MAJOR ARTICLE

Early Removal of Central Venous Catheter in Patients with Candidemia Does Not Improve Outcome: Analysis of 842 Patients from 2 Randomized Clinical Trials

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(See the editorial commentary by Brass and Edwards, on pages 304–306.)

Background. Patients with candidemia frequently have a central venous catheter (CVC) in place, and its early removal is considered the standard of care.

Methods. We performed a subgroup analysis of 2 phase III, multicenter, double-blind, randomized, controlled trials of candidemia to examine the effects of early CVC removal (within 24 or 48 h after treatment initiation) on the outcomes of 842 patients with candidemia. Inclusion criteria were candidemia, age >16 years, CVC at diagnosis, and receipt of ⩾1 dose of the study drug. Six outcomes were evaluated: treatment success, rates of persistent and recurrent candidemia, time to mycological eradication, and survival at 28 and 42 days. Univariate and multivariate analyses were performed, controlling for potential confounders.

Results. In univariate analysis, early CVC removal did not improve time to mycological eradication or rates of persistent or recurrent candidemia but was associated with better treatment success and survival. These benefits were lost in multivariate analysis, which failed to show any beneficial effect of early CVC removal on all 6 outcomes and identified Acute Physiology and Chronic Health Evaluation II score, older age, and persistent neutropenia as the most significant variables. Our findings were consistent across all outcomes and time points (removal within 24 or 48 h and survival at 28 and 42 days). The median time to eradication of candidemia was similar between the 2 study groups.

Conclusions. In this cohort of 842 adults with candidemia followed up prospectively, early CVC removal was not associated with any clinical benefit. These findings suggest an evidence-based re-evaluation of current treatment recommendations.

Candidemia is a common nosocomial bloodstream infection and is associated with high mortality [1]. Patients with candidemia usually have a central venous catheter (CVC) in place, and prompt CVC removal is considered by some to be critical to a successful outcome. Recent guidelines for the management of candidiasis strongly recommend early CVC removal in all nonneutropenic patients with candidemia [2] or in patients with CVC-related candidemia [3]. These recommendations were based on selected studies suggesting that prompt CVC removal was associated with improved outcomes, including better treatment success, faster mycological eradication, decreased rates of recurrent and persistent candidemia, and improved survival [4–7]. However, these studies had serious limitations: small sample size, retrospective data collection, inclusion of patients without candidemia, lack of a def-

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inition for what constitutes "early" CVC removal, and suboptimal statistical analyses including no adjustment for important potential host confounders, such as a high severity of illness score and persistent neutropenia. Not cited in these guidelines are studies that made such adjustments and failed to confirm the reported association between early CVC removal and improved outcomes [8–11]. The findings in these latter studies prompted some to recommend against CVC removal and replacement in critically ill patients because of the risks of serious complications [12].

The optimal strategy to resolve this controversial issue is a randomized, controlled trial (RCT) in which patients with candidemia are randomized to have early CVC removal versus no removal, after patient stratification by key baseline variables; uniform antifungal therapy would be provided, and serial blood cultures would be performed at predefined time points to ascertain the time to mycological eradication. Because such a study is unlikely to be conducted in the near future, the next best approach relies on appropriate subgroup analysis of a large cohort of patients enrolled in recent RCTs of candidemia in which the effect of early CVC removal on various outcomes is evaluated [13]. The newer and more precise methods for grading evidence-based medicine give such subgroup analyses higher-quality grading than purely observational studies [14], provided the following requirements are fulfilled: (a) a representative patient population for which these evidence-based recommendations are applied, (b) direct comparison of 2 groups (eg, CVC removal or retention), (c) evaluation of clinically important outcomes, and (d) statistically significant results in a positive study or adequate sample size to rule out a β error in a negative study [15].

We present the results of a study in which we evaluated the effects of early CVC removal on clinically important outcomes among 842 patients enrolled in 2 recent large multicenter, multinational RCTs of treatment of candidemia [7, 16]. We specifically examined whether early CVC removal—defined as removal within 24 or 48 h after initiation of antifungal therapy—was associated with the beneficial outcomes that form the basis for current recommendations for early CVC removal [2, 3]—namely, better treatment success, faster mycological eradication, lower rates of recurrent and persistent candidemia, and improved survival.

Table 1. Study Design and Characteristics of the 2 Double-Blind, Randomized Clinical Trials of Candidemia That Enrolled the Patients Evaluated in the Current Study of Early Removal of the Central Venous Catheter (CVC)

Characteristic	2-Arm study[a]	3-Arm study[b]
Inclusion criteria	Age ⩾16 years, clinical signs of systemic *Candida* infection, and ⩾1 positive culture from blood or another sterile site within the previous 4 days	Same criteria as the 2-arm study, except for age ⩾18 years
Exclusion criteria	Positive cultures from nonsterile site or urine, 2 days of systemic antifungal therapy, and elevated aminotransferases (10× ULN) or bilirubin (5× ULN)	Same criteria as the 2-arm study, except also Child-Pugh score >9 and receipt of cyclosporine
Recruitment period	January 2003–November 2004	August 2004–April 2006
No. of centers (geographic locations)	115 (Europe, India, Brazil, North America, Thailand, South Africa, and Australia)	128 (Europe, India, Brazil, and North America)
Duration of therapy (minimum; maximum)	14 days; 28 days	Same as the 2-arm study
CVC recommendations	Remove CVC before the first dose of therapy	No recommendation given
Frequency of repeat blood cultures	3 times per week until sterilization of blood cultures	Daily until sterilization of blood cultures
Duration of follow-up after start of therapy	2 and 6 weeks	12 weeks
Stratification	Center and neutropenic status	APACHE II score (⩽20 vs >20) and region (North America, Europe, Brazil, and India)
Method of randomization	Computer-generated, at each center	Same as the 2-arm study
Primary end point	Rate of overall treatment success[c]	Same as the 2-arm study[c]
Clinical success	Resolution of symptoms of candidemia	Same as the 2-arm study
Mycological success	Eradication of baseline candidemia	Same as the 2-arm study
Recurrence	Reemergence of baseline fungal infection (same species) during follow-up	Same as the 2-arm study

NOTE. CVC, central venous catheter; ULN, upper limit of normal value.

[a] Study of micafungin at 100 mg/day versus liposomal amphotericin B at 3 mg/kg/day.

[b] Study of micafungin at 100 mg/day versus micafungin at 150 mg/day versus caspofungin at 50 mg/day after a loading dose of 70 mg on the first day.

[c] Overall treatment success was defined as clinical and mycological success at the end of blinded therapy.

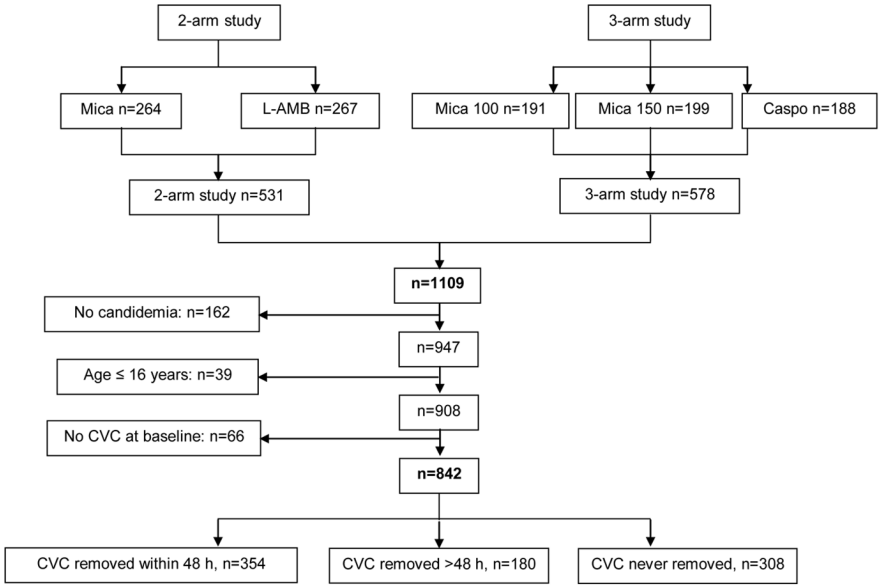

Figure 1. Randomization of the 2 original candidemia treatment trials (1109 patients) and eligibility for the analysis of early central venous catheter (CVC) removal (48 h refers to 48 h after treatment initiation). Caspo, caspofungin; L-AMB, liposomal amphotericin B; Mica 100, micafungin at 100 mg/day; Mica 150, micafungin at 150 mg/day.

PATIENTS AND METHODS

This analysis of early CVC removal represents a subgroup analysis of data pooled from 2 phase III, double-blind, multicenter/multinational RCTs of therapy for candidemia [7, 16]. Study details are presented in the original publications (Table 1). Briefly, patients were randomized to receive micafungin at 100 mg/day or liposomal amphotericin B at 3 mg/kg/day in one study [16] and micafungin at 100 mg/day, micafungin at 150 mg/day, or caspofungin at 50 mg/day (after a 70-mg loading dose on day 1) in the other study [7].

Inclusion criteria and end points for the analysis of early CVC removal. Inclusion criteria were documented candidemia, age >16 years, presence of a CVC at diagnosis of candidemia, and receipt of at least 1 dose of study drug. Prior to the analysis, we defined the 2 time points for early CVC removal (within 24 h and 48 h after initiation of antifungal therapy), the 6 outcomes of interest, and the planned statistical analyses. The 2 time points we selected for early CVC removal are in keeping with the recent Infectious Diseases Society of America (IDSA) guidelines [2, 3] and within the usual time frame when clinicians consider removing the CVC in a patient with candidemia [9, 17–21].

The outcomes we selected were those advanced in support of early CVC removal [2, 3], including all 4 that were prospectively examined in the original RCTs [7, 16]—that is, overall treatment success, rates of recurrent candidemia, and survival at 28 days and 42 days after treatment initiation. In addition, because survival is frequently related to the underlying disease, we also evaluated outcomes that are thought to be closely related to CVC status (removal or retention)—that is, time to mycological eradication and rates of persistent candidemia.

Definitions. Treatment success was defined as clinical success (resolution of clinical signs of infection) and mycological success (eradication of the baseline pathogen) at the end of therapy. Death during receipt of antifungal therapy and missing evaluations were considered treatment failures. Recurrent candidemia was defined as documented candidemia with the baseline *Candida* species during the posttreatment follow-up period. These definitions were similar to those applied in the original trials [7, 16]. Persistent candidemia referred to any blood culture obtained during antifungal therapy and that yielded the same *Candida* species recovered at baseline. Time to mycological eradication represented the number of days from initiation of treatment to the first day of blood cultures negative for *Candida* species.

Statistical analyses. Patients with early CVC removal were compared with those whose CVC was not removed within 48 h after treatment initiation or was never removed during the course of therapy. Univariate analysis was performed to evaluate the association between each outcome and CVC status (removal within 24 or 48 h after treatment initiation). To explore the association between our predefined outcomes and the potential confounding factors, the following prospectively collected baseline variables were examined: age, sex, neutropenia (absolute neutrophil count, <500 cells/mm^3), liver failure (a di-

Table 2. Characteristics of 842 Patients with Candidemia according to Time of Removal of the Central Venous Catheter (CVC) after Treatment Initiation, for Univariate Analysis

Characteristic	CVC removed within 24 h		CVC removed within 48 h		All patients (n = 842)
	Yes (n = 318)	No (n = 524)	Yes (n = 354)	No (n = 488)	
Baseline characteristics					
Age, median years (range)	58 (18–92)	56 (17–95)	58 (18–92)	56 (17–95)	57 (17–95)
Male-to-female ratio	180:138	305:219	199:155	286:202	485:357
Neutropenia	16 (5.0)	69 (13.2)[a]	21 (5.9)	64 (13.1)[b]	85 (10.1)
Liver failure	4 (1.3)	10 (1.9)	5 (1.4)	9 (1.8)	14 (1.7)
Renal failure	32 (10.1)	114 (21.8)[a]	42 (11.9)	104 (21.3)[b]	146 (17.3)
Diabetes	70 (22.0)	112 (21.4)	78 (22.0)	104 (21.3)	182 (21.6)
Solid-organ transplantation	9 (2.8)	17 (3.2)	9 (2.5)	17 (3.5)	26 (3.1)
Concomitant bacteremia	40 (12.6)	107 (20.4)[a]	51 (14.4)	96 (19.7)[b]	147 (17.5)
Receipt of corticosteroids	64 (20.1)	121 (23.1)	72 (20.3)	113 (23.2)	185 (22.0)
Surgery	51 (16.0)	99 (18.9)	63 (17.8)	87 (17.8)	150 (17.8)
APACHE II score, median (range)	13 (0–39)	15 (0–47)[a]	13 (0–39)	15 (0–47)[b]	14 (0–47)
Pathogen					
Candida albicans	139 (43.7)	227 (43.3)	152 (42.9)	214 (43.9)	366 (43.5)
Candida tropicalis	54 (17.0)	97 (18.5)	62 (17.5)	89 (18.2)	151 (17.9)
Candida parapsilosis	55 (17.3)	83 (15.8)	62 (17.5)	76 (15.6)	138 (16.4)
Other *Candida* species	41 (12.9)	63 (12.0)	49 (13.8)	55 (11.3)	104 (12.4)
Disseminated candidiasis	29 (9.1)	53 (10.1)	29 (8.2)	53 (10.9)	82 (9.7)
Characteristics after enrollment					
Persistent neutropenia	9 (2.8)	26 (5.0)	10 (2.8)	25 (5.1)	35 (4.2)
Treatment regimen					
Micafungin at 100 mg/day	135 (42.5)	200 (38.2)	151 (42.7)	184 (37.7)	335 (39.8)
Micafungin at 150 mg/day	48 (15.1)	119 (22.7)[a]	56 (15.8)	111 (22.7)[b]	167 (19.8)
Caspofungin	49 (15.4)	111 (21.2)[a]	61 (17.2)	99 (20.3)	160 (19.0)
Liposomal amphotericin B	86 (27.0)	94 (17.9)[a]	86 (24.3)	94 (19.3)	180 (21.4)

NOTE. Data are no. (%) of patients, unless indicated otherwise. APACHE, Acute Physiology and Chronic Health Evaluation.

[a] $P < .05$ for comparison of patients whose CVC was removed within 24 h after treatment initiation with those whose CVC was not removed within this time frame, by univariate analysis.

[b] $P < .05$ for comparison of patients whose CVC was removed within 48 h after treatment initiation with those whose CVC was not removed within this time frame, by univariate analysis.

agnosis of cirrhosis), renal failure (serum creatinine level, >2 mg/dL), diabetes mellitus, concomitant bacteremia, solid-organ transplantation, receipt of corticosteroids (within 2 weeks prior to the first dose of study drug), surgery (requiring anesthesia other than local and occurring within 2 weeks prior to the first dose of study drug), Acute Physiology and Chronic Health Evaluation (APACHE) II score, pathogen (*Candida albicans* vs. *Candida tropicalis* vs. *Candida parapsilosis* vs. other *Candida* species; *C. albicans* vs. other *Candida* species; *C. parapsilosis* vs. other *Candida* species), disseminated candidiasis (as previously defined [22]), and treatment regimen (micafungin at 100 mg/day, micafungin at 150 mg/day, caspofungin, or liposomal amphotericin B). We also examined the effects of persistent neutropenia, defined as neutropenia for ⩾3 days after the last dose of antifungal treatment.

All variables with $P < .1$ by univariate analysis were entered in a multivariate model. Categorical data were analyzed using χ^2 or Fisher's exact tests, as appropriate, and continuous variables (age and baseline APACHE II score) were compared using the Wilcoxon test. Time-to-event variables were analyzed by the log-rank test. Multivariate analysis was performed by logistic regression analysis. All analyses were conducted using SAS statistical software (SAS Institute).

RESULTS

Patient characteristics. A total of 1109 patients were enrolled in the original RCTs, 842 of whom fulfilled inclusion criteria for the analysis of early CVC removal (Figure 1). We excluded 267 patients because a diagnosis of candidemia was not established (n = 162), a CVC was not present at diagnosis of candidemia (n = 66), or the patient was aged ⩽16 years (n = 39). Patient characteristics are detailed in Table 2. The median age was 57 years (range, 19–95 years), and 485 patients were

Table 3. Univariate Analysis of 5 Predefined Outcomes among 842 Patients with Candidemia according to Time of Removal of the Central Venous Catheter (CVC) (within 24 or 48 h after Treatment Initiation)

	CVC removed within 24 h			CVC removed within 48 h		
Outcome	Yes (n = 318)	No (n = 524)	P	Yes (n = 354)	No (n = 488)	P
Overall treatment success	237 (74.5)	360 (68.7)	.07	266 (75.1)	331 (67.8)	.02
Persistent candidemia[a]	30/292 (10.3)	66/493 (13.4)	.20	34/328 (10.4)	62/457 (13.6)	.18
Recurrent candidemia	18 (5.7)	42 (8.0)	.21	22 (6.2)	38 (7.8)	.42
Survival at 28 days	244 (76.7)	369 (70.4)	.046	274 (77.4)	339 (69.4)	.01
Survival at 42 days	228 (71.6)	341 (65.0)	.046	256 (72.3)	313 (64.1)	.01

NOTE. Data are no. (%) of patients, unless indicated otherwise.

[a] Data were missing for 57 patients.

male. Baseline risk factors were receipt of corticosteroids (22%), diabetes mellitus (21.6%), surgery (17.8%), renal failure (17.3%), and neutropenia (10.1%). *C. albicans* was the most frequent species (43.5%), and 9.7% of patients had disseminated candidiasis. Early CVC removal was observed in 354 patients (318 patients within 24 h after treatment initiation and 36 patients between 24 and 48 h). The CVC was removed >48 h after treatment initiation or was retained throughout the course of treatment in 180 and 308 patients, respectively. The median time from candidemia to CVC removal was 2 days in both cohorts (patients with removal within 24 h and patients with removal within 48 h), compared with 9 days in patients whose CVC was removed >48 h after treatment initiation. Early CVC removal was associated with significantly lower baseline APACHE II score for both the 24 and 48 h time points and was less likely in patients who had baseline neutropenia, renal failure, or concomitant bacteremia.

Univariate analysis of the effect of early CVC removal on outcome. Early CVC removal within 24 or 48 h had no effect on persistent or recurrent candidemia and treatment success (Table 3) or time to mycological eradication (Figure 2). By contrast, early CVC removal was associated with increased survival at 28 and 42 days and with higher treatment success.

Univariate analysis of potential confounders. Persistent candidemia was associated with diabetes mellitus, receipt of corticosteroids, and *C. parapsilosis* candidemia, whereas baseline neutropenia was the only variable associated with recurrent candidemia. Longer time to mycological eradication was more likely among patients with *C. parapsilosis* candidemia, diabetes mellitus, and concomitant bacteremia. Because overall treatment success and 28-day and 42-day survival were influenced by early CVC removal in the univariate analysis, the potential confounders for these 3 outcomes were examined. Higher APACHE II score, persistent neutropenia, and corticosteroid use were associated with treatment failure, whereas these same variables in addition to older age, renal failure, recent surgery, and baseline pathogen predicted poor survival (Table 4).

Multivariate analysis of outcome predictors. The improved treatment success and survival associated with early CVC removal by univariate analysis was lost when multivariate analysis was applied; in the multivariate analysis, early CVC removal failed to influence any of these outcomes (Table 5). This lack of benefit from early CVC removal was in contrast to the significant negative association between these outcomes and certain host factors: higher APACHE II score, persistent neutropenia, and older age.

DISCUSSION

In this cohort of 842 patients with candidemia followed up prospectively, we could not identify a beneficial effect of early

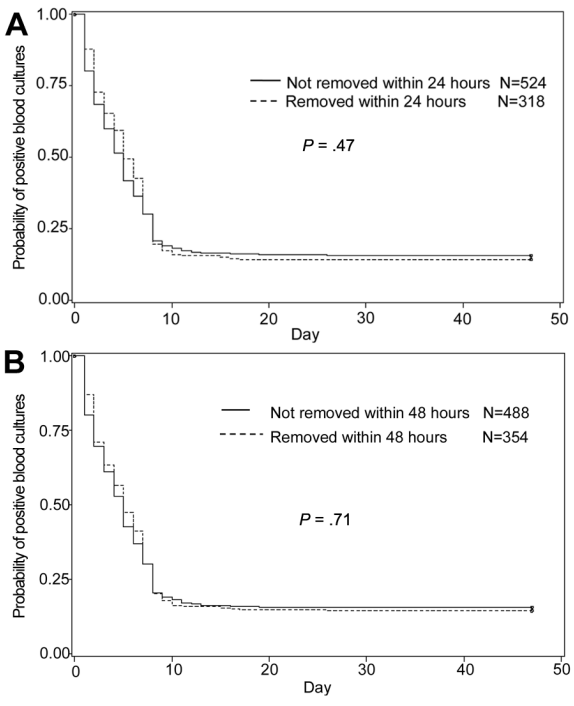

Figure 2. Time to mycological eradication for patients whose central venous catheter (CVC) was removed within 24 h (*A*) or 48 h (*B*) after initiation of antifungal therapy, compared with patients whose CVC was not removed within this time frame.

Table 4. Univariate Analysis of the Association between Potential Confounding Variables and Overall Treatment Success and Survival at 28 and 42 Days after Treatment Initiation

	Treatment success			Survival at 28 days			Survival at 42 days		
Variable	Yes	No	*P*	Yes	No	*P*	Yes	No	*P*
Baseline characteristics									
Age, median years (range)	56 (17–95)	59 (18–92)	.04	55 (17–90)	61 (18–95)	<.001	55 (17–90)	61 (18–95)	<.001
Male-to-female ratio	343:254	142:103	.93	348:265	137:92	.43	329:240	156:117	.88
Neutropenia	50 (8.4)	35 (14.3)	.01	54 (8.8)	31 (13.5)	.05	49 (8.6)	36 (13.2)	.049
Liver failure	9 (1.5)	5 (2.0)	.56	7 (1.1)	7 (3.1)	.07	7 (1.2)	7 (2.6)	.16
Renal failure	102 (17.1)	44 (17.9)	.76	89 (14.5)	57 (24.9)	.004	83 (14.6)	63 (23.1)	.003
Diabetes	140 (23.4)	42 (17.1)	.04	133 (21.7)	49 (21.4)	1.00	120 (21.1)	62 (22.7)	.59
Solid-organ transplantation	19 (3.2)	7 (2.9)	1.00	19 (3.1)	7 (3.1)	1.00	17 (2.9)	9 (3.3)	.83
Concomitant bacteremia	111 (18.6)	36 (14.7)	.19	111 (18.1)	36 (15.7)	.47	105 (18.4)	42 (15.4)	.29
Receipt of corticosteroids	115 (19.3)	70 (28.6)	.004	122 (19.9)	63 (27.5)	.02	109 (19.2)	76 (27.8)	.006
Surgery	116 (19.4)	34 (13.9)	.06	122 (19.9)	28 (12.2)	.01	119 (20.9)	31 (11.4)	<.001
APACHE II score, median (range)	13 (0–38)	18 (0–47)	<.001	12 (0–38)	19 (2–47)	<.001	12 (0–38)	19 (1–47)	<.001
Pathogen			.04			<.001			.006
Candida albicans	262 (43.9)	104 (42.4)		270 (44.1)	96 (41.9)		244 (42.9)	122 (44.7)	
Candida glabrata	85 (14.3)	19 (7.8)		84 (13.7)	20 (8.7)		79 (13.9)	25 (9.2)	
Candida tropicalis	101 (16.9)	50 (20.4)		95 (15.5)	56 (24.4)		89 (15.7)	62 (22.7)	
Candida parapsilosis	97 (16.3)	41 (16.7)		111 (18.1)	27 (11.8)		105 (18.5)	33 (12.1)	
Other *Candida* species	51 (8.6)	31 (12.6)		52 (8.5)	30 (13.1)		51 (8.9)	31 (11.4)	
Disseminated candidiasis	23 (3.8)	12 (4.9)	.57	25 (4.1)	10 (4.4)	.85	24 (4.2)	11 (4.0)	1.00
Characteristics after enrollment									
Persistent neutropenia	16 (2.7)	19 (7.8)	<.001	17 (2.8)	18 (7.9)	.002	15 (2.6)	20 (7.3)	.003
Treatment regimen			.28			.07			.15
Micafungin at 100 mg/day	242 (40.5)	93 (37.9)		243 (39.6)	92 (40.2)		220 (38.7)	115 (42.1)	
Micafungin at 150 mg/day	121 (20.3)	46 (18.7)		123 (20.1)	44 (19.2)		117 (20.6)	50 (18.3)	
Caspofungin	117 (19.6)	43 (17.5)		127 (20.7)	33 (14.4)		118 (20.7)	42 (15.4)	
Liposomal amphotericin B	117 (19.6)	63 (25.7)		120 (19.6)	60 (26.2)		114 (20.0)	66 (24.2)	

NOTE. Data are no. (%) of patients, unless indicated otherwise. Analysis of time to mycological eradication and rates of persistent or recurrent candidemia was not performed because of the lack of significant effect of CVC removal on these outcomes by univariate analysis (Figure 1 and Table 3). APACHE, Acute Physiology and Chronic Health Evaluation.

CVC removal on any of the 6 predefined outcomes—treatment success, survival at 28 and 42 days, rates of persistent or recurrent candidemia, and time to mycological eradication. Importantly, these findings were consistent across all examined outcomes and at both time points of CVC removal (within 24 h and 48 h after treatment initiation). Notably, the curves comparing the time to eradication of candidemia between the group with early CVC removal and the control group were almost superimposable (Figure 2). This lack of benefit from early CVC removal on all outcomes was in sharp contrast to the key role that host factors played in these outcomes. Indeed, severity of illness (APACHE II) score, persistent neutropenia, older age, and other host factors were independent outcome determinants, in accordance with several prior reports [8–11, 17, 23, 24].

The current analysis differs from previous studies of candidemia (including ours) that evaluated the effect of CVC removal on outcomes [4, 8–11, 17, 23–25]. Differences include the very large sample size of our current study, its multicenter and multinational enrollment, and the prospective and standardized evaluation and follow-up as predefined in the 2 RCTs [7, 16]. The prospective collection of blood cultures at predetermined time points allowed us to study 4 outcomes thought to be directly related to CVC status (removal or retention) [2]—namely, time to mycological eradication, treatment success, and rates of persistent and recurrent candidemia. Our predefined time points for early CVC removal (within 24 and 48 h after treatment initiation) are also in keeping with the guidelines advocating "prompt" removal of CVCs [2].

Our findings are supported by several retrospective studies [8–11] but differ from others [4, 17, 23–25] and from the 2 recent IDSA guidelines [2, 3]; in one set of IDSA guidelines, a recommendation for early CVC removal is made for all nonneutropenic patients with candidemia [2], whereas the other

Table 5. Multivariate Analysis of the Effect of Early Removal of the Central Venous Catheter (CVC) on Treatment Success and Survival at 28 and 42 Days after Treatment Initiation in 842 Patients with Candidemia

	Treatment success		Survival at 28 days		Survival at 42 days	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
CVC removal within 24 h after treatment initiation						
CVC removal	NT	NT	1.15 (0.79–1.67)	.45	1.19 (0.84–1.67)	.33
Persistent neutropenia	NT	NT	0.36 (0.15–0.88)	.03	0.38 (0.16–0.90)	.03
Higher APACHE II score	NT	NT	0.90[a] (0.88–0.93)	<.001	0.91[a] (0.89–0.93)	<.001
Liver failure	NT	NT	0.23 (0.07–0.72)	.01	NT	NT
Surgery	NT	NT	1.46 (0.87–2.47)	.16	1.97 (1.23–3.18)	.005
Older age	NT	NT	0.98[a] (0.97–0.99)	.02	0.98[a] (0.97–0.99)	.02
CVC removal within 48 h after treatment initiation						
CVC removal	1.20 (0.86–1.69)	.26	1.23 (0.85–1.75)	.27	1.25 (0.88–1.75)	.20
Receipt of corticosteroids	0.64 (0.44–0.94)	.02	0.77 (0.51–1.16)	.21	0.70 (0.47–1.02)	.06
Persistent neutropenia	0.42 (0.18–0.98)	.04	0.36 (0.15–0.89)	.03	0.38 (0.16–0.90)	.03
Higher APACHE II score	0.93[a] (0.91–0.96)	<.001	0.90[a] (0.88–0.93)	<.001	0.91[a] (0.89–0.93)	<.001
Liver failure	NT	NT	0.22 (0.07–0.72)	.01	NT	NT
Surgery	1.25 (0.80–1.95)	.33	1.46 (0.86–2.46)	.16	1.96 (1.22–3.17)	.006
Older age	0.99[a] (0.98–1.01)	.31	0.98[a] (0.97–0.99)	.02	0.98[a] (0.97–0.99)	.02

NOTE. Analysis of time to mycological eradication, success rate, and rates of persistent and recurrent candidemia was not performed because of the lack of significant effect of CVC removal on these outcomes by univariate analysis (Figure 1 and Table 2). APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; NT, not tested because this variable was not significant by univariate analysis; OR, odds ratio.

[a] The OR is the incremental increased risk for each additional point in the scale.

limits this recommendation to patients with CVC-related candidemia only [3]. In the present study, no attempt was made to distinguish between CVC-related and -unrelated candidemia, because the former is a diagnosis of exclusion ("no other source for candidemia") for which a minimum workup required to fulfill this essential criterion was not provided. Moreover, this definition is meant to identify CVC-related infections to apply a targeted CVC-removal strategy as opposed to removal in all patients. Because this diagnosis almost always requires a positive CVC tip culture, and thus CVC removal, it has limited clinical usefulness. Quantitative blood cultures and time to culture positivity have been advanced as alternative means for diagnosing CVC-related candidemia without requiring CVC removal. However, neither has been validated in a large cohort of patients with candidemia, and quantitative blood cultures are expensive and not widely used.

Removal of CVCs has been thought to benefit patients with candidemia, under the assumption that removal of this potential focus of infection improves clinical success, decreases time to mycological eradication and rates of persistent and recurrent candidemia, and improves survival [2, 3]. However, these recommendations were based on studies that had several limitations, including retrospective data collection, evaluation of patients without candidemia and/or without a CVC in place, lack of specific time points for "early" CVC removal, and no adjustment for key confounders known to influence the outcomes [4, 5, 26]. An important and often-overlooked confounder in these studies is the inclusion of patients who died before the diagnosis of candidemia was even made and thus before they could receive optimal antifungal therapy and undergo CVC removal [4, 8, 11, 23–25]. Comparing the outcome of such patients with those of patients who survived long enough to receive antifungal therapy and have their CVC removed introduces a significant bias favoring the latter group. Some studies attempted to analyze time to mycological eradication and/or rates of persistent or recurrent candidemia without the essential prerequisite of serial blood cultures at predefined intervals to establish a precise time to eradication [4].

Of the 6 RCTs of candidemia that examined the effect of CVC removal on outcome [6, 7, 16, 20, 27, 28], 4 trials [6, 16, 20, 27] failed to identify a beneficial role for CVC removal. In 1 of the 2 remaining studies, faster mycological eradication was associated with early CVC removal; however, the APACHE score was significantly higher among patients whose CVC was not promptly removed, and no adjustment for this important confounder was made [5, 28]. The importance of controlling for confounders is exemplified by 1 of the 2 RCTs analyzed in our report, in which the authors concluded that early CVC removal led to a higher rate of overall clinical success [7]. When we applied multivariate analysis to the same patient population (excluding those without candidemia), this higher rate of clinical success was lost (data not shown).

The echinocandins and liposomal amphotericin B penetrate well in biofilms and exhibit similar minimal inhibitory concentrations in biofilm and in planktonic stage [29]. In a rabbit model of *C. albicans* biofilm infection, *Candida* colony counts were significantly reduced with lipid amphotericin B but not with fluconazole [30]. Given these properties, we cannot rule out the possibility that the lack of benefit from early CVC removal may be caused by the antifungal therapy received, because all patients were treated with either an echinocandin or liposomal amphotericin B. However, early CVC removal did not improve outcome in a large RCT of candidemia that used fluconazole with or without amphotericin B deoxycholate [6], suggesting that the lack of benefit from early CVC removal is observed across all classes of antifungal agents regardless of their differential in vitro activity on biofilms.

Our study was not specifically designed to assess the effect of CVC removal on outcome; a large prospective RCT of CVC retention versus removal as the primary end point can better address this question. Because such a study has never been conducted, we applied the next best methodology [13], a subgroup analysis of a large cohort of patients enrolled in recent RCTs of candidemia that fulfilled the key requirements for high-quality grading—namely, the evaluation of a representative patient population for which these evidence-based recommendations are applied, a direct comparison of the 2 groups of interest (eg, CVC removal or retention), a focus on clinically important outcomes, and the largest sample size ever published, to minimize the chance of a β error [15]. Unlike purely observational studies lacking these requirements, such subgroup analysis is now given high-quality grading, at times even superior to that of some RCTs [15].

Our findings imply that immediate CVC removal is not warranted in adults with candidemia treated with an echinocandin or liposomal amphotericin B. Because our patients were adults (age >16 years) and because only 10% were neutropenic, our findings cannot be extrapolated to younger patients and those who are neutropenic.

Future evaluations of the role of early CVC removal on the outcome of patients with candidemia should rely on prospective studies, should limit the analysis to patients with candidemia and a CVC in place at diagnosis, and should exclude those who die before candidemia is diagnosed. Future studies should also rely on a large sample size to minimize the chance of a β error. Specifically, a β error may miss a potential difference in favor of CVC retention, because CVC removal and replacement may impart a worse outcome as a result of potentially serious complications.

The time points for "early" CVC removal should also be predefined and should be limited to the early period (within the first 48 h after initiation of therapy), and the outcomes should include those directly related to a CVC, such as time to mycological eradication and rates of persistent and/or recurrent candidemia, provided that serial blood cultures are performed at predefined intervals. Finally, statistical analyses should always account for potential outcome confounders.

We conclude that early CVC removal in nonneutropenic adults with candidemia does not influence patient outcomes and that the recommendation to remove all CVCs in nonneutropenic patients [2] may not be justified. Instead, CVC management should be individualized, taking into consideration several factors, such as the need for a CVC and the risks versus benefits of CVC replacement in a patient who is not responding to optimal antifungal therapy and who, after proper evaluation, does not appear to have a focus of infection other than the CVC.

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