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Empirical antifungal therapy for patients with neutropenia and persistent fever: Systematic review and meta-analysis

Elad Goldberg[a,b,*], *Anat Gafter-Gvili*[b,c], *Eyal Robenshtok*[a,b], *Leonard Leibovici*[a,b], *Mical Paul*[b,d]

[a]*Department of Medicine E, Rabin Medical Center, Beilinson Campus, 49100 Petah-Tiqva, Israel*
[b]*Sackler School of Medicine, Tel Aviv University, Ramat Aviv, Israel*
[c]*Hematology Department, Rabin Medical Center, Beilinson Campus, Petah-Tiqva, Israel*
[d]*Infectious Disease Unit, Rabin Medical Center, Beilinson Campus, Petah-Tiqva, Israel*

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ABSTRACT

Objectives: To assess the evidence for the current standard of practice of using empirical antifungal treatment in febrile neutropenic cancer patients.

Methods: Systematic review and meta-analysis of randomised controlled trials comparing empirical or preemptive antifungal treatment with placebo, no intervention, or another antifungal. The primary outcomes were all-cause mortality and invasive fungal infections (IFI) (documented or probable). Relative risks (RR) with 95% confidence intervals (CI) were pooled.

Results: Six trials assessed the efficacy of empirical treatment compared to no treatment and one compared empirical to preemptive therapy. Empirical treatment did not decrease mortality significantly (RR 0.82, 95% CI 0.50–1.34), but significantly decreased IFIs (RR 0.25, 0.12–0.54). Twenty-three trials assessed the efficiency of different antifungals. All-cause mortality was lower with azoles compared to amphotericin B (AB) (RR 0.81, 0.65–1.01); IFI rates were not different while adverse events were less frequent with azoles (RR 0.40; 0.34–0.66). Liposomal AB was associated with lower mortality and IFIs than other AB formulations (RR 1.57, 1.10–2.23 and 1.48, 0.98–2.25, respectively). Caspofungin was associated with fewer adverse events, but otherwise comparable to liposomal AB. All trials included patients with haematological malignancies. Major limitations included per-protocol analysis, non-blinded design and inconsistent definitions of IFIs.

Conclusions: Empirical antifungal treatment is associated with a lower rate of IFIs but no significant difference in overall mortality. The assessment of IFIs in these trials may have been biased, offering only weak support to standard practice. Azoles, liposomal amphotericin B or caspofungin should be preferred. Pre-emptive antifungal therapy should be considered and further investigated.

* *Corresponding author:* Address: Department of Medicine E, Rabin Medical Center, Beilinson Campus, 49100 Petah-Tiqva, Israel. Tel.: +972 3 9376500/8; fax: +972 3 9376512.
E-mail addresses: eladgo@clalit.org.il, eladgol310@yahoo.com (E. Goldberg).
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1. Introduction

Administration of empirical antifungal therapy for persistent fever in neutropenic patients is standard practice.[1–3] As a result, as many as 40–50% of high-risk neutropenic patients receive empirical antifungal therapy.[4] The rationale for this approach is based on several reasons. The percentage of fungal infections in neutropenic patients with persistent fever is estimated at 15–45%.[4,5] We currently lack the ability to diagnose fungal infections early.[6,7]. In addition, evidence from previous studies demonstrates that withholding antifungal treatment until a definite diagnosis is established frequently leads to disseminated infection.[8,9] Finally, evidence from retrospective studies shows decreased mortality due to IFIs in patients receiving antifungal agents during periods of neutropenia and persistent fever when compared with historical control groups.[10,11]

Conflicting data concerning the efficacy of empirical antifungal treatment and of different agents as empiric treatment have been published.[12–16] Furthermore, the standard of care for cancer patients and the methods to diagnose and treat fungal infections have changed dramatically over the years. A new approach to the neutropenic patient with persistent fever is that of preemptive treatment directed by a combination of radiological tests and non-culture-based assays. This may allow us to treat only high-risk patients and avoid serious adverse reactions in other patients, but the available data on this approach are scarce.

A previous systematic review assessed empirical or prophylactic antifungal therapy combined.[16] Antifungals did not affect mortality and significantly reduced IFIs. In order to address the question of empirical treatment separately and expand the available data, we performed a systematic review and meta-analysis of randomised controlled trials assessing empirical or preemptive anti-fungal treatment for cancer patients with persistent fever and neutropenia.

2. Patients and methods

2.1. Data sources

We searched The Cochrane Cancer Network register of trials (current), CENTRAL (The Cochrane Library, Issue 3, 2007), EMBASE (January 1980 to October 2007), PubMed (January 1966 to October 2007) and conference proceedings in infectious diseases and haematology for the last 3 years. The terms '*neutropenia*' and similar, '*empiric*' and similar, '*persistent*' and similar, specific antifungals or '*antifungal*' and similar were searched. References of all identified studies were inspected for more trials.

2.2. Study selection

We attempted to identify all trials assessing empirical or preemptive antifungal treatment regimens. Thus, we included randomised controlled trials comparing different types of antifungals administered as empirical or preemptive therapy for neutropenic cancer patients with placebo, no intervention, preemptive treatment or with other antifungals. Neutropenia was defined as absolute neutrophil count < 500/mm^3 or < 1000/mm^3 and expected to decline to <500/mm^3. Empirical treatment was defined as that given non-selectively to all patients and preemptive treatment was defined as that administered selectively to patients with a positive diagnostic test (e.g. PCR, radiography, etc.) To delineate from the assessment of antifungal prophylaxis, both strategies had to begin with or after the onset of fever. In case the trial included patients with proven fungal infections, only the data concerning patients with persistent fever with no diagnosis were analysed. If data were not given separately, only trials in which 10% or less of the patients had a proven fungal infection were included. Trials were included irrespective of publication status, language and blinding.

Two reviewers independently inspected each reference identified by the search and applied inclusion criteria. For possibly relevant articles, or in cases of disagreement between the two reviewers, the full article was obtained and inspected independently by the two reviewers.

2.3. Comparisons

Since we included trials assessing all types of antifungals, we defined *a priori* the following comparisons for meta-analysis:

1. Empirical antifungal treatment versus placebo, no treatment or pre-emptive therapy (control), stratified by the type of antifungal agent and control.
2. Azoles versus amphotericin B-based preparations, stratified by the type of azole and polyene.
3. Different formulations of amphotericin B.
4. Echinocandins versus other antifungals, stratified by the comparator.

2.4. Data extraction and quality assessment

Two reviewers independently extracted data from included trials. In case of any disagreement between the two reviewers, a third reviewer extracted the data. Data extraction was discussed, decisions were documented and, where necessary, the authors of the trials were contacted for clarification and complementary information on their trials. Mortality data for Walsh 2002[17] were obtained from previous correspondence between the authors of a Cochrane review and the pharmaceutical company.[18]

Two reviewers independently assessed trials for methodological quality. We individually assessed the following methodological quality measures: allocation generation, concealment and blinding. We graded allocation generation as A (adequate: a random component in the sequence generation process), B (unclear: insufficient information about the sequence generation, or C (inadequate: a non-random component in the sequence generation process); and allocation concealment as A (adequate: enrollment could not be foreseen by participants or investigators), B (unclear: insufficient information about allocation concealment) or C (inadequate: enrollment could be foreseen by participants or investigators), using the definitions given in the Cochrane handbook.[19] Data were collected preferentially by intention to treat (ITT) and the type of analysis (ITT or per-protocol) and number of

exclusions after randomisation was recorded. We performed sensitivity analysis on allocation concealment for mortality.[20]

2.5. Outcomes

The primary outcome measures were all-cause mortality at the end of follow-up and invasive fungal infections (IFIs) (proven or probable) during the study period. IFIs were categorised as documented, probable or possible according to consensus criteria.[21] We assessed all IFIs occurring during the study, including baseline IFIs (documented within 48 h of randomisation) and breakthrough IFIs (occurring >48–72 h after randomisation). Secondary outcomes included treatment failure (a composite outcome) as defined in each study, fungal-related mortality, mould and yeast fungal infections, durations of fever and hospitalisation. We assessed all adverse events, those requiring treatment discontinuation, acute infusion-related events, nephrotoxicity and hypokalaemia. We attempted to extract primary outcome data for the subgroups of high-risk cancer patients, defined as those with acute leukaemia or allogeneic bone marrow transplantation and for patients receiving antifungal prophylaxis.

2.6. Data synthesis and analysis

Dichotomous data were analysed by calculating the relative risk (RR) for each trial with 95% confidence intervals (CI) (Review Manager [RevMan], version 4.2 for Windows, The Cochrane Collaboration, Oxford, UK). For the main outcome, all-cause mortality, we performed an ITT analysis in which we included all known events in both nominator and denominator, even if excluded from the trial's original analysis. We did not conduct full ITT analysis in trials that did not report ITT, since we could not input assumptions regarding the primary outcomes, mortality and IFIs. We assessed heterogeneity of trial results by calculating a chi-square test of heterogeneity and the I^2 measure of inconsistency.[22] We used a fixed-effect model by using the Mantel–Haenszel method for pooling trial results throughout the review unless statistically significant heterogeneity was found ($p<0.10$ or $I^2>50\%$), in which case we chose a random-effects model and used the DerSimonian and Laird method. Numbers needed to treat (NNT) were calculated as 1/pooled risk difference and given with the unadjusted control event rate (CER). Heterogeneity was investigated through subgroup and sensitivity analyses as defined above.

3. Results

The search yielded 865 potentially relevant studies of which 40 were considered for further evaluation. Ten studies were excluded;[23–31] reasons for exclusion are detailed in Fig. 1. Thirty trials fulfilled inclusion criteria and 6303 patients were evaluated in these trials. Six trials compared empirical antifungal treatment with placebo or no treatment,[12–15,32,33] one trial compared empirical versus pre-emptive therapy,[34] nine trials compared empirical treatment with amphotericin B versus azoles (fluconazole, ketoconazole or itraconazole),[35–43] one compared liposomal amphotericin to voriconazole,[17] 11 trials compared different polyenes[44–54] and two trials compared liposomal amphotericin versus caspofungin[55,56] (Table 1). All the trials included patients with haematological malignancies, and four trials [13,15,47,55] included patients with solid tumours as well. Ten trials reported the use of antifungal prophylaxis. Ten trials reported adequate allocation generation and ten reported adequate allocation concealment. Seven trials were double or triple-blinded and the remaining were open trials. ITT analysis was not performed in most of the trials.

Empirical antifungal treatment was initiated between 1–7 days following initiation of empirical anti-bacterial treatment in 21 trials. Two trials did not report the exact timing of treatment initiation. Our primary outcomes, all-cause mortality and IFIs, were reported separately in 22 trials and 21 trials, respectively. Other trials assessed a composite endpoint.

3.1. Antifungals versus no treatment/ placebo (seven trials, 1043 patients)

3.1.1. All-cause mortality

Six trials (955 patients) reported all-cause mortality. Empirical antifungal treatment did not decrease mortality compared with placebo, no treatment or pre-emptive treatment (RR 0.82 [95%CI 0.50–1.34]), with no heterogeneity, I^2 =0% (separate analyses shown in Fig. 2). Excluding the trial of empirical versus pre-emptive treatment [34] resulted in a smaller relative risk reduction (RR 0.93 [95% CI 0.55–1.58]). Excluding the two trials in which antifungal treatment was administered on the first day of fever[12,32] did not affect results, RR 0.94 [95% CI 0.52–1.71].

Trials reporting adequate allocation concealment and generation methods yielded a point estimate for all cause mortality (RR 0.52 [95% 0.16–1.70]) lower than trials reporting unclear or inadequate methods (RR 0.89 [95% CI 0.59–1.53]), but with wide confidence intervals and without reaching statistical significance.

3.1.2. Invasive fungal infections

Data from five trials (800 patients) demonstrated that empiric antifungal treatment significantly decreased IFIs (RR 0.25 [95% CI 0.12–0.54], Fig. 3); NNT to prevent one IFI 17 (95% CI 11–33). The CER was 7.7%, without a major difference between trials published between 1982 and 1994 (6.9%) and the preemptive trial published in 2006 (9.1%). This is based on a small number of events: eight events in the treatment group versus 31 in the control group. We extracted the onset time of IFI occurrence. In the control group, seven of the 14 IFIs reported with their time of onset occurred within 2 weeks of randomisation and seven occurred subsequently. In the treatment group, of three IFIs reported with timing, one occurred within 2 weeks of empirical therapy and two occurred subsequently.

3.1.3. Composite failure and secondary outcomes

Six trials (769 patients) reported a composite failure outcome, defined most commonly as persistence of fever, microbiological failure or breakthrough fungal infection, any discontinuation of the assigned antifungal agent and death during treatment. Failure was significantly lower with empiric treatment (RR 0.71 [95% CI 0.59–0.85], six trials). Fungal related

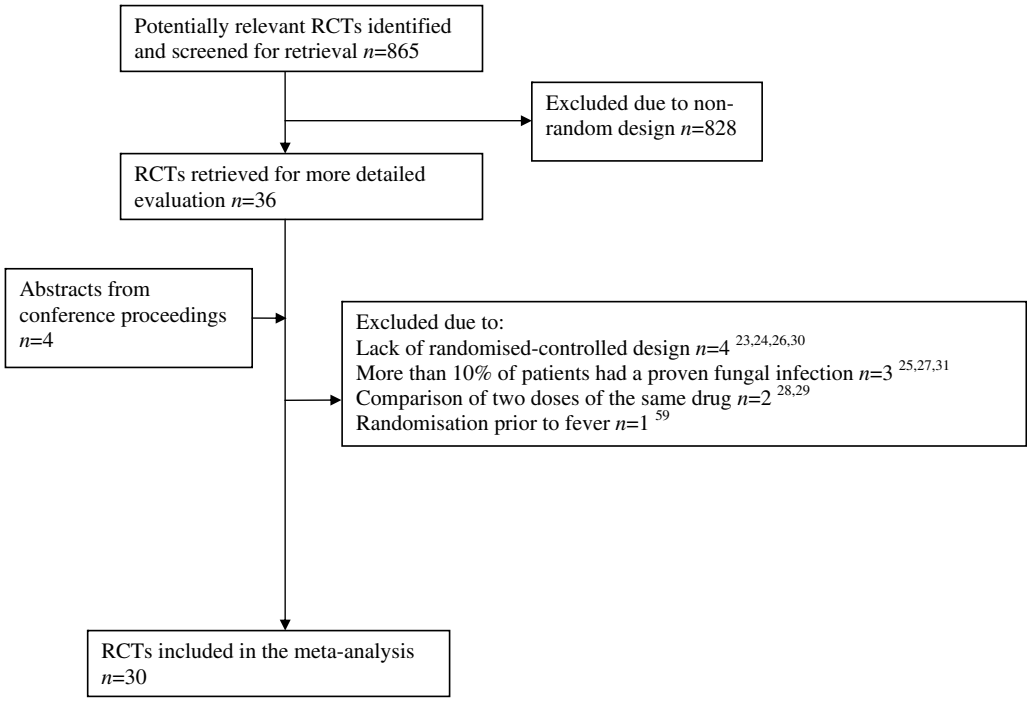

Fig. 1 – Trial flow, RCT – randomised controlled trial.

mortality was significantly lower in the empiric treatment group (RR 0.18 [95% CI 0.05–0.71], four trials); numbers needed to treat 33 patients (95% CI 17–100, CER 3.5%). Reductions in both mould (RR 0.58 [95% CI 0.14–2.30], three trials) and yeast infections (RR 0.19 [95% CI 0.05–0.73], three trials) were noted. Persistence of fever during neutropenia was reported in two trials only and favoured empirical treatment (RR 0.60 [95% CI 0.44–0.81]). Duration of hospitalisation was not reported in these trials.

3.1.4. *Adverse events*

There were non-significantly more adverse events in the treatment group when compared to placebo or no intervention, including nephrotoxicity (RR 1.76 [95% CI 0.58–5.30]) but only two trials (166 patients) provided data.

3.1.5. *Subgroup analysis*

Only one of the trials that compared empirical antifungal treatment to placebo or no treatment reported prior use of antifungal prophylaxis.[15] There was no difference in the risk for composite failure between empirical therapy and no intervention in the subgroup of patients who received prophylaxis in both groups (RR 1.01 [95% CI 0.56–1.82]). All cause mortality was not reported separately for this subgroup. Outcome data for high-risk patients only were not available.

3.2. *Azoles versus amphotericin B-based preparations (11 trials, 2308 patients)*

3.2.1. *All-cause mortality*

All-cause mortality was reported in eight trials (1371 patients) that compared azoles to amphotericin B. Mortality was lower with azoles, without statistical significance, RR 0.81 [95% CI 0.65–1.01], Fig. 4. Mortality was lower with each of the azoles: fluconazole (RR 0.83 [95% CI 0.59–1.15], four trials), ketoconazole (RR 0.73 [95% CI 0.50–1.07], two trials) and itraconazole (RR 0.87 [95% CI 0.57–1.35] two trials). One trial compared voriconazole versus liposomal amphotericin B. All-cause 30-day mortality was higher with voriconazole without statistical significance (RR 1.35 [95% CI 0.94–1.93]). Effect estimates were similar for trials with adequate and unclear allocation concealment.

3.2.2. *Invasive fungal infections*

There were no statistically significant differences in the risk for IFI between fluconazole and amphotericin B (RR 0.84 [95%CI 0.51–1.38], four trials, 627 patients), ketoconazole and amphotericin B (RR 1.50 [95%CI 0.47–4.82], one trial, 64 patients), itraconazole and amphotericin B (RR 0.94 [95%CI 0.64–1.38], two trials, 522 patients) and voriconazole and liposomal amphotericin B (RR 0.79 [95%CI 0.45–1.38], one trial, 837 patients).

3.2.3. *Composite failure and secondary outcomes*

There was no significant difference in composite failure between azoles and amphotericin B-based preparations: fluconazole and amphotericin B (RR 0.95 [95%CI 0.77–1.16], six trials, 788 patients), ketoconazole and amphotericin B (RR 1.09 [95%CI 0.49–2.43], one trial, 58 patients), voriconazole and liposomal amphotericin B (RR 1.07 [95%CI 0.98–1.16], one trial, 837 patients). Itraconazole was significantly superior to amphotericin B in two trials (RR 0.77 [95%CI 0.66–0.89], two trials, 517 patients). Fungal-related mortality was not significantly different for each of the azoles and all combined versus amphotericin B (combined RR 0.83, 95% CI 0.43–1.59). Persistence of fever during neutropenia occurred more frequently

Table 1 – Description of randomized controlled trials included in the review

Study, year (reference)	Group 1		Group 2		Group 3		Age	Underlying Haematologic Condition-%	Antifungal initiation time[a], days	Antifungal prophylaxis (%)	Allocation concealment, Allocation generation	Blinding	ITT
	Drug, dose	Patients randomised	Drug, dose	Patients randomised	Drug, dose	Patients randomised							
Empirical antifungal therapy versus placebo/ no treatment/ pre-emptive treatment													
EORTC, 1989	Ampho B, 0.6mg/kg/d	77	No intervention	80	NA	NA	Mean – 39	Leu-75%, ST-9%	4	Amphotericin B – 45 Placebo - 61	B,B	N	Y
Pizzo, 1982	Ampho B, 0.5mg/kg/d	18	No intervention	16	NA	NA	Median – 17	Leu-44%, Ly-18%, ST- 38%	7	-	B,B	N	Y
Goldstone, 1994	Ambisome, 2mg/kg/d	64	No intervention	69	NA	NA	-	HSCT-37%, Leu-44%	1	-	B,B	N	N
Fukuda, 1994	Fluconazole, 400mg/d	37	No intervention	26	NA	NA	Mean – 53	Leu-65%	2	-	B,B	N	N
Wingard, 1987	Miconazole, 15mg/kg/d	97[b]	Placebo	111	NA	NA	Mean – 34	Leu-47%, HSCT-33%	1	-	B,B	DB	N
Schiel, 2006	Ampho B, 0.75mg/kg/d	45	Fluconazole, 400mg/d	56	No intervention	54	Mean – 46	Leu-38%	4-5	-	A,A	N	Y
Cordonnier, 2006	Empirical Ampho B / Lip. Ampho B	150	Pre-emptive Ampho B / Lip. Ampho B	143	NA	NA	Mean - 52	ALL – 68%	4	-	B,B	N	
Amphotericin B-based preparations versus azoles													
Malik, 1998	Ampho B, 0.5mg/kg/d	48	Fluconazole, 400mg/d	52	NA	NA	Mean – 34	Leu-60%	7	-	B,B	N	N
Viscoli, 1996	Ampho B, 0.8mg/kg/d	57	Fluconazole, 6mg/kg/d	57	NA	NA	Mean – 26	Leu-63%, HSCT-42%	4	-	A,A	N	N
Winston, 2000	Ampho B, 0.5mg/kg/d	162	Fluconazole, 400mg/d	160	NA	NA	Mean – 47	Leu-46%, HSCT-38%	4	Ampho – 77 Fluconazole - 82	B,B	N	N
Corneli, 2001	Ampho B, -	31	Fluconazole,-	29	NA	NA	-	Leu-64%, Ly-36%	3-4	-	A,B	N	N
Fainstein, 1987	Ampho B, 0.6-1mg/kg/d	32	Ketoconazole, 800mg/d	26	NA	NA	-	Leu-95%	3-4	-	B,A	N	N
Boogaerts, 2001	Ampho B, 0.7-1mg/kg/d	192	Itraconazole, 200mg/d	192	NA	NA	Median – 48	Leu-63%,	3	Ampho B – 77 Itraconazole - 74	A,A	N	N
Schuler, 2007	Ampho B, 0.7-1mg/kg/d	81	Itraconazole, 200mg/d	81	NA	NA	Medan – 53	Leu-64%, HSCT-15%	3	-	A,B	N	N
Walsh, 2002	Lip. Ampho B, 3mg/kg/d	422[c]	Voriconazole, 3mg/kg/d	415	NA	NA	Mean – 46	Leu-40%, HSCT-19%	4	Lip. Ampho B – 59 Voriconazole - 54	B,A	N	N
Walsh, 1991	Ampho B, 0.5mg/kg/d	36	Ketoconazole, 800mg/d	36	NA	NA	Mean – 27	Leu and Ly-63%	7	-	B,B	N	N
Silling, 1999	Ampho B, 0.75mg/kg/d	47	Fluconazole, 5.7mg/kg/d	51	NA	NA	Mean – 46	Leu-85%	3	-	B,B	N	Y

Comparisons between different formulations of amphotericin B													
Wingard, 2000	Lip. Ampho B, 5mg/kg/d	81	Lip. Ampho B, 3mg/kg/d	85	ABLC, 5mg/kg/d	78	Mean – 42	Leu non HSCT-31%, HSCT-16%	3	-	B,B	TB	N
Subira, 2004	Ampho B, 0.6mg/kg/d	56	ABLC, 1mg/kg/d	49	NA	NA	Median – 45	Leu-69%	5	Ampho B – 14 ABLC - 24	B,B	N	N
Moreau, 1992	Ampho B, 0.7-1mg/kg/d	16	Ampho B + intralipid 0.7-1mg/kg/d	16	NA	NA	Mean – 42	-	-	-	B,B	N	Y
White, 1998	Ampho B, 0.8mg/kg/d	104	ABCD, 4mg/kg/d	109	NA	NA	Median – 36	Leu-27%	3	Ampho B – 75 ABCD - 80	A,A	DB	N
Fleming, 2001	Lip. Ampho B, 3-5mg/kg/d	13	ABLC, 3-5mg/kg/d	17	NA	NA	Median – 58	Leu-79%	2	-	A,A	N	Y
Nucci, 1999	Ampho B, 1mg/kg/d	33	Ampho B + intralipid, 1mg/kg/d	28	NA	NA	Median – 18	Leu-73%	-	-	B,B	N	Y
Prentice, 1997	Ampho B, 1mg/kg/d	102	Lip. Ampho B, 1mg/kg/d	118	Lip. Ampho B, 3mg/kg/d	118	Median – 21	Leu-57%	4	Ampho B – 31 Lip. Ampho B - 28	A,A	N	N
Walsh, 1999	Ampho B, 0.6mg/kg/d	344	Lip. Ampho B, 3mg/kg/d	343	NA	NA	Mean – 42	Leu-49%	5	-	A,A	TB	N
Schoffski, 1998	Ampho B, 0.75mg/kg/d	24	Ampho B + intralipid, 0.75mg/kg/d	27	NA	NA	Mean – 44	Leu-69%	4	-	B,B	N	Y
Caillot, 1994	Ampho B, 1-1.1mg/kg/d	20	Ampho B + intralipid, 1-1.1mg/kg/d	19	NA	NA	Mean – 52	Leu-57%	1-2	-	B,B	N	Y
Sandler, 2000	Ampho B, 0.8mg/kg/d	22	ABCD, 4mg/kg/d	27	NA	NA	Mean – 7	HSCT-67%	3	Ampho B – 45% ABCD – 63%	B,B	DB	N
Amphotericin B-based preparations versus echinocandins													
Walsh, 2004	Lip. Ampho B, 3mg/kg/d	550	Caspofungin, 50mg/d	573	NA	NA	Median – 50	Leu-74%, HSCT-7%	4	Lip. Ampho B - 56% Caspofungin-56%	B,B	DB	N
Maertens, 2007	Lip. Ampho B, 3mg/kg/d	25	Caspofungin, 70mg/m^2/d	56	NA	NA	2-17	-	4	51 (both groups)	A,A	DB	N

NA – not applicable, Med – median, A – adequate, B – unknown, ITT – intention to treat, Y – yes, N – no, DB – double blind, TB – triple blind, ST – solid tumour, HSCT- haematopoietic stem cell transplantation, Leu – leukaemia, Ly – lymphoma, AML- acute myelogenic leukaemia, ALL- acute lymphatic leukaemia, MDS- myelodysplastic syndrome, Ampho B – amphotericin B, Lip. Ampho B – liposomal amphotericin B, ABLC – amphotericin B lipid complex, ABCD – amphotericin B colloidal dispersion.

a Time elapsing from initiation of empiric antibiotic treatment.

b Number of episodes.

c Number of evaluated patients; number of randomised patients per group not given.

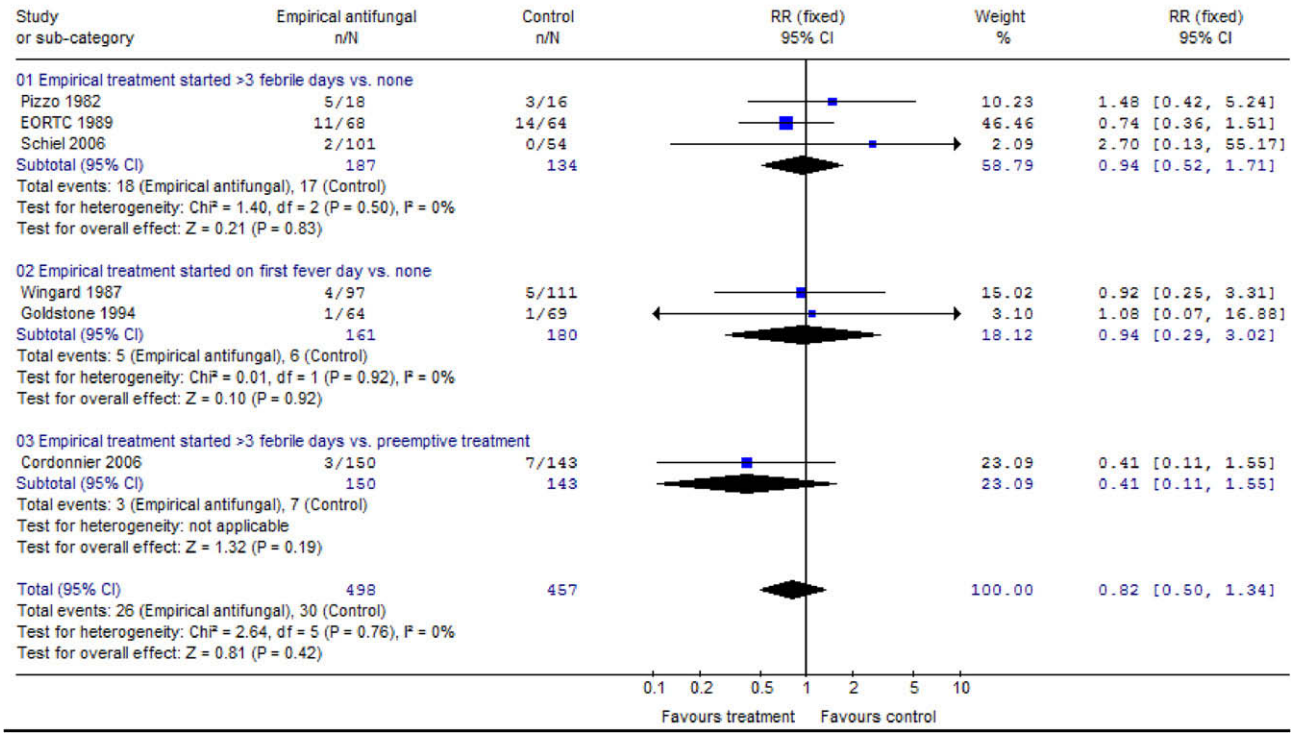

Fig. 2 – All-cause mortality for trials comparing empirical antifungal therapy versus control (placebo, no treatment or pre-emptive treatment). Studies are identified by name of first author and year of publication and sorted by their weight. Relative risks are pooled using the fixed effect model and shown on a logarithmic scale of 0.1–10.

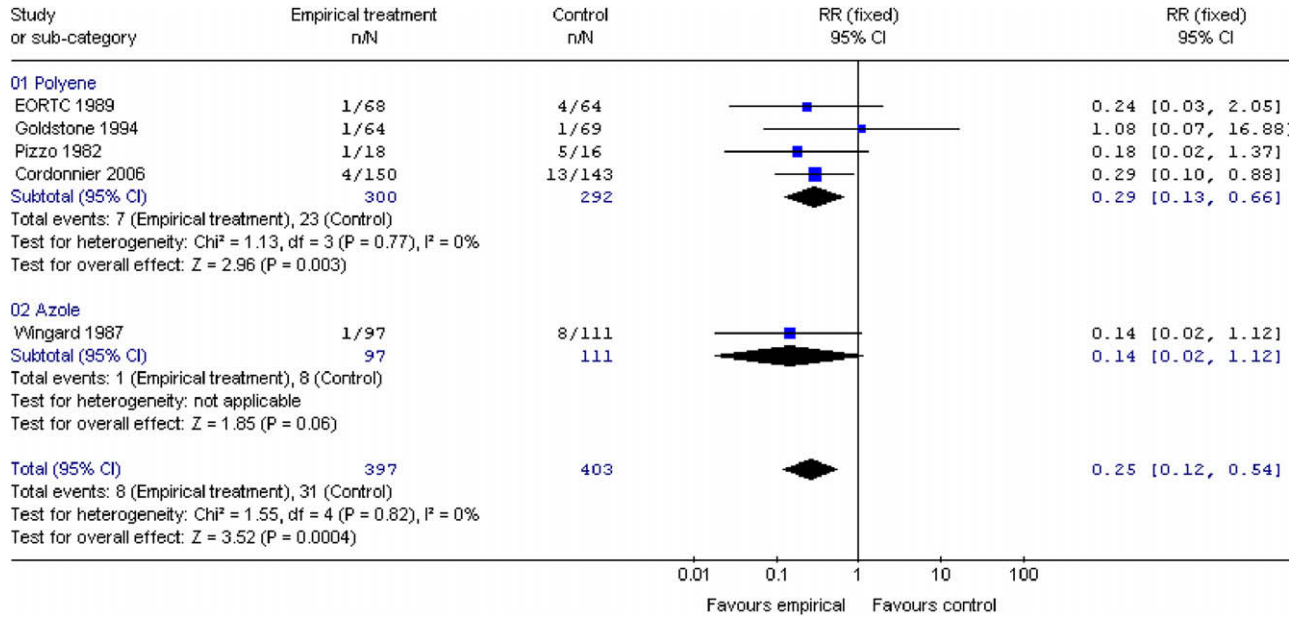

Fig. 3 – Invasive fungal infections (proven and probable) for trials comparing empirical antifungal therapy versus control (placebo, no treatment or pre-emptive treatment). Fixed effect model on a logarithmic scale of 0.01–100.

with amphotericin B compared to fluconazole (RR 1.60 [95% CI 1.09–2.36]) and did not differ significantly in the other comparisons.

3.2.4. *Adverse events*

Significantly less adverse events occurred with azoles compared to all polyenes combined: overall adverse events RR 0.40 [95% CI 0.34–0.46], adverse events requiring treatment discontinuation RR 0.48 [95% CI 0.38–0.62], acute infusion-related events RR 0.52 [95% CI 0.48–0.57], nephrotoxicity RR 0.32 [95% CI 0.24– 0.42] and hypokalaemia RR 0.41 [95% CI 0.34–0.49]. The number needed to harm for an adverse event that required treatment discontinuation was 12 patients (95% CI 9–17).

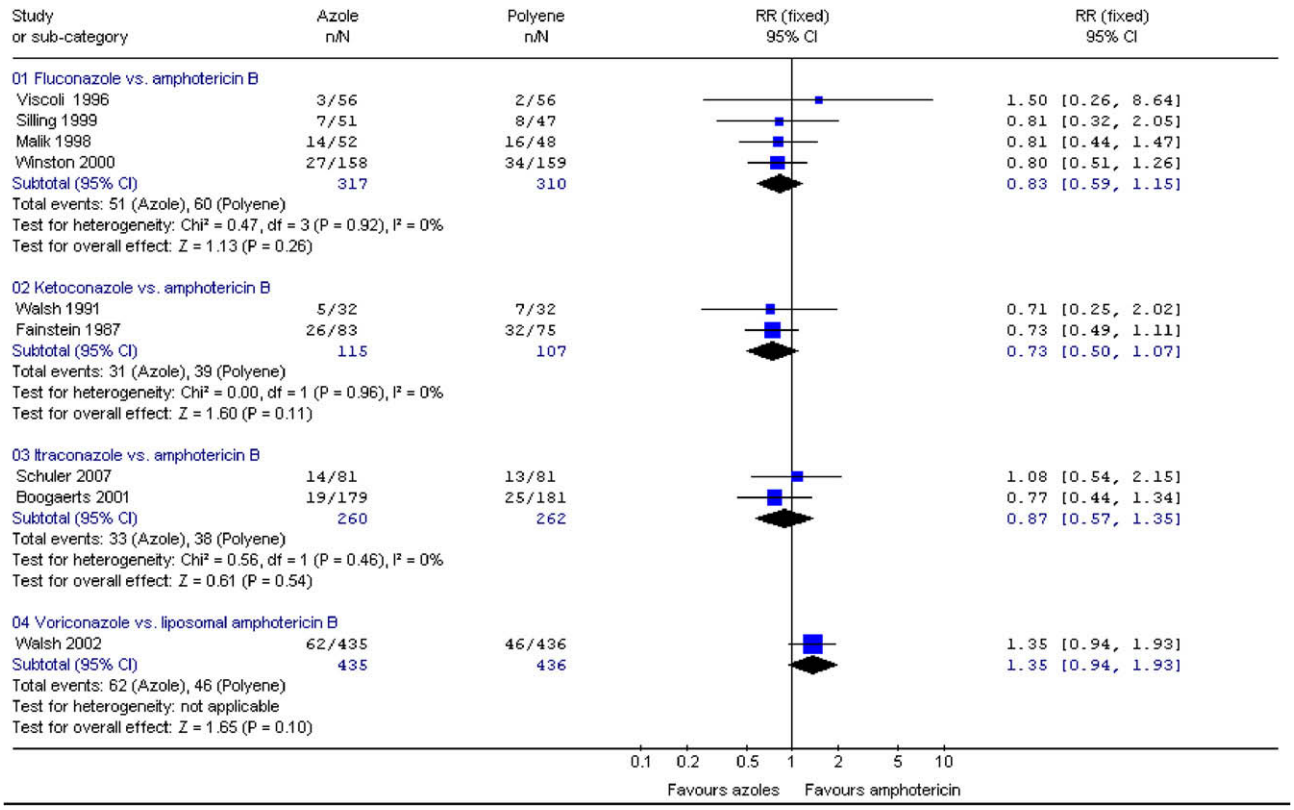

Fig. 4 – All-cause mortality for trials comparing empirical antifungal therapy using azoles versus polyenes (stratified by type of azole and polyene). Relative risks for the subcategories are pooled using the fixed effect model, on a logarithmic scale of 0.1–10. The combined relative risk for all trials comparing azoles versus amphotericin B (non-lipid) is 0.81 [95% CI 0.65–1.01].

3.3. *Different amphotericin B-based preparations (11 trials, 2193 patients)*

Two trials compared liposomal amphotericin B versus amphotericin B. All-cause mortality was non-significantly higher with amphotericin B (RR 1.36 95% CI [0.92–2.01]). Two trials compared liposomal amphotericin B to amphotericin B lipid complex (ABLC), but only one reported mortality and IFIs. All-cause mortality was significantly higher with ABLC (RR 3.34 [95% CI 1.35–8.3]). The combined mortality comparison for liposomal amphotercin B versus any other amphotericin B formulations significantly favoured liposomal amphotercin B (RR 1.57 [95% CI 1.10–2.23]). There was no significant difference in all-cause mortality between amphotericin B and amphotericin B lipid formulations excluding liposomal amphotericin B (overall RR 0.90 [0.59–1.39], values <1 in favour of amphotericin B, four trials).

Amphotericin B was associated with a higher rate of IFIs than all amphotericin B lipid formulations combined, RR 1.49 [95% CI 0.99–2.24], and amphotericin B or other amphotericin B lipid formulation were associated with a higher rate when compared to liposomal amphotercin B, RR 1.48 [95% CI 0.98–2.25].

The different formulations could be ranked with regard to toxicity. Amphotericin B was associated with higher rate of adverse events compared to all amphotericin B lipid formulations combined: RR 2.79 [95% CI 1.94– 4.01] for adverse events requiring treatment discontinuation and RR 1.70 [95% CI 1.49–1.95] for nephrotoxicity. Amphotericin B and lipid formulations other than liposomal amphotericin B were associated with a higher rate of adverse events than liposomal amphotercin B: (RR 3.69 [95% CI 2.54–5.35] for adverse events requiring discontinuation and RR 1.86 [95% CI 1.59–2.17] for nephrotoxicity.

3.4. *Caspofungin versus liposomal amphotericin B (two trials, 1204 patients)*

Two trials compared caspofungin versus liposomal amphotericin B.[55,56] One was conducted in adult patients and the other in paediatric patients. There was no difference in all-cause mortality (RR 0.79 [95% CI 0.57–1.08]) and IFI (RR 1.05 [95% CI 0.73–1.50], RR<1 favour caspofungin). There were less adverse events overall in the caspofungin group, RR 0.79 [95% CI 0.72–0.87] as well as less adverse events requiring discontinuation, RR 0.60 [95% CI 0.37–0.95].

4. Discussion

We compiled all trials assessing empirical antifungal therapy for febrile neutropenic patients. Compared to no treatment, empirical antifungals did not reduce all-cause mortality significantly RR 0.82 [95% CI 0.50–1.34]. Significantly less IFIs were detected during follow-up in the empirical treatment arm (RR 0.25 [95% CI 0.12–0.54]) and fungal-related mortality was lower at the expense of a higher rate of adverse events.

The comparisons of different antifungal agents showed a significant disadvantage to amphotericin B compared to azoles and liposomal amphotericin B, both with regard to efficacy and adverse events. No significant differences in efficacy between all other antifungals assessed were detected. Caspofungin compared favourably with liposomal amphotericin B with regard to adverse events.

Several issues concerning our analysis merit consideration. We included a recently completed trial comparing empirical antifungal treatment to pre-emptive treatment together with trials comparing empirical treatment versus no treatment. All but one.[32] of the 'no treatment' trials were open-label. Undoubtedly, physicians employed their best available resources to investigate fever in the openly untreated group. Thus, the design of these open trials is probably similar to the pre-emptive strategy comparison, albeit a major difference in the technologies available for investigation in older trials compared to the newer pre-emptive trial. We assessed all IFIs rather than limiting the analysis to baseline or breakthrough infections. Even with the best current modalities, our ability to diagnose IFIs early is limited and thus the distinction between baseline and breakthrough infections is difficult. Furthermore, selecting specific IFIs for outcome reporting may introduce bias, while randomisation should ensure an equal distribution of IFIs already present at the time of randomisation. Empirical treatment was initiated variably in included trials between 1 and 7 days of fever and neutropenia. We included trials initiating early antifungal treatment of febrile neutropenia since this approach is closer to empirical treatment than to prophylaxis, which is usually started at the time of chemotherapy (generally more than 10 days prior to onset of neutropenia and fever). Exclusion of these trials did not alter results. Finally, the reported NNT to prevent one IFI of 17 (95% CI 11–33). depends on the CER. The rate of IFIs has increased during the last years. Using a CER of 15.7%, as observed in a recently published RCT assessing prophylaxis using liposomal amphotericin inhalations in high-risk patients,[57] gives a NNT of 8 (95% CI 7–14) patients. The incidence of IFIs outside the setting of RCTs may be higher.

Antifungal prophylaxis significantly reduces all-cause mortality among cancer patients with a relative risk of 0.84 [95% CI 0.74–0.95],[58] similar to the effect estimate observed with empirical antifungal therapy. We examined whether empirical antifungal therapy serves as 'enhanced' prophylaxis, or has an independent therapeutic merit due to undetected IFIs presenting with persistent fever alone. Only one trial reported on the effect of empirical treatment in a small subgroup of patients given antifungal prophylaxis and there was no advantage to empirical antifungal treatment in this subgroup with regard to treatment failure. All other trials did not even report on the percentage of patients given antifungal prophylaxis. We extracted data on the time of occurrence of IFIs in the control group. Half of IFIs occurred early and the other half occurred 2 weeks after randomisation, supporting both a therapeutic and prophylaxis gain with empirical treatment. Thus, with currently available evidence, we cannot answer the question of whether empirical antifungal treatment offers an advantage over antifungal prophylaxis.

Three major studies have recently evaluated pre-emptive antifungal therapy. In a prospective non-comparative study, Maertens et al. evaluated a pre-emptive strategy among high-risk patients with acute leukaemia or allogeneic bone-marrow transplantation.[26] Only patients with positive microbiological results (culture or microscopy) plus supportive radiological findings on high-resolution CT, or those with two or more consecutive positive galactomannan essays received antifungal treatment (liposomal amphotericin B). With this approach, 7.7% of febrile neutropenic patients received antifungal treatment, compared to 35% who would have been treated with the classic empirical approach. Survival at 12 weeks was 63.6% overall and 76.9% for patients in complete or partial remission of their haematological disease, an encouraging figure although no comparator group was available. In the pre-emptive trial we included, Cordonnier et al. randomised 293 adult patients with haematological malignancies at high risk for IFIs to receive empirical antifungal therapy (amphotericin B or liposomal amphotericin B) on the fourth day of fever, or pre-emptive therapy based on clinical criteria and galactomannan screening. Antifungal therapy was given to 66% versus 46% of patients, respectively. All-cause mortality was non-significantly higher and more IFIs occurred in the pre-emptive treatment group. Finally, another randomised trial compared PCR-based pre-emptive treatment with empirical treatment using liposomal amphotericin B among 408 patients undergoing allogeneic stem cell transplantation.[59] All patients received fluconazole prophylaxis. This trial was not included in our analysis, since patients were randomised to PCR screening at the time of transplantation and not at the appearance of fever. Less patients in the empirical group received antifungal treatment than in the pre-emptive group (37% versus 56%). A significant reduction in all-cause mortality and a trend for fewer IFIs were demonstrated in the pre-emptive group at 30 days post-transplantation. No significant differences in mortality at days 100 and 180 were demonstrated. The different designs of these trials preclude a combined conclusion regarding pre-emptive therapy.

Most of the trials included in the drug versus no treatment meta-analysis are old, and at least one of them [13] relies on outdated diagnostic criteria. The definitions for fungal infections we used for the present review were only introduced in 2002,[21] while many of the trials were designed and conducted prior to that. Moreover, IFIs constitute a biased and unreliable outcome in non-blinded 'no treatment'-controlled trials or in the trial comparing empirical to pre-emptive treatment, since it is likely that a more aggressive search for IFIs was performed in the control group and post-mortem studies were not performed systematically in these trials to assess the cause of death. It is to be expected that more IFIs will be detected in the control group. We have, therefore, defined all-cause mortality as the primary outcome, but the power of our analysis was limited by the small number of trials and the low number of events in these trials. The small number of trials also limited our ability to assess reporting bias. Furthermore, most trials, including all trials that assessed azoles, reported results per protocol, a fact which limits the validity of their results. Several patient-related morbidity outcomes, such as length of hospital stay, days with fever and patients' satisfaction were not assessed in these trials, although extraction of these outcomes was planned. Thus,

we cannot be sure how empirical treatment affects patients' wellbeing.

4.1. *Implications for practice*

Our main finding was that empirical antifungal therapy, while universally practiced, does not reduce all-cause mortality significantly. A statistically significant reduction in IFIs is based on a small number of events and the data are derived mostly from studies conducted 10–20 years ago, before the advent of potent antifungal prophylaxis and using outdated diagnostic criteria for IFIs. Current guidelines recommend empirical antifungal therapy for persistent fever and neutropenia.[1] The evidence presented offers no solid backing for current guidelines, although cautious interpretation of the trend in mortality and the clinical significance of IFIs in high-risk patients support rather that refute these guidelines. Better outcomes with pre-emption should be shown before a change in current practice can be recommended.

Amphotericin B should not be used for empirical treatment based on a trend for lower efficacy and a higher rate of adverse events. Treatment with azoles, caspofungin or liposomal amphotericin B seems to be equivalent in terms of efficacy and adverse events. The specific agents should be chosen locally, according to local epidemiology and cost considerations.

4.2. *Implications for research*

Further studies should pursue the pre-emptive approach. A large randomised controlled trial comparing empirical antifungal treatment versus a pre-emptive approach in patients receiving antifungal prophylaxis is needed. The optimal pre-emptive strategy with regard to screening methods and time of screening initiation should be determined.

Conflict of interest statement

None declared.

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