Antifungal prophylaxis for severely neutropenic chemotherapy recipients: a meta-analysis of randomized-controlled clinical trials

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Authors' objectives
To assess the clinical efficacy ofazole antifungal agents and low-dose intravenous amphotericin B for antifungal chemoprophylaxis in patients with malignant disease who have severe neutropenia.

Searching
MEDLINE and EMBASE were searched from 1966 to 2000. The key terms included 'neutropenia', 'granulocytopenia', 'carcinoma', 'leukemia', 'bone marrow transplantation', 'fungal infection' and 'prophylaxis'. The bibliographies of retrieved studies and reviews were examined, and pharmaceutical companies and researchers in the field were contacted for additional studies. Studies reported in any language were considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Comparisons of regimens that included azoles (fluconazole, itraconazole, ketoconazole and miconazole) or polyenes (intravenous low-dose amphotericin B deoxycholate or lipid-based formulations of amphotericin B) with control regimens that included placebo, no treatment or polyene-based treatment (oral or intravenous amphotericin B deoxycholate or oral nystatin with or without additional agents) were eligible for inclusion. The daily drug doses used in the included studies were as follows: fluconazole, 50 to 400 mg; ketoconazole, 200 to 400 mg; miconazole, 2,000 mg or 15 mg/kg intravenously; itraconazole, from 200 mg or 5 mg/kg; amphotericin B, from 40 to 4,000 mg or 100 mg/kg, or 0.1 to 0.5 mg/kg intravenously; ambisome, 0.1 to 2 mg/kg intravenously; nystatin, 2 to 72 MU; and clotrimazole, 20 mg. The study duration per treatment arm, where stated, ranged from 14 to 81 days.

Participants included in the review
Patients who received cytotoxic therapy for acute leukaemia or haemopoietic stem cell transplantation (HSCT), which was sufficient to produce a period of neutropenia (absolute neutrophil count less than 1.0E09/L) lasting one week or more, were eligible for inclusion.

Outcomes assessed in the review
The inclusion criteria were not defined in terms of the outcomes. The five primary outcomes assessed in the review were:

prophylaxis success, defined by study completion without the administration of parenteral, full-dose antifungal therapy for patients with suspected or proven invasive fungal infection;

superficial fungal infection, defined by infection of integumentary surfaces attributable to fungi;

proven invasive fungal infection, requiring microbiological or histological identification of fungal pathogen from normally sterile body area plus clinical evidence of infection;

overall mortality (death from any cause during the study period); and

fungal infection-related mortality (association between death and fungal infection reported by the authors).

The incidence of invasive aspergillosis (proven fungal infection attributed by investigators to Aspergillus species) was also assessed.
How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Validity was assessed and scored using a five-point scale that assessed randomisation, blinding, handling of withdrawals and concealment of allocation (see Other Publications of Related Interest nos.1-2). Three reviewers independently assessed validity.

Data extraction
Three reviewers independently extracted the data onto standardised forms and data from each trial were checked. The following information were tabulated: author, drugs used, the number of patients in each treatment arm, daily dose of study drug, diagnosis, duration of neutropenia, and duration of study. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each study.

Methods of synthesis
How were the studies combined?
Pooled weighted ORs and 95% CIs were calculated for each outcome using fixed-effect models, or random-effects models where statistical heterogeneity was detected. Where zero events occurred, 0.5 was substituted. The relative risk reduction (RRR) of the outcomes was also estimated, along with the 95% CI. The number-needed-to-prevent or promote an outcome was also calculated. Publication bias was assessed for each outcome using the method described by Egger et al. (see Other Publications of Related Interest no.3).

How were differences between studies investigated?
Statistical heterogeneity was tested using the chi-squared test (threshold value, P<0.1). The OR and 95% CI were re-calculated for each outcome for the following subgroups: after excluding RCTs with validity scores of less than 3 (the median); sequential exclusion of paediatric and adult RCTs; sequential exclusion of HSCT-related and non-HSCT RCTs; exclusion of RCTs according to duration of neutropenia (either less than 14 days or greater than 22 days, representing the 25th and 75th quartiles, respectively); exclusion of each RCT in turn; drug regimens compared (azoles versus placebo or no treatment, azoles versus active polyene-based control, and low-dose amphotericin B formulations versus placebo); and study drug. The influence of the following factors on the outcomes was assessed using meta-regression: study drug; drug regimes compared; proportion of patients in study undergoing HSCT; dose of azole; duration of neutropenia; use of haematopoietic growth factors; rates of proven invasive fungal infection in the control group; and the proportion of patients receiving treatment for acute leukaemia.

Results of the review
Thirty-eight RCTs (7,014 patients) were included.

The mean quality score was 2.87 (median 3.0, range: 0 to 5 points). There was no evidence for publication bias across any of the five primary outcomes (P = 0.2198 to 0.9255).

Antifungal prophylaxis significantly reduced the use of parenteral antifungal therapy, superficial fungal infection, invasive fungal infection, and fungal infection-related mortality. The OR for use of antifungal therapy was 0.57 (95% CI: 0.48, 0.68), the RRR was 19% and the NNT was 10 patients; significant heterogeneity was detected (P=0.007). The OR for superficial fungal infection was 0.29 (95% CI: 0.20, 0.43), the RRR was 16% and the NNT was 12 patients; significant heterogeneity was detected (P=0.0003). The OR for invasive fungal infection was 0.13 (95% CI: 0.36, 0.53), the RRR was 56% and the NNT was 22 patients; no significant heterogeneity was detected (P=0.31). The OR for fungal infection-related mortality was 0.58 (95% CI: 0.41, 0.82), the RRR was 47% and the NNT was 52 patients; no significant heterogeneity was detected (P=0.91).

There was no significant difference between antifungal prophylaxis and control in overall mortality or invasive
aspergillosis. The OR was 0.87 (95% CI: 0.74, 1.03) for overall mortality and 1.03 (95% CI: 0.62, 1.44) for invasive aspergillosis; no significant heterogeneity was detected (P=0.44 and P=0.99, respectively).

In the sensitivity analysis, similar results were found for subgroups of studies with quality scores above the median, for comparisons of azoles versus placebo or no treatment controls, and after excluding each study in turn. The subgroup analysis found that antifungal prophylaxis significantly reduced mortality in patients with prolonged neutropenia (OR 0.72, 95% CI: 0.55, 0.95) and patients who underwent HSCT (OR 0.77, 95% CI: 0.59, 0.99). In the meta-regression, the factors associated with increased effect of antifungal prophylaxis were HSCT (P=0.085), prolonged neutropenia (P=0.824), acute leukaemia with prolonged neutropenia (P=0.0178) and higher azole dose (P=0.0131).

Authors’ conclusions
Antifungal prophylaxis reduced morbidity, superficial fungal infection, invasive fungal infection and fungal infection-related mortality. The effects were greater in people with malignant disease who had prolonged neutropenia and HSCT.

CRD commentary
The aims of the review were stated and the inclusion criteria were defined in terms of the participants, study design and intervention. Studies were sought from several sources and attempts were made to locate unpublished material, but the methods used to select the studies were not described. Validity was assessed using a validated scale and the methods used to assess validity were described.

Relevant data were extracted and tabulated, and details were provided of the methods used to extract the data. Statistical heterogeneity was assessed and the influence of various factors on the results was explored. However, it is unclear whether the studies in the subgroup analyses were statistically homogeneous. Potential reasons for the finding of no difference in overall mortality and a reduced fungal infection-related mortality were not discussed. The evidence presented appears to support the authors’ conclusions.

Implications of the review for practice and research
Practice: The authors state that the Center for Disease Control, the Infectious Diseases Society of America, and the American Society for Blood and Marrow Transplantation recommend the use of fluconazole 400 mg daily (orally or intravenously) to prevent invasive disease due to fluconazole susceptible Candida spp. during neutropenia until engraftment in HSCT patients. They further recommend the use of low-dose intravenous amphotericin B as antifungal prophylaxis.

Research: The authors state that further research is required to identify the patients who are most susceptible to invasive antifungal infection.

Bibliographic details

PubMedID
12115356

DOI
10.1002/cncr.10610

Other publications of related interest
Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. BMJ 1997;315:629-34.

Indexing Status
Subject indexing assigned by NLM

MeSH
Antifungal Agents /therapeutic use; Antineoplastic Agents /adverse effects; Hematopoietic Stem Cell Transplantation; Humans; Mycoses /prevention & control; Neoplasms /complications /drug therapy; Neutropenia /complications; Randomized Controlled Trials as Topic

AccessionNumber
12002001532

Date bibliographic record published
31/08/2003

Date abstract record published
31/08/2003

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.