

Antifungal Prophylaxis for Severely Neutropenic Chemotherapy Recipients

A Meta-Analysis of Randomized-Controlled Clinical Trials

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BACKGROUND. The overall clinical efficacy of the azoles antifungal agents and low-dose intravenous amphotericin B for antifungal chemoprophylaxis in patients with malignant disease who have severe neutropenia remains unclear.

METHODS. Randomized-controlled trials of azoles (fluconazole, itraconazole, ketoconazole, and miconazole) or intravenous amphotericin B formulations compared with placebo/no treatment or polyene-based controls in severely neutropenic chemotherapy recipients were evaluated using meta-analytical techniques.

RESULTS. Thirty-eight trials that included 7014 patients (study agents, 3515 patients; control patients, 3499 patients) were analyzed. Overall, there were reductions in the use of parenteral antifungal therapy (prophylaxis success: odds ratio [OR], 0.57; 95% confidence interval [95% CI], 0.48–0.68; relative risk reduction [RRR], 19%; number requiring treatment for this outcome [NNT], 10 patients), superficial fungal infection (OR, 0.29; 95% CI, 0.20–0.43; RRR, 61%; NNT, 12 patients), invasive fungal infection (OR, 0.44; 95% CI, 0.35–0.55; RRR, 56%; NNT, 22 patients), and fungal infection-related mortality (OR, 0.58; 95% CI, 0.41–0.82; RRR, 47%; NNT, 52 patients). Invasive aspergillosis was unaffected (OR, 1.03; 95% CI, 0.62–1.44). Although overall mortality was not reduced (OR, 0.87; 95% CI, 0.74–1.03), subgroup analyses showed reduced mortality in studies of patients who had prolonged neutropenia (OR, 0.72; 95% CI, 0.55–0.95) or who underwent hematopoietic stem cell transplantation (HSCT) (OR, 0.77; 95% CI, 0.59–0.99). The multivariate meta-regression analyses identified HSCT, prolonged neutropenia, acute leukemia with prolonged neutropenia, and higher azole dose as predictors of treatment effect.

CONCLUSIONS. Antifungal prophylaxis reduced morbidity, as evidenced by reductions in the use of parenteral antifungal therapy, superficial fungal infection, and invasive fungal infection, as well as reducing fungal infection-related mortality. These effects were most pronounced in patients with malignant disease who had prolonged neutropenia and HSCT recipients. *Cancer* 2002;94:3230–46.

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KEYWORDS: meta-analysis, antifungal prophylaxis, neutropenia, azoles, amphotericin B, randomized-controlled trials.

Patients with neutropenia who are receiving intensive cytotoxic therapy for malignant disease are at risk for life-threatening invasive fungal infections.^{1,2} This risk is related to the intensity of the cytotoxic regimen and the duration of neutropenia.^{3,4} Mortality rates associated with documented invasive fungal infections due to opportunistic yeasts and filamentous fungi have been high, ranging from 50% to 90%.^{1,3,4}

Strategies for preventing excess morbidity and mortality associated with superficial and invasive fungal infections have focused primarily on the use of antifungal agents to suppress the acquisition of opportunistic yeasts and filamentous fungi that colonize mucosal

surfaces damaged by the effects of cytotoxic therapy and environmental control of air-borne conidia.^{1,5} Although early clinical trials examining orally administered, polyene-based antifungal regimens demonstrated reductions in the incidence of superficial fungal infections, the results for invasive infections have been mixed.⁶⁻¹³ Furthermore, oral intolerance has been a significant problem.^{7,11,13-15} Orally or intravenously administered imidazole and triazole antifungal agents, including ketoconazole, miconazole, fluconazole, and itraconazole, have been the main focus of antifungal prophylaxis strategies because of their spectrum of activity, systemic antifungal effect, ease of administration, and tolerability. Moreover, these agents have been effective in reducing mucosal colonization by opportunistic yeasts.¹⁶⁻²⁰ More recently, the results of studies examining low-dose parenteral amphotericin B as the deoxycholate-based or lipid-based formulations also have been promising.²¹⁻²⁵ However, the results of clinical trials have been inconsistent with respect to clinically important outcomes, including superficial and invasive fungal infections, the use of parenteral therapeutic antifungal therapy, overall mortality, and fungal infection-related mortality. The use of multiple agents, differing study designs with variable power, differing dosing schedules, antifungal resistance, hematopoietic growth factor-induced early bone marrow recovery, heterogeneous patient populations, and variable cytotoxic therapy dose intensities have been cited as factors linked to the mixed results derived from these studies.

Meta-analytical techniques have been used to systematically pool the results of clinical trials, thereby increasing the statistical power of analyses examining the efficacy of therapeutic interventions.²⁶⁻²⁸ A meta-analysis reported by the Cochrane Collaboration examining prophylactic and empiric antifungal therapy in neutropenic patients with malignant disease suggested a reduction in invasive fungal infection; however, the conclusions were biased by the inclusion in the overall analysis of both prophylactic and empiric treatment studies.²⁹ A recently reported meta-analysis examining the prophylactic efficacy of fluconazole was able to demonstrate treatment effects in hematopoietic stem cell transplantation (HSCT) recipients but not for the more heterogeneous non-HSCT patient population.²⁰ That study did not address the issue of overall mortality or the roles of other antifungal agents. A recent Canadian trial reported prophylactic efficacy in specific patient subgroups, such as patients with acute myeloid leukemia who were undergoing remission induction therapy with standard cytarabine plus anthracycline-based or high-dose, cytarabine-based regimens, but not patients who were undergoing postremission consolidation or autologous HSCT supported by hematopoietic growth fac-

tors.³⁰ Accordingly, questions about the relative merits of different available agents and the overall value of antifungal prophylaxis in the treatment of different populations of neutropenic patients with malignant disease as a strategy remain unsettled. Prior to the publication of the report by Kanda et al.,²⁰ we had conducted a systematic review of the literature between 1966 and 2000 to examine the overall efficacy of antifungal prophylaxis with azole-based or intravenous, low-dose amphotericin B regimens in neutropenic patients with malignant disease regarding the incidence of superficial and invasive fungal infection, the use of parenteral therapeutic antifungal therapy, overall mortality, and fungal infection-related mortality.³¹ We now report the results of that analysis, including expanded subgroup analyses emphasizing the patient groups in which the protective benefits were demonstrated best.

MATERIALS AND METHODS

Literature Review

The literature pertaining to antifungal prophylaxis in neutropenic patients with malignant disease between 1966 and 2000 was searched, independent of language, with the use of the MEDLINE and EMBASE data bases. The search keyed on specific terms, including neutropenia, granulocytopenia, carcinoma, leukemia, bone marrow transplantation, fungal infection, and prophylaxis. Additional studies were identified from the bibliographies of articles that were retrieved in the search, from topical reviews, and from information made available by the pharmaceutical industry and other investigators in the field. Permission to access and use data derived from unpublished trials identified by the search strategy was obtained through correspondence with the principal investigators and study sponsors. Study selection criteria included a randomized-controlled study design; study regimens that included azoles (fluconazole, itraconazole, ketoconazole, and miconazole) or polyenes (intravenous low-dose amphotericin B deoxycholate or lipid-based formulations of amphotericin B); control regimens that included placebo or no treatment controls or polyene-based (oral or intravenous amphotericin B deoxycholate or oral nystatin with or without additional agents, such as clotrimazole) controls; and the inclusion of patients who received cytotoxic therapy for acute leukemia or hematopoietic stem cell transplantation sufficient to produce a period of neutropenia (absolute neutrophil count $< 1.0 \times 10^9/L$) lasting ≥ 1 week.

Review Protocol

Trials that were selected for inclusion in the analysis were reviewed independently by three investigators (E.J.B., M.L., and N.L.). Data from each trial were entered onto standardized case report forms, verified for consistency and accuracy, and entered into a comput-

TABLE 1
Characteristics of the Studies Included in the Analysis

Reference (TQS)	Agent(s)	No. of Patients	Daily dose	Diagnosis			Duration of neutropenia (days)	On study (days)
				AL	HSCT	Other		
Schiason et al. ¹⁶ (0)								
Study	Flu	23	400 mg	22	0	1	22.9 ^a	NR
Control	NT	23	—	23	0	0	24.0 ^a	NR
Goodman et al. ⁶⁶ (4)								
Study	Flu	179	400 mg	0	179	0	NR	22.6
Control	Plac	177	—	0	177	0	NR	19.7
Winston et al. ⁶⁷ (5)								
Study	Flu	123	400 mg	123	0	0	NR	NR
Control	Plac	132	—	132	0	0	NR	NR
Schaffner and Schaffner ⁶⁹ (5)								
Study	Flu	75	400 mg	55	8	20	23.8 ^b	25
Control	Plac	76	—	54	9	22	19.5 ^b	20
Yamaç et al. ⁷⁰ (1)								
Study	Flu	41	400 mg	13	0	28	25 ± 17 ^c	NR
Control	NT	29	—	10	0	19	17 ± 16 ^c	NR
Slavin et al. ⁷¹ (5)								
Study	Flu	152	400 mg	0	152	0	20 ^b	75
Control	Plac	148	—	0	148	0	20 ^b	75
Kern et al. ⁷² (0)								
Study	Flu	36	400 mg	36	0	0	35 ^a	23
Control	NT	32	—	32	0	0	34 ^a	23
Rostein et al. ³⁰ (5)								
Study	Flu	141	400 mg	79	62	0	NR	21
Control	Plac	133	—	75	58	0	NR	18
Vreugdenhil et al. ⁷³ (5)								
Study	Itra/AmB-PO	46	400 mg/4000 mg	37	0	9	28 ^b	81
Control	Plac/AmB-PO	47	—/4000 mg	45	0	2	25 ^b	80
Menichetti et al. ⁷⁴ (0)								
Study	Itra (os)/Nyst	201	5 mg/kg/2 Mu	149	37	15	13 ^a	19
Control	Plac/Nyst	204	—/2Mu	157	37	10	13 ^a	19
Nucci et al. ⁷⁵ (5)								
Study	Itra (cap)	104	200 mg	83	15	6	12 ^a	19.5
Control	Plac	106	—	84	16	6	11 ^a	17
Brincker ⁷⁶ (2)								
Study	Keto	19	400 mg	19	0	0	NR	NR
Control	Plac	19	—	19	0	0	NR	NR
Estey et al. ⁷⁷ (1)								
Study	Keto	75	400 mg	75	0	0	26 ^b	38
Control	NT	70	—	70	0	0	28 ^b	38
Hansen et al. ⁷⁹ (3)								
Study	Keto	27	400 mg	18	4	5	22 ^a	NR
Control	Plac	29	—	15	3	11	21 ^a	NR
Benhamou et al. ⁸⁰ (4)								
Study	Keto	63	200 mg	0	60	3	32.9 ^b	30
Control	Plac	62	—	0	55	7	29.7 ^b	30.4
Palmblad et al. ⁸¹ (3)								
Study	Keto	50	200 mg	50	0	0	21 ± 18 ^d	58.2 ± 11.9
Control	Plac	57	—	57	0	0	17 ± 15 [‡]	59.2 ± 10.6
Brincker ⁸² (3)								
Study	Mic	15	2000 mg	15	0	0	NR	NR
Control	Plac	15	—	15	0	0	NR	NR
Wingard et al. ⁸³ (4)								
Study	Mic	97	15 mg/kg IV	41	42	14	21 ^b	NR
Control	Plac	111	—	56	41	14	23 ^b	NR
Ninane ⁵⁰ (0)								
Study	Flu	245	3 mg/kg	133	58	54	NR	27.8
Control	AmB-PO/Nyst	257	100 mg/kg/0.2 MU/kg	132	64	61	NR	29.2
Brammer ⁸⁴ (1)								
Study	Flu	126	50 mg	93	33	0	NR	25.3
Control	AmB-PO/Nyst	122	2000 mg/4 MU	97	25	0	NR	28.2
Rozenberg-Arska et al. ⁸⁵ (1)								
Study	Flu	25	50 mg	25	0	0	19.4 ^b	19.4
Control	AmB-PO	25	1600 mg	25	0	0	19.8 ^b	19.8

(continued)

TABLE 1
(continued)

Reference (TQS)	Agent(s)	No. of Patients	Daily dose	Diagnosis			Duration of neutropenia (days)	On study (days)
				AL	HSCT	Other		
Akiyama et al. ⁸⁶ (2)								
Study	Flu	71	200 mg	70	0	1	10 ^b	NR
Control	AmB-PO	59	2400 mg	58	0	1	17 ^b	NR
Philpott-Howard et al. ⁸⁷ (1)								
Study	Flu	256	50 mg	195	0	74	NR	NR
Control	AmB-PO/Nyst	255	2000 mg/4 MU	210	0	57	NR	NR
Menichetti et al. ⁸⁸ (3)								
Study	Flu	420	150 mg	420	0	0	19 ^a	26
Control	AmB-PO	400	2000 mg	400	0	0	18 ^a	25
Ellis et al. ⁸⁹ (3)								
Study	Flu	42	200 mg	28	10	4	18.5 ^a	24
Control	Nyst/Clot	48	2 MU/20 mg	31	13	4	15 ^a	19
Bodey et al. ⁹⁰ (2)								
Study	Flu	41	400 mg	41	0	0	20 ^a	24
Control	AmB-IV	36	0.5 mg/kg MWF	36	0	0	16 ^a	19
Egger et al. ⁹¹ (3)								
Study	Flu	43	400 mg	16	14	13	8.0 ^b	26
Control	Nyst/Mic inhaled	46	72 MU/? mg tid	21	19	6	7.5 ^b	21
Boogaerts et al. ⁹² (3)								
Study	Itra (os)	144	200 mg	88	15	41	11 ^b	22
Control	AmB-PO/Nyst	133	750 mg/8 MU	95	10	28	12 ^b	20
Harousseau et al. ⁹³ (5)								
Study	Itra (os)	281	5 mg/kg	199	0	82	18 ^b	19
Control	AmB-PO	276	250 mg	195	0	81	20 ^b	18
Vogler et al. ⁷⁸ (1)								
Study	Keto	22	400 mg	22	0	0	21 ^b	24
Control	Nyst	24	2 MU	24	0	0	22 ^b	23
Hann et al. ⁹⁴ (2)								
Study	Keto	37	400 mg	21	13	3	11.5 ± 1.6 ^d	63.2 ± 6.3
Control	AmB-PO/Nyst	35	40 mg/12 MU	21	12	2	8.6 ± 7.3 ^d	61.1 ± 7.3
Donnelly et al. ⁹⁵ (0)								
Study	Keto	17	400 mg	15	2	0	20 ± 6 ^b	29 ± 7
Control	AmB-PO	19	1760 mg	18	1	0	15 ± 7 ^b	27 ± 5
Jones et al. ⁹⁶ (1)								
Study	Keto	18	200 mg	15	0	3	18.3 ± 2.7 ^b	NR
Control	Nyst	18	2 MU	11	0	7	16.0 ± 2.9 ^b	NR
Shepp et al. ⁹⁷ (2)								
Study	Keto	27	400 mg	0	27	0	23 ^b	31
Control	Nyst	29	12 MU	0	29	0	23 ^b	32
Perfect et al. ²¹ (5)								
Study	AmB-IV	91	0.1 mg/kg	0	91	0	16.2 ^b	16
Control	Plac	91	—	0	91	0	13.9 ^b	14
Tollema et al. ²² (5)								
Study	Ambisome IV	36	1 mg/kg	0	36	0	14 ± 1 ^b	20
Control	Plac	40	—	0	40	0	16 ± 1 ^b	19
Riley et al. ²³ (5)								
Study	AmB-IV	17	0.1 mg/kg	0	17	0	19 ^b	NR
Control	Plac	18	—	0	18	0	20 ^b	NR
Kelsey et al. ²⁴ (5)								
Study	Ambisome IV	74	2 mg/kg ^e	11	63	0	NR	NR
Control	Plac	87	—	15	72	0	NR	NR

TQS: trial quality score out of a possible five points, one each for details of randomization, double-blinding, details of the double-blinding procedure, concealment of allocation, and handling of withdrawals;^{32,33} AL: acute leukemia; HSCT: hematopoietic stem cell transplantation; Other: other diagnoses; Keto: ketoconazole; Flu: fluconazole; Itra: itraconazole; Mic: miconazole; Clot: clotrimazole; Nyst: nystatin; AmB-PO: oral amphotericin B; AmB-NT: intranasal amphotericin B; AmB-IV: intravenous amphotericin B; NR: not reported; NT: no treatment control; Plac: placebo control; cap: capsules; os: oral solution.

^a Neutrophils < 1.0 × 10⁹/liter.

^b Neutrophils < 0.5 × 10⁹/liter.

^c Neutrophils < 2.0 × 10⁹/liter.

^d Neutrophils < 0.1 × 10⁹/liter.

^e The dosing schedule was thrice weekly.

erized data base. A methodical quality review of each trial was undertaken to include specification of details of randomization, the use of double-blinding, details of the double-blinding procedure, handling of withdrawals, and concealment of allocation. One point was awarded for the specification of each criterion, for a maximum achievable score of 5 points, as described previously.^{32,33}

Definition of Outcomes

Five major outcomes (prophylaxis success; superficial fungal infection; proven invasive fungal infection; overall mortality; and, where reported, fungal infection-related mortality) were assessed. In addition, the incidence of invasive aspergillosis also was evaluated. Prophylaxis success was defined by study completion without the administration of parenteral, full-dose, antifungal therapy for patients with suspected or proven invasive fungal infection. Superficial fungal infection was defined by infections of integumentary surfaces attributable to fungi. Proven invasive fungal infection required the microbiologic or histologic identification of a fungal pathogen from normally sterile body sites in association with clinical evidence of infection. Invasive aspergillosis was defined as a proven fungal infection that was attributed by the investigators to *Aspergillus* spp. Overall mortality was defined as death from any cause that occurred over the study period. Fungal infection-related mortality was defined by the association between death and the fungal infection as reported by the study authors. Because not all studies reported all outcomes, outcomes were recorded whenever they were available.

Statistical Analysis

The analyses were performed using both fixed models³⁴ and random-effects models³⁵ with SAS software (SAS Institute, Cary, NC). Random-effects models were used when intertrial heterogeneity was detected. The risk differences in each study were defined by the *odds ratio* (OR; i.e., a measure of the association between a dichotomized factor and a binary outcome, such as response; the OR is defined by the ratio of the odds of experiencing the outcome of interest in the presence of the factor to the odds of experiencing an outcome in the absence of the factor) with 95% confidence intervals [95%CI] of the categoric outcome frequencies in the study groups and the control groups, respectively. ORs less than unity indicated a treatment effect that favored the study agent. Pooled, weighted ORs and their respective 95%CIs were then estimated separately for each outcome for each meta-analysis. When zero events occurred, the ORs were estimated by substituting a value of 0.5 in the calculation. Intertrial differences for each outcome in pa-

tients who received the same treatments were assessed using a chi-square test for homogeneity derived from the Q statistic.³⁶ A low probability of homogeneity ($P < 0.1$) implied that the variances for the treatment effects for individual trials contributing to the pooled results differed significantly from one another.

For each outcome, *publication bias* (defined as selection bias as a result of the inclusion of published data that tend to be positive and may ignore the contribution of unpublished negative trials, resulting in an overestimate of a given treatment effect) was assessed by regressing the natural logarithm of the OR against the estimate's precision (1/standard error of the OR).³⁷ Subgroup analyses for each outcome were performed by recalculating the ORs and 95%CIs based on the following criteria: exclusion of studies with quality review scores less than the median of 3, sequential exclusion of pediatric and adult studies, sequential exclusion of HSCT-related and non-HSCT trials, exclusion of trials according to the duration of neutropenia (either $<$ the 25th quartile/14 days or $>$ the 75th quartile/22 days), exclusion of each individual trial in sequence, evaluation of trials of differing study designs (that is, azoles compared with placebo or no treatment controls, trials of azoles compared with an active polyene-based control, and trials of low-dose amphotericin B formulations compared with placebo controls), and study agent (that is, fluconazole, itraconazole, ketoconazole, miconazole, and low-dose intravenous amphotericin B formulations). The prophylaxis benefits also were estimated by the percent *relative risk reduction* (RRR; i.e., the reduction of adverse events achieved by a treatment, expressed as a proportion of the control rate; the formula is [event rate, control group – event rate, study group]/event rate, control group) and the number of patients who required treatment to prevent or promote a particular outcome compared with control participants according to the methods described previously.^{26,38} The effects of predictor variables on outcome were evaluated by metaregression analysis based on a general, linear-measures modeling procedure for least-squares means. The independent variables evaluated included study drug (that is, fluconazole, itraconazole, ketoconazole, miconazole, or intravenous low-dose amphotericin B formulation); study design (that is, azoles vs. placebo/no treatment controls, azoles vs. polyene controls, or low-dose amphotericin B formulations vs. placebo); proportion of patients in the trials undergoing HSCT, including autologous and allogeneic HSCT; proportion of patients receiving treatment for acute leukemia; azole dosing; duration of neutropenia; the use of hematopoietic growth factors; and the incidence of proven, invasive fungal infection in the control group.

TABLE 2
Demographics of the Study Populations

Characteristic	Study group		Control group		Total
	No.	%	No.	%	
No. of patients					
Fluconazole trials	2052	58	2010	57	4062
Itraconazole trials	776	22	765	22	1541
Ketoconazole trials	357	10	362	10	719
Miconazole trials	112	3	126	4	238
Low-dose amphotericin B trials	218	6	236	7	454
Totals	3515	—	3499	—	7014
Gender					
Males	1797	51	1674	48	3471
Females	1396	40	1485	42	2881
Not stated	322	9	340	10	662
Total	3515	—	3499	—	7014
Age in yrs (no. of studies in which age data were provided)					
Mean \pm SD	38.9 \pm 12.5	—	38.7 \pm 13.1	—	—
Median (range)	42 (6.8–57.0)	—	41 (6.8–65.0)	—	—
Diagnoses ^a					
Acute leukemia, NOS	2141	59	2160	60	—
Hematopoietic stem cell transplant	982	27	979	27	—
Other, NOS	509	14	480	13	—
Days on study (mean \pm SD) ^b	29.3 \pm 15.1 ^c	—	27.8 \pm 15.7 ^c	—	—
Duration of neutropenia in days \pm SD of the mean (no. of studies in which data were provided) ^b					
< 0.5 \times 10 ⁹ /L, (<i>n</i> = 21 studies) ^d	19.3 \pm 6.2	—	19.0 \pm 7.5	—	—
< 1.0 \times 10 ⁹ /L, (<i>n</i> = 7 studies) ^e	21.3 \pm 7.0	—	19.9 \pm 7.5	—	—

SD: standard deviation; NOS: not otherwise specified.

^a Some patients may be represented in more than one group^b Collated from Table 1.^c *P* = 0.001.^d *P* = 0.57.^e *P* = 0.06.

RESULTS

Characteristics of the Data Set

The literature search identified 69 trials of antifungal prophylaxis in patients with malignant disease.^{8,10,16,21–25,28,30,39–97} Thirty-one studies were excluded for lack of a randomized-controlled design (16 trials);^{39–42,44,46,47,52–60} because the comparison was between azoles (4 trials);^{61–64} because the trial was of early empiric therapy rather than prophylaxis;⁴⁸ because the study patients were reported in larger multicenter trials (2 trials);^{51,68} or because of insufficient myelosuppression or outcome information (7 trials).^{8,43,45–47,49,65} Drug-related toxicity necessitated early closure of one other trial, and no meaningful data were available.²⁵ Thirty-eight trials^{16,21–24,30,50,66,67,69–97} remained in the analysis, including 18 placebo-controlled trials, 4 no treatment-controlled trials, and 16 polyene-controlled trials. Study regimens included fluconazole (17 trials that included 58% of randomized patients), itraconazole (5 trials that included 22% of randomized patients), ketoconazole (10 trials that included 10% of randomized patients), miconazole (2

trials that included 3% of randomized patients), and low-dose intravenous amphotericin B (4 trials that included 6% of randomized patients). One multiple-treatment study⁹⁵ that involved ketoconazole versus oral amphotericin B versus ketoconazole plus oral amphotericin B comparisons was retained for the analysis; however, the ketoconazole plus amphotericin B arm was excluded to avoid the azole:azole comparison. The results of one large, unpublished, randomized trial of itraconazole was included in the analyses with the permission of the Janssen Research Foundation and the primary investigator.⁹² The mean trial quality score for all 38 trials was 2.87 \pm 1.77 (median, 3.0; range, 0–5).

The characteristics of the trials that were included in the analyses are detailed in Table 1. The patient demographic information compiled in Table 2 demonstrates the comparability between the study group and the control group overall. Patients in the study group remained on study longer than patients in the control group (29.3 days \pm 15.2 days vs. 27.8 days \pm 15.7 days, respectively; *P* = 0.001).

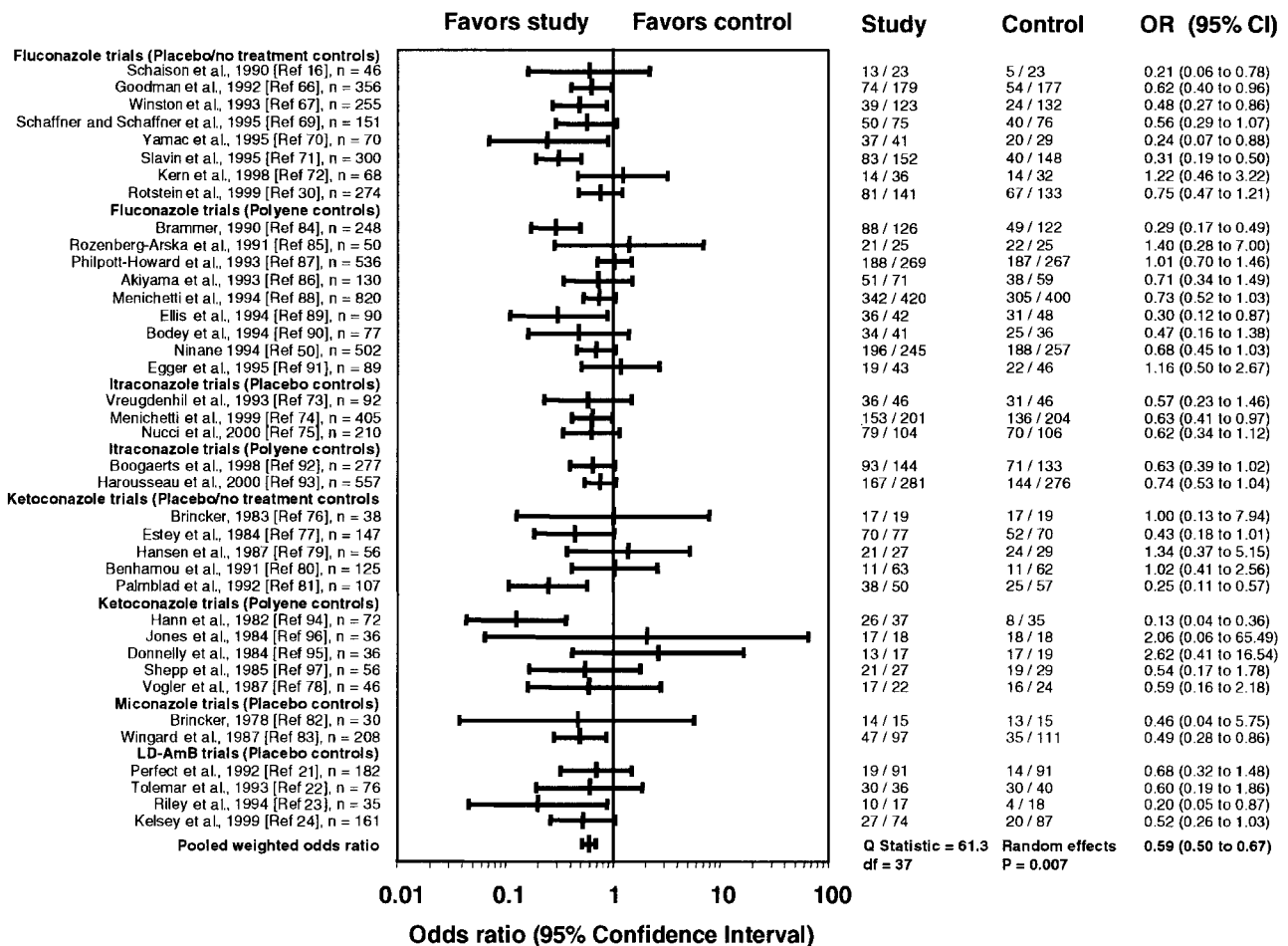


FIGURE 1. Treatment effects for prophylaxis success. Results are shown as the odds ratio (OR) with 95% confidence interval (95% CI) for 38 individual trials together with the pooled, weighted OR based on a random-effects model and the results of the homogeneity testing (Q statistic, chi-square test). Ref: reference number; LD-AmB: low-dose intravenous amphotericin B; df: degrees of freedom.

Publication bias, which was estimated from the correlation between effect size (natural logarithm of the OR) and sample size (estimate's precision), was not detected in any of the five primary outcomes examined (prophylaxis success: adjusted correlation coefficient $[R^2] = -0.0281, P = 0.9009$; superficial fungal infection: adjusted $R^2 = 0.0076, P = 0.2819$; proven invasive fungal infection: adjusted $R^2 = -0.0183, P = 0.5570$; overall mortality: adjusted $R^2 = 0.0181, P = 0.2198$; fungal infection-related mortality: adjusted $R^2 = -0.0354, P = 0.9255$).

Analyses of Outcomes

The pooled, weighted ORs with their 95% CIs derived from the overall analysis of the 7014 randomized patients for each of the 6 outcomes together with the results of the chi-square (Q) statistic for homogeneity are illustrated in Figures 1–6. The analyses are presented according to the study agent and the study

design. Intertrial heterogeneity was observed for prophylaxis success and superficial fungal infection; accordingly, the results are presented based on random-effects modeling for these outcomes, which takes this heterogeneity into account. The analyses of the remaining outcomes were based on fixed-effects modeling.

Prophylaxis reduced the use of parenteral antifungal therapy (prophylaxis success: OR, 0.57; 95% CI, 0.48–0.68; RRR, 19%; *number requiring treatment* for this outcome [NNT; i.e., the number of patients who must be treated to prevent the occurrence of one event, expressed as the reciprocal of the *absolute risk reduction*, which is the difference in event rates between the control group and the study group; expressed as the event rate in the control group minus the event rate in the study group], 10 patients), superficial fungal infection (OR, 0.29; 95% CI, 0.20–0.43; RRR, 61%; NNT, 12 patients), invasive fungal infection

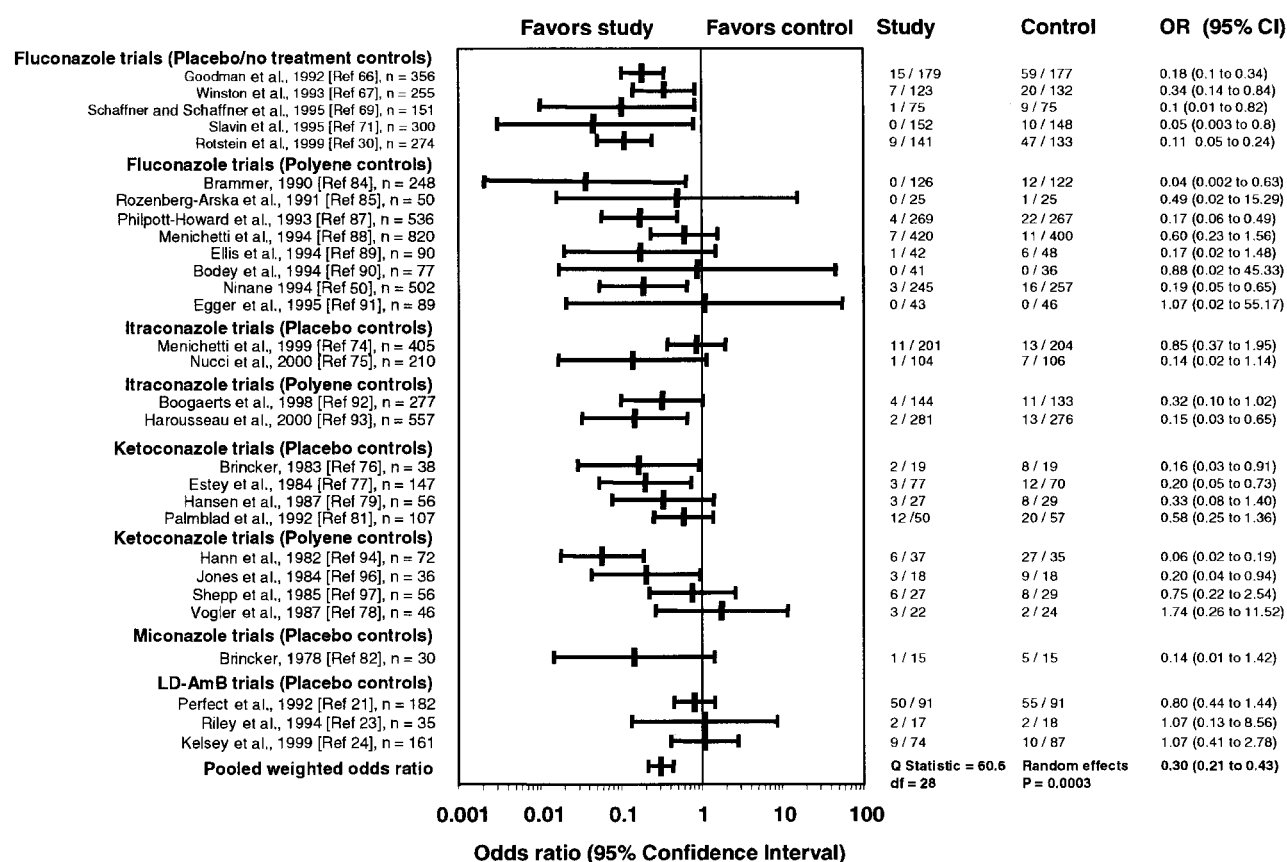


FIGURE 2. Treatment effects for superficial fungal infection. Results are shown as the odds ratios (OR) with 95% confidence intervals (95% CI) for 29 individual trials together with the pooled, weighted OR based on a random-effects model and the results of the homogeneity testing (Q statistic, chi-square test). Ref: reference number; LD-AmB: low-dose intravenous amphotericin B; df: degrees of freedom.

(OR, 0.44; 95% CI, 0.35–0.55; RRR, 56%; NNT, 22 patients), and fungal infection-related mortality (OR, 0.58; 95% CI, 0.41–0.82; RRR, 47%; NNT, 52 patients). Overall mortality and the incidence of aspergillosis (which was very low; 1% in both groups) were unaffected.

Subgroup Analyses

The results of the subgroup analyses are shown in Table 3. The overall patterns of treatment effects observed for all 6 outcomes for the 38 trials were similar to the trials that were characterized by quality scores above the median, trials that compared azoles with placebo or no treatment controls, and analyses in which the outcome treatment effects were recalculated after excluding 1 trial at a time (data not shown).

Treatment effects for prophylaxis success were observed for all analyses. Superficial fungal infections were not reduced in studies in which the majority of patients were HSCT recipients; in the trials of low-dose intravenous amphotericin B formulations (in which the study populations were largely HSCT recip-

ients); or in a single, small miconazole trial.⁸² However, among six HSCT trials that were evaluable for superficial fungal infection, a treatment effect was observed among the three azole-based studies (OR, 0.23; 95% CI, 0.13–0.39) but not among the three studies that evaluated low-dose amphotericin B formulations (OR, 0.87; 95% CI, 0.54–1.42). A reduction in proven invasive fungal infection was observed in all analyses except for miconazole trials. In contrast to the overall results for mortality, a protective treatment effect was observed in trials with adult patients and trials in which the mean duration of neutropenia was longer than 2 weeks. A reduction in fungal infection-related mortality was not observed among pediatric trials; non-HSCT trials; trials with study designs that compared azoles with polyene controls or compared low-dose intravenous amphotericin B formulations with placebo; or itraconazole-based, ketoconazole-based, or miconazole-based trials. However, there was a reduction in fungal infection-related mortality in fluconazole-based trials. No treatment effects were observed for invasive aspergillosis in any subgroup analysis.

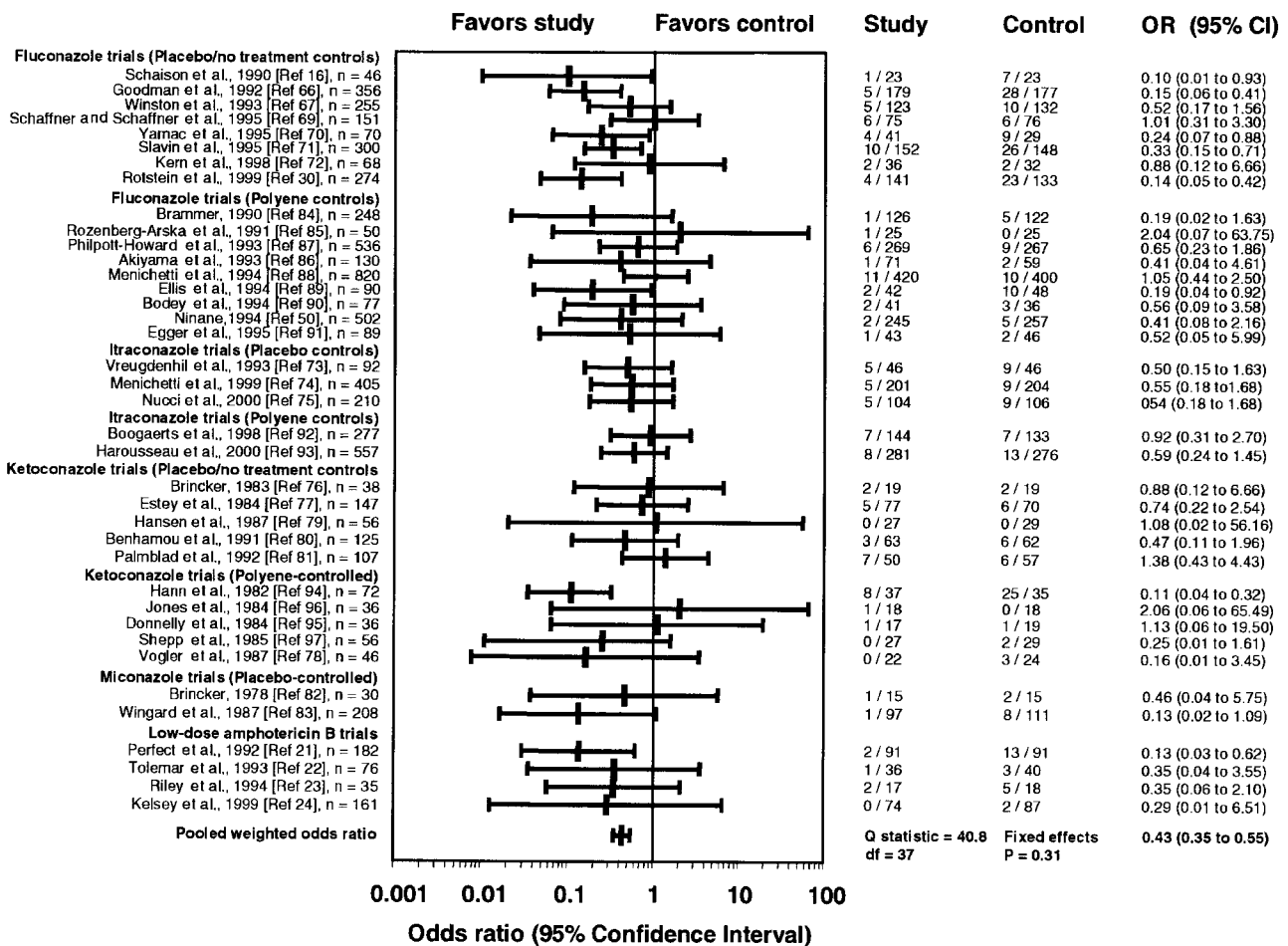


FIGURE 3. Treatment effects for proven invasive fungal infection. Results are shown as the odds ratio (OR) with 95% confidence interval (95% CI) for 38 individual trials together with the pooled, weighted OR based on a fixed-effects model and the results of the homogeneity testing (Q statistic, chi-square test). Ref: reference number; LD-AmB: low-dose intravenous amphotericin B; df: degrees of freedom.

Metaregression Analyses

We attempted to explore factors that may otherwise explain the observed correlations between treatment effects and outcome. Although the univariate meta-regression analysis detected no correlation between study agent and prophylaxis success ($P = 0.45$), proven invasive fungal infection ($P = 0.43$), overall mortality ($P = 0.73$), or fungal infection-related mortality ($P = 0.73$), there was an effect for superficial fungal infection ($P = 0.0004$) in which it was found that fluconazole was more protective than itraconazole ($P = 0.04$) or low-dose amphotericin B formulations ($P < 0.0001$). Table 4 details the variables that were correlated independently with treatment effect for each outcome in the multivariate metaregression analyses. Treatment effects for prophylaxis success, invasive fungal infection, and overall mortality were more likely to be observed in trials in which the rate of proven invasive fungal infection among control par-

ticipants was high and in which the majority of patients were undergoing HSCT, particularly allogeneic HSCT. Furthermore, prophylaxis success was more likely to be observed in trials that were associated with prolonged neutropenia. A reduction in overall mortality was observed among HSCT trials in which there was also prolonged neutropenia. Daily azole doses > 200 mg also were associated with a greater likelihood of prophylaxis success and fewer invasive fungal infections. It is noteworthy that a treatment effect for superficial fungal infection was observed only among trials that were characterized by patients who did not undergo HSCT. Trials in which the rate of invasive fungal infection was high (≥ 75 th percentile; 14.7%) among control participants tended to be of higher quality ($P = 0.026$) and were characterized by younger adult patients ($P = 0.045$) and HSCT recipients ($P = 0.002$) in a multivariate regression model ($P = 0.007$).

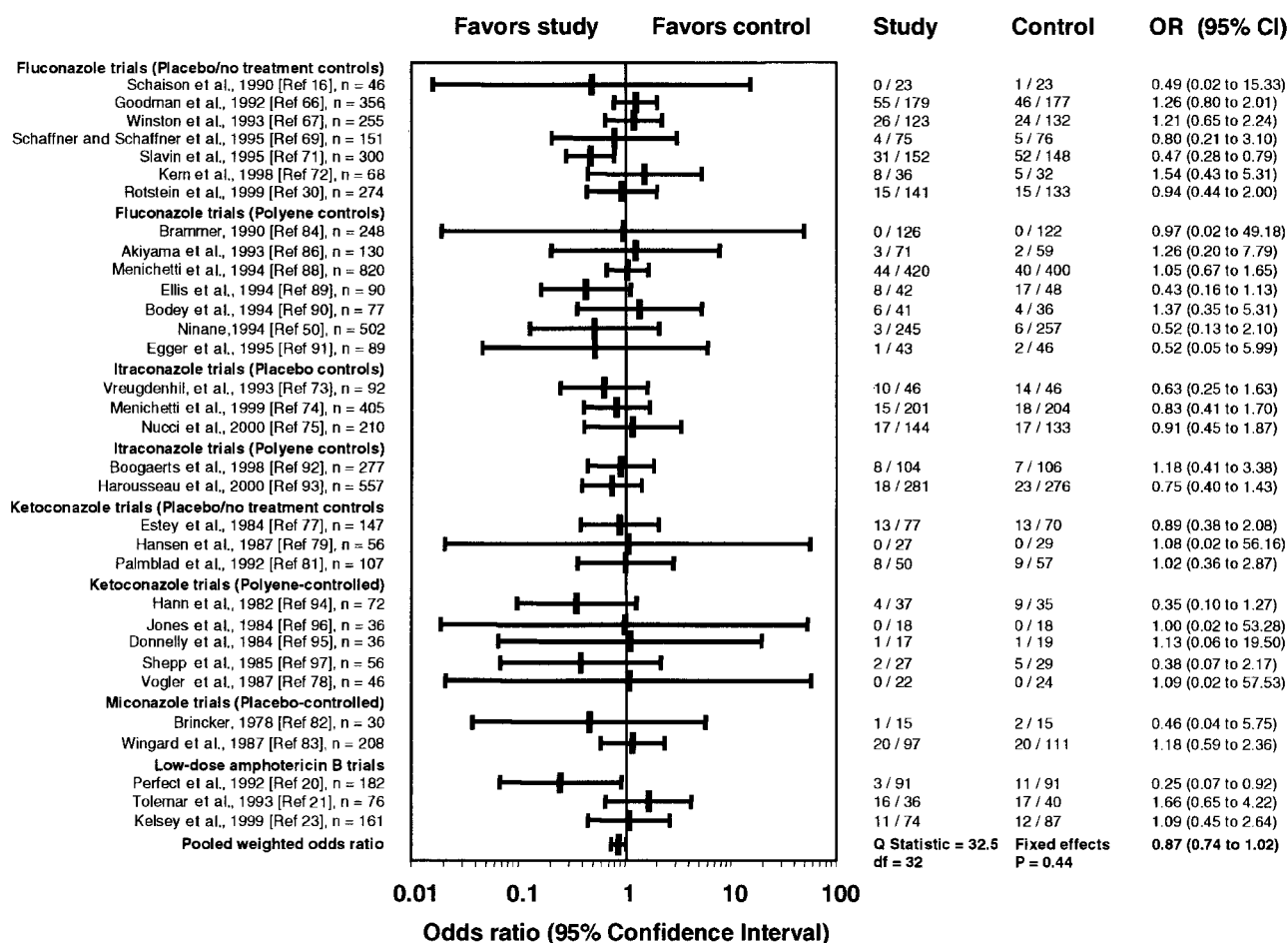


FIGURE 4. Treatment effects for overall mortality. Results are shown as the odds ratio (OR) with 95% confidence interval (95% CI) for 33 individual trials together with the pooled, weighted OR based on a fixed-effects model and the results of the homogeneity testing (Q statistic, chi-square test). Ref: reference number; LD-AmB: low-dose intravenous amphotericin B; df: degrees of freedom.

DISCUSSION

This meta-analysis of antifungal prophylaxis in neutropenic patients with malignant disease represents the largest systematic review of this subject to date. We sought to determine whether antifungal prophylaxis as a supportive strategy could affect a variety of clinically important outcomes. In the analyses of all study agents, we identified important treatment effects similar to the effects reported previously only for fluconazole,²⁰ namely, reductions in the use of parenteral antifungal therapy, superficial fungal infection, invasive fungal infection, and fungal infection-related mortality, despite the inclusion in our analysis of many underpowered, heterogeneous, and less well-controlled trials. Although, like Gøtzsche and Johansen,²⁹ we found no overall effect on mortality, in subgroup analyses, we were able to demonstrate a treatment-related reduction in overall mortality for high-risk patients with prolonged neutropenia. We also confirmed the observations of Marr and col-

leagues⁹⁸ demonstrating a reduction in overall mortality among HSCT recipients. Despite the sample size, the incidence of invasive aspergillosis was too low to detect a treatment effect, even among itraconazole-based trials (OR, 0.91; 95% CI, 0.19–1.64).

The factors associated with increased risk of fungal infection include the use of indwelling central venous access devices,^{99,100} fungal colonization,^{19,101} prolonged neutropenia,^{30,102,103} cytotoxic therapy-induced intestinal mucosal damage,^{3,4} remission induction therapy for patients with acute myeloid leukemia,³⁰ allogeneic HSCT,⁴ treatment for patients with suspected or proven graft-versus-disease,¹⁰⁴ management of patients undergoing allogeneic HSCT outside of a high-efficiency particulate air-filtered/laminar air-flow-protected environment,^{98,105} and autologous HSCT unsupported by hematopoietic growth factors.³⁰ Although we attempted to examine factors that were correlated with outcome, a complete analysis in this regard was not possible because of the lack

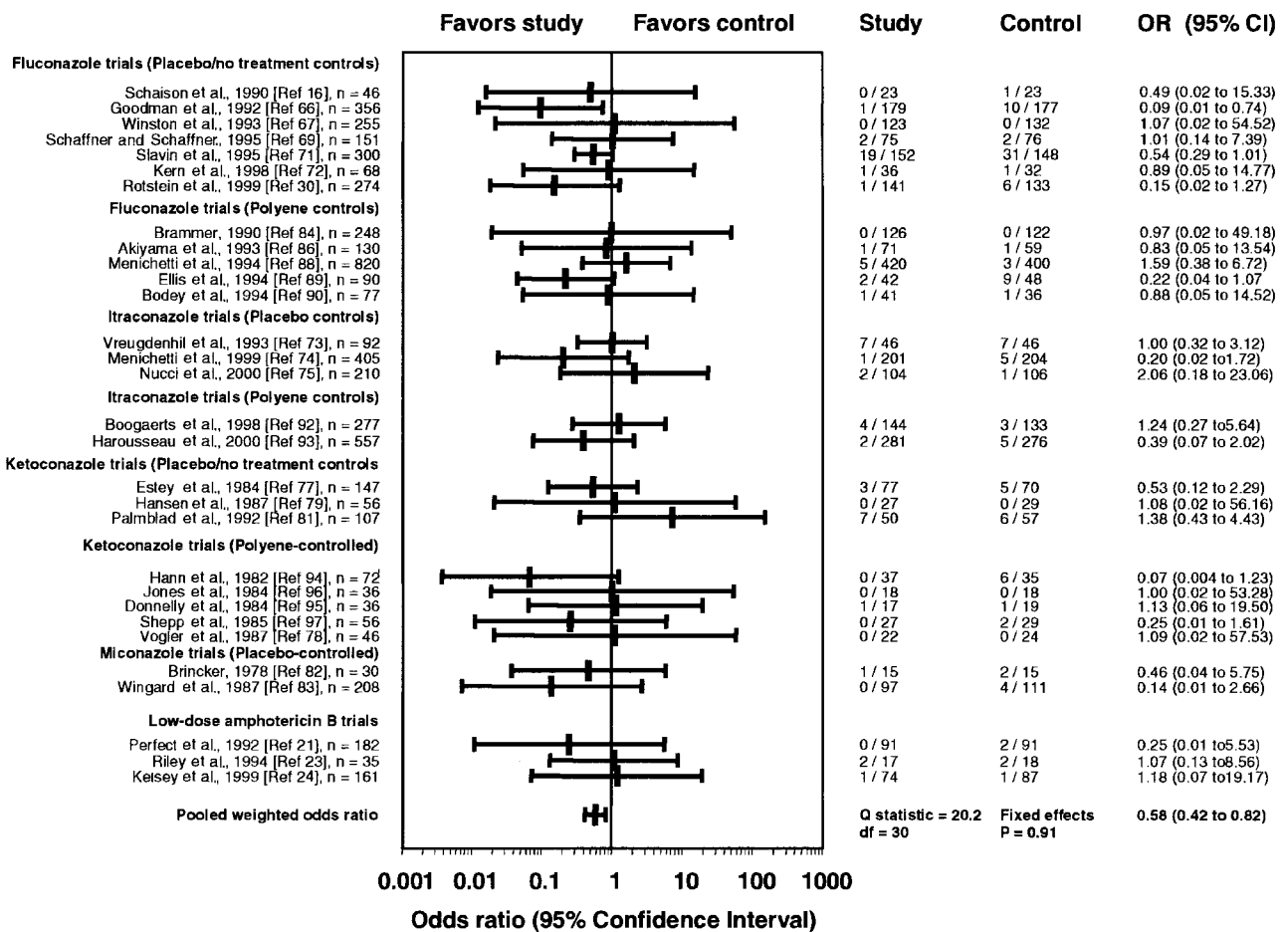


FIGURE 5. Treatment effects for fungal infection-related mortality. Results are shown as the odds ratio (OR) with 95% confidence interval (95% CI) for 31 individual trials together with the pooled, weighted Or based on a fixed-effects model and the results of the homogeneity testing (Q statistic chi-square test). Ref: reference number; LD-AmB: low-dose intravenous amphotericin B; df: degrees of freedom.

of information in the trials reviewed for this study. Despite these limitations, we were able to examine the correlations between treatment effects and outcome for patient-related factors, such as age and gender; disease-related factors, such as a diagnosis of acute leukemia; treatment-related factors, such as HSCT and duration of neutropenia; and study design-related factors, such as trial quality and active versus placebo or no treatment controls. However, we did not evaluate fungal colonization, because this had been evaluated in two previous meta-analyses.^{20,29}

Like the meta-analysis of Kanda and colleagues,²⁰ we identified HSCT recipients as a group for which a prophylaxis-related reduction in empiric parenteral antifungal therapy (prophylaxis success), proven invasive fungal infection, and fungal infection-related mortality could be demonstrated. Kanda et al. demonstrated reductions in invasive fungal infections for trials in which the event rate among control participants was $\geq 15\%$.²⁰ We extended those observations to

include prophylaxis success, overall mortality, and fungal infection-related mortality. Unlike Kanda et al.,²⁰ however, we were unable to detect a reduction in superficial fungal infection in HSCT trials. Our analysis of superficial fungal infection in HSCT recipients included trials that evaluated low-dose intravenous amphotericin B formulations,²¹⁻²⁴ a ketoconazole trial,⁸⁰ and two fluconazole trials.^{66,71} The amphotericin B-based trials failed to reduce superficial fungal infections, whereas the azole-based trials demonstrated a treatment effect on superficial fungal infections, suggesting a possible treatment advantage for this latter class of antifungal agents.

Only one direct comparison of fluconazole and a lipid-based formulation of amphotericin B has been published; however, that trial was inconclusive because of early termination due to toxicity.²⁵ Accordingly, the question of the relative benefits of these agents must await further, well-designed, randomized-controlled trials.

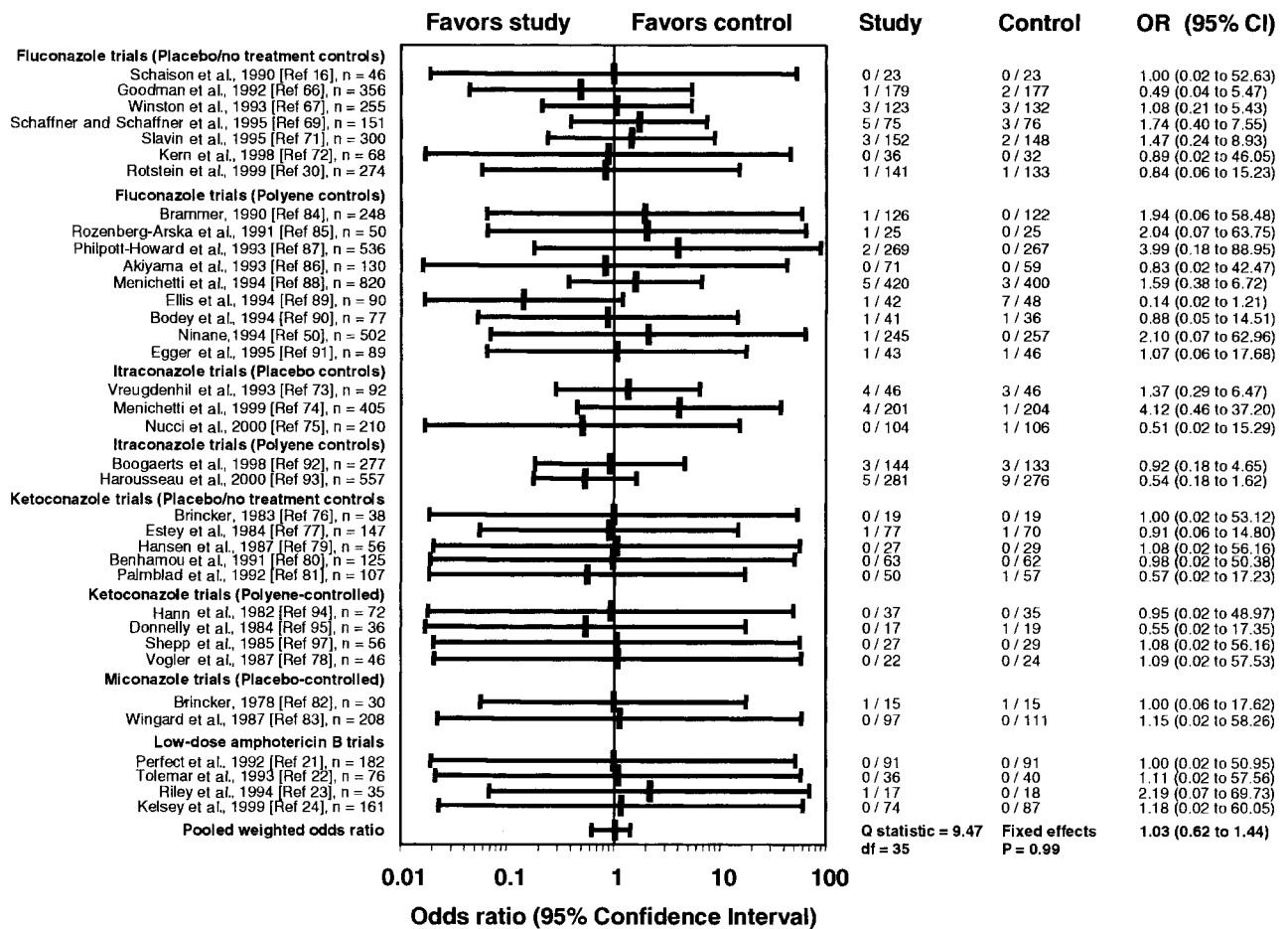


FIGURE 6. Treatment effects for proven invasive aspergillosis. Results are shown as the odds ratio (OR) with 95% confidence interval (95% CI) for 36 individual trials together with the pooled, weighted OR based on a fixed-effects model and the results of the homogeneity testing (Q statistic, chi-square test). Ref: reference number; LD-AmB: low-dose intravenous amphotericin B; df: degrees of freedom.

We were able to demonstrate a prophylaxis benefit in non-HSCT trials with respect to prophylaxis success and proven invasive fungal infection, whereas others had not.²⁰ These differences may be related to relatively larger differences in event rates for these outcomes among the control groups in the HSCT and non-HSCT trials evaluated in our study compared with the study by Kanda et al.²⁰

There has been concern that antifungal prophylaxis with agents like fluconazole would lead to a selection for and infection by azole-resistant fungi.^{55,106,107} This has not been observed in clinical practice, however.^{18-20,108} In fact, recent observations suggest that patients who had been receiving azole-based or polyene-based, antifungal prophylaxis and who require empiric antifungal therapy for persistent fever may respond very well to empiric administration of broad-spectrum triazole agents, such as itraconazole or voriconazole.^{109,110} Although an increased rate of invasive aspergillosis among fluconazole prophylaxis recipi-

ents, compared with itraconazole, has been reported,⁶⁴ our analysis failed to demonstrate any such tendency, again suggesting that the clinical consequences of prophylaxis-related selection toward more resistant fungi may not be as dire as once feared.

We failed to detect treatment effects among the azoles, except for the fluconazole-related reduction in fungal infection-related mortality, the possible advantage of fluconazole over itraconazole with respect to superficial fungal infection, and the failure of miconazole to affect invasive fungal infection. We were unable to detect evidence that antifungal chemoprophylaxis affected the incidence of invasive aspergillosis. This observation is surprising and stands in contrast to the results of a recent, large, multicenter British study,⁶⁴ suggesting the superiority of itraconazole oral solution (5 mg/kg per day) over fluconazole oral solution (100 mg per day) for preventing aspergillosis in neutropenic patients with malignant disease. The difference in this trial, however, was related to an outbreak of invasive aspergillosis at

TABLE 3
Subgroup Analyses: Treatment Effects by Analysis and Outcome

Analysis	Pooled, weighted odds ratio for each outcome (95% confidence interval)					
	Prophylaxis success	Superficial fungal infection	Invasive fungal infection	Overall mortality	Fungal infection-related mortality	Aspergillosis
TQS > 3	0.61 (0.53–0.69)	0.35 (0.23–0.54)	0.46 (0.35–0.59)	0.88 (0.74–1.04)	0.59 (0.41–0.86)	0.99 (0.63–1.56)
Pediatric trials excluded	0.56 (0.48–0.67)	0.32 (0.21–0.48)	0.47 (0.37–0.60)	0.83 (0.70–0.99)	0.62 (0.44–0.88)	1.04 (0.68–1.60)
Adult trials excluded	0.66 (0.51–0.87)	0.19 (0.12–0.32)	0.25 (0.13–0.48)	1.11 (0.73–1.70)	0.26 (0.07–1.01)	0.91 (0.24–3.41)
HSCT excluded	0.60 (0.50–0.71)	0.26 (0.17–0.37)	0.50 (0.39–0.65)	0.91 (0.75–1.11)	0.67 (0.43–1.03)	1.02 (0.66–1.59)
Non-HSCT excluded	0.51 (0.40–0.65)	0.51 (0.22–1.16)	0.26 (0.16–0.42)	0.62 (0.33–1.17)	0.48 (0.28–0.82)	1.10 (0.38–3.18)
Duration of neutropenia > 15 days	0.55 (0.45–0.68)	0.54 (0.40–0.74)	0.51 (0.38–0.69)	0.76 (0.62–0.94)	0.65 (0.44–0.95)	0.95 (0.57–1.59)
Duration of neutropenia < 22 days	0.58 (0.49–0.69)	0.27 (0.19–0.40)	0.43 (0.34–0.55)	0.85 (0.71–1.01)	0.56 (0.39–0.83)	1.01 (0.65–1.57)
Study design:						
1. Azoles vs. placebo/NT	0.54 (0.44–0.66)	0.25 (0.15–0.40)	0.41 (0.31–0.56)	0.92 (0.75–1.14)	0.56 (0.37–0.85)	1.22 (0.68–2.20)
2. Azoles vs. polyenes	0.63 (0.49–0.81)	0.26 (0.15–0.45)	0.51 (0.35–0.74)	0.82 (0.62–1.08)	0.64 (0.34–1.21)	0.85 (0.47–1.53)
3. LD-AmB vs. placebo	0.54 (0.34–0.84)	0.87 (0.54–1.42)	0.23 (0.09–0.61)	0.51 (0.15–1.68)	0.63 (0.18–2.16)	1.35 (0.20–9.01)
4. Fluconazole trials	0.58 (0.46–0.74)	0.20 (0.15–0.28)	0.39 (0.29–0.54)	0.91 (0.73–1.13)	0.53 (0.34–0.83)	1.13 (0.63–2.03)
5. Itraconazole trials	0.67 (0.54–0.82)	0.43 (0.24–0.79)	0.61 (0.38–0.98)	0.83 (0.59–1.17)	0.78 (0.38–1.60)	0.91 (0.44–1.88)
6. Ketoconazole trials	0.56 (0.32–0.97)	0.24 (0.12–0.49)	0.49 (0.28–0.83)	0.74 (0.44–1.26)	0.63 (0.24–1.63)	0.86 (0.26–2.89)
7. Miconazole trials	0.49 (0.28–0.85)	0.14 (0.01–1.42)	0.22 (0.04–1.12)	1.11 (0.57–2.15)	0.28 (0.04–1.90)	1.05 (0.10–10.64)

TQS: trial quality score; HSCT: hematopoietic stem cell transplantation; NT: no-treatment; LD-AmB: low-dose intravenous amphotericin B.

TABLE 4
Predictors of Treatment Effects in Clinical Trials of Antifungal Prophylaxis

Outcome and predictors	Multivariate P value
Prophylaxis success (model $P < 0.0001$)	
High rates of proven IFI in controls	< 0.0001
Higher azole doses	0.0131
HSCT	0.085
Allogeneic HSCT	0.0327
Prolonged neutropenia	0.0824
Superficial fungal infection (model $P = 0.0012$)	
Non-HSCT	0.0012
Invasive fungal infections (model $P = 0.0043$)	
High rates of proven IFI in controls	0.0012
HSCT	0.0021
Higher azole doses	0.0043
Allogeneic HSCT	0.009
Overall mortality (model $P = 0.0073$)	
HSCT with prolonged neutropenia	0.0341
High rates of proven IFI in controls	0.0063
Fungal infection-related mortality (model $P = 0.0178$)	
Acute leukemia with longer duration of neutropenia	0.0178

IFI: invasive fungal infection; HSCT: hematopoietic stem cell transplantation.

one institution. Itraconazole would be expected to have the greatest treatment effect among HSCT recipients; however, the proportion of such patients among participants in the itraconazole trials reviewed in our study was low. Accordingly, the overall incidence of aspergil-

losis in the control groups in our analysis was too low to detect any treatment effect.

Fungal infection-related mortality was included in our analyses, because we felt that it was important to evaluate investigators' impressions about the role fungal infection played in the mortality rates in their respective studies. Although overall mortality is viewed by some as a more sensitive, less biased measure of treatment effect,²⁹ other factors independent of the antifungal treatment effect, including the type of cytotoxic therapy, patient age, or status of the underlying disease, may influence the risk of death during the study period. Previous meta-analyses have not demonstrated a treatment effect on overall mortality^{20,29} despite observations to the contrary among different populations of HSCT recipients from single centers.^{98,111} The metaregression analyses in this study detected treatment effects for overall mortality among studies characterized by a high proportion of acute leukemia patients as well as in HSCT recipients, particularly in the setting of prolonged neutropenia. These observations and those of other authors⁹⁸ underscore the need to accurately define patient groups with the greatest risk for invasive fungal infection.

The Centers for Disease Control, the Infectious Diseases Society of America, and the American Society for Blood and Marrow Transplantation have recommended the use of fluconazole at 400 mg daily orally or intrave-

nously to prevent invasive disease due to fluconazole-susceptible *Candida* spp. during neutropenia until engraftment among HSCT recipients.¹¹² Some of the accrued benefits from this strategy also may be due to a treatment effect related to prolonged prophylaxis beyond engraftment on the event rate for graft-versus-host disease, particularly gut-related, which, in turn, may reduce the risk for invasive fungal infection and mortality.⁹⁸ This may become more important with the increased use of unrelated donors and peripheral blood as stem cell sources that have been associated with a greater risk for acute or chronic graft-versus-host disease.^{98,104,113–118} Our observations regarding the use of azoles, particularly fluconazole, at doses > 200 mg daily and HSCT support these recommendations. The use of other oral agents, such as ketoconazole tablets and itraconazole capsules or solution,¹¹⁹ which may be influenced by problems of absorption and drug interactions, are not recommended currently in HSCT recipients.¹¹² Our observations also support the use of low-dose, intravenous amphotericin B as antifungal prophylaxis to prevent the administration of full-dose, parenteral amphotericin B and invasive fungal infection but not to reduce overall mortality or fungal infection-related mortality.

Finally, it appears that antifungal prophylaxis may have measurable benefits for other specified groups of neutropenic, non-HSCT patients with malignant disease, including patients who are undergoing remission induction therapy for acute myeloid leukemia, particularly if a cytarabine plus anthracycline, 7 + 3-type regimen or a high-dose, cytarabine-based regimen is prescribed,³⁰ as we demonstrated in our subgroup analysis. Further study is needed to provide clinicians with a more precise identification of the patients who are most susceptible to invasive fungal infection and, thus, will benefit most from antifungal chemoprophylaxis.

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