Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients (Review)

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[Intervention Review]

Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients

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ABSTRACT

Background

Invasive fungal infections, important causes of morbidity and mortality in critically ill patients, may be preventable with the prophylactic administration of antifungal agents.

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.

Search methods

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 handsearched reference lists, abstracts of conference proceedings and scientific meetings (1998 to 2004), and contacted authors of included studies and pharmaceutical manufacturers.

Selection criteria

We included 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.

Data collection and analysis

Two authors independently applied selection criteria, performed quality assessment, and extracted data using an intention-to-treat approach. We resolved differences by discussion. We synthesized data using the random effects model and expressed results as relative risk with 95% confidence intervals.

Main results

We included 12 unique trials (eight comparing fluconazole and four ketoconazole with no antifungal or a nonabsorbable agent) involving 1606 randomized patients. 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 about 25% (relative risk 0.76, 95% confidence interval 0.59 to 0.97) and invasive fungal infections by about 50% (relative risk 0.46, 95% confidence interval 0.31 to 0.68). We identified no significant increase in the incidence of infection or colonization with the azole-resistant fungal pathogens *Candida glabrata* or *C. krusei*, although the confidence intervals of the summary effect measures were wide. Adverse effects were not more common amongst patients receiving prophylaxis. Results across all trials were homogeneous despite considerable heterogeneity in clinical and methodological characteristics.

Authors' 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.

PLAIN LANGUAGE SUMMARY

Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients

Critically ill patients are at risk of invasive fungal infections, such as those affecting the bloodstream and other organs. Once established, such infections are difficult to treat and result in a high mortality. Results from 12 randomized trials demonstrate that the administration of antifungal drugs to critically ill patients reduces the incidence of invasive fungal infections by about one half and reduces mortality by about one quarter. Although no increase in adverse effects or resistance amongst fungi was reported by these studies, such effects are not excluded. However, concerns that the widespread use of antifungal drugs may promote resistance amongst fungi justify their selective use in patients at greatest risk of fungal infections.

BACKGROUND

The morbidity and mortality caused by invasive fungal infections amongst hospitalized patients has increased over recent decades (Beck-Sague 1993; Jarvis 1995). Immunocompromised patients, such as those with neutropenia (low white blood cells) and organ transplant recipients, are at particular risk. However, the incidence of invasive fungal infections in critically ill intensive care unit (ICU) and surgical patients is increasingly recognized, amongst whom up to one half of all cases of invasive candidiasis occur (Ostrosky 2003). *Candida* species rank as the fourth commonest cause of bloodstream infection with a reported incidence of 0.5 to 2% of admissions in unselected ICU patients (Borzotta 1999; McKinnon 2001; Petri 1997; Pittet 1994; Rangel-Frausto 1999). Patients in ICUs represent a heterogeneous group amongst whom certain factors, such as recent abdominal surgery, perforation of the gastrointestinal tract, dialysis, central venous catheterization, parenteral nutrition, broad-spectrum antibiotic therapy, and colonization with *Candida* species, are associated with increased risk of invasive fungal infections (Blumberg 2001; Borzotta 1999; Fridkin 1996; McKinnon 2001;Pittet 1994).

The clinical and economic consequences of invasive fungal infections in critically ill patients are considerable. Crude mortality rates of 30 to 40% for candidaemia are commonly reported (Blumberg 2001; Edmond 1999; Fridkin 1996; Petri 1997), but uncertainty exists regarding the attributable mortality (Blot 2002; Leleu 2002; Pelz 2000). Candidaemia has been reported to be associated with prolonged length of ICU stay (Leleu 2002; Pelz 2000) and excess economic costs as high as US$44,000 per episode (Rentz 1998). Unfortunately invasive candidiasis is often recognized and treated late, given the non-specific clinical features and the poor sensitivity and specificity of currently available diagnostic tests. Recent interest has therefore focused on preventative strategies. Antifungal prophylaxis, defined as the commencement of antifungal therapy on the basis of risk factors for infection or colonization with fungi or both, but without clinical, microbiological, or radiological evidence of a fungal infection, reduces the incidence of invasive fungal infections in other high-risk patient groups, such as neutropenic patients (Gøtzsche 2002; Kanda 2000) and solid organ transplant recipients (Playford 2004). Antifungal prophylaxis, encompassing the terms 'prophylaxis', 'pre-emptive treatment', and 'empiric treatment', indicates the initiation of antifungal therapy prior to the definitive diagnosis of a fungal infection. However, the relative benefits, harms, and cost-effectiveness of antifungal prophylaxis in non-neutropenic critically ill patients remain undefined. Poten-

tial ecological effects of widespread antifungal use, including the selection and spread of resistant fungal strains or species, a well-recognized phenomenon in bacteria consequent upon antibiotic use (McGowan 1983), are of particular concern. As a result of this uncertainty, there is no consensus regarding the use of antifungal prophylaxis in critically ill patients (Calandra 2002; Ostrosky 2003; Rex 2001; Sobel 2001). However, considerable variability in clinical practice, with respect to the indications for prophylaxis, the agents used and the duration of prophylaxis, occurs (Gauzit 2003). Given that the overwhelming majority of fungal pathogens in non-neutropenic critically ill patients involves *Candida* species, the azole drugs, fluconazole and ketoconazole, have been the agents in most widespread use for the prophylaxis and treatment of these infections.

OBJECTIVES

The objectives of this review were to determine the benefits and harms of the prophylactic administration of antifungal agents in non-neutropenic critically ill patients.

We examined the following primary questions:

1. Is prophylaxis with any antifungal agent(s) associated with reduced proven invasive fungal infections and total mortality compared with no prophylaxis?

2. Are some agent(s) alone or in combination more efficacious than others?

3. For each agent, does the efficacy depend upon dose, route of administration, and duration of prophylaxis?

4. Do some patient subgroups (e.g. medical versus surgical) derive greater benefit from antifungal prophylaxis than others?

We examined the following secondary questions:

1. Is antifungal prophylaxis associated with reduced suspected invasive fungal infections?

2. Is antifungal prophylaxis associated with reduced superficial fungal infections?

3. Is antifungal prophylaxis associated with reduced fungal colonization?

4. Is antifungal prophylaxis associated with increased colonization or infection with azole-resistant fungal strains or species?

5. Is prophylaxis with antifungal agent(s) associated with clinically significant toxicity?

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomized controlled trials (RCTs) that evaluated the effect of any prophylactic antifungal agent (alone or in combination with other interventions) in non-neutropenic critically ill patients.

Types of participants

We considered trials involving adult patients (aged 18 years or over) and paediatric patients (aged less than 18 years), classified as critically ill (such as those admitted to an ICU or having recently undergone an abdominal or other major surgical procedure). We excluded trials involving neutropenic, neonatal or HIV-infected patients; patients predominantly with malignancies; or solid organ transplant recipients, as systematic reviews have been or will be performed for these patient groups (Gøtzsche 2002; Holmes 2003; McGuire 2004; Playford 2004; Worthington 2004). We included trials including non-neutropenic critically ill patients along with other patient groups if the proportion of these is less than 25% or if data on non-neutropenic patients were separately provided.

Types of interventions

We considered trials if they involved the randomized comparison of any antifungal regimen with placebo, no antifungal or another antifungal regimen.
The study groups were required to differ only for the antifungal regimen under investigation; other cointerventions and aspects of care, including the routine use of other prophylactic antimicrobial agents, were required to be the same to avoid potentially confounded comparisons.

Types of outcome measures

Primary outcomes

Primary outcome measures included:
1. Total (all-cause) mortality.
2. Proven invasive fungal infection. The criteria for proven invasive fungal infection included a clinical illness consistent with the diagnosis and either histopathological evidence of invasive fungal infection, or a positive fungal culture from one or more sterile site specimens (including blood). Funguria (as indicated by a positive urine fungal culture), in the absence of a complicated urinary tract infection, and fungal oesophagitis were classified as superficial fungal infections. Where insufficient information was available to classify infections, we contacted study authors for clarification. Otherwise we used the classification and definitions used in individual studies.

Secondary outcomes

Secondary outcome measures included:

1. Proven or suspected invasive fungal infection. This outcome measure incorporated both proven invasive fungal infection cases (defined above) and suspected invasive fungal infection cases (defined as the initiation of systemic antifungal therapy without the fulfillment of the criteria for a proven invasive fungal infection) in trials that reported both outcomes.
2. Superficial fungal infection. Superficial fungal infections were defined as superficial cutaneous, oropharyngeal, oesophageal or uncomplicated urinary tract fungal infections.
3. Fungal colonization. Fungal colonization was defined as a positive fungal culture from any body site that either developed (if not present at baseline) or persisted (if present at baseline) during prophylaxis.
4. Proven invasive fungal infection caused by an azole-resistant *Candida* species (defined as *Candida glabrata*, *C. krusei*, or another species with documented azole resistance) or a filamentous fungus (such as *Aspergillus* species). Note: although newer azole antifungal agents (such as voriconazole and posiconazole) have activity against these fungal pathogens, we will use the term azole-resistant *Candida* spp. in this review to denote fluconazole/ketoconazole resistance.
5. Fungal colonization at any body site with azole-resistant *Candida* species.
6. Adverse events requiring cessation of study drug(s).

We analysed all outcome measures according to intention-to-treat. The time point of assessment of outcome measures was at the time of discharge from ICU or at the end of prophylaxis, whichever was longer.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases:

The Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 3 2005): the search strategy incorporated MeSH terms for antifungal agents and for fungal infections.

MEDLINE (OVID: 1966 to 2 September 2005): the search strategy incorporated MeSH terms and textwords for antifungal agents and for fungal infections, combined with the Cochrane highly sensitive search strategy for identifying randomized controlled trials in MEDLINE (Dickersin 1994).

EMBASE (OVID: 1980 to week 36 2005): the search strategy incorporated MeSH terms and textwords for antifungal agents and for fungal infections combined with a highly sensitive search strategy for identifying randomized controlled trials in EMBASE (Lefebvre 1996).

We have included the full electronic database search strategies as presented in Appendix 1.

Searching other resources

We searched the proceedings of major relevant conferences (including, but not limited to: Interscience Congress of Antimicrobial Agents and Chemotherapy; American Society for Microbiology; Infectious Diseases Society of America; European Congress of Clinical Microbiology and Infectious Diseases; American Society of Anaesthesiologists; European Society of Intensive Care Medicine; and Society of Critical Care Medicine).

We searched the reference lists of identified trials and major reviews.

We contacted researchers active in the field and primary authors of identified relevant trials for additional published and unpublished trial data.

We contacted manufacturers of the study drugs for additional published or unpublished trial data.

We did not apply a language restriction. We accepted letters, abstracts, and unpublished trials to reduce publication bias. If we suspected duplicate publication, we contacted the study authors for clarification, and if confirmed, used the publication with the longest follow-up data for the review.

Data collection and analysis

Four authors undertook the review (EGP, ACW, TCS, JCC).

Selection of studies

One author (EGP) performed the above search strategy to identify potentially relevant trials. Two authors (EGP and ACW) then independently performed each subsequent step of the selection and review process. The titles and abstracts of identified studies were initially screened for eligibility. Potentially eligible studies were subjected to full-text review for methodological quality assessment (see below) and data extraction (see below). The authors were not blinded to author, source institution, or publication source of trials. Discrepancies were resolved by discussion with two additional authors (EGP with TCS and JCC).

Data extraction

Two authors independently extracted and collected data on a standardized paper form. Where important data regarding trial results were not provided in the primary papers, we contacted the study authors for clarification. We extracted data, wherever possible for all randomized patients on an intention-to-treat basis. One author (EGP) then entered the data into Review Manager (RevMan 4.2) twice.

Evaluation of study methodological quality

We evaluated the validity and design characteristics of each study for major potential sources of bias (random sequence generation, allocation concealment, blinding, intention-to-treat analysis, and completeness of follow-up) (Higgins 2005). We assessed each study quality factor separately.

Random sequence generation:

Adequate: Method used that would generate random sequence (e.g. random number generator, toss of coin).
Unclear: No information on random sequence generation available.
Inadequate: Alternate medical record numbers or other nonrandom sequence generation.

Allocation concealment:

Adequate: Allocation method described that would not allow investigator or participant to know or influence intervention group before eligible participant entered into study (e.g. central allocation, sealed opaque envelopes).
Unclear: No information on allocation method available.
Inadequate: Allocation method such as alternate medical record numbers or unsealed envelopes, open allocation sequence, or any information in the study that indicated that investigators or participants could influence intervention group.

Blinding:

We evaluated whether patients, study investigators, outcome assessors, or data analysis personnel were blinded to treatment allocation.

Intention-to-treat (ITT) analysis:

Yes: Specifically reported by authors that ITT analysis was undertaken and confirmed on study assessment, or not stated but evident from study assessment that ITT analysis was undertaken.
Unclear: Reported by authors that ITT analysis was undertaken but unable to be confirmed on study assessment, or not reported and unable to be confirmed on study assessment.
No: Lack of ITT analysis confirmed on study assessment (patients who were randomized were not included in the analysis because they did not receive study intervention, they withdrew from the study, or were not included because of protocol violation) regardless of whether ITT analysis was reported.

Completeness of follow-up:

Percentage of randomized participants with outcome data at defined study endpoint.

Data analysis

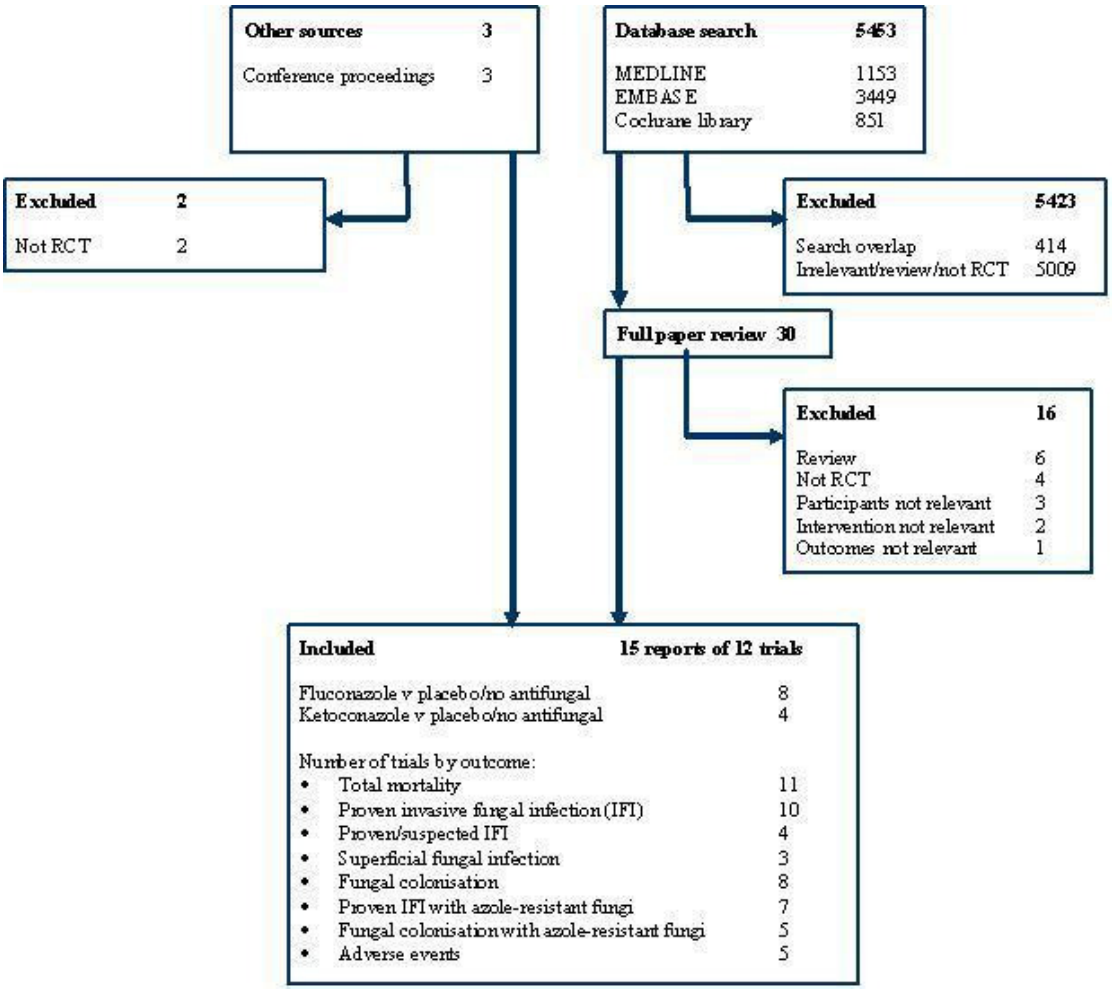
We analysed data using relative risks and 95% confidence intervals (CI). We assessed heterogeneity across trials with a test of homogeneity (χ^2 on k-1 degrees of freedom), with $p < 0.1$ considered significant. We also applied a test of inconsistency (I^2) measuring the proportion of total variation in the estimates of treatment effect due to heterogeneity between trials (Higgins 2003). We pooled the results from different trials using a random effects model and compared with a fixed effect model in a sensitivity analysis. We performed subgroup analyses according to clinical characteristics (such as definition of invasive fungal infection, proportion of surgical patients, and medical versus surgical patients) and antifungal prophylaxis regimens (different agents, systemic versus nonabsorbable, dose, duration, and route of administration). We performed sensitivity analyses comparing the random effects model with a fixed effect model. In a further sensitivity analysis, we assessed the effect of study methodological quality.
We assessed for publication bias using a funnel plot (log relative risk for efficacy versus 1/standard error) (Egger 1997).
We calculated the number needed to treat (NNT) using the pooled estimate of relative risk and various assumptions of baseline risk, whereby NNT = 1 [(baseline risk - (baseline risk · RR)]. We calculated the 95% confidence intervals of the NNT as described (Altman 1998).

RESULTS

Description of studies

From the initial search strategy (2228 potential studies), we identified 33 references as potentially relevant and retrieved these for further assessment (Additional Figure 1). Of these, 15 references (publications and abstracts) reporting twelve trials were eligible for inclusion in this review (see 'Characteristics of included studies': Ables 2000; ARDS Network 2000; Eggimann 1999; Garbino 2002; He 2003; Jacobs 2003; Parizkova 2000; Pelz 2001; Sandven 2002; Savino 1994; Slotman 1987; Yu 1993). These twelve trials involved 1606 randomized patients (range, 38 to 292 patients per trial). Although pharmaceutical companies provided some information, no unique trials were identified. All identified trials were published in full: 11 in English and one in Czech (Parizkova 2000).

Figure 1. Search results



Eight trials compared fluconazole with no antifungal (Ables 2000; Eggimann 1999; Garbino 2002; He 2003; Jacobs 2003; Parizkova 2000; Pelz 2001; Sandven 2002) and four ketoconazole with no antifungal or a nonabsorbable agent (Savino 1994; Slotman 1987; ARDS Network 2000; Yu 1993). All trials but two (He 2003; Sandven 2002) were restricted to ICU patients. Post-surgical patients comprised more than 75% of trial participants in six trials (Eggimann 1999; Pelz 2001; Sandven 2002; Savino 1994; Slotman 1987; Yu 1993), 50 to 75% in two (Garbino 2002; Jacobs 2003), 30 to 50% in two (Ables 2000; Parizkova 2000), and not stated in two (ARDS Network 2000; He 2003). No trials directly compared different marketed systemic antifungal agents, although one trial compared fluconazole and control with "garlicin" (He 2003). Reporting of outcomes was variable (see Additional Table 1). Invasive fungal infections were reported in ten trials. Six trials (Eggimann 1999; Garbino 2002; Jacobs 2003; Parizkova 2000; Pelz 2001; Slotman 1987) reported criteria that were consistent with our definition (i.e. restricted to positive culture or histological findings,or both, from sterile site/deep tissue specimens), whereas four trials (Ables 2000; He 2003; Sandven 2002; Savino 1994) included positive cultures from one or more superficial sites as evidence of invasive infection, which we would consider representing either colonization or superficial infection (Additional Table 1). Other outcomes were even more variably reported, particularly with respect to the fungal species causing infection, colonization, or both.

Ables et al (Ables 2000) included patients at least 14 years of age admitted to a single ICU either with a diagnosis of trauma ("code trauma", "trauma consult" or "trauma alert") or who had undergone intra-abdominal or intrathoracic surgery. Furthermore, patients were required to have an anticipated length of ICU stay of

more than 48 hours and at least one "risk factor" manifest within 48 hours of ICU admission (central venous catheter placement, administration of total parenteral nutrition (TPN), artificial ventilation for more than 24 hours, or treatment with broad-spectrum antibiotics). Reported baseline characteristics included mean age (44 years), mean APACHE II score (18), trauma (70%), intra-abdominal or intra-thoracic surgery, or both (30%), and malignancy (3%). Patients were randomized to receive either fluconazole (800 mg initially followed by 400 mg daily intravenously, orally, or enterally) or placebo (given by same route of administration) for the duration of ICU stay.

The ARDS Network trial (ARDS Network 2000) included patients aged at least 18 years admitted to 24 ICUs who were ventilated and who developed acute lung injury or ARDS (impaired oxygenation and bilateral pulmonary infiltrates). Reported baseline characteristics included mean age (53 years), mean APACHE III score (81.3), sepsis (31%), and trauma (10%).Patients were randomized to receive either ketoconazole (400 mg daily enterally) or placebo for 21 days or until more than 48 hours of unassisted ventilation was achieved.

Eggimann et al. (Eggimann 1999) included patients at least 16 years of age admitted to two ICUs with recent abdominal surgery and who had recurrent gastrointestinal perforation or anastomotic leakages that were either suspected or confirmed by surgery. Reported baseline characteristics included median age (57 to 63 years), median APACHE II score (13), gastrointestinal malignancy (37%), pancreatitis (10%), antibiotics (100%), and fungal colonization (40%). Patients were randomized to receive either fluconazole (400 mg daily intravenously) or placebo until "complete resolution of the intra-abdominal disease".

Garbino et al. (Garbino 2002) included patients over 18 years of age admitted to a single ICU who were mechanically ventilated for at least 48 hours and expected to remain so for an additional 72 hours. All patients received selective decontamination of the digestive tract with oral polymyxin B, neomycin, and vancomycin. Reported baseline characteristics included mean age (54.3 years), mean APACHE II score (19.4), abdominal surgery (20%), other surgery (40%), malignancy (15%), antibiotics (39%), TPN (28%), and fungal colonization (48%). Patients were randomized to receive fluconazole (100 mg daily intravenously) or placebo until withdrawal from mechanical ventilation.

He et al. (He 2003) included patients with pancreatitis and at least one "predisposing factor" for fungal infection ("gerontism", diabetes, "dysfunction of one or more organs", hyperglycaemia, central venous catheter, TPN, urinary catheterization, "operation", gastrointestinal fistula, "ICU", ventilated at least five days, broad-spectrum antibiotics at least five days, or "super" broad-spectrum antibiotics at least three days). Reported baseline characteristics included mean age (50.2 years) and mean APACHE II score (12.2), Patients were randomized to receive fluconazole (100 mg daily intravenously), "garlicin" (120 mg daily intravenously), or neither. Treatment was continued "until relief of predisposing factors".

Jacobs et al. (Jacobs 2003) included patients admitted a single ICU with a diagnosis of septic shock (according to criteria established by the American Society of Chest Physicians/Critical Care Society Consensus Conference) within 24 hours of onset, from either intra-abdominal sepsis or nosocomial pneumonia. Reported baseline characteristics included pneumonia (52%), intraabdominal sepsis (48%), surgery (65%), mean APACHE II score (18.4), and fungal colonization (6%). Patients were randomized to receive either fluconazole (200 mg daily intravenously) or placebo for the duration of the septic shock.

Parizkova et al. (Parizkova 2000) included patients aged at least 18 years of age admitted to a single ICU within five days of admission who had received at least 24 hours of antibiotic therapy and at least 48 hours of mechanical ventilation. Reported baseline characteristics included mean age (44.5 years), mean APACHE II score (23), gastrointestinal surgery (37%), TPN (97%), broad-spectrum antibiotics (66%), and central venous access (100%). Patients were randomized to receive either fluconazole (100 mg daily intravenously) or no fluconazole until ICU discharge.

Pelz et al. (Pelz 2001) included patients admitted to a single ICU with an expected length of stay of at least 3 days. Reported baseline characteristics included median age (63 to 66 years), median APACHE III score (63 to 65), surgery (91%), TPN (9%), antibiotics within 48 hours of ICU admission (29%), central venous access (95%), malignancy (29%), and fungal colonization (79%). Patients were randomized to receive either fluconazole (800 mg loading then 400 mg daily enterally) or placebo until ICU discharge.

Sandven et al. (Sandven 2002) included patients from 13 hospitals with intraabdominal perforation or anastomotic leakage. Reported baseline characteristics included median age (60 to 68 years), surgery (100%), antibiotics for at least three days (14%), and malignancy (40%). Patients were randomized to receive either fluconazole (400 mg intravenously) or placebo as a single dose.

Savino et al. (Savino 1994) included all patients admitted to a single ICU for more than 48 hours with an expected ICU length of stay of at least 48 hours. Reported baseline characteristics included mean age (54 years), mean APACHE II score (11.3), TPN (42%), surgery (79%), and malignancy (27%). Patients were randomized to receive ketoconazole (200 mg daily enterally), clotrimazole (10 mg three times daily enterally), nystatin (2 million units four times daily enterally), or no antifungal until ICU discharge.

Slotman and Burchard (Slotman 1987) included patients admitted to a single surgical ICU with at least three of the following: age greater than 40 years, second- and third-degree burns covering greater than 30% of body surface area, antibiotics greater than seven days, three or more antibiotics, severe sepsis unresponsive to antibiotics, diabetes, steroids greater than seven days, acute renal failure, immunosuppressive therapy or chemotherapy, advanced malignancy, TPN, multitrauma, serum glucose greater than 11.1 mmol/L, intra-abdominal abscess, peritonitis, or se-

vere head injury. Patients with fungal colonization at baseline were excluded post-randomization. Reported baseline characteristics included median age (59 to 65 years), intra-abdominal surgery (39%), other surgery (59%), TPN (25%), antibiotics greater than seven days (26%), malignancy (11%), and corticosteroids (5%). Patients were randomized to receive either ketoconazole (200 mg daily enterally) or placebo for 21 days or until ICU discharge.
Yu and Tomasa (Yu 1993) included patients aged at least 16 years admitted to a single surgical ICU with a diagnosis of sepsis. Reported baseline characteristics included mean age (53.2 years), mean APACHE II score (13), and mean number of surgical procedures (1.6 per patient). Patients were randomized to receive either ketoconazole (400 mg daily enterally) or placebo for 21 days or until ICU discharge.

Risk of bias in included studies

Although imperfect, the overall methodological quality of the included trials was high (see 'Characteristics of included studies').

Random sequence generation

Adequate random sequence generation was specifically reported in five trials (Ables 2000; ARDS Network 2000; Eggimann 1999; Pelz 2001; Sandven 2002) and unclear in the other seven.

Allocation concealment

Adequate allocation concealment was specifically reported in seven trials (ARDS Network 2000; Eggimann 1999; Garbino 2002; Jacobs 2003; Pelz 2001; Sandven 2002; Savino 1994) and unclear in the other five.

Blinding

Blinding of study participants and investigators was reported in nine trials (Ables 2000; ARDS Network 2000; Eggimann 1999; Garbino 2002; Jacobs 2003; Pelz 2001; Sandven 2002; Slotman 1987; Yu 1993), with three of these also specifically reporting blinding of outcome assessors (ARDS Network 2000; Eggimann 1999; Pelz 2001).

Intention-to-treat analysis

Intention-to-treat analysis was apparent in seven trials (ARDS Network 2000; He 2003; Jacobs 2003; Parizkova 2000; Pelz 2001; Sandven 2002; Yu 1993).

Completeness of follow-up

Post-randomization exclusions were greater than 10% in two trials (Eggimann 1999; Slotman 1987).

Effects of interventions

Total mortality

(see Analysis 1.1)

Although total mortality rates were very variable in the control arms of the seven fluconazole trials reporting this outcome (range 0-54%, mean 26%), there was no significant heterogeneity in the observed effect of fluconazole across these trials (χ^2 = 8.73, df = 6, p = 0.19; I^2 = 31.3%). One trial (Jacobs 2003) demonstrated a significant mortality reduction (RR 0.41, 95% CI 0.2 to 0.83) with fluconazole, with four other trials (Eggimann 1999; Garbino 2002; Pelz 2001; Sandven 2002) showing a small, non-significant benefit. The summary relative risk favoured fluconazole, but was not significantly less than 1.0 (RR 0.77, 95% CI 0.56 to 1.07).
Mortality in the control arms of the four ketoconazole trials ranged from 16-42% (mean 25%), with some heterogeneity evident (χ^2 = 6.28, df = 3, p = 0.1, I^2 = 52.3%). The results of three trials (Savino 1994; Slotman 1987; Yu 1993) favoured ketoconazole, with the pooled analysis demonstrating a non-significant mortality reduction (RR 0.68, 95% CI 0.42 to 1.12).
Across all eleven trials, the results were homogeneous (χ^2 = 14.81, df = 10, p = 0.14, I^2 = 32.5%), demonstrating a significant reduction in total mortality by about 25% (RR 0.76, 95% CI 0.59 to 0.97).

Invasive fungal infections

(see Analysis 1.2)

Fluconazole significantly reduced the incidence of proven invasive fungal infections by about one half (RR 0.47, 95% CI 0.32 to 0.71). One trial (Parizkova 2000) did not report any proven infections, whereas amongst the other seven fluconazole trials, the incidence ranged from 3% to 41% (mean 15%). 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 (χ^2 = 1.12, df = 6, p = 0.98, I^2 = 0%).
Amongst the two ketoconazole trials that reported invasive infections, no significant reduction was demonstrated, although confidence intervals were wide (RR 0.3, 95% CI 0.07 to 1.31).
Across all trials of both fluconazole and ketoconazole, the results were homogeneous (χ^2 = 1.82, df = 8, p = 0.99, I^2 = 0%), with a significant reduction in invasive infections by about one half (RR 0.46, 95% CI 0.31 to 0.68).

Proven or suspected invasive fungal infections

(see Analysis 1.5 and Analysis 1.6)

Fluconazole prophylaxis did not significantly reduce the incidence of suspected invasive fungal infections (empiric antifungal use) amongst the four trials that reported this outcome, although some heterogeneity was evident (χ^2 = 6.72, df = 3, P = 0.08, I^2 = 55.4%) and the confidence intervals were wide (RR 1.14, 95% CI 0.25 to 5.13). The incidence of suspected invasive fungal infections in the control arms of the fluconazole trials ranged from 1% to 5% (mean 3%).

The combined incidence of proven and suspected invasive fungal infections in the control arms of the four fluconazole trials reporting this outcome ranged from 14% to 22% (mean 17%). Fluconazole prophylaxis was associated with a nonsignificant reduction in their incidence (RR 0.64, 95% CI 0.4 to 1.02).

Superficial fungal infections

(see Analysis 1.7)

The incidence of superficial fungal infections in the control arm of the three fluconazole trials that reported this outcome ranged from 3% to 12% (mean, 6%). Fluconazole prophylaxis demonstrated a non-significant reduction in superficial fungal infections (RR 0.59, 95% CI 0.27 to 1.29), with no significant heterogeneity demonstrated across these three trials (χ^2 = 1.12, df = 2, P = 0.57, I^2 = 0%).

Fungal colonization

(see Analysis 1.8)

Fluconazole prophylaxis reduced the incidence of fungal colonization by about one half (RR 0.55, 95% CI 0.42 to 0.74): this effect was homogenous across the four trials reporting fungal colonization (χ^2 = 3.61, df = 3, P=0.31, I^2 = 16.9%). Ketoconazole also reduced fungal colonization (RR 0.66, 95% CI 0.47 to 0.94), with no significant heterogeneity demonstrated across the three trials (χ^2 = 0.83, df = 2, P = 0.66, I^2 = 0%). Across the fluconazole and ketoconazole trials, the effect on fungal colonization was homogenous (χ^2 = 4.72, df = 6, P = 0.58, I^2 = 0%). Reporting of fungal colonization did not allow for stratification of colonized patients into those with or without fungal infection.

Infection and colonization with azole-resistant fungi

(see Analysis 1.3, Analysis 1.4 and Analysis 1.9)

Infections with *C. glabrata* or *C. krusei* were documented in four of the six fluconazole trials that provided data on the species of invasive fungal pathogens (Ables 2000; Eggimann 1999; Garbino 2002; Pelz 2001). 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 azole-resistant *Candida* species was not significantly increased with either fluconazole (RR 0.66, 95% CI 0.22 to 1.96) or ketoconazole prophylaxis (RR 0.34, 95% CI 0.01 to 8.14).

Fungal colonization with *C. glabrata* or *C. krusei* occurred in 6% and 15% in the control and fluconazole arms, respectively. Although no significant effect of fluconazole on colonization with azole-resistant *Candida* species was demonstrated, three of the four fluconazole trials did report greater colonization rates and the confidence intervals around the pooled estimate were very wide (RR 1.74, 0.64 to 4.71).

Adverse events

(see Analysis 1.10)

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

Subgroup and sensitivity analyses

(see Additional Table 2)

In subgroup analyses, no obvious effect of clinical characteristics or antifungal prophylaxis regimen was evident. Sensitivity analyses similarly did not demonstrate an effect of analysis method (random effects or fixed effect models) or study methodological quality.

Publication bias

(see Additional Figure 2 and Additional Figure 3)

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 trials reporting a lack of benefit from antifungal prophylaxis.

Figure 2. Funnel plot for systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal; outcome = total mortality

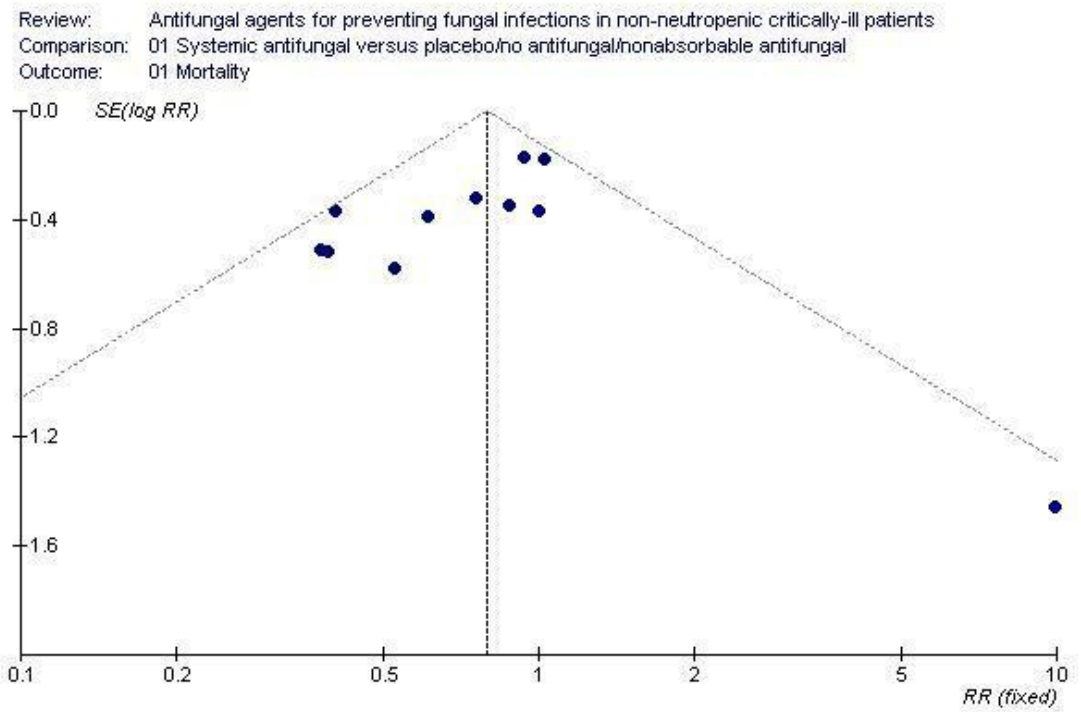
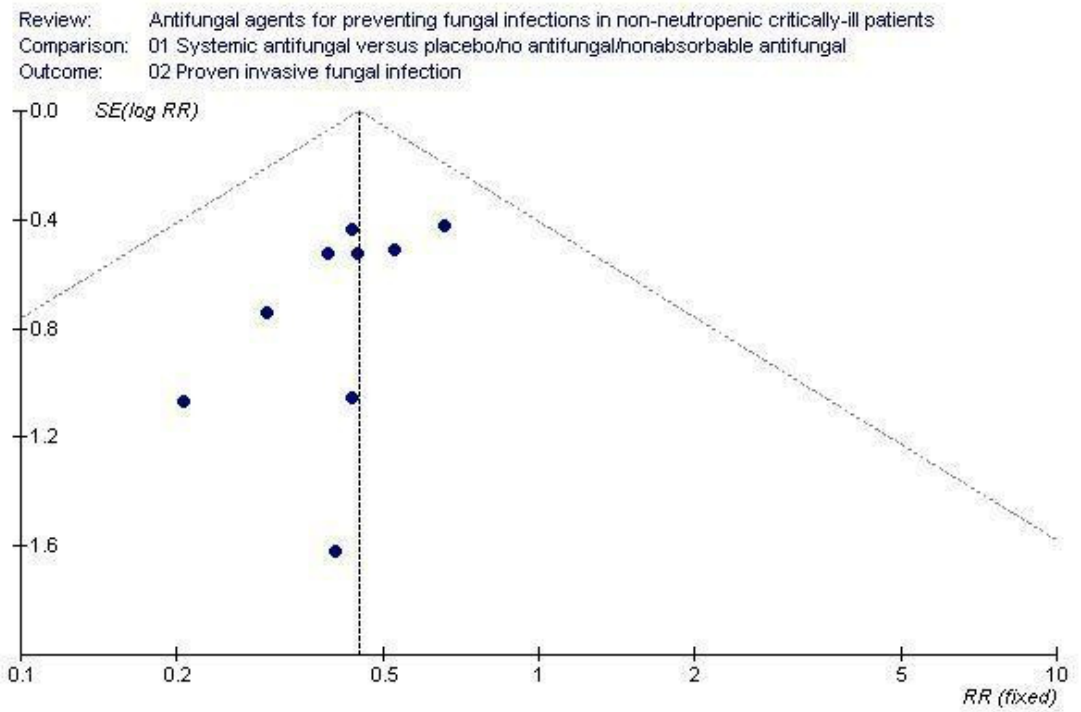


Figure 3. Funnel plot for systemic antifungal agent versus placebo/no antifungal/nonabsorbable antifungal agents; outcome = proven invasive fungal infection



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 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 administration, and other clinical and methodological aspects. This suggests that the results are generalizable to a diverse range of clinical situations. Assuming a baseline incidence of invasive fungal infections amongst unselected critically ill patients of 2% (Rex 2001), 94 patients would require fluconazole prophylaxis to prevent one infection. This estimate varies according to risk (see Additional 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 non-significant - effect was observed with ketoconazole on the basis of two trials reporting this outcome.

Demonstration of a beneficial effect of antifungal prophylaxis on total mortality is novel and important. The point estimates of seven of the 11 trials favoured antifungal prophylaxis, whereas two showed no benefit. Overall there was no significant heterogeneity with results across the trials. The pooled analysis for fluconazole prophylaxis suggests a 23% mortality benefit, with relatively wide confidence intervals (from a 7% hazard to a 44% benefit). However, inclusion of the ketoconazole trials in the pooled analysis demonstrates a significant result of about the same magnitude (24% mortality benefit, 95% CI 3% to 41%). These findings are highly encouraging. Although the confidence intervals are wide and individually only one trial reported a significant mortality benefit, seven of the other ten trials did demonstrate a non-significant benefit. However, whether this mortality benefit is mediated through preventing invasive fungal infections remains uncertain. Reported crude mortality rates associated with such infections in critically ill ICU patients which range between 40% and 60% (Blumberg 2001; Edmond 1999; Fridkin 1996; Petri

1997) do not account for the confounding effect of severity of illness. Estimates of the attributable mortality from epidemiological studies comparing the mortality of infected with uninfected patients matched for severity of illness, have yielded conflicting results. We must note the difficulties of adequately accounting for the influence of all factors confounding the association between critical illness, fungal infections, and mortality: two studies demonstrated no significant attributable mortality (Blot 2002; Pelz 2000) whereas one demonstrated a 31% attributable mortality (Leleu 2002). Given an uncertain attributable mortality, it remains possible that merely preventing fungal infections may not prevent deaths in critically ill patients who are at risk of death from other underlying conditions. Of note is that antifungal prophylaxis has not been demonstrated to reduce total mortality in other high-risk patients, such as neutropenic patients (Gøtzsche 2002) or solid organ transplant recipients (Playford 2004). Fungal-related mortality may be reduced with antifungal prophylaxis amongst neutropenic patients (Kanda 2000); however we deliberately did not assess this outcome in this study, as we considered the attribution of deaths to fungal infections imprecise and subjective, and therefore prone to bias. Ketoconazole and fluconazole exert anti-inflammatory and immunomodulatory effects in addition to their antifungal activity (Williams 1992; Zervos 1996), and other mechanisms may therefore contribute to any mortality benefit. 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 (ARDS Network 2000; Jacobs 2003; Slotman 1987; Yu 1993). In summary, this systematic review suggests that azole prophylaxis reduces total mortality in critically ill ICU patients consistently across the available trials and, when pooled, this mortality benefit is significant. Although promising and potentially clinically important, the identification of those patient subsets, amongst the typically heterogeneous ICU population, that are likely to derive the greatest benefit remains an important objective. Confirmation of this mortality benefit in appropriately powered clinical trials amongst such patients is warranted.

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 de novo development of fluconazole-resistance amongst susceptible species and the emergence of intrinsically resistant species have been associated with the use of antifungal agents, particularly amongst neutropenic or HIV-infected patients (Abi-Said 1997; Gleason 1997; Johnson 1995; Law 1994; Nguyen 1996). 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 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 confidence intervals 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 characterisation 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 the trials, adequate allocation concealment, an important potential source of bias if inadequate (Schultz 1995) 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 (Ascioglu 2002), a varied, and often conflicting, range of diagnostic criteria for invasive fungal infections has been published (Ascioglu 2001). 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, culture, or both. Four trials also included positive cultures from nonsterile 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, posiconazole, 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.

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 (Ostrosky 2003; Paphitou 2005) and should be incorporated into decisions regarding prophylaxis (see Additional Table 3). However, the accurate identification of patients at increased risk requires the further refinement and validation of predictive risk assessment algorithms (Ostrosky 2003; Paphitou 2005). Furthermore, the cost-effectiveness of antifungal prophylaxis strategies has 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 study quantifying such potential ecological effects is 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. Although no significant difference in the effect of fluconazole and ketoconazole was demonstrated, fluconazole is preferred given the greater available evidence-base, its more favourable pharmacokinetic properties, its availability in either parenteral or enteral formulation, and its safer toxicity and drug interaction profile.

AUTHORS' CONCLUSIONS

Implications for practice

Our results demonstrate that antifungal prophylaxis, particularly with fluconazole, is effective in preventing invasive fungal infections and total mortality in non-neutropenic critically ill patients, although the optimal dose and duration of prophylaxis remain uncertain. Antifungal prophylaxis with fluconazole should therefore be considered for patients at increased risk of invasive fungal infections.

Implications for research

The prospective identification of patients at increased risk, who may most benefit from antifungal prophylaxis, from amongst the general population of critically ill patients requires further research. Although many risk factors for fungal infections have been defined, these require integration into risk predictive algorithms (Ostrosky 2003; Paphitou 2005). The cost-effectiveness of antifungal prophylaxis strategies also has not been defined - awaiting, in part, a clearer understanding of the attributable clinical and economic consequences of invasive fungal infections in critically ill patients.

The selection or generation of resistance to antifungal agents among fungal pathogens remains a major potential concern and further study quantifying such potential ecological effects is required before the widespread adoption of antifungal prophylaxis can be recommended.

The significant effect of antifungal prophylaxis with fluconazole and ketoconazole on total mortality demonstrated in this study is promising and potentially clinically important; this requires confirmation in appropriately powered trials.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ables 2000

Methods	Random sequence generation: Yes (block) Allocation concealment: Unclear Blinding (subjects/investigators): Yes Blinding (outcome assessors): Unclear Intention-to-treat analysis: No Number excluded /number randomized: 6/125 (5%)
Participants	Inclusion: trauma or surgical patients, expected length of stay >48 hours, >1 risk factor (e.g. central venous line, total parenteral nutrition, mechanical ventilation, antibiotics etc) Number randomised: 125 Percentage post-surgical: >30%Candida at baseline: 24% Percentage colonized with Candida at baseline: 24%
Interventions	1. Fluconazole 800 mg/day intravenously (IV) initially then 400 mg/day IV or orally 2. Placebo Intervention duration: until ICU discharge (maximum 6 weeks)
Outcomes	Mortality Proven IFI Suspected IFI Proven IFI with azole-resistant species Superficial FI Fungal colonization Fungal colonization with azole-resistant species Adverse events Follow-up duration: until hospital discharge
Notes	Country: USA Setting: single hospital, adult ICU

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

ARDS Network 2000

Methods	Random sequence generation: Yes (computer) Allocation concealment: Yes (central allocation) Blinding (subjects/investigators): Yes Blinding (outcome assessors): Yes Intention-to-treat analysis: Yes Number excluded /number randomized: 0/234 (0%)
Participants	Inclusion: acute lung injury Number randomized: 234 Percentage post-surgical: not stated Percentage colonized with Candida at baseline: not stated
Interventions	1. Ketoconazole 400 mg/day orally 2. Placebo Intervention duration: until 48 hours post-extubation
Outcomes	Mortality Adverse events Follow-up duration: not stated
Notes	Country: USA Setting: 24 hospitals, adult ICU

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Eggimann 1999

Methods	Random sequence generation: Yes (block) Allocation concealment: Yes (pharmacy allocation) Blinding (subjects/investigators): Yes Blinding (outcome assessors): Yes Intention-to-treat analysis: No Number excluded /number randomized: 6/49 (12%)
Participants	Inclusion: recent abdominal surgery, recurrent gastrointestinal tract perforation, or anastomotic leakage Number randomized: 49 Percentage post-surgical: 100% Percentage colonized with Candida at baseline: 40%
Interventions	1. Fluconazole 400 mg/day IV 2. Placebo Intervention duration: until "complete resolution of intra-abdominal disease" (median 15-17 days)

Eggimann 1999 (*Continued*)

Outcomes	Mortality Proven IFI Proven IFI with azole-resistant species. Fungal colonization Fungal colonization with azole-resistant species Adverse events Follow-up duration: until one week post-prophylaxis
Notes	Country: Switzerland Setting: two hospitals, adult surgical/medical ICU

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Garbino 2002

Methods	Random sequence generation: Unclear Allocation concealment: Yes ("blinded list") Blinding (subjects/investigators): Yes Blinding (outcome assessors): Unclear Intention-to-treat analysis: Unclear Number excluded /number randomized: 16/220 (7%)
Participants	Inclusion: mechaniscal ventilation >48 hours and expected further 72 hours Number randomized: 220 Percentage post-surgical: 60% Percentage colonized with Candida at baseline: 48%
Interventions	1. Fluconazole 100 mg/day IV 2. Placebo Intervention duration: until withdrawal from mechanical ventilation
Outcomes	Mortality Proven IFI Suspected IFI Proven IFI with azole-resistant species Superficial FI Fungal colonization Fungal colonization with azole-resistant species Adverse events Follow-up duration: at least 30 days
Notes	Country: Switzerland Setting: single hospital, adult surgical/medical ICU

Garbino 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

He 2003

Methods	Random sequence generation: Unclear Allocation concealment: Unclear Blinding (subjects/investigators): Unclear Blinding (outcome assessors): Unclear Intention-to-treat analysis: Yes Number excluded /number randomized: 0/70 (0%)
Participants	Inclusion: severe pancreatitis with at least one of "elderly", organ dysfunction, total parenteral nutrition, corticosteroids, gastrointestinal fistula, broad-spectrum antibiotics) Number randomized: 70 Percentage post-surgical: not stated Percentage colonized with Candida at baseline: not stated
Interventions	1. Fluconazole 100 mg/day IV 2. "Garlicin" 120 mg/day IV 3. Control (neither fluconazole or "garlicin") Intervention duration: "until relief of predisposing condition"
Outcomes	Proven IFI Follow-up duration: not stated
Notes	Country: China Setting: ?single hospital, ?ward and/or ICU

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Jacobs 2003

Methods	Random sequence generation: Uclear Allocation concealment: Yes (pharmacy allocation) Blinding (subjects/investigators): Yes Blinding (outcome assessors): Unclear Intention-to-treat analysis: Yes Number excluded /number randomized: 0/71 (0%)
Participants	Inclusion: septic shock from gastrointestinal tract perforation or nosocomial pneumonia Number randomized: 71 Percentage post-surgical: 65% Percentage colonized with Candida at baseline: 6%
Interventions	1. Fluconazole 200 mg/day IV 2. Placebo Intervention duration: for duration of septic shock
Outcomes	Mortality Proven IFI Proven IFI with azole-resistant species Fungal colonization Follow-up duration: 30 days
Notes	Country: Saudi Arabia Setting: single hospital, adult surgical/medical ICU

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Parizkova 2000

Methods	Random sequence generation: Unclear Allocation concealment: Unclear (envelopes ?sealed) Blinding (subjects/investigators): Unclear Blinding (outcome assessors): Unclear Intention-to-treat analysis: Yes Number excluded /number randomized: 0/38 (0%)
Participants	Inclusion: admitted to ICU <5 days, receipt of antibiotics >24 hours, mechaniscal ventilation >48 hours Number randomized: 38 Percentage post-surgical: >37% Percentage colonized with Candida at baseline: not stated
Interventions	1. Fluconazole 100 mg/day IV 2. Control (no fluconazole) Intervention duration: for duration of ICU admission

Parizkova 2000 (*Continued*)

Outcomes	Mortality Proven IFI Proven IFI with azole-resistant species Fungal colonization Fungal colonization with azole-resistant species Follow-up duration: not stated
Notes	Country: Czech Republic Setting: single hospital, adult ICU

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pelz 2001

Methods	Random sequence generation: Yes (block) Allocation concealment: Yes (pharmacy allocation) Blinding (subjects/investigators): Yes Blinding (outcome assessors): Yes Intention-to-treat analysis: Yes Number excluded /number randomized: 0/260 (0%)
Participants	Inclusion: expected length of ICU stay >3 days Number randomized: 260 Percentage post-surgical: 91% Percentage colonized with Candida at baseline: 75%
Interventions	1. Fluconazole 800 mg orally then 400 mg/day orally 2.Placebo Intervention duration: until ICU discharge (mean 5 days)
Outcomes	Mortality Proven IFI Suspected IFI Proven IFI with azole-resistant species Superficial FI Follow-up duration: until 3 days post-ICU discharge
Notes	Country: USA Setting: single hospital, adult surgical ICU

Risk of bias

Bias	Authors' judgement	Support for judgement

Pelz 2001 (*Continued*)

Allocation concealment?	Low risk	A - Adequate

Sandven 2002

Methods	Random sequence generation: Yes (computer) Allocation concealment: Yes (computer allocation) Blinding (subjects/investigators): Yes Blinding (outcome assessors): Unclear Intention-to-treat analysis: Yes Number excluded /number randomized: 8/117 (7%)
Participants	Inclusion: gastrointestinal perforation Number randomized: 117 Percentage post-surgical: 100% Percentage colonized with Candida at baseline: not stated
Interventions	1. Fluconazole 400 mg IV single dose 2. Placebo Intervention duration: single dose
Outcomes	Mortality Proven IFI Suspected IFI Follow-up duration: not stated
Notes	Country: Norway Setting: 13 hospitals, adult surgical patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Savino 1994

Methods	Random sequence generation: Unclear Allocation concealment: Yes (sealed envelopes) Blinding (subjects/investigators): No Blinding (outcome assessors): Unclear Intention-to-treat analysis: No Number excluded /number randomized: 0/292 (0%)
Participants	Inclusion: expected length of stay >48 hours Number randomized: 292 Percentage post-surgical: 79% Percentage colonized with Candida at baseline: not stated

Savino 1994 (*Continued*)

Interventions	1. Ketoconazole 200 mg/day orally 2. Clotrimazole 30 mg/day orally 3. Nystatin 8 million units/day orally 4. Control (no antifungal) Intervention duration: until ICU discharge (mean 8-16 days)
Outcomes	Mortality Proven IFI Fungal colonization Follow-up duration: not stated
Notes	Country: USA Setting: single hospital, adult surgical ICU

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Slotman 1987

Methods	Random sequence generation: Unclear Allocation concealment: Unclear Blinding (subjects/investigators): Yes Blinding (outcome assessors): Unclear Intention-to-treat analysis: No Number excluded /number randomized: 17/74 (23%)
Participants	Inclusion: >2 risk factors, no fungal colonization Number randomized: 74 Percentage post-surgical: 97% Percentage colonized with Candida at baseline: 20%
Interventions	1. Ketoconazole 200 mg/day orally 2. Placebo Intervention duration: until ICU discharge (maximum 21 days)
Outcomes	Mortality Proven IFI Proven IFI with azole-resistant species Fungal colonization Fungal colonization with azole-resistant species Follow-up duration: not stated
Notes	Country: USA Setting: single hospital, adult surgical ICU

Slotman 1987 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Yu 1993

Methods	Random sequence generation: Unclear Allocation concealment: Unclear Blinding (subjects/investigators): Yes Blinding (outcome assessors): Unclear Intention-to-treat analysis: Yes Number excluded /number randomized: 0/56 (0%)
Participants	Inclusion: sepsis Number randomized: 56 Percentage post-surgical: ?100% Percentage colonized with Candida at baseline: not stated
Interventions	1. Ketoconazole 400 mg/day orally 2. Placebo Intervention duration: until ICU discharge (maximum 21 days)
Outcomes	Mortality Fungal colonization Adverse events Follow-up duration: not stated
Notes	Country: USA Setting: single hospital, adult surgical ICU

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

FI = fungal infections
IFI = invasive fungal infections
IV = intraveneous
ICU = intensive care unit

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Allen 2000	Intervention (glutamine-containing total parenteral nutrition fluid) not relevant
Bellman 1995	Commentary
DeVries 1998	Review
Earl-Salotti 1995	Review
Evans 1975	Not randomized
Frazee 1995	Review
Kicklighter 2001	Participants not relevant (neonates)
Moral 1994	Not randomized
Ohnmacht 2001	Participants not relevant (patients receiving interleukin-2)
Rosemurgy 1995	Outcomes not relevant
Schilling 2001	Not randomized
Van Saene 2002	Review
Vandewoude 1997	Not randomized
Wainer 1992	Participants not relevant (neonates)
Weydert 1971	Intervention not relevant (selective decontamination of the digestive tract)
Yahwak 2002	Review

DATA AND ANALYSES

Comparison 1. Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal

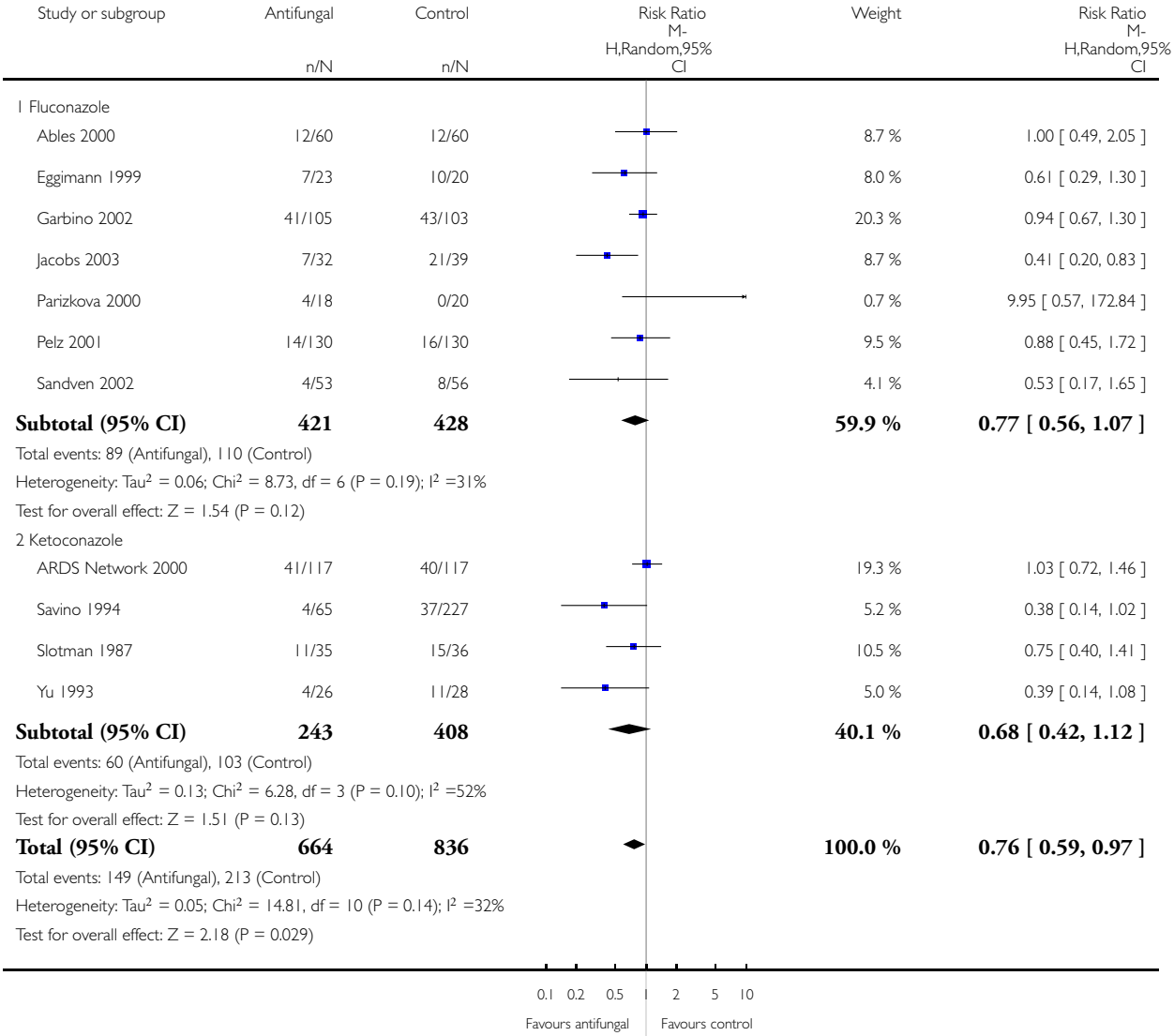
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	11	1500	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.59, 0.97]
1.1 Fluconazole	7	849	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.56, 1.07]
1.2 Ketoconazole	4	651	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.42, 1.12]
2 Proven invasive fungal infection	10	1260	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.31, 0.68]
2.1 Fluconazole	8	897	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.32, 0.71]
2.2 Ketoconazole	2	363	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.07, 1.31]
3 Proven invasive fungal infection (azole-resistant Candida species)	7	805	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.22, 1.72]
3.1 Fluconazole	6	734	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.22, 1.96]
3.2 Ketoconazole	1	71	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.14]
4 Proven invasive fungal infection (moulds)	7	805	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.1 Fluconazole	6	734	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Ketoconazole	1	71	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Suspected invasive fungal infection	4	696	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.25, 5.13]
5.1 Fluconazole	4	696	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.25, 5.13]
5.2 Ketoconazole	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Proven or suspected invasive fungal infection	4	696	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.40, 1.02]
6.1 Fluconazole	4	696	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.40, 1.02]
6.2 Ketoconazole	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Superficial fungal infection	3	587	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.27, 1.29]
7.1 Fluconazole	3	587	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.27, 1.29]
7.2 Ketoconazole	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Fungal colonization	8	792	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.50, 0.73]
8.1 Fluconazole	5	375	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.42, 0.74]
8.2 Ketoconazole	3	417	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.47, 0.94]
9 Fungal colonization (azole-resistant Candida species)	5	309	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.44, 2.95]
9.1 Fluconazole	4	252	Risk Ratio (M-H, Random, 95% CI)	1.74 [0.64, 4.71]
9.2 Ketoconazole	1	57	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.02, 1.44]
10 Adverse effects requiring cessation	5	655	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.37, 1.94]
10.1 Fluconazole	3	367	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.22, 2.57]
10.2 Ketoconazole	2	288	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.20, 7.59]

Analysis 1.1. Comparison 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal, Outcome 1 Mortality.

Review: Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients

Comparison: 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal

Outcome: 1 Mortality



Analysis 1.2. Comparison 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal, Outcome 2 Proven invasive fungal infection.

Review: Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients

Comparison: 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal

Outcome: 2 Proven invasive fungal infection

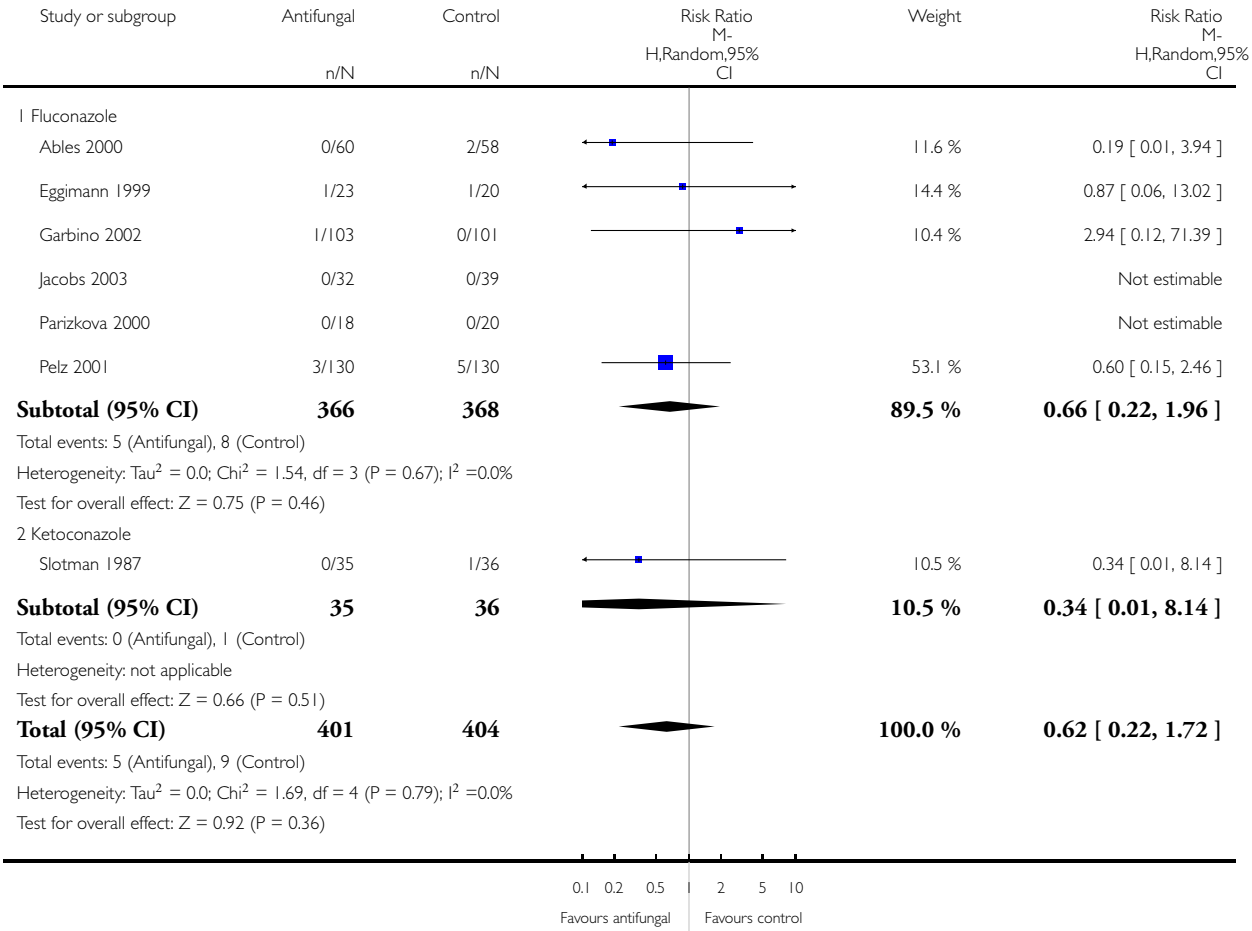
Study or subgroup	Antifungal n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Fluconazole					
Ables 2000	8/61	12/60		21.9 %	0.66 [0.29, 1.49]
Eggimann 1999	4/25	9/22		13.9 %	0.39 [0.14, 1.09]
Garbino 2002	5/104	11/102		14.1 %	0.45 [0.16, 1.24]
He 2003	2/22	7/23		6.9 %	0.30 [0.07, 1.28]
Jacobs 2003	0/32	1/39		1.5 %	0.40 [0.02, 9.59]
Parizkova 2000	0/18	0/20			Not estimable
Pelz 2001	7/130	16/130		20.2 %	0.44 [0.19, 1.03]
Sandven 2002	5/53	10/56		14.6 %	0.53 [0.19, 1.44]
Subtotal (95% CI)	**445**	**452**		**93.2 %**	**0.47 [0.32, 0.71]**
Total events: 31 (Antifungal), 66 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.22$, df = 6 (P = 0.98); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.67 (P = 0.00024)					
2 Ketoconazole					
Savino 1994	1/65	8/227		3.5 %	0.44 [0.06, 3.43]
Slotman 1987	1/35	5/36		3.4 %	0.21 [0.03, 1.67]
Subtotal (95% CI)	**100**	**263**		**6.8 %**	**0.30 [0.07, 1.31]**
Total events: 2 (Antifungal), 13 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.25$, df = 1 (P = 0.62); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.60 (P = 0.11)					
Total (95% CI)	**545**	**715**		**100.0 %**	**0.46 [0.31, 0.68]**
Total events: 33 (Antifungal), 79 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.82$, df = 8 (P = 0.99); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.96 (P = 0.000074)					

Analysis 1.3. Comparison 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal, Outcome 3 Proven invasive fungal infection (azole-resistant Candida species).

Review: Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients

Comparison: 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal

Outcome: 3 Proven invasive fungal infection (azole-resistant Candida species)



Analysis 1.4. Comparison 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal, Outcome 4 Proven invasive fungal infection (moulds).

Review: Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients

Comparison: 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal

Outcome: 4 Proven invasive fungal infection (moulds)

Study or subgroup	Antifungal n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Fluconazole					
Ables 2000	0/60	0/58			Not estimable
Eggimann 1999	0/23	0/20			Not estimable
Garbino 2002	0/103	0/101			Not estimable
Jacobs 2003	0/32	0/39			Not estimable
Parizkova 2000	0/18	0/20			Not estimable
Pelz 2001	0/130	0/130			Not estimable
Subtotal (95% CI)	**366**	**368**			**Not estimable**
Total events: 0 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Ketoconazole					
Slotman 1987	0/35	0/36			Not estimable
Subtotal (95% CI)	**35**	**36**			**Not estimable**
Total events: 0 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**401**	**404**			**Not estimable**
Total events: 0 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 1.5. Comparison 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal, Outcome 5 Suspected invasive fungal infection.

Review: Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients

Comparison: 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal

Outcome: 5 Suspected invasive fungal infection

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Fluconazole					
Ables 2000	5/61	1/60		23.9 %	4.92 [0.59, 40.86]
Garbino 2002	1/104	3/102		22.5 %	0.33 [0.03, 3.09]
Pelz 2001	2/130	6/130		30.2 %	0.33 [0.07, 1.62]
Sandven 2002	4/53	1/56		23.4 %	4.23 [0.49, 36.61]
Subtotal (95% CI)	**348**	**348**		**100.0 %**	**1.14 [0.25, 5.13]**
Total events: 12 (Treatment), 11 (Control)					
Heterogeneity: Tau^2 = 1.29; Chi^2 = 6.72, df = 3 (P = 0.08); I^2 =55%					
Test for overall effect: Z = 0.18 (P = 0.86)					
2 Ketoconazole					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**348**	**348**		**100.0 %**	**1.14 [0.25, 5.13]**
Total events: 12 (Treatment), 11 (Control)					
Heterogeneity: Tau^2 = 1.29; Chi^2 = 6.72, df = 3 (P = 0.08); I^2 =55%					
Test for overall effect: Z = 0.18 (P = 0.86)					

Analysis 1.6. Comparison 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal, Outcome 6 Proven or suspected invasive fungal infection.

Review: Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients

Comparison: 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal

Outcome: 6 Proven or suspected invasive fungal infection

Study or subgroup	Antifungal n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Fluconazole					
Ables 2000	13/61	13/60		29.6 %	0.98 [0.50, 1.94]
Garbino 2002	6/104	14/102		19.6 %	0.42 [0.17, 1.05]
Pelz 2001	9/130	22/130		26.8 %	0.41 [0.20, 0.85]
Sandven 2002	9/53	11/56		24.0 %	0.86 [0.39, 1.92]
Subtotal (95% CI)	**348**	**348**		**100.0 %**	**0.64 [0.40, 1.02]**
Total events: 37 (Antifungal), 60 (Control)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 4.35$, df = 3 (P = 0.23); $I^2 = 31\%$					
Test for overall effect: Z = 1.89 (P = 0.059)					
2 Ketoconazole					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**348**	**348**		**100.0 %**	**0.64 [0.40, 1.02]**
Total events: 37 (Antifungal), 60 (Control)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 4.35$, df = 3 (P = 0.23); $I^2 = 31\%$					
Test for overall effect: Z = 1.89 (P = 0.059)					

Analysis 1.7. Comparison 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal, Outcome 7 Superficial fungal infection.

Review: Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients

Comparison: 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal

Outcome: 7 Superficial fungal infection

Study or subgroup	Antifungal n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Fluconazole					
Ables 2000	4/61	7/60		43.5 %	0.56 [0.17, 1.82]
Garbino 2002	2/104	6/102		24.2 %	0.33 [0.07, 1.58]
Pelz 2001	4/130	4/130		32.3 %	1.00 [0.26, 3.91]
Subtotal (95% CI)	**295**	**292**		**100.0 %**	**0.59 [0.27, 1.29]**
Total events: 10 (Antifungal), 17 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.12$, df = 2 (P = 0.57); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.32 (P = 0.19)					
2 Ketoconazole					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**295**	**292**		**100.0 %**	**0.59 [0.27, 1.29]**
Total events: 10 (Antifungal), 17 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.12$, df = 2 (P = 0.57); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.32 (P = 0.19)					

Analysis 1.8. Comparison 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal, Outcome 8 Fungal colonization.

Review: Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients

Comparison: 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal

Outcome: 8 Fungal colonization

Study or subgroup	Antifungal n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Fluconazole					
Ables 2000	14/60	32/57		14.4 %	0.42 [0.25, 0.69]
Eggimann 1999	7/23	14/20		8.2 %	0.43 [0.22, 0.86]
Garbino 2002	29/55	40/51		45.5 %	0.67 [0.50, 0.90]
Jacobs 2003	2/32	4/39		1.4 %	0.61 [0.12, 3.12]
Parizkova 2000	18/18	20/20			Not estimable
Subtotal (95% CI)	**188**	**187**		**69.6 %**	**0.55 [0.42, 0.74]**
Total events: 70 (Antifungal), 110 (Control)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.61$, df = 3 (P = 0.31); $I^2 = 17\%$					
Test for overall effect: Z = 4.02 (P = 0.000059)					
2 Ketoconazole					
Savino 1994	9/65	50/227		8.9 %	0.63 [0.33, 1.21]
Slotman 1987	16/35	23/36		19.9 %	0.72 [0.46, 1.11]
Yu 1993	2/26	6/28		1.7 %	0.36 [0.08, 1.62]
Subtotal (95% CI)	**126**	**291**		**30.4 %**	**0.66 [0.47, 0.94]**
Total events: 27 (Antifungal), 79 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.83$, df = 2 (P = 0.66); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.28 (P = 0.023)					
Total (95% CI)	**314**	**478**		**100.0 %**	**0.60 [0.50, 0.73]**
Total events: 97 (Antifungal), 189 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.73$, df = 6 (P = 0.58); $I^2 = 0.0\%$					
Test for overall effect: Z = 5.11 (P < 0.00001)					

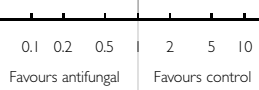
Analysis 1.9. Comparison 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal, Outcome 9 Fungal colonization (azole-resistant Candida species).

Review: Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients

Comparison: 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal

Outcome: 9 Fungal colonization (azole-resistant Candida species)

Study or subgroup	Antifungal n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Fluconazole					
Ables 2000	2/60	2/57		21.5 %	0.95 [0.14, 6.52]
Eggimann 1999	2/23	1/20		15.4 %	1.74 [0.17, 17.78]
Garbino 2002	3/24	2/30		26.5 %	1.88 [0.34, 10.33]
Parizkova 2000	3/18	1/20		17.4 %	3.33 [0.38, 29.25]
Subtotal (95% CI)	**125**	**127**		**80.8 %**	**1.74 [0.64, 4.71]**
Total events: 10 (Antifungal), 6 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.73$, df = 3 (P = 0.87); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.09 (P = 0.28)					
2 Ketoconazole					
Slotman 1987	1/27	6/30		19.2 %	0.19 [0.02, 1.44]
Subtotal (95% CI)	**27**	**30**		**19.2 %**	**0.19 [0.02, 1.44]**
Total events: 1 (Antifungal), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.61 (P = 0.11)					
Total (95% CI)	**152**	**157**		**100.0 %**	**1.13 [0.44, 2.95]**
Total events: 11 (Antifungal), 12 (Control)					
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 4.54$, df = 4 (P = 0.34); $I^2 = 12\%$					
Test for overall effect: Z = 0.26 (P = 0.80)					

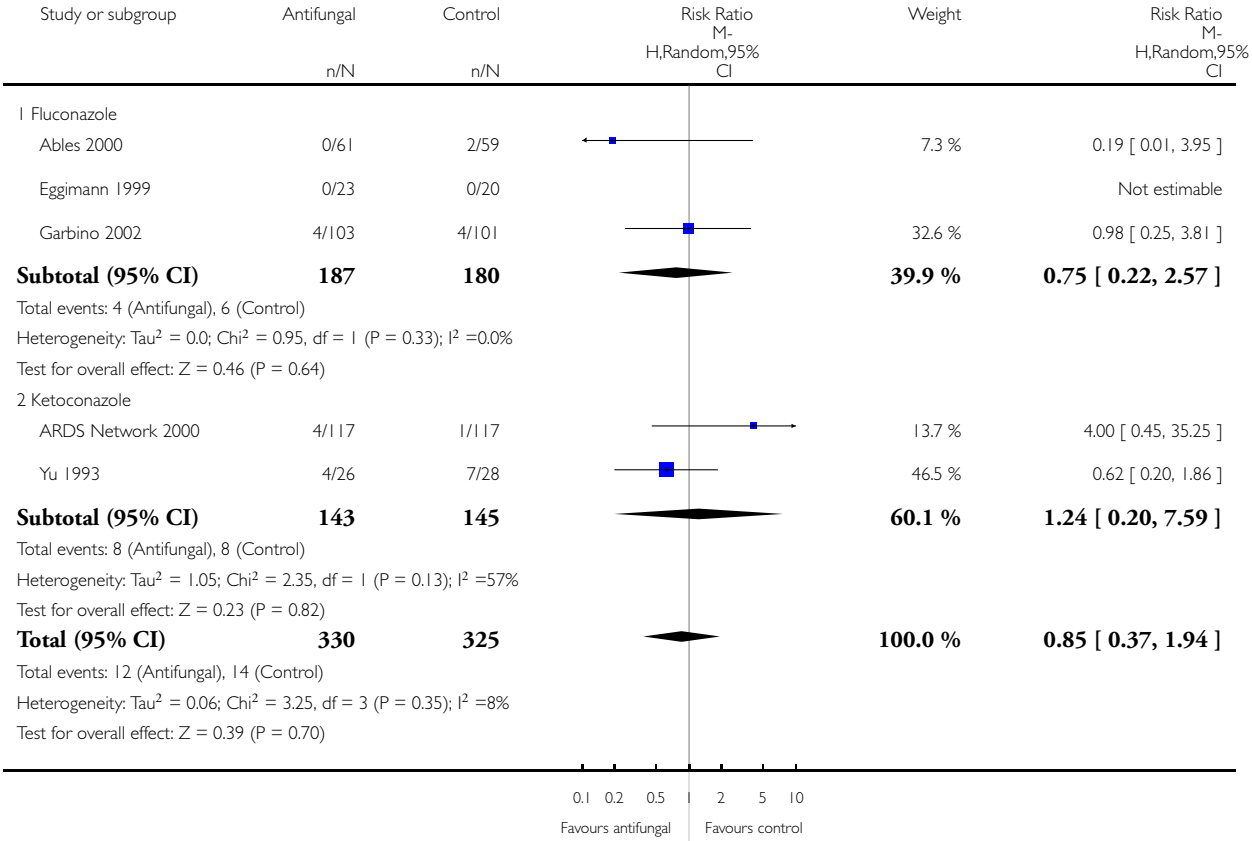


Analysis 1.10. Comparison 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal, Outcome 10 Adverse effects requiring cessation.

Review: Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients

Comparison: 1 Systemic antifungal versus placebo/no antifungal/nonabsorbable antifungal

Outcome: 10 Adverse effects requiring cessation



ADDITIONAL TABLES

Table 1. Definitions of fungal infections used in included studies

Trial	Proven IFI	Suspected IFI	Superficial FI
Ables 2000	"Documented candidiasis": positive culture from respiratory, mucosal, or peritoneal specimens	Compatible clinical illness (including SIRS) but no evidence of bacterial or other cause	Fungal UTI, thrush, skin lesions

Table 1. Definitions of fungal infections used in included studies (*Continued*)

Eggimann 1999	Clinical plus positive culture/histology of sterile site specimen or abdominal drain effluent	NA	NA
Garbino 2002	Clinical plus positive culture of sterile site specimen or BAL (>10,000 cfu/mL) with radiological infiltrates	Commencement of systemic antifungal therapy with clinical but no microbiological evidence of IFI	Fungal superficial wound, UTI, or mucocutaneous infection
He 2003	Clinical plus positive culture from sterile site specimen or bile, sputum, pus, throat, urine, or stool	NA	NA
Jacobs 2003	Positive culture/histology of sterile site specimen	NA	Culture of mucosal surface specimens
Parizkova 2000	Clinical plus positive culture/histology of sterile site specimen	NA	Clinical plus culture of superficial site specimens
Pelz 2001	Clinical plus positive culture/histology of sterile site specimen, intradermal catheter tip (>15 cfu), or deep surgical site specimen (on debridement)	Commencement of antifungal therapy with clinical evidence of IFI and fungal colonisation	Fungal UTI
Sandven 2002	Clinical plus positive culture of blood, intrabdominal drain fluid, or other (unspecified) sites	Commencement of systemic antifungal therapy with clinical but no microbiological evidence of IFI	NA
Savino 1994	Positive culture of sterile site specimen or > 2 other (unspecified) sites	NA	NA
Slotman 1987	Positive culture of sterile site or invasive burn wound	NA	NA
Weidemann 2000	NA	NA	NA
Yu 1993	NA	NA	NA

Table 2. Subgroup and sensitivity analyses

Variable	Category	No. studies	RR (95%CI) IFI
SUBGROUP ANALYSES:			
Definition of invasive fungal infection conforms to that used in this review	Yes	5	0.41 (0.24 to 0.69)

Table 2. Subgroup and sensitivity analyses (*Continued*)

	No	4	0.53 (0.30 to 0.93)
Fluconazole dose	>/=400 mg/day	4	0.50 (0.30 to 0.80)
	<400 mg/day	3	0.39 (0.17 to 0.88)
Post-surgical patients (%)	>/=75%	5	0.43 (0.26 to 0.71)
	<75%	3	0.56 (0.03 to 1.04)
SENSITIVITY ANALYSES:			
Analysis model	Random effects		0.46 (0.31 to 0.68)
	Fixed effects		0.45 (0.31 to 0.66)
Randomized sequence generation	Adequate	4	0.50 (0.32 to 0.80)
	Uncertain	5	0.37 (0.18 to 0.75)
Allocation concealment	Adequate	6	0.45 (0.28 to 0.71)
	Uncertain	3	0.49 (0.25 to 0.97)
Blinding of outcome assessors	Yes	2	0.42 (0.22 to 0.81)
	No	7	0.48 (0.30 to 0.78)
Intention-to-treat analysis	Yes	4	0.44 (0.24 to 0.78)
	No	5	0.48 (0.29 to 0.80)

Table 3. Applicability of meta-analysis results

Estimated risk	Examples	Incid. w/o prophylax	Incid. w/ prophylax	No. avoided	NNT (95%CI)
Low (1%)	Absence of risk factors (based on Rex 2001)	1	0.47	0.53	188 (147-345)
Average (2%)	Unselected ICU population (based on Rex 2001)	2	0.94	1.06	94 (74-172)

Table 3. Applicability of meta-analysis results (*Continued*)

High (11%)	One of new onset haemodialysis, diabetes, total parenteral nutrition prior to ICU entry, or broad-spectrum antibiotics (based on Paphitou 2005)	11	5.2	5.8	17 (13-31)
High (17%)	One of new onset haemodialysis, diabetes, or total parenteral nutrition prior to ICU entry (based on Paphitou 2005)	17	8.0	9.0	11 (9-20)
Highest (20%)	One of new onset haemodialysis, diabetes, or total parenteral nutrition prior to ICU entry AND broad-spectrum antibiotics (based on Paphitou 2005)	20	9.4	10.6	9 (7-17)

APPENDICES

Appendix 1. Search strategies for electronic databases

Database	Search strategy
Cochrane Central Register of Controlled Trials	#1 MeSH descriptor Antifungal Agents explode all trees in MeSH products #2 antifungal in All Fields, from 1800 to 2004 in all products #3 fluconazole in All Fields, from 1800 to 2004 in all products #4 itraconazole in All Fields, from 1800 to 2004 in all products #5 ketoconazole in All Fields in all products #6 voriconazole in All Fields in all products #7 amphotericin in All Fields in all products #8 ambisome in All Fields in all products

(*Continued*)

	#9 amphotec in All Fields in all products #10 amphocil in All Fields in all products #11 abelcet in All Fields in all products #12 caspofungin in All Fields in all products #13 flucytosine in All Fields in all products #14 miconazole in All Fields in all products #15 econazole in All Fields in all products #16 clotrimazole in All Fields in all products #17 nystatin in All Fields in all products #18 MeSH descriptor Mycoses explode all trees in MeSH products #19 fung* in All Fields in all products #20 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19) #21 MeSH descriptor Critical Care explode all trees in MeSH products #22 intensive in All Fields in all products #23 critic* in All Fields in all products #24 surg* in All Fields in all products #25 (#21 OR #22 OR #23 OR #24) #26 (#20 AND #25)
MEDLINE (OVID)	1 exp antifungal agents/ 2 exp mycoses/ 3 fung$.tw. 4 fluconazole.tw. 5 diflucan.tw. 6 itraconazole.tw. 7 sporanox.tw. 8 ketoconazole.tw. 9 nizoral.tw. 10 voriconazole.tw. 11 amphotericin.tw. 12 ambisome.tw. 13 amphotec.tw. 14 abelcet.tw. 15 flucytosine.tw. 16 nystatin.tw. 17 miconazole.tw. 18 (echinocandin$ or caspofungin).tw. 19 (select$ adj5 decontam$).tw. 20 or/1-19 21 exp Intensive Care Units/ 22 intensive care.tw. 23 critical$.tw. 24 surg$.tw. 25 or/21-24 26 20 and 25 27 randomized controlled trial.pt. 28 controlled clinical trial.pt. 29 randomized controlled trials/

(*Continued*)

	30 Random allocation/ 31 Double-blind method/ 32 Single-blind method/ 33 exp Evaluation studies/ 34 exp clinical-trials/ 35 clinical trial.pt. 36 (clin$ adj5 trial$).tw. 37 ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw. 38 exp Placebos/ 39 placebo$.tw. 40 random$.tw. 41 exp Research design/ 42 or/27-41 43 26 and 42
EMBASE (OVID)	1 exp antifungal agent/ 2 fluconazole.tw. 3 diflucan.tw. 4 itraconazole.tw. 5 sporanox.tw. 6 ketoconazole.tw. 7 nizoral.tw. 8 voriconazole.tw. 9 vfend.tw. 10 amphotericin.tw. 11 ambisome.tw. 12 amphotec.tw. 13 amphocil.tw. 14 abelcet.tw. 15 fungizone.tw. 16 flucytosine.tw. 17 nystatin.tw. 18 miconazole.tw. 19 echinocandin$.tw. 20 caspofungin.tw. 21 (select$ adj decontam$).tw. 22 exp mycosis/ 23 fung$.tw. 24 or/1-23 25 exp intensive care unit/ 26 intensive.tw. 27 critic$.tw. 28 surg$.tw. 29 or/25-28 30 24 and 29 31 exp controlled study/ or controlled study.ti,ab,hw,tn,mf. 32 exp statistical analysis/ or clinical study.ti,ab,hw,tn,mf. 33 exp major clinical study/ or major clinical study.ti,ab,hw,tn,mf. 34 exp randomized controlled trial/ or randomised controlled study.ti,ab,hw,tn,

(*Continued*)

	mf. 35 exp randomized controlled trial/ or randomized controlled study.ti,ab,hw,tn, mf. 36 random$.ti,ab,hw,tn,mf. 37 exp double blind procedure/ or double blind procedure.ti,ab,hw,tn,mf. 38 exp single blind procedure/ or single blind procedure.ti,ab,hw,tn,mf. 39 exp multicenter study/ or multicenter study.ti,ab,hw,tn,mf. 40 exp placebo/ or placebo.ti,ab,hw,tn,mf. 41 or/31-40 42 (human not animal).sh,de,hw. 43 41 and 42 44 30 and 43

WHAT'S NEW

Last assessed as up-to-date: 8 November 2005.

Date	Event	Description
31 May 2012	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 1, 2006

Date	Event	Description
25 July 2008	Amended	Converted to new review format.
8 November 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Elliott Geoffrey Playford (EGP) wrote the protocol, developed the search strategy, identified trials and coordinated trial results, extracted and entered data into RevMan, and wrote the final review.

Angela Webster (ACW) assisted in creating the search strategy, reviewed the protocol, identified trials, extracted data, and reviewed the final review.

Tania Sorrell (TCS) assisted writing the background and the protocol, assisted in identifying trials, and assisted in writing the final review.

Jonathan Craig (JCC) assisted with all aspects of the protocol, methodology, and review.

DECLARATIONS OF INTEREST

EGP: is a member of the Mycology Interest Group of the Australasian Society for Infectious Diseases, which is sponsored by Gilead, Pfizer, and Merck.

ACW: none declared.

TCS: has advisory board involvement with Pfizer, has received unrelated project funding from Pfizer, Merck, and Gilead, and is a member of the Mycology Interest Group of the Australasian Society for Infectious Diseases, which is sponsored by Gilead, Pfizer, and Merck.

JCC: none declared.

NOTES

Please note: The author originally published:"Antifungal agents for preventing fungal infections in non-neutropenic critically- ill patients and solid organ transplant recipients" with the Cochrane Gynaecological Cancer Group. The author then split the title and published a further protocol: "Antifungal agents for preventing fungal infections in solid organ transplant recipients" with the Cochrane Renal Group. The Cochrane Gynaecological Cancer Group has kindly agreed to the author splitting the original published protocol again and registering it with the Anaesthesia Group as: "Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients".

INDEX TERMS

Medical Subject Headings (MeSH)

*Critical Illness [mortality]; Amphotericin B [therapeutic use]; Antifungal Agents [*therapeutic use]; Fluconazole [therapeutic use]; Immunocompromised Host; Mycoses [mortality; *prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans