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Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, *Candida* Colonization, and Multiple Organ Failure

The EMPIRICUS Randomized Clinical Trial

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IMPORTANCE Although frequently used in treating intensive care unit (ICU) patients with sepsis, empirical antifungal therapy, initiated for suspected fungal infection, has not been shown to improve outcome.

OBJECTIVE To determine whether empirical micafungin reduces invasive fungal infection (IFI)–free survival at day 28.

DESIGN, SETTING, AND PARTICIPANTS Multicenter double-blind placebo-controlled study of 260 nonneutropenic, nontransplanted, critically ill patients with ICU-acquired sepsis, multiple *Candida* colonization, multiple organ failure, exposed to broad-spectrum antibacterial agents, and enrolled between July 2012 and February 2015 in 19 French ICUs.

INTERVENTIONS Empirical treatment with micafungin (100 mg, once daily, for 14 days) (n = 131) vs placebo (n = 129).

MAIN OUTCOMES AND MEASURES The primary end point was survival without proven IFI 28 days after randomization. Key secondary end points included new proven fungal infections, survival at day 28 and day 90, organ failure, serum (1-3)-β-D-glucan level evolution, and incidence of ventilator-associated bacterial pneumonia.

RESULTS Among 260 patients (mean age 63 years; 91 [35%] women), 251 (128, micafungin group; 123, placebo group) were included in the modified intent-to-treat analysis. Median values were 8 for Sequential Organ Failure Assessment (SOFA) score, 3 for number of *Candida*-colonized sites, and 99 pg/mL for level of (1-3)-β-D-glucan. On day 28, there were 82 (68%) patients in the micafungin group vs 79 (60.2%) in the placebo group who were alive and IFI free (hazard ratio [HR], 1.35 [95% CI, 0.87-2.08]). Results were similar among patients with a (1-3)-β-D-glucan level of greater than 80 pg/mL (n = 175; HR, 1.41 [95% CI, 0.85-2.33]). Day-28 IFI–free survival in patients with a high SOFA score (>8) was not significantly different when compared between the micafungin vs placebo groups (HR, 1.69 [95% CI, 0.96-2.94]). Use of empirical micafungin decreased the rate of new invasive fungal infection in 4 of 128 patients (3%) in the micafungin group vs placebo (15/123 patients [12%]) (P = .008).

CONCLUSIONS AND RELEVANCE Among nonneutropenic critically ill patients with ICU-acquired sepsis, *Candida* species colonization at multiple sites, and multiple organ failure, empirical treatment with micafungin, compared with placebo, did not increase fungal infection–free survival at day 28.

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Supplemental content

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Despite the development of effective and safer drugs, invasive candidiasis and candidemia remain associated with high and increasing mortality,[1] particularly when complicated by septic shock.[2] The optimal management of *Candida* species infections includes early awareness of patients at risk, control of the infection source, and timely administration of appropriate antifungal agents.[2-5] Consequently, antifungal agents have been widely used as empirical therapy, ie, for treating suspected fungal infection in patients at risk for invasive candidiasis or patients with unresolved sepsis.[6-9]

Two multicenter randomized clinical trials evaluated empirical antifungal therapy for fungal infection suspicion in patients with a central catheter and persistent fever despite treatment with broad-spectrum antibacterial agents. One study demonstrated that empirical fluconazole did not improve clinical outcomes vs placebo in patients at high risk for invasive candidiasis.[5] Another trial evaluated antifungal prophylaxis using caspofungin among intensive care unit (ICU) patients with at least 2 risk factors for candidemia.[10] Caspofungin failed to significantly improve the primary end point, as proven or probable invasive candidiasis occurred in 16.7% of the placebo recipients vs 9.8% of the caspofungin recipients. There was no difference in mortality across groups. Subsequently, empirical antifungal therapy was incorporated into guidelines for nonimmunocompromised critically ill patients with unresolved ICU-acquired sepsis.[11] Despite lack of evidence-based data, as much as 8% of ICU patients without documented *Candida* infection receive antifungal agents.[12,13] The number of organ system failures and incidences of *Candida* colonization at multiple sites and high serum (1-3)-β-D-glucan levels have been well established as risk factors for candidemia.[14,15] To our knowledge, no randomized clinical trial of colonization-driven empirical therapy has been performed in critically ill patients at risk for invasive candidiasis.

The multicenter, double-blind, placebo-controlled EMPIRICUS (Empirical Antifungal Treatment in ICUS) trial was designed to evaluate whether micafungin, as compared with placebo, increases 28-day invasive fungal infection–free survival among patients with ICU-acquired sepsis, *Candida* colonization at multiple sites, and multiple organ failure.

Key Points

Question Does empirical antifungal therapy increase invasive fungal infection–free survival at day 28 in nonneutropenic critically ill patients with sepsis, multiple *Candida* colonization, and multiple organ failure exposed to broad-spectrum antibacterials?

Findings In this randomized clinical trial of 260 adults, there was no significant difference in the rate of survivors without any fungal infection at day 28 between micafungin-treated (87/128 [68%]) and placebo-treated (74/123 [60.2%]) groups.

Meaning The use of micafungin as a routine empirical treatment in critically ill patients with suspected fungal infection did not improve fungal infection–free survival at 28 days.

Methods

Study Design and Oversights

The study design has been published elsewhere[16] and the trial protocol is reported in Supplement 1.

EMPIRICUS, a multicenter, randomized, double-blind, and parallel-group study, compared the benefit from a 14-day empirical treatment with micafungin (100 mg administered intraveneously, 1×/d) vs placebo associated with day-28 survival without invasive fungal infection among adult patients with suspected invasive candidiasis.

Empirical treatment was defined as an antifungal treatment for suspected nondocumented invasive fungal infection in patients with unresolved sepsis despite broad-spectrum antibacterial therapy for at least 4 days and multiple sites colonized with *Candida* species.

The study involved 19 ICUs in France and was approved by an authorized ethics committee (Comité de Protection des Personnes CPP Sud Est V; December 7, 2011; see the trial protocol in Supplement 1) and the French Health Authorities (AFSSAPS; December 2, 2011).

Written informed consent was obtained from all participants or their proxies (in cases of impaired decision-making capacity) at the time of enrollment.

Patients and Randomization

Inclusion Criteria

Critically ill adult patients were eligible for the study if they met the following criteria: (1) mechanically ventilated at least 5 days; (2) with at least 1 colonization site (other than rectal swab or stool) positive for *Candida* species using traditional culture methods; (3) at least 1 additional organ dysfunction; (4) previous treatment for more than 4 days using broad-spectrum antibacterial agents within the last 7 days; (5) 1 arterial or central vein catheter, and (6) 1 new finding of ICU-acquired sepsis of unknown origin (eBox in Supplement 2).

Exclusion Criteria

Main exclusion criteria were as follows: (1) neutrophil count of less than 500/mm^3; (2) previous bone marrow or solid organ transplantation; (3) ongoing systemic immunosuppressant agent therapy other than corticosteroids at doses lower than 2 mg/kg/d of prednisolone or equivalent; and (4) antifungal treatment with an echinocandin agent for more than 1 day or with any other antifungal agent for more than 72 hours during the week prior to inclusion[16] (see trial protocol in Supplement 1 and the statistical analysis plan in Supplement 3).

Randomization

Permuted-block randomization with varying block sizes between groups used a web-based system programmed by an independent statistician. Immediately after randomization and for 14 days, the research pharmacists prepared reconstituted opaque bags of micafungin or placebo according to the randomization list and provided it to the site for infusion. [16]

A set for blood culture inoculated with 10 mL of blood in aerobic, anaerobic, and selective milieu were drawn at inclusion before administration of the study drug. During the opening visit of each center, investigators were instructed to perform blood cultures, puncture or evacuation of possible infected sites, funduscopy, and echocardiography to confirm the fungal nature of any subsequent episodes of sepsis during the follow-up.

If the invasive candidiasis at inclusion was evidenced after randomization by the analysis of baseline samples (ie, results not available at randomization), or if the investigator started another antifungal treatment, the study treatment was withdrawn and the antifungal treatment usually prescribed at the investigation site was administered to the patient. However, blinding was not compromised, and the patient remained in the modified intent-to-treat (ITT) analysis. The end point was judged as the occurrence of a new invasive fungal infection or death within 28 days of inclusion.

Data collection and study management are detailed elsewhere (Supplement 1).[16] Database lock and adjudication of all suspected or proven invasive candidiasis were performed before unblinding of the study. The independent adjudication committee reviewed records of all patients with new antifungal treatment and with positive culture from blood, operative room, or direct percutaneous puncture of sterile sites. Additionally, the committee reviewed records of patients with suspicion of documented infections and interviewed investigators by phone when questions were not solved by e-mail. Final judgment was unanimous in all cases.

End Points

The primary end point was 28-day survival free of proven invasive fungal infection, as defined according to adapted version of Tissot et al of the EORTC/MSG (European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group) definitions from 2008.[17]

Prespecified secondary end points included new proven invasive fungal infections during the follow-up, survival at day 28 and at day 90 (3 months after randomization), antifungal-free survival at day 28, incidence of ventilator-associated bacterial pneumonia, and evolution throughout the 28-day study period of the Sequential Organ Failure Assessment (SOFA) score (range, 0-24 with higher scores indicating worse outcome) and of the serum level of (1-3)-β-D-glucan (a fungal cell antigen identified in blood of patients with fungal infection). The primary end point was assessed also in prespecified patient subgroups at increased risk of fungal infection (medical vs surgical, low vs high SOFA score, low vs high (1-3)-β-D-glucan level, low vs high colonization index, Candida score <3 vs ≥3) and the pharmacokinetic and safety profiles of micafungin. The pharmacokinetics of micafungin were assessed after the first intravenous administration through the evaluation of the plasmatic peak (Cmax) and plasmatic trough (Cmin), which enabled calculation of parameters such as the area under the curve (AUC) of the plasmatic concentrations. Other additional outcomes not reported in the text were hospital survival, mechanical ventilation–free days, and colonization index during follow-up. Molecular biomarkers and molecular markers of resistance of recovered strains from blood cultures will need further analyses.

Statistical Analysis

Sample Size Calculation

As previously published,[16] it was estimated that (1) the mortality of patients fulfilling the selection criteria would be between 30% and 37%; (2) the candidemia-related mortality in case of early treatment would be 12% instead of 35% when the treatment is delayed (current practice); (3) according to Schuster et al,[5] invasive fungal infection would be diagnosed in 7.1% of patients receiving antifungal therapy and 20.8% of those receiving placebo (absolute difference 13.7%); and (4) the sensitivity of conventional diagnostic tests (blood cultures, culture of sterile site) of invasive fungal infection diagnosis would be 60%.[18] Therefore, in the micafungin group, the actual incidence of invasive fungal infections would be estimated at 11.8% (7.1%/0.6), the rate of candidemia-related mortality at 1.4% (11.8% × 12%), and the rate of overall events between 31.4% and 38.4%. In the placebo group, the rate of candidemia-related mortality would be estimated at 4.13% (11.8% × 35%), the number of additional invasive fungal infections diagnosed after randomization at 13.7%,[5] and the rate of overall events between 49.4% and 56.4%. A difference of 18%, considering the lower and upper estimations of overall event rates in both groups, was therefore hypothesized.

A 2-sided log-rank test with an overall sample size of 235 patients (118 in the micafungin group and 117 in the placebo group) would achieve an ability to detect a difference of 18% in the primary end point with an 80% power at a 0.05 significance level. The hypothesis used was then to increase the proportion of patients surviving free of proven invasive fungal infection from 37% in the placebo group to 55% in the micafungin group. To account for secondary dropouts, 260 patients (130 in each group) were needed.

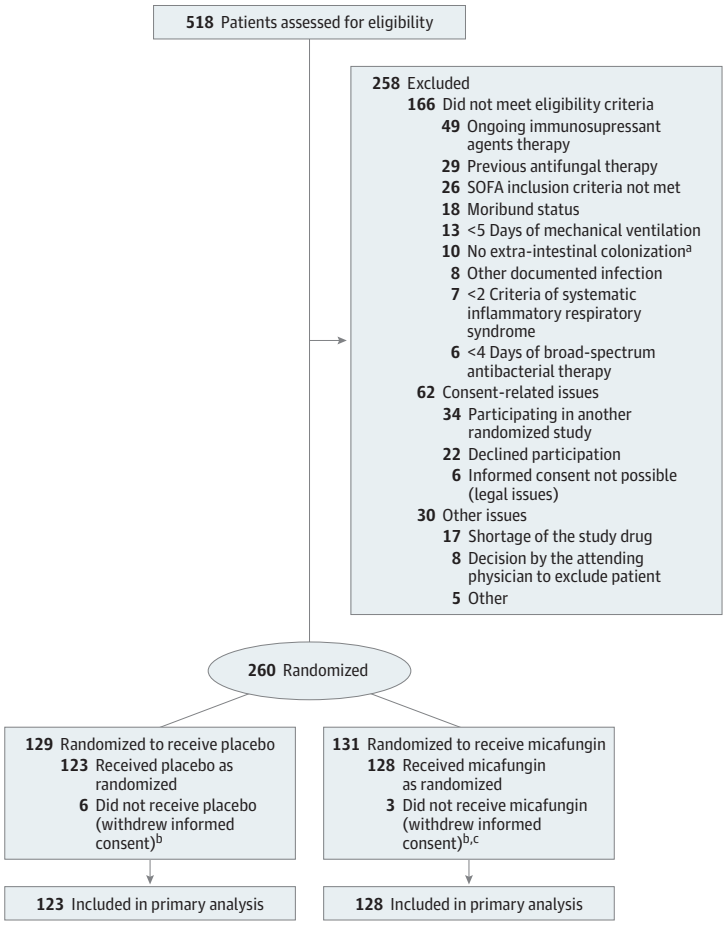
Statistical Analyses Performed by Data

Analyses were calculated using SAS 9.4 (SAS, Inc) and R (R Foundation for Statistical Computing) software. Comparisons were performed with a modified ITT population. A 2-sided *P* value of .05 or less was considered statistically significant.

All patients who received at least 1 dose of study treatment were included in the modified ITT analysis.

Missing, unused, or outlying data were checked with investigators via queries. For instances in which missing values were confirmed, data concerning the independent variables were replaced using multiple-imputation methods. Data were reported as numbers (percentages) or medians (interquartile ranges [IQRs]). Continuous variables were compared using the Wilcoxon rank-sum test, and the Fisher exact test was used for proportions. Death or proven invasive fungal infection (primary end point) were evaluated at day 28 and analyzed using survival methods and the Kaplan-Meier estimate (stratified by center). A Cox model was used for adjustment of parameters imbalanced between groups.

Figure 1. Flow of EMPIRICUS Patients From Eligibility Assessment to Primary Analysis



[a] No other colonization sites than the stools or rectal swab were positive with *Candida*.

[b] According to the French law, data from patients who withdrew informed consent after inclusion (3 in the micafungin group and 6 in the placebo group) was destroyed and not taken into account in the modified intent-to-treat analysis.

[c] One patient (micafungin group) from the modified intent-to-treat population had only 1 dose of study drug administered.

EMPIRICUS indicates Empirical Antifungal Treatment in ICUS; SOFA, Sequential Organ Failure Assessment.

Proportionality assumption was tested using cumulative sums of martingale-based residuals. Analyses were 2-tailed and stratified by center. A generalized estimating equation, stratified by centers, was used to estimate the effect of the study drug on (1-3)-β-D-glucan. The statistical analysis plan was previously published[16] (Supplement 3). Pharmacokinetic assessment used a population approach to obtain individual Bayesian estimates of micafungin clearance (used to calculate the AUC of micafungin for each patient pie, AUC = dose/clearance]).[19,20]

Results

Study Patients

From July 20, 2012, to February 7, 2015, a total of 260 patients in 19 ICUs were randomized. After database lock (September 30, 2015), 251 of them were included in the modified ITT analysis (**Figure 1**). Patients' characteristics were well-balanced between groups, except for diabetes and body mass index (**Table 1**). The study patients were severely ill, as reflected by their overall Simplified Acute Physiology Score (SAPS II) (range, 0-124 with higher scores indicating worse outcome), with a median score of 48 (IQR, 39-57) and an overall median SOFA score of 8 (IQR, 6-11) at randomization. Vasopressors were administered to more than 50% of the patients, and renal replacement therapy to 1 of 3. All patients had multiple risk factors for invasive fungal infection. The median number of sites colonized at inclusion were 3 (IQR, 2-4 [range, 1-7]; eTable 1 in Supplement 2). The (1-3)-β-D-glucan level was greater than 80 pg/mL in 175 (70%) patients (**Figure 2**).

Eighty-seven (68%) patients in the micafungin group vs 74 (60.2%) patients in the placebo group were alive and free from invasive fungal infection at day 28 (hazard ratio [HR], 1.35 [95% CI, 0.87-2.08]; Figure 2). Results of the primary end point regarding various predefined subgroups of interest are reported in Figure 2 for the modified ITT population (with HRs substantially favoring the micafungin group for patients with [1-3]-β-D-glucan levels >80 pg/mL, [1-3]-β-D-glucan levels of 250 pg/mL, Candida scores at ≥3, and colonization index ≥50%). Unadjusted analyses provided similar results (eFigures 1 and 2; eTable 2 in Supplement 2). A posthoc analysis, not taking into account the 12 patients with invasive fungal infection at inclusion, had similar results (HR, 1.39 [95% CI, 0.88-2.22]; P = .15).

Day-28 survival was not significantly different between micafungin and placebo groups (**Figure 3**; eFigures 3 and 4 in Supplement 2). Similar results were observed for day-90 survival

Table 1. Characteristics of Patients With ICU-Acquired Sepsis, Multiple *Candida* Colonization, and Multiple Organ Failure

	No. (%)[a]		
	All Patients N = 251)	Micafungin (n = 128)	Placebo (n = 123)
Age, median (IQR), y	64 (53-74)	65 (56-74)	64 (52-74)
Men	163 (65)	81 (66)	82 (64)
Weight, median (IQR), kg	82 (70-96)	84 (72-97)	80 (68-95)
Body mass index[b]			
Not recorded	42 (17)	24 (20)	18 (14)
≤30	121 (48)	49 (40)	72 (56)
>30	88 (35)	50 (41)	38 (30)
Chronic disease categories[c]			
Cardiac	64 (26)	30 (24)	34 (27)
Respiratory	53 (21)	20 (16)	33 (26)
Hepatic	25 (10)	11 (9)	14 (11)
Renal	22 (9)	15 (12)	7 (6)
Immunosuppression	12 (5)	4 (3)	8 (6)
Diabetes	67 (27)	42 (34)	25 (20)
Cancer	13 (5)	4 (3)	9 (7)
Receiving corticosteroids	22 (9)	11 (9)	11 (9)
SAPS II score at admission, median (IQR)[d]	48 (39-57)	49 (37-57)	48 (41-58)
Admission category			
Medical	186 (74)	92 (75)	94 (73)
Emergency surgery	60 (24)	29 (24)	31 (24)
Scheduled surgery	5 (2)	2 (2)	3 (2)
Main surgical procedures			
Cardiac	50 (20)	25 (20)	25 (20)
Abdominal	13 (5)	5 (4)	8 (6)
Other surgery or trauma	6 (2)	2 (2)	4 (3)
Main reason for ICU admission			
Acute respiratory failure	102 (40)	48 (39)	54 (41)
Septic shock	85 (34)	37 (31)	48 (37)
Cardiogenic shock	38 (15)	21 (17)	17 (13)
Coma	25 (10)	15 (12)	10 (8)
Acute pancreatitis	14 (6)	7 (6)	7 (6)
Duration of ICU stay prior to inclusion, median (IQR), d	10 (7-16)	11 (7-17)	10 (7-15)
Variables assessed at inclusion			
SOFA score, median (IQR)[d]	8 (6-11)	8 (5-12)	8 (6-11)
Candida score, median (IQR)	3 (2-4)	3 (2.5-4)	3 (2-4)
No. of positive colonization sites, median (IQR)	3 (2-4)	3 (2-4)	3 (2-4)
Epinephrine or norepinephrine use	141 (56)	70 (57)	71 (56)
Dialysis or hemofiltration	82 (33)	42 (34)	40 (31)
Parenteral nutrition	65 (26)	30 (24)	35 (27)

Abbreviations: ICU, intensive care unit; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

[a] Values are reported as No. (%) unless otherwise indicated.

[b] Body mass index was calculated as weight in kilograms divided by height in meters squared. Nine missing values of weight were imputed.

[c] Chronic diseases used Knaus definitions.[21]

[d] Higher scores indicate worse outcome (SAPS II range, 0-124; SOFA range, 0-24).

(eFigure 5 and eTable 3 in Supplement 2) and for the antifungal therapy-free survival rate (eFigure 6 in Supplement 2).

After inclusion, during the study follow-up, 15 (12%) patients in the placebo group and 4 (3%) patients in the micafungin group developed at least 1 new proven invasive fungal infection (P = .008) (**Table 2**). Of these 19 patients, 1 out of 4 (25%) in the micafungin group and 3 out of 15 (20%) in the placebo group died before day 28.

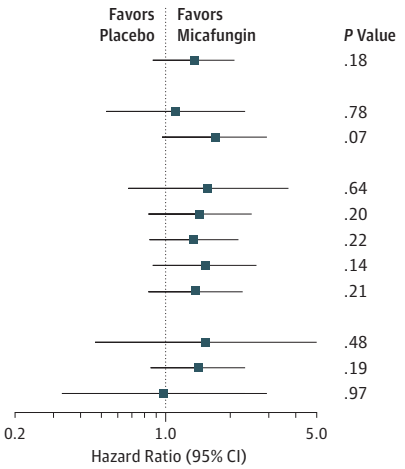
Other secondary end points, such as the number of organ failure–free days and the rate of ventilator-acquired pneumonia, were not significantly different between both groups (eTable 3 in Supplement 2).

After the first dose of micafungin, the mean (SD) Cmax level was 7.26 (2.43) mg/L (median, 7.4 [IQR, 5.4-9.2]), the mean (SD) Cmin level was 1.6 (0.54) mg/L (median, 2.1 [IQR, 1.4-3.1]), and the mean (SD) AUC was 78.2 (33.2) mg.h/L.

The drug was well tolerated with few adverse events; especially, liver enzymes variations were similar between micafungin and control groups (eTables 4 and 5; eFigures 7 and 8 in Supplement 2).

Figure 2. Comparison of Fungal Infection–Free Survival at Day 28 in the Modified Intent-to-Treat Population and in Predefined Subgroups

	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	*P* Value
All patients	87	128	74	123	1.35 (0.87-2.08)	.18
SOFA score						
≤8	51	66	52	68	1.11 (0.53-2.33)	.78
>8	36	62	22	55	1.69 (0.96-2.94)	.07
Admission category						
Surgical	22	34	16	31	1.56 (0.67-3.70)	.64
Medical	65	94	58	92	1.43 (0.83-2.50)	.20
Colonization index ≥0.5[a]	68	101	58	99	1.35 (0.84-2.17)	.22
Corrected colonization index ≥0.4[b]	52	76	45	80	1.52 (0.87-2.63)	.14
Candida score ≥3	64	96	47	85	1.37 (0.83-2.27)	.21
(1-3)-ß-D-glucan, pg/mL[c]						
>250	14	21	14	25	1.52 (0.47-5.00)	.48
>80	58	91	47	84	1.41 (0.85-2.33)	.19
≤80	29	37	27	39	0.98 (0.30-2.94)	.97



All analyses are stratified by center and adjusted on parameters imbalanced between groups (ie, diabetes and body mass index).

[a] Colonization index (range, 0-1) indicates the number of positive sites colonized with *Candida* divided by the number of sites sampled.

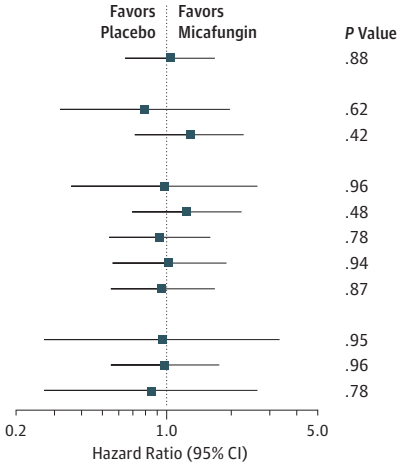
[b] Corrected colonization index (range, 0-1) indicates the number of heavily colonized sites divided by the number of sites sampled.

[c] Candida score (range, 0-5) items are surgical admission (1 point), severe sepsis (2 points), multiple sites positive with *Candida* species (1 point), and parenteral nutrition (1 point).

SOFA indicates Sequential Organ Failure Assessment.

Figure 3. Comparison of Survival at Day 28 in the Modified Intent-to-Treat Population and in Predefined Subgroups

	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	*P* Value
All patients	90	128	86	123	1.04 (0.64-1.67)	.88
SOFA score						
≤8	53	66	58	68	0.79 (0.32-1.96)	.62
>8	37	62	28	55	1.28 (0.71-2.27)	.42
Admission category						
Surgical	23	34	23	31	0.97 (0.36-2.63)	.96
Medical	67	94	63	92	1.23 (0.69-2.22)	.48
Colonization index ≥0.5[a]	70	101	70	99	0.93 (0.54-1.59)	.78
Corrected colonization index ≥0.4[b]	54	76	56	80	1.02 (0.56-1.89)	.94
Candida score ≥3	66	96	58	85	0.95 (0.55-1.67)	.87
(1-3)-ß-D-glucan, pg/mL[c]						
>250	14	21	17	25	0.96 (0.27-3.33)	.95
>80	61	91	58	84	0.98 (0.55-1.75)	.96
≤80	29	37	28	39	0.85 (0.27-2.63)	.78



All analyses are stratified by center and adjusted on parameters imbalanced between groups (ie, diabetes and body mass index).

[a] Colonization index (range, 0-1) indicates the number of positive sites colonized with *Candida* divided by the number of sites sampled.

[b] Corrected colonization index (range, 0-1) indicates the number of heavily colonized sites divided by the number of sites sampled.

[c] Candida score (range, 0-5) items are surgical admission (1 point), severe sepsis (2 points), multiple sites positive with *Candida* species (1 point), and parenteral nutrition (1 point).

SOFA indicates Sequential Organ Failure Assessment.

Discussion

In this multicenter, double-blind, placebo-controlled trial in critically ill nonimmunocompromised patients with ICU-acquired severe sepsis, *Candida* colonization at multiple sites, and multiple organ failure, micafungin did not significantly improve the primary outcome of 28-day invasive fungal infection-free survival. There were no significant differences in the mortality rates, patient severity of illness following randomization, or in ICU or hospital lengths of stay. However, micafungin-treated patients had a significant reduction in the number of ICU-acquired invasive fungal infections following randomization.

Table 2. Proven Invasive Fungal Infection at Inclusion and 28-Day Follow-up[a]

	No. (%)			
	All Patients (N = 251)	Micafungin (n = 128)	Placebo (n = 123)	Absolute Difference (95% CI)
No. of invasive fungal infections from inclusion to day 28[b]				
≥1	27 (11)	12 (9)	15 (12)	2.82 (−5.0 to 10.8)
2	3 (1)	0	3 (2)	2.44 (−0.9 to 6.9)
Invasive fungal infections by species at inclusion	12 (5)	8 (6)	4 (3)	3.00 (−2.7 to 8.9)
Candida albicans	7 (50)	4 (44)	3 (60)	15.6 (−31.3 to 53.7)
Candida glabrata	5 (36)	4 (44)	1 (20)	24.4 (−25.1 to 57.7)
Candida tropicalis	1 (7)	0	1 (20)	20.0 (−14.1 to 62.5)
Aspergillus fumigatus	1 (7)	1 (11)	0	11.0 (−36.2 to 82.4)
No. of invasive fungal infections at follow-up (day 28)[b]				
≥1[c]	19 (8)	4 (3)	15 (12)	9.1 (2.5 to 16.3)
2	2 (1)	0	2 (2)	1.6 (−1.5 to 5.7)
Invasive fungal infections by species				
Candida albicans	13 (59)	3 (75)	10 (55)	19.4 (−29.7 to 49.4)
Candida glabrata	2 (9)	0	2 (9)	11.1 (−38.5 to 32.8)
Candida parapsilosis	3 (14)	0	3 (14)	16.7 (−33.5 to 39.2)
Candida inconspicua	1 (4)	1 (25)	0	25.0 (−2.0 to 69.9)
Trichosporon[d]	2 (9)	0	2 (11)	11.1 (−38.5 to 32.8)
Aspergillus fumigatus	1 (4.5)	0	1 (6)	5.6 (−43.7 to 25.8)

[a] Incidence was reported per 1000 days of follow-up.

[b] Values may not sum as more than 1 infection is possible per patient.

[c] *P* value was .008 using the Fisher exact test.

[d] Both cases occurred in patients with candidaemia documented at inclusion and treated by candins.

The study failed to demonstrate that an empirical antifungal therapy with micafungin is able to improve, by at least 18%, the rate of survival free from proven fungal infection at day 28. This finding is unlikely to be from a lack of statistical power because the event rates were within the expected ranges, in line with the high severity of illness at admission or inclusion, also reflected by the number of patients receiving life-sustaining therapies. Furthermore, the intervention failed to improve outcomes overall, as well as in specific patient subsets such as those with high colonization index, high Candida score, or high (1-3)-β-D-glucan concentrations. The nonsignificant improvement of day-28 survival without invasive fungal infections among patients with high SOFA scores deserve further discussion. Because inclusion criteria for this trial comprised ICU-acquired sepsis, multiple organ dysfunctions, and other risk factors for candidemia, this finding suggests that among these selected patients, those who are most ill may benefit from antifungal agents. On one hand, this decreases the biological plausibility that supports the present intervention, limiting its benefit to a super niche. Conversely, because single-target interventions failed in this population, it can be assumed that reducing the incidence of invasive fungal infection could be seen as a therapeutic intervention that will ultimately improve survival in patients with established multiple organ dysfunctions. However the effect of this intervention on mortality is probably lower than suggested by previous literature.

This trial on empirical antifungals in ICU patients with *Candida* extra-intestinal colonization, unresolved sepsis, and multiple organ failure adds to the 2 previously published studies regarding 3 aspects. First, it shows that sepsis occurring in patients with multiple organ dysfunction and multiple-sites colonization in patients receiving broad-spectrum antibacterials agents is rarely due to invasive fungal infection. Second, it sheds light on the discrimination power of *Candida* colonization. Indeed, in the present trial, which included heavily colonized patients, questions remain about the relevance of sampling patients for *Candida* colonization when such sampling leads to financial burden from laboratory testing and also excessive antifungal consumption[22] without any apparent clinical benefits. A study by Throughton et al reported that *Candida* colonization failed to guide empirical therapy,[23] and a study by Barenfanger et al demonstrated significantly reduced antifungal consumption when clinicians were not provided with *Candida* colonization results.[24] Altogether, these results call into question the routine use of systematic surveillance for *Candida* colonization. Besides sparing unnecessary use of health care resources, it may also avoid inducing resistances to antifungals.[25-27] Whether this trial closes 3 decades of clinical research on *Candida* colonization deserves consideration. Furthermore, the observation that the intervention failed, irrespective of the patients' (1-3)-β-D-glucan levels, is in line with previous publications showing that (1-3)-β-D-glucan was not significantly different between patients with candidemia vs those with multiple colonization.[17] As for documented infections, (1-3)-β-D-glucan kinetics was not influenced by micafungin therapy, which did not support its use for guiding antifungal de-escalation.[28,29]

In addition, this trial adds to the 2 others by reporting micafungin plasma concentrations. The observed median AUC is strictly similar to the value of 78.6 mg.h/L that was previously observed in ICU patients.[30] It confirms a decreased exposure by approximately 50% compared with healthy patients and by approximately 25% compared with non-ICU patients, suggesting

that higher doses may be necessary in critically ill patients. The assumption that the present intervention would have proven benefits by using higher micafungin dosages is not supported by the significant reduction of ICU-acquired candidemia, unless considering that micafungin may have decreased blood culture sensitivity without clinical benefit.

Strengths of this study include the multicenter design and high adherence to the intervention started immediately after randomization. The proportion of ICU-acquired invasive candidiasis is within previously published ranges,[2,13,31-33] as is mortality.[1] Also, no patient was lost to follow-up. The risk of bias was also minimized by the blinded nature of the design, use of central randomization, concealment of study-group assignments before randomization to avoid selection bias, and a robust primary outcome that could not be influenced by observer bias. Because the centers belonged to a large study group that included university and non-university hospitals, the study may have external validity.

This study has a number of limitations. The first is its low rate of patients with a very high risk of invasive candidiasis, such as patients with postoperative gastrointestinal leakage of acute necrotizing pancreatitis.[17] Also, micafungin underdosing cannot be ruled out because therapeutic drug monitoring was not performed after day 1.

Although maximal efforts were made to homogenize the diagnosis of invasive fungal infection, the procedure that was used daily in each center to diagnose fungal infections during the follow-up period might have slightly varied. However, the consequence of this information bias is limited by the stratification of the random process and the statistical analyses. The adapted EORTC definition for documented infection used in this study was previously used in studies by Tissot et al[17] and Ostrosky-Zeichner et al[10]; however, this definition might possibly miss true fungal infections.

Besides having *Candida* species colonization, the inclusion criteria were similar to those used in previous trials of empirical antifungal use in critically ill patients[5,10,13] (in whom illness severity at randomization and mortality rates were similar). There was no evidence that micafungin influenced mortality estimates or was beneficial in treating specific subgroups. However, empirical treatment should be further evaluated in similar patients with a SOFA score greater than 8 at randomization.

Conclusions

Among nonneutropenic critically ill patients with ICU-acquired sepsis, *Candida* species colonization at multiple sites, and multiple organ failure, empirical treatment with micafungin, compared with placebo, did not increase fungal infection–free survival at day 28.

ARTICLE INFORMATION

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