

A Meta-analysis of Fluconazole versus Amphotericin B for Treatment of Invasive *Candida* Infections

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- **Objective:** To compare the efficacy of amphotericin B and fluconazole in the eradication of invasive *Candida* infections.
- **Design:** Meta-analysis.
- **Data sources:** Published and unpublished randomized controlled trials comparing amphotericin B to fluconazole in the treatment of invasive *Candida* infections were identified by searches of MEDLINE, the Cochrane Clinical Trials Registry, EMBASE, and the Medical Editors' Trial Amnesty. The bibliographies of all identified articles and relevant review articles also were examined.
- **Study selection:** For inclusion in the meta-analysis, articles had to meet the following criteria: (1) random allocation of patients, (2) objective inclusion criteria for documented *Candida* infections, and (3) subject-level data collection regarding mortality, microbiological failure, clinical success, and adverse events.
- **Outcome measures:** Mortality, microbiological failure, clinical success, and adverse event rates.
- **Results:** 4 trials with 457 subjects were selected for inclusion in the final analysis. There were no statistically significant differences between the 2 therapies. The relative risk (RR) of death was 0.99 (95% confidence interval [CI], 0.75 to 1.29) when fluconazole subjects were compared with amphotericin B subjects. In the fluconazole-treated group, there was a trend toward microbiological failure (RR = 1.34 [95% CI, 0.77 to 2.34]) and clinical failure (RR = 1.18 [95% CI, 0.90 to 1.52]). In the fluconazole-treated groups, there were also trends toward clinical failure among immunocompetent patients (RR = 1.31 [95% CI, 0.96 to 1.67]) and among those who did not receive flucytosine (RR = 1.19 [95% CI, 0.90 to 1.57]).
- **Conclusions:** While there were no statistically significant differences in death, clinical failure, or microbiological failure between the 2 agents, the RRs for clinical failure and microbiological failure favored amphotericin B for the treatment of invasive *Candida* infections.

Over the past 20 years, the number of invasive infections caused by *Candida* species has increased in frequency due to advances in the care and prolonged survival of patients with malignancy and end-stage organ diseases [1–3]. Until recently, amphotericin B was the only effective therapy for invasive fungal infections. However, a high incidence of renal toxicity and other side effects associated with this agent have limited its use and led to the development of the better-tolerated azole antifungal drugs, such as fluconazole. Since the late 1980s, there have been a number of randomized controlled trials comparing amphotericin B with fluconazole for the treatment of invasive *Candida* infections. Although these individual studies found no statistically significant differences in cure or survival frequencies between the 2 treatment groups, the studies were relatively small and therefore may have lacked sufficient power to detect significant differences. Furthermore, other factors such as underlying immunosuppression and catheter exchange practices might affect outcome without being apparent in studies with small sample size and heterogeneous patient populations. We conducted this meta-analysis to derive a more precise comparison of the 2 treatment groups.

Methods

Study Selection

Literature searches of the following computerized bibliographic databases were conducted: MEDLINE database (January 1966 to July 1999), the Cochrane Clinical Trials Registry (CCTR, up to July 1999), and EMBASE (January 1990 to July 1999). Searches for unpublished trials were limited to the Medical Editors' Trial Amnesty. The search terms "fluconazole" and "amphotericin" were used. The searches

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Table 1. Characteristics of Trials Included in Meta-analysis

Study	No. of Patients		Study Criteria		Outcomes Measured
	Fluconazole	Amphotericin B	Inclusion	Exclusion	
Rex [9]	103	103	CAN	NEU, LIVER, PRE, HIV	MORT, MIC, CLIN, CR, LE, K
Abele-Horn [7]	36	36	CAN	NEU, LIVER	MORT, MIC, CLIN, CR, LE, K
Anaïssie [6]*	37	37	CAN, PRES	LIVER, PRE, RENAL, HIV	MORT, CLIN, CR, LE, K
Phillips [8]	50	53	CAN	NEU, LIVER, PRE, CATH	MORT, MIC, CLIN, CR, K

CAN = documented invasive candidal infection; CATH = removal of vascular catheter not expected to occur within 72 hours of enrollment; CLIN = clinical failure; CR = creatinine levels; HIV = AIDS or HIV+; K = hypokalemia; LE = liver enzymes; LIVER = decreased liver function; MIC = microbiological failure; MORT = mortality; NEU = neutropenic; PRE = previous unsuccessful therapy; PRES = presumed candidiasis; RENAL = renal failure.

*Patients with presumed *Candida* infections, wound infection, and lower urinary tract infections were excluded from the meta-analysis.

Table 2. Characteristics of Enrolled Patients by Study

Study	Mean or Median Age, yr		Mean APACHE II Score		Malignancy, %*		<i>C. albicans</i> Infection, %†	
	FLUC	AMB	FLUC	AMB	FLUC	AMB	FLUC	AMB
Rex [9]	58	60	16	16	32	31	68	61
Abele-Horn [7]	58	60	20	20	14	11	72	64
Anaïssie [6]‡	62	58			56	63	58	46
Phillips [8]	65	58	15	13	20	22	80	62

AMB = amphotericin B; FLUC = fluconazole.

*The remainder had underlying disorders, including gastrointestinal disease, cardiovascular disease, respiratory disease, pancreatitis, trauma, diabetes, pulmonary disease, and renal failure.

†The remainder had non-*albicans Candida* species or *Candida* species that were not determined.

‡Results for Age and Malignancy refer to the total study population, not the portion with confirmed infection.

of MEDLINE and EMBASE were also limited to articles identified as randomized controlled trials; however, no language restrictions were imposed on the searches. In addition, the bibliographies of all identified articles and relevant review articles were examined. Study titles and abstracts were evaluated, and prospective trials comparing fluconazole to amphotericin B in patients with invasive *Candida* infections were selected for further review.

These selected articles were independently reviewed by 2 authors (DC and DZ). At this stage, the investigators were blinded to the journal and author names to avoid bias. To be included in the meta-analysis, articles had to meet the following criteria: (1) random allocation of patients to fluconazole and amphotericin B, (2) objective inclusion criteria for documented *Candida* infections, including pure *Candida* growth from a culture of a normally sterile site and/or histopathology indicative of *Candida* infection, and (3) collection of data at the subject level regarding mortality, microbiological failure, clinical success, and/or adverse effects of therapy. Disagreements were resolved through discussion, and consensus was achieved in the selection of articles for analy-

sis. All studies included in this meta-analysis met these criteria for at least 2 of the outcomes measured. Data were then independently abstracted by 3 authors (DC, MG, and DZ) using a standardized reporting form, and any disagreements were again resolved by consensus. Attempts to contact authors for unpublished data as needed were unsuccessful.

Outcome Measures

Mortality, microbiological failure, clinical success, and adverse effect rates were chosen as *a priori* outcome measures. When trials measured mortality at multiple time-points, the measure closest to 4 weeks after initiation of therapy was selected for the analysis. Microbiological failure was measured as the proportion of patients in each group who had positive objective tests (blood culture or biopsy) for systemic fungal infection after treatment. Clinical failure data were abstracted as reported in the individual articles. Adverse effect rates were abstracted from the studies for elevated creatinine, elevated liver enzymes, and hypokalemia.

The primary analysis included all trials with available outcome data that passed the quality review. Two subanalyses

Table 3. Antifungal Dosing and Duration

Study	Fluconazole	Amphotericin B	Duration
Rex [9]	400 mg/day IV x 7 days then PO*	0.5–0.6 mg/kg/day [†]	≥ 14 days after resolution of symptoms or last positive culture, which ever was longer
Abele-Horn [7]	400 mg/day 1, then 200 mg/day	1–1.5 mg/kg every other day [‡]	14 days
Anaïssie [6]	400 mg/day IV x 5 days then PO	25–50 mg/day [§]	FLUC: not specified AMB: ≥ 250 mg total dose
Phillips [8]	800 mg/day 1, then 400 mg/day IV x ≥ 10 days then PO	0.6 mg/kg/day	FLUC: 4–8 weeks AMB: 8–20 mg/kg total dose

AMB = amphotericin B; FLUC = fluconazole; IV = intravenously; PO = orally.

*If patient's weight is > 90 kg or < 50 kg, dosed at multiples of 50 closest to but not > 6 mg/kg.

[†]0.5–0.6 mg/kg/day x 7 days, then dosing could be adjusted to approximately 3 times per week as long as the average daily dose was 0.5–0.6 mg/kg.

[‡]5-flucytosine was used in addition to amphotericin.

[§]Neutropenic patients: 0.67 mg/kg/day.

^{||}Neutropenic patients: total dose ≥ 750 mg.

Table 4. Criteria for Clinical Failure

Study	Criteria
Rex [9]	Unresponsive or progressive infection after 5 or more days of therapy; drug toxicity requiring change of therapy; patient withdrawal from study
Abele-Horn [7]	Absence of complete clinical resolution of infection
Anaïssie [6]	No change or worsening of laboratory and clinical signs of infection; relapse of infection; drug toxicity requiring change of therapy
Phillips [8]	Death within first week of treatment; evidence of progressive candidal infection; withdrawal from study due to drug toxicity, fungal superinfections, or inadequate clinical response

were also performed; 1 involving studies that did not use 5-flucytosine in the amphotericin B group, and 1 involving studies that restricted trial entry to, or provided stratified data on, immunocompetent patients.

Statistical Methods

Because all of the study outcomes were dichotomous measures, we calculated Mantel-Haenszel adjusted relative risks comparing patients who received fluconazole with those who received amphotericin B. Two-tailed *P* values of less than 0.05 were used as the level of statistical significance, and 95% confidence intervals (CIs) were calculated. A chi-square test of homogeneity was also employed for each analysis to determine if the data were similar enough to be appropriately pooled into an adjusted relative risk. Studies were reviewed for quality, but no scoring or weighting was applied. Additionally, the potential for publication bias was investigated with the test of Begg and Mazumdar, using a continuity correction for ties [4,5]. All statistical analyses were performed using Stata 6.0 (Stata Corporation, College Station, TX).

Results

Search Results

The literature search returned 42 articles from the MEDLINE database, 53 articles from EMBASE, and 61 articles from CCTR. No additional articles were detected from the searches of the Medical Editors' Trial Amnesty or from review of the bibliographies of the included and relevant review articles. Of these articles, 6 were selected for blinded review on the basis that they appeared to meet the initial selection criteria of being prospective randomized trials comparing fluconazole and amphotericin B in the treatment of documented invasive *Candida* infections. Two of these articles included other fungal isolates in addition to *Candida* species; therefore, only the remaining 4 were included the analysis [6–9]. The Begg and Mazumdar test [4,5] showed no statistical evidence of publication bias (*P* = 1.0) among the 4 trials.

Characteristics of Individual Trials

The 4 trials included in this analysis [6–9] randomized 226 patients to fluconazole and 229 to amphotericin B

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Table 5. Mortality, Microbiological Failure, and Clinical Failure Rates

Study	Mortality, n (%)		Microbiological Failure, n (%)		Clinical Failure, n (%)	
	FLUC	AMB	FLUC	AMB	FLUC	AMB
Rex [9]	34 (33)	41 (40)	15 (15)	12 (12)	31 (30)	22 (21)
Abele-Horn [7]	13 (36)	14 (39)			16 (44)	14 (38)
Anaïssie [6]	6 (16)	3 (8)			14 (35)	15 (40)
Phillips [8]	17 (34)	14 (26)	10 (20)	6 (13)	25 (50)	22 (42)

AMB = amphotericin B; FLUC = fluconazole.

Table 6. Adjusted Relative Risks for Mortality, Clinical Failure, and Adverse Events

Analysis/Subanalyses	RR	95% CI	Studies*
Mortality	0.99	0.75–1.29	1,2,4
Without flucytosine	0.94	0.69–1.28	1,4
Immunocompetent	0.94	0.71–1.24	1,2,4
Clinical failure	1.18	0.90–1.52	1,2,3,4
Without flucytosine	1.19	0.90–1.57	1,3,4
Immunocompetent	1.31	0.96–1.67 [†]	1,2,4
Microbiological failure	1.34	0.77–2.34	1,4
Adverse events			
Elevated creatinine levels [‡]	0.17	0.10–0.30	1,2,4
Elevated liver enzymes	1.35	0.76–2.41	1,2
Hypokalemia	0.75	0.47–1.22	1,2,4

CI = confidence interval; RR = relative risk.

*1 = Rex [9]; 2 = Abele-Horn [7]; 3 = Anaïssie [6]; 4 = Phillips [8].

[†]P value = 0.09; all other P values were > 0.10.

[‡]Significant heterogeneity.

(Table 1). Inclusion criteria for all 4 studies included a positive blood culture; 3 of the studies additionally required signs of systemic illness, such as fever and low blood pressure [6,7,9]. Furthermore, 2 studies included individuals with organ system infections, as defined by a pure *Candida* culture of a normally sterile site accompanied by systemic signs of infection and/or inflammation at the site of the infection [6,7]. One of these studies also included patients with histologic evidence of blastomycetes in a tissue sample [7]. Another study included patients with presumed *Candida* infections [6], but results excluding these patients for the outcomes mortality and clinical failure were reported and these results were included in the meta-analysis. Neutropenic patients were excluded from 3 of the trials [7–9], and the fourth provided stratified data by white blood cell count [6]. All trials were conducted in primarily adult populations with underlying medical problems, and the majority of yeast isolates were *Candida albicans*

(Table 2). Dosing regimens of antifungal agents varied between studies (Table 3); 1 trial [7] used 5-flucytosine in addition to amphotericin B.

All 4 trials measured mortality and clinical failure (Table 1), while 3 measured microbiological failure [7–9]. One trial measured microbiological failure by *Candida* species rather than by patient [7], and was thus excluded from this analysis for this outcome. The criteria for clinical failure were similar among trials (Table 4). The most commonly measured adverse events were elevated creatinine levels, hypokalemia, and elevated liver enzymes [6–9].

Analysis of Pooled Data

Case fatality ranged from 16% to 36% in the fluconazole groups and from 8% to 40% in the amphotericin B groups (Table 5). The Mantel-Haenszel adjusted relative risk for mortality was 0.99 (95% CI, 0.75 to 1.29) (Table 6 and Figure 1). The 2 secondary subanalyses of mortality showed similar results, neither of which reached statistical significance (Table 6). The frequency of microbiological failure was 15% and 20% in the fluconazole groups and 12% and 13% in the amphotericin groups. The adjusted relative risk was 1.34 (95% CI, 0.77 to 2.34), but this was not statistically significant. Clinical failure ranged from 30% to 50% in the fluconazole groups and from 21% to 42% in the amphotericin groups. The adjusted relative risk for clinical failure was 1.18 (95% CI, 0.90 to 1.52) (Table 6 and Figure 2). Again, the 2 subanalyses revealed similar results.

There was wide variation in the adverse event rates reported by the individual trials (Table 7). No significant differences between groups were detected in the prevalence of elevated liver enzymes or hypokalemia. While considerably more patients who received amphotericin had elevated creatinine levels, the data were too heterogenous to make a pooled analysis appropriate (Table 7). Testing revealed no significant heterogeneity for the other comparisons performed.

Discussion

This meta-analysis attempted to summarize the current state of knowledge with respect to the comparative efficacies of

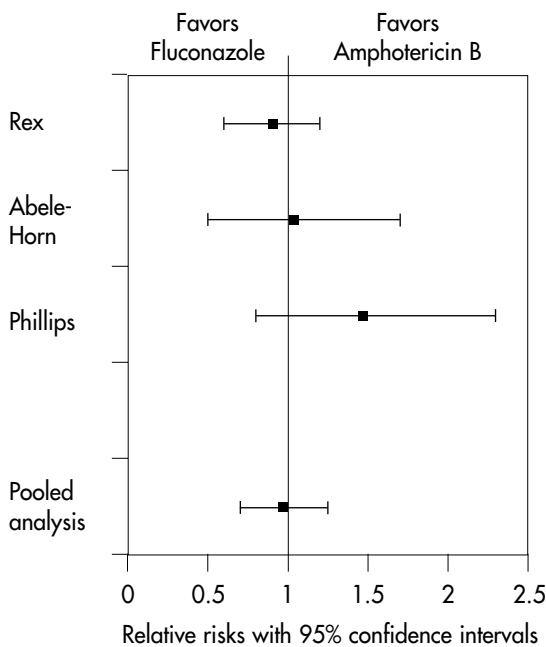


Figure 1. Individual and pooled relative risks (with 95% confidence intervals) for mortality.

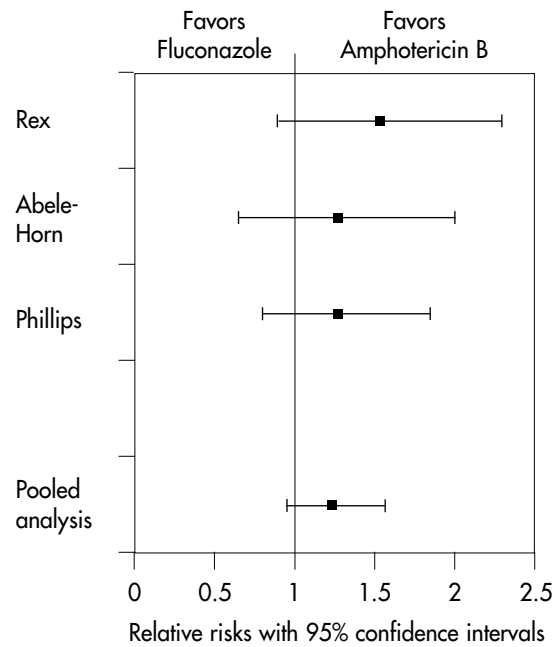


Figure 2. Individual and pooled relative risks (with 95% confidence intervals) for clinical failure.

Table 7. Adverse Event Rates

Study	Elevated Creatinine, n (%)		Elevated Liver Enzymes, n (%)		Hypokalemia, n (%)	
	FLUC	AMB	FLUC	AMB	FLUC	AMB
Rex [9]	2 (2)	38 (37)	14 (14)	10 (10)	2 (2)	10 (10)
Abele-Horn [7]	0 (0)	11 (31)	9 (25)	7 (19)	2 (6)	5 (14)
Anaissie [6]*						
Phillips [8]	10 (20)	23 (43)	17 (34)	17 (32)		

AMB = amphotericin B; FLUC = fluconazole.

*Did not stratify adverse event data by presumed versus documented *Candida* infections.

fluconazole and amphotericin B in the treatment of invasive fungal disease. We found no statistically significant differences with respect to mortality; however, we did find a statistical trend favoring amphotericin with respect to clinical failure.

Another meta-analysis published recently did not find a difference between amphotericin and fluconazole in the treatment of *Candida* infections [10]. A trend in favor of amphotericin B was noted only in non-albicans *Candida* infections. These investigators evaluated candidemia only and used different inclusion criteria, analyzing observational trials in addition to randomized, controlled trials. This different methodology may explain the modest differences between their results and the results of our analysis.

The estimated effect size for clinical failure shown in the present analysis would be clinically meaningful if it were statistically significant. Unfortunately, neither the individual trials included in this analysis nor this meta-analysis itself was powered to detect a difference of this magnitude. A randomized controlled trial would require 1738 patients, or 869 in each arm ($\alpha = 0.05, 1-\beta = 0.80$), to detect this difference. Similarly, a study would require 1020 patients, or 510 in each arm ($\alpha = 0.05, 1-\beta = 0.80$), to detect the effect size we estimated for immunocompetent patients.

A large-scale randomized controlled study to determine whether amphotericin B is more effective than fluconazole in the treatment of invasive *Candida* disease is warranted if

amphotericin B and fluconazole are to remain the mainstays of therapy for *Candida* infections, especially given the rising incidence of nosocomial fungal infections [1] and the emergence of more drug-resistant *Candida* strains [11,12]. Such a study would by design eliminate the concerns accompanying a meta-analysis such as this; for instance, dosing of the antifungal agents would be standardized as would inclusion criteria and outcomes. The study would ideally include mortality, clinical and microbiological failure, and treatment side effects. With the ongoing development of broader spectrum, low-toxicity antifungal agents, it seems unlikely that such a large study comparing amphotericin and fluconazole will take place. However, future studies evaluating the newer agents against the standard of care will face similar concerns.

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