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EC MICROBIOLOGY
Research Article

Current Situation of Candidemia in Non-Neutropenic Critically Ill Patients: Results of On-Line Survey

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Received: February 06, 2021; **Published:** September 29, 2021

Abstract

Purpose: To determine the epidemiology, risk factors and impact on mortality of candidemia in non neutropenic critical patients and to describe the used diagnostic tools and management of candidemia.

Patients and Methods: a cross-sectional observational study using an online questionnaire that assessed an 8-month period (January - August 2014). Eleven departments of medical and surgical ICU and severe burns participated in this study. All the medical records of admitted patients during this period were consulted: those who presented a candidemia were the cases and the others were the control.

Results: 87 episodes of candidemia were recorded in 73 among 2500 patients admitted during the study period. The overall incidence of candidemia was 34.8/1000 admissions and it was higher in medical and burn units. *Candida* albicans (58.3%) and C. glabrata (21%) were the most isolated species. Sensitivity of the isolates to fluconazole and amphotericin B was maintained at 80% (70/87) and 87% (76/87), respectively. Invasive procedures, pre-exposure to antibiotics and antifungals, severe burns and an ICU stay > 7 days were independent factors associated with candidemia. Mortality at 28 days was 42.5% and no effect of *Candida* species on mortality was revealed. Candidemia was a significant mortality factor (OR = 4.16, IC95% [1.77 - 15.05], p = 0.005).

Conclusion: The incidence of candidemia was elevated outside neutropenia with a significant association with mortality.

Keywords: *Candidemia; Candida spp; Mortality; Intensive Care; Risk Factors*

Introduction

Candidemia is a common infection in intensive care units (ICU) associated with increased morbidity and mortality. *Candida* species are the microorganisms in cause. *Candida spp* may be present as commensals on human skin or mucus membranes including the upper airways, the gastrointestinal tract and the genitourinary tract. *Candida* overgrowth in such non-sterile sites manifests clinically as thrush. However, translocation to sterile sites such as the blood stream results in candidemia or in invasive candidiasis (IC) when *Candida spp* affect several organs such as the peritoneal cavity, brain, eyes or bones [1].

Candida albicans, C. parapsilosis, C. glabrata, C. tropicalis and *C. krusei* are the most common species in humans [2]. A major change in the global epidemiology of candidemia over the past two decades is a shift towards the predominance of non-albicans *Candida* species in many parts of the world, especially amongst patients with hematological malignancies and transplant recipients [3-5].

Risk factors for candidemia include the presence of central venous catheters, exposure to broad-spectrum antibiotics and abdominal surgery. Such risk factors are prevalent amongst patients in intensive care units and hence such patients are at an increased risk of can-

didemia [2]. Candidemia is associated with poor clinical outcomes, including mortality, as well prolonged hospital stays and considerably increased healthcare costs [6,7]. Early recognition and appropriate treatment for candidemia are associated with improved outcomes [1]. Currently available diagnostic tools for candidemia include culture, biomarkers and molecular assays. However, their diagnostic utility is limited by their suboptimal sensitivity and specificity [1,2]. Therefore, management continues to rely on critical assessment for the presence of risk factors and any clinical evidence of Candidemia. A detailed understanding of the local epidemiology and the clinical and mycological patterns of candidemia is essential to support such assessments.

In Tunisia and to the best of our knowledge, available data on the epidemiology of candidemia are mainly focused on immunocompromised patients. There have been no published data describing the epidemiology of candidemia in non-neutropenic patients.

Herein, we report the results of a multicenter study from 11 Tunisian ICUs. We describe the epidemiology of candidemia in those units, mycological features, the diagnostic and therapeutic strategies deployed.

Patients and Methods

Study design: This was a multicenter, cross sectional observational on-line survey involving 11 ICUs in 5 different Tunisian cities. All patients aged 18 years or more who were admitted to ICU during the period from January 1 to August 31, 2014 were included. Patients with neutropenia (absolute neutrophil count less than 1,5 x 10^9/L) at the time of admission to ICU were excluded.

The electronic microbiology databases in the participating hospitals were searched for blood cultures yielding a growth of *Candida* species over the study period. Demographic and clinical details, including clinical presentation, risk factors, treatment received and outcomes were extracted from the hospital records. Moreover, details of participating hospitals and intensive care units (total admissions over the study period, available mycological investigations and typical turnaround times) were also recorded.

Candidemia was defined as the isolation of *Candida spp*. from the blood culture in the presence of systemic inflammatory response syndrome (SIRS), manifested by ≥ 2 out of the following: body temperature < 36°C or > 38°C, heart rate > 90/min; respiratory rate > 20/min or $PaCO_2$ < 32 mmHg; peripheral white blood cells count > 12 x 10^9/L, < 4 x 10^9/L or > 10% of circulating immature forms [8]. The isolation of *Candida* species from blood cultures taken 14 days or more from the date of the first candidemia in the same patient was considered as a separate episode of candidemia. The detection of *Candida spp*. from catheter tip culture in presence of SIRS without concomitant evidence of bacterial infection was also considered an episode of candidemia.

Mycological procedures

Commonly, the detection and identification of *Candida strains* were performed using the transplanting CandiID® and Sabouraud chloramphenicol actidione media. *Candida* blood isolates (CBI) were detected using the automated blood culture of Bactec system. Chromogenic *Candida* Agar and CHROMagar *Candida* were used for identification of CBI. Susceptibility testing for fluconazole, voriconazole and caspofungin was performed using the microtitre broth dilution method with the Sensi-titre YeastOne™ test panel (version 4.0 from 2004 to 2007; version 7.0 from 2007 to 2009). Interpretation of susceptibility was performed by applying the clinical interpretive breakpoints defined by the antifungal susceptibility testing/European Committee on Antimicrobial Susceptibility Testing: AFST-EUCAST ("EUCAST breakpoints"; http://www.eucast.org/clinical_breakpoints/; version 6.1).

Statistical analysis: Continuous and normally distributed quantitative variables were expressed as mean and standard deviation (SD) and compared using the Student t test or Z test. Quantitative variables with non-Gaussian distribution were expressed as median and inter-quartile ranges (IQR [25 - 75]) and compared using the Mann-Whitney U test. Categorical variables were expressed as percentages and compared using the Chi Squared or Fisher exact test as appropriate.

The assessment of association (between risk factors and candidemia and between candidemia and mortality) was performed by the logistic regression method (stepwise regression model) and expressed as odds ratio. The studied factors in the first analysis (risk fac-

tors and candidemia) were: age, gender, co-morbidities, SAPS II, admission reason, invasive procedures and an ICU stay > 7 days. For the second analysis (candidemia and mortality), the covariates were: age > 50 years, SAPSII > 35, co-morbidities, septic shock and reason of admission. The factors with a significance < 0.2 in the univariate analysis were included in the multivariate analysis.

A p values of < 0.05 were considered statistically significant. Data were analyzed by the Statistical Package for Social Sciences (SPSS) Version 20.

Ethics statement: This study was approved by the local institutional review boards of the participating hospitals. The requirement for written consent was waived.

Results

Two thousand and five hundred patients were admitted during the study period. A total of 87 episodes of candidemia were documented in 73 patients. The diagnosis of candidemia was established by a positive blood culture in 63 cases (72%) and a positive catheter tip culture in 24 cases (28%). The overall incidence of candidemia was 34.8 per 1000 admissions. The incidence in medical and burns ICU was 59 per 1000 admissions, whereas it was only 10.2 per 1000 admissions in surgical ICUs (p = 0.03). A second episode of candidemia was documented in 14 patients (19%); of these, 11 (79%) were in ICU for ≥ 21 days, 10 (71%) had previous exposure to fluconazole or amphotericin B and 8 (57%) had the same *Candida* species in both episodes.

The most frequent reason of admission in ICU was medical pathology. The occurrence of candidemia was more observed in severe burns. The demographic data and severity scores were similar between patients with candidemia compared with those without. Co-morbidities, such solid tumors, cardiac failure and diabetes, were more common in patients with candidemia. The septic shock occurred more frequently in the candidemia group with a difference near to significance (Table 1).

	Patients with candidemia (n = 73)	**Patients without candidemia (n = 2427)**	**p value**
Age (years), mean ± SD	46 ± 15	48 ± 18	1
Sex ratio (M/F)	1.33	1.09	0.63
SAPS II on admission, median, IQR	38 ± 11	32 ± 16	0.8
Co-morbidities, n (%)			
Diabetes	33 (45.2%)	840 (34.6%)	0.09
chronic respiratory failure	19 (26%)	522 (21.5%)	0.75
chronic renal failure	13 (18%)	364 (15%)	0.2
cardiac failure	8 (11%)	186 (7.7%)	0.056
Solid Tumor	4 (5.4%)	23 (0.94%)	0.01
No co-morbidities	0	492 (20.3%)	NC
Admission typology, n (%)			
Medical pathology	45 (62%)	1747 (72%)	0.46
Surgical -Trauma pathology	7 (10%)	437 (18%)	0.5
Severe burns	21 (28%)	243 (10%)	0.02
Predisposing factors, n (%)			
Central venous catheter	69 (94%)	1747 (72%)	0.06
Mechanical ventilation	67 (92%)	1577 (65%)	0.04
Previous antibiotic therapy	58 (80%)	1116 (46%)	0.009
Parenteral nutrition	61 (84%)	922 (38%)	0.038
Steroid therapy	38 (52%)	1092 (45%)	0.9
Previous antifungal	33 (45%)	218 (9%)	< 0.001
Septic shock, n (%):	46 (63%)	1092 (45%)	0.072
LOS in ICU (days), median (IQR)	24 (19-32)	13 (8-21)	0.01
Length of mechanical ventilation, (days), median (IQR)	15 (10-23)	7 (5-16)	0.048
ICU all cause mortality	42.5%	26%	0.016

Table 1: *Patient's demographic and clinical characteristics.*
SD: Standard Deviation, IQR: Inter-Quartile Range, LOS: Length of Stay, SAPS II: *Simplified Acute Physiology Score II, ICU: Intensive Care Unit, NC: Not Calculated.*

Culture results were received >72 hours from presentation in 72% of episodes. *C. albicans* (58.3%) and *C. glabrata* (21%) were the most commonly isolated species (Figure 1).

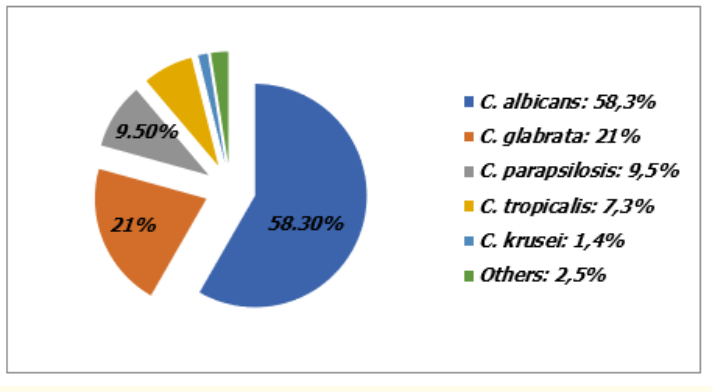

Figure 1: *Distribution of isolated Candida species.*

Legend: *Candida albicans was the predominant strain in 58.3% of cases followed by C. glabrata in 21%. Third position was divided between C. parapsilosis and C. tropicalis in 9.5% and 7.3% respectively. The krusei species was rarely detected (1.4%).*

The majority of isolates were susceptible to fluconazole (70/87, 80%) and amphotericin B (76/87, 87%).

Regarding the risk factors, invasive procedures (central venous catheter and mechanical ventilation), previous antibiotic therapy, previous antifungal therapy, a solid tumor, severe burns and an ICU stay higher than 7 days were the independent factors associated to candidemia. Results of the univariate and multivariate analysis are summarized in table 2.

	Un-adjusted analysis	Adjusted analysis	
	Odds Ratio (95% confidence interval)	**Odds Ratio (95% confidence interval)**	**p value**
Age ≥50 years	1.02 (0.62-2.80)	-	0.45
Male gender	0.77 (0.20-3.69)	-	0.8
SAPS II >35	1.65 (1.20-2.06)	1.04 (0.87-1.25)	0.23
Type of admission			
Medical	1.27 (1.13-1.87)	1.09 (0.89-1.15)	0.18
Burns	2.30 (1.19-2.95)	1.42 (1.20-1.67)	0.024
Comorbidities			
Diabetes	1.54 (0.90-2.25)	1.32 (0.68-1.67)	0.45
Chronic respiratory failure	1.20 (0.79-4.22)	-	0.5
Chronic renal failure	1.09 (0.86-2.07)	-	0.33
Cardiac failure	1.78 (0.74-2.66)	1.15 (0.86-1.57)	0.1
Solid Tumor	2.59 (1.34-4.15)	1.88 (1.20-2.45)	0.017

Iatrogenic factors			
Central venous catheter	2.65 (1.99-3.71)	1.40 (1.12-1.64)	0.05
Mechanical ventilation	2.98 (2.02-4.10)	1.62 (1.18-1.97)	0.032
Previous antibiotic	1.96 (1.25-3.48)	1.64 (1.20-2.06)	0.011
Parenteral nutrition	1.77 (1.29-3.26)	1.18 (0.92-1.54)	0.15
Steroid therapy	1.11 (0.74-2.26)	-	0.28
Previous antifungal	2.44 (1.92-4.08)	1.85 (1.40-2.16)	<0.001
LOS in ICU (>7 days)	2.06 (1.35-3.99)	1.45 (1.14-1.97)	0.018

Table 2: *Factors associated with candidemia by stepwise logistic regression.*
SAPS II: Simplified Acute Physiology Score; LOS: Length of Stay.

Fluconazole was the most commonly prescribed systemic antifungal (38%), followed by amphotericin B deoxycholate (32%). Voriconazole was used in 24% of cases, while caspofungin in only 7% of cases. Oral voriconazole was mostly used in patients with chronic renal impairment while caspofungin was usually reserved for patients with recurrent candidemia who had previous fluconazole exposure. Nephrotoxicity, defined as serum creatinine rise by ≥ 50% from baseline, was reported in 8/23 (38%) of patients who received amphotericin b deoxycholate. Four among them required renal replacement therapy. Furthermore, two patients developed a severe anaphylaxis due to amphotericin B deoxycholate. In addition to the antifungal treatment, catheter removal was performed in 54% of the cases.

The overall all-cause mortality at day 28 was 42.5%. The logistic regression showed that candidemia was a significant mortality factor (OR = 4.16, IC95% [1.77-15.05], p = 0.005).

The comparison of mortality according to the *Candida* species found no impact of the *Candida* gender on mortality (Table 3).

	Alive at 28 days (n = 56)	**Not alive at 28 days (n = 31)**	**p**
Candida albicans	33/56 (59%)	18/31 (58%)	0.39
Candida glabrata	8/56 (14%)	10/31 (32%)	0.5
Candida parapsilosis	6/56 (11%)	3/31 (10%)	0.23
Candida. tropicalis	5/56 (9%)	1/31 (3%)	0.14
Candida krusei	1/56 (2%)	0	-
Others	2/56 (4%)	0	-

Table 3: *Mortality according to Candida species.*

Discussion

Our main findings, candidemia was a frequent infection in non-neutropenic critical patients and that was higher in medical and burns units. The significant risk factors were central catheter, mechanical ventilation, previous antibacterial and/or antifungal therapy and an ICU stay > 7 days. The diagnosis of candidemia was established by a positive blood culture in 63 cases (72%) and a positive catheter tip culture in 24 cases (28%). A second episode of candidemia was showed in 14 cases and the same *Candida* species was isolated in 8/14 of cases. *C. albicans* was the major isolate (58.3%) followed by *C. glabrata* (21%). The isolated *Candida* strains were susceptible to fluconazole and amphotericin B in 80% and 87% respectively. The most prescribed drugs were fluconazole and amphotericin B. Amphotericin B

was the most antifungal agent in cause of side effects. The all-cause mortality was 42.5%. Candidemia was an independent factor related to mortality and no effect of *Candida* gender on mortality.

The incidence of candidemia varied from 1.5 to 39 per 1000 admissions [9-12]. Our incidence was similar to that of a multicenter French study performed in septic shock patients (EPISS study) with an incidence of 32 per 1000 admissions [13]. Indeed, a steady increase in candidemia rates has been noted over the past 10 years in France [14].

The differences of incidences of candidemia may reflect the heterogeneity of studied populations. It was recognized that surgery exposed to *Candida* infections by the risk of fungal translocation. Our results and others [10,11] do not agree with this hypothesis. This could be explained by the shorter length of stay in intensive surgical units than in medical units. The major risk factors reported in our survey were invasive procedures, severe burns, previous antibacterial or antifungal and ICU stay > 7 days. These results were consistent with previous literature review [7].

The fungal ecology changes according to the patient environment. Indeed, in North America an increase of *non-albicans Candida species* was reported in the recent years [15,16]. The reasons for the emergence of *non-albicans* species are not clear, but some conditions may increase their growing. For example, a high growth of *C. parapsilosis was associated* with vascular catheterization and parenteral nutrition, whereas a high growth of *C. krusei* and *C. glabrata* was associated with pre exposure to azoles [17]. Different data were reported in Europe regarding the predominance of *C. albicans* reaching 70% [18-22]. In the same way, *C. albicans* was the major isolate in our survey (58.3%). The dominance of *C. parapsilosis* was noted in the Mediterranean regions with 77.1% and 36.4% in Turkey and Greece respectively [12,23]. The prevalence of *C. glabrata* varied from 13.2 to 31.2% in European studies [24,25].

In routine practice, the laboratory diagnosis of candidemia is established by repeated blood cultures. Nevertheless, the identification of some species of *Candida* may require specific techniques. When invasive candidiasis without candidemia is suspected, the dosage of mannan antigens or better the 1,3-β-D-glucan (in reason of its high negative predictive value) is recommended for the diagnosis of candidiasis [26,27]. The dosage of mannan antigens/anti mannan antibodies is available in only 3/11 of the present studied centers.

It is now admitted that the early antifungal treatment is a determinant prognostic factor for candidemia [28,29]. The choice of antifungal agent must take into account the fungal ecology of each unit, properties and availability of this antifungal. The expert societies recommend an echinocandin as a first line therapy in patients with severe invasive fungal infection [30]. Later, if the isolated strain is sensitive to azoles with a clinical improvement, de-escalation to fluconazole is recommended. In case of recent exposure to azole, echinocandin should be continued. Voriconazole is proposed in specific situations, such as oral relay in candidemia due to fluconazole-resistant *Candida spp.* The recent opinions tend to the abandonment of amphotericin B because of its side effects. In our survey, the antifungal drugs most commonly prescribed as first line were fluconazole and amphotericin B. No therapeutic strategy was followed later and this could be explained by the high costs of echinocandin that are outside hospital nomenclature in low income countries.

The ESCMID guidelines recommend the removal of any central catheter during candidemia. In fact, it was demonstrated that catheter removal was associated to the successful treatment rate [31] and to decreasing of mortality [32]. In our series, catheter removal was performed in 54% of cases.

The mortality in patients with candidemia remains considerable at 40 or even 60%; as reported by different series [9,11]. The most reported poor prognosis factors were organ failure and later treatment [33] and septic shock [34]. An inappropriate, probabilistic antifungal treatment was shown to be an independent risk factor of mortality [34]. The mortality rate in our series was also crucial (42.5%) and candidemia increased the risk of death by four times.

The literature data differ regarding the mortality by *Candida* specie. In the AURORA cohort, the specific mortality of different species varied from 26.5% for *C. parapsilosis* to 77.8% for *C. tropicalis* [9]. For the Prospective Antifungal Therapy Alliance registry, *C. parapsilosis* was the least linked to death, whereas *C. krusei* was the most [35]. Some species become more virulent after exposure to azoles or echinocandins and that may be due to resistance's acquisition [22,36,37]. The mortality was not influenced by the type of *Candida* in our series.

The strength of this article is, to our knowledge, the first multicentre study focusing on candidemia in non-neutropenic patients and involving medical and surgical ICIs. The weakness is the lack of longitudinal follow-up of the included patients.

Conclusion

The incidence of candidemia was considerable and significantly associated to mortality. *C. albicans and C. glabrata* were the most isolated strains. Severe burns, invasive procedures, previous antibacterial and/or antifungal and ICU stay longer than 7 days were the independent factors related to candidemia. The diagnostic of candidemia was mainly established by the isolation of *Candida* strain in blood culture. The management was based on the prescription of fluconazole and amphotericin B in addition to the removal catheter. The inconsistence with the guidelines regarding the diagnostic and therapeutic management of candidemia may be explained by the insufficiency of biological diagnostic techniques and the difficulty to obtain echinocandin. This should set priorities for the clinical investigations and therapeutic tools that need to be performed.

Acknowledgments

The authors express their warm thanks to the colleagues who participated in the survey: Pr Amel Moklin, Pr Amen Allah Messadi, Pr Mounir Bouaziz, Pr Fahmi Dachraoui, Pr Fekri Abroug, Pr Hatem Elghord, Pr Mustapha Ferjani, Pr Mouldi Amamou, Pr Amira Jammoussi, Pr Mohamed Besbes, Pr Souheil Elatrous, Pr Mohamed Sami Mebazaa, Pr Zouheir Jerbi.

Conflict of Interest

No conflict of interest to declare.

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Volume 17 Issue 10 October 2021