Antifungal agents for preventing fungal infections in non-neutropenic critically ill and surgical patients: systematic review and meta-analysis of randomized clinical trials

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Objectives: This study aims to systematically identify and summarize the effects of antifungal prophylaxis in non-neutropenic critically ill adult patients on all-cause mortality and the incidence of invasive fungal infections.

Methods: Systematic review and meta-analysis of randomized controlled trials in all languages comparing the prophylactic use of any antifungal agent or regimen with placebo, no antifungal or another antifungal agent or regimen in non-neutropenic critically ill adult patients. We searched the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 3, 2005), MEDLINE (1966 to 2 September 2005) and EMBASE (1980 to week 36, 2005). We also hand-searched reference lists, abstracts of conference proceedings and scientific meetings (1998–2004) and contacted authors of included studies and pharmaceutical manufacturers. The primary outcomes assessed were all-cause mortality and proven invasive fungal infections. Two reviewers independently applied selection criteria, performed quality assessment and extracted data using an intention-to-treat approach. Data were synthesized using the random effects model and expressed as relative risk with 95% confidence intervals.

Results: Twelve unique trials (eight comparing fluconazole and four ketoconazole with no antifungal or a non-absorbable agent) involving 1606 randomized patients were included. For both outcomes of total mortality and invasive fungal infections, almost all trials of fluconazole and ketoconazole separately showed a non-significant risk reduction with prophylaxis. When combined, fluconazole/ketoconazole reduced total mortality by one-quarter (relative risk 0.76, 95% confidence interval 0.59–0.97) and invasive fungal infections by about one-half (relative risk 0.46, 95% confidence interval 0.31–0.68). No significant increase in the incidence of infection or colonization with the azole-resistant fungal pathogens Candida glabrata or Candida krusei was demonstrated, although the confidence intervals of the summary effect measures were wide. Adverse effects requiring treatment discontinuation were not more common amongst patients receiving prophylaxis. Results across all trials were homogeneous despite considerable heterogeneity in clinical and methodological characteristics.

Conclusions: Prophylaxis with fluconazole or ketoconazole in critically ill patients reduces invasive fungal infections by one-half and total mortality by one-quarter. Although no significant increase in azole-resistant Candida species associated with prophylaxis was demonstrated, trials were not powered to exclude such an effect. In patients at increased risk of invasive fungal infections, antifungal prophylaxis with fluconazole should be considered.

Keywords: mycoses, candidiasis, fungaemia, antifungals, fluconazole, ketoconazole, intensive care, critical care
Introduction

The incidence of invasive fungal infections in critically ill intensive care unit (ICU) and surgical patients has been increasingly recognized over recent decades. Although the incidence of candidaemia amongst unselected ICU patients is only 0.5–2%, those with certain risk factors, such as recent abdominal surgery, gastrointestinal tract perforation, dialysis, central venous catheterization, total parenteral nutrition, broad-spectrum antibiotic therapy and colonization with Candida species are at increased risk. Invasive fungal infections in such patients are associated with crude mortality rates of 30–40%, prolonged lengths of ICU stay, and excess economic costs. As these infections are often recognized and treated late, given their non-specific clinical features and the poor sensitivity of diagnostic tests, recent interest has therefore focused on preventative strategies. Although antifungal prophylaxis reduces the incidence of invasive fungal infections in high-risk patient groups, the relative benefits and harms, and the cost-effectiveness of antifungal prophylaxis in non-neutropenic critically ill patients remain incompletely defined, which is reflected by observed variability in clinical practice. Potential ecological effects of widespread antifungal use, including the selection and spread of resistant fungal strains or species, are of particular concern. Although recent guidelines from the Infectious Diseases Society of America have endorsed an ‘A-1’ recommendation for antifungal prophylaxis for ‘carefully selected patients’ in ICUs with high rates of invasive candidiasis, until recently, a systematic synthesis of the benefits and harms of antifungal prophylaxis has not been published.

Materials and methods

Inclusion criteria

We included randomized controlled trials that evaluated the effect of any antifungal regimen with placebo, no antifungal or another antifungal regimen in non-neutropenic critically ill patients (such as those admitted to an ICU or having recently undergone abdominal or another major surgical procedure). Trials including non-neutropenic critically ill patients together with such other patient groups were included if the proportion of these was <25% or if data on non-neutropenic patients were separately provided. The study groups were required to differ only for the antifungal regimen under investigation; other co-interventions and aspects of care, including the routine use of other prophylactic antimicrobial agents, were required to be the same to avoid potentially confounded comparisons.

Search strategy

We searched MEDLINE (OVID: 1966 to 2 September 2005), EMBASE (OVID: 1980 to week 36, 2005) and CENTRAL (Issue 3, 2005) using a search strategy (see Supplementary data available at JAC Online) that incorporated MeSH terms and textwords for antifungal agents and for fungal infections, combined with highly sensitive search strategies for identifying randomized controlled trials in MEDLINE and EMBASE. We also searched the proceedings of major relevant conferences, trial databases, the reference lists of identified trials and major reviews, and the manufacturers of the study drugs for additional published or unpublished trial data. We did not apply a language restriction. Letters, abstracts and unpublished trials were accepted to reduce publication bias. If duplicate publication was suspected, we contacted the study authors for clarification, and, if confirmed, the publication with the longest follow-up data were used for the review.

Outcomes

Primary outcomes included total (all-cause) mortality and proven invasive fungal infection. Criteria for proven invasive fungal infection were a compatible clinical illness with either histopathological evidence of invasive fungal infection or a positive fungal culture from at least one sterile site (including blood) specimen. Funguria in the absence of a complicated urinary tract infection, and mucocutaneous fungal infections, including fungal oesophagitis, were classified as superficial, rather than invasive, infections. Secondary outcomes were suspected invasive fungal infections (systemic antifungal therapy without criteria for proven invasive fungal infection), fungal colonization at any site (that either developed or persisted during prophylaxis) and adverse events requiring study drug cessation. The incidence of invasive infection or colonization with intrinsically or relatively fluconazole-resistant fungal species, such as Candida glabrata, Candida krusei and filamentous fungi were also assessed. Outcome data were extracted and analysed for all randomized patients on an intention-to-treat basis wherever possible and were assessed at the time of discharge from ICU or at the end of prophylaxis, whichever was longer.

Quality assessment

Trials were assessed for methodological quality, including randomized sequence generation, allocation concealment, blinding, intention-to-treat analysis and completeness of follow-up. Each study quality factor was assessed separately and no composite scoring system was applied.

Data analysis

Data were analysed using relative risks (RRs) and 95% confidence intervals (CIs). Heterogeneity across trials was assessed with a test of homogeneity ($\chi^2$ on $k$ – 1 degrees of freedom), with $P <0.1$ considered significant. A test of inconsistency ($I^2$), measuring the proportion of total variation in the estimates of treatment effect due to heterogeneity between trials, was also applied. Treatment effects across trials were combined using a random effects model and compared with a fixed effect model in a sensitivity analysis. Further sensitivity analyses assessed the effect of study methodological quality. Subgroup analyses according to clinical characteristics (such as definition of invasive fungal infection and the proportion of surgical patients) and antifungal prophylaxis regimens (different agents and dose) were performed. Publication bias was assessed using a funnel plot (log relative risk for efficacy versus 1/standard error).

Results

Description and assessment of studies

From the search strategy (Figure 1), 12 unique trials were included (Table 1). Eight compared fluconazole with no antifungal and four ketoconazole with no antifungal or a non-absorbable agent. All trials but two were restricted to ICU patients. Post-surgical patients comprised >75% of trial participants in six trials, 50–75% in two, and not stated in two. No trials directly compared different marketed systemic antifungal agents, although one trial compared fluconazole and control with ‘garlicin’.

Outcome reporting was variable [Table 1 and Table A1 (Supplementary Table A1 is available at JAC Online)]. Invasive
Fungal infections were reported in ten trials: six \cite{30,31,33-35,38} reported criteria that were consistent with our definition (i.e. requiring positive cultures and/or histological findings from sterile site/deep tissue specimens), whereas four \cite{29,32,36,37} included positive cultures from one or more superficial sites as evidence of invasive infection, which we would consider representing either colonization or superficial infection. Other outcomes were even more variably reported, particularly with respect to the fungal species associated with infection and/or colonization.

Adequate methods of random sequence generation and allocation concealment were reported in five and seven trials respectively [Table A2 (Supplementary Table A2 is available at JAC Online)]. Although blinding of trial subjects and investigators was reported in nine trials, only three also reported blinding of outcome assessors. Intention-to-treat analysis was apparent in seven trials, although post-randomization exclusions >10% occurred in only two.

**Total mortality (Figure 2)**

Although total mortality rates in the control arms in the seven fluconazole trials reporting this outcome was very variable (range 0–54%, mean 26%), there was no significant heterogeneity in the observed effect of fluconazole across these trials. One trial \cite{33} demonstrated a significant mortality reduction (RR 0.41, 95% CI 0.2–0.83) with fluconazole, with four other trials \cite{30,31,35,36} showing a small, albeit statistically non-significant, benefit. The summary relative risk favoured fluconazole, but was not significantly less than 1.0 (RR 0.77, 95% CI 0.56–1.07). Mortality in the control arms
<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting/inclusion criteria</th>
<th>Baseline characteristics</th>
<th>Intervention(s)</th>
<th>Intervention duration</th>
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<tbody>
<tr>
<td><strong>Fluconazole versus placebo/no antifungal agent</strong></td>
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<tr>
<td>Ables et al. 29</td>
<td>USA, single hospital, ICU; patients ≥14 years; trauma, intraabdominal or intrathoracic surgery; expected LOS &gt;48 h; ≥1 ‘risk factor’</td>
<td>age (mean, 44 years); APACHE II score (mean, 18); trauma (70%); intraabdominal or intrathoracic surgery (30%); malignancy (3%); fungal colonization (24%)</td>
<td>fluconazole 800 mg initially, then 400 mg/day iv/po (n = 63); placebo (n = 62)</td>
<td>until ICU discharge until withdrawal of mechanical ventilation (maximum 6 weeks)</td>
</tr>
<tr>
<td>Eggimann et al. 30</td>
<td>Switzerland, two hospitals, mixed ICUs; patients ≥16 years; recent abdominal surgery and recurrent gastrointestinal perforation or anastomotic leakage</td>
<td>age (median 57–63 years); APACHE II score (median, 13); gastrointestinal malignancy (37%); pancreatitis (10%); antibiotic exposure (100%); fungal colonization (40%)</td>
<td>fluconazole 400 mg/day iv (n = 25); placebo (n = 24)</td>
<td>until ‘complete resolution of intraabdominal disease’ (median, 15–17 days)</td>
</tr>
<tr>
<td>Garbino et al. 31</td>
<td>Switzerland, single hospital, mixed ICU; patients &gt;18 years; mechanically ventilated ≥48 h and expected further ≥72 h</td>
<td>age (mean, 54.3 years); APACHE II (19.4); abdominal surgery (20%); other surgery (40%); malignancy (15%); selective decontamination of digestive tract (100%); systemic antibiotic exposure (39%); TPN (28%); fungal colonization (48%)</td>
<td>fluconazole 100 mg/day iv (n = 110); placebo (n = 110)</td>
<td>until withdrawal of mechanical ventilation</td>
</tr>
<tr>
<td>He et al. 32</td>
<td>China, ?single hospital, ?ward and/or ICU; pancreatitis; ≥1 ‘predisposing factor’</td>
<td>age (mean, 50.2 years); APACHE II (mean, 12.2)</td>
<td>fluconazole 100 mg/day iv (n = 22); ‘garlicin’ 120 mg/day (n = 25); control (neither fluconazole nor ‘garlicin’) (n = 23)</td>
<td>until ‘relief of predisposing condition’</td>
</tr>
<tr>
<td>Jacobs et al. 33</td>
<td>Saudi Arabia, single hospital, mixed ICU; septic shock within 24 h of onset from nosocomial pneumonia or intraabdominal sepsis</td>
<td>pneumonia (52%); intraabdominal sepsis (48%); surgery (65%); APACHE II (mean, 18.4); fungal colonization (6%)</td>
<td>fluconazole 200 mg/day iv (n = 32); placebo (n = 39)</td>
<td>for duration of septic shock</td>
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<tr>
<td>Parizkova et al. 34</td>
<td>Czech Republic, single hospital, ICU; in ICU &lt;5 days with ≥24 h antibiotic exposure and ≥48 h mechanical ventilation</td>
<td>age (mean, 44.5 years); APACHE II (mean, 23); gastrointestinal surgery (37%); TPN (97%); broad-spectrum antibiotics (66%); central venous access (100%)</td>
<td>fluconazole 100 mg/day iv (n = 18); control (no fluconazole) (n = 20)</td>
<td>until ICU discharge</td>
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</tbody>
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### Table 1. Continued

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting/inclusion criteria</th>
<th>Baseline characteristics</th>
<th>Intervention(s)</th>
<th>Intervention duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelz et al. [35]</td>
<td>USA, single hospital, surgical ICU; expected length of ICU stay ≥3 days</td>
<td>age (median, 63–66 years); APACHE III (median, 63–65); surgery (91%); TPN (9%); antibiotics exposure (29%); central venous access (95%); malignancy (29%); fungal colonization (79%)</td>
<td>fluconazole 800 mg/day po initially, then 400 mg/day po thereafter (n = 130); placebo (n = 130)</td>
<td>until ICU discharge (mean, 5 days)</td>
</tr>
<tr>
<td>Sandven et al. [36]</td>
<td>Norway, 13 hospitals, ICU and/or ward; gastrointestinal perforation or anastomotic leakage</td>
<td>age (median, 60–68 years); surgery (100%); antibiotics ≥3 days (14%); malignancy (40%)</td>
<td>fluconazole 400 mg single dose iv (n = 53); placebo (n = 56)</td>
<td>single dose</td>
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<tr>
<td><strong>Ketoconazole versus placebo/no antifungal/non-absorbable antifungal agents</strong></td>
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<tr>
<td>ARDS Network [39]</td>
<td>USA, 24 hospitals, ICUs; patients ≥18 years; acute lung injury or ARDS on mechanical ventilator</td>
<td>age (mean, 53 years); APACHE III (mean, 81.3); sepsis (31%); trauma (10%)</td>
<td>ketoconazole 400 mg/day po (n = 117); placebo (n = 117)</td>
<td>until 48 h post-extubation</td>
</tr>
<tr>
<td>Savino et al. [37]</td>
<td>USA, single hospital, surgical ICU; expected length of ICU stay ≥48 h</td>
<td>age (mean, 54 years); APACHE II (mean, 11.3); TPN (42%); surgery (79%); malignancy (27%)</td>
<td>ketoconazole 200 mg/day po (n = 65); clotrimazole 10 mg every 8 h po (n = 80); nystatin 8 million units/day po (n = 75); control (no antifungal) (n = 72)</td>
<td>until ICU discharge (mean, 8–16 days)</td>
</tr>
<tr>
<td>Slotman and Burchard [38]</td>
<td>USA, single hospital, surgical ICU; ≥3 ‘risk factors’; no fungal colonization</td>
<td>age (median, 59–65 years); intraabdominal surgery (39%); other surgery (59%); TPN (25%); antibiotics ≥7 days (26%); malignancy (11%); corticosteroids (5%)</td>
<td>ketoconazole 200 mg/day po (n = 35); placebo (n = 36)</td>
<td>until ICU discharge (maximum 21 days)</td>
</tr>
<tr>
<td>Yu and Tomasa [40]</td>
<td>USA, single hospital, surgical ICU; patients ≥16 years; sepsis</td>
<td>age (mean, 53.2 years); APACHE II (13); number of surgical procedures (mean, 1.6 per patient)</td>
<td>ketoconazole 400 mg/day po (n = 26); placebo (n = 28)</td>
<td>until ICU discharge (maximum 21 days)</td>
</tr>
</tbody>
</table>

LOS, length of stay; TPN, total parenteral nutrition; iv, intravenous; po, orally/enterally.

*Figures represent numbers of patients who were treated in each arm; eight patients randomized to receive ketoconazole subsequently allocated to other arms.*
of the four ketoconazole trials ranged from 16 to 42% (mean, 25%), with some heterogeneity evident ($P = 0.1$, $I^2 = 52.3\%$). The results of three trials$^{37,38,40}$ favoured ketoconazole, with the pooled analysis demonstrating a statistically non-significant mortality reduction (RR 0.68, 95% CI 0.42–1.12). Across all 11 trials, the results were homogeneous and a significant reduction in total mortality of around one-quarter (RR 0.76, 95% CI 0.59–0.97) was demonstrated.

### Invasive fungal infections (Figure 3)

Fluconazole significantly reduced the incidence of proven invasive fungal infections by about one-half (RR 0.47, 95% CI 0.32–0.7). One trial$^{34}$ did not report any proven infections, whereas amongst the other seven fluconazole trials, the incidence ranged from 3 to 41% (mean, 15%). All infections were caused by Candida spp. Despite differences in the dose, route of administration and duration of fluconazole prophylaxis, there was no significant heterogeneity in the relative risk reduction across studies. Amongst the two ketoconazole trials that reported invasive infections, no statistically significant reduction was demonstrated, although CIs were wide (RR 0.3, 95% CI 0.07–1.31). Across all trials of both fluconazole and ketoconazole, the results were homogeneous, with a significant reduction in invasive infections of about one-half (RR 0.46, 95% CI 0.31–0.68).

### Suspected invasive infections, superficial infections and fungal colonization (Table 2)

Fluconazole prophylaxis did not reduce the incidence of suspected invasive fungal infections amongst the four trials that reported this outcome, although was associated with a statistically non-significant reduction in the combined incidence of proven and suspected invasive fungal infections (RR 0.64, 95% CI 0.4–1.02). Fluconazole prophylaxis was associated with a non-significant reduction in superficial fungal infections (RR 0.59, 95% CI 0.27–1.29). Both fluconazole and ketoconazole prophylaxis reduced the incidence of fungal colonization (RR 0.55, 95% CI 0.42–0.74 and RR 0.66, 95% CI 0.47–0.94 respectively).

### Infection and colonization with azole-resistant fungi (Table 2 and Figure 4)

Infections with C. glabrata and C. krusei were documented in four of the six fluconazole trials that provided data on the species of invasive fungal pathogens.$^{29–31,35}$ Amongst these four trials, infections with C. glabrata or C. krusei accounted for 16% of all invasive infections in the control arms and 21% in the fluconazole arms. The incidence of proven invasive infections caused by these species was not significantly increased with either fluconazole (RR 0.66, 95% CI 0.223–1.96) or ketoconazole prophylaxis (RR 0.34, 95% CI 0.01–8.14). Fungal colonization with C. glabrata or C. krusei occurred in 6 and 15% in the control and fluconazole arms respectively. Although no statistically significant effect of fluconazole on colonization with these species was demonstrated, three of the four fluconazole trials did report greater colonization rates and the CIs around the pooled estimate were very wide (RR 1.74, 95% CI 0.64–4.71).

### Adverse events (Table 2)

Adverse events requiring cessation of systemic antifungal prophylaxis were very uncommon and did not occur more frequently than in the control arms.

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**Figure 2.** Total mortality.

**Table 2.** Fungal colonization with azole-resistant fungi.
In subgroup analyses, no obvious effect of clinical characteristics or antifungal prophylaxis regimen was evident. The mortality benefit for the two trials assessing hospital mortality appeared less than for the seven trials assessing ICU or 30-day mortality. Sensitivity analyses did not demonstrate an effect of analysis method (random effects or fixed effect models) or study methodological quality.

Publication bias (Figure 5)
Although trial numbers were relatively small, some degree of asymmetry in the funnel plot of precision by effect size was evident, with a relative absence of smaller trials reporting a lack of benefit from antifungal prophylaxis.

Discussion
This meta-analysis demonstrates that antifungal prophylaxis in non-neutropenic critically ill patients reduces proven invasive fungal infections by approximately one-half and total mortality by approximately one-quarter.

Although none of the individual fluconazole trials demonstrated a statistically significant reduction in invasive infections, the pooled result was highly significant. Furthermore, the efficacy
of fluconazole was remarkably consistent across the studies despite considerable differences in the dose, duration, route of its administration and in other clinical and methodological aspects. This suggests that these results may be generalizable to a diverse range of clinical situations. Assuming a baseline incidence of invasive fungal infections amongst unselected critically ill patients of 2%, 94 patients would require fluconazole prophylaxis to prevent one infection. This estimate varies according to risk (Table 3): ranging, for example, from nine amongst higher risk patients (with an approximate 20% incidence) to 188 amongst lower risk patients (with an approximate 1% incidence). A similar—albeit statistically non-significant—effect was observed with ketoconazole on the basis of two trials reporting this outcome. The pooled analysis for fluconazole prophylaxis suggests a 23% mortality benefit, with relatively wide CIs (from a 7% hazard to a 44% benefit). However, inclusion of the ketoconazole trials in the pooled analysis demonstrates a statistically significant result of about the same magnitude (24% mortality benefit, 95% CI 3–41%). Using this effect estimate, the number of patients requiring antifungal prophylaxis to prevent one death ranges from 83 (95% CI 49–667) amongst those with a 5% mortality risk to 9 (95% CI 5–67) amongst those with a 50% risk. These findings are thus highly encouraging. However, whether this mortality benefit is mediated through preventing invasive fungal infections remains uncertain. Although crude mortality rates of 40–60% have been reported for critically ill ICU patients with candidaemia, estimates of attributable mortality from epidemiological studies accounting for the confounding effect of underlying severity of illness have yielded conflicting results. Thus, it remains possible that the prevention of fungal infections, in itself, may not be the sole mechanism by which deaths are prevented in otherwise critically ill patients. Of note is the lack of total mortality benefit from antifungal prophylaxis in other high-risk patients, such as neutropenic patients or solid organ transplant recipients. Although a reduction in fungal-related mortality has been reported with antifungal prophylaxis amongst neutropenic patients, we did not consider this outcome, as we considered the attribution of deaths to fungal infections too imprecise and subjective and therefore prone to bias, particularly in trials without blinded outcome assessors. Other mechanisms, independent of antifungal activity, may contribute to a mortality benefit: both fluconazole and ketoconazole may exert anti-inflammatory and immunomodulatory effects. Indeed such effects provided the rationale for three of the ketoconazole and one of the fluconazole trials in patients with acute respiratory distress syndrome or septic shock. Although a mortality benefit of antifungal prophylaxis is promising and potentially clinically important, further appropriately powered clinical trials to both confirm this mortality benefit and to identify specific patient subsets, amongst the typically heterogeneous ICU population, whom are likely to derive the greatest benefit are required.

The selection of resistant fungal species is a major potential adverse consequence of widespread antifungal use. Certain Candida species, such as C. glabrata and C. krusei, and most filamentous fungi, including Aspergillus species, are intrinsically or relatively fluconazole-resistant. The development of fluconazole-resistance amongst susceptible species and the emergence of intrinsically resistant species have been associated with...
Systematic review

Table 3. Applicability of meta-analysis results

<table>
<thead>
<tr>
<th>Estimated risk</th>
<th>Examples</th>
<th>Incidence without fluconazole prophylaxis (IFIs/100 patients)</th>
<th>Incidence with fluconazole prophylaxis (IFIs/100 patients)</th>
<th>Number avoided/100 patients</th>
<th>Number needed to treat to prevent one episode of IFI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (≤1%)</td>
<td>absence of risk factors(^b)</td>
<td>1</td>
<td>0.47</td>
<td>0.53</td>
<td>188 (147–345)</td>
</tr>
<tr>
<td>Average (2%)</td>
<td>unselected ICU population(^b)</td>
<td>2</td>
<td>0.94</td>
<td>1.06</td>
<td>94 (74–172)</td>
</tr>
<tr>
<td>High (11%)</td>
<td>one of diabetes, new onset haemodialysis, TPN prior to ICU entry or broad-spectrum antibiotics(^b)</td>
<td>11</td>
<td>5.2</td>
<td>5.8</td>
<td>17 (13–31)</td>
</tr>
<tr>
<td>High (17%)</td>
<td>one of diabetes, new onset haemodialysis or TPN prior to ICU entry(^b)</td>
<td>17</td>
<td>8.0</td>
<td>9.0</td>
<td>11 (9–20)</td>
</tr>
<tr>
<td>Highest (20%)</td>
<td>one of diabetes, new onset haemodialysis or TPN prior to ICU entry, and broad-spectrum antibiotics(^b)</td>
<td>20</td>
<td>9.4</td>
<td>10.6</td>
<td>9 (7–17)</td>
</tr>
</tbody>
</table>

IFI, invasive fungal infection; TPN, total parenteral nutrition.
\(^a\)Calculation based on RR 0.47 (0.32–0.71).
\(^b\)Based on ref. 18.
\(^c\)Based on ref. 54.

The use of antifungal agents, particularly amongst neutropenic or HIV-infected patients.\(^{43-48}\) Whether such use amongst critically ill ICU patients has resulted, or will result, in a similar phenomenon remains uncertain. In the fluconazole trials reporting the species of infecting fungal pathogens, no statistically significant increase in invasive infections or colonization caused by C. glabrata or C. krusei was demonstrated, although more patients were colonized with these species in the fluconazole arms of three of four trials. The wide CIs around these pooled estimates reflect relatively small event rates and insufficient sample sizes. Thus, that fluconazole prophylaxis may predispose to infection or colonization with azole-resistant fungal species cannot be excluded from the available studies and further studies involving the characterization and susceptibility testing of fungal isolates, an appropriate timeframe, and sufficient statistical power are required.

The trials included in this review are insufficiently powered to exclude adverse toxic events. Ketoconazole—and to a lesser extent fluconazole—have been associated with hepatotoxicity and clinically important drug interactions. The likelihood and severity of such events with routine antifungal prophylaxis require careful consideration.

The major limitation of this systematic review is the relatively small number of trials and their small sample sizes causing imprecision of pooled estimates. We sought to maximize study retrieval by employing a comprehensive search strategy encompassing the major computerized databases without language restriction, major conference proceedings, unpublished studies and review articles. We approached major pharmaceutical companies marketing antifungal agents, but identified no additional or unpublished studies. Despite these efforts, some degree of funnel plot asymmetry was evident, which suggests the possibility of publication bias.

The methodological quality of studies in this review, as reported, was generally of high standard. In more than half of trials adequate allocation concealment, an important potential source of bias if inadequate,\(^{49}\) was reported. As invasive fungal infections are often diagnosed with some degree of uncertainty and subjectivity, blinding of outcome assessors with respect to treatment allocation would be an important precaution to minimize bias. However, this precaution was specifically reported in only three trials. Despite progress toward standardization,\(^{25}\) a varied, and often conflicting, range of diagnostic criteria for invasive fungal infections have been published.\(^{50}\) This problem was evident amongst the trials reviewed here. We therefore, wherever possible, restricted the diagnosis to patients with compatible clinical features in whom fungi were demonstrated in blood or deep tissue specimens by histopathology and/or culture. Four trials also included positive cultures from non-sterile site specimens as evidence of invasive infections making independent classification of infections impossible. Although in this review, the direction and magnitude of trial results did not appear to correlate with the presence or absence of reported study methodological quality parameters, we urge the incorporation and reporting of methodological quality parameters and the adoption of standardized diagnostic criteria for future trials.

Despite heterogeneity of the clinical as well as the methodological aspects of the trials, the results for the major outcomes were remarkably homogeneous. This finding suggests that pooled estimates are both robust and applicable across a wide range of clinical situations encountered with critically ill patients. Although likely that different antifungal regimens have different efficacies, the results of this meta-analysis suggest that, overall, they are of a similar magnitude. Nevertheless, given the lack of head-to-head comparative trials, inferences regarding the superiority of different doses, routes of administration, and durations of antifungal prophylaxis are not possible. Fewer data are available for ketoconazole, although the results of this review indicate an overall similar effect to fluconazole. This is an interesting result given the poor and erratic bioavailability of the oral formulation. However, firm conclusions regarding the relative efficacies of fluconazole and ketoconazole are restricted by the lack of direct head-to-head comparative trials.

Other antifungal agents, such as itraconazole, voriconazole, posaconazole, caspofungin and amphotericin B, possess broader spectra of activity than fluconazole, but have not been assessed in randomized controlled trials of prophylaxis in non-neutropenic critically ill patients. Given that Candida species cause the overwhelming majority of infections in such patients and the demonstrated efficacy and safety of fluconazole, there may be little rationale for their use. Such agents may be justified in situations...
where fluconazole-resistant *Candida* infections are prevalent, although their routine use may simply exert additional selection pressure and an increase in resistant isolates.

This review is distinguished from three recently published reviews in this area\(^\text{1}^{1-5}\) by a number of factors. We adopted a more comprehensive approach with respect to patients (including trials performed on all non-neutropenic critically ill and surgical patients), interventions (with any systemic antifungal agent), and outcomes (using a variety of outcomes to assess both the benefits, including all invasive fungal infections rather than just candidaemia, and harms, including colonization and infection with azole-resistant fungal species). We identified and included several eligible trials\(^\text{32,34,40}\) not included in some or all of the other reviews, and have analysed outcomes using an intention-to-treat approach. Finally, in addition to demonstrating reduced invasive fungal infections, we demonstrated a significant total mortality benefit and a trend toward increased colonization with fluconazole/ketoconazole-resistant *Candida* species.

Given its demonstrated efficacy in preventing fungal infections, should fluconazole prophylaxis be adopted in critically ill patients? Amongst such patients, the risk of fungal infections varies from patient-to-patient and antifungal prophylaxis should therefore be instituted selectively to patients at increased risk, rather than universally. Many risk factors for fungal infections have been defined\(^\text{1,5}\) and should be incorporated into decisions regarding prophylaxis. However the accurate identification of patients at increased risk requires the further refinement and validation of predictive risk assessment algorithms. This conclusion supports recent guidelines from the Infectious Diseases Society of America,\(^\text{72}\) advocating careful patient selection for prophylaxis. Furthermore, the cost-effectiveness of antifungal prophylaxis strategies have not been defined—awaiting, in part, a clearer understanding of the attributable clinical and economic consequences of invasive fungal infections in critically ill patients. Finally, as the selection or generation of resistance to antifungal agents among fungal pathogens remains a major potential concern, further studies quantifying such potential ecological effects are required before the widespread adoption of antifungal prophylaxis can be recommended.

In summary, this systematic review and meta-analysis demonstrates that antifungal prophylaxis with fluconazole or ketoconazole reduces invasive fungal infections and total mortality across a broad range of clinical settings in non-neutropenic critically ill patients. Antifungal prophylaxis is thus recommended for critically ill patients at increased risk of invasive fungal infections, such as those with multiple clinical risk factors and candida colonization.\(^\text{4,18,5}\)\(^4\) Although no significant difference in the effect of fluconazole and ketoconazole was demonstrated, fluconazole is preferred given the greater available evidence-base, more favourable pharmacokinetic properties, availability in both parenteral and enteral formulations, and safer toxicity and drug interaction profile.

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### Transparency declarations

E. G. P. is a member of the Mycology Interest Group of the Australasian Society for Infectious Diseases, which is sponsored by Gilead, Pfizer and Merck, and has received funding from Pfizer for attendance at scientific conferences where he has given presentations. A. C. W.: none declared. T. C. S. is/has been on product advisory boards for Pfizer, Merck and Gilead; has received untied, unrelated project funding from Pfizer, Merck and Gilead; is a member of the Mycology Interest Group of the Australasian Society for Infectious Diseases, which is sponsored by Gilead, Pfizer and Merck; and has accepted funding from Pfizer, Gilead and Merck for attendance at symposia/scientific conferences where she has given presentations. J. C. C.: none declared.

### Supplementary data

Supplementary data are available at JAC Online (http://jac.oxfordjournals.org).

### References


Systematic review


