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[Intervention Review]

Routine versus selective antifungal administration for control of fungal infections in patients with cancer

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pcg@cochrane.dk.**Editorial group:** Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group**Publication status and date:** Stable (no update expected for reasons given in 'What's new'), published in Issue 3, 2017.**Citation:** Gøtzsche PC, Johansen HK. Routine versus selective antifungal administration for control of fungal infections in patients with cancer. *Cochrane Database of Systematic Reviews* 2014, Issue 9. Art. No.: CD000026. DOI: [10.1002/14651858.CD000026.pub2](https://doi.org/10.1002/14651858.CD000026.pub2).

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ABSTRACT

Background

Systemic fungal infection is considered to be an important cause of morbidity and mortality in cancer patients, particularly those with neutropenia. Antifungal drugs are often given prophylactically, or empirically to patients with persistent fever.

Objectives

To assess whether commonly used antifungal drugs decrease mortality in cancer patients with neutropenia.

Search methods

We searched PubMed from 1966 to 7 July 2014 and the reference lists of identified articles.

Selection criteria

Randomised clinical trials of amphotericin B, fluconazole, ketoconazole, miconazole, itraconazole or voriconazole compared with placebo or no treatment in cancer patients with neutropenia.

Data collection and analysis

The two review authors independently assessed trial eligibility and risk of bias, and abstracted data.

Main results

Thirty-two trials involving 4287 patients were included. Prophylactic or empirical treatment with amphotericin B significantly decreased total mortality (relative risk (RR) 0.69, 95% confidence interval (CI) 0.50 to 0.96), whereas the estimated RRs for fluconazole, ketoconazole, miconazole, and itraconazole were close to 1.00. No eligible trials were found with voriconazole. Amphotericin B and fluconazole decreased mortality ascribed to fungal infection (RR 0.45, 95% CI 0.26 to 0.76 and RR 0.42, 95% CI 0.24 to 0.73, respectively). The incidence of invasive fungal infection decreased significantly with administration of amphotericin B (RR 0.41, 95% CI 0.24 to 0.73), fluconazole (RR 0.39, 95% CI 0.27 to 0.57) and itraconazole (RR 0.53, 95% CI 0.29 to 0.97), but not with ketoconazole or miconazole. Effect estimates were similar for those 13 trials that had adequate allocation concealment and were blinded. The reporting of harms was far too variable from trial to trial to allow a meaningful overview. For the 2011 and 2014 updates no additional trials were identified for inclusion.

Authors' conclusions

Intravenous amphotericin B was the only antifungal agent that reduced total mortality. It should therefore be preferred when prophylactic or empirical antifungal therapy is introduced in cancer patients with neutropenia.

PLAIN LANGUAGE SUMMARY

Prevention of fungal infections in patients with cancer with antifungal drugs

Cancer patients receiving chemotherapy or a bone marrow transplant are at risk of fungal infections. These can be life-threatening, especially when they spread throughout the body. Those patients with low white cell counts (neutropenia) are particularly at risk. Antifungal drugs are often given as a routine preventive measure, or when people who are at risk have a fever. The review found that intravenous amphotericin B could reduce the number of deaths. Three of the drugs, amphotericin B, fluconazole and itraconazole, reduced fungal infections.

BACKGROUND

Bacterial infections are an important cause of death in cancer patients (Inagaki 1974), and patients with low white blood cell counts are particularly at risk (Estey 1982). Systemic fungal infection, with wide dissemination of infection throughout the body, is also considered to be an important cause of morbidity and mortality (Meyers 1990; Verfaillie 1991). This type of infection is mainly caused by *Candida* or *Aspergillus* species (Walsh 1991). The mortality rate in patients with *Candida* sepsis or deep tissue involvement is around 75% (Meyers 1990; Verfaillie 1991), and a positive blood culture or histologic signs of invasion were found before death in 37% of the patients in one series of patients (Estey 1982).

Antifungal agents are often given prophylactically in conjunction with chemotherapy or bone marrow transplantation, or empirically to patients without documented fungal infection but with persisting fever despite antibiotic treatment. The rationale for these approaches is to start therapy before it is too late, since it is difficult to diagnose an invasive fungal infection with certainty (Verfaillie 1991; Walsh 1990).

Studies with historical controls have shown a positive effect of antifungal agents on mortality (Stein 1986; Walsh 1991) but such non-randomised comparisons have been shown to overestimate the effect of cancer treatments considerably (Berlin 1989). We performed a meta-analysis of trials in which commonly used antifungal agents were compared with an untreated control group.

OBJECTIVES

The primary aim was to assess whether commonly used antifungal agents decrease mortality in cancer patients with neutropenia.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised trials were included. We accepted reports in any language. Studies concerned with the treatment or prevention of oral candidiasis were excluded.

Types of participants

Cancer patients with neutropenia caused by chemotherapy or bone marrow transplantation, as defined by the researchers within each study.

Types of interventions

Experimental: amphotericin B (including lipid soluble formulations), fluconazole, ketoconazole, miconazole, itraconazole or voriconazole given orally or intravenously. Control: placebo or no treatment.

Types of outcome measures

- Mortality
- Mortality ascribed to fungal infection
- Invasive fungal infection (defined as positive blood culture, oesophageal candidiasis, lung infection or microscopically confirmed deep tissue involvement)

- Colonisation
- Use of additional (escape) antifungal therapy
- Harms

Search methods for identification of studies

Electronic searches

We searched PubMed from 1966 to 7 July 2014 and the reference lists of identified articles.

The search strategy used is in Appendix 1.

The search strategies have been developed and executed by the authors.

Searching other resources

This has not been carried out since 2007 as we have not found it worthwhile.

Data collection and analysis

Data extraction and management

Decisions on which trials to include, and also which variables to use when a number of options were available for the same outcome, were based on the methods sections of the trials. Details on diagnosis, drug, dose, rules for use of additional (rescue) antifungal therapy, average length of treatment with placebo, length of follow-up, randomisation (Schulz 1995) and blinding methods, number of randomised patients, number of patients excluded from analysis, deaths, invasive fungal infections, colonisation and use of rescue drug were independently extracted by both review authors; differences in the data extracted were resolved by consensus.

We defined invasive fungal infection as a positive blood culture, oesophageal candidiasis, lung infection or microscopically confirmed deep tissue infection. We excluded cases of oropharyngeal and vulvovaginal candidiasis, skin infections, *Candida* in the urine and vaguely described infections.

We asked the trial authors to confirm the extracted information and to answer additional questions; numbers in the tables may therefore be different from those given in the published articles. To increase the response rate, the authors' most recent addresses were located in PubMed. In an attempt to increase the power of the meta-analyses and avoid reporting bias, the trial authors were specifically asked for the three months mortality data for all randomised patients, also secondarily excluded patients. We asked the trial authors for details on the randomisation process, especially whether it was concealed and irreversible so that an allocation could not be known beforehand or changed later.

Data synthesis

The outcomes were weighted by the inverse variance. Since heterogeneity of the studies was expected because of various designs; diagnoses; drugs; doses and routes of administration; and criteria for fungal invasion, colonisation and use of rescue drug a random-effects model was used. A fixed-effect analysis was preferred, however, if the P value was greater than 0.10 for the test of heterogeneity. Ninety-five per cent confidence intervals (CI) were presented.

RESULTS

Description of studies

We identified 44 potentially eligible trials of which 12 were excluded: two were not randomised ([Hiddemann 1991](#); [Schaison 1990](#)); one concerned oropharyngeal candidiasis only ([Samonis 1990](#)); one had a control group receiving active drugs ([Wang 2003](#)); in one only 14 of 146 patients had neutropenia and only data on oropharyngeal candidiasis were provided ([Bodey 1990](#)); one only reported a subgroup of 72 of 298 randomised patients who underwent autopsy ([Ezdinli 1979](#)); one used a surrogate outcome (resolution of fever) and only one patient developed candidaemia ([Schiel 2006](#)); one was published as an abstract without useful data and where no fungal diseases were found ([Reed 1993](#)); and four were excluded since they were unpublished and we could not obtain any data from them ([Benhamou 1991b](#); [Brincker 1990](#); [Prentice 1989](#); [Siegel 1982b](#)).

Two of the included 32 trials were published only as abstracts ([Acuna 1981](#); [Siegel 1982a](#)); one was an interim analysis ([Goldstone 1994](#)); and two were published in Japanese ([Fukuda 1994](#); [Suda 1980](#)).

Finally, we found a conference abstract describing a small placebo-controlled trial of voriconazole (25 patients) ([Cornely 2006](#)). This trial awaits assessment and may not be eligible as the primary outcome was lung infiltrates, which have other causes than fungal infection.

For the 2011 and 2014 updates no additional trials were identified for inclusion.

Risk of bias in included studies

We adopted broad quality assessment criteria and considered the risk of bias as low if the randomisation method was concealed, if central randomisation, use of sealed envelopes, a code provided by a pharmacy or a company was described; generation of the allocation sequence was adequate (for example random numbers); and the trial was placebo controlled and blinded. On one occasion what seemed to be a sound randomisation, provided by a pharmacy, on further questioning proved to result in medicine packages labelled A or B ([Vreugdenhil 1993](#)), which one would not have expected for a trial published in 1993. Such a procedure is risky as code breaking for just one patient would make it possible to predict all future allocations. Thirteen trials had adequate allocation concealment and were blinded ([Brincker 1978](#); [Brincker 1983](#); [Goodman 1992](#); [Kelsey 1999](#); [Nucci 2000](#); [Perfect 1992](#); [Riley 1994](#); [Rotstein 1999](#); [Schaffner 1995](#); [Tollema 1993](#); [Vreugdenhil 1993](#); [Wingard 1987](#); [Winston 1993](#)). One trial maintained the blinding during data analysis ([Schaffner 1995](#)).

The antifungal agent was given prophylactically in 29 trials and empirically in three. Acute leukaemia was the most common indication in 21 trials, bone marrow transplantation in 11. The length of the follow-up period was often not reported; it probably varied for different patients even within the same study since many trial authors stated that the trial drugs had been given till the neutropenia had resolved.

Effects of interventions

Thirty-two trials involving 4287 patients were included. Prophylactic or empirical treatment with amphotericin B significantly decreased total mortality (relative risk (RR) 0.69, 95% confidence interval (CI) 0.50 to 0.96). The point estimate was the same for those four trials that had adequate allocation concealment and were blinded (RR 0.69, 95% CI 0.41 to 1.19). Intravenous administration of amphotericin B was used in the trials apart from one in which the drug was given orally ([Suda 1980](#)). RRs for the other drugs were close to 1.00: fluconazole, RR of 1.04 (95% CI 0.84 to 1.30); ketoconazole, RR of 0.97 (95% CI 0.63 to 1.49); miconazole, RR of 1.16 (95% CI 0.71 to 1.87); and itraconazole, RR of 0.94 (95% CI 0.63 to 1.40).

Amphotericin B and fluconazole decreased mortality ascribed to fungal infection (RR 0.45, 95% CI 0.26 to 0.76 and RR 0.42, 95% CI 0.24 to 0.73, respectively).

The incidence of invasive fungal infection decreased significantly with administration of amphotericin B (RR 0.41, 95% CI 0.24 to 0.73), fluconazole (RR 0.39, 95% CI 0.27 to 0.57) and itraconazole (RR 0.53, 95% CI 0.29 to 0.97); but not with ketoconazole (RR 1.32, 95% CI 0.68 to 2.54) or miconazole (RR 0.52, 95% CI 0.20 to 1.31). Effect estimates were similar for those 13 trials that had adequate allocation concealment and were blinded. We did not find any eligible trials with voriconazole.

The trial authors' definitions of fungal colonisation and their methods varied widely and there was considerable heterogeneity between the trials for the effects of the drugs. The overall reduction in fungal colonisation was statistically significant for prophylactic amphotericin B, fluconazole and ketoconazole.

Use of rescue antifungal agents tended to be more common in the untreated groups. There was considerable heterogeneity for those drugs that were used in most of the studies.

The reporting of harms was far too variable from trial to trial to allow a meaningful overview. Usually no treatment discontinuations because of harms were reported in the fluconazole trials, whereas 16% discontinued in one trial with itraconazole ([Menichetti 1999](#)) and only 3% in another trial with this drug ([Nucci 2000](#)). We have listed the most important harms that were reported in [Table 1](#).

DISCUSSION

Amphotericin B was the only antifungal agent among those we studied that significantly decreased total mortality. The trials were relatively small but this finding is supported by another review in which we reported on three trials that compared intravenous lipid soluble amphotericin B (AmBisome) with smaller doses of standard intravenous amphotericin B ([Johansen 2001](#)). The relative risk (RR) for total mortality in these trials was 0.74 (95% CI 0.52 to 1.07).

The advantage of using total mortality as an outcome measure is not only that it is unbiased but it may also be the most relevant outcome since the drugs could have important harms leading to drug-related mortality. Ketoconazole, for example, is immunosuppressive and in all three trials in which bacterial infections were reported they were more common with ketoconazole than with placebo; 37 versus 21 patients ([Palmlblad 1992](#)), 33 versus 24 patients ([Estey 1984](#)), and 20% of neutropenic

courses versus 15% (Hansen 1987). Interestingly this adverse effect could be a class effect related to azoles as an increased incidence of bacteraemias has also been reported with fluconazole, 27 versus 16 patients (Schaffner 1995) and 15 versus 7 patients (Kern 1998); and with itraconazole, 47 versus 31 patients (Menichetti 1999). Fluconazole has been associated with an excess of graft-versus-host disease or organ failure in the two large studies of bone marrow transplant recipients; 29 versus 16 deaths (Goodman 1992), or 44 versus 24 according to later correspondence (Goodman 1992), and 102 versus 85 cases of graft-versus-host disease (Slavin 1995). It is noteworthy that the largest trial of fluconazole found no difference in total mortality, 55 versus 46 deaths (RR 1.18, 95% CI 0.85 to 1.65), whereas fewer deaths were ascribed to acute systemic fungal infections in the group receiving fluconazole compared to the group receiving placebo (1 of 179 versus 10 of 177 patients, P value 0.01) (Goodman 1992). This indicates that fluconazole increases mortality from other causes (54 versus 36 deaths, P value 0.04). Itraconazole has been associated with congestive heart failure, which does not seem to be a class effect (Ahmad 2001).

In an eight year follow-up of the only study that has reported a significant but possibly flawed effect of fluconazole on total mortality (Slavin 1995) the trial authors ascribe this finding to the fact that most of their patients (88%) had received allogeneic grafts. They write that the other large trial (Goodman 1992) primarily included autologous graft recipients, but in fact 48% of the patients in that trial had also received allogeneic grafts and the trial had three times as many deaths as the trial authors' own trial. Commentators (Slavin 1995) have suggested that the trial authors' positive result on mortality might represent a statistical aberration. We agree that this seems more likely than the tentative explanation based on type of graft offered by the trial authors. Furthermore, we suspect that a biased decision on length of follow-up may have been made in this trial. A conference abstract notes a follow-up period of 75 days (maximum length of treatment) plus an additional two weeks, that is 89 days (Slavin 1995). The final article gives no explanation why the follow-up period had been extended to 110 days. We used the data after 89 days (21 versus 28 deaths), which came closest to the three months follow-up we aimed for in the meta-analysis and which we assume was also the time frame stipulated in the trial protocol for the study.

Another bias that involves reporting at favourable time points relates to informal interim analyses. Concern about bias in cancer trials that is caused by lax stopping rules has previously been raised (Pocock 1978) and a survey showed that the majority of cancer cooperative groups perform annual interim analyses of their trials without formal stopping rules (Buyse 1993). A trial author informed us that one of his studies was stopped prematurely after 30 patients when an interim analysis showed a significant effect, but the trial report did not describe that this had occurred or that the study was planned to include more patients (Brincker 1978). A third study report did not mention any interim analysis, although an earlier conference abstract reported an interim analysis (Riley 1994); a fourth study described interim analyses but gave no rules (Estey 1984); and a fifth study has only been published as an interim analysis (Goldstone 1994).

Publication bias (Stern 1997), which is a well documented phenomenon in cancer trials (Berlin 1989; Simes 1986), is also of concern. A study on fluconazole was stopped by the company in 1990 when 32 patients had been entered; the

investigator never learned about the results (Brincker 1990, personal communication). Our efforts to make contact with the medical companies were disappointing; Pfizer and Janssen-Cilag did not wish to share their unpublished reports with us, or even to give us a list of the trials so that we could approach the investigators. This secrecy, which we have previously reported for Pfizer's trials that compared fluconazole with amphotericin B (Johansen 1999), and which other meta-analysts have reported when they approached Janssen (Huston 1996), is unethical and must be changed (Chalmers 1990). Clinical trial data can only be assembled through the patients' willingness to contribute to science for the benefit of future patients; the data should therefore be regarded as public property to be used for the common good. It has been amply documented that the withholding of data that are not favourable for the drug in question may be harmful to patients.

It should be noted that a possible effect on total mortality may be overlooked if rescue antifungal therapy is instituted too quickly in the control group. The positive effect of amphotericin B was seen despite the fact that rescue antifungal therapy was introduced rather quickly in the control group, for example after an average of 10, 10 and 15 days in three of the most positive trials (Perfect 1992; Pizzo 1982; Riley 1994); there were no data on this in the trial by Penack 2006. This problem was hardly the reason for the lack of effect of fluconazole as the three largest studies with fluconazole 400 mg daily reported the use of rescue antifungal therapy after an average of 14 days (Winston 1993), 20 days (Goodman 1992) and 55 days (Slavin 1995).

In previous versions of this review we did not include death attributed to fungal infection as an outcome measure. It is difficult to determine the cause of death in these severely ill patients and we therefore suspected that disease-specific mortality would be unreliable. As we could not confirm this suspicion in a study of disease-specific mortality (Due 2006), we have now included this outcome.

The harms we have listed in Table 1 should be interpreted cautiously. Biased reporting of harms is very common (Chan 2004; Gøtzsche 1989), and we suspected that biased reporting had occurred in several of the trials we reviewed. For example, arbitrary cut-offs delineating what constitutes a clinically relevant increase in creatinine and liver enzymes can have a major impact on what is found. We have described this type of biased reporting in a pivotal trial that compared voriconazole with liposomal amphotericin B (Jørgensen 2006). The investigators found that 29 versus 32 patients had a two-fold increase in S-creatinine. They also found that 43 versus 80 patients experienced a 1.5-fold increase (P value < 0.001), which is the result they reported in the abstract. This case was unusual as the bias was so obvious. We have never seen a 1.5-fold increase in S-creatinine reported in other trials, and the lack of clinical relevance of the trivial difference in S-creatinine was underlined by the fact that two patients in the voriconazole group and one in the amphotericin B group died from renal failure.

Amphotericin B, fluconazole and itraconazole all had an effect on invasive fungal infection. The data on mortality that we have presented in this review suggest that amphotericin B is a better drug than fluconazole. The comparisons are indirect, however. Unfortunately it is not possible to make a direct judgement on whether fluconazole is of similar effectiveness as amphotericin B on mortality or invasive infection despite the fact that more than a dozen comparative trials have been published (Johansen

1999; Johansen 2002a). First, most of the trials have used oral amphotericin B, which is not absorbed from the gastrointestinal tract and which is poorly documented. Second, the results for amphotericin B were combined with those for nystatin in large three-armed trials despite the fact that nystatin is no better than placebo when given to patients with severe immunodeficiency, such as those with cancer complicated by neutropenia (Johansen 1999; Johansen 2002b). It is also of concern that widespread use of fluconazole could lead to the development of resistance or to infection with inherently resistant species of fungi, for example *Candida krusei* and *Candida (Torulopsis) glabrata* (Working Party 1995). For itraconazole, little data is available at present to judge its efficacy compared with amphotericin B.

AUTHORS' CONCLUSIONS

Implications for practice

Intravenous amphotericin B was the only antifungal agent that reduced total mortality. It should therefore be preferred when prophylactic or empirical antifungal therapy is instituted in cancer patients with neutropenia.

Implications for research

It may be difficult to justify further placebo-controlled trials whereas there is a need for unbiased trials comparing intravenous amphotericin B with other antifungal drugs. Such trials should

comprise at least 1000 patients and they should include data on length of hospital stay and similar measures, allowing cost-benefit analyses to be performed. Data on the incidence of bacterial infections should be collected since azole compounds might increase the risk of such infections.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Acuna 1981

Methods	Allocation concealment: NA Blinding of study: yes
Participants	52 participants total, excluded: NA BMT
Interventions	Ketoconazole 200 mg/d oral Prophylactic
Outcomes	Infections Colonisation Use of escape drug
Notes	Follow-up period (days): NA Days on placebo: NA

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	

Benhamou 1991a

Methods	Allocation concealment: not described Blinding of study: yes
Participants	125 participants total, excluded: none BMT
Interventions	Ketoconazole 600 mg/d oral Prophylactic
Outcomes	Death Infections Colonisation Use of escape drug
Notes	Follow-up period (days): 36 Days on placebo: 30 3 viral infections included in 25 bacterial infections as they could not be separated

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias)	Low risk	

Benhamou 1991a (Continued)

All outcomes

Brincker 1978

Methods	Allocation concealment: computer generated numbers Blinding of study: yes
Participants	30 participants total, excluded: none AL
Interventions	Miconazole 2 g/d oral Prophylactic
Outcomes	Death Infections Colonisation Use of escape drug
Notes	Follow-up period (days): 90 Days on placebo: 23

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	

Brincker 1983

Methods	Allocation concealment: computer Blinding of study: yes
Participants	38 participants total, excluded: none AL
Interventions	Ketoconazole 400 mg/d oral Prophylactic
Outcomes	Death Infections Colonisation Use of escape drug
Notes	Follow-up period (days): 28 Days on placebo: 28

Risk of bias

Brincker 1983 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	

Caselli 1990

Methods	Allocation concealment: not described Blinding of study: NA
Participants	40 participants total, excluded: none AL
Interventions	Itraconazole 2 mg/kg/d oral (not stated whether it was suspension), ketoconazole 5 mg/kg/d, or amphotericin B 50 mg/kg/d Prophylactic
Outcomes	Infections Colonisation
Notes	Follow-up period (days): NA Days on placebo: NA

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

EORTC 1989

Methods	Allocation concealment: not described Blinding of study: no
Participants	157 participants total, excluded: 25 AL
Interventions	Amphotericin B 0.6 mg/kg/d iv Empiric
Outcomes	Death Infections
Notes	Follow-up period (days): 30 Days on placebo: NA

Risk of bias

EORTC 1989 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	

Estey 1984

Methods	Allocation concealment: not described Blinding of study: NA
Participants	150 participants total, excluded: 3 AL
Interventions	Ketoconazole 400 mg/d oral Prophylactic
Outcomes	Death Infections Colonisation
Notes	Follow-up period (days): 56 Days on placebo: 39

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Fukuda 1994

Methods	Allocation concealment: envelopes Blinding of study: no
Participants	63 participants total, excluded: none AL
Interventions	Fluconazole 400 mg/d iv Prophylactic
Outcomes	Death Infections Colonisation
Notes	Follow-up period (days): NA Days on placebo: 7

Risk of bias

Fukuda 1994 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	High risk	

Goldstone 1994

Methods	Allocation concealment: not described Blinding of study: no
Participants	137 participants total, excluded: 4 BMT
Interventions	AmBisome 2 mg/kg/d iv Empiric
Outcomes	Death Infections Use of escape drug
Notes	Follow-up period (days): NA Days on placebo: NA

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	

Goodman 1992

Methods	Allocation concealment: sequence list by pharmacy Blinding of study: yes
Participants	356 participants total, excluded: 1 BMT
Interventions	Fluconazole 400 mg/d oral Prophylactic
Outcomes	Death Infections Colonisation Use of escape drug

Goodman 1992 (Continued)

Notes Follow-up period (days): 90
Days on placebo: 20

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	

Hansen 1987

Methods	Allocation concealment: blinded random scheme Blinding of study: NA
Participants	60 participants total, excluded: 4 AL
Interventions	Ketoconazole 400 mg/d oral Prophylactic
Outcomes	Infections Colonisation Use of escape drug
Notes	Follow-up period (days): NA Days on placebo: NA

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Hughes 1983

Methods	Allocation concealment: not described Blinding of study: yes
Participants	64 participants total, excluded: 8 AL
Interventions	Ketoconazole 400 mg/d oral Prophylactic
Outcomes	Colonisation
Notes	Follow-up period (days): NA

Hughes 1983 (Continued)

Days on placebo: 14

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	

Kaptan 2003

Methods	Allocation concealment: NA ('randomized blindly'). Blinding of study: no
Participants	61 participants (113 episodes), excluded: 6 (16 episodes) AL
Interventions	Itraconazole capsules 400 mg/d Prophylactic
Outcomes	Death Infections Use of escape drug
Notes	Follow-up period (days): NA

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	

Kelsey 1999

Methods	Allocation concealment: sealed envelopes Blinding of study: yes
Participants	170 participants total, excluded: 9 BMT
Interventions	AmBisome 2 mg/kg 3 times a week iv Prophylactic
Outcomes	Death Infections

Routine versus selective antifungal administration for control of fungal infections in patients with cancer (Review)

Kelsey 1999 (Continued)

	Colonisation Use of escape drug
Notes	Follow-up period (days): NA Days on placebo: NA
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment (selection bias)	Low risk A - Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk

Kern 1998

Methods	Allocation concealment: central computer Blinding of study: no
Participants	84 participants total, excluded: 16 AL
Interventions	Fluconazole 400 mg/d oral Prophylactic
Outcomes	Death Infections Use of escape drug
Notes	Follow-up period (days): 42 Days on placebo: NA
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment (selection bias)	Low risk A - Adequate
Blinding (performance bias and detection bias) All outcomes	High risk

Menichetti 1999

Methods	Allocation concealment: NA Blinding of study: yes
Participants	405 participants total, excluded: none AL

Menichetti 1999 (Continued)

Interventions	Itraconazole 5 mg/kg/d oral solution Prophylactic
Outcomes	Death Infections Colonisation Use of escape drug
Notes	Follow-up period (days): NA Days on placebo: 19

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	

Nucci 2000

Methods	Allocation concealment: sealed envelopes Blinding of study: yes
Participants	219 participants total, excluded: none from analysis of deaths AL
Interventions	Itraconazole capsules 200mg/d oral Prophylactic
Outcomes	Death Infections Colonisation Use of escape drug
Notes	Follow-up period (days): 60 Days on placebo: 17 Data on colonisation not used as they were given only as percentages, and it is clear from the confidence interval that data were not available for all patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	

Palmblad 1992

Methods	Allocation concealment: pharmacy Blinding of study: NA
Participants	116 participants total, excluded: 9 AL
Interventions	Ketoconazole 200 mg/d oral Prophylactic
Outcomes	Death Infections Colonisation Use of escape drug
Notes	Follow-up period (days): 59 Days on placebo: 56

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Penack 2006

Methods	Allocation concealment: central computer system Blinding of study: none
Participants	140 participants total, excluded: 8 AL
Interventions	Lipid amphotericin B 50 mg every other day iv Prophylactic
Outcomes	Death Infections Use of escape drug
Notes	Follow-up period (days): 17 Days on no treatment: NA

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	High risk	

Perfect 1992

Methods	Allocation concealment: pharmacy codes Blinding of study: yes
Participants	188 participants total, excluded: 6 BMT
Interventions	Amphotericin B 0.1 mg/kg/d iv Prophylactic
Outcomes	Death Infections Colonisation Use of escape drug
Notes	Follow-up period (days): 42 Days on placebo: 10

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	

Pizzo 1982

Methods	Allocation concealment: sealed envelopes Blinding of study: no
Participants	34 participants total, excluded: none AL
Interventions	Amphotericin B 0.5 mg/kg/d iv Empiric
Outcomes	Death Infections
Notes	Follow-up period (days): 50 Days on placebo: 10 Numbers of deaths are inconsistently reported, 2 or 3 on study drug, 3, 4 or 5 on control; we used 3 versus 4 deaths for the analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Pizzo 1982 (Continued)

Blinding (performance bias and detection bias)
All outcomes

High risk

Riley 1994

Methods	Allocation concealment: random numbers, handled by pharmacy Blinding of study: yes
Participants	35 participants total, excluded: none BMT
Interventions	Amphotericin B 0.1 mg/kg/d iv Prophylactic
Outcomes	Death Infections Colonisation Use of escape drug
Notes	Follow-up period (days): 30 Days on placebo: 15

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	

Rotstein 1999

Methods	Allocation concealment: computer generated, sequentially numbered Blinding of study: yes
Participants	304 participants total, excluded: 30 AL
Interventions	Fluconazole 400 mg/d oral Prophylactic
Outcomes	Death Infections Colonisation Use of escape drug
Notes	Follow-up period (days): NA Days on placebo: NA

Rotstein 1999 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	

Schaffner 1995

Methods	Allocation concealment: consecutive numbers, prepared by pharmacy Blinding of study: yes, data analysis was also blinded Mycosis diagnosed by external observer
Participants	96 participants total, but randomised more than once. Total of 154 episodes, excluded: 3 episodes AL
Interventions	Fluconazole 400 mg/d oral or iv Prophylactic
Outcomes	Death Infections Colonisation Use of escape drug
Notes	Follow-up period (days): NA, but sufficient (till symptom resolution or failure) Days on placebo: 20

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	

Siegel 1982a

Methods	Allocation concealment: NA Blinding of study: NA
Participants	25 participants total, excluded: NA BMT
Interventions	Ketoconazole 200 mg/d oral Prophylactic

Siegel 1982a (Continued)

Outcomes	Infections Colonisation Use of escape drug
Notes	Follow-up period (days): NA Days on placebo: NA
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment (selection bias)	Unclear risk B - Unclear

Slavin 1995

Methods	Allocation concealment: stratified Blinding of study: yes
Participants	301 participants total, excluded: 1 BMT
Interventions	Fluconazole 400 mg/d oral Prophylactic
Outcomes	Death Infections Colonisation Use of escape drug
Notes	Follow-up period (days): 89 Days on placebo: 55
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment (selection bias)	Unclear risk B - Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk

Suda 1980

Methods	Allocation concealment: NA Blinding of study: no
Participants	70 participants total, excluded: none AL
Interventions	Amphotericin B 600 mg/d oral

Suda 1980 (Continued)

Prophylactic

Outcomes	Death Infections Use of escape drug
Notes	Follow-up period (days): NA Days on placebo: NA

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	High risk	

Tollemar 1993

Methods	Allocation concealment: pharmacy Blinding of study: yes
Participants	84 participants total, excluded: 8 BMT
Interventions	AmBisome 1 mg/kg/d iv Prophylactic
Outcomes	Death Infections Use of escape drug
Notes	Follow-up period (days): NA Days on placebo: 19

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	

Vreugdenhil 1993

Methods	Allocation concealment: A and B; risk of breaking the code Blinding of study: yes

Vreugdenhil 1993 (Continued)

Participants	98 participants total, excluded: 6 AL
Interventions	Itraconazole 400 mg/d oral, capsules Prophylactic
Outcomes	Death Infections Colonisation Use of escape drug
Notes	Follow-up period (days): 80 Days on placebo: 80

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	

Wingard 1987

Methods	Allocation concealment: computer generated Blinding of study: yes
Participants	208 participants total, excluded: 15 BMT
Interventions	Miconazole 15 mg/kg/d oral Prophylactic
Outcomes	Death Infections Colonisation Use of escape drug
Notes	Follow-up period (days): NA Days on placebo: 9

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	

Winston 1993

Methods	Allocation concealment: computer generated Blinding of study: yes
Participants	257 participants total, excluded: 2 AL
Interventions	Fluconazole 400 mg/d oral Prophylactic
Outcomes	Death Infections Colonisation Use of escape drug
Notes	Follow-up period (days): 90 Days on placebo: 14

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	

Yamac 1995

Methods	Allocation concealment: not described Blinding of study: no
Participants	70 participants total, excluded: NA AL
Interventions	Fluconazole 400 mg/d oral Prophylactic
Outcomes	Infections
Notes	Follow-up period (days): NA Days on placebo: NA

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias)	High risk	

Yamac 1995 (Continued)

All outcomes

AL: acute leukemia (main disease)
BMT: bone marrow transplantation (main disease)
NA: not available

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Benhamou 1991b	An unpublished study mentioned in the reference. No data available
Bodey 1990	Only 14 of 146 patients had neutropenia
Brincker 1990	An unpublished study mentioned in personal communication. No data available
Caselli 2012	All patients in the untreated control group were deliberately at low risk for getting an invasive fungal infection, and outcome data were unclear. Small trial, with only 31 patients potentially eligible out of 104 patients that 'provided sufficient data.'
Ezdinli 1979	Autopsy subgroup of RCT
Hiddemann 1991	Not an RCT
Prentice 1989	An unpublished study mentioned in the reference. No data available
Reed 1993	Only published as abstract, 96 patients randomised to fluconazole, amphotericin B or no treatment. No fungal disease was documented in any group, colonisation data insufficient for inclusion in the review
Samonis 1990	Study of oropharyngeal candidiasis
Schaison 1990	Not truly randomised
Schiel 2006	Used a surrogate outcome (resolution of fever) and only one patient developed candidaemia
Siegel 1982b	An unpublished study mentioned in the reference. No data available
Vehreschild	Trial of 'pulmonary infiltrates', not of verified antifungal infections. Trial stopped after only 25 patients for ethical reasons
Wang 2003	Control group was not untreated (ranitidine and an antibiotic were used)

Characteristics of studies awaiting assessment [ordered by study ID]

Cornely 2006

Methods	Prospective, randomized, double-blind, placebo-controlled phase III trial
Participants	Patients with AML undergoing first remission induction chemotherapy
Interventions	Voriconazole 200 mg bid or placebo
Outcomes	Detection of a lung infiltrate or end of neutropenia

Routine versus selective antifungal administration for control of fungal infections in patients with cancer (Review)

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Cornely 2006 (Continued)

Notes

DATA AND ANALYSES

Comparison 1. Antifungals versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	26	3902	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.81, 1.09]
1.1 Amphotericin	9	988	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.50, 0.96]
1.2 Fluconazole	7	1470	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.84, 1.30]
1.3 Ketoconazole	4	429	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.63, 1.49]
1.4 Miconazole	2	238	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.71, 1.87]
1.5 Itraconazole	4	777	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.63, 1.40]
2 Death related to fungal infection	23	3490	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.38, 0.71]
2.1 Amphotericin	9	988	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.26, 0.76]
2.2 Fluconazole	6	1213	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.24, 0.73]
2.3 Ketoconazole	3	304	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.55, 4.04]
2.4 Miconazole	1	208	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.33]
2.5 Itraconazole	4	777	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.31, 1.56]
3 Invasive infections	30	4044	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.39, 0.64]
3.1 Amphotericin	8	855	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.24, 0.73]
3.2 Fluconazole	8	1539	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.27, 0.57]
3.3 Ketoconazole	7	562	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.68, 2.54]
3.4 Miconazole	2	238	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.20, 1.31]
3.5 Itraconazole	4	810	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.29, 0.97]
3.6 Itraconazole/ketoconazole/amphotericin	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Colonisation	22		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Amphotericin	3	378	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.33, 0.77]
4.2 Fluconazole	6	1393	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.33, 0.90]
4.3 Ketoconazole	8	626	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.51, 0.87]
4.4 Miconazole	2	238	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.37, 2.24]
4.5 Itraconazole	2	503	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.57, 1.45]
4.6 Itraconazole/ketoconazole/amphotericin	1	40	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.31, 1.04]
5 Use of escape drug	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Amphotericin	6	636	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.35, 1.03]
5.2 Fluconazole	7	1469	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.02]
5.3 Ketoconazole	6	412	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.58, 1.44]
5.4 Miconazole	2	238	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.94, 1.46]
5.5 Itraconazole	3	712	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.57, 0.95]

Analysis 1.1. Comparison 1 Antifungals versus placebo or no treatment, Outcome 1 Death.

Analysis 1.2. Comparison 1 Antifungals versus placebo or no treatment, Outcome 2 Death related to fungal infection.

Analysis 1.3. Comparison 1 Antifungals versus placebo or no treatment, Outcome 3 Invasive infections.

Analysis 1.4. Comparison 1 Antifungals versus placebo or no treatment, Outcome 4 Colonisation.

Analysis 1.5. Comparison 1 Antifungals versus placebo or no treatment, Outcome 5 Use of escape drug.

ADDITIONAL TABLES

Table 1. Harms

Trial	Trial drug	Number of patients	Harms
EORTC 1989	amphotericin B	80 versus 77	Treatment discontinuations: 6 pts on trial drug (infusion-related toxicity, allergic reactions); Nephrotoxicity: 8 versus 3, none required dialysis and renal function restored later; Hypokalaemia: 33 versus 16
Goldstone 1994	amphotericin B	64 versus 69	Treatment discontinuations: 4 on trial drug (chills, rigour, hypotension, rash and bronchospasm); Elevated liver function tests: 26 versus 32; Nephrotoxicity: 1 on trial drug that did not require withdrawal of therapy
Kelsey 1999	amphotericin B	74 versus 87	Treatment discontinuations: 5 on trial drug, 1 on placebo because of immediate reactions; Nephrotoxicity: 9 versus 6; Hypokalaemia: 1 versus 0; Clinical adverse events were very similar in the two groups
Penack 2006.	amphotericin B	75 versus 57	Treatment discontinuations: 2 (1 skin rash, 1 chills) versus 0; Other harms: "no differences in ... liver function tests, renal function parameters and hypokalaemia"
Perfect 1992	amphotericin B	91 versus 91	More infusion-related harms on active drug, but no data provided; No significant differences in renal function, hepatic enzymes or electrolytes (no data provided)
Pizzo 1982	amphotericin B	18 versus 16	Treatment discontinuations: none; Rash: 2 versus 1; Azotaemia: 1 versus 0; liver enzyme elevations: 2 versus 3; Electrolyte abnormalities: 18 versus 16
Riley 1994	amphotericin B	17 versus 18	Treatment discontinuations: none; Renal function: no difference (P value 0.82 for blood urea, P value 0.63 for creatinine); Potassium supplements: no difference; Infusion reactions: none
Suda 1980	amphotericin B	39 versus 31	Article is in Japanese
Tollemar 1993	amphotericin B	42 versus 42	Treatment discontinuations: 4 versus 0 for infusion reactions; Potassium supplementation: no difference; Renal function: no useful data, but only small changes reported, compared to normal ranges
Fukuda 1994	fluconazole	37 versus 26	Article is in Japanese
Goodman 1992	fluconazole	179 versus 177	Treatment discontinuations: 1 on trial drug, 2 on placebo for clinical side effects, and 17 versus 11 for elevated liver function tests; in 7 versus 3, hepatic dysfunction contributed to death; Graft-versus-host disease or organ failure: 44 versus 24 deaths; Nausea: 13 versus 9; Skin rash: 9 versus 9; Eosinophilia in 6 versus 0

Table 1. Harms (Continued)

Kern 1998	fluconazole	36 versus 32	Bacteraemia: 15 versus 7; Other harms similar: 5 versus 6 elevations in transaminases, 19 versus 17 nausea or vomiting, 3 versus 0 allergy
Rotstein 1999	fluconazole	141 versus 133	Treatment discontinuations: none reported; Elevated liver enzymes: 17 versus 19; Rash: 51 versus 59; Nausea: 106 versus 95; Vomiting: 68 versus 85
Schaffner 1995	fluconazole	76 versus 76 episodes	Treatment discontinuations: none reported; No data on harms ("no significant differences were found")
Slavin 1995	fluconazole	152 versus 148	Treatment discontinuations: 32 versus 31 for abnormal liver function; Graft-versus-host disease: 102 versus 85; Nausea: 33 versus 22; Seizures: 8 versus 9; Liver enzymes: no differences
Winston 1993	fluconazole	124 versus 133	Treatment discontinuations: none reported; Elevated liver enzymes: 25 versus 14; Nausea and vomiting: 9 versus 5; Rash: 13 versus 7; Other harms were similarly distributed
Yamac 1995	fluconazole	41 versus 29	Treatment discontinuations: none reported; Other harms: no data
Acuna 1981	ketoconazole	28 versus 24	No data
Benhamou 1991	ketoconazole	63 versus 62	Treatment discontinuations: 38 versus 14 (among them 2 patients with veno-occlusive disease, 1 hepatitis, 3 skin rash in active group; none in placebo group); Severe gastrointestinal intolerance: 4 versus 7; Three-fold greater values than normal for transaminases: 13 versus 8
Brincker 1983	ketoconazole	19 versus 19	One patient on trial drug stopped treatment because of universal exanthema
Estey 1984	ketoconazole	77 versus 73	Bacterial infections: 33 versus 24
Hansen 1987	ketoconazole	27 versus 29	Treatment discontinuations: 2 on trial drug (1 skin rash and 1 elevated liver function tests); Bacterial infections: 20% versus 15% of neutropenic episodes
Hughes 1983	ketoconazole	42 versus 22	Treatment discontinuations: 1 on trial drug (nausea and anorexia); Other harms: 2 nausea and anorexia, 1 abdominal pain, 1 transient rash, all on trial drug
Palmblad 1992	ketoconazole	55 versus 61	Treatment discontinuations: 2 (elevated transaminases) versus 6 (1 elevated transaminases, 5 exanthema); Bacteraemias: 37 versus 21
Siegel 1982a	ketoconazole	12 versus 13	No data
Brincker 1978	miconazole	15 versus 15	None ascribable to trial drug
Wingard 1987	miconazole	97 versus 111	Treatment discontinuations: 1 (pruritis and flushing) versus 2 (1 rash, 1 nausea); Severe hypotension: 2 on trial drug
Caselli 1990	itraconazole, amphotericin B, ketoconazole	30 versus 10	No data

Table 1. Harms (Continued)

Kaptan 2003	itraconazole	31 versus 24	Treatment discontinuations: 2 on trial drug (cardiac arrhythmia and gastric irritation); "there was a clinical impression that hypokalaemia occurred at a greater rate in patients with itraconazole"
Menichetti 1999	itraconazole	201 versus 204	Treatment discontinuations: 37 versus 27; Bacteraemia: 47 versus 31; Elevated transaminases: 5 versus 3
Nucci 2000	itraconazole	104 versus 106	Treatment discontinuations: 3 versus 4; Skin rash: 3 versus 1; Elevated liver enzymes: 3 versus 4; Nausea: 2 on placebo
Vreugdenhil 1993	itraconazole	49 versus 49	Treatment discontinuations: 1 (nausea) versus 1 (liver function deterioration); Liver function deterioration: 28 versus 22 episodes; Renal function deterioration: 4 versus 2 episodes

APPENDICES

Appendix 1. PubMed search strategy

#1: random* OR control* OR blind*

#2: nystatin OR amphotericin OR fluconazol* OR itraconazol* OR ketoconazol* OR miconazol* OR voriconazol*

#3: bone-marrow OR cancer* OR fungemia OR hematologic* OR malignan* OR neoplas* OR neutropeni* OR granulocytopeni* OR leukemi* OR lymphom*

#4: #1 AND #2 AND #3.

WHAT'S NEW

Date	Event	Description
8 March 2017	Review declared as stable	Intervention no longer in general use.

HISTORY

Protocol first published: Issue 3, 1996

Review first published: Issue 2, 1997

Date	Event	Description
7 July 2014	New search has been performed	Literature searches updated
7 July 2014	New citation required but conclusions have not changed	No new trials identified for inclusion, one study excluded
14 September 2011	New search has been performed	Review updated with new search details. No new studies were identified for inclusion.
18 July 2011	Amended	Searches re-run July 2011
5 February 2008	New search has been performed	Minor update. One new drug added (voriconazole); one new trial added (Penack); two new excluded trials added (Schiel, Vehreschild); two new outcomes added (death ascribed to fungal infection and harms).

Date	Event	Description
5 November 2007	New search has been performed	New studies found and included or excluded
9 January 2002	New search has been performed	Substantive amendment
8 January 2002	New search has been performed	Conclusions changed

CONTRIBUTIONS OF AUTHORS

PCG wrote the protocol and the draft manuscript, did the searches and performed the statistical analyses. Both authors read the papers and extracted the data independently. HKJ commented on the various versions of the draft.

DECLARATIONS OF INTEREST

Peter C Gøtzsche - nothing to declare

Helle Krogh Johansen - nothing to declare

SOURCES OF SUPPORT

Internal sources

- Rigshospitalet, Copenhagen, Denmark.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have not recorded dropouts due to toxicity as they were reported rarely and inconsistently. We have added harms and also death ascribed to fungal infection as our research has shown that this outcome is reliable ([Due 2006](#)), contrary to our expectations.

INDEX TERMS

Medical Subject Headings (MeSH)

Antifungal Agents [*therapeutic use]; Immunocompromised Host; Mycoses [complications] [mortality] [*prevention & control]; Neoplasms [*complications] [immunology] [mortality]; Neutropenia [complications]; Opportunistic Infections [complications] [mortality] [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans