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Original Article

Timing for Step-Down Therapy of Candidemia in Non-Neutropenic Patients: An International Multi-Center Study

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Abstract. ***Background*: Candida bloodstream infection (BSI) remains one of the leading causes of BSI in critically ill and immunosuppressed cancer patients. In light of the changing epidemiology and rising resistant species, duration of treatment and appropriate timing of stepdown therapy from intravenous (IV) to oral antifungal agents are crucial for utmost disease control and overall survival.**
***Method*: We performed a multicenter retrospective study, with 119 non-neutropenic patients enrolled from four different medical institutions in Brazil, Lebanon, Spain and the United States, to assess the duration of IV therapy and appropriate time to step-down to oral therapy in adult patients, 14 years of age and older, with documented candidemia. The analysis was done using the statistical program R and SAS v9.4. Descriptive statistics are presented as frequencies and tables and the Fisher exact test was used to test the association between the categorical variables: organism, cancer, country, antifungal drug and duration of therapy, and time of step-down.**
***Results*: *Candida albicans* contributed to 45% of bloodstream infection versus 55% of infection caused by Candida non-albicans. The three most common Candida non-albicans are: *Candida glabrata* 24%, *Candida parapsilosis* 13% and *Candida tropicalis* 8%. Most (57%) of the patients were admitted to ICU, whereas 52% had underlying malignancy. Multivariate analysis showed that a stay at ICU or an underlying cancer requiring chemotherapy were independently associated with failure and death (p <0.001). The average total duration of therapy was 14 days in all patients and 16 days in those who responded and survived. Forty-five patients were stepped down to either fluconazole and/or voriconazole in association with clinical and microbiologic resolution of the candidemia. The average (and median) day of step-down was 5 days. Patients who had a stepdown had more favorable outcomes (78% survival) as compared to those with no stepdown (56% survival) (P = 0.022). However, the 20 patients who received 1-4 days of first IV treatment before a stepdown to oral azoles had a comparable outcome (20% mortality) to the 25 patients who received ≥5 days of treatment (24% mortality - p = 0.75).**
***Conclusion*: Our data support the IDSA guidelines in that the total duration of treatment for**

candidemia should be at least 14 days after a negative blood culture. However, in non-neutropenic cancer patients with candidemia, a step-down to oral azole therapy can safely take place early (within 4 days of initiating IV therapy) as long as the patient had clinical and microbiologic resolution of the bloodstream infections.

Keywords: Candida infections; Neutropenia; Bloodstream infection.

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Introduction. Candida bloodstream infections have become one of the leading causes of bloodstream infections (BSI) in critically ill and immunosuppressed patients.[1,2] They are also associated with high morbidity and mortality rates, which range from 10 to 47%.[3,4] The main objective of this multicenter study was to examine the real-world use of antifungal agents in the treatment of candidemia and assess the appropriate duration of treatment as well as the outcome on patients who were step-down to oral therapy in non-neutropenic patients with BSI caused by candida

Given the seriousness of the infection, determining the appropriate type of therapy with step-down, and ensuring timely treatment is both essential and crucial.

The most recent guidelines published in 2016 by the Infectious Disease Society of America (IDSA) for the management of candidemia recommend a minimum of 14 days of antifungal therapy after a negative blood culture in clinically stable patients.[5] Furthermore, the IDSA guidelines suggest a step-down strategy from intravenous (IV) antifungals to oral therapy within five to seven days as long as the signs and symptoms associated with the candidemia resolve with negative blood cultures.[5] However, these recommendations have become a routine practice over the last few decades, even though there have not been prospective randomized studies that evaluated and determined the appropriate total duration of therapy and time to step-down to oral therapy.[6-9]

The early initiation of antifungal agents has been associated with favorable survival outcomes,[10] but the question remains when it should be stopped. To the best of our knowledge, there are no randomized studies comparing the different durations of treatment, and a limited number of studies have examined the appropriate timing to step-down from IV to oral antifungal therapy.

Therefore, the objective of this multicenter international study was to describe the epidemiology of candidemia cases over the past five years in four centers located in four different countries and continents (Brazil, Lebanon, Spain, and USA) in order to evaluate the duration of IV therapy and determine the appropriate time to step-down to oral therapy in non-neutropenic adult patients with documented candidemia.

Methodology. A multicenter, retrospective study was conducted with 119 patients enrolled with approximately 20-30 patients from four different international institutions, including Lebanon, Brazil, Spain, and USA. Patients 14 years and older with documented candidemia and received at least one dose of antifungal therapy were included. Patients with neutropenia at the onset of infection diagnosis or with documented candida endocarditis, osteomyelitis, meningitis, or disseminated candidiasis diagnosed within 72 hours from the first positive blood culture for candida were excluded from the study. Data on demographic measures, in addition to the occurrence of cancer, other underlying diseases, and different treatment types, duration and outcomes, were collected. Step-down therapy refers to switching from IV to oral antifungal therapy. Response to therapy was defined by clinical improvement and microbiological eradication of patients with candidemia treated with appropriate antifungal therapy.

Cox regression analysis was used to identify the independent predictors of the response to antifungal therapy (success vs. failure). In both multivariate analyses, factors with a p-value <0.2 in univariate analysis were included in each initial multivariate model, and then the full model was reduced to the final model by a backward variable elimination procedure. A p-value of less than .05 was considered statistically significant.

The study was approved by the IRB at the different sites. The analysis was performed using the statistical program R, and SAS v 9.4 (SAS Institute Inc., Cary, NC, USA), descriptive statistical software. The Fisher exact test was used to test the association between the categorical variables organism, cancer, country, antifungal drug, and duration of therapy and the results are presented in tables as frequencies.

Table 1. Patient Demographics and Characteristics by Countries (>5%)

	Lebanon (n=34)	Brazil (n=33)	Spain (n=32)	USA (n=20)	Total (n=119)
Characteristics	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Age in years, median (range)	69 (40 - 86)	71 (33 - 89)	71 (39 - 91)	53 (19 - 70)	68 (19 - 91)
Diabetes mellitus	9 (26.4)	8 (24.2)	17 (53.1)	9 (45.0)	43 (36.1)
Liver disease mild	3 (8.8)	0	6 (18.7)	3 (15.0)	12 (10.0)
Chronic kidney disease	5 (14.7)	3 (9.1)	8 (25.0)	3 (15.0)	19 (16.0)
Congestive Heart Failure	1 (2.9)	1 (3.0)	10 (31.3)	3 (15.0)	15 (12.6)
Myocardial Infarction*	3 (8.8)	2 (6.1)	4 (12.5)	3 (15.0)	12 (10.1)
COPD†	2 (5.9)	0	7 (21.9)	2 (10.0)	11 (9.2)
Peripheral Vascular Disease	1 (2.9)	0	4 (12.5)	2 (10.0)	7 (5.9)
Stroke*	1 (2.9)	3 (9.1)	10 (31.3)	1 (5.0)	15 (12.6)
Surgery*	11 (32.4)	19 (57.6)	16 (50.0)	9 (45.0)	55 (46.2)
Cancer	20 (58.8)	18 (54.5)	19 (59.4)	5 (25.0)	62 (52.1)
Leukemia/Lymphoma	5 (14.7)	2 (6.1)	1 (3.1)	0	8 (6.7)
Solid tumor	16 (47.1)	14 (42.4)	16 (50.0)	4 (20.0)	50 (42)
ICU Admission	22 (64.7)	22 (66.7)	11 (34.4)	13 (65)	68 (57.1)

*Developed myocardial infarct, stroke or underwent surgery within a month of the onset of the candidemia.
†COPD = Chronic obstructive pulmonary disease.

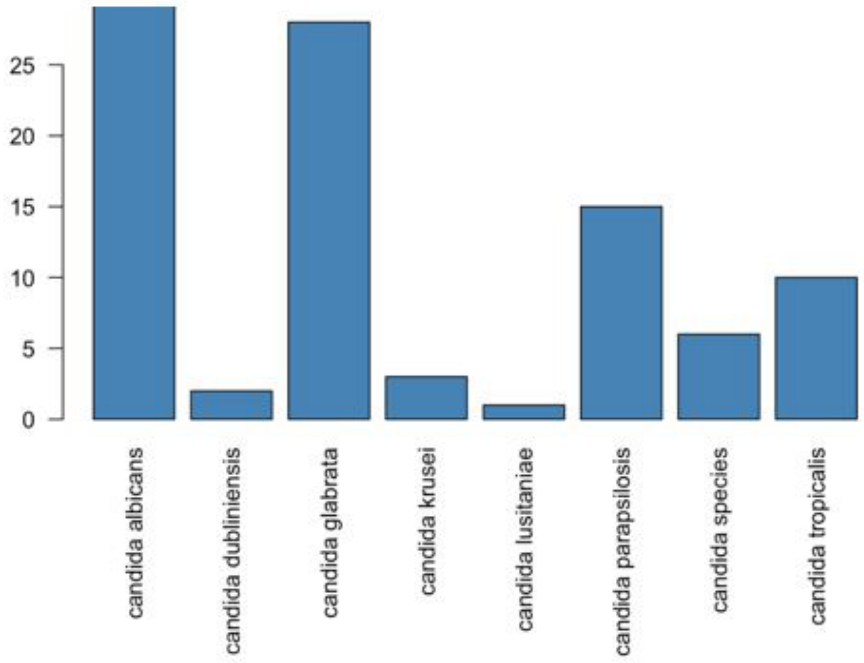

Figure 1. Histogram showing the number of people (vertically) according to the type of Candida infection (horizontally).

Results. In this retrospective study, a total of 119 patients were enrolled from 4 different countries: Lebanon (34 patients), Brazil (33), Spain (32), and the USA (20). **Table 1** outlines the demographics of study patients from the four reported country centers. The median age for 119 patients was 68 years (range, 19 - 91), and the median duration for their total treatment was 14 days (range, 1 - 36). *Candida albicans* was prominent among 45% of the patients, and 55% were infected with *Candida non-albicans*. The three most common *Candida non-albicans* reported were *Candida glabrata* (24%), *Candida parapsilosis* (13%), and *Candida tropicalis* (8%) (**Figure 1**). The two most common identified sources of infection were the central line (50%) and abdomen (18%). *Candida albicans* was notably the most commonly isolated species (spp), causing candidemia in the centers located in Brazil (67%) and in Spain (53%), whereas *Candida non-albicans* was predominant in the USA (85%) and Lebanon (68%). There was a significant association between the *Candida* organism type and geographical area (Fisher exact test p-value=<0.001).

Candida glabrata was more commonly found in the

Table 2. Survival Status for All Patients by Countries

	Lebanon (n=34)	Brazil (n=33)	Spain (n=32)	USA (n=20)	Total (n=119)
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Survival					
Survived/success	19 (55.9)	12 (36.4)	27 (84.4)	16 (80.0)	74 (62.1)
Deaths/Failure	15 (44.1)	21 (63.6)	5 (15.6)	4 (20.0)	45 (37.9)

Table 3. Sources of Infection for All Patients by Countries

	Lebanon (n=34)	Brazil (n=33)	Spain (n=32)	USA (n=20)	Total (n=119)
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Sources of Infection					
Catheter Related	15 (44.1)	24 (73)	20 (62)	2 (10)	61 (51)
GI*		6 (18)	6 (19)	10 (50)	22 (19)
Others - Not Catheter Related Sources	19 (56)	3(9)	6 (9)	8 (40)	36 (30)

*Gastrointestinal

Lebanese and American samples compared with samples obtained from patients in Brazil and Spain. *Candida albicans* had a much higher frequency in Brazil (67%) compared with the USA (15%) and Lebanon (32%). **Figure 1** gives the distribution of organisms by country.

Echinocandins (48%) were the most commonly used antifungal medications, followed by azoles (39%) and amphotericin B (6%). Most patients (97%) received their first antifungal through the IV route, while 3% were treated with oral antifungals. In hospitals in USA and Lebanon, echinocandins were mainly used as the first antifungal drug, whereas azoles were predominantly used in Brazil and Spain. No combination therapy was used in this study.

The mortality rate was 38% but ranged from a high of 64% in Brazil to a low of 16% in Spain (**Table 2**). Of the patients who died, 29% were definitely attributable to the candidemia, 35% of the cases were caused by the infection and 36% of cases were not attributed to the Candida infection. The highest mortality rate was observed in Brazil (64%) (**Table 2**) despite the fact that most (73%) of the candidemia cases in Brazil originated from a removable catheter-related source (**Table 3**). In contrast, the USA's mortality rate was more than three-fold lower than Brazil's (20%) despite the fact that only 10% of the candidemia in the US was line related (**Table 3**).

Of the 119 patients with candidemia, 57% were admitted to the ICU and 52% had underlying cancer during their hospitalization (**Table 1**). The median duration of stay in ICU was 15 days (range, 1 – 34). Of the 107 patients treated for at least 24 hours, 70 (65%) patients responded to treatment and survived. Of those responders, 32 (46%) were admitted to ICU ($p < 0.001$). However, 36/37 (97%) of the patients who were treated and died were admitted to ICU. There was a significant association between overall mortality and ICU stay (p-value < 0.01). Of the 45 patients who died (including the 8 not treated), 80% were admitted to the ICU for an average of 15 days. Multivariate analysis showed that a stay at ICU or an underlying cancer requiring chemotherapy were independently associated with failure and death outcome (HR (95% CI), 5.90 (2.22, 15.71) for ICU, and 6.63 (2.43, 18.11) for chemotherapy $P < 0.001$).

Among treated patients, the overall average duration of therapy was 14 days and 16 days in those who had a response to therapy. The median time on treatment for patients who died was 13 days (range, 1 – 24). The mean total duration of ICU hospital stay of the patients who did not receive stepdown therapy was 12 days, with a standard deviation of 8.76. Of the 107 treated patients whose antifungal was changed due to clinical response, 45 (42%) were stepped down to oral therapy. Those 45 patients, who were stepped down to oral antifungal drugs, received either fluconazole or voriconazole, while 13% and 3% of patients were stepped up to echinocandins, and amphotericin B, respectively. The median and mean duration for the step-down from IV to oral antifungal therapy was 5 days of IV treatment.

Looking at the total population, patients who were treated and had a stepdown medication had more favorable outcomes (78% survival) as compared to those with no stepdown (56% survival) ($P = 0.022$). However, the 20 patients who received 1-4 days of first IV treatment before a stepdown to oral azoles had an outcome (20% mortality) which is comparable to the 25 patients who received $\geq$5 days of treatment (24% mortality - $p = 0.75$).

Discussion. Current practice in the treatment of candidemia, when it comes to therapy duration and the time to step-down from IV antifungal therapy to oral drugs, has been based on inference rather than evidence**.** For example, in a milestone study by Rex et al. published in 1994 in the New England Journal of Medicine

whereby fluconazole and amphotericin B were shown to be equally effective in the treatment of candidemia, the duration of therapy in both arms was mandated to be 2 weeks after the last negative blood culture.[7] This treatment duration (2 weeks) has become a routine practice for years to come in the absence of hard data that would highlight the appropriate total duration of therapy and time to step-down to oral therapy.

Hence, the recent IDSA guidelines recommended a total duration of treatment for candidemia of at least 14 days after a negative blood culture. The guidelines also recommend a step-down to oral azole therapy within 5-7 days as long as the patient has achieved clinical stability characterized by resolution of signs and symptoms associated with the infection and clearance of the candida (which should be susceptible to the azole to be used orally) from the bloodstream.[5] In 2012 the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) suggested stepping down to oral after 10 days of IV therapy if the patient was stable clinically and isolated candida demonstrated susceptibility to the oral antifungal drug.[11]

Patients in the present study were treated according to the IDSA guidelines[5] because the overall average duration of treatment for candidemia in this current trial was 14 days, and it was 16 days in those patients who responded to therapy and survived. Furthermore our data do support step-down to oral azoles in patients with clinical and microbiologic resolution since patients, who had a step-down, presented a favorable outcome, even with a more favorable outcome and better survival compared to those patients who did not undergo any stepdown [$p = 0.022$]. This improved outcome associated with stepdown to oral therapy could be related to the fact that a stepdown is dependent on clinical improvement and microbiologic eradication of the candida from the bloodstream, and supports de-escalation in selected patients with good prognostic factors such as the ones described.

However, although our data show that the mean and median duration for stepdown to oral antifungal therapy was 5 days (which is in line with the IDSA guidelines of 5-7 days), there was no indication that a particular minimal time period of IV therapy is necessary before the stepdown should occur. When we compared the 20 patients in our study who received 1–4 days of IV therapy before stepping down to oral azoles with the 25 patients who received 5 days or more of IV therapy before the stepdown, there was no difference in outcome and survival. Hence, stepdown could occur early and at any point in time as long as the patient demonstrates clinical and microbiologic resolution of the bloodstream infection.

In an open label non-comparative trial that evaluated the response to intravenous anidulafungin followed by stepdown to oral fluconazole, the step-down criteria consisted of 24 hours without fever associated with hemodynamic stability and documentation of negative blood cultures as well as resolution of the neutropenia. The time range for the stepdown was 1–6 days in that study.[12] Another multicenter prospective randomized trial compared voriconazole IV to amphotericin B and allowed a stepdown from IV voriconazole to oral voriconazole as well as a stepdown from IV amphotericin to oral fluconazole. Based on the data, a stepdown on day 3 was proposed if the patient was clinically stable with negative blood cultures.[13] Hence it is clear from our study and the literature that the documented clinical and microbiologic resolution of the candidemia is what determines appropriate timing for the stepdown to oral antifungal therapy.

Traditionally, *Candida albicans* has been the most common *Candida* infection worldwide, followed by *candida non-albicans* species in both pediatric and adult patients.[14,15] However, over the past 10 years, there has been a change in the epidemiology of candidemia. Specifically, a decrease in the *candida albicans* infection rate and an increase in the *Candida non-albicans* infection rate has been reported, particularly for *C. parapsilosis*, *C. glabrata, C.tropicalis*, and *C. krusei*.[15,16] In this study, we found that *Candida albicans* infections are still the most common *Candida* species, with 45% of patients being infected with *Candida albicans* and 55% with *Candida non-albicans*. The three most common *Candida non-albicans* were *Candida glabrata* (24%), *Candida parapsilosis* (13%), and *Candida tropicalis* (8%), which are consistent with the literature (**Figure 1**).[14-17]

Our data showed that 57% of our patients were admitted to the ICU and 52% had an underlying cancer (**Table 1**). Hence, the main micro-epidemiological changes in the intensive care and oncology units (to which most of our patients belonged) has been the change in the main type of candida species from *C. albicans* to *C. non-albicans* species, such as *C. glabrata, C. tropicalis, C. krusei, and C. parapsilosis*.[18-21] In the past, fluconazole, have shown efficacy in preventing invasive candida infections in cancer patients, however, their use has been associated with the emergence of resistant candida species, particularly candida non-albicans, such as *Candida glabrata* and *Candida krusei*.[19,20] Sun et al. revealed a global decline in *Candida albicans* infection rates with an associated rise in *Candida parapsilosis* infections among adult patients with malignancy.[22] In our current study, Lebanon and the USA had higher cases of non-albicans candida spp. compared to Brazil and Spain, where albicans spp. remained the most common, which is also consistent with the literature.[23-26]

The two most common sources of candidemia in our study were the central line (possible skin origin) (50%) and gastrointestinal (18%). Since 57% of our patients

were admitted to the ICU where central venous catheters are commonly used, it is not surprising that the vascular catheter was implicated as a source for the candidemia in more than half of our patients (**Tables 1** and **2**). Candida species also belong to the normal gastrointestinal flora, and several risk factors lead to overgrowth of candida and their consequent spread into the bloodstream. Patients with underlying malignancies are at an increased risk of invasive candida infections because chemotherapeutic agents disrupt the gastrointestinal normal flora. More than half of our patients had underlying malignancy and hence it is not unusual to have 18% of our patient having a gastrointestinal source for the candidemia.

As shown in the present study, the mortality rate associated with candidemia was around 38% which is similar to the published literature in high-risk patients. By multivariate analysis we have demonstrated that patients with an ICU admission or with underlying cancer requiring chemotherapy were significantly associated with the highest mortality. Hence, the high mortality rate in this study is likely related to the fact that the majority of the population analyzed were very sick (57% admitted to the ICU), and have multiple comorbidities (52% with underlying cancer, 46% with prior surgery and 36% with underlying diabetes mellitus).

However, similar to the epidemiological distribution of invasive candida infections, mortality and cure rates may also vary among populations and geographical areas.[30] For instance, the rate of death increased from 29% in the USA to 60% in South Africa and 54-72% in Brazil.[30] Similar findings were observed in our study, in which Lebanon and Brazil had higher rates of death compared to the USA and Spain. In some ways, these results are not surprising because of the numerous factors that would likely affect the nature, effectiveness, and accuracy of care given in developing countries.[31,32]

Andes et al. conducted an individual patient-level review to assess the clinical outcome, mortality, and factors associated with the success of treatment.[33] Many factors were identified to affect the success of treatment and survival of patients, such as early removal of the central venous catheter and early use of antifungals, specifically echinocandin.[31,33-35] In contrast, other studies suggested that advanced age, the presence of comorbidities, and delaying treatment until positive blood cultures, are factors that could increase mortality.[32-34,36]

Conclusions. In summary, our study showed that the mortality associated with candidemia may be high especially among high-risk patients who are critically ill or cancer patients receiving chemotherapy. Our data support the IDSA guidelines and previous reviews[37] in that the total duration of treatment for candidemia should be at least 14 days after a negative blood culture. However, our data showed that in non-neutropenic cancer patients with candidemia, a step-down to oral azole therapy can safely take place early as long as the patient had clinical and microbiologic resolution of the bloodstream infection.

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