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[Intervention Review]

Amphotericin B lipid soluble formulations versus amphotericin B in cancer patients with neutropenia

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ABSTRACT

Background

Patients with cancer who are treated with chemotherapy or receive a bone marrow transplant have an increased risk of acquiring fungal infections. Such infections can be life-threatening. Antifungal drugs are therefore often given prophylactically to such patients, or when they have a fever.

Objectives

To compare the benefits and harms of lipid soluble formulations of amphotericin B with conventional amphotericin B 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 comparing lipid soluble formulations of amphotericin B with conventional amphotericin B.

Data collection and analysis

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

Main results

We found 13 trials (1960 patients). Lipid-based amphotericin B was not more effective than conventional amphotericin B on mortality (relative risk (RR) 0.5; 95% confidence interval (CI) 0.64 to 1.14) but decreased invasive fungal infection (RR 0.65; 95% CI 0.44 to 0.97), nephrotoxicity defined as a 100% increase in serum creatinine (RR 0.45; 95% CI 0.37 to 0.54), and number of dropouts (RR 0.78; 95% CI 0.62 to 0.97).

For the drug used in most patients, AmBisome (4 trials, 1214 patients), there was no significant difference in mortality (RR 0.77; 95% CI 0.54 to 1.10) whereas it tended to be more effective than conventional amphotericin B on invasive fungal infection (RR 0.63; 95% CI 0.39 to 1.01, P value 0.053).

AmBisome, amphotericin B in Intralipid (6 trials, 379 patients), amphotericin B colloidal dispersion (ABCD) (2 trials, 262 patients), and amphotericin B lipid complex (ABLC) (1 trial, 105 patients) all decreased the occurrence of nephrotoxicity, but conventional amphotericin B was rarely administered under optimal circumstances.

Authors' conclusions

It is not clear whether there are any advantages of lipid-based formulations if conventional amphotericin B is administered under optimal circumstances, and their high cost prohibits routine use in most settings. There is a need for large trials comparing lipid-based formulations of amphotericin B with conventional amphotericin B given in the same dose, with routine premedication for prevention of infusion-related toxicity, and with supplementation with fluid, potassium, and magnesium for prevention of nephrotoxicity.

PLAIN LANGUAGE SUMMARY**Prevention of fungal infections in patients with cancer with amphotericin B**

Patients with cancer who are treated with chemotherapy or receive a bone marrow transplant have an increased risk of acquiring fungal infections. Such infections can be life-threatening. Antifungal drugs are therefore often given prophylactically to such patients, or when they have a fever. The review found that lipid formulations of amphotericin B had fewer adverse effects (less nephrotoxicity and fewer dropouts) than conventional amphotericin B. However, it is not clear whether there are any advantages of these formulations if conventional amphotericin B is administered under optimal circumstances.

BACKGROUND

Opportunistic fungal infections are a major cause of morbidity and mortality in neutropenic patients (Richardson 1998). The mortality rate in patients with candidaemia or deep tissue infection is around 50% (Edwards 1997). Therefore, some clinicians use antifungal agents prophylactically in patients undergoing antileukaemic chemotherapy or bone marrow transplantation, or empirically in patients with persistent fever of unknown origin where the effect is relatively modest. In a meta-analysis of prophylactic or empirical antifungal treatment versus placebo or no treatment we found that it was necessary to treat more than 50 patients to prevent one case of fungal invasion in patients who survived the neutropenic episode (Gøtzsche 1997; Gøtzsche 2002).

Amphotericin B has proven antimicrobial activity against *Candida* and *Aspergillus* species, which are the most prevalent fungal pathogens in cancer patients with neutropenia (Edwards 1997). Lipid formulations of amphotericin B such as AmBisome, amphotericin B lipid complex (ABLC), or amphotericin B colloidal dispersion (ABCD) are sometimes preferred over conventional amphotericin B because of less nephrotoxicity (Richardson 1998; Tang 1997). It is uncertain, however, how important this is, for example whether the use of such agents leads less often to renal failure. Furthermore, studies have shown that the nephrotoxicity of conventional amphotericin B can be reduced to a very low level by continuous infusion (Imhof 2003) and by appropriate supplementation with fluid, potassium, and magnesium (Mayer 1999; Nath 1999). For a proper assessment of the value of these drugs, it is also relevant to consider the considerable differences in cost. In some hospitals the costs for the new lipid formulations have accounted for a significant proportion of all expenditure on antimicrobial agents (Tang 1997).

OBJECTIVES

To compare the benefits and harms of lipid soluble formulations of amphotericin B with conventional amphotericin B in cancer patients with neutropenia.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised trials, irrespective of language, which compared lipid soluble formulations of amphotericin B with conventional amphotericin B in cancer patients with neutropenia were eligible. Trials using quasi-randomisation methods were not accepted.

Types of participants

Patients with cancer complicated by neutropenia caused by cancer chemotherapy or bone marrow transplantation.

Types of interventions

Experimental: lipid soluble formulations of amphotericin B. Control: conventional amphotericin B. The drugs were given intravenously.

Types of outcome measures

- Mortality

- Invasive fungal infection (defined as positive blood culture, oesophageal candidiasis, lung infection, or microscopically confirmed deep tissue involvement)
- Nephrotoxicity (defined as a doubling of serum creatinine)
- Other harms
- Serum creatinine ($\mu\text{mol/l}$)
- Dropouts

Search methods for identification of studies

We searched PubMed (from 1966 to 18 July 2011).

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 which variables to use when a number of options were available for the same outcome were based on the methods sections of the trials only. Details on diagnosis, drug, dose, randomisation and blinding methods, number of randomised patients, number of patients excluded from the analysis, deaths, invasive fungal infections, nephrotoxicity, serum creatinine, and number of dropouts were extracted by both authors independently. When baseline and breakthrough fungal infections were reported separately, we combined the data. 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 (Gøtzsche 1997). We excluded cases of oropharyngeal and vulvovaginal candidiasis, skin infections, *Candida* in the urine, and vaguely described infections. The authors were contacted for supplementary information on their trials.

Data synthesis

The outcomes were weighted by the inverse variance; 95% CIs are presented. A fixed-effect model analysis was used unless P value was less than 0.10 for the test of heterogeneity.

RESULTS

Description of studies

We identified 13 relevant trials. Conventional amphotericin B was compared with AmBisome (Fugisome) in four trials (Jadhav 2012; Leenders 1998; Prentice 1997; Walsh 1999), with amphotericin B in Intralipid in six trials (Caillot 1994; Moreau 1992; Nath 1999; Nucci 1999; Pascual 1995; Schöffski 1998), with amphotericin B colloidal dispersion (ABCD) in two trials (Sandler 2000; White 1998), and with

amphotericin B lipid complex (ABLC) in one trial (Subira 2004). The trial drugs were given as an intravenous infusion. Premedication to prevent infusion-related toxicity was allowed in the AmBisome trials but in one of them only after the first day (Jadhav 2012) and in another only after the first dose (Walsh 1999). For other lipid formulations premedication was routine in four studies (Moreau 1992; Nath 1999; Subira 2004; White 1998), was only used in the control group (Nucci 1999), according to the investigator's preference (Sandler 2000), or not at all in three studies (Caillot 1994; Pascual 1995; Schöffski 1998).

The drugs were given empirically in 11 trials, mainly empirically in one trial (Nucci 1999), and in an intended treatment trial (Leenders 1998). In the intended treatment trial, 109 patients were randomised but 43 were subsequently excluded, 40 of them according to the protocol as a suspected infection could not be confirmed. However, as this criterion applied to only 26 of the remaining 66 patients we included data from all 109 patients whenever possible.

Acute leukaemia was the most common disease in 11 trials; two trials were in patients who had undergone bone marrow or stem cell transplantation (Sandler 2000; White 1998). Two studies included children as well as adults (Jadhav 2012; Prentice 1997) and two only children (Nath 1999; Sandler 2000). The doses were 1 to 5 mg/kg/day of AmBisome, 0.7 to 4.0 mg/kg/day of amphotericin B in Intralipid, 4.0 mg/kg/day of ABCD, 1 mg/kg/day of ABLC, and 0.6 to 1 mg/kg/day of conventional amphotericin B.

Risk of bias in included studies

We adopted broad quality assessment criteria and considered the randomisation method to be concealed if central randomisation, sealed envelopes, or a code provided by a pharmacy or a company was described. Treatment allocation was adequately concealed in seven trials (Caillot 1994; Jadhav 2012; Leenders 1998; Nath 1999; Prentice 1997; Subira 2004; Walsh 1999) and blinding of the drugs was reported for three trials (Sandler 2000; Walsh 1999; White 1998). Few patients were excluded from analysis apart from the intended treatment trial (see above) (Leenders 1998).

The length of the follow-up period was not always reported, and it sometimes varied for different patients within the same study since some authors stated that the follow-up ended one week after the last dose of trial drug (see the table 'Characteristics of included studies').

Effects of interventions

We included 13 trials (1960 patients). Supplementation with potassium to prevent nephrotoxicity was used in only one of the trials (Nath 1999). Lipid-based amphotericin B was not more effective than conventional amphotericin B on mortality (RR 0.85; 95% CI 0.64 to 1.14) but decreased invasive fungal infection (RR 0.65; 95% CI 0.44 to 0.97), nephrotoxicity defined as a 100% increase in serum creatinine (RR 0.45; 95% CI 0.37 to 0.54), and number of dropouts (RR 0.78; 95% CI 0.62 to 0.97). There were only 12 deaths ascribed to fungal infection (RR 0.56; 95% CI 0.29 to 1.09).

AmBisome versus conventional amphotericin B (4 trials, 1214 patients)

There was no significant difference in mortality (RR 0.77; 95% CI 0.54 to 1.10) whereas AmBisome tended to be more effective than

conventional amphotericin B on invasive fungal infection (RR 0.63; 95% CI 0.39 to 1.01, P value 0.053) and decreased significantly the incidence of nephrotoxicity defined as a 100% increase in serum creatinine (RR 0.51; 95% CI 0.40 to 0.64). None of the trials reported on serum creatinine values. Fewer patients dropped out on AmBisome but the difference was not significant (RR 0.78; 95% CI 0.56 to 1.08). There were fewer infusion-related reactions to AmBisome (Table 1).

Amphotericin B in Intralipid versus conventional amphotericin B (6 trials, 379 patients)

There were no significant differences in clinical effect whereas the patients treated with the lipid soluble formulation experienced significantly less nephrotoxicity (RR 0.44; 95% CI 0.24 to 0.81) and smaller increases in serum creatinine (weighted mean difference 19 µmol/l, 95% CI 5 to 34 µmol/l). In one of the studies (Schöffski 1998), nephrotoxicity was not defined as a 100% increase in serum creatinine but as the numbers of patients with severe renal dysfunction. Two studies reported on renal dysfunction after therapy. In one, two patients in the lipid formulated amphotericin B group and one patient in the amphotericin B group underwent haemodialysis (Schöffski 1998); in the other, one patient had a high serum creatinine (250 µmol/l) eight months after amphotericin B therapy (Moreau 1992). There were fewer infusion-related reactions with the lipid formulation but more cases of severe dyspnoea (Table 1).

Amphotericin B colloidal dispersion (ABCD) versus conventional amphotericin B (2 trials, 262 patients)

There were no significant differences in clinical effect whereas the patients treated with ABCD experienced significantly less nephrotoxicity (RR 0.35; 0.23 to 0.53). There were more infusion-related reactions and more cases of hypoxic events with ABCD (Table 1).

Amphotericin B lipid complex (ABLC) versus conventional amphotericin B (1 trial, 105 patients)

There were no significant differences in clinical effect whereas the patients treated with ABLC experienced significantly less nephrotoxicity (RR 0.25; 95% CI 0.09 to 0.70) and fewer dropouts (RR 0.21; 95% CI 0.05 to 0.89). There was a tendency for fewer infusion-related reactions with ABLC (Table 1).

DISCUSSION

All of the four different lipid soluble formulations of amphotericin B were associated with less nephrotoxicity than conventional amphotericin B. These results were seen even though the dose of AmBisome was two to five times higher than that for conventional amphotericin B, and for a trial in which the dose of ABCD was five times higher (Sandler 2000). The studies were generally small, and it could therefore not be ascertained with certainty whether the higher doses of the individual drugs also led to better clinical effect, although the summary estimate suggested that this might be the case at least for some of them. We reported only on nephrotoxicity but AmBisome was also better tolerated with respect to other well-known adverse effects of amphotericin B. For example, in the only double-blind trial that compared the two drugs, the percentage of patients with an adverse reaction after the first infusion was 17% versus 44% for infusion-related fever and 18% versus 54% for chills (Walsh 1999). The clinical importance of these differences

is less clear, however. Premedication for prevention of infusion-related toxicity was not permitted before the first infusion and when all infusions were considered together 38% versus 74% of the patients had chills (Walsh 1999). Thus, after the first infusion an additional 20% of the patients had chills in both groups, which suggests that the occurrence of chills might have been more similar if premedication had been allowed before all infusions. The relevance of equating a doubling in serum creatinine with nephrotoxicity is also not clear, and conventional amphotericin B was rarely given under optimal conditions (see below). It may be necessary to reduce the dosage of drugs which are excreted by the kidneys but no cases of renal failure were reported in the AmBisome trials and the nephrotoxicity seems to be reversible.

The authors of one of the Intralipid studies reported that pulmonary events, such as acute respiratory distress, were significantly more common in the Intralipid group and suggested that this could be due to fat overload or chemical incompatibility (Schöffski 1998). This observation is in the opposite direction to that of the biggest AmBisome study (Walsh 1999) where hypoxia occurred significantly less often (1 versus 22 cases) among patients receiving AmBisome. The clinical relevance of this finding is doubtful, however, as the hypoxia was predominantly diagnosed by pulse oximetry and not by clinical symptoms. The two published trials with ABCD reported more chills and fever, and in one more clinical hypoxia, on this drug than on conventional amphotericin B (Sandler 2000; White 1998). Another multicentre trial of ABCD was stopped prematurely by the company despite objections from the investigators; data from one of the centres showed no differences in clinical effect, nephrotoxicity, or chills (Winston 1999). We excluded a fourth trial of ABCD as only 50% of the patients had cancer. This trial had considerable statistical power as it was a treatment trial in 231 patients with haematogenous and invasive candidiasis but it has only been published as an abstract (Anaissie 1995). There were no differences in clinical effect or adverse effects apart from less nephrotoxicity with ABCD. In the ABLC study there was no difference in infusion-related adverse events; one patient in the conventional amphotericin B group required haemodialysis (Subira 2004).

Amphotericin B is an old drug but because of its broad antimycotic activity it is still widely regarded as the drug of choice for treatment of life-threatening mycoses (Viscoli 1997), and as empirical therapy in febrile patients with neutropenia (Hughes 1997). The present meta-analysis, like the previous ones, renders support for this practice. In a meta-analysis of the placebo controlled trials of antifungal agents, intravenous amphotericin B was the only antifungal agent that reduced total mortality (Gøtzsche 1997; Gøtzsche 2002). It should be noted, however, that most of the trials were small, both in our review of the placebo controlled trials and in the present review. Survival estimates in small trials in cancer patients are often biased (Berlin 1989); furthermore, bias in reporting of mortality differences can occur when trials have no formal stopping rules or when the length of follow-up was not determined in advance. One of the AmBisome trials illustrates the importance of length of follow-up (Leenders 1998). An unpublished company trial report noted 5 versus 6 deaths during the study and 21 versus 19 deaths in total among its 109 patients. The published version of this trial is more favourable for AmBisome than the company report as it notes 7 versus 13 deaths based on a subsample of only 66 patients. Because of the uncertainty, we included the lowest number of deaths in our analysis as we did not find it reasonable to give this trial the same weight as the two

larger AmBisome trials. Taken together, the results of the present review and those of the review of the placebo controlled trials show that amphotericin B decreases mortality. It would be interesting to analyse the numbers of deaths after extended follow-up, for example one and three months after randomisation, for all the studies that compare higher doses of amphotericin B with lower doses, preferably in an individual patient data meta-analysis. The study by Walsh, for example, reported the number of deaths after only seven days, despite the fact that many of the patients were neutropenic and therefore at risk of dying from a fungal infection, and under treatment with trial drug for much longer. The median follow-up in the placebo controlled trials of antifungal agents was much longer (Gøtzsche 1997; Gøtzsche 2002) and in the three other AmBisome trials it was 30 days (Prentice 1997), 42 days (Leenders 1998), and 49 days (Jadhav 2012), respectively.

The studies we reviewed indicate that some lipid soluble formulations of amphotericin B may be better drugs than conventional amphotericin B but there are two important caveats. First, is the benefit worth the extra cost? The high costs prohibit routine use in most settings. Second, it is not clear whether there are any advantages of AmBisome if conventional amphotericin B is administered under optimal circumstances. We noted above that one of the large trials of AmBisome did not use effective premedication and the drugs seem not to have been infused slowly. Infusion-related toxicity could possibly be reduced by infusing conventional amphotericin B over 4 hours (Ellis 1992), and further reduced if the infusion-time is 24 hours (Eriksson 2001; Imhof 2003). It is also important to supplement the therapy with fluid, potassium, and magnesium to prevent nephrotoxicity. It is remarkable that in a study where 32 patients received sufficient substitution to cover the losses induced by a mean dose of amphotericin B of 0.9 mg/kg/d over 20 days no increase in serum creatinine was observed (Mayer 1999). And in one of the trials in the present review, where potassium supplementation was used, only one patient out of 78 on conventional amphotericin B experienced a doubling of serum creatinine (Nath 1999). Furthermore, the chosen doses in the reviewed trials can be discussed. Conventional amphotericin B has been given in similarly high doses as those used for AmBisome (2 to 5 mg/kg/d) (Hiddemann 1991), and the trial by Walsh et al (Walsh 1999) has been criticised for using only 0.6 mg/kg/d of conventional amphotericin B (Fischer 1999). Conversely, it is possible that AmBisome could be given in smaller doses than those used in the trials we reviewed without loss of effect. In one of the studies we included in our review (Prentice 1997) the patients on AmBisome were randomised to 1 or 3 mg/kg/d (118 patients in both groups) and there was a similar clinical effect. In an EORTC study of patients with invasive Aspergillosis, a partial or complete clinical response was obtained in 26 patients randomised to 1 mg AmBisome and in 22 patients receiving 4 mg (Ellis 1998). In a third study of Aspergillosis, the clinical effect was similar for AmBisome 3 mg/kg/d (107 patients) as for 10 mg/kg/d (94 patients) (Cornely 2007). It would be interesting to compare lipid formulations of amphotericin B with conventional amphotericin B in the same doses and with optimal conditions for the use of amphotericin B.

AUTHORS' CONCLUSIONS

Implications for practice

Some lipid soluble formulations of amphotericin B may be better drugs than conventional amphotericin B but their high cost prohibits routine use in most settings. Furthermore, it is not

clear whether there are any advantages of these formulations if conventional amphotericin B is administered under optimal circumstances.

Implications for research

There is a need for large trials comparing lipid formulations of amphotericin B with conventional amphotericin B given in the same dose, with routine premedication for prevention of infusion-related toxicity, and with supplementation with fluid, potassium, and magnesium for prevention of nephrotoxicity.

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REFERENCES

References to studies included in this review

Caillot 1994 {published and unpublished data}

- * Caillot D, Reny G, Solary E, Casasnovas O, Chavanet P, Bonnotte B. A controlled trial of the tolerance of amphotericin B infused in dextrose or in Intralipid in patients with haematological malignancies. *Journal of Antimicrobial Chemotherapy* 1994;**33**(3):603-13.

Jadhav 2012 {published data only}

- * Jadhav MP, Shinde VM, Chandrakala S, et al. A randomized comparative trial evaluating the safety and efficacy of liposomal amphotericin B (Fungisome) versus conventional amphotericin B in the empirical treatment of febrile neutropenia in India. *Indian Journal of Cancer* 2012;**49**:107-13.

Leenders 1998 {published and unpublished data}

- * Leenders AC, Daenen S, Jansen RL, Hop WC, Lowenberg B, Wijermans PW. Liposomal amphotericin B compared with amphotericin B deoxycholate in the treatment of documented and suspected neutropenia-associated invasive fungal infections. *British Journal of Haematology* 1998;**103**(1):205-12.

Leenders ACAP, Daenen S, Jansen R, Hop WCJ, Löwenberg B, Wijermans PW, et al. Ambisome compared with amphotericin B deoxycholate in the treatment of neutropenia-associated invasive fungal infections. The Tenth International Symposium on Infections in the Immunocompromised Host. Davos, Switzerland, 21-24 June 1998. International Immunocompromised Host Society. 1998:Abstract 100.

Leenders ACAP, Daenen S, Jansen RHL, Hop WCJ, Löwenberg B, Cornelissen J, et al. Liposomal amphotericin B (AmBisome) compared with amphotericin B in the treatment of neutropenia-associated invasive fungal infections. Trends in Invasive Fungal Infections 4. Final Programme and Abstract Book, November 5-8, 1997, Barcelona, Spain. 1997:54 (P-6).

Leenders ACAP, Daenen S, Schouten H, Lelie J, Herbrecht R, Hop WCJ, et al. AmBisome 5 mg/kg versus conventional amphotericin B (AmB) 1 mg/kg in the treatment of neutropenia associated invasive aspergillosis. *Clinical Microbiology and Infection* 1997;**3 Suppl 2**:336 (P1356).

Moreau 1992 {published data only}

- * Moreau P, Milpied N, Fayette N, Ramee JF, Harousseau JL. Reduced renal toxicity and improved clinical tolerance of amphotericin B mixed with intralipid compared with conventional amphotericin B in neutropenic patients [see comments]. *Journal of Antimicrobial Chemotherapy* 1992;**30**(4):535-41.

Moreau P, Milpied N, Fayette N, Ramée JF, Casassus P, Harousseau JL. Amphotericin B mixed with IntralipidR: reduction of nephrotoxicity in neutropenic patients. Proceedings of the Annual Meeting of the American Society of Clinical Oncology. 1992; Vol. 11:380 (abstract 1319).

Nath 1999 {published and unpublished data}

- * Nath CE, Shaw PJ, Gunning R, McLachlan AJ, Earl JW. Amphotericin B in children with malignant disease: a comparison of the toxicities and pharmacokinetics of amphotericin B administered in dextrose versus lipid emulsion. *Antimicrobial Agents and Chemotherapy* 1999;**43**(6):1417-23.

Nucci 1999 {published and unpublished data}

- * Nucci M, Loureiro M, Silveira F, Casali AR, Bouzas LF, Velasco E. Comparison of the toxicity of amphotericin B in 5% dextrose with that of amphotericin B in fat emulsion in a randomized trial with cancer patients. *Antimicrobial Agents and Chemotherapy* 1999;**43**(6):1445-8.

Pascual 1995 {published data only}

- * Pascual B, Ayestaran A, Montoro JB, Oliveras J, Estibalez A, Julia A. Administration of lipid-emulsion versus conventional amphotericin B in patients with neutropenia. *Annals of Pharmacotherapy* 1995;**29**(12):1197-201.

Prentice 1997 {published data only}

- * Prentice HG, Hann IM, Herbrecht R, Aoun M, Kvaloy S, Catovsky D. A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. *British Journal of Haematology* 1997;**98**(3):711-8.

Sandler 2000 {published data only}

- * Sandler ES, Mustafa MM, Tkaczewski I, Graham ML, Morrison VA, Green M. Use of amphotericin B colloidal dispersion in children. *Journal of Pediatric Hematology/Oncology* 2000;**22**(3):242-6.

Schöffski 1998 {published data only}

- * Schoffski P, Freund M, Wunder R, Petersen D, Kohne CH, Hecker H. Safety and toxicity of amphotericin B in glucose 5% or intralipid 20% in neutropenic patients with pneumonia or fever of unknown origin: randomised study. *BMJ* 1998;**317**(7155):379-84.

Schöffski P, Freund M, Wunder R, Petersen D, Ganser A. No evidence of improved toxicity of amphotericin B in intralipid: results of a confirmatory randomized phase II-trial. *Clinical Microbiology and Infection. Abstracts of 8th European Congress of Clinical Microbiology and Infectious Diseases. May 25-28, 1997, Lausanne, Switzerland.* 1997;**3 Suppl 2**:305 (P1237).

Subira 2004 {published data only}

- * Subira M, Martino R, Gomez L, Marti JM, Estany C, Sierra J. Low-dose amphotericin B lipid complex versus conventional amphotericin B for empirical antifungal therapy of neutropenic fever in patients with hematologic malignancies - a randomized, controlled trial. *European Journal of Haematology* 2004;**72**(5):342-7.

Walsh 1999 {published data only}

- Cagnoni PJ. Liposomal amphotericin B versus conventional amphotericin B in the empirical treatment of persistently febrile

neutropenic patients. *Journal of Antimicrobial Chemotherapy* 2002;**49** Suppl 1:81-6.

Cagnoni PJ, Walsh TJ, Prendergast MM, Bodensteiner D, Hiemenz S, Greenberg RN. Pharmacoeconomic analysis of liposomal amphotericin B versus conventional amphotericin B in the empirical treatment of persistently febrile neutropenic patients. *Journal of Clinical Oncology* 2000;**18**:2476-83.

Walsh T, Bodensteiner D, Hiemenz J, Thaler S, Greenberg R, Arndt C. A randomized, double-blind trial of ambisome (liposomal amphotericin B) versus amphotericin B in the empirical treatment of persistently febrile neutropenic patients. *Annals of Hematology* 1999;**78** Suppl 1:S3 (abstract 10).

Walsh TJ, Bodensteiner D, Hiemenz J, Thaler S, Greenberg RN, Arndt C et al The mycoses study group (MSG) and the empirical antifungal study group. A randomised, double-blind trial of AmBisome (liposomal amphotericin B) versus amphotericin B in the empirical treatment of persistently febrile neutropenic patients. Abstracts in Clinical Trials of Antimicrobials & Unique and Instructive Clinical Observations. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy 1997, September 28-October 1, Toronto, Canada. 381 (Poster LM-90).

* Walsh TJ, Finberg RW, Arndt C, Hiemenz J, Schwartz C, Bodensteiner D. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *The New England Journal of Medicine* 1999;**340**(10):764-71.

White 1998 {published data only}

* White MH, Bowden RA, Sandler ES, Graham ML, Noskin GA, Wingard JR. Randomized, double-blind clinical trial of amphotericin B colloidal dispersion vs. amphotericin B in the empirical treatment of fever and neutropenia. *Clinical Infectious Diseases* 1998;**27**(2):296-302.

References to studies excluded from this review

Anaissie 1995 {published data only}

* Anaissie EJ, White M, Uzun O. Amphotericin B lipid complex (ABLC) versus amphotericin B (AMB) for treatment of hematogenous and invasive candidiasis: a prospective, randomized, multicenter trial. 35th Interscience Conference on Antimicrobial Agents and Chemotherapy. 1995:330 (LM21).

Bowden 2002 {published data only}

Bowden R, Chandrasekar P, White M, van Burik J-A, Wingard J. The Multicenter Aspergillus Study Group. A double-blind, randomized controlled trial of Amphocil (ABCD) versus amphotericin B (AmB) for treatment of invasive aspergillosis in immunocompromised patients. The Tenth International Symposium on Infections in the Immunocompromised Host. Davos, Switzerland, 21-24 June 1998. International Immunocompromised Host Society. 1998:Abstract 091.

Bowden R, Chandrasekar P, White MH, Li X, Pietrelli L, Gurwith M, et al. A double-blind, randomized, controlled trial of amphotericin B colloidal dispersion versus amphotericin B

for treatment of invasive aspergillosis in immunocompromised patients. *Clinical Infectious Diseases* 2002;**35**(4):359-66.

Richard 1999 {published data only}

Richard J. Ambisome treatment for empiric treatment of fungal infections in haematology. Trends in invasive fungal infections 5, Malta, 14-16 October. 1999:128 (P6.08).

Uhlenbrock 2001 {published data only}

Uhlenbrock S, Zimmermann M, Fegeler W, Jurgens H, Ritter J. Liposomal amphotericin B for prophylaxis of invasive fungal infections in high-risk paediatric patients with chemotherapy-related neutropenia: interim analysis of a prospective study. *Mycoses* 2001;**44**(11-12):455-63.

Winston 1999 {unpublished data only}

Winston DW, Schiller GJ, Territo MC. Liposomal amphotericin B for fever and neutropenia (letter). *The New England Journal of Medicine* 1999;**341**:1154.

Zoubek 1992 {published data only}

* Zoubek A, Emminger W, Emminger Schmidmeier W, Peters C, Pracher E, Grois N. Conventional versus liposomal amphotericin B in immunosuppressed children [letter]. *Pediatric Hematology and Oncology* 1992;**9**(2):187-90.

Additional references

Berlin 1989

Berlin JA, Begg CB, Louis TA. An assessment of publication bias using a sample of published clinical trials. *Journal of the American Statistical Association* 1989;**84**:381-92.

Cornely 2007

Cornely OA, Maertens J, Bresnik M, Ebrahimi R, Ullmann AJ, Bouza E, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). *Clinical Infectious Diseases* 2007;**44**(10):1289-97.

Due 2006

Due AK, Johansen HK, Gøtzsche PC. Fungal infection-related mortality versus total mortality as an outcome in trials of antifungal agents. *BMC Medical Research Methodology* 2006;**6**:40.

Edwards 1997

Edwards JE, Bodey GB, Bowden RA, Büchner T, de Pauw BE, Filler SG. International conference for the development of a consensus on the management and prevention of severe candidal infections. *Clinical Infectious Diseases* 1997;**25**:43-59.

Ellis 1992

Ellis ME, al-Hokail AA, Clink HM, Padmos MA, Ernst P, Spence DG. Double-blind randomized study of the effect of infusion rates on toxicity of amphotericin B. *Antimicrobial Agents and Chemotherapy* 1992;**36**:172-9.

Ellis 1998

Ellis M, Spence D, de Pauw B. An EORTC international multicenter randomized trial (EORTC number 19923) comparing two dosages of liposomal amphotericin B for treatment of invasive aspergillosis. *Clinical Infectious Diseases* 1998;**27**:1406-12.

Eriksson 2001

Eriksson U, Seifert B, Schaffner A. Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial. *BMJ* 2001;**322**(7286):579-82.

Fischer 1999

Fischer T, Heubel G, Huber C. Liposomal amphotericin B for fever and neutropenia (letter). *The New England Journal of Medicine* 1999;**341**:1152.

Gøtzsche 1997

Gøtzsche PC, Johansen HK. Meta-analysis of prophylactic or empirical antifungal treatment versus placebo or no treatment in patients with cancer complicated by neutropenia. *BMJ* 1997;**314**:1238-44.

Gøtzsche 2002

Gøtzsche PC, Johansen HK. Routine versus selective antifungal administration for control of fungal infections in patients with cancer. *Cochrane Database of Systematic Reviews* 2002, Issue 2. [DOI: [10.1002/14651858.CD000026](https://doi.org/10.1002/14651858.CD000026)]

Hiddemann 1991

Hiddemann W, Essink ME, Fegeler W, Zuhlsdorf M, Sauerland C, Buchner T. Antifungal treatment by amphotericin B and 5-fluorocytosine delays the recovery of normal hematopoietic cells after intensive cytostatic therapy for acute myeloid leukemia. *Cancer* 1991;**68**:9-14.

Hughes 1997

Hughes WT, Armstrong D, Bodey GP. 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Infectious Diseases Society of America. *Clinical Infectious Diseases* 1997;**25**:551-73.

Imhof 2003

Imhof A, Walter RB, Schaffner A. Continuous infusion of escalated doses of amphotericin B deoxycholate: an open-label observational study. *Clinical Infectious Diseases* 2003;**36**:943-51.

Mayer 1999

Mayer J, Doubek M, Vorlicek J. Must we really fear toxicity of conventional amphotericin B in oncological patients?. *Support Care Cancer* 1999;**7**(1):51-5.

Richardson 1998

Richardson MD, Kokki MH. Antifungal therapy in "bone marrow failure". *British Journal of Haematology* 1998;**100**:619-28.

Tang 1997

Tang CM, Bowler ICJW. Do the new lipid formulations of amphotericin B really work?. *Clinical Microbiology and Infection* 1997;**3**:283-8.

Viscoli 1997

Viscoli C, Castagnola E, Machetti M. Antifungal treatment in patients with cancer. *Journal of Internal Medicine* 1997;**242** Suppl 740:89-94.

References to other published versions of this review

Johansen 2000

Johansen HK, Gøtzsche PC. Amphotericin B lipid soluble formulations versus amphotericin B in cancer patients with neutropenia. *Cochrane Database of Systematic Reviews* 2000, Issue 1. [DOI: [10.1002/14651858.CD000969](https://doi.org/10.1002/14651858.CD000969)]

Johansen 2002a

Johansen HK, Gøtzsche PC. Amphotericin B lipid soluble formulations vs amphotericin B in cancer patients with neutropenia. *Cochrane Database of Systematic Reviews* 2002, Issue 2. [DOI: [10.1002/14651858.CD000969](https://doi.org/10.1002/14651858.CD000969)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Caillot 1994

Methods	Allocation concealment: random table, opaque envelopes Blinding of study: none
Participants	42 patients with AL Excluded: NA
Interventions	Experimental: amphotericin B + 20% intralipid 1.0 to 1.1 mg/kg/d as a 2 hour infusion Control: amphotericin B same dose Premedication to prevent infusion-related toxicity was not used Empiric
Outcomes	Deaths Infections

Amphotericin B lipid soluble formulations versus amphotericin B in cancer patients with neutropenia (Review)

Caillot 1994 (Continued)

Dropouts
Nephrotoxicity
Serum creatinine

Notes
Follow-up period (days): 30
Days on amphotericin B + 20% intralipid: 12.8
Days on amphotericin B: 8.4
All got nystatin or fluconazole prophylactically

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	

Jadhav 2012

Methods	Computer generated central randomisation list, blocks of 6, sealed envelopes. No blinding
Participants	65 patients with AL Excluded: 8
Interventions	Experimental: liposomal amphotericin B (Fungisome) at either 1 or 3 mg/kg/d as a 2 hour infusion (2 groups) Control: amphotericin B 1 mg/kg/d Premedication to prevent infusion-related toxicity was not used on the first day Empiric
Outcomes	Primary outcome: "Investigator assessment of overall treatment success" (criteria for this were stated) Fever resolution
Notes	This trial was heavily biased. A test dose of 1 ml was used for Fungisome but not for amphotericin B, no premedication was used for amphotericin B, and in one of the Fungisome groups, the dose was three times as large as for amphotericin B. The trial was seriously underpowered, with a one-sided alpha of 0.20 and beta also of 0.20. It was planned to randomise 150 patients, but only 65 were enrolled. There were no data on mycology Follow-up period (days): 49 Days on Fungisome: 17 Days on amphotericin B: 15

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding (performance bias and detection bias)	High risk	No blinding

Amphotericin B lipid soluble formulations versus amphotericin B in cancer patients with neutropenia (Review)

Jadhav 2012 (Continued)

All outcomes

Leenders 1998

Methods	Allocation concealment: sealed envelopes Blinding of study: none
Participants	109 patients with neutropenia Excluded: 43, 40 of which did not have fungal infection (20 were randomised to AmBisome, 20 to amphotericin B). We included those patients after obtaining information from the author and the company
Interventions	Experimental: AmBisome 5 mg/kg/d as infusion Control: amphotericin B 1 mg/kg/d as infusion over 6 h; premedication to prevent infusion-related toxicity was allowed Mainly empiric (only 26 patients had documented infection)
Outcomes	Deaths Dropouts Nephrotoxicity
Notes	Follow-up period (days): 42 Days on AmBisome: 14.5 Days on amphotericin B: 16.5

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	

Moreau 1992

Methods	Allocation concealment: NA Blinding: none
Participants	32 patients with AL Excluded: 0
Interventions	Experimental: amphotericin B + 20% Intralipid 0.7-1.0 mg/kg/d as a 4 hour infusion Control: amphotericin B same dose Premedication to prevent infusion-related toxicity was routine Empiric
Outcomes	Infections Nephrotoxicity Serum creatinine
Notes	Follow-up period (days): NA

Amphotericin B lipid soluble formulations versus amphotericin B in cancer patients with neutropenia (Review)

Moreau 1992 (Continued)

Days on amphotericin B + 20% Intralipid: 18
Days on amphotericin B: 11

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	

Nath 1999

Methods	Allocation concealment: consecutively numbered, sealed and opaque envelopes. Computer generated random numbers Blinding: none
Participants	130 children, mostly with AL (162 courses; 20 versus 12 patients were entered into the study a second time) Excluded: 0
Interventions	Experimental: amphotericin B + 20% intralipid 1.0 mg/kg/d as a 2 hour infusion Control: amphotericin B, same dose Premedication: hydrocortisone, 3 mg/kg Potassium supplements were given to maintain serum level above 3 mmol/l. Empiric
Outcomes	Deaths Infections Nephrotoxicity Serum creatinine
Notes	Follow-up period (days): NA Days on amphotericin B + 20% Intralipid: 6.9 Days on amphotericin B: 6.3 Only two cases of nephrotoxicity (doubling of serum creatinine from baseline)

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	

Nucci 1999

Methods	Allocation concealment: sealed envelopes Blinding: none
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Nucci 1999 (Continued)

Participants	72 patients with AL Excluded: 11
Interventions	Experimental: amphotericin B + 20% intralipid 1.0 mg/kg/d as a 1 hour infusion Control: amphotericin B, same dose Premedication only in control group: promethazine plus antipyretic Empiric in 49 patients, treatment in 11 and secondary prophylaxis in one
Outcomes	Infections Nephrotoxicity Serum creatinine
Notes	Follow-up period: one week after stop treatment Days on amphotericin B + 20% Intralipid: 7.5 Days on amphotericin B: 9 Fungal invasive infections as defined by authors, not specified by species or location. Not clear how many infections there were at follow-up. Data not useable for our meta-analysis

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	

Pascual 1995

Methods	Allocation concealment: NA Blinding: none
Participants	20 patients with AL Excluded: NA
Interventions	Experimental: amphotericin B + 20% Intralipid 1.0 mg/kg/d as a one hour infusion Control: amphotericin B 0.1 mg/kg/d as a one hour infusion Premedication to prevent infusion-related toxicity was not used Empiric
Outcomes	Serum creatinine
Notes	Follow-up period: NA Days on amphotericin B + 20% Intralipid: 7.0 Days on amphotericin B: 7.4

Risk of bias

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

Pascual 1995 (Continued)

Blinding (performance bias and detection bias)
All outcomes

High risk

Prentice 1997

Methods	Allocation concealment: central randomisation, blinded, numbered envelopes Blinding: none
Participants	338 patients with AL (204 were children) Excluded: 3
Interventions	Experimental: AmBisome 1 mg/kg/d to 118 patients and 3 mg/kg/d to 118 patients, as infusion Control: amphotericin B 1 mg/kg/d as infusion to 102 patients; gradual dose increase and premedication to prevent infusion-related toxicity was allowed Empiric
Outcomes	Deaths Infections Nephrotoxicity
Notes	Follow-up period (days): 30 Days on drugs: till neutrophil count above 0.5×10^9 /l for 3 days

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	

Sandler 2000

Methods	Allocation concealment: NA Blinding: double-blind
Participants	49 children undergoing BMT Excluded: 3
Interventions	Experimental: amphotericin B colloidal dispersion (ABCD) 4 mg/kg/d as infusion Control: amphotericin B 0.8 mg/kg/d as infusion Premedication: according to investigator's preference Empiric
Outcomes	Deaths Infections Nephrotoxicity
Notes	Follow-up period: 7 days after last dose of trial drug Days on ABCD: 9.6

Amphotericin B lipid soluble formulations versus amphotericin B in cancer patients with neutropenia (Review)

Sandler 2000 (Continued)

Days on amphotericin B: 8.5
Sponsored by SEQUUS Pharmaceutical
No data on mortality: "No drug-related mortality was seen"

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	

Schöffski 1998

Methods	Allocation concealment: NA Blinding: none
Participants	51 patients with AL Excluded: NA
Interventions	Experimental: amphotericin B + 20% Intralipid 0.75 mg/kg/d as a 1-4 hour infusion Control: amphotericin B 0.75 mg/kg/d as a 1-4 hour infusion Premedication to prevent infusion-related toxicity was not used Empiric
Outcomes	Deaths Nephrotoxicity Serum creatinine
Notes	Follow-up period (days): NA Days on amphotericin B + 20% Intralipid: 9.9 Days on amphotericin B: 11.3 Nephrotoxicity was not defined. Two patients on amphotericin B + Intralipid and one on amphotericin B underwent haemodialysis

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	

Subira 2004

Methods	Allocation concealment: blinded numbered envelopes, sequential opening Blinding: none
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Subira 2004 (Continued)

Participants	105 patients with AL Excluded: 9
Interventions	Experimental: amphotericin B lipid complex (ABLC) 1 mg/kg/d as a 2 hour infusion. Control: amphotericin B 0.6 mg/kg/d as a 6 hour infusion. Premedication in all cases
Outcomes	Deaths Nephrotoxicity Dropouts Infections
Notes	Follow-up period (days): NA. Days on amphotericin B lipid complex (ABLC): 8 Days on amphotericin B: 6

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	

Walsh 1999

Methods	Allocation concealment: central randomisation Blinding: double-blind
Participants	702 patients with AL Excluded: 15
Interventions	Experimental: AmBisome 3 mg/kg/d as infusion Control: amphotericin B 0.6 mg/kg/d as infusion; premedication to prevent infusion-related toxicity was allowed after the first infusion Empiric
Outcomes	Deaths Infections Dropouts Nephrotoxicity
Notes	Follow-up period (days): 7 Days on AmBisome: 10.8 Days on amphotericin B: 10.3

Risk of bias

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

Amphotericin B lipid soluble formulations versus amphotericin B in cancer patients with neutropenia (Review)

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Walsh 1999 (Continued)

All outcomes

White 1998

Methods	Allocation concealment: NA Blinding: double-blind
Participants	213 patients undergoing BMT Excluded: 20
Interventions	Experimental: Amphotec (ABCD, amphotericin B cholesteryl sulfate complex) 4.0 mg/kg/d as infusion Control: amphotericin B 0.8 mg/kg/d as infusion Premedication to prevent infusion-related toxicity was routine Empiric
Outcomes	Deaths Infections Dropouts Nephrotoxicity
Notes	Follow-up period (days): 28 Days on Amphotec: 9 Days on amphotericin B: 7.5

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	

AL: acute leukaemia
BMT: bone marrow transplantation
NA: not available

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Anaissie 1995	Only 50% of patients had cancer, unpublished trial. Treatment of invasive candidiasis, 153 patients received amphotericin B lipid complex (ABLC), 5 mg/kg/d, and 78 amphotericin B, 0.6 to 1.0 mg/kg/d. Response rates 63% versus 68%; more cases with doubling of baseline creatinine with conventional amphotericin B, 28% versus 47% (P value 0.007)
Bowden 2002	More than two-thirds of the patients did not have neutropenia. Trial of 174 patients that compared amphotericin B colloidal dispersion, 6 mg/kg/d, with amphotericin B, 1.0 to 1.5 mg/kg/d. Response rates 52% versus 51%; more cases with nephrotoxicity (doubling of baseline creatinine, and similar) with conventional amphotericin B, 25% versus 49% (P value 0.002)

Study	Reason for exclusion
Richard 1999	Published as an abstract, no useful data. Empiric treatment with AmBisome (N = 19) or amphotericin B (N = 11)
Uhlenbrock 2001	Only 14 of the patients were randomised. For the other 15 patients, treatment was assigned according to the wishes of the parents, patients or physicians
Winston 1999	Multicentre trial that compared amphotericin B lipid complex (ABLC) with amphotericin B. Despite objections from the investigators, the trial was prematurely discontinued by the sponsor, the Lipo-some Company, Princeton, New Jersey. An analysis of the patients at the University of California, Los Angeles, showed no difference in clinical responses or in nephrotoxicity
Zoubeck 1992	Not an RCT (personnal communication with first author)

DATA AND ANALYSES

Comparison 1. Lipid-based amphotericin B versus standard amphotericin B

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	9	1742	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.64, 1.14]
1.1 AmBisome	4	1198	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.54, 1.10]
1.2 Intralipid	3	255	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.23, 1.59]
1.3 ABCD	1	193	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.61, 2.34]
1.4 ABLC	1	96	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.46, 7.16]
2 Death ascribed to fungal infection	7	1297	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.29, 1.09]
2.1 AmBisome	2	753	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.21, 0.92]
2.2 Intralipid	3	255	Risk Ratio (M-H, Fixed, 95% CI)	4.46 [0.22, 88.61]
2.3 ABCD	1	193	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.06, 15.28]
2.4 ABLC	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Invasive fungal infection	9	1711	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.44, 0.97]
3.1 AmBisome	3	1131	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.39, 1.01]
3.2 Intralipid	3	236	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.18, 1.22]
3.3 ABCD	2	239	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.28, 5.16]
3.4 ABLC	1	105	Risk Ratio (M-H, Fixed, 95% CI)	3.42 [0.14, 82.08]

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
4 Nephrotoxicity	11	1782	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.37, 0.54]
4.1 AmBisome	3	1110	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.40, 0.64]
4.2 Intralipid	5	328	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.24, 0.81]
4.3 ABCD	2	239	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.23, 0.53]
4.4 ABLC	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.09, 0.70]
5 Serum creatinine	6	303	Mean Difference (IV, Random, 95% CI)	-19.28 [-33.97, -4.60]
5.1 Intralipid	6	303	Mean Difference (IV, Random, 95% CI)	-19.28 [-33.97, -4.60]
6 Dropouts	6	1199	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.62, 0.97]
6.1 AmBisome	2	795	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.56, 1.08]
6.2 Intralipid	2	103	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.55]
6.3 ABCD	1	196	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.72, 1.38]
6.4 ABLC	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.05, 0.89]

Analysis 1.1. Comparison 1 Lipid-based amphotericin B versus standard amphotericin B, Outcome 1 Death.

Analysis 1.2. Comparison 1 Lipid-based amphotericin B versus standard amphotericin B, Outcome 2 Death ascribed to fungal infection.

Analysis 1.3. Comparison 1 Lipid-based amphotericin B versus standard amphotericin B, Outcome 3 Invasive fungal infection.

Analysis 1.4. Comparison 1 Lipid-based amphotericin B versus standard amphotericin B, Outcome 4 Nephrotoxicity.

Analysis 1.5. Comparison 1 Lipid-based amphotericin B versus standard amphotericin B, Outcome 5 Serum creatinine.

Analysis 1.6. Comparison 1 Lipid-based amphotericin B versus standard amphotericin B, Outcome 6 Dropouts.

ADDITIONAL TABLES

Table 1. Harms

Trial	Experimental drug	Control drug	Number of patients	Harms
Leenders 1998	AmBisome	Amphotericin B	52 versus 54	Chills/fever: 5 versus 12; Other acute reactions: 5 versus 3; Other clinical events and laboratory values similar
Prentice 1997	AmBisome	Amphotericin B	236 versus 102	Severe test-drug-related side-effects: 3 (encephalopathy, convulsions, hypokalaemia) versus 11 (7 renal toxicity, 2 rigors, rash and fever, 1 hypokalaemia, 1 dyspnoea); Clinical adverse events: 40% versus 64%
Walsh 1999	AmBisome	Amphotericin B	343 versus 344	Chills or rigors: 63 versus 187; Fever: 58 versus 150; Nausea: 42 versus 35; Vomiting: 21 versus 28; Hypotension: 12 versus 28
Caillot 1994	Amphotericin B + 20% Intralipid	Amphotericin B	21 versus 21	Chills: 5 versus 16
Moreau 1992	Amphotericin B + 20% Intralipid	Amphotericin B	16 versus 16	Rigors and fever: 5 versus 12
Nath 1999	Amphotericin B + 20% Intralipid	Amphotericin B	84 versus 78	Rigors or fever, or both: 21 versus 19

Table 1. Harms (Continued)

Nucci 1999	Amphotericin B + 20% Intralipid	Amphotericin B	28 versus 33	Fever: 19 versus 28; Rigors: 6% versus 33% of administrations; Hypotension: 1 versus 3
Pascual 1995	Amphotericin B + 20% Intralipid	Amphotericin B	10 versus 10	Fever: 3 versus 5; Chills: 7 versus 8; Nausea: 3 versus 4
Schöffski 1998	Amphotericin B + 20% Intralipid	Amphotericin B	27 versus 24	Severe dyspnoea: 11 versus 4 (see Discussion); Other harms: very detailed presentation, only minor differences
Sandler 2000	ABCD	Amphotericin B	25 versus 21	Data not reliable, eg 50.0% of 21 patients had chills on amphotericin B, which is 11.5 patients
White 1998	ABCD	Amphotericin B	109 versus 104	Chills: 87 versus 68; Hypoxic events: 16 versus 3
Subira 2004	ABLC	Amphotericin B	49 versus 56	Chills/rigors: 31 versus 33; Fever: 27 versus 37; Nausea/vomiting: 4 versus 7

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 1, 1998

Review first published: Issue 3, 2000

Date	Event	Description
7 July 2014	New citation required but conclusions have not changed	One new trial added, conclusions not changed
7 July 2014	New search has been performed	Literature searches re-run
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 in July 2011

Date	Event	Description
5 February 2008	New search has been performed	Minor update: Two new outcomes added in November 2007 (death ascribed to fungal infection and harms).
5 November 2007	New search has been performed	New studies found and included or excluded: Two new outcomes added in (death ascribed to fungal infection and harms).
30 September 2004	Amended	New studies found and included or excluded
3 April 2000	New search has been performed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

HKJ wrote the draft meta-analysis protocol, HKJ and PCG contributed equally to selection of trials, data extraction, and writing of the manuscript. Guarantors: both authors.

DECLARATIONS OF INTEREST

Helle Krogh Johansen - nothing to declare

Peter C Gøtzsche - nothing to declare

SOURCES OF SUPPORT

Internal sources

- Rigshospitalet, Denmark.

External sources

- JASCHA-fonden, Denmark.
- Nordic Council of Ministers, Denmark.
- Swedish Society of Medicine, Sweden.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Need for additional antifungal treatment was dropped because it was rarely reported; we have reported on dropouts instead and added harms. Also, we have added death ascribed to fungal infection as our research has shown that this outcome is reliable, contrary to our expectations ([Due 2006](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

Amphotericin B [chemistry] [therapeutic use]; Antifungal Agents [chemistry] [*therapeutic use]; Chemistry, Pharmaceutical; Neoplasms [*complications] [mortality]; Neutropenia [complications] [*drug therapy] [mortality]; Randomized Controlled Trials as Topic

MeSH check words

Humans