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REVIEW ARTICLE

CANDIDEMIA IN INTENSIVE CARE UNIT: EPIDEMIOLOGY AND PROGNOSTIC FACTORS

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ABSTRACT

Background: Candidemia, recognized as a fairly common disease in intensive care unit (ICU) patients, is of poor prognosis. Our study aimed to study the epidemiology of a series of candidemia and the factors favoring their aggravation in the intensive care unit (USI) of the Military Hospital of Tunis. ***Methodology:*** It is a retrospective study carried out in the laboratory of Parasitology-Mycology and the UCI of the Military Hospital of Tunis over six years. Blood cultures were performed in the MYCOSIS-IC/F® Becton Medium from Deckinson. The identification of the species was made by the chlamydosporulation test and the YST Vitek®2 card. These data were analyzed by SPSS version 22 software. ***Results****:* Of 3298 ICU admissions, 58 presented with candidemia resulting in an attack rate of 1.7%, or 17.5 episodes of candidemia per 1000 admissions. The average annual incidence was 9.6 cases/year. The mean age of the patients was 55 ± 15.9 years. We noted a male predominance in 59% of cases with a sex ratio of 1.4. The study of the pathological antecedents showed that these patients were followed mainly for pancreatitis (98.3%), diabetes (37.9%), and arterial hypertension (34.5%). The predominantly isolated species was *C. albicans* (48.33%). Multivariate analysis revealed that isolation of *Candida albicans* from blood cultures and arterial hypertension are significant factors of high mortality. ***Conclusion****:* This study allowed us to observe epidemiology and prognostic factors of candidemia in a Tunisian series. It can help resuscitators by allowing an optimization of the recommendations for the treatment of candidemia according to the prognostic factors.

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INTRODUCTION

Candidemia is defined by the presence of at least one blood culture positive for the yeast of the genus *Candida*. Currently, it is increasing and ranking fourth among nosocomial infections. They represent 70 to 90% of invasive fungal infections (IFI) (Gürcüoğlu *et al*., 2010). These opportunistic infections lead to significant hospital mortality (30 to 60%) and considerable economic costs (Huttunen *et al*., 2010). Patients at risk are mainly found in an intensive care unit (ICU), medical or surgical resuscitation, onco-hematology, neonatology, in severe burns, or after organ transplantation. Only early diagnosis and treatment can improve the prognosis. Due to the geographic disparity in the epidemiology of candidemia found through studies, the data in the literature are not necessarily superimposable and are even less applicable to local issues. We, therefore, conducted this study, which aims to study the epidemiology of a series of candidemia and the factors favoring their aggravation in the ICU of the Military Hospital of Tunis.

METHODS

Study design and setting: Our study is a retrospective conducted in the laboratory of Parasitology-Mycology of the Military Hospital of Tunis in collaboration with the ICU of the same hospital for 6 years, from January 2013 to December 2018.

Study population: Patients older than 18 years, hospitalized in the ICU with at least one positive *Candida* strain in their blood culture, were included in this study. For each patient, an observation sheet was completed from the clinical records of the patients: age, gender, medical and surgical history, reasons for hospitalization in intensive care, and risk factors.

Laboratory analysis: Blood cultures were performed in MYCOSIS-IC/F® Becton-Deckinson medium in the presence of an infectious syndrome. Species identification was made by the chlamydosporulation test (subculture on Agar Tween medium) and the YST Vitek®2 card.

Mannan antigenemia and anti-mannan antibodies were performed using the Platelia™ *Candida* Ag Plus and Platelia™ *Candida* Ab plus kits, respectively.

Statistical analysis: These data were entered and analyzed using SPSS version 22 software. We studied the prognostic factors of candidemia by univariate analysis added to a multivariable analysis. For all statistical tests, the significance level was $p<0.05$.

RESULTS

Among 3298 admissions into ICU between 2013 and 2018, 58 presented candidemia resulting in an attack rate of 1.7%, or 17.5 episodes of candidemia per 1000 admissions.

Table 1. Distribution of patients according to the reason for hospitalization (n = 58)

Reasons for admission	Percentage (%)
Septic shock	27 (46,6%)
Post-operative resuscitation	15 (25,8%)
Polytrauma	4 (6,9%)
Cardiogenic shock	4 (6,9 %)
Neurological distress	4 (6,9%)
Altered state of consciousness	3
Cerebrovascular accident	1
Hemodynamic shock	3 (5,1%)
Respiratory distress	1(1,8%)

Table 2. Distribution of patients according to personal pathological history (n = 58)

Pathological history	Percentage (%)
Pancreatitis	57 (98,3 %)
Diabetes	22 (37,9 %)
Arterial hypertension	20 (34,5 %)
Chemotherapy	8 (13,8 %)
Chronic renal failure	6 (10,3 %)
Malignant hemopathy	5 (8,6%)
Solid tumor	5 (8,6%)

Table 3. Distribution of immunological diagnostic results in study patients (n=42)

Results	Anti-Mannan antibody Percentage (%)	Mannan antigen Percentage (%)
Negative	21 (50%)	30 (71%)
Doubtful	3 (7%)	5 (12%)
Positive	18 (43%)	7 (17%)
Total	42 (100%)	42 (100%)

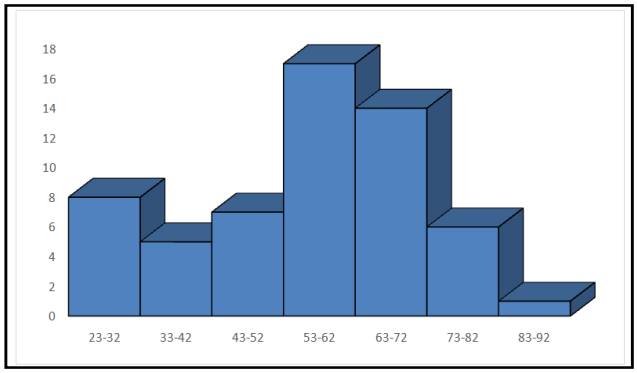

Figure 1. Distribution of candidemia cases by age group (n = 58)

The mean annual incidence was 9.6 cases/year. The mean age of patients during the study period was 55 years ± 15.9 years, with age ranges from 23 years to 88 years. The age group (53-62 years) was the most affected (29.3%) (Figure1).

In addition, we noted a male predominance in 59% of cases with a sex ratio of 1.4. The admission to the ICU was mainly represented by septic shock and postoperative resuscitation (Table 1). The study of pathological history showed that these patients were followed mainly for pancreatitis (98.3%), diabetes (37.9%), and arterial hypertension (34.5%) (Table 2). Six species of *Candida* have been isolated. *C. albicans* was the most common species isolated from 29 blood cultures (48.3%). *Non-albicans Candida* species, isolated from 31 blood cultures (51.7%), were represented by *C. glabrata* (n = 11), *C. parapsilosis* (n = 9), *C. tropicalis* (n = 8), *C. krusei* (n = 2), and *C. Kefyr* (n = 1) (Figure 2).

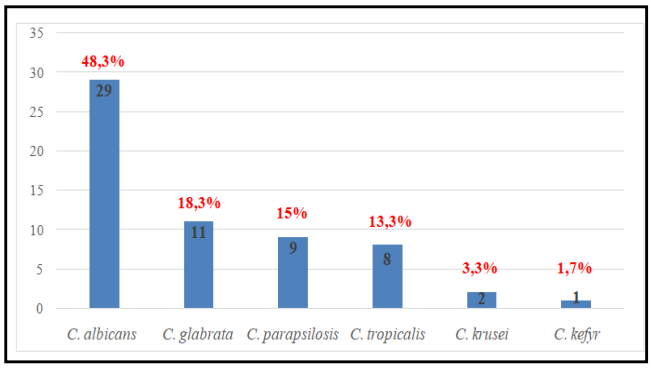

Figure 2. Distribution of species of the genus *Candida* isolated in blood cultures (n = 60)

The association of the genus *Candida* yeast species was noted in two blood cultures (3.4%). It was an association of *C. tropicalis* with *C. albicans* in 1 case and with *C. glabrata* in the other case. Among the candidemia cases, five had an association with yeasts of the genus other than *Candida* (8.6%). These were three patients with *C. albicans* and *Geotrichum capitatum* and the other two patients with *C. tropicalis* and *Trichosporon asahii*. In the present study, the association with bacteria was frequent and reported in 39 cases (67.2%) with a predominance of Gram-negative bacteria in 74% of cases compared to Gram-positive bacteria in 26%. The main bacteria involved are represented in Figure 3.

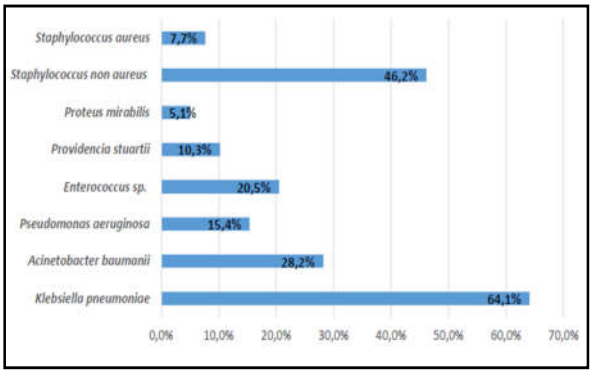

Figure 3. Distribution according to the bacterial species isolated in association with yeasts of the genus *Candida*

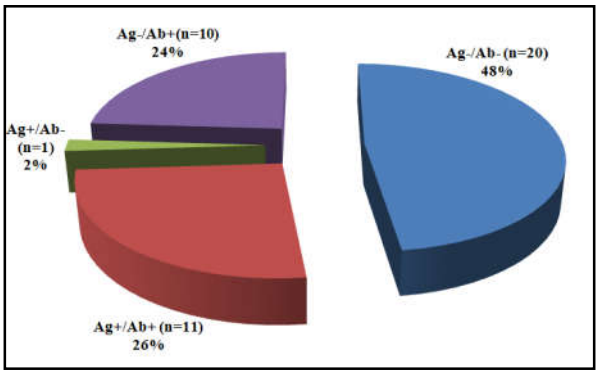

Figure 4: Distribution of patients according to the results of the mannan antigen and anti-mannan antibody

Table 4. Univariate analytical study of prognostic factors

Prognostic factors	Groups with and without prognostic factor	Dead	Living	p value
Gender	Male :34	22	12	0,263
	Female : 24	12	12	
Age	≥ 65 ans : 22	16	6	0,081
	<65 ans : 36	18	18	
Diabetes	Yes : 22	16	6	0,088
	No : 36	18	18	
Arterial hypertension	Yes : 20	16	4	0,016
	No : 38	18	20	
Long-term antibiotherapy	Yes : 56	32	24	0,227
	No : 2	2	0	
Corticosteroid therapy	Yes : 15	9	6	0,906
	No : 43	25	18	
Chemotherapy	Yes : 8	5	3	0,812
	No : 50	29	21	
Malignant hemopathy	Yes : 5	5	0	0,07
	No : 53	29	24	
Solid Tumor	Yes : 5	1	4	0,149
	No : 53	33	20	
Fungal colonization	Yes : 30	15	15	0,018
	No : 17	15	2	
Parenteral nutrition	Yes : 47	28	19	0,765
	No : 11	6	5	
Major surgery	Yes : 23	11	12	0,176
	No : 35	23	12	
Neutropenia	Yes : 3	3	0	0,260
	No : 55	31	24	
Candiduria	Yes : 17	9	8	0,822
	No : 23	13	10	
Dialysis	Yes : 35	23	12	0,176
	No : 23	11	12	
Renal failure	Yes : 40	26	14	0,141
	No : 18	8	10	
Extended stay in intensive care	Yes : 49	29	20	0,813
	No : 9	5	4	
Mechanical ventilation	Yes : 48	29	19	0,726
	No : 10	5	5	
Urinary catheter	Yes : 56	34	22	0,167
	No : 2	0	2	
Central venous catheter	Yes : 57	33	24	0,391
	No : 1	1	0	
Central arterial catheter	Yes : 56	32	24	0,227
	No : 2	2	0	
Drain	Yes : 12	10	2	0,091
	No : 46	24	22	
Mannan antigenemia	Negative : 30	15	15	0,443
	Doubtful to positive:12	7	5	
Anti-mannan antibody	Negative: 21	10	11	0,379
	Doubtful to positive : 21	12	9	
Abundance of culture	1 to 2 crosses : 22	16	6	0,271
	3 to 4 crosses : 23	13	10	
Score APACHE II	≥20 : 8	7	1	0,223
	<20: 50	18	32	
Candida albicans species	Yes : 29	17	12	0,032
	No : 29	11	18	

C: Candida, APACHE II: Acute Physiological and Chronic Health Evaluation.

The mannan antigen (Ag) and the anti-mannan antibody (Ab) were tested concomitantly in 42 patients. Ag and Ab were doubtful to positive in 12cases and 21 cases, respectively (Table 4). The mean concentrations of positive mannan antigenemia were 268.7pg/ml with extremes of 125 and 655 pg/ml. The distribution of the results of the Ag/Ab pair of our patients is shown in Figure 4. Day 0 is considered the date of the first positive blood culture. In patients with dubious to positive Ab and/or Ag serologies, the time between Day 0 and the date of serological sampling was, on average, 7.8 days before Day 0. Thirty-four patients died, corresponding to a mortality rate of 58.6%. In univariate analysis, the factors of poor prognosis retained were: arterial hypertension (p=0.016), fungal colonization (p= 0.018) and isolation of *C. albicans* species in blood cultures (p = 0.032). The results of this analysis are detailed in Table 3. Multivariate analysis revealed that the isolation of *Candida albicans* from blood cultures (ORa 3.9; 95% CI 1.2-54.2) and arterial hypertension (ORa 4.4; 95% CI 1.2-15.7) are significant factors in high mortality.

DISCUSSION

Epidemiological data on candidemia in Tunisia are rarely reported. In our 6-year study, the incidence of candidemia was 17.5 episodes per 1000 ICU admissions. It is 16.5/1000 admissions in Italy (Montagna *et al*., 2013) and 6.7/1000 admissions in France (Sasso *et al*., 2017). It is 26/1000 admissions in Saudi Arabia (Aldorzi *et al*., 2018), 2.49/1000 admissions in Brazil (Yapar, 2014), and 0.026/ 1000 admissions in Norway (Berdal *et al*., 2014). Our series studied candidemia in adults; the mean age of patients was 55 ± 15.9 years, with age extremes ranging from 23 to 88 years. The sex ratio of our population was 1.4. This male predominance in candidemia is reported in several studies around the world (Colombo *et al*., 2006; Nucci *et al*., 2013). The maximum difference between men and women is found in patients over 50 years old and in those aged 20 to 29 years (Arendrup *et al*., 2009).

The reasons for the difference in incidence by sex are not identified. Favorable circumstances such as blood diseases and gastrointestinal cancers or serious trauma are more frequent in men aged 20-29, which could partly explain this difference (Arendrup *et al*., 2009). Determining the personal pathological history is important because patients admitted to intensive care are often immunocompromised and therefore likely to develop opportunistic infections, including candidemia. In the present study, 98.3% of our patients were followed for pancreatitis. In other studies, this rate varies between 0 and 40% (Kochhar *et al*., 2009; Rasch *et al*., 2016). Invasive fungal infections associated with acute pancreatitis are very common, particularly those caused by *Candida albicans* (Rasch *et al*., 2016). In our study, 37.9% of the patients were diabetic. High blood pressure was noted in 34.5% of our patients. The rate of arterial hypertension in patients with candidemia was estimated at 37% in China and 39% in France, which gives values close to those found in our study (Ruiz *et al*., 2018).

In our series, *C. albicans* was the most frequent species, isolated in 48.3% of cases. Several studies confirm that *C. albicans* is the main species although its incidence has been declining in recent years in favor of *non-albicans Candida* (Kawano *et al*., 2017; Lortholary*et al*., 2014). *C. glabrata* was isolated from 18.3% of our patients. This result is in agreement with the data in the literature. In fact, in 87 French ICUs, *C. glabrata* was responsible for 18.6% of all cases of invasive candidiasis occupying second place after *C. albicans* (Arsic, 2018). These data are close to those found in a Moroccan study carried out in 2016 in Rabat, where *Candida glabrata* was isolated in 24% of cases (Achich, 2016). In our study, the association of yeast species of the genus Candida was noted in two cases (3.4%). These data are similar to those found in a study carried out in Leuven-Belgium, reporting a percentage of 4% (Lagrou *et al*., 2007). In the review of 529 cases of candidemia in Barcelona, two species of *Candida* were associated in 1.7% of cases (Ortega *et al*., 2011). In the series of 186 candidemia in France, 7 cases of candidemia (3.8%) concerned associations of yeasts of the *Candida* genus (Talarmin *et al*., 2009). Furthermore, we also noted two associations of *Candida* yeasts with *Trichosporon asahii* and three with *Geotrichum capitatum*. Mixed fungemia, defined by the simultaneous isolation of two or more fungal genera in the same blood culture or two blood cultures were taken less than 72 hours apart, is rare and remains poorly documented. The usefulness of *Candida* serology and antigenemia is proven when these two markers are associated. In fact, the antibody must be solicited several times to follow its kinetics: an increase in titer or a seroconversion. As for the antigen, its positivity is frequent 5 to 6 days before the positivity of the blood culture (Gaspar *et al*., 2015). This result was demonstrated in our study: the time between day 0 and the date of the serological sample was, on average, 7.8 days before day 0. These tests can be used both for screening and for the early diagnosis of invasive candidiasis. The sensitivity of mannan antigenemia in our study was 29%, and that of anti-mannan antibody was 50%. A meta-analysis of 14 studies, including 7 conducted in non-neutropenic patients, reported a sensitivity of mannan antigenemia and anti-mannan IgG of 58% and 59%, respectively (Bailly *et al*., 2017). The combined detection of the two biomarkers improves the sensitivity and specificity to 83% and 86%, respectively, with the best performances obtained for infections with *C. albicans*, *C. glabrata*, and *C. tropicalis* (Cuenca, 2012). In our series, the death rate was 58.6%. This rate is consistent with the study by Lortholary *et al*. conducted on 1206 patients hospitalized in ICUs in 24 hospitals in the Paris region from 2002 to 2010, where the overall mortality rate was 41.5% (Arsic, 2018). Mortality attributable to invasive candidiasis reported in retrospective cohorts ranges from 26.5 to 76.7% (Kalai, 2019; Takesue *et al*., 2015). We identified three prognostic factors which were isolation of *C. albicans* species from blood cultures ($p = 0.032$), high blood pressure ($p = 0.016$) and fungal colonization ($p = 0.018$). The SCOPE study showed that the overall mortality was lowest for *C. parapsilosis* (27.9%) and highest for *C. krusei* (59%) (Wisplinghoff *et al*., 2004). An Italian study found a 55.5% mortality in *C. krusei* septicemia (Takesue *et al*., 2015). In a Spanish study, this higher mortality for *C. krusei* is also found (39%), while it is lower for the species *C. parapsilosis* (23%) (Bassetti *et al*., 2011).

Other prognostic factors associated with candidemia have been reported in the literature. In a study in western France, overall mortality, 49% was significantly higher in septic shock, advanced age, and no catheter removal (Ortega *et al*., 2011). Indeed, the presence of a central venous catheter is a well-identified risk factor for candidemia (Talarmin *et al*., 2009). In the univariate analysis and multivariate analysis, catheter ablation significantly reduced the risk of mortality. This improvement in the prognosis of candidemia in the event of central passage removal has been reported in other studies (Raad *et al*., 2004), and both American and French recommendations strongly encourage catheter removal in the event of candidemia (Reboli *et al*., 2011).

CONCLUSION

Candidemia occupies an important place in the infections of patients staying in intensive care. It is associated with high mortality and morbidity. Through this study, we have contributed to the knowledge of epidemiology and prognostic factors of candidemia in a Tunisian series which could provide support to resuscitators, allowing an optimization of the recommendations for the treatment of candidemia according to prognostic factors. Indeed, despite the complexity of the diagnosis, the early initiation of antifungal treatment remains a key factor in the management of these invasive infections.

Declarations

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Availability of data and material: not applicable

Code availability: not applicable

Ethics approval: The global rules of ethics relating to the respect for confidentiality and the protection of patient-specific data were taken into consideration during this work.

Author Contributions: All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by (Tasnim Labiedh), (Latifa Mtibaa), and (Aicha Rebai). The first draft of the manuscript was written by (Tasnim Labiedh), (Latifa Mtibaa), (Nawel Baccouchi) and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent to participate: not applicable

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