Review: Prophylactic antifungal treatment decreases systemic fungal infection but not mortality in cancer complicated by neutropenia

Gotzsche PC, Johansen HK. Meta-analysis of prophylactic or empirical antifungal treatment versus placebo or no treatment in patients with cancer complicated by neutropenia. BMJ. 1997 Apr 26;263:1238-44.

Objective
To determine the effectiveness of antifungal agents given prophylactically or empirically in patients with cancer complicated by neutropenia.

Data sources
Studies were identified by searching MEDLINE (1966 to 1996) using the terms random, control, blind, clinical trial, placebo, comparative study, amphotericin, AmBisome, fluconazole, itraconazole, ketoconazole, miconazole, bone marrow, transplant, cancer, fungemia, haematologic, malignancy, neoplasms, neutropenia, granulocytopenia, leukemia, lymphoma, sepsis, septic, intensive care, and immunodeficiency. Pharmaceutical companies and authors were contacted, and conference proceedings and references were scanned.

Study selection
Studies were selected if they were randomised trials comparing empirical (n = 3) or prophylactic (n = 21) amphotericin B, various lipid soluble formula- tions of amphotericin B, fluconazole, ketoconazole, miconazole, or itracon-azole with placebo or no treatment in patients with cancer complicated by neutropenia. Studies of treatment or prevention of oral candidiasis were excluded.

Data extraction
Data were extracted on diagnosis, drug, dose, rules for use of additional antifungal agents, length of treatment with placebo, length of follow-up, randomisation and blinding, number of patients randomised and excluded from analysis, deaths, invasive fungal infections, colonisation, and use of rescue treatment.

Main results
24 studies (2758 patients) met the selection criteria. The mortality rate was compared between antifungal therapy and control groups.

Antifungal vs control therapy*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Antifungal weighted EER</th>
<th>Control weighted CER</th>
<th>RRR (95% CI)</th>
<th>Weighted ARR</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>17.2%</td>
<td>18.4%</td>
<td>6%</td>
<td>1.2%</td>
<td>Not significant</td>
</tr>
<tr>
<td>Infection</td>
<td>6.2%</td>
<td>10.0%</td>
<td>3.8%</td>
<td>18%</td>
<td>(18 to 32)</td>
</tr>
<tr>
<td>Colonisation</td>
<td>38.2%</td>
<td>54.1%</td>
<td>15.9%</td>
<td>7%</td>
<td>(5 to 18)</td>
</tr>
</tbody>
</table>

*Abbreviations defined in Glossary; RRR, ARR, NNT, and CI calculated from data in article.

Commentary
Gotzsche and Johansen conclude that prophylactic or empirical antifungal treatment in cancer patients with neutropenia does not reduce overall mortality despite reducing the incidence of invasive fungal infection (IFI) by about 50%. How can this be?

The low incidence of IFI in patients who did not receive prophylaxis may be the explanation. Despite the poor outcome of IFI, any differences in mortality from IFI with treatment will be small and greatly overshadowed by the more common causes of death in these patients.

The applicability of this meta-analysis to clinical practice depends on the incidence of IFI in a given patient population and the value attached to IFI prevention. If reduction of overall mortality is the principal goal, antifungal prophylaxis is likely to be effective only in patient populations with high rates of IFI, possibly only in those with rates exceeding 20%. The patients at highest risk are probably allogeneic bone marrow transplant recipients treated without laminar airflow rooms. However, most cancer treatment programs do not have such a high incidence of IFI. Whether the costs and risks associated with antifungal therapy are justifiable to reduce the incidence of IFI without reducing overall mortality is debatable. I do not endorse antifungal prophylaxis in patient populations with an IFI incidence of < 10%.

This meta-analysis also questions the common practice of empirical antifungal therapy in patients who remain febrile with neutropenia despite 4 to 7 days of broad spectrum antibacterial therapy, a practice endorsed by the Infectious Diseases Society of America.

18%. The overall mortality rates did not differ between antifungal therapy and control groups (P = 0.44) (Table 1). However, amphotericin was associated with increased mortality (odds ratio 0.58, 95% CI 0.37 to 0.93). Antifungal treatment decreased the risk of invasive fungal infection (P < 0.001) and colonisation (P < 0.001) (Table 2).

References

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