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Short Course of Antifungal Therapy in Patients With Uncomplicated *Candida* Bloodstream Infection: Another Case of Less Is More in the Clinical Setting?

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Background. The objective of this study was to compare the clinical outcomes of patients receiving a short course (SC) vs a prolonged course (PC) of antifungal therapy for uncomplicated *Candida* bloodstream infections (BSIs).

Methods. All episodes of uncomplicated *Candida* BSI from September 1, 2018, to August 31, 2020, were reviewed. We compared the primary (all-cause 90-day mortality) and secondary study end points (1-year recurrent *Candida* BSI and all-cause 1-year mortality) among patients who underwent SC (5–11 days) or PC (12–24 days) therapy using propensity score analysis with the inverse probability of treatment weighting (IPTW) method.

Results. A total of 114 patients with uncomplicated *Candida* BSI were included: 35 (30.7%) were classified into the SC group (median [interquartile range {IQR}], 9 [7–11] days) and 79 (69.3%) into the PC group (median [IQR], 14 [14–16] days). Patients in the SC group compared with the PC group had a higher rate of hospitalization in the surgical ward (40.0% vs 19.0%; *P* = .02) or septic shock at the time of *Candida* BSI onset (11.4% vs 1.3%; *P* = .03). The risk of 90-day mortality was not different between the SC and PC groups (n = 8 [22.9%] vs 17 [21.5%], respectively; IPTW-adjusted subdistribution hazard ratio [sHR], 0.67; 95% CI, 0.31–1.47; *P* = .20). The risk for recurrent *Candida* BSI within 1 year of completing therapy (IPTW-adjusted sHR, 1.07; 95% CI, 0.20–5.80; *P* = .94) or for all-cause 1-year mortality (IPTW-adjusted HR, 0.72; 95% CI, 0.35–1.50; *P* = .38) did not differ between groups.

Conclusions. Receiving a short vs prolonged course of antifungal therapy did not affect mortality or BSI recurrence in patients with uncomplicated candidemia.

Keywords. short course; 90-day mortality; prolonged course; recurrent *Candida* BSI; uncomplicated candidemia.

Shortening the duration of antimicrobial therapy in patients with bloodstream infection (BSI) is an important strategy for maximizing benefits while reducing drug-related adverse events, duration of hospitalization, emergence of resistance, and overall health care costs [1]. Several recent studies have demonstrated no significant differences in mortality or infection relapse between short and prolonged antibiotic therapy for a wide range of uncomplicated BSIs, including those caused by *Staphylococcus aureus* [2], *Enterobacterales* [3], and *Pseudomonas aeruginosa* [4].

Candida species cause 3%–9% of all episodes of BSI in many hospitals, and *Candida* ranks fourth as a cause of hospital-acquired BSI in studies carried out in the United States [5, 6]. Currently, a minimum of 14 days of antifungal therapy after the first negative blood cultures (BCs) is recommended for patients with uncomplicated candidemia (eg, episodes without metastatic spread to other organs) [7, 8]. However, adequate duration of antifungal therapy in *Candida* BSI is a neglected topic in the medical literature, with the available evidence supporting guideline recommendations primarily based on old randomized controlled trials not specifically designed to address this issue [9–16].

In the present study, we retrospectively compared the clinical outcomes of patients with uncomplicated *Candida* BSI receiving either a short course (SC; 5–11 days) or prolonged course (PC; 12–24 days) of antifungal therapy.

METHODS

Setting

Policlinico San Martino hospital is a large teaching institution serving a population of ∼400 000 inhabitants in Genoa, Northern Italy. During the study period, the number of beds available was 1200. We have all the services of a general hospital, with active programs directed to HIV-infected patients, transplant recipients, immunosuppressed hosts, and sophisticated surgical procedures.

Study Design

We performed a retrospective cohort study of patients admitted to our hospital between September 1, 2018, and August 31, 2020. We included all consecutive adult patients (aged ≥18 years) with uncomplicated *Candida* BSI, defined as the exclusion of clinically evident metastatic infection or deep-seated infection (eg, endophthalmitis, endocarditis, thrombophlebitis, arthritis, or other secondary manifestations involving a foreign body). Exclusion criteria were (i) polymicrobial BSI; (ii) failure to receive in vitro active therapy against the *Candida* isolate; (iii) follow-up blood cultures not performed every 48 hours, as it was not possible to establish the time point at which *Candida* BSI resolved; and (iv) death while receiving antifungal therapy for *Candida* BSI.

Data Collection

Medical charts were retrospectively reviewed according to a pre-established protocol including the following variables: sex, age, underlying conditions according to the Charlson comorbidity index [17], risk factors for *Candida* BSI, clinical features, source of infection, *Candida* species, antifungal therapy, appropriate source control, diagnostic procedures (ophthalmological examination and echocardiography), duration of antifungal therapy, and clinical outcomes.

Variable Exposure

The primary exposure was the duration of antifungal treatment, defined as the number of consecutive days during which the patients received an appropriate antifungal therapy, counting from the first negative follow-up BCs. According to our study protocol, the duration of antifungal therapy was dichotomized, before the start of data collection, as short (5–11 days) or prolonged (12–24 days).

End Points

The primary end point was all-cause mortality within 90 days after discontinuation of antifungal therapy. The secondary end points were analyzed after following patients for up to 1 year and included (i) recurrent *Candida* BSI and (ii) all cause 1-year mortality.

Definitions

An episode of *Candida* BSI was defined as at least 1 peripheral BC positive for *Candida* spp., obtained from a patient with signs and/or symptoms of infection. Polymicrobial BSI was defined as the growth of >1 microorganism, excluding potential contaminants (eg, coagulase-negative staphylococci, *Corynebacterium* spp., *Propionibacterium* spp.). *Candida* BSI onset was defined as the date of collection of the first blood culture yielding the study isolate. Regarding underlying conditions, we classified patients' prognosis as rapidly fatal, ultimately fatal, and non-fatal according to the criteria of McCabe and Jackson [18]. Sepsis and septic shock were recorded on the day of *Candida* BSI onset [19]. Severity of illness was classified according to the Pitt score [20]. As for the source of infection, patients were considered to have primary candidemia if there was no apparent portal of entry or if the infection was probably catheter related [21]. Central venous catheter–related candidemia was defined according to current guidelines [22]. The urinary tract was considered the portal of entry in patients with urological predisposing conditions (ie, manipulation or obstruction of the urinary tract) and evidence of urinary tract infection caused by the same *Candida* spp. [23]. The abdomen was considered the origin of the *Candida* BSI when a patient had evidence of abdominal infection and (i) a positive culture from the intra-abdominal space was obtained during surgery or by needle aspiration or (ii) no other apparent sources of candidemia were detected [23]. Early antifungal therapy was considered *appropriate* if a recommended dose of an antifungal drug was administered within 72 hours after *Candida* BSI onset and it was found to be effective by in vitro susceptibility testing [23]. Source control of the infection included central venous catheter withdrawal or invasive procedures to resolve urinary tract obstruction or intra-abdominal abscess drainage, depending on the source of candidemia. Source control was considered appropriate when performed within 72 hours of *Candida* BSI onset [23]. An episode of *Candida* BSI was defined as persistent when patients had positive follow-up BCs at least 48 hours after the initiation of antifungal therapy [24]. Recurrent *Candida* BSI was defined as a new episode of BSI due to the same *Candida* species occurring within 1 year after the end of antifungal therapy.

Microbiological Studies

During the entire study period, we recommended at least 2 samples of blood (∼20 mL in each for adults) to evaluate each episode of suspected BSI. Blood from each extraction was equally divided between an aerobic and anaerobic atmosphere bottle. All samples were transported to our laboratory as soon as they were collected. Blood samples were processed using a BACTEC FX blood culture system (Becton-Dickinson Microbiology Systems, Franklin Lakes, NJ, USA) with an incubation period of 5 days. If yeast cells were observed after microscopic examination of a gram stain, blood bottles were

subcultured into Sabouraud and chromogenic agar plates (Liofilchem, Roseto degli Abruzzi, Italy). Pathogens were identified by MALDI-TOF MS using the VITEK MS system (BioMerieux SA, Paris, France). In vitro antifungal activity was studied by a commercial microdilution method (Sensitre YeastOne, ThermoFisher Scientifics Inc., Waltham, MA, USA), in accordance with the manufacturer's instructions. Results were interpreted according to Clinical and Laboratory Standards Institute performance standards for antifungal susceptibility testing of yeasts (M60, 2nd edition).

Patient Consent

The study was approved by the Ethics Committee of the Liguria region (CER Liguria 562/2022). Specific informed consent for this study was waived due to the retrospective nature of the study.

Statistical Analysis

Continuous variables were compared using the Mann-Whitney U test, and categorical variables were compared using the chi-square or Fisher exact test, as appropriate. The standardized mean difference (SMD) was calculated according to Cohen d effect size to evaluate a possible imbalance between treatment duration groups. A Cohen d effect size >0.1 denotes meaningful imbalance in the baseline covariates [25]. We compared all-cause mortality (at 90 days and 1 year) and recurrence at 1 year in patients treated with PC of antifungal therapy with those who underwent SC. An inverse probability weighting (IPW) approach based on propensity score (PS) was used to minimize biases with respect to baseline characteristics between the 2 groups. The weights correspond to the inverse of the conditional PS of receiving the SC of antifungal therapy. The PS for each patient was calculated as a probability from a logistic regression model that had duration of antifungal therapy as the dependent variable (SC vs PC) and the following baseline variables as independent covariates: sex, age, hospital ward stay at the time of candidemia onset, Charlson comorbidity index, cardiovascular disease, neurological disease, solid tumor, chronic lung disease, hematological malignancy, solid organ transplantation, HIV infection, hematopoietic stem cell transplantation, McCabe scale, antibiotic therapy, total parenteral nutrition, surgery (all types <3 months), abdominal surgery (within previous 3 months), previous antifungal therapy, sepsis, septic shock, PITT score, source of infection, *Candida* species, infectious disease consultation, empirical antifungal therapy, initial antifungal therapy, early appropriate antifungal therapy, ophthalmological examination, intensive care unit admission, and need for hemodialysis after *Candida* BSI. We used stabilized trimmed weights to mitigate the impact of extremely higher or lower weights on the variability of the estimated treatment effect. The threshold (5%) was based on the quantiles of the distribution of the weights. Risk factors for mortality were analyzed using a Cox regression model, while risk factors for recurrence were analyzed using the Fine and Gray competing risk analysis, taking risk of death into account. All the variables with a P value <.2 at univariable analysis were entered into a multivariable model. Subdistribution hazard ratios (sHRs) and relative 95% CIs were shown for Fine and Gray models. An IPW Cox regression model was used to assess therapy duration effect differences on outcomes.

RESULTS

During the study period, 420 patients were diagnosed with an episode of candidemia. Of those, 114 patients met the inclusion criteria: 35 (30.7%) were classified into the SC group and 79 (69.3%) into the PC group. Figure 1 shows the study flowchart. The median duration of antifungal therapy in the SC group and PC group (interquartile range [IQR]) was 9 (7–11) days and 14 (14–16) days, respectively ($P < .0001$).

The main demographic characteristics and risk factors for *Candida* BSI in both groups are shown in Table 1. Groups did not differ regarding sex, age, underlying conditions, *Candida* species distribution, and management of candidemia. However, patients in the SC group compared with the PC group were more likely to be hospitalized in the surgical ward at the time of candidemia (40.0% vs 19.0%; $P = .02$) or to have septic shock at the time of *Candida* BSI onset (11.4% vs 1.3%; $P = .03$).
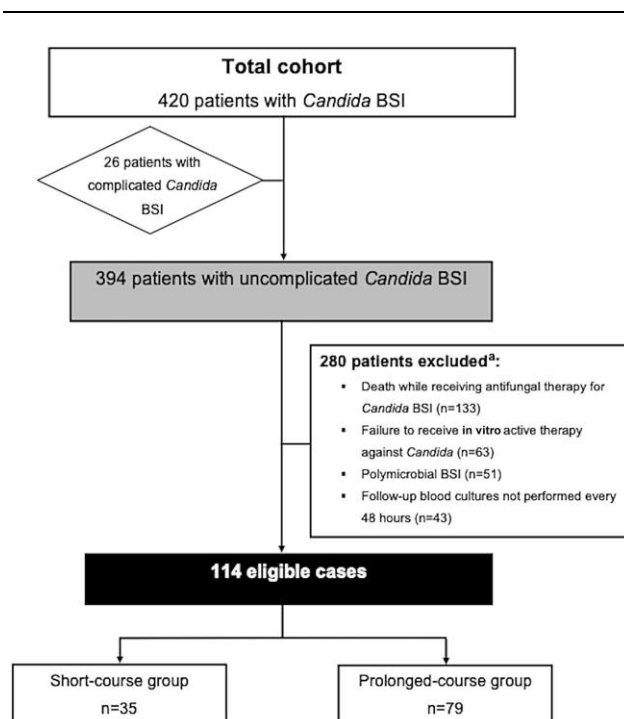
Figure 1. Study flowchart. [a]Ten out of 280 patients (3.6%) had >1 exclusion criterion. Abbreviation: BSI, bloodstream infection.

Table 1. Comparison of the Main Demographic and Clinical Characteristics of the Study Population, by Duration of Antifungal Therapy

Variable	All Episodes (n = 114)	Short-Course Group (n = 35)	Prolonged-Course Group (n = 79)	P Value[a]	SMD[b]
Demographics					
Male sex, No. (%)	67 (58.8)	67 (58.8)	45 (57.0)	.55	1.12
Age, mean (SD), y	67.1 (15.6)	65.9 (12.5)	67.6 (16.8)	.20	0.11
Hospital ward stay at the time of candidemia onset, No. (%)					
Internal medicine ward	50 (43.9)	10 (28.6)	40 (50.6)	.03	0.46
Surgical ward	29 (25.4)	14 (40.0)	15 (19.0)	.02	0.47
Intensive care unit	29 (25.4)	8 (22.9)	21 (26.6)	.67	0.09
Onco-hematology unit	6 (5.3)	3 (8.6)	3 (3.8)	.29	0.20
Underlying conditions, No. (%)					
Cardiovascular disease	57 (50.0)	13 (37.1)	44 (55.7)	.07	0.38
Neurological disease	37 (32.5)	8 (22.9)	29 (36.7)	.14	0.31
Gastrointestinal disease	33 (28.9)	10 (28.6)	23 (29.1)	.95	0.01
Solid tumor	25 (21.9)	10 (28.6)	15 (19.0)	.25	0.23
Diabetes mellitus	24 (21.0)	7 (20.0)	17 (21.5)	.85	0.04
Chronic lung disease	21 (18.4)	5 (14.3)	16 (20.3)	.45	0.16
Chronic kidney failure	17 (14.9)	6 (17.1)	11 (13.9)	.66	0.09
Chronic liver disease	11 (9.6)	3 (8.6)	8 (10.1)	1.00	0.05
Hematological malignancy	10 (8.8)	4 (11.4)	6 (7.6)	.49	0.13
Solid organ transplantation	2 (1.7)	0 (0.0)	2 (2.5)	1.00	0.23
HIV infection	2 (1.7)	0 (0.0)	2 (2.5)	1.00	0.23
Hematopoietic stem cell transplantation	1 (0.9)	1 (2.9)	0 (0.0)	.31	0.24
Charlson comorbidity index, median (IQR)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	.84	0.11
McCabe scale, No. (%)					
Non-fatal	50 (43.8)	18 (51.4)	32 (40.5)	.28	0.22
Ultimately fatal	54 (47.4)	14 (40.0)	40 (50.6)	.29	0.01
Rapidly fatal	10 (8.8)	3 (8.6)	7 (8.9)	.96	0.21
Risk factors for candidemia, No. (%)					
Antibiotic therapy	107 (93.9)	32 (91.4)	75 (94.9)	.67	0.14
Central venous catheter	100 (87.7)	31 (88.6)	69 (87.3)	1.00	0.04
Total parenteral nutrition	76 (66.7)	19 (54.3)	57 (72.2)	.06	0.38
Surgery (all types <3 mo)	58 (50.9)	22 (62.9)	36 (45.6)	.09	0.35
Corticosteroid therapy	29 (25.4)	10 (28.6)	19 (24.1)	.61	0.10
Abdominal surgery (within previous 3 mo)	28 (24.6)	12 (34.3)	16 (20.3)	.11	0.32
Immunosuppressive therapy	9 (7.9)	3 (8.6)	6 (7.6)	1.00	0.04
Previous antifungal treatment, No. (%)	14 (12.3)	3 (8.6)	11 (13.9)	.54	0.17
Clinical features, No. (%)					
Sepsis	51 (44.7)	19 (54.3)	32 (40.5)	.17	0.28
Septic shock	5 (4.4)	4 (11.4)	1 (1.3)	.03	0.43
Pitt score, median (IQR)	1.0 (0.0–2.0)	1.0 (0.0–3.0)	1.0 (0.0–2.0)	.27	0.21
Source of infection, No. (%)					
Primary/central venous catheter	112 (98.2)	34 (97.1)	78 (98.7)	.52	0.11
Abdomen	1 (0.9)	0 (0.0)	1 (1.3)	1.00	0.16
Other	1 (0.9)	1 (2.9)	0 (0.0)	.31	0.24
Candida species, No. (%)					
C. parapsilosis	60 (52.6)	20 (57.1)	40 (50.6)	.52	0.13
C. albicans	44 (38.6)	13 (37.1)	31 (39.2)	.83	0.04
C. tropicalis	6 (5.2)	1 (2.9)	5 (6.3)	.66	0.17
C. glabrata	2 (1.7)	1 (2.9)	1 (1.3)	.52	0.11
Other	3 (2.6)	0 (0.0)	3 (3.8)	.55	0.28
Infectious disease consultation, No. (%)	104 (91.2)	31 (88.6)	73 (92.4)	.49	0.13
Empirical antifungal therapy (before positive BC), No. (%)	51 (44.7)	11 (31.4)	40 (50.6)	.06	0.40
Time between first positive BC and initial antifungal therapy, median (IQR), d	2 (1–3)	2 (1–4)	2 (1–3)	.48	0.03
Initial antifungal therapy, No. (%)					
Echinocandins	101 (88.6)	29 (82.9)	72 (91.1)	.19	0.25
Azoles	11 (9.6)	5 (14.3)	6 (7.6)	.31	0.22

Table 1. Continued

Variable	All Episodes (n = 114)	Short-Course Group (n = 35)	Prolonged-Course Group (n = 79)	P Value[a]	SMD[b]
Liposomal amphotericin B	2 (1.7)	1 (2.9)	1 (1.3)	.52	0.11
Early appropriate antifungal therapy, No. (%)	86 (75.4)	25 (71.4)	61 (77.2)	.51	0.13
Time between first positive BC and source control of the infection, median (IQR), d	3 (1–5)	3 (1–5)	3 (1–5)	.93	0.03
Appropriate source control, No. (%)	59/95 (62.1)	19 (61.3)	40 (62.5)	.91	0.02
Persistent candidemia, No. (%)	35 (30.7)	23 (29.1)	12 (34.3)	.66	0.02
Ophthalmologic examination, No. (%)	21 (18.4)	9 (25.7)	12 (15.2)	.18	0.26
Echocardiography, No. (%)	66 (57.9)	16 (45.7)	50 (63.3)	.08	0.04
Complications, No. (%)					
Intensive care unit admission	2 (1.7)	0 (0.0)	2 (2.5)	1.00	0.23
Need for hemodialysis after *Candida* BSI	2 (1.7)	1 (2.9)	1 (1.3)	.52	0.11

Abbreviations: BC, blood culture; IQR, interquartile range.

[a]P values refer to pairwise comparisons based on the chi-square or Fisher exact test or Mann-Whitney *U* test, as appropriate.

[b]Cohen's *d* values (effect sizes) represent standardized mean or proportion differences. Absolute values of *d* > 0.10 were considered clinically meaningful.

By 90 days after discontinuation of therapy, all-cause mortality occurred in 26/114 patients (22.8%) overall, 8/35 patients (22.9%) in the SC group and 18/79 (22.8%) patients in the PC group, respectively. Factors associated with 90-day mortality are reported in Table 2. At univariable analysis, receiving a PC of antifungal therapy was not associated with a lower 90-day mortality compared with SC therapy (HR, 1.00; 95% CI, 0.43–2.30; *P* = .997) (Figure 2). PC therapy was not associated with an increased probability of all-cause 90-day mortality in either the multivariable (HR, 0.47; 95% CI, 0.14–1.55; *P* = .22) or weighted model (IPTW-adjusted HR for 90-day mortality, 0.67; 95% CI, 0.31–1.47; *P* = .32) compared with SC therapy (Table 3).

During the following year, patients who underwent SC therapy were less likely to receive any additional course of antifungal treatment, although this difference was not statistically significant (3/35 [8.6%] vs 11/79 [13.9%]; *P* = .54). Recurrent *Candida* BSI within 1 year of completing therapy occurred in 8/114 (7.0%) patients, 3/35 (8.6%) in the SC group and 5/79 (6.6%) in the PC group. Factors associated with recurrence of *Candida* BSI are reported in Table 2. At univariable analysis, a PC course of antifungals was not associated with recurrence of candidemia (sHR, 0.70; 95% CI, 0.17–2.93) (Figure 3). After IPTW adjustment and considering death as a competing risk, a longer course of therapy did not reduce the risk of recurrent infection (IPTW-adjusted sHR, 1.07; 95% CI, 0.20–5.80; *P* = .940) (Table 3).

Analyzing the end point at 1-year mortality showed consistent findings. Duration of antifungal therapy was not associated with higher 1-year mortality in either univariate (HR, 0.97; 95% CI, 0.46–20.60; *P* = .95) (Figure 3) or multivariate analysis (HR, 0.58; 95% CI, 0.20–1.67; *P* = .32), nor was it associated with higher 1-year mortality after adjusting the model for the propensity scores (IPTW-adjusted HR, 0.72; 95% CI, 0.35–1.50; *P* = .38) (Table 3).

DISCUSSION

Among patients treated for uncomplicated candidemia, we were not able to show any differences in 90-day mortality between patients receiving a short course of antifungals (5–11 days) vs those treated with a prolonged course of antifungal therapy (12–24 days). In addition, the lack of differences between these 2 groups persisted even when we analyzed the rate of recurrent *Candida* BSI and all-cause mortality within the following year after discontinuing antifungal therapy.

This study has several strengths. To our knowledge, this is the first retrospective study to analyze the influence of the length of antifungal treatment on the short- and long-term outcomes of patients with uncomplicated candidemia. Moreover, it is the largest study published to date in which state-of-art statistical methods designed for casual inference on observational data have been applied.

Current guidelines recommend duration of therapy for candidemia without documented metastatic complication of at least 14 days after documented clearance of *Candida* species from the bloodstream [7, 8]. However, the quality of the evidence supporting this recommendation is moderate, as it is mainly based on the results of old randomized trials in which "this rule has been universally and successively applied" [9–16]. This weakness in recommendation is reflected in the low rate of appropriate length of antifungal therapy reported by us and other authors (32%–78%) [23, 26–29], thus highlighting an unmet need to produce new evidence regarding adequate duration of antifungal therapy in patients with uncomplicated candidemia. Our results support and extend the findings from a previous study in which patients with uncomplicated transient candidemia (<1 day of documented positive BCs) were safely treated with 5–7 days of amphotericin B [30]. However, in that study a smaller number of patients were included in the SC group (n = 29), and none of them had septic shock at the

Table 2. Comparison of Factors Associated With All-Cause 90-Day Mortality, 1-Year Recurrent *Candida* Bloodstream Infection, and All-Cause 1-Year Mortality

Variable	All-Cause 90-Day Mortality	P Value	1-Year Recurrent *Candida* BSI	P Value	All-Cause 1-Year Mortality	P Value
Demographics						
Male sex,	1.05 (0.48–2.28)	.904	0.47 (0.09–2.29)	.35	0.98 (0.48–1.98)	.94
Age, y	1.03 (1.00–1.06)	.051	1.00 (0.94–1.07)	.91	1.03 (1.01–1.06)	.02
Hospital ward stay at the time of candidemia onset						
Internal medicine ward	1.89 (0.87–4.11)	.110	0.41 (0.08–1.98)	.27	2.37 (1.16–4.85)	.02
Surgical ward	0.67 (0.25–1.78)	.426	3.08 (0.78–12.13)	.11	0.64 (0.26–1.56)	.33
Intensive care unit	0.86 (0.34–2.13)	.738	0.99 (0.20–4.89)	.99	0.65 (0.27–1.58)	.35
Onco-hematology unit	…	…	…	…	…	…
Charlson comorbidity index	1.15 (1.01–1.31)	.029	0.89 (0.72–1.11)	.31	1.15 (1.02–1.30)	.02
Underlying conditions						
Cardiovascular disease	2.10 (0.94–4.71)	.072	1.72 (0.42–7.04)	.45	2.51 (1.19–5.30)	.02
Neurological disease	1.12 (0.50–2.51)	.784	1.24 (0.30–5.07)	.77	1.12 (0.54–2.32)	.76
Gastrointestinal disease	1.38 (0.61–3.09)	.435	0.34 (0.04–2.66)	.30	1.58 (0.77–3.24)	.21
Solid tumor	1.10 (0.44–2.74)	.838	0.50 (0.06–4.12)	.52	1.43 (0.66–3.09)	.36
Diabetes mellitus	0.85 (0.32–2.27)	.753	3.92 (1.00–15.37)	.05	1.01 (0.44–2.34)	.98
Chronic lung disease	1.79 (0.75–4.25)	.189	0.63 (0.08–5.06)	.66	1.37 (0.59–3.17)	.46
Chronic kidney failure	1.94 (0.78–4.84)	.155	1.92 (0.40–9.17)	.41	1.84 (0.80–4.27)	.15
Chronic liver disease	1.93 (0.66–5.60)	.226	3.31 (0.69–15.91)	.13	2.56 (1.05–6.23)	.04
Hematological malignancy	0.40 (0.05–2.95)	.368	…	…	0.31 (0.04–2.28)	.25
McCabe scale	0.28 (0.16–0.51)	<.0001	0.57 (0.23–1.44)	.23	0.28 (0.17–0.48)	<.001
Risk factors for candidemia						
Antibiotic therapy	0.87 (0.20–3.68)	.848	0.43 (0.05–3.52)	.43	1.06 (0.25–4.42)	.94
Central venous catheter	0.42 (0.17–1.04)	.061	1.00 (0.13–7.68)	.99	0.43 (0.18–0.99)	.05
Total parenteral nutrition	1.43 (0.60–3.39)	.421	0.48 (0.12–1.90)	.29	1.59 (0.72–3.55)	.25
Corticosteroid therapy	1.42 (0.62–3.27)	.409	…	…	1.06 (0.47–2.35)	.89
Abdominal surgery (within previous 3 mo)	0.48 (0.22–1.09)	.080	2.95 (0.60–14.56)	.18	0.70 (0.35–1.41)	.32
Immunosuppressive therapy	0.43 (0.06–3.20)	.412	…	…	0.34 (0.05–2.50)	.29
Previous antifungal treatment	1.96 (0.74–5.19)	.177	1.03 (0.13–8.26)	.98	1.53 (0.59–3.98)	.38
Clinical features	…	…	…	…	…	…
Sepsis	0.89 (0.41–1.94)	.776	0.72 (0.18–2.95)	.65	1.23 (0.61–2.45)	.56
Septic shock	2.35 (0.55–9.95)	.246	…	…	1.87 (0.45–7.83)	.39
Pitt score	1.14 (0.96–1.34)	.127	0.90 (0.60–1.35)	.62	1.11 (0.95–1.29)	.17
Candida species						
C. parapsilosis	0.91 (0.42–1.96)	.805	1.54 (0.37–6.34)	.55	0.69 (0.34–1.39)	.30
C. albicans	0.79 (0.35–1.77)	.570	0.94 (0.23–3.86)	.93	1.03 (0.51–2.09)	.93
C. tropicalis	…	…	…	…	…	…
C. glabrata	3.63 (0.49–26.86)	.206	…	…	6.97 (1.65–29.44)	<.01
Other	9.11 (2.67–31.06)	.0004	…	…	9.11 (2.67–31.06)	<.01
Infectious disease consultation	0.70 (0.21–2.35)	.569	…	…	0.88 (0.27–2.90)	.84
Empirical antifungal therapy (before positive BC)	0.91 (0.42–1.99)	.818	0.17 (0.02–1.33)	.09	0.96 (0.48–1.94)	.92
Time between first positive BC and initial antifungal therapy, d	0.98 (0.85–1.14)	.800	0.97 (0.86–1.10)	.67	0.98 (0.86–1.13)	.80
Initial antifungal therapy						
Echinocandins	0.52 (0.20–1.39)	.195	…	…	0.52 (0.21–1.27)	.15
Azoles	1.77 (0.61–5.15)	.291	…	…	1.85 (0.71–4.81)	.20
Liposomal amphotericin B	2.17 (0.29–16.07)	.446	…	…	1.88 (0.26–13.79)	.39
Early appropriate antifungal therapy	0.56 (0.25–1.25)	.158	2.32 (0.29–18.70)	.43	0.64 (0.30–1.35)	.24
Time between first positive BC and source control of the infection, d	1.10 (1.02–1.18)	.015	1.04 (0.88–1.24)	.64	1.07 (1.00–1.15)	.05
Appropriate source control	0.29 (0.12–0.73)	.009	1.22 (0.23–6.58)	.81	0.34 (0.15–0.77)	<.01

Abbreviation: BC, blood culture.

time of candidemia onset, compared with 11% of the present study. Moreover, our study includes older patients (median, 66 years vs 58 years in the earlier study) mainly treated with echinocandins as initial antifungal therapy (~82%), thus reflecting the changes in demographic characteristics and in management of candidemia during recent years. We found

an all-cause 90-day mortality of 21.9%, which is significantly lower than the mortality rate reported by other authors in recent series including comparable study populations, where the mortality rate remained around 40% and 75% [31, 32]. This is sought because a large proportion of patients who did not receive or complete antifungal therapy were excluded from our analysis.

Importantly, Fichtenbaum et al. [30] did not include in the short treatment course patients with persistent candidemia. Despite appropriate antifungal therapy and appropriate source control of the infection, follow-up blood cultures were commonly positive in our study population, which agrees with the findings of others [23, 24]. Persistent follow-up BC in patients with uncomplicated candidemia is associated with a risk that the infection might take a more severe course [33], but it is not necessarily associated with treatment failure [34], even with a shorter course of antifungals, as shown in our study.

Late-onset complications, including recurrent *Candida* BSI and new diagnosis of deep-seated infection, probably represent the most significant consequences among patients who survive an episode of candidemia [35]. Recognized risk factors for recurrence of *Candida* BSI include underlying gastrointestinal disease [36–38], *Candida parapsilosis* candidemia [37], intravenous drug use [36], and drug resistance or inadequate source control of the infection [38]. In the present study, 7% of patients with uncomplicated candidemia developed recurrent *Candida* BSI, a rate consistent with that reported in larger series [36–38]. Despite theoretical concerns, the results of our study suggest that a short course of antifungal therapy is not a decisive factor predisposing to recurrent candidemia in patients with *Candida* BSI. These findings were observed despite a greater proportion of patients belonging to the prolonged-course group requiring new antifungal administration over the 1-year follow-up period.

Our study has several limitations that should be considered when interpreting the results. First, as observed in recent studies using comparable methodology [2, 4], the rigorous exclusion criteria we adopted also led us to exclude many patients (~75%) from the original cohort. Accordingly, the statistical results must be interpreted with caution. Second, because of its retrospective design, it is possible that confounding factors associated with treatment decisions and clinical outcomes were not included in the multivariable analysis. Although we tried to account for this through use of propensity score matching to isolate the effect of length of antifungal therapy, some characteristics remained slightly unbalanced even after the IPW adjustment (Supplementary Data). Third, this was a single-center study, and our findings may not be generalized to other settings. Fourth, we did not monitor the adverse events related to antifungals in both study groups; unfortunately, our study
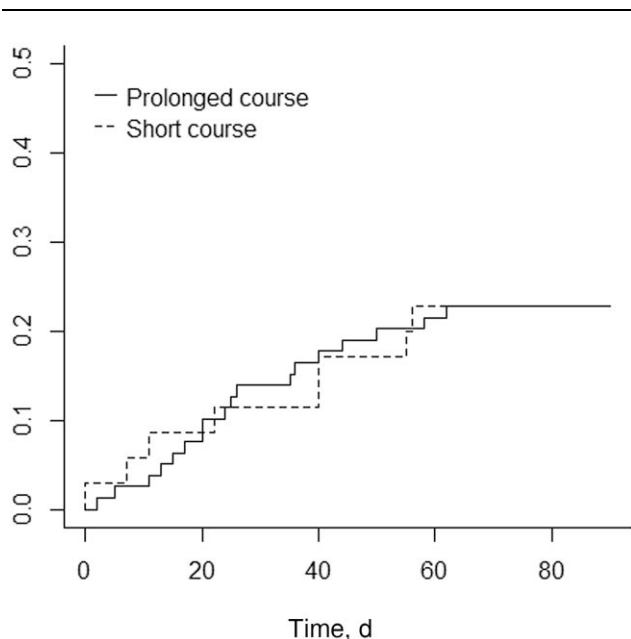
Figure 2. Cumulative incidence of all-cause 90-d mortality among patients with uncomplicated *Candida* bloodstream infection receiving a prolonged or short course of antifungal therapy.

Table 3. Clinical Outcomes (90-Day and 1-Year All-Cause Mortality and Relapse) of Prolonged-Course Antifungal Therapy vs Short-Course Antifungal Therapy

|	Univariable Analysis		Multivariable Analysis		IPTW-Adjusted HR	
Primary End Point	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
All-cause 90-d mortality	1.00 (0.43–2.30)	.99	0.47 (0.14–1.55)[a]	.22	0.67 (0.31–1.47)	.32
Secondary end points						
1-y recurrent *Candida* BSI	0.70 (0.17–2.93)[b]	.63	1.33 (0.30–6.00)[b,c]	.71	1.07 (0.20–5.80)[b]	.94
All-cause 1-y mortality	0.97 (0.46–20.60)	.95	0.58 (0.20–1.67)[d]	.32	0.72 (0.35–1.50)	.38

Abbreviations: BSI, bloodstram infection; HR, hazard ratio.

[a]Twenty events/95 patients.

[b]Subdistribution hazard ratio was shown for the Fine and Gray model.

[c]Eight events/114 patients.

[d]Twenty-five events/95 patients.
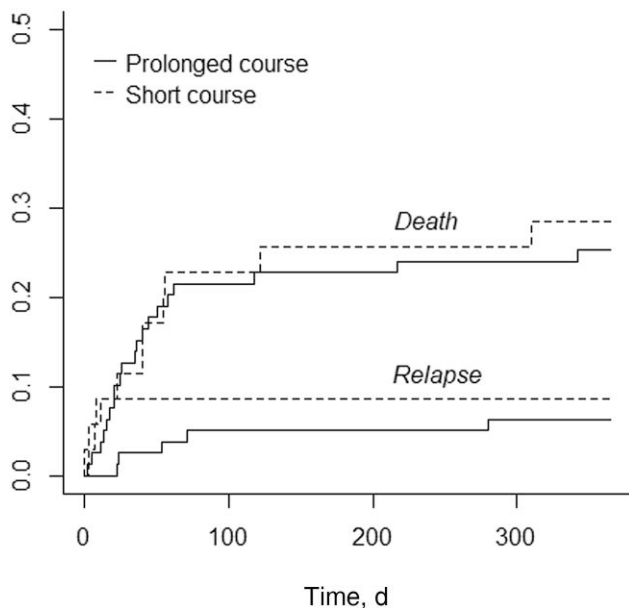
Figure 3. Cumulative incidence of 1-year recurrent bloodstream infection and all-cause 1-year mortality among patients with uncomplicated *Candida* bloodstream infection receiving a prolonged or short course of antifungal therapy.

was not designed to address this issue. Fifth, ophthalmoscopic examination and echocardiograms were not consistently performed. Thus, some cases of complicated *Candida* BSI could have been potentially misclassified as uncomplicated disease. Finally, we followed the patients with *Candida* BSI through their medical charts reporting whether they had made subsequent visits related to the candidemia episodes, but we were not able to determine whether any patient was cared for in another hospital or consulted with another physician because of signs or symptoms related to recurrent *Candida* BSI. We can only assume they did not because in our region patients usually attend their reference hospital.

In conclusion, short-course antifungal therapy for uncomplicated candidemia yielded similar outcomes as prolonged-course antifungal therapy in terms of 90-day mortality and long-term outcomes including 1-year recurrent *Candida* BSI and 1-year mortality, with the precautions imposed by the applied methodology of our study. These observations merit further evaluation in a randomized controlled trial.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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