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[Intervention Review]

Antifungal agents for preventing fungal infections in solid organ transplant recipients

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ABSTRACT

Background

Invasive fungal infections (IFIs) are important causes of morbidity and mortality in solid organ transplant recipients.

Objectives

This study aims to systematically identify and summarise the effects of antifungal prophylaxis in solid organ transplant recipients.

Search methods

The Cochrane Central Register of Controlled Trials, MEDLINE (from 1966), and EMBASE (from 1980) were searched. Reference lists, abstracts of conference proceedings and scientific meetings (1998-2003) were handsearched. Authors of included studies and pharmaceutical manufacturers were contacted.

Selection criteria

Randomised controlled trials (RCTs) in all languages comparing the prophylactic use of any antifungal agent or regimen with placebo, no antifungal, or another antifungal agent or regimen.

Data collection and analysis

Two reviewers independently applied selection criteria, performed quality assessment, and extracted data using an intention-to-treat approach. Differences were resolved by discussion. Data were synthesised using the random effects model and expressed as relative risk (RR) with 95% confidence intervals (95% CI).

Main results

Fourteen unique trials with 1497 randomised participants were included. Antifungal prophylaxis did not reduce mortality (RR 0.90, 95% CI 0.57 to 1.44). In liver transplant recipients, a significant reduction in IFIs was demonstrated for fluconazole (RR 0.28, 95% CI 0.13 to 0.57). Although less data were available for itraconazole and liposomal amphotericin B, indirect comparisons and one direct comparative trial suggested similar efficacy. Fluconazole prophylaxis did not significantly increase invasive infections or colonisation with fluconazole-resistant fungi. In renal and cardiac transplant recipients, neither ketoconazole nor clotrimazole significantly reduced invasive infections. Overall, the strength and precision of comparisons however were limited by a paucity of data.

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Authors' conclusions

For liver transplant recipients, antifungal prophylaxis with fluconazole significantly reduces the incidence of IFIs with no definite mortality benefit. Given a 10% incidence of IFI, 14 liver transplant recipients would require fluconazole prophylaxis to prevent one infection. In transplant centres where the incidence of IFIs is high, or in situations where the individual risk is great, antifungal prophylaxis should be considered.

PLAIN LANGUAGE SUMMARY

Antifungal drugs used for prevention can significantly reduce the number of invasive fungal infections in liver transplant patients

Invasive fungal infections - infections of the bloodstream and organs within the body (e.g. meningitis, pneumonia, peritonitis) - are important causes of morbidity and mortality in liver, pancreas, heart, kidney and lung (i.e. solid organ) transplant recipients. This review found that fluconazole, used as a preventive drug, significantly reduced the number of invasive fungal infections in liver transplant patients. More studies are needed to determine how effective antifungal drugs are for pancreas, heart, kidney and lung transplant patients.

BACKGROUND

Invasive fungal infections (IFIs) are an emerging problem and an important cause of morbidity and mortality amongst the increasing populations of immunocompromised and otherwise debilitated patients. Amongst North American hospitalised patients their incidence increased from 2.0 to 3.8 infections/1000 discharges during the decade 1980 to 1990 (Beck-Sague 1993).

Patient groups at particular risk for IFIs include those with cancer that have undergone chemotherapy and/or bone marrow transplantation, solid organ transplant recipients, critically-ill patients in Intensive Care Units, and very low birth weight neonates. Amongst solid organ transplant recipients, IFIs remain a relatively common and clinically important complication. The risk is greatest during the early post-transplant period (Singh 2000) and varies with transplant type; liver (7 to 42%), heart (5 to 21%), lung (15 to 35%), and pancreas (18 to 38%) transplant recipients are at greater risk than renal transplant recipients (1 to 14%) (Paya 1993; Singh 2000). Many other risk factors for the development of IFIs have also been identified, including hepatic and renal dysfunction, retransplantation, greater degrees of immunosuppression, surgical complications, and post-transplant bacterial or cytomegalovirus infections (Castaldo 1991; George 1997; Nieto-Rodriguez 1996; Paya 1993; Patel 1996; Paterson 1999; Singh 2000).

Although a wide range of fungal pathogens cause IFIs in solid organ transplant recipients, *Candida* and *Aspergillus* species account for the vast majority, with the former causing more than three-quarters (Singh 2000). They include bloodstream and other deep organ infections, such as peritonitis, hepatosplenic candidiasis, meningitis, and pneumonia. Invasive aspergillosis generally presents within the first four weeks following transplantation. The lungs are the most common initial site of infection, although dissemination to other organs, particularly the brain, occurs in more than half (Paterson 1999). The clinical consequences of IFIs in solid organ transplant recipients are considerable, with attributable mortality rates reported as high as 70% for invasive candidiasis (Nieto-Rodriguez 1996) and 100% for invasive aspergillosis despite antifungal therapy (Paterson 1999).

IFIs are often diagnosed late because of their nonspecific clinical features and the poor sensitivity and specificity of currently available diagnostic tests. Given the high mortality and morbidity associated with such infections, particularly where the institution of antifungal therapy is delayed, attention has focused on preventative strategies. Antifungal prophylaxis with amphotericin B, fluconazole, and itraconazole reduces IFIs in neutropenic patients (Gotzsche 2002; Kanda 2000). In these settings, antifungal prophylaxis has become a standard strategy in high-risk neutropenic patients. However, the benefit of antifungal prophylaxis in high-risk non-neutropenic patients remains uncertain (Paya 2002; Singh 2000; Sobel 2001).

The prophylactic use of antifungal agents is associated with actual and potential problems. Although several antifungal agents are available, the choice is not straightforward, as each has differing spectra of activity, pharmacological properties, toxicities, and costs. Amphotericin B is active against a broad spectrum of fungi,

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but requires intravenous administration and is associated with renal toxicity and infusion-related febrile reactions. Although lipid preparations of amphotericin B have reduced toxicity (Johansen 2002), they are significantly more expensive. Azole antifungal agents, such as ketoconazole, fluconazole, and itraconazole, may be administered orally and are overall well tolerated, but have important interactions with many drugs, particularly immunosuppressant agents commonly used in solid organ transplantation. Furthermore, ketoconazole and fluconazole are inactive against *Aspergillus* species and other filamentous fungi and itraconazole has poor gastrointestinal absorption. Nonabsorbable antifungal agents given by the oral route, such as amphotericin B and nystatin, are relatively nontoxic. Although their use is based on the rationale that the most invasive C*andida* infections are derived from the gastrointestinal tract colonisation (Nucci 2001), they have no activity against other important portals of entry, such as the skin or respiratory tract.

An important potential problem of antifungal prophylaxis relates to selective pressure, whereby susceptible strains or species of fungi are simply replaced by resistant ones. This phenomenon is well-recognised in bacteria as a consequence of antibiotic use (McGowan 1983). There is some evidence that increases in azole-resistant invasive candida infections have resulted from increases in azole use (Abi-Said 1997; Fortun 1997; Gleason 1997; Nguyen 1996). In HIV-positive patients, thrush with azole-resistant candida strains and species has been selected for by azole use (Johnson 1995; Law 1994). Thus, antifungal prophylaxis in solid organ transplant recipients requires consideration of toxicity, ecological effects, resistance selection, and cost, as well as efficacy.

OBJECTIVES

To evaluate the benefits and harms of prophylactic antifungal agents for the prevention of fungal infections in solid organ transplant recipients.

The following primary questions were examined:

- Is prophylaxis with any antifungal agent(s) associated with reduced IFIs and mortality compared with no prophylaxis?
- Are some agent(s) alone or in combination more efficacious than others?
- For each agent, does the efficacy depend upon dose, route of administration, and duration of prophylaxis?
- Do some patient subgroups derive greater benefit from antifungal prophylaxis than others?

Secondary questions were examined:

- Is antifungal prophylaxis associated with reduced superficial fungal infections?
- Is antifungal prophylaxis associated with colonisation or infection with azole-resistant fungal strains or species?
- Is prophylaxis with antifungal agent(s) associated with clinically-significant toxicity?

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs that evaluate the effect of any prophylactic antifungal agent (alone or in combination with other interventions) in solid organ transplant recipients.

Types of participants

Studies involving patients who have received one or more solid organ transplants (heart, lung, kidney, liver, or pancreas) were considered. Studies involving patients with neutropenia or HIV-infected patients were excluded; the former patient group has already been the subject of a systematic review and the latter involves a different spectrum of fungal infections. Where studies include solid organ transplant recipients, together with neutropenic and/or HIV-infected patients, they were included, providing the proportion of the latter groups is less than 25%.

Types of interventions

Studies were considered if they involved the randomised comparison of any antifungal agent with placebo, no antifungal, or another antifungal agent, dose, route of administration, or duration. The study groups were required to differ only for the antifungal regimen under investigation; other aspects of care, including the routine use of other prophylactic antimicrobial agents, should be the same to avoid confounded comparisons. Secondary "prevention" trials (i.e. trials examining antifungal agents to prevent the relapse of an established fungal infection) were not considered, as the objective of this review was to assess interventions to prevent primary fungal infections.

Types of outcome measures

Primary outcome measures included:

- Proven IFI. The definition of proven IFI included a compatible clinical illness with either histological evidence of IFI

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or a positive fungal culture from one or more deep/sterile site specimen. Funguria (as indicated by a positive urine fungal culture), in the absence of a complicated urinary tract infection, and fungal oesophagitis was classified as superficial fungal infections. The definitions used in individual studies however were used, as they are likely to vary from study-to-study. Where uncertainty regarding the definitions or the validity of the classification of patients existed, authors were contacted for clarification.

- Total mortality.

Secondary outcome measures included:

- Proven or suspected IFI. The definition of proven or suspected IFI included all patients classified as proven IFI together with those with possible infection. This was defined as the initiation of systemic antifungal therapy without fulfilment of the criteria for a proven IFI.
- Superficial fungal infection. Superficial fungal infections were defined as superficial cutaneous, oropharyngeal, oesophageal or uncomplicated urinary tract fungal infections.
- Fungal colonisation. Fungal colonisation was defined as a positive culture from any body site for fungi from any site that develops (if not present at baseline) or persists (if present at baseline).
- Proven IFI caused by an azole-resistant *Candida* species (defined as *Candida glabrata, Candida krusei*, or another species with documented azole resistance) or a filamentous fungi (including *Aspergillus* species).
- Fungal colonisation at any body site with azole-resistant *Candida* species.
- Adverse events requiring cessation of study drug(s).

The time point of assessment of outcome measures was at three months after commencement of prophylaxis or at the end of prophylaxis (whichever is longer). All outcome measures were analysed according to intention-to-treat.

Search methods for identification of studies

Initial search

Relevant studies were identified by searching electronic databases (Table 1 - *Electronic search strategy*) and other resources:

1. Cochrane Central Register of Controlled Trials (Issue 4, 2003)
2. MEDLINE (OVID: 1966-August 2003): the search strategy incorporated the Cochrane highly sensitive search strategy for identifying RCTs in MEDLINE (Dickersin 1994)
3. EMBASE (OVID: 1980-August 2003): the search strategy incorporated a sensitive strategy for identifying RCTs in EMBASE (Lefebvre 1996)
4. Proceedings of major relevant conferences (including, but not limited to Interscience Conference of Antimicrobial Agents and Chemotherapy, American Society for Microbiology, Infectious Diseases Society of America, European Congress of Clinical Microbiology and Infectious Diseases, and American Society of Transplant Physicians)
5. Reference lists of identified studies and major reviews
6. Contact with researchers active in the field and primary authors of identified relevant trials for details of unpublished trials
7. Contact with manufacturers of the study drugs (including Pfizer, Gilead, Merck) for additional published or unpublished trials.

No language restrictions were applied. Letters, abstracts, and unpublished trials were accepted to reduce publication bias. If duplicate publication was suspected, authors were contacted for clarification, and if confirmed, the publication with the most and/or the longest follow-up data was used for the review.

Review update

For this update the Cochrane Renal Group's specialised register and The Cochrane Central Register of Controlled Trials (CENTRAL, in *The Cochrane Library*) was searched. CENTRAL and the Renal Group's specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective (http://www.cochrane.us/masterlist.asp). Please refer to The Cochrane Renal Review Group's Module in *The Cochrane Library* for the complete lis of nephrology conference proceedings searched.

Date of most recent search: November 2005

Data collection and analysis

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

Data extraction

Data were extracted and collected on a standardised paper form. Where important data regarding study results were not provided

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in the primary papers, the authors were contacted for clarification. Data was extracted wherever possible for all randomised patients on an intention-to-treat basis. Data was then entered into RevMan twice (EGP).

Evaluation of study methodological quality

The validity and design characteristics of each study was evaluated for major potential sources of bias (generation of random allocation sequence, allocation concealment, blinding, intention-to-treat analysis, and completeness of follow-up) (Clarke 2001). Each study quality factor was assessed separately, but not with a composite score.

Randomised sequence generation

- Adequate: Random number generation used
- Unclear: No information on randomised sequence generation available
- Inadequate: Alternate medical record numbers or other nonrandom sequence generation

Allocation concealment

- Adequate (A): Allocation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered into study
- Unclear (B): No information on allocation method available
- Inadequate (C): 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

- Subjects: yes/no/not stated
- Investigators: yes/no/not stated
- Outcome assessors: yes/no/not stated
- Data analysis: yes/no/not stated

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 randomised 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 randomised participants with outcome data at defined study endpoint

Data analysis

Dichotomous data was analysed using RR and 95% CI.
Heterogeneity in trial results was graphically inspected and assessed with a test of homogeneity (χ^2 on N-1 degrees of freedom), with $P < 0.1$ considered as indicating significant heterogeneity and with a test of inconsistency (I^2) (Higgins 2003). Potential causes for significant heterogeneity, such as study design, drug type, drug dose, drug administration route, population, outcome measure definitions, or other factors were explored. Results from different studies, where clinically appropriate, were pooled using a random effects model and compared with the fixed effect model.
Subgroup analysis was performed to assess the influence of study methodology quality and clinical parameters (such as type of antifungal agent, dose and duration of prophylaxis, transplant type, outcome measure definition, and follow-up duration). Although variations in treatment effect may be explained by differences in the background risk of developing IFIs, assessing this variation through the simple relationship between the observed treatment effect and the observed background risk in individual studies is flawed (Davey Smith 2001; Sharp 2001).
Publication bias was assessed using a funnel plot (log relative risk for efficacy versus 1/standard error) (Egger 1997).

RESULTS

Description of studies

From the initial search strategy (1926 potential studies), 114 studies were identified as potentially relevant and retrieved for further assessment (Figure 1). Although pharmaceutical companies provided some information, no unique studies were identified from that source. No useable data or information regarding one potentially eligible study (Rossi 1995), available only as an abstract, other than its title was able to be retrieved despite extensive efforts, including contact with the corresponding author.

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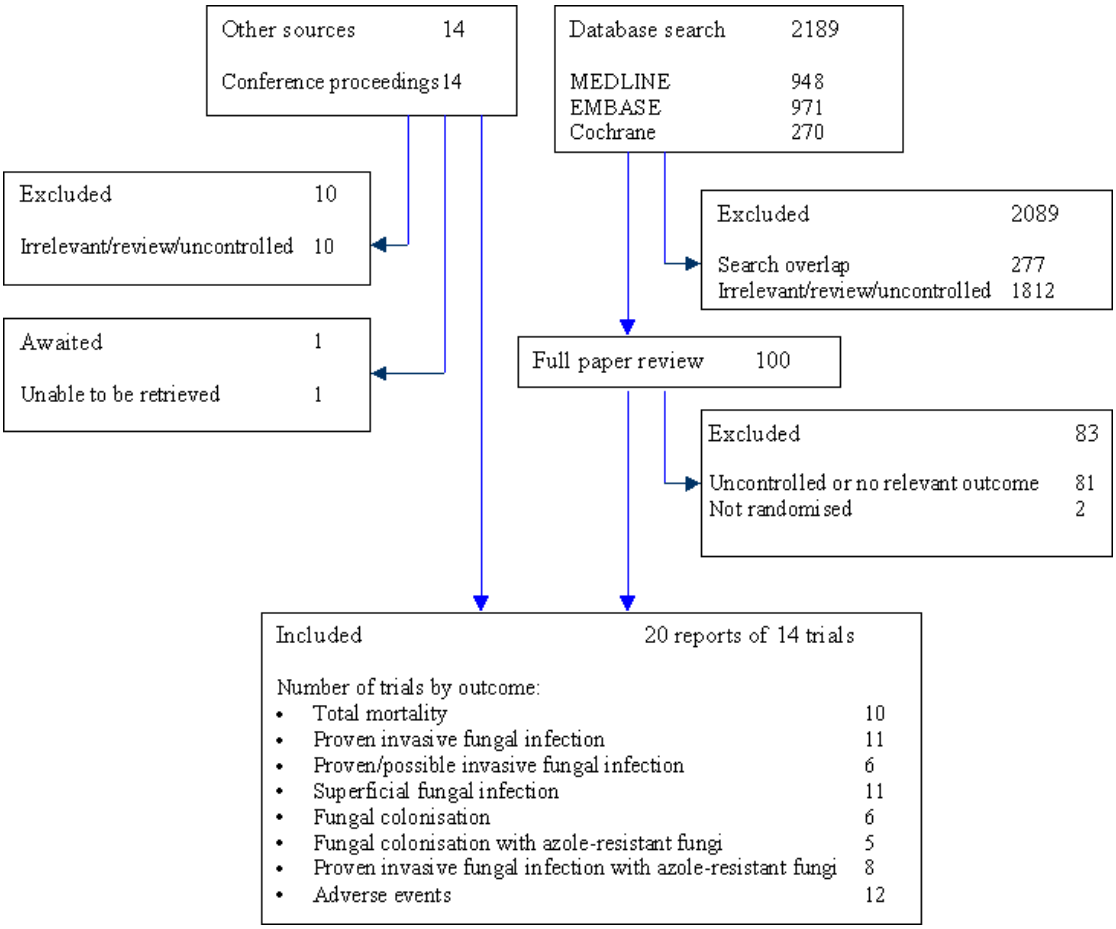
Figure 1. Search strategy results



Twenty references reporting 14 trials (Biancofiore 2002; Gombert 1987; Keogh 1995; Lumbreras 1996; Meyers 1997; Owens 1984; Patton 1994; Ruskin 1992; Sharpe 2003; Sobh 1995; Tollemar 1995; Tortorano 1995; Winston 1999; Winston 2002) involving 1497 randomised patients (range, 34 to 236 patients/study) were included in the review. All studies were in English. One study was available only as an abstract (Meyers 1997).

Eleven trials evaluated systemic antifungal agents. Ten trials compared a systemic antifungal regimen with placebo, no antifungal, or an oral nonabsorbable agent: four involved fluconazole (Lumbreras 1996; Meyers 1997; Tortorano 1995; Winston 1999), two itraconazole (Biancofiore 2002; Sharpe 2003), one liposomal amphotericin B (Tollemar 1995), and three ketoconazole (Keogh 1995; Patton 1994; Sobh 1995). One study directly compared two systemic regimens: fluconazole versus itraconazole (Winston 2002). Additionally, one of the placebo-controlled studies compared two different itraconazole-based regimens with placebo (Biancofiore 2002), which we assessed both separately and together. Three studies evaluated only oral nonabsorbable agents: one compared clotrimazole with placebo (Owens 1984) and two compared clotrimazole with nystatin (Gombert 1987; Ruskin 1992). Nine studies involved liver transplant recipients (Biancofiore 2002; Lumbreras 1996; Meyers 1997; Ruskin 1992; Sharpe 2003; Tollemar 1995; Tortorano 1995; Winston 1999; Winston 2002), four renal transplant recipients (Gombert 1987; Owens 1984; Patton 1994; Sobh 1995), and one cardiac transplant recipients (Keogh 1995).

Reporting of outcomes was variable (Table 2; Table 3). Total mortality was reported for all but one of the trials assessing systemic antifungal agents (Sobh 1995), but none of those assessing only nonabsorbable agents. Eleven trials reported proven IFIs, with the diagnostic criteria for this outcome provided in six of these. The reported criteria was consistent with our definition in six (Lumbreras 1996; Sharpe 2003; Tollemar 1995; Tortorano 1995; Winston 1999; Winston 2002), but not in the other which included posi-

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tive cultures from three or more peripheral sites as evidence of an invasive infection (Biancofiore 2002), which we would regard as consistent with either colonisation or superficial infection. Of the four trials without explicit criteria, three provided sufficient information in the results to classify infections (Owens 1984; Patton 1994; Sobh 1995), but not the other, which was presented only in abstract form (Meyers 1997). The other three trials (Gombert 1987; Ruskin 1992; Sobh 1995) did not report IFIs. Other outcomes were even more variably reported, particularly with respect to the fungal species causing infection and/or colonisation. Overall, most data were available for the fluconazole trials.

Risk of bias in included studies

Methodological quality parameters were incompletely reported for most trials (Table 2; Table 3)

Random sequence generation

As reported, random sequence generation was adequate in three trials (Gombert 1987; Lumbreras 1996; Winston 2002) and unclear in the other 11.

Allocation concealment

Allocation concealment was adequate in two trials (Sharpe 2003; Tollemar 1995) and unclear in 12.

Blinding

Blinding of study participants was evident in six trials (Biancofiore 2002; Meyers 1997; Owens 1984; Sharpe 2003; Tollemar 1995; Winston 1999), and of investigators in five (Meyers 1997; Owens 1984; Sharpe 2003; Tollemar 1995; Winston 1999). Three trials reported that outcome assessors were blinded (Sharpe 2003; Tollemar 1995; Winston 1999).

Intention-to-treat analysis

Intention-to-treat analysis was confirmed in seven trials (Biancofiore 2002; Keogh 1995; Lumbreras 1996; Ruskin 1992; Sobh 1995; Winston 1999; Winston 2002).

Completeness of follow-up

Post-randomisation exclusions were 10% or greater for two trials (Patton 1994; Sharpe 2003; Tollemar 1995) and unstated for one (Meyers 1997).

Effects of interventions

Systemic antifungal agents versus placebo/no antifungal/nonabsorbable agents

Total mortality

Total mortality rates in the control arms of the trials ranged from 3 to 16% (mean, 12%). Total mortality was not reduced with any systemic antifungal regimen compared with placebo, no treatment, or nonabsorbable antifungal agents. Results were homogeneous across different antifungal agents and transplant types (χ^2 = 9.01, df = 8, P = 0.34, I^2 = 11.3%) . Pooled estimates for all trials combined (Analysis 1.1: RR 0.90, 95% CI 0.57 to 1.44) and for those in liver transplant recipients combined (RR 0.84, 95% CI 0.54 to 1.30) did not demonstrate a significant mortality benefit, although confidence intervals were wide.

Proven invasive fungal infections (IFIs)

Fluconazole significantly reduced the risk of proven IFIs in liver transplant recipients compared with placebo or nonabsorbable antifungal agents by about three-quarters (Analysis 1.2.1: RR 0.28, 95% CI 0.13 to 0.57). The overall rate of proven infections in the control arm of these four studies was 13% (range 4 to 23%). Despite differences in the prophylactic regimens, such as dose, route of administration, and duration, the relative risk reductions across these studies were homogeneous (χ^2 = 1.04, df= 3, P = 0.79; I^2 = 0%).

Proven IFIs were reported to occur in only one of the two itraconazole trials: in this, no significant reduction in infections was demonstrated, although confidence intervals were wide (Analysis 1.2.2: RR 0.80, 95% CI 0.44 to 1.45).
Liposomal amphotericin B prevented all proven invasive infections in one trial in liver transplant recipients, but similarly confidence intervals were very wide (Analysis 1.2.3: RR 0.07, 95% CI 0.00 to 1.26).
No significantly heterogeneity was demonstrated amongst the seven studies that compared fluconazole, itraconazole, or amphotericin B with no antifungal or a nonabsorbable antifungal agent in liver transplant recipients (χ^2 = 8.44, df = 5, P = 0.13, I^2 = 40.7%). This suggests a similar underlying efficacy for the prevention of proven IFIs in such patients, which is not critically dependent on the antifungal agent, dose, duration, or route of administration (pooled estimate, RR 0.39, 95% CI 0.18 to 0.85).
Ketoconazole did not significantly reduce infections in the single study in renal transplant recipients (RR 7.67, 95% CI 0.32 to 182.44) and that in cardiac transplant recipients (RR 0.43, 95% CI 0.09 to 2.93), although only a total of seven infections occurred amongst 137 randomised patients in these two trials.

Proven or suspected invasive fungal infections

Fluconazole prophylaxis reduced the incidence of combined proven and suspected IFIs (Analysis 1.7.1: RR 0.46, 95% CI 0.28 to 0.76). The incidence of suspected invasive infections (empiric antifungal use) ranged from 3% to 8% in the control arms of

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these trials and was not significantly reduced by fluconazole prophylaxis. In the single itraconazole study reporting this outcome, the incidence of suspected infections was not significantly reduced (Analysis 1.7.2: RR 0.25, 95% CI 0.03 to 1.93). Similarly, liposomal amphotericin B did not significantly reduce the incidence of suspected infections (Analysis 1.6.3: RR 1.27, 95% CI 0.30 to 5.34) or that of suspected and proven infections combined (Analysis 1.7.3: RR 0.42, 95% CI 0.14 to 1.27). However, for both of these studies, the confidence intervals were wide.

Superficial fungal infections

Fluconazole significantly reduced superficial fungal infections in liver transplant recipients (Analysis 1.8.1: RR 0.24, 95% CI 0.10 to 0.59). Amongst these three studies, the overall rate of superficial fungal infections was 29% (range, 25% to 31%), with no significant heterogeneity in the effect of fluconazole prophylaxis demonstrated (χ^2 = 3.9, df = 2, P = 0.14, I^2 = 48.8%). No superficial infections occurred in the itraconazole arm of the single trial reporting this outcome. Amongst renal transplant recipients, ketoconazole reduced superficial infections (RR 0.19, 95% CI 0.04 to 0.86), although the rate of superficial infections in the control groups of these two studies were considerably different (18% and 64%) and heterogeneity was demonstrated between them (χ^2 = 2.83, df = 1, P = 0.09, I^2 = 64.7%). In the single study of ketoconazole in cardiac transplant recipients, all superficial infections were prevented.

Fungal colonisation

Fluconazole reduced fungal colonisation in liver transplant recipients (Analysis 1.9.1: RR 0.47, 95% CI 0.37 to 0.61). Results were homogeneous across the three trials reporting this outcome (χ^2 = 1.58, df = 2, P = 0.45, I^2 = 0%). Itraconazole prophylaxis similarly reduced colonisation (Analysis 1.9.2: RR 0.57, 95% CI 0.41 to 0.80), although only one study was available.

Infection and colonisation with azole-resistant fungi

Invasive infections with *C. glabrata*, *C. krusei*, or moulds were reported in three fluconazole trials, causing 6% and 3% of invasive infections in the control and fluconazole arms respectively. No significant increase in their incidence was associated with fluconazole (Analysis 1.5.1:RR 0.50, 95% CI 0.19 to 1.33). Based on single studies, no significant increases were associated with itraconazole (Analysis 1.5.2:RR 5.76, 95% CI 0.33 to 101.77), liposomal amphotericin B (Analysis 1.5.3: RR 0.32, 95% CI 0.01 to 7.59), or ketoconazole (Analysis 1.5.4: RR 0.58, 95% CI 0.11 to 3.13), although confidence intervals were wide.

Fungal colonisation with *C. glabrata* or *C. krusei* was reported in three fluconazole trials and occurred in 7% of patients in the control arms and 16% in the fluconazole arms. In all three, *C. glabrata* or *C. krusei* colonisation was greater in the fluconazole arms, although the pooled effect was not significant (Analysis 1.10.1:RR 1.82, 95%CI 0.66 to 5.03). Itraconazole, in a single study, did not increase such colonisation (Analysis 1.10.2:RR 1.04, 95%CI 0.20 to 5.43).

Adverse effects (Analysis 1.11)

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

Subgroup and sensitivity analyses

Subgroup and sensitivity analyses were performed using the pooled results from the seven studies assessing systemic antifungal agents versus no antifungal in liver transplant recipients. No obvious effect of reported study methodology quality, publication status, or analysis method (random effects versus fixed effect model) was evident (Table 4), although the magnitude of the risk reduction was greater for studies employing diagnostic criteria for IFIs that were both explicit and consistent with our definitions than otherwise.

Direct comparisons of systemic antifungal agents

Two trials directly compared systemic antifungal prophylactic regimens in liver transplant recipients: one compared itraconazole with fluconazole and the other intravenous liposomal amphotericin B with fluconazole for one week, each followed by oral itraconazole for three weeks. These studies did not demonstrate any significant differences in total mortality, proven or proven or suspected IFIs, superficial fungal infections, fungal colonisation, or adverse effects requiring antifungal cessation (Analysis 2.1, Analysis 2.2, Analysis 2.7, Analysis 2.8, Analysis 2.9, Analysis 2.11). The incidence of IFIs with filamentous fungi or azole-resistant *Candida* species and of colonisation with azole-resistant *Candida* species were also similar (Analysis 2.5, Analysis 2.10).

Nonabsorbable antifungal agents

Amongst liver transplant recipients, superficial fungal infections were significantly reduced by clotrimazole compared with placebo in the single available study (Analysis 3.8: RR 0.17, 95% CI 0.04 to 0.67). Although no proven IFIs in the clotrimazole arm, the effect was not significant given the small overall event rate (Analysis 3.2: RR 0.12, 95% CI 0.01 to 2.19).

In the two studies directly comparing clotrimazole with nystatin in renal transplant recipients, no significant differences in the incidence of superficial fungal infection, fungal colonisation, or adverse effects were demonstrated (Analysis 4.8).

DISCUSSION

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This meta-analysis demonstrates that antifungal prophylaxis with fluconazole reduces IFIs in liver transplant recipients by about three-quarters although only one of four trials individually demonstrated a significant effect, the other three yielded a similar but non-significant benefit. Furthermore, the efficacy of fluconazole was remarkably consistent across the studies despite considerable clinical heterogeneity (including differences in dose, duration, and route of administration of fluconazole as well as the comparator and underlying risk of infection) and methodological heterogeneity (including differences in diagnostic criteria and reported study methodological parameters). This suggests that the pooled estimates are robust and generalizable to a diverse range of clinical settings. Assuming an overall average 10% incidence of IFI in liver transplant recipients (Fung 2002), 14 patients would require fluconazole prophylaxis to prevent one infection (Table 5). For lower risk recipients, with an approximate 5% incidence, this would increase to 28 patients. However, for highest risk patients, such as those undergoing retransplantation, and/or those with fulminant hepatitis, preoperative immunosuppressive therapy, operative or infective complications, with a risk of fungal infections around 25% (Collins 1994; George 1997; Patel 1996), only six patients would require prophylaxis to prevent one fungal infection (Table 5).

Itraconazole and liposomal amphotericin B both have broader antifungal spectra than fluconazole. Although neither agent demonstrated a significant reduction in invasive infections (based on only three studies), their efficacies are likely to be similar to that of fluconazole. The results of the single study directly comparing itraconazole with fluconazole reinforce this finding. No direct comparisons of liposomal amphotericin B with other antifungals are available, although one study comparing liposomal amphotericin B with fluconazole for one initial week - each then followed by itraconazole for three weeks - demonstrated no significant difference (Winston 2002). Recently marketed systemic antifungal agents, such as caspofungin and voriconazole, offer potential advantages, such as wider spectrum of activity, improved pharmacological properties, and greater safety, however no data are available regarding their prophylactic efficacy. Given the demonstrated efficacy of fluconazole, the justification for the use of such broader-spectrum agents depends on the incidence of infections with fluconazole-resistant pathogens. However from the trials reviewed here and from other reports (Singh 2000), such infections account for 25% or less of all invasive infections in solid organ transplant recipients.

The significant reduction in IFIs in liver transplant recipients with antifungal prophylaxis has not been confirmed in other settings, such as heart, lung, or pancreas recipients, because of a lack of formal evaluation in RCTs. Three trials, designed principally to assess the cyclosporine-sparing effect of ketoconazole in cardiac and renal transplant recipients, were available, did not demonstrate a significant reduction in invasive infections. Although wide confidence intervals reflected a very low event rate, poor bioavailability and a lack of demonstrated efficacy in neutropenic patients (Gotzsche 2002), would suggest little benefit for ketoconazole. Similarly, despite limited data, nonabsorbable agents are unlikely to be effective (Gotzsche 2002a).

Given the significant reduction in IFIs and their high attributable mortality, the lack of significant mortality benefit associated with antifungal prophylaxis is noteworthy. As the number of available studies was limited, this result may reflect type II error. However, there are other possible explanations for this finding. Patients at risk of fungal infections most likely share risks for other serious complications and may have died from other causes. It is also possible that any mortality benefit provided by antifungal prophylaxis was matched by the institution of early empirical antifungal therapy in the control arm. The overall results are consistent with those in neutropenic patients, where despite similar reductions in IFIs, no significant mortality benefit was demonstrated for fluconazole or itraconazole, and only a marginal benefit was demonstrated for amphotericin B (Gotzsche 2002). Although concerns regarding possible increased mortality associated with fluconazole prophylaxis in bone marrow transplant recipients have been raised (Gotzsche 2002), there was no evidence of this amongst solid organ transplant recipients. A reduction in fungal-related mortality has been reported in a meta-analysis of fluconazole prophylaxis in neutropenic patients (Kanda 2000). We did not assess this outcome, as we, like others (Gotzsche 2002), considered the attribution of deaths to fungal infections too imprecise and subjective, and therefore prone to bias, particularly in studies without blinded outcome assessors.

The selection of resistant fungal species is a major potential adverse consequence of widespread prophylactic antifungal use. Certain *Candida* species, such as *C. glabrata* and *C. krusei,* and most moulds, including *Aspergillus* species, are intrinsically fluconazole-resistant. The *de novo* development of fluconazole-resistance amongst susceptible species and the emergence of intrinsically resistant species have been associated with its use (Law 1994; Johnson 1995; Nguyen 1996; Abi-Said 1997; Fortun 1997; Gleason 1997). Amongst the three fluconazole studies containing sufficient information, no increase in fluconazole-resistant fungal infections was demonstrated, although only eight infections with fluconazole-resistant *Candida* spp. and ten with moulds were reported. However, all three trials reported an increase, albeit non-significant, in colonisation with *C. glabrata* and *C. krusei*. The confidence intervals around the point estimates were very wide, reflecting the relatively small event rate. Thus, given the relatively small sample sizes in these studies, a significant effect of fluconazole on the either the spectrum of fungal species or their antifungal susceptibility cannot be excluded. Further studies involving the characterisation and susceptibility testing of fungal isolates, an appropriate timeframe, and sufficient statistical power are therefore required.

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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 maximise our study retrieval by employing a comprehensive search strategy encompassing the major computerised databases without language restriction, major conference proceedings, and review articles. Unpublished studies ('grey literature') were also sought despite the potential for inflated estimates of intervention efficacy (McAuley 2000). We also approached major pharmaceutical companies marketing antifungal agents, but identified no additional or unpublished studies. Publication bias was recognised previously in trials of antifungal prophylaxis in neutropenic patients (Johansen 1999). Examination of funnel plots for systemic antifungal agents versus control shows asymmetry around the point estimate of effect (Figure 2; Figure 3), which may indicate publication bias.

Figure 2. Funnel plot for systemic antifungal agents versus placebo/no antifungal/nonabsorbable antifungal agent; outcome=proven invasive fungal infections

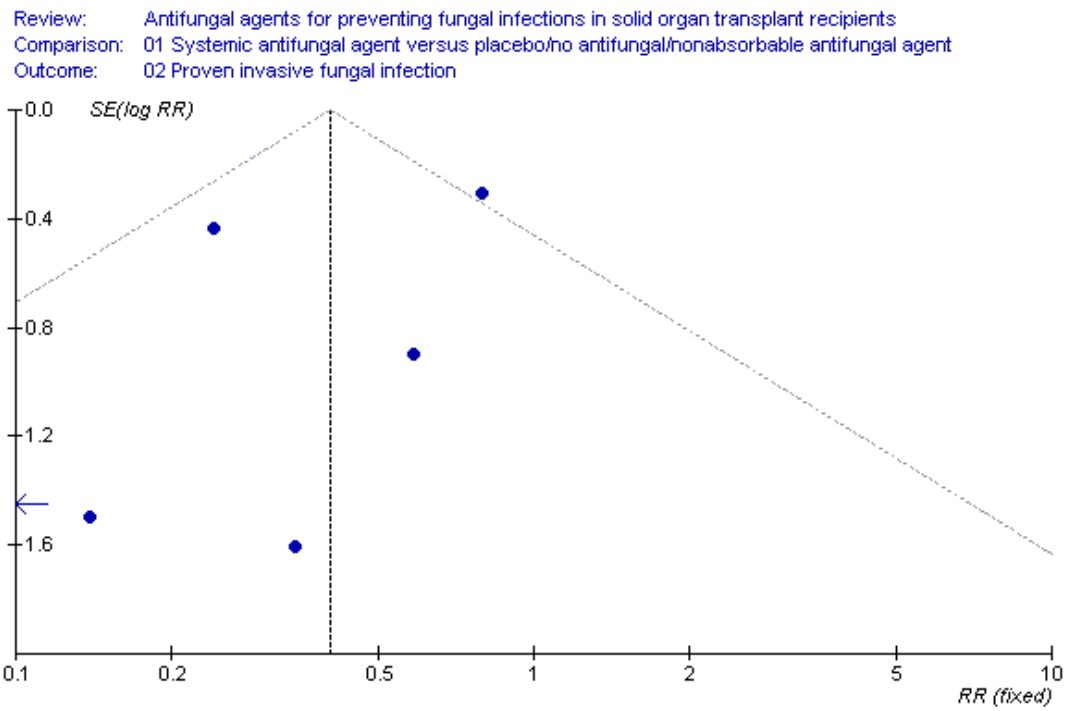

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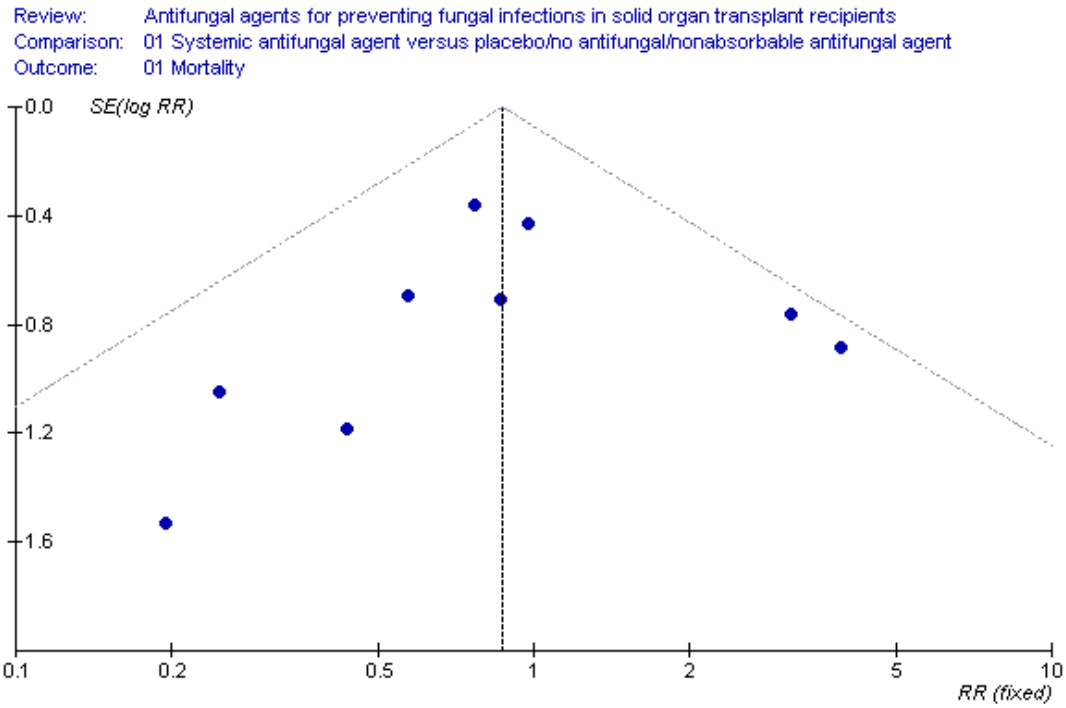
Figure 3. Funnel plot for systemic antifungal agents versus placebo/no antifungal/nonabsorbable antifungal agent; outcome=mortality



The reporting of methodological quality of studies in this review was generally suboptimal. Allocation concealment, an important potential source of bias if inadequate (Schultz 1995), was adequate in only one study. IFIs are often diagnosed with at least some degree of uncertainty and subjectivity. Blinding of outcome assessors with respect to treatment allocation would therefore be an important precaution to minimise bias, although this was reportedly taken in only two studies. Despite progress toward standardisation (Ascioglu 2002), a varied - and often conflicting - range of diagnostic criteria for IFIs have been published (Ascioglu 2001). This problem was evident amongst the studies 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. We classified uncomplicated funguria and fungal oesophagitis as superficial, not invasive, infections. However one trial included positive cultures of nonsterile specimens as evidence of invasive infections and another did not provide either the criteria or sufficient details to allow independent classification. Despite these shortcomings in reported study methodology, they did not appear to obviously influence the direction or magnitude of trial results.

AUTHORS' CONCLUSIONS

Implications for practice

Our results demonstrate that antifungal prophylaxis, particularly with fluconazole, is effective in preventing IFIs in liver transplant recipients. Although the optimal dose and duration of prophylaxis remains uncertain, it should be considered particularly for high-risk patients or in centres experiencing a high rate of IFIs. Given that the risk of fungal infections in transplant recipients varies from patient-to-patient, prophylaxis would be logically applied selectively and individually according to that risk, rather than universally.

Implications for research

Many risk factors for fungal infections have been defined and could be incorporated into decisions regarding prophylaxis. A more detailed risk assessment associated with cost-effectiveness analyses of antifungal prophylaxis will further rationalise decisions on antifungal prophylaxis. To that end, studies modelling the risk factors for IFIs amongst solid organ transplant recipients with examination of their clinical and economic consequences are required. Studies of newer antifungal agents or of prophylaxis in other organ

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transplant recipients should be specifically targeted to patients at increased risk. Such studies should incorporate standardised definitions of IFIs and basic methodological quality measures.

The potential for selection or generation of resistance to antifungal agents amongst fungal pathogens remains a major concern associated with antifungal use. Further study is required to quantify the occurrence and consequences of such ecological effects before the prophylactic use of antifungal agents can be more widely recommended.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Biancofiore 2002

Methods	Country: Italy Setting: Single centre
Participants	Liver transplant (consecutive patients, at time of transplantation) 131 randomised 2 excluded (pretransplant fungal infection)
Interventions	1. Liposomal amphotericin B 1mg/kg/d IV for 7 days then itraconazole 200mg/d oral for 3 weeks 2. Fluconazole 400mg/d IV for 7 days then itraconazole (prep. not stated) 200mg/d oral for 3 weeks 3. Placebo
Outcomes	1. Mortality 2. Proven IFI 3. Proven IFI with azole-resistant species 4. Colonisation 5. Colonisation with azole-resistant species 6. Adverse effects
Notes	Duration of prophylaxis: 28 days F/U period: NS

Risk of bias

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

Gombert 1987

Methods	Country: USA Setting: Single centre
Participants	Renal transplant (within 24 hours post-transplantation) 62 randomised 2 excluded (rejection & nausea)
Interventions	1. Nystatin 1.5MU x5/d oral for 60 days 2. Clotrimazole 10mg tds oral for 60 days
Outcomes	1. SFI 2. Adverse effects
Notes	Duration of prophylaxis: 60 days F/U period: ?60 days

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Gombert 1987 (*Continued*)

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

Keogh 1995

Methods	Country: Australia Sestting: Single centre
Participants	Cardiac transplant (consecutive adult patients, at time of transplantation) 43 randomised 0 excluded
Interventions	1. Ketoconazole 200mg/d oral for 1year 2. No ketoconazole
Outcomes	1. Mortality 2. Proven IFI 3. Proven IFI with azole-resistant species 4. SFI 5. Adverse effects
Notes	Duration of prophylaxis: 1 year F/U period: 1 year

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

Lumbreras 1996

Methods	Country: Spain Setting: 3 hospitals
Participants	Liver transplant (consecutive adult and paediatric patients, at time of transplantation) 143 randomised 0 excluded
Interventions	1. Fluconazole 100mg/d oral for 4 weeks 2. Nystatin 1M qid oral for 4 weeks

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Outcomes	1. Mortality 2. Proven IFI 3. Proven IFI with azole-resistant species 4. Suspected IFI 5. SFI 6. Colonisation 7. Colonisation with azole-resistant species 8. Adverse effects	
Notes	Duration of prophylaxis: 4 weeks F/U period: 3 months	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Meyers 1997

Methods	Country: USA Setting; ?Single centre Abstract only available	
Participants	Liver transplant (at time of transplantation) ? randomised ? excluded 55 analysed	
Interventions	1. Fluconazole ?dose oral/iv for 10 weeks plus clotrimazole 100,000U qid oral/nystatin per vagina for 3 months 2. Placebo plus clotrimazole 100,000U qid oral/nystatin per vagina for 3 months	
Outcomes	1. Mortality 2. Proven IFI 3. Suspected IFI 4. SFI 5. Adverse effects	
Notes	Duration of prophylaxis: 10 weeks F/U period: NS	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

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Owens 1984

Methods	Country: USA Setting: Single study	
Participants	Renal transplant (adults, ?timing post-transplantation) 47 randomised 3 excluded (renal transplant infarction, ?other reasons)	
Interventions	1. Clotrimazole 10mg tds oral until steroids tapered to 20mg/d 2. Placebo	
Outcomes	1. Proven IFI 2. Proven IFI with azole-resistant species 3. SFI 4. Adverse effects	
Notes	Duration of prophylaxis: NS F/U period: NS	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Patton 1994

Methods	Country: USA setting: Single centre	
Participants	Renal transplant (within 1 week post-transplantation) 110 randomised 16 excluded (side effects, protocol violations, erratic cyclosporin levels, others)	
Interventions	1. Ketoconazole 200mg/d oral for 1 year 2. No ketoconazole	
Outcomes	1. Proven IFI 2. SFI 3. Mortality 4. Adverse effects	
Notes	Duration of prophylaxis: 1 year F/U period: 1 year	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Patton 1994 (*Continued*)

Allocation concealment?	Unclear risk	B - Unclear

Ruskin 1992

Methods	Country: USA Sestting: Single centre
Participants	Liver transplant (aged 3 years or greater, at time of transplantation) 34 randomised 0 excluded
Interventions	1. Nystatin 500,000 U qid oral until hospital discharge 2. Clotrimazole 10mg x5/d oral until hospital discharge
Outcomes	1. SFI 2. Colonisation
Notes	Duration of prophylaxis: NS F/U period: NS

Risk of bias

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

Sharpe 2003

Methods	Country: Canada Setting: Single centre
Participants	Liver transplant (consecutive adults, at time of transplantation) 71 randomised 9 excluded (5 "retracted consent", 2 transplant cancelled, 1 "protocol violation", 1 "lost consent")
Interventions	1. Itraconazole 5mg/kg/d (prep. not stated) oral for 8 weeks 2. Placebo
Outcomes	1. Mortality 2. Proven IFI 3. Suspected IFI 4. SFI
Notes	Duration of prophylaxis: 8 weeks F/U period: NS

Risk of bias

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Sharpe 2003 (*Continued*)

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

Sobh 1995

Methods	Country: Egypt Setting: Single centre
Participants	Renal transplant (?timing post-transplantation) 100 randomised 0 excluded
Interventions	1. Ketoconazole 100mg/d oral for 1 year 2. No ketoconazole
Outcomes	1. SFI 2. Adverse events
Notes	Duration of prophylaxis: 1 year F/U period: 1 year

Risk of bias

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

Tollemar 1995

Methods	Country: Sweden & Finland Setting: 2 hospitals
Participants	Liver transplant (consecutive adults and children, at time of transplantation) 86 randomised 9 excluded (4 suspected FI, 3 intercurrent complications, 1 no preop data, 1 intraop death)
Interventions	1. Liposomal amphotericin B 1mg/kg/d iv for 5 days 2. Placebo
Outcomes	1. Mortality 2. Proven IFI 3. Proven with azole-resistant species 4. Suspected IFI 5. Adverse effects

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Tollemar 1995 (*Continued*)

Notes	Duration of prophylaxis: 5 days F/U period: 30 days and 1 year	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Tortorano 1995

Methods	Country: Italy Setting: Single centre	
Participants	Liver transplant (consecutive adults and children, at time of transplantation) 75 randomised 3 excluded (2 deaths within 9 days, 1 IFI)	
Interventions	1. Fluconazole 100mg/d oral/iv for 4 weeks 2. Amphotericin B 1500mg qid oral for 4 weeks	
Outcomes	1. Mortality 2. Proven IFI 3. Proven IFI with azole-resistant species 4. Colonisation 5. Colonisation with azole-resistant species 6. Adverse effects	
Notes	Duration of prophyalxis: 4 weeks F/U period: 8 weeks	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Winston 1999

Methods	Country: USA Setting: Single centre
Participants	Liver transplant (consecutive adults, at time of transplantation) 236 randomised 24 excluded (18 transplant cancelled/intraop death, 1 pregnant, 1 child, 1 dialysis, 1 baseline IFI, 2 retransplant)

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Winston 1999 (*Continued*)

Interventions	1. Fluconazole 400mg/d iv then oral for 10 weeks 2. Placebo	
Outcomes	1. Mortality 2. Proven IFI 3. Proven IFI with azole-resistant species 4. Suspected IFI 5. SFI 6. Colonisation 7. Colonisation with azole-resistant species 8. Adverse effects	
Notes	Duration of prophylaxis: 10 weeks F/U period: NS (?10 weeks)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Winston 2002

Methods	Country: USA Setting: Single centre	
Participants	Liver transplant (consecutive adults, at time of transplantation) 204 randomised 16 excluded (14 transplant cancelled/intraop death, 1 baseline suspected IFI, 1 islet cell transplant)	
Interventions	1. Itraconazole 200mg bd oral for 10 weeks 2. Fluconazole 400mg/d iv then oral for 10 weeks	
Outcomes	1. Mortality 2. Proven IFI 3. Proven IFI with azole-resistant species 4. Suspected IFI 5. SFI 6. Colonisation 7. Colonisation with azole-resistant species 8. Adverse events	
Notes	Duration of prophylaxis: 10 weeks F/U period: 1 year	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Winston 2002 (*Continued*)

Allocation concealment?	Unclear risk	B - Unclear

IFI = invasive fungal infection; SFI = superficial fungal infection

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DATA AND ANALYSES

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	9	889	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.57, 1.44]
1.1 Fluconazole	4	477	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.53, 1.82]
1.2 Itraconazole	2	191	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.18, 1.85]
1.3 Liposomal amphotericin B	1	84	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.15, 2.24]
1.4 Ketoconazole	2	137	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.18, 12.87]
2 Proven invasive fungal infection	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Fluconazole	4	477	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.13, 0.57]
2.2 Itraconazole	2	191	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.44, 1.45]
2.3 Liposomal amphotericin B	1	84	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.26]
2.4 Ketoconazole	2	137	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.08, 20.41]
3 Proven invasive fungal infection (azole-resistant Candida species)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Fluconazole	3	430	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.14, 2.36]
3.2 Itraconazole	1	129	Risk Ratio (M-H, Random, 95% CI)	3.66 [0.19, 69.37]
3.3 Liposomal amphotericin B	1	84	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Ketoconazole	1	43	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Proven invasive fungal infection (moulds)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Fluconazole	3	430	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.11, 1.92]
4.2 Itraconazole	1	129	Risk Ratio (M-H, Random, 95% CI)	2.62 [0.13, 53.34]
4.3 Liposomal amphotericin B	1	84	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.59]
4.4 Ketoconazole	1	43	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.11, 3.13]
5 Proven invasive fungal infection (azole-resistant Candida species or moulds)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Fluconazole	3	430	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.19, 1.33]
5.2 Itraconazole	1	129	Risk Ratio (M-H, Random, 95% CI)	5.76 [0.33, 101.77]
5.3 Liposomal amphotericin B	1	84	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.59]
5.4 Ketoconazole	1	43	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.11, 3.13]
6 Suspected invasive fungal infection	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Fluconazole	4	477	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.48, 2.34]
6.2 Itraconazole	1	62	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 1.93]
6.3 Liposomal amphotericin B	1	84	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.30, 5.34]
6.4 Ketoconazole	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

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7 Proven or suspected invasive fungal infection	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Fluconazole	4	477	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.28, 0.76]
7.2 Itraconazole	1	62	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 1.93]
7.3 Liposomal amphotericin B	1	84	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.14, 1.27]
7.4 Ketoconazole	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Superficial fungal infection	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Fluconazole	3	402	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.10, 0.59]
8.2 Itraconazole	1	62	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.01, 3.87]
8.3 Liposomal amphotericin B	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.4 Ketoconazole	3	237	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.06, 0.51]
9 Fungal colonisation	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Fluconazole	3	360	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.37, 0.61]
9.2 Itraconazole	1	129	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.41, 0.80]
9.3 Liposomal amphotericin B	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.4 Ketoconazole	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Fungal colonisation (azole-resistant Candida species)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Fluconazole	3	360	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.66, 5.03]
10.2 Itraconazole	1	129	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.20, 5.43]
10.3 Liposomal amphotericin B	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.4 Ketoconazole	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Adverse effects requiring cessation	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Fluconazole	4	474	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.65, 2.10]
11.2 Itraconazole	1	127	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.3 Liposomal amphotericin B	1	84	Risk Ratio (M-H, Random, 95% CI)	1.91 [0.18, 20.24]
11.4 Ketoconazole	3	237	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Systemic antifungal agent versus another systemic antifungal agent

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Itraconazole versus fluconazole	1	188	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.66, 3.91]
1.2 Liposomal amphotericin/itraconazole versus Fluconazole/itraconazole	1	85	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.27, 8.73]
2 Proven invasive fungal infection	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Itraconazole versus fluconazole	1	188	Risk Ratio (M-H, Random, 95% CI)	2.19 [0.58, 8.21]

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2.2 Liposomal amphotericin/itraconazole versus Fluconazole/itraconazole	1	85	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.48, 2.20]
3 Proven invasive fungal infection (azole-resistant Candida species)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Itraconazole versus fluconazole	1	188	Risk Ratio (M-H, Random, 95% CI)	1.88 [0.35, 10.00]
3.2 Liposomal amphotericin/itraconazole versus Fluconazole/itraconazole	1	85	Risk Ratio (M-H, Random, 95% CI)	2.05 [0.19, 21.74]
4 Proven invasive fungal infection (moulds)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Itraconazole versus fluconazole	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Liposomal amphotericin/ itraconazole versus Fluconazole/itraconazole	0		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Proven invasive fungal infection (moulds or azole-resistant Candida species)	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Itraconazole versus fluconazole	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Liposomal amphotericin/itraconazole versus Fluconazole/itraconazole	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Suspected invasive fungal infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Itraconazole versus fluconazole	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Liposomal amphotericin/ itraconazole versus Fluconazole/itraconazole	0		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Proven or suspected invasive fungal infection	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Itraconazole versus fluconazole	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Liposomal amphotericin/ itraconazole versus Fluconazole/itraconazole	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Superficial fungal infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 Itraconazole versus fluconazole	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Liposomal amphotericin/ itraconazole versus Fluconazole/itraconazole	0		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Fungal colonisation	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1 Itraconazole versus fluconazole	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

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9.2 Liposomal amphotericin/itraconazole versus Fluconazole/itraconazole	1	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Fungal colonisation (azole-resistant Candida species)	2	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10.1 Itraconazole versus fluconazole	1	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Liposomal amphotericin/itraconazole versus Fluconazole/itraconazole	1	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Adverse effects requiring cessation	2	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.1 Itraconazole versus fluconazole	1	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Liposomal amphotericin/itraconazole versus Fluconazole/itraconazole	1	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Nonabsorbable antifungal agent versus no antifungal agent

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	0		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Proven invasive fungal infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Clotrimazole	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Proven invasive fungal infections (azole-resistant Candida species)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Clotrimazole	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Proven invasive fungal infection (moulds)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Clotrimazole	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Proven invasive fungal infection (azole-resistant Candida species and moulds)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Clotrimazole	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Suspected invasive fungal infection	0		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7 Proven or suspected invasive fungal infection	0		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8 Superficial fungal infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 Clotrimazole	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Fungal colonisation	0		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10 Fungal colonisation (azole-resistant Candida species)	0		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11 Adverse effects requiring cessation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

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11.1 Clotrimazole	1	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. Nonabsorbable antifungal agent versus another nonabsorbable antifungal agent

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	0		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Proven invasive fungal infection	0		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Proven invasive fungal infections (azole-resistant Candida species)	0		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Proven invasive fungal infections (moulds)	0		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5 Proven invasive fungal infection (azole-resistant Candida species or moulds)	0		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6 Suspected invasive fungal infection	0		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7 Proven or suspected invasive fungal infection	0		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8 Superficial fungal infection	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 Nystatin versus clotrimazole	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Fungal colonisation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1 Nystatin versus clotrimazole	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Fungal colonisation (azole-resistant Candida species)	0		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11 Adverse effects requiring cessation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.1 Nystatin versus nystatin	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

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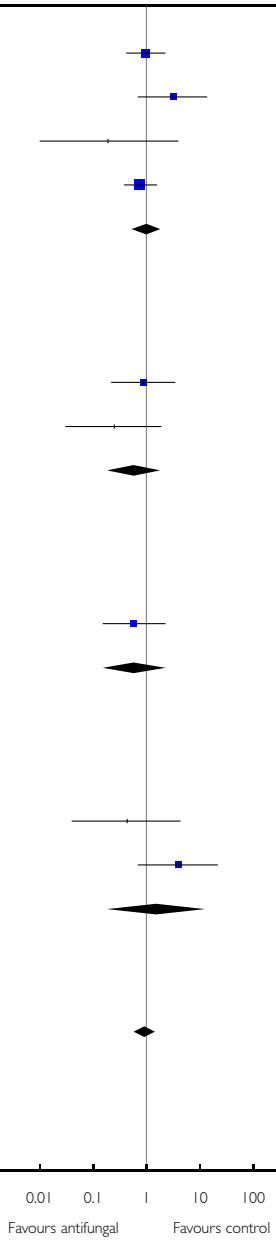
Analysis 1.1. Comparison 1 Systemic antifungal agent versus placebo/no antifungal/nonabsorbable antifungal agent, Outcome 1 Mortality.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

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

Outcome: 1 Mortality

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					
Lumbreras 1996	10/76	9/67		23.3 %	0.98 [0.42, 2.27]
Meyers 1997	6/23	2/24		8.8 %	3.13 [0.70, 13.95]
Tortorano 1995	0/38	2/37		2.3 %	0.19 [0.01, 3.93]
Winston 1999	12/108	15/104		29.7 %	0.77 [0.38, 1.57]
Subtotal (95% CI)	**245**	**232**		**64.2 %**	**0.98 [0.53, 1.82]**
Total events: 28 (Antifungal), 28 (Control)					
Heterogeneity: Tau^2 = 0.09; Chi^2 = 3.85, df = 3 (P = 0.28); I^2 =22%					
Test for overall effect: Z = 0.07 (P = 0.94)					
2 Itraconazole					
Biancofiore 2002	5/85	3/44		10.1 %	0.86 [0.22, 3.44]
Sharpe 2003	1/25	6/37		4.9 %	0.25 [0.03, 1.93]
Subtotal (95% CI)	**110**	**81**		**14.9 %**	**0.58 [0.18, 1.85]**
Total events: 6 (Antifungal), 9 (Control)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 1.02, df = 1 (P = 0.31); I^2 =1%					
Test for overall effect: Z = 0.92 (P = 0.36)					
3 Liposomal amphotericin B					
Tollemar 1995	3/43	5/41		10.3 %	0.57 [0.15, 2.24]
Subtotal (95% CI)	**43**	**41**		**10.3 %**	**0.57 [0.15, 2.24]**
Total events: 3 (Antifungal), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
4 Ketoconazole					
Keogh 1995	1/23	2/20		3.8 %	0.43 [0.04, 4.44]
Patton 1994	3/26	2/68		6.7 %	3.92 [0.69, 22.15]
Subtotal (95% CI)	**49**	**88**		**10.5 %**	**1.50 [0.18, 12.87]**
Total events: 4 (Antifungal), 4 (Control)					
Heterogeneity: Tau^2 = 1.35; Chi^2 = 2.23, df = 1 (P = 0.14); I^2 =55%					
Test for overall effect: Z = 0.37 (P = 0.71)					
Total (95% CI)	**447**	**442**		**100.0 %**	**0.90 [0.57, 1.44]**
Total events: 41 (Antifungal), 46 (Control)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 9.01, df = 8 (P = 0.34); I^2 =11%					
Test for overall effect: Z = 0.43 (P = 0.67)					



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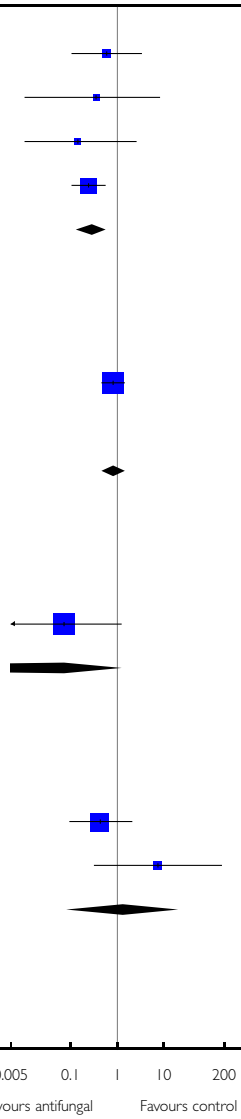
Analysis 1.2. Comparison 1 Systemic antifungal agent versus placebo/no antifungal/nonabsorbable antifungal agent, Outcome 2 Proven invasive fungal infection.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

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

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					
Lumbreras 1996	2/76	3/67		24.6 %	0.59 [0.10, 3.41]
Meyers 1997	0/23	1/24		9.5 %	0.35 [0.01, 8.11]
Tortorano 1995	0/38	3/37		10.8 %	0.14 [0.01, 2.60]
Winston 1999	6/108	24/104		55.2 %	0.24 [0.10, 0.57]
Subtotal (95% CI)	**245**	**232**		**100.0 %**	**0.28 [0.13, 0.57]**
Total events: 8 (Antifungal), 31 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.04, df = 3 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 3.49 (P = 0.00048)					
2 Itraconazole					
Biancofiore 2002	20/85	13/44		100.0 %	0.80 [0.44, 1.45]
Sharpe 2003	0/25	0/37			Not estimable
Subtotal (95% CI)	**110**	**81**		**100.0 %**	**0.80 [0.44, 1.45]**
Total events: 20 (Antifungal), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.75 (P = 0.45)					
3 Liposomal amphotericin B					
Tollemar 1995	0/43	6/41		100.0 %	0.07 [0.00, 1.26]
Subtotal (95% CI)	**43**	**41**		**100.0 %**	**0.07 [0.00, 1.26]**
Total events: 0 (Antifungal), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.80 (P = 0.072)					
4 Ketoconazole					
Keogh 1995	2/23	4/20		75.2 %	0.43 [0.09, 2.13]
Patton 1994	1/26	0/68		24.8 %	7.67 [0.32, 182.44]
Subtotal (95% CI)	**49**	**88**		**100.0 %**	**1.30 [0.08, 20.41]**
Total events: 3 (Antifungal), 4 (Control)					
Heterogeneity: Tau^2 = 2.53; Chi^2 = 2.55, df = 1 (P = 0.11); I^2 =61%					
Test for overall effect: Z = 0.19 (P = 0.85)					



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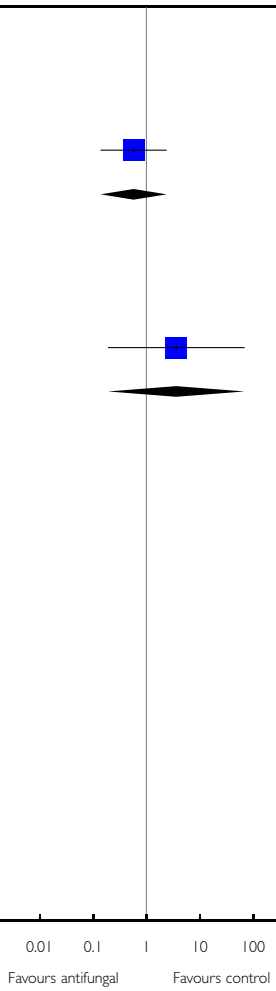
Analysis 1.3. Comparison 1 Systemic antifungal agent versus placebo/no antifungal/nonabsorbable antifungal agent, Outcome 3 Proven invasive fungal infection (azole-resistant Candida species).

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

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

Outcome: 3 Proven invasive fungal infection (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					
Lumbreras 1996	0/76	0/67			Not estimable
Tortorano 1995	0/38	0/37			Not estimable
Winston 1999	3/108	5/104		100.0 %	0.58 [0.14, 2.36]
Subtotal (95% CI)	**222**	**208**		**100.0 %**	**0.58 [0.14, 2.36]**
Total events: 3 (Antifungal), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.76 (P = 0.44)					
2 Itraconazole					
Biancofiore 2002	3/85	0/44		100.0 %	3.66 [0.19, 69.37]
Subtotal (95% CI)	**85**	**44**		**100.0 %**	**3.66 [0.19, 69.37]**
Total events: 3 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.87 (P = 0.39)					
3 Liposomal amphotericin B					
Tollemar 1995	0/43	0/41			Not estimable
Subtotal (95% CI)	**43**	**41**			**Not estimable**
Total events: 0 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Ketoconazole					
Keogh 1995	0/23	0/20			Not estimable
Subtotal (95% CI)	**23**	**20**			**Not estimable**
Total events: 0 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					



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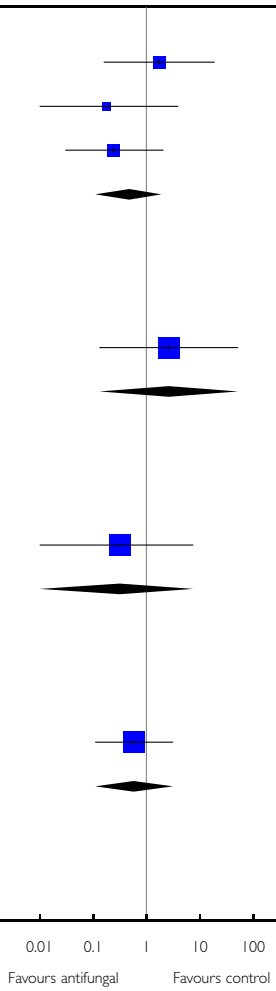
Analysis 1.4. Comparison 1 Systemic antifungal agent versus placebo/no antifungal/nonabsorbable antifungal agent, Outcome 4 Proven invasive fungal infection (moulds).

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

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

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					
Lumbreras 1996	2/76	1/67		35.4 %	1.76 [0.16, 19.01]
Tortorano 1995	0/38	2/37		22.2 %	0.19 [0.01, 3.93]
Winston 1999	1/108	4/104		42.4 %	0.24 [0.03, 2.12]
Subtotal (95% CI)	**222**	**208**		**100.0 %**	**0.47 [0.11, 1.92]**
Total events: 3 (Antifungal), 7 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 1.89, df = 2 (P = 0.39); I² =0.0%					
Test for overall effect: Z = 1.06 (P = 0.29)					
2 Itraconazole					
Biancofiore 2002	2/85	0/44		100.0 %	2.62 [0.13, 53.34]
Subtotal (95% CI)	**85**	**44**		**100.0 %**	**2.62 [0.13, 53.34]**
Total events: 2 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					
3 Liposomal amphotericin B					
Tollemar 1995	0/43	1/41		100.0 %	0.32 [0.01, 7.59]
Subtotal (95% CI)	**43**	**41**		**100.0 %**	**0.32 [0.01, 7.59]**
Total events: 0 (Antifungal), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.71 (P = 0.48)					
4 Ketoconazole					
Keogh 1995	2/23	3/20		100.0 %	0.58 [0.11, 3.13]
Subtotal (95% CI)	**23**	**20**		**100.0 %**	**0.58 [0.11, 3.13]**
Total events: 2 (Antifungal), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					



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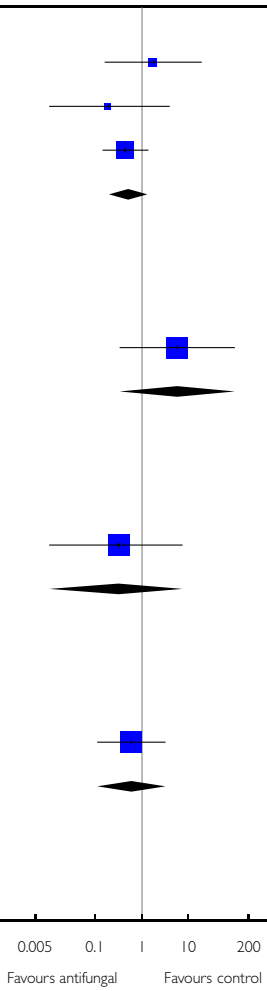
Analysis 1.5. Comparison 1 Systemic antifungal agent versus placebo/no antifungal/nonabsorbable antifungal agent, Outcome 5 Proven invasive fungal infection (azole-resistant Candida species or moulds).

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

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

Outcome: 5 Proven invasive fungal infection (azole-resistant Candida species or 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					
Lumbreras 1996	2/76	1/67		16.9 %	1.76 [0.16, 19.01]
Tortorano 1995	0/38	2/37		10.6 %	0.19 [0.01, 3.93]
Winston 1999	4/108	9/104		72.6 %	0.43 [0.14, 1.35]
Subtotal (95% CI)	**222**	**208**		**100.0 %**	**0.50 [0.19, 1.33]**
Total events: 6 (Antifungal), 12 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 1.53, df = 2 (P = 0.47); I² =0.0%					
Test for overall effect: Z = 1.39 (P = 0.16)					
2 Itraconazole					
Biancofiore 2002	5/85	0/44		100.0 %	5.76 [0.33, 101.77]
Subtotal (95% CI)	**85**	**44**		**100.0 %**	**5.76 [0.33, 101.77]**
Total events: 5 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.19 (P = 0.23)					
3 Liposomal amphotericin B					
Tollemar 1995	0/43	1/41		100.0 %	0.32 [0.01, 7.59]
Subtotal (95% CI)	**43**	**41**		**100.0 %**	**0.32 [0.01, 7.59]**
Total events: 0 (Antifungal), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.71 (P = 0.48)					
4 Ketoconazole					
Keogh 1995	2/23	3/20		100.0 %	0.58 [0.11, 3.13]
Subtotal (95% CI)	**23**	**20**		**100.0 %**	**0.58 [0.11, 3.13]**
Total events: 2 (Antifungal), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					



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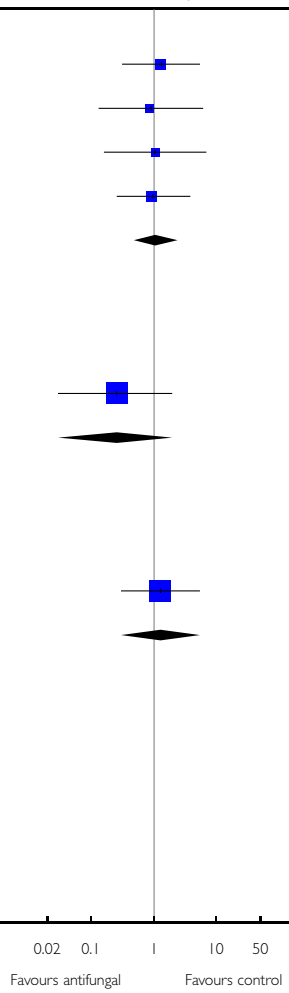
Analysis 1.6. Comparison 1 Systemic antifungal agent versus placebo/no antifungal/nonabsorbable antifungal agent, Outcome 6 Suspected invasive fungal infection.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

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

Outcome: 6 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					
Tortorano 1995	4/38	3/37		31.0 %	1.30 [0.31, 5.41]
Lumbreras 1996	2/76	2/67		16.9 %	0.88 [0.13, 6.09]
Meyers 1997	2/23	2/24		18.0 %	1.04 [0.16, 6.80]
Winston 1999	4/108	4/104		34.1 %	0.96 [0.25, 3.75]
Subtotal (95% CI)	**245**	**232**		**100.0 %**	**1.06 [0.48, 2.34]**
Total events: 12 (Antifungal), 11 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 0.13, df = 3 (P = 0.99); I² =0.0%					
Test for overall effect: Z = 0.13 (P = 0.89)					
2 Itraconazole					
Sharpe 2003	1/25	6/37		100.0 %	0.25 [0.03, 1.93]
Subtotal (95% CI)	**25**	**37**		**100.0 %**	**0.25 [0.03, 1.93]**
Total events: 1 (Antifungal), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.33 (P = 0.18)					
3 Liposomal amphotericin B					
Tollemar 1995	4/43	3/41		100.0 %	1.27 [0.30, 5.34]
Subtotal (95% CI)	**43**	**41**		**100.0 %**	**1.27 [0.30, 5.34]**
Total events: 4 (Antifungal), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					
4 Ketoconazole					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					



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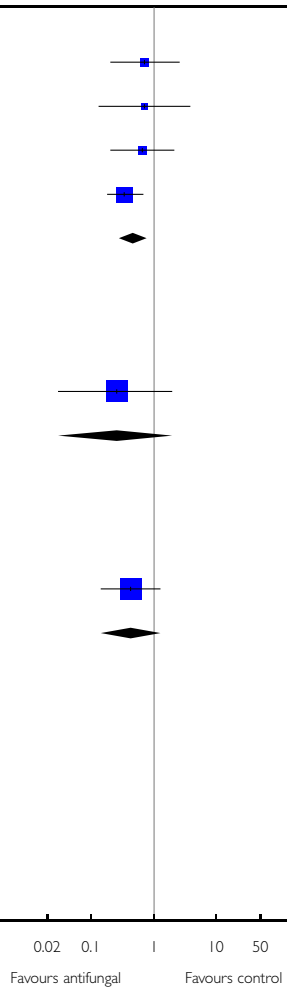
Analysis 1.7. Comparison 1 Systemic antifungal agent versus placebo/no antifungal/nonabsorbable antifungal agent, Outcome 7 Proven or suspected invasive fungal infection.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

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

Outcome: 7 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					
Lumbreras 1996	4/76	5/67		15.8 %	0.71 [0.20, 2.52]
Meyers 1997	2/23	3/24		8.9 %	0.70 [0.13, 3.79]
Tortorano 1995	4/38	6/37		18.3 %	0.65 [0.20, 2.12]
Winston 1999	10/108	28/104		57.0 %	0.34 [0.18, 0.67]
Subtotal (95% CI)	**245**	**232**		**100.0 %**	**0.46 [0.28, 0.76]**
Total events: 20 (Antifungal), 42 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.71, df = 3 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 3.00 (P = 0.0027)					
2 Itraconazole					
Sharpe 2003	1/25	6/37		100.0 %	0.25 [0.03, 1.93]
Subtotal (95% CI)	**25**	**37**		**100.0 %**	**0.25 [0.03, 1.93]**
Total events: 1 (Antifungal), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.33 (P = 0.18)					
3 Liposomal amphotericin B					
Tollemar 1995	4/43	9/41		100.0 %	0.42 [0.14, 1.27]
Subtotal (95% CI)	**43**	**41**		**100.0 %**	**0.42 [0.14, 1.27]**
Total events: 4 (Antifungal), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.53 (P = 0.13)					
4 Ketoconazole					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					



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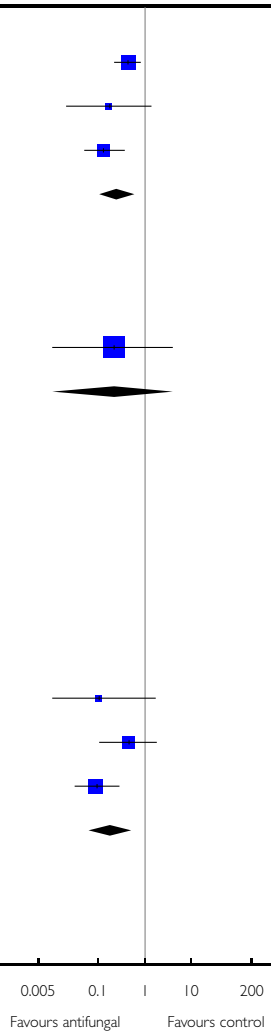
Analysis 1.8. Comparison 1 Systemic antifungal agent versus placebo/no antifungal/nonabsorbable antifungal agent, Outcome 8 Superficial fungal infection.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

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

Outcome: 8 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					
Lumbreras 1996	10/76	21/67		52.8 %	0.42 [0.21, 0.83]
Meyers 1997	1/23	6/24		12.1 %	0.17 [0.02, 1.34]
Winston 1999	4/108	29/104		35.0 %	0.13 [0.05, 0.36]
Subtotal (95% CI)	**207**	**195**		**100.0 %**	**0.24 [0.10, 0.59]**
Total events: 15 (Antifungal), 56 (Control)					
Heterogeneity: Tau^2 = 0.29; Chi^2 = 3.90, df = 2 (P = 0.14); I^2 =49%					
Test for overall effect: Z = 3.15 (P = 0.0016)					
2 Itraconazole					
Sharpe 2003	0/25	3/37		100.0 %	0.21 [0.01, 3.87]
Subtotal (95% CI)	**25**	**37**		**100.0 %**	**0.21 [0.01, 3.87]**
Total events: 0 (Antifungal), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					
3 Liposomal amphotericin B					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Ketoconazole					
Keogh 1995	0/23	4/20		11.2 %	0.10 [0.01, 1.70]
Patton 1994	2/26	12/68		36.8 %	0.44 [0.10, 1.82]
Sobh 1995	3/51	31/49		52.1 %	0.09 [0.03, 0.28]
Subtotal (95% CI)	**100**	**137**		**100.0 %**	**0.17 [0.06, 0.51]**
Total events: 5 (Antifungal), 47 (Control)					
Heterogeneity: Tau^2 = 0.32; Chi^2 = 2.96, df = 2 (P = 0.23); I^2 =32%					
Test for overall effect: Z = 3.17 (P = 0.0015)					



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Analysis 1.9. Comparison 1 Systemic antifungal agent versus placebo/no antifungal/nonabsorbable antifungal agent, Outcome 9 Fungal colonisation.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

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

Outcome: 9 Fungal colonisation

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					
Lumbreras 1996	19/76	35/67		30.2 %	0.48 [0.30, 0.75]
Tortorano 1995	9/38	11/34		11.0 %	0.73 [0.35, 1.55]
Winston 1999	29/85	47/60		58.8 %	0.44 [0.32, 0.60]
Subtotal (95% CI)	**199**	**161**		**100.0 %**	**0.47 [0.37, 0.61]**
Total events: 57 (Antifungal), 93 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.58, df = 2 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 5.88 (P < 0.00001)					
2 Itraconazole					
Biancofiore 2002	33/85	30/44		100.0 %	0.57 [0.41, 0.80]
Subtotal (95% CI)	**85**	**44**		**100.0 %**	**0.57 [0.41, 0.80]**
Total events: 33 (Antifungal), 30 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.30 (P = 0.00097)					
3 Liposomal amphotericin B					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Ketoconazole					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

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Analysis 1.10. Comparison 1 Systemic antifungal agent versus placebo/no antifungal/nonabsorbable antifungal agent, Outcome 10 Fungal colonisation (azole-resistant Candida species).

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

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

Outcome: 10 Fungal colonisation (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					
Lumbreras 1996	5/76	4/67		30.6 %	1.10 [0.31, 3.94]
Tortorano 1995	9/38	0/34		7.6 %	17.05 [1.03, 282.36]
Winston 1999	18/85	8/60		61.8 %	1.59 [0.74, 3.41]
Subtotal (95% CI)	**199**	**161**		**100.0 %**	**1.82 [0.66, 5.03]**
Total events: 32 (Antifungal), 12 (Control)					
Heterogeneity: Tau² = 0.35; Chi² = 3.46, df = 2 (P = 0.18); I² =42%					
Test for overall effect: Z = 1.16 (P = 0.25)					
2 Itraconazole					
Biancofiore 2002	4/85	2/44		100.0 %	1.04 [0.20, 5.43]
Subtotal (95% CI)	**85**	**44**		**100.0 %**	**1.04 [0.20, 5.43]**
Total events: 4 (Antifungal), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.04 (P = 0.97)					
3 Liposomal amphotericin B					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 Ketoconazole					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

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Analysis 1.11. Comparison 1 Systemic antifungal agent versus placebo/no antifungal/nonabsorbable antifungal agent, Outcome 11 Adverse effects requiring cessation.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

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

Outcome: 11 Adverse effects requiring cessation

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					
Lumbreras 1996	1/76	0/67		3.3 %	2.65 [0.11, 63.96]
Meyers 1997	12/23	10/24		89.9 %	1.25 [0.68, 2.31]
Tortorano 1995	0/38	0/34			Not estimable
Winston 1999	1/108	3/104		6.7 %	0.32 [0.03, 3.04]
Subtotal (95% CI)	**245**	**229**		**100.0 %**	**1.17 [0.65, 2.10]**
Total events: 14 (Antifungal), 13 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.62, df = 2 (P = 0.44); I^2 =0.0%					
Test for overall effect: Z = 0.53 (P = 0.59)					
2 Itraconazole					
Biancofiore 2002	0/85	0/42			Not estimable
Subtotal (95% CI)	**85**	**42**			**Not estimable**
Total events: 0 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Liposomal amphotericin B					
Tollemar 1995	2/43	1/41		100.0 %	1.91 [0.18, 20.24]
Subtotal (95% CI)	**43**	**41**		**100.0 %**	**1.91 [0.18, 20.24]**
Total events: 2 (Antifungal), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.54 (P = 0.59)					
4 Ketoconazole					
Keogh 1995	0/23	0/20			Not estimable
Patton 1994	0/26	0/68			Not estimable
Sobh 1995	0/51	0/49			Not estimable
Subtotal (95% CI)	**100**	**137**			**Not estimable**
Total events: 0 (Antifungal), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

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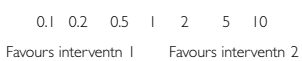
Analysis 2.1. Comparison 2 Systemic antifungal agent versus another systemic antifungal agent, Outcome 1 Mortality.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 2 Systemic antifungal agent versus another systemic antifungal agent

Outcome: 1 Mortality

Study or subgroup	Intervention 1 n/N	Intervention 2 n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Itraconazole versus fluconazole					
Winston 2002	12/97	7/91		100.0 %	1.61 [0.66, 3.91]
Subtotal (95% CI)	**97**	**91**		**100.0 %**	**1.61 [0.66, 3.91]**
Total events: 12 (Intervention 1), 7 (Intervention 2)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					
2 Liposomal amphotericin/itraconazole versus Fluconazole/itraconazole					
Biancofiore 2002	3/42	2/43		100.0 %	1.54 [0.27, 8.73]
Subtotal (95% CI)	**42**	**43**		**100.0 %**	**1.54 [0.27, 8.73]**
Total events: 3 (Intervention 1), 2 (Intervention 2)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					



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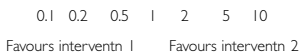
Analysis 2.2. Comparison 2 Systemic antifungal agent versus another systemic antifungal agent, Outcome 2 Proven invasive fungal infection.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 2 Systemic antifungal agent versus another systemic antifungal agent

Outcome: 2 Proven invasive fungal infection

Study or subgroup	Intervention 1 n/N	Intervention 2 n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Itraconazole versus fluconazole					
Winston 2002	7/97	3/91		100.0 %	2.19 [0.58, 8.21]
Subtotal (95% CI)	**97**	**91**		**100.0 %**	**2.19 [0.58, 8.21]**
Total events: 7 (Intervention 1), 3 (Intervention 2)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.16 (P = 0.25)					
2 Liposomal amphotericin/itraconazole versus Fluconazole/itraconazole					
Biancofiore 2002	10/42	10/43		100.0 %	1.02 [0.48, 2.20]
Subtotal (95% CI)	**42**	**43**		**100.0 %**	**1.02 [0.48, 2.20]**
Total events: 10 (Intervention 1), 10 (Intervention 2)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.95)					



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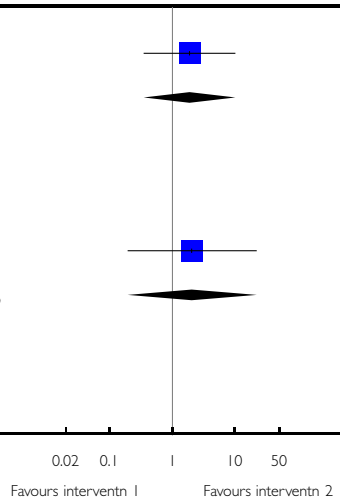
Analysis 2.3. Comparison 2 Systemic antifungal agent versus another systemic antifungal agent, Outcome 3 Proven invasive fungal infection (azole-resistant Candida species).

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 2 Systemic antifungal agent versus another systemic antifungal agent

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

Study or subgroup	Intervention 1 n/N	Intervention 2 n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Itraconazole versus fluconazole					
Winston 2002	4/97	2/91		100.0 %	1.88 [0.35, 10.00]
Subtotal (95% CI)	**97**	**91**		**100.0 %**	**1.88 [0.35, 10.00]**
Total events: 4 (Intervention 1), 2 (Intervention 2)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.74 (P = 0.46)					
2 Liposomal amphotericin/itraconazole versus Fluconazole/itraconazole					
Biancofiore 2002	2/42	1/43		100.0 %	2.05 [0.19, 21.74]
Subtotal (95% CI)	**42**	**43**		**100.0 %**	**2.05 [0.19, 21.74]**
Total events: 2 (Intervention 1), 1 (Intervention 2)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.59 (P = 0.55)					



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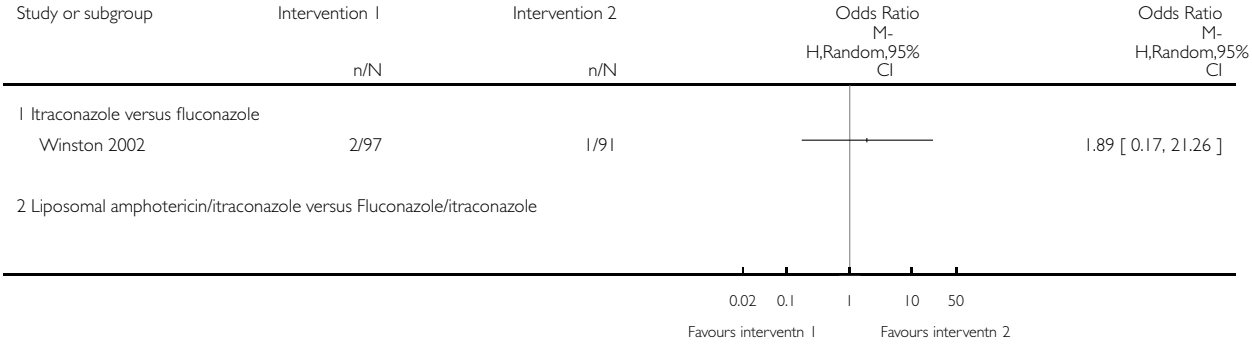
Analysis 2.4. Comparison 2 Systemic antifungal agent versus another systemic antifungal agent, Outcome 4 Proven invasive fungal infection (moulds).

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 2 Systemic antifungal agent versus another systemic antifungal agent

Outcome: 4 Proven invasive fungal infection (moulds)

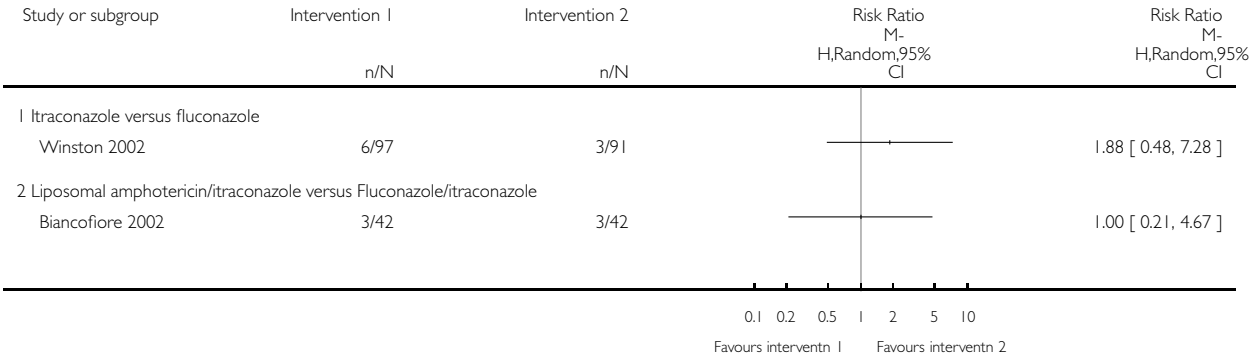


Analysis 2.5. Comparison 2 Systemic antifungal agent versus another systemic antifungal agent, Outcome 5 Proven invasive fungal infection (moulds or azole-resistant Candida species).

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 2 Systemic antifungal agent versus another systemic antifungal agent

Outcome: 5 Proven invasive fungal infection (moulds or azole-resistant Candida species)



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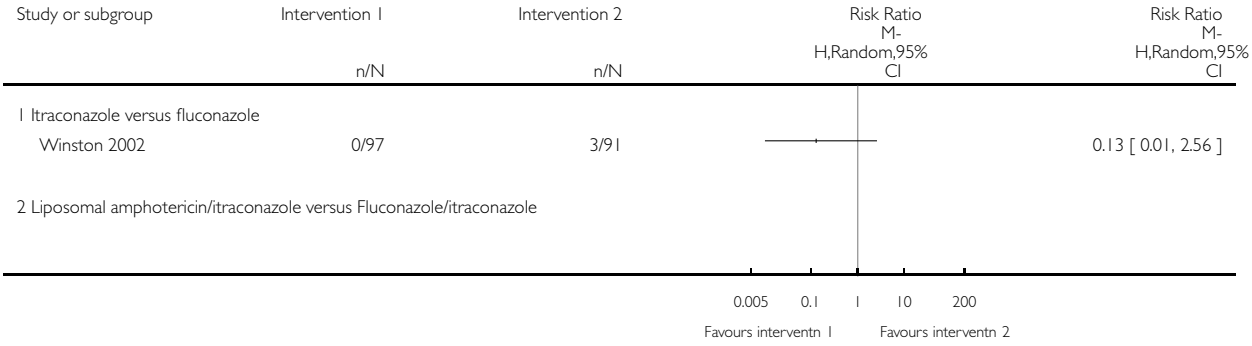
Analysis 2.6. Comparison 2 Systemic antifungal agent versus another systemic antifungal agent, Outcome 6 Suspected invasive fungal infection.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 2 Systemic antifungal agent versus another systemic antifungal agent

Outcome: 6 Suspected invasive fungal infection

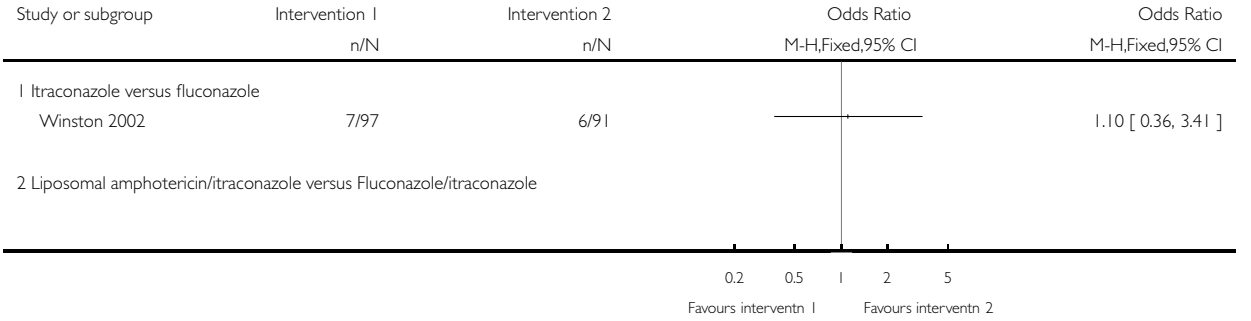


Analysis 2.7. Comparison 2 Systemic antifungal agent versus another systemic antifungal agent, Outcome 7 Proven or suspected invasive fungal infection.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 2 Systemic antifungal agent versus another systemic antifungal agent

Outcome: 7 Proven or suspected invasive fungal infection



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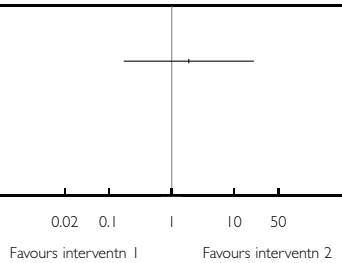
Analysis 2.8. Comparison 2 Systemic antifungal agent versus another systemic antifungal agent, Outcome 8 Superficial fungal infection.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 2 Systemic antifungal agent versus another systemic antifungal agent

Outcome: 8 Superficial fungal infection

Study or subgroup	Intervention 1 n/N	Intervention 2 n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Itraconazole versus fluconazole				
Winston 2002	2/97	1/91		1.88 [0.17, 20.34]
2 Liposomal amphotericin/itraconazole versus Fluconazole/itraconazole				



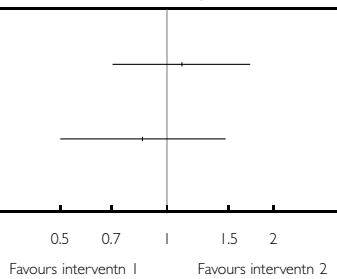
Analysis 2.9. Comparison 2 Systemic antifungal agent versus another systemic antifungal agent, Outcome 9 Fungal colonisation.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 2 Systemic antifungal agent versus another systemic antifungal agent

Outcome: 9 Fungal colonisation

Study or subgroup	Intervention 1 n/N	Intervention 2 n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Itraconazole versus fluconazole				
Winston 2002	29/87	24/79		1.10 [0.70, 1.72]
2 Liposomal amphotericin/itraconazole versus Fluconazole/itraconazole				
Biancofiore 2002	15/42	18/43		0.85 [0.50, 1.46]



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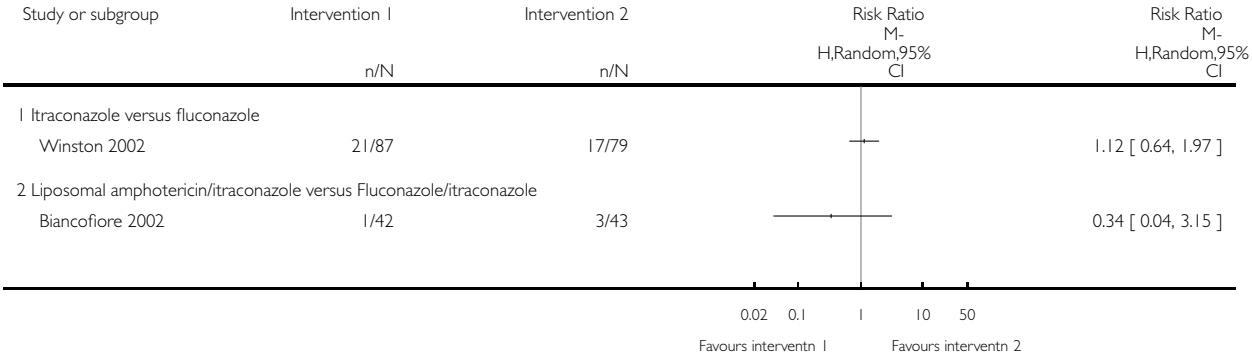
Analysis 2.10. Comparison 2 Systemic antifungal agent versus another systemic antifungal agent, Outcome 10 Fungal colonisation (azole-resistant Candida species).

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 2 Systemic antifungal agent versus another systemic antifungal agent

Outcome: 10 Fungal colonisation (azole-resistant Candida species)

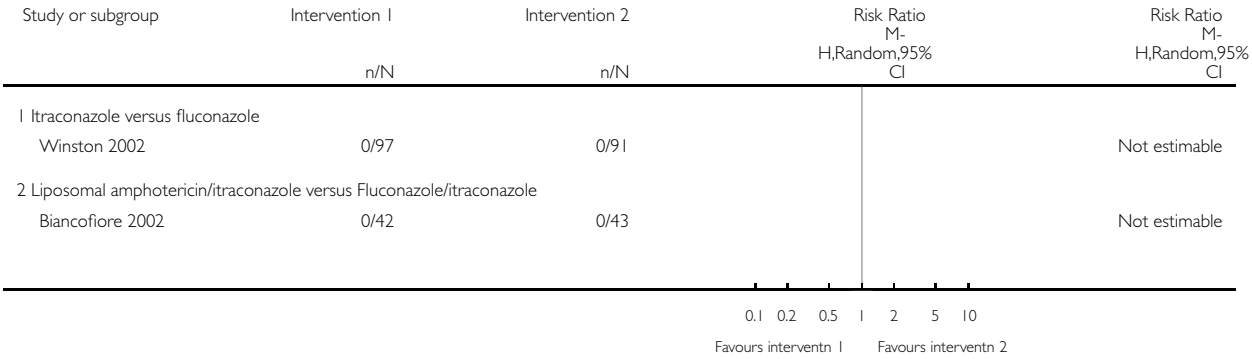


Analysis 2.11. Comparison 2 Systemic antifungal agent versus another systemic antifungal agent, Outcome 11 Adverse effects requiring cessation.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 2 Systemic antifungal agent versus another systemic antifungal agent

Outcome: 11 Adverse effects requiring cessation



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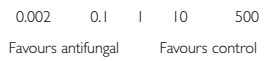
Analysis 3.2. Comparison 3 Nonabsorbable antifungal agent versus no antifungal agent, Outcome 2 Proven invasive fungal infection.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 3 Nonabsorbable antifungal agent versus no antifungal agent

Outcome: 2 Proven invasive fungal infection

Study or subgroup	Antifungal n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Clotrimazole				
Owens 1984	0/24	3/20		0.12 [0.01, 2.19]



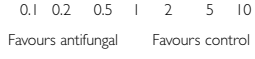
Analysis 3.3. Comparison 3 Nonabsorbable antifungal agent versus no antifungal agent, Outcome 3 Proven invasive fungal infections (azole-resistant Candida species).

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 3 Nonabsorbable antifungal agent versus no antifungal agent

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

Study or subgroup	Antifungal n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Clotrimazole				
Owens 1984	0/24	0/23		Not estimable



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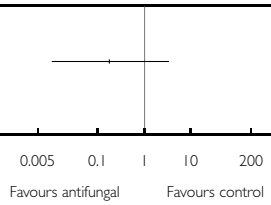
Analysis 3.4. Comparison 3 Nonabsorbable antifungal agent versus no antifungal agent, Outcome 4 Proven invasive fungal infection (moulds).

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 3 Nonabsorbable antifungal agent versus no antifungal agent

Outcome: 4 Proven invasive fungal infection (moulds)

Study or subgroup	Antifungal n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Clotrimazole				
Owens 1984	0/24	2/20		0.17 [0.01, 3.31]



Analysis 3.5. Comparison 3 Nonabsorbable antifungal agent versus no antifungal agent, Outcome 5 Proven invasive fungal infection (azole-resistant Candida species and moulds).

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 3 Nonabsorbable antifungal agent versus no antifungal agent

Outcome: 5 Proven invasive fungal infection (azole-resistant Candida species and moulds)

Study or subgroup	Antifungal n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Clotrimazole				
Owens 1984	0/24	2/20		0.17 [0.01, 3.31]

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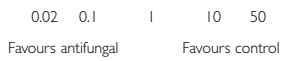
Analysis 3.8. Comparison 3 Nonabsorbable antifungal agent versus no antifungal agent, Outcome 8 Superficial fungal infection.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 3 Nonabsorbable antifungal agent versus no antifungal agent

Outcome: 8 Superficial fungal infection

Study or subgroup	Antifungal n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Clotrimazole				
Owens 1984	2/24	10/20		0.17 [0.04, 0.67]



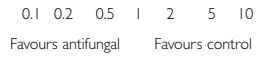
Analysis 3.11. Comparison 3 Nonabsorbable antifungal agent versus no antifungal agent, Outcome 11 Adverse effects requiring cessation.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 3 Nonabsorbable antifungal agent versus no antifungal agent

Outcome: 11 Adverse effects requiring cessation

Study or subgroup	Antifungal n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Clotrimazole				
Owens 1984	0/24	0/20		Not estimable



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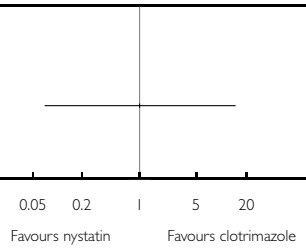
Analysis 4.8. Comparison 4 Nonabsorbable antifungal agent versus another nonabsorbable antifungal agent, Outcome 8 Superficial fungal infection.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 4 Nonabsorbable antifungal agent versus another nonabsorbable antifungal agent

Outcome: 8 Superficial fungal infection

Study or subgroup	Nystatin n/N	Clotrimazole n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Nystatin versus clotrimazole				
Gombert 1987	0/28	0/32		Not estimable
Ruskin 1992	1/17	1/17		1.00 [0.07, 14.72]



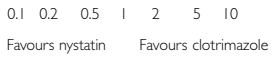
Analysis 4.9. Comparison 4 Nonabsorbable antifungal agent versus another nonabsorbable antifungal agent, Outcome 9 Fungal colonisation.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 4 Nonabsorbable antifungal agent versus another nonabsorbable antifungal agent

Outcome: 9 Fungal colonisation

Study or subgroup	Nystatin n/N	Clotrimazole n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Nystatin versus clotrimazole				
Ruskin 1992	2/17	2/17		1.00 [0.16, 6.30]



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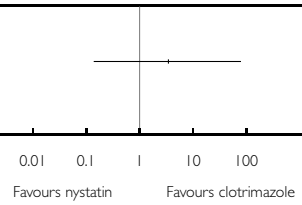
Analysis 4.11. Comparison 4 Nonabsorbable antifungal agent versus another nonabsorbable antifungal agent, Outcome 11 Adverse effects requiring cessation.

Review: Antifungal agents for preventing fungal infections in solid organ transplant recipients

Comparison: 4 Nonabsorbable antifungal agent versus another nonabsorbable antifungal agent

Outcome: 11 Adverse effects requiring cessation

Study or subgroup	Nystatin n/N	Clotrimazole n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Nystatin versus nystatin				
Gombert 1987	1/29	0/33		3.40 [0.14, 80.36]



ADDITIONAL TABLES

Table 1. Search strategies for electronic databases

Database	Search strategy
CENTRAL	1. fung* 2. antifungal 3. fluconazole 4. itraconazole 5. ketoconazole 6. voriconazole 7. amphotericin 8. ambisome 9. amphotec 10. abelcet 11. caspofungin 12. flucytosine 13. miconazole 14. clotrimazole 15. econazole 16. nystatin 17. transplant* 18. or/1-16 19. 17 and 18
MEDLINE (OVID)	1. antifungal agents/ 2. exp clotrimazole/

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Table 1. Search strategies for electronic databases (*Continued*)

	3. exp econazole/ 4. exp fluconazole/ 5. exp flucytosine/ 6. exp itraconazole/ 7. exp ketoconazole/ 8. exp miconazole/ 9. antibiotics, antifungal/ 10. exp amphotericin b/ 11. fluconazole.tw. 12. diflucan.tw. 13. itraconazole.tw. 14. sporanox.tw. 15. ketoconazole.tw. 16. nizoral.tw. 17. voriconazole.tw. 18. amphotericin.tw. 19. ambisome.tw. 20. amphotec.tw. 21. abelcet.tw. 22. flucytosine.tw. 23. nystatin.tw. 24. miconazole.tw. 25. (echinocandin$ or caspofungin).tw. 26. (select$ adj5 decontam$).tw. 27. exp nystatin/ 28. or/1-27 29. randomized controlled trial.pt. 30. controlled clinical trial.pt. 31. randomized controlled trials/ 32. Random allocation/ 33. Double-blind method/ 34. Single-blind method/ 35. exp Evaluation studies/ 36. exp clinical-trials/ 37. clinical trial.pt. 38. (clin$ adj5 trial$).tw. 39. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw. 40. exp Placebos/ 41. placebo$.tw. 42. random$.tw. 43. exp Research design/ 44. or/29-43 45. animal.sh. 46. 44 not 45 47. 28 and 46 48. exp HIV/ or exp HIV infections/ 49. exp leukopenia/ 50. exp bone marrow transplantation/

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Table 1. Search strategies for electronic databases (*Continued*)

	51. exp leukemia/ or exp lymphoma/ 52. exp tinea/ or exp tinea versicolor/ 53. or/48-52 54. 47 not 53 55. exp PRIMARY PREVENTION/ 56. prevent$.tw. 57. exp ANTIBIOTIC PROPHYLAXIS/ 58. prophyl$.tw. 59. or/55-58 60. 47 and 59 61. exp renal transplantation/ or liver transplantation/ or transplant$.tw. 62. 47 and 61 63. 60 or 62
EMBASE (OVID)	1.exp amphotericin b/ 2. exp amphotericin b cholesterol sulfate/ 3. exp amphotericin b deoxycholate/ 4. exp amphotericin b derivative/ 5. exp amphotericin b lipid complex/ 6. exp amphotericin b methyl ester/ 7. exp echinocandin b/ 8. exp echinocandin b derivative/ 9. exp econazole/ 10. exp fluconazole/ 11. exp flucytosine/ 12. exp itraconazole/ 13. exp ketoconazole/ 14. exp miconazole/ 15. exp nystatin/ 16. exp voriconazole/ 17. or/1-16

Table 2. Quality assessment of included studies: liver transplant recipients

Trial	Random sequence generation	Allocation concealment	Blinding (subjects/ investigators)	Blinding (assessors)	Intention-to-treat	Number excluded/number randomised
Tortorano 1995	Unclear	Unclear	No	Unclear	No	3/75 (4%)
Lumbreras 1996	Yes (permuted blocks)	Unclear	No	Unclear	Yes	0/143 (0)
Meyers 1997	Unclear	Unclear	Yes	Unclear	No	Unclear
Winston 1999	Yes (computer generated)	Unclear	Yes	Yes	Yes	24/236 (10%)

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Table 2. Quality assessment of included studies: liver transplant recipients *(Continued)*

Sharpe 2003	Unclear	Yes (pharmacy allocation)	Yes	Yes	No	9/71 (13%)
Biancofiore 2002	Unclear	Unclear (unclear whether envelopes sealed or opaque)	Yes (subjects only)	Unclear	Yes	2/131 (2%)
Tollemar 1995	Unclear	Yes (pharmacy allocation)	Yes	Yes	No	9/86 (10%)
Winston 2002	Unclear	Unclear	No	Unclear	Yes	16/304 (5%)
Ruskin 1992	Unclear	Unclear	No	Unclear	Yes	0/34 (0)

Table 3. Quality assessment of included studies: renal and cardiac transplant recipients

Trial	Random sequence generation	Allocation concealment	Blinding (subjects/investigators)	Blinding (assessors)	Intention-to-treat	Loss to follow-up
Patton 1994	Unclear	Unclear	No	Unclear	No	16/110 (15%)
Sobh 1995	Unclear	Unclear	No	Unclear	Yes	0/100 (0)
Owens 1984	Unclear	Unclear	Yes	Unclear	No	3/47 (6%)
Gombert 1987	Yes (computer generated)	Unclear	No	Unclear	No	2/60 (3%)
Keogh 1995	Unclear	Unclear	No	Unclear	Yes	0/43 (0)

Table 4. Subgroup and sensitivity analyses

Variable	Category	Studies	RR (95% CI) of IFI
Publication status	Published Unpublished	6 1	0.38 (0.16 to 0.91) 0.35 (0.01 to 8.11)
Randomised sequence generation	Adequate Uncertain	2 5	0.29 (0.13 to 0.61) 0.38 (0.11 to 1.37)
Allocation concealment	Adequate Uncertain	2 4	0.07 (0 to 1.26) 0.45 (0.22 to 0.93)

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Table 4. Subgroup and sensitivity analyses *(Continued)*

Blinding	Any None	5 2	0.37 (0.13 to 1.03) 0.4 (0.09 to 1.81)
Diagnostic criteria	Explicit Unclear	5 2	0.25 (0.12 to 0.51) 0.77 (0.43 to 1.39)
Analysis model	Random effects Fixed effect		0.39 (0.18 to 0.85) 0.41 (0.26 to 0.63)

Table 5. Applicability of meta-analysis results

Estimated risk	Examples	Incidence without prophlaxis	Incidence with prophylaxis	Number avoided	NNT to prevent 1 IFI
Low (5%)	Elective transplant, no operative/post-operative complications	5	2	3	28
Intermediate (10%)		10	3	7	14
High (25%)	Retransplant, fulminant hepatitis, preoperative steriods, dialysis, renal failure, difficult operation, re-operation, high transfusion requirement, postoperative bacterial/CMV infection	25	7	18	6

IFI = invasive fungal infection

WHAT'S NEW

Last assessed as up-to-date: 21 November 2005.

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Date	Event	Description
13 May 2009	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 3, 2004

Date	Event	Description
15 September 2008	Amended	Converted to new review format.
22 November 2005	Amended	New studies sought, but none found

CONTRIBUTIONS OF AUTHORS

- EGP wrote the protocol, developed the search strategy, identified trials and coordinated trial results, data extraction, RevMan data entry, and wrote final review
- ACW reviewed the protocol, identified trials, extracted data, and reviewed the final review
- TCS reviewed the protocol, identified trials, reviewed the results and the final review
- JCC reviewed the protocol, identified trials, reviewed the results and the final review

DECLARATIONS OF INTEREST

- EGP: none declared
- 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.
- JCC: none declared

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INDEX TERMS

Medical Subject Headings (MeSH)

*Organ Transplantation [mortality]; Antifungal Agents [*therapeutic use]; Fluconazole [therapeutic use]; Immunocompromised Host; Liver Transplantation [mortality]; Mycoses [mortality; *prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans

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