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ARTICLE

Candidemia in immunocompromised and immunocompetent critically ill patients: a prospective comparative study

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Abstract The purpose of this study was to compare the risk factors, clinical manifestations, and outcome of candidemia in immunocompromised (IC) and nonimmunocompromised (NIC) critically ill patients. Data were collected prospectively over a 2-year period (02/2000–01/2002) from patients in a 25-bed, medical–surgical intensive care unit (ICU). Eligible for participation in this study were patients who developed candidemia during their ICU stay. Patients under antifungal therapy and with a confirmed systemic fungal infection prior to the diagnosis of candidemia were excluded. Cultures of blood, urine, and stool were performed for all patients in the study, and all patients underwent endoscopy/biopsy of the esophagus for detection of *Candida*. Smears and/or scrapings of oropharyngeal and esophageal lesions were examined for hyphae and/or pseudohyphae and were also cultured for yeasts. During the study period, 1,627 patients were hospitalized in the ICU, 57% for primary medical reasons and 43% for surgical reasons. After application of the study's inclusion and exclusion criteria, 24 patients with candidemia (9 IC and 15 NIC) were analyzed. Total parenteral nutrition was more common in IC than in NIC patients (9/9 [100%] vs 8/15 [53%], $p=0.02$). Oropharyngeal candidiasis was detected in 5 of 9 (55.5%) IC patients and in 1 of 15 (6.5%) NIC patients ($p=0.015$). Esophageal candidiasis was also more common in IC than in NIC patients (4/9 [44%] vs 0/15 [0%], $p=0.012$). Among the 9 IC patients, all except 2 died, resulting in a crude mortality of 78%; among the 15 NIC patients, 9 died, resulting in a crude mortality of 60% ($p>0.05$). Autopsy was performed in two IC and in six NIC patients, with disseminated candidiasis found in one IC patient. Oropharyngeal and esophageal candidiasis are frequent in IC patients with candidemia. In contrast, this coexistence is rare in NIC critically ill patients with *Candida* bloodstream infections. A high mortality was noted in both IC and NIC critically ill patients with candidemia.

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Introduction

Bloodstream infections (BSIs) due to *Candida* spp. have become common in both adult and pediatric intensive care units (ICUs), accounting for 10–15% of hospital-acquired BSIs [1–3]. This rising incidence has been attributed to several risk factors that are prevalent in critically ill patients, such as debility, underlying malignancy, blood and marrow transplantation, acquired immunodeficiency syndrome (AIDS), prolonged ICU and hospital stay, neutropenia, use of antibiotics and corticosteroids, and administration of parenteral alimentation [4–10]. In most

cases, the yeast's portal of entry is the gut, yet in other patients, especially those with central venous catheters (CVCs), skin is the most likely culprit [11, 12].

Candidemia may occur in both immunocompromised (IC) and nonimmunocompromised (NIC) patients. The development of candidemia, however, strongly implies immunodeficiency, since it often occurs in IC patients and, more specifically, in 10–20% of those with myeloproliferative disorders or leukemia and in up to 74% of patients with AIDS [13]. In immunocompetent patients, *Candida* esophagitis is quite rare and is associated with certain predisposing factors, such as use of H2-receptor antagonists, antacids, prior vagotomy producing hypochlorydria, administration of antibiotics and systemic or inhaled corticosteroids, functional or mechanical obstruction of the esophagus, malnutrition, metabolic disorders, and alcoholism [14–16]. However, it is unclear if *Candida* esophagitis is unusual in the general population because its occurrence in that setting has never been investigated prospectively.

No study to date has been specifically designed to compare risk factors, manifestations, and outcome of candidemia in IC and NIC critically ill patients. Thus, we performed the present study to assess possible clinically significant differences between IC and NIC patients with candidemia receiving care in the ICU setting.

Materials and methods

Study design

This was a prospective study that was conducted over 2 years (February 2000–January 2002) in a 25-bed, medical–surgical ICU in a tertiary hospital in Greece. The "G. Gennimatas" General Hospital in Athens is a 750-bed general hospital that mainly serves the north-northeastern part of Athens. The study protocol was approved by the hospital's ethics committee. Because of the patients' inability to give informed consent for participation in the study, consent was obtained from their next of kin. Eligible for participation in the study were patients who had been hospitalized for >48 h and had developed candidemia during their ICU stay. Blood cultures were ordered at the discretion of the attending physicians, when clinically indicated. Patients with severe thrombocytopenia (platelets <60,000/μl) or coagulopathy were excluded because our study included a biopsy procedure. Patients receiving or who had received prior antifungal therapy the last month before the ICU admission and patients with a confirmed systemic fungal infection prior to the diagnosis of candidemia also were excluded because the focus of the study was to be a population with ICU-acquired canidemia.

Data collection

One of the authors (G.D.) collected the data in a standard manner and was responsible for the follow-up of the patients during the study period. Patients were evaluated in terms of age, Acute Physiology and Chronic Health Evaluation-II (APACHE II) and Sequestrial Organ Failure Assessment (SOFA) scores, mean duration of ICU stay, main predisposing factors for fungal infection development, and clinical outcome. For the purposes of the study, patients without underlying malignancy or neutropenia (leukocyte count >4,000/μl and neutrophil count >1,000/μl) and with human immunodeficiency virus (HIV) seronegative status who had not received corticosteroids orally, intravenously, or by nebulization within the last 30 days prior to ICU admission were defined as nonimmunocompromised (NIC). Patients who received systemic corticosteroids for ICU indications, such as sepsis or adult respiratory distress syndrome (ARDS), after their ICU admission were classified in the NIC group. The study population did not include transplant patients, since our center is a trauma-oriented general hospital. Oral thrush was clinically diagnosed by the presence of typical creamy lesions and whitish plaques or pseudomembranes in the oropharyngeal mucosa and on the tongue.

A complete laboratory evaluation, which included a hemogram as well as biochemical and coagulation profiles, urinalysis, serologic testing for HIV, radiological studies, and an electrocardiogram, was performed. Blood, urine, and stool cultures, in addition to cultures of scrapings obtained from the oropharynx, were performed for all study patients. Oropharyngeal scrapings were also immediately examined microscopically for the presence of yeasts and/or hyphae/pseudohyphae, using 10% potassium hydroxide.

The investigational work-up for invasive candidiasis in our patients (other than blood cultures, esophageal endoscopy, and oral scrapings) included (a) identification of predisposing factors, (b) surveillance cultures to detect possible colonization, (c) eye exam, and (d) CT scans of the suspected site of infection.

Pathological examinations

All endoscopies were performed by the same gastroenterologist. Endoscopies were performed during the first 24 h after the diagnosis of candidemia, using a Pentax EG 2901 videoscope. During endoscopy, brushing specimens and tissue biopsies were obtained for microbiological and histological examination. *Candida* esophagitis was diagnosed by the presence of visible esophageal lesions (white plaques with hyperemia and edema, linear and nodular elevated plaques with ulceration, plaques with increased friability of the mucous membrane) using a modified Kodsi

method and was verified by biopsy showing hyphae in histological sections and/or *Candida* growth on agar plates [17, 18].

Microbiological investigations

Additionally, the brushing specimens were evaluated immediately for yeasts and hyphae/pseudohyphae after the addition of 10% potassium hydroxide and were cultured on Sabouraud dextrose agar plates for *Candida* growth. Biopsy samples were fixed with 10% formalin and paraffin followed by acid-Schiff staining to detect mucosal invasion by the fungus.

Cultures were considered positive if there was growth of *Candida* on Sabouraud dextrose agar plates. Yeasts were identified using the API 20 C AUX system (bioMérieux, Marcy l'Etoile, France). Candidemia was defined by at least one positive blood culture for *Candida* spp., and candiduria by a urine culture with *Candida* spp. growth of $\geq 10^5$ cfu/ml. Candidemia was identified using BacTalert (bioMérieux, USA). Table 1 shows the number of sites (besides blood) colonized by *Candida* spp. Disseminated candidiasis was diagnosed when *Candida* was identified by culture and/or biopsy from two or more organs. We used *Candida* ID2 agar (bioMérieux) to discriminate between *Candida albicans*, *Candida* non-*albicans*, and *Candida tropicalis*. Additionally, we used the germ-tube method and the API 32C (assimilation of 32 carbohydrates) for identification of all species of *Candida*.

Statistical analysis

IC and NIC patients were compared for certain variables of interest by Mann–Whitney *U* test, chi-squared test, and Fisher exact test. The level of significance was set at $p<0.05$.

Results

During the study period, 1,627 patients were hospitalized in the ICU, 57% for primary medical reasons and 43% for primary surgical reasons. Twenty-four patients (9 IC and 15 NIC) met the eligibility criteria. Of these, 18 (75%) were

Table 1 *Candida* spp. isolated from various body sites of the patients in the study

Patient no.	Blood	Esophagus	Urine	Oropharynx	Stools	No. of sites (except blood) colonized
Immunocompromised						
01	*C. albicans*	*C. albicans*	*C. albicans*	*C. albicans*	*C. albicans*	4
02	*C. albicans*	NG	NG	*C. albicans*	*C. albicans*	2
03	*C. albicans*	NG	NG	NG	*C. albicans*	1
04	*C. krusei*	*C. albicans*	*C. albicans*	*C. albicans*	NG	3
05	*C. albicans*	*C. albicans*	NG	*C. albicans*	NG	2
06	*C. albicans*	NG	NG	NG	NG	0
07	*C. parapsilosis*	*C. albicans*	*C. parapsilosis*	*C. albicans*	*C. albicans*	4
08	*C. dubliniensis*	NG	NG	NG	NG	0
09	*C. lusitaniae*	NG	NG	NG	*C. albicans*	1
09						
Nonimmunocompromised						
10	*C. albicans*	NG	*C. albicans*	NG	*C. albicans*	2
11	*C. albicans*	NG	*C. albicans*	*C. albicans*	*C. albicans*	3
12	*C. albicans*	NG	NG	NG	*C. albicans*	1
13	*C. albicans*	NG	*C. albicans*	NG	NG	1
14	*C. albicans*	NG	NG	NG	NG	0
15	*C. albicans*	NG	NG	NG	*C. albicans*	1
16	*C. albicans*	NG	*C. albicans*	NG	*C. albicans*	2
17	*C. albicans*	NG	*C. albicans*	NG	NG	1
18	*C. albicans*	NG	NG	NG	*C. albicans*	1
19	*C. albicans*	NG	NG	NG	NG	0
20	*C. tropicalis*	NG	NG	NG	NG	0
21	*C. tropicalis*	NG	NG	NG	*C. albicans*	1
22	*C. tropicalis*	NG	*C. albicans*	NG	NG	0
23	*C. parapsilosis*	NG	*C. albicans*	NG	NG	1
24	*C. krusei*	NG	NG	NG	NG	0

NG Cultures with no growth

medical patients and 6 (25%) surgical patients. Their demographic and clinical characteristics are shown in Table 2. Among the IC and NIC patients, 6 (40%) and 4 (44%) were females, respectively ($p>0.05$). The median age of the IC and NIC patients was 50 years (range 34–55) and 52 years (range 34–68), respectively ($p>0.05$). The median duration of ICU stay for IC and NIC patients was 17.8 and 16.7 days, respectively ($p>0.05$).

Among the nine IC patients, all had underlying primary medical pathology, since three had leukaemia/lymphoma, three AIDS, and one each had liver cirrhosis complicated by septic shock, pneumonia following chemotherapy for lung cancer, and rheumatoid arthritis complicated by pneumonia. None of the patients in the study with leukemia/lymphoma received chemotherapy during the study or for 2 weeks prior to the diagnosis of candidemia. The patients with lung cancer and rheumatoid arthritis (patient nos. 2 and 3 in IC group, Table 1) received treatment with glucocorticosteroids. Among the 15 NIC patients, the underlying diagnosis was pneumonia/ARDS in 6, trauma/head injury in 3, peritonitis in 3, pancreatitis in 2, and pulmonary embolism in 1. Six of the 15 NIC patients had surgical pathology: three with trauma/head injury and three with peritonitis. Most patients with pneumonia had community-acquired infection but needed ICU admission due to respiratory failure. Patient numbers 19 and 23 in the NIC group (Table 1) developed ventilator-associated pneumonia.

The mean time from ICU admission to the isolation of *Candida* from blood specimens was 9 days (range 5–11 days). The mean time between drawing blood specimens for culture and isolation of *Candida* was 3 days. The presence of known predisposing factors for development of candidiasis in these patients is shown in Table 3. The 9 IC patients with candidemia had higher mean APACHE II (24±3 vs 20±3) and SOFA (8±1 vs 6±2) scores during ICU admission compared to the 15 NIC patients ($p=0.04$ for both scores). In addition, the administration of total parenteral nutrition was more common in IC patients ($p=0.02$).

Oropharyngeal candidiasis was detected in 5 of 9 (55.5%) IC patients and in 1 of 15 (6.5%) NIC patients ($p=0.015$). In the IC patients, the diagnosis of oral thrush was confirmed prior to the ICU admission, while in the single NIC patient with oral thrush, the diagnosis was established on the eighth ICU day. Four of the nine (44%) IC patients and none of the NIC patients presented with esophageal candidiasis ($p=0.012$). All patients with esophageal candidiasis manifested symptoms (mainly odynophagia; dysphagia in one patient) before ICU admission, but the diagnosis

Table 2 Demographic and clinical characteristics of the study population

Patient no.	Sex	Age (years)	Comorbid factors
Immunocompromised			
01	M	34	AIDS, PCP
02	F	48	Rheumatoid arthritis, pneumonia
03	M	55	Lung cancer, pneumonia
04	F	53	Leukemia, protein C deficiency
05	M	38	AIDS, MRSA bacteremia
06	F	52	Leukemia, pneumonia
07	M	54	AIDS, pneumonia
08	F	50	Lymphoma, pneumonia
09	M	50	Alcoholic cirrhosis, sepsis
Nonimmunocompromised			
10	M	52	Pneumonia/ARDS
11	F	62	Pancreatitis
12	M	48	Pneumonia/ARDS
13	M	53	Trauma
14	M	34	Peritonitis
15	M	34	Cocaine overdose, ARDS
16	M	54	Trauma, splenectomy
17	F	45	Peritonitis
18	F	56	Pneumonia
19	M	68	Head injury, pneumonia
20	F	54	Pancreatitis, ARDS
21	M	65	Pulmonary embolism, PCD
22	F	43	Peritonitis
23	F	45	Charcot disease, pneumonia
24	M	34	Heroin overdose, ARDS

ARDS Adult respiratory distress syndrome, *MRSA* methicillin-resistant *Staphylococcus aureus*, *PCP Pneumocystis carinii* pneumonia

Table 3 Presence of factors predisposing to the development of candidemia in the study population

Factor	Immunocompromised patients (n=9)	Nonimmunocompromised patients (n=15)	p value
Age in years, mean±SD	50±5.9	58±9.6	>0.05
Apache II score, mean±SD	24±3	20±3	0.04
SOFA score, mean±SD	8±1	6±2	0.04
Broad-spectrum antibiotics, no. (%)	9 (100)	15 (100)	>0.05
Central venous catheter, no. (%)	9 (100)	15 (100)	>0.05
Total parenteral nutrition, no. (%)	9 (100)	8 (53)	0.02
CVVH, no. (%)	4 (44)	5 (33)	>0.05
Diabetes mellitus, no. (%)	1 (11)	4 (27)	>0.05
Systemic corticosteroids, no. (%)	7 (47)	6 (40)	>0.05

SOFA Sequestrial Organ Failure Assessment score, *CVVH* continuous venovenous hemofiltration

of esophageal candidiasis was not confirmed until after their ICU admission.

Table 1 shows the results of the fungal cultures in IC and NIC patients. *C. albicans* was isolated from the blood in 5 of 9 (55.5%) IC patients and in 10 of 15 (66.5%) NIC patients, while non-*albicans Candida* spp. were isolated in the remaining 9 patients of the two study groups (p>0.05). Among NIC patients, *C. tropicalis* was isolated from the blood of three patients and *Candida krusei* and *Candida parapsilosis* from one patient each. Among IC patients, *C. krusei*, *C. parapsilosis*, *Candida dubliniensis*, and *Candida lusitaniae* were isolated from the blood of one patient each. The same *Candida* spp. were isolated in at least two different body sites in eight of ten NIC patients and in four of five IC patients with candidemia due to *C. albicans*. There was one patient (Table 1) who had concomitant and persistent methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia during the ICU hospitalization.

Patients with *C. albicans* candidemia received fluconazole 400 mg every 12 h intravenously and patients with non-*albicans* candidemia liposomal amphotericin B intravenously (mean duration of therapy, 16.5 days; range 14–24 days).

No statistically significant difference in clinical outcome was detected between NIC and IC patients with candidemia. Among the nine IC patients, all except two (patient nos. 2 and 8; Table 1) died, resulting in a crude mortality of 78%. Among the 15 NIC patients, 9 (patient nos. 10, 11, 13, 14, 16, 17, 18, 20, and 24; Table 1) died, resulting in a crude mortality of 60% (p>0.05). When IC and NIC patients were combined, the mortality among patients with primary medical pathology and patients with surgical pathology was identical, at 67%. More specifically, of the 18 patients with medical pathology (9 IC and 9 NIC), 12 (7 IC and 5 NIC) died, while 4 of the 6 patients with surgical pathology (all NIC) died. Autopsy after consent was performed in eight patients (two IC and six NIC) and showed disseminated candidiasis in one IC patient (oropharyngeal, esophageal, and gastric candidiasis).

Discussion

The main findings of our study of critically ill patients with candidemia are that IC patients had higher APACHE II and SOFA scores and were more likely to receive total parenteral nutrition than NIC patients. In addition, oropharyngeal and esophageal candidiasis was considerably more common in IC than in NIC ICU patients with candidemia. Of importance, a high mortality was noted in both IC and NIC critically ill patients with candidemia.

The recent advances in intensive care have improved the survival of critically ill patients at the cost of the emergence of nosocomial infections of the bloodstream and other sites. Candidemia is the most common hematogenous fungal infection and the fourth most common BSI overall in the USA, accounting for 8% of all nosocomial BSIs [19]. In Greece, there are no relevant data from large multicenter studies regarding candidal BSI, although there are data from a single-center study reporting that 3.3–4.9% of BSIs during a 5-year period (2000–2005) were due to *Candida* spp. [20]. Risk factors for invasive candidiasis in the ICU have been defined by several studies and include a prolonged hospital stay; the use of broad-spectrum antibiotics, corticosteroids or other immunosuppressants; the administration of total parenteral nutrition, hemodialysis or multiple blood transfusions; prolonged mechanical ventilation; diabetes mellitus; gastrointestinal perforation or surgery; and pancreatitis [5, 7–10, 21].

Candida spp. colonize the gastrointestinal tract of healthy individuals and, although they are most frequently recovered from the oropharynx, they have also been isolated from the stool of 10–30% of healthy adults [22]. Colonization of the gastrointestinal tract or the oropharynx with *Candida* spp. has been shown to invariably precede hematogenous or systemic disease, although in recent years the improved survival of burn victims and the widespread use of CVCs has allowed direct invasion of the bloodstream by *Candida* spp. that colonize the skin [11, 12]. *Candida* colonization as a risk factor is still controversial. It has been

studied as a predictor of invasive candidiasis in the ICU setting; in fact, a "colonization index" has been proposed to predict invasive candidiasis in ICU patients, although guidelines for identifying patients who would best benefit from antifungal prophylaxis are not established [23, 24]. It is unclear, however, whether differences exist between IC and NIC patients in the way candidemia and/or systemic candidiasis is acquired in relation to the presence of prior mucosal candidiasis.

One of the purposes of the present prospective clinical study was to assess a possible correlation between the development of candidemia and/or systemic candidiasis and the pre-existence of oropharyngeal or esophageal candidiasis in critically ill patients. We showed that oropharyngeal and esophageal candidiasis was rare in NIC critically ill patients with candidemia, but often the two entities coexisted in IC patients.

A prior diagnosis of oral thrush due to *Candida* spp. in conjunction with a *Candida*-positive stool culture was a sensitive marker for the presence of esophageal candidiasis. The development of *Candida* esophagitis is a two-step process that includes colonization of the esophagus and invasion of the epithelial layer. When the intraluminal concentration of *Candida* spp. is high, the fungus is able to transmigrate the wall of the digestive tract and gain access to the circulation, a process known as persorption [25]. In NIC patients, this process, although rare, has been associated with certain predisposing factors and as-yet-unknown mechanisms of infection [25]. The NIC patients in our study developed candidemia during their ICU hospitalization, and none manifested esophageal candidiasis, although one developed oral thrush. Our autopsy findings, which showed that six NIC patients had no organ involvement, suggest that candidemia probably resulted from transient fungal translocation across the gastrointestinal tract without affecting the mucosal membranes. However, we performed autopsies in only 40% of the NIC patients.

A correlation between oral thrush and esophageal candidiasis has been shown in a number of studies in IC patients with AIDS or cancer [26–28]. In our study, the simultaneous diagnosis of oral thrush and a stool culture positive for *Candida* spp. in IC patients was associated with a 67% specificity and a positive predictive value for development of esophageal candidiasis. The lack of correlation between candidemia/systemic candidiasis and mucosal candidiasis in NIC in comparison to IC patients can likely be explained by the defective primary defense mechanisms against tissue invasion and dissemination that are common in IC patients. We would like to emphasize that oral candidiasis that presents as erythematous candidiasis (in the absence of other specific symptoms and signs) could be difficult to diagnose in critically ill patients and might be occasionally misleading because (a) tubes and other devices placed in the oral cavity are themselves able to produce mild inflammatory lesions, and (b) the increased respiratory secretions and, often, the regurgitated enteral nutrition content may cause inflammation of the oral mucosa.

The clinical characteristics of the eligible NIC and IC patients of the study were well balanced between the groups, except for the more frequent use of parenteral alimentation and the higher Apache II scores in the IC patients. Total parenteral nutrition has been a known risk factor for BSI due to *Candida* spp., and its use has recently been associated with candidemia due to *C. parapsilosis* in both children and adults [29, 30]. Interestingly, candidemia due to *C. parapsilosis* in non-neutropenic patients with an intravenous hyperalimentation catheter has a low mortality rate and a good prognosis [30]. In our study, *C. parapsilosis* was isolated from the blood cultures of two patients, one NIC and one IC, making it the third most common *Candida* sp. encountered, after *C. albicans* (15 blood isolates total; 10 in NIC patients) and *C. tropicalis* (3 blood isolates, all in NIC patients). The NIC patient with *C. parapsilosis* candidemia in our series had Charcot disease complicated by pneumonia, but she survived. The other patient with *C. parapsilosis* candidemia had AIDS and succumbed to his disease. The higher Apache II scores in our IC patients are suggestive of an increased severity of the underlying critical illness. Lower (<21 points) Apache II scores have been associated with a higher probability of survival in a multicenter study of non-neutropenic critically ill patients with candidemia [31], and higher Apache III scores have been associated with increased mortality in cancer patients with candidemia in a study of 479 episodes at the M.D. Anderson Cancer Center [32].

C. albicans was the *Candida* sp. most commonly isolated from the blood of our patients (15 of 24 isolates, or 62.5%), followed by *C. tropicalis* (3 isolates, or 12.5%), *C. parapsilosis* (2 isolates, or 8.3%), *C. krusei* (2 isolates or 8.3%), *C. dubliniensis*, and *C. lusitaniae* (1 isolate each, or 4.2%). In one patient (Table 1), persistent MRSA bacteremia was observed concomitantly with candidemia. There are sporadic reports indicating a small but significant proportion of patients who have ICU-acquired candidemia concomitantly with bacteremia [33]. In our patients, fungemia due to *C. tropicalis* was not preceded by colonization with the same species. It is well known that *C. tropicalis*, part of the normal human mucocutaneous flora, is a major cause of septicemia/disseminated candidiasis, mainly in patients with lymphoma, leukemia, and diabetes [34]. Accordingly, a possible explanation for the development of *C. tropicalis* candidemia in our patients could be the uncontrolled diabetes combined with the severe septic syndrome.

We did not have any cases of candidemia due to *Candida glabrata*, a common pathogen in the USA and Israel [35, 36]. This finding is in accordance with the data of the Sentry Antimicrobial Surveillance Program, which surveyed episodes of BSI due to *Candida* spp. in patients hospitalized in European ICUs. Overall, 53% of the BSIs due to *Candida* spp. were attributable to *C. albicans*, followed by *C. parapsilosis* (21%), *C. glabrata* (12%), *C. tropicalis* (6%), *C. famata* (2%), *C. krusei* (1%), and *Candida inconspicua* (1%) [37].

With regards to *C. albicans*, our figures are very close to both European [37] and American studies. For example, Trick et al. [35], who described the secular trend of hospital-acquired candidemia among ICU patients in the USA during 1989–1999, found that among cases of monomicrobial and polymicrobial candidemia, *C. albicans* was isolated in 59 and 57%, respectively. The high crude mortality among our patients (60% for NIC and 78% for IC) was not unexpected, given the severity of their underlying diseases, and is comparable to the mortality rate for adults with candidemia reported by Lark et al. [38] (67%), Gudlaugsson et al. [39] (61%), Karlowsky et al. [40] (52%), Colombo et al. [41] (50%), and Pappas et al. [42] (47%). Although we saw no difference in outcome between medical and surgical patients, others have described a poorer outcome for medical patients with candidemia [43].

In our study population, patients with ARDS and sepsis were classified in the NIC group because we believe that these patients have a temporary immunosuppression (if they survive), while the patients classified in the IC group had a certain degree of chronic immunosuppression, despite the differences in the underlying disease. The patient with alcoholic cirrhosis and sepsis (Table 1) was classified in the IC group because he had received glucocorticosteroids due to exacerbations of chronic obstructive pulmonary disease for 2 months before admission to the ICU.

The design of the study did not allow for all patients admitted to the ICU to be evaluated for the presence of oropharyngeal and esophageal candidiasis. Additionally, we focused on a subset of patients with ICU-acquired candidemia without prior systemic fungal infection who had not been exposed to prophylactic antifungal drugs. Since, by definition, the term "ICU-acquired candidemia" means that the fungal infection is acquired in the ICU, we excluded from our study those patients with previous invasive fungal infection.

We should acknowledge that our study has several limitations. First, we were unable to pinpoint the exact time of onset of the esophageal candidiasis, especially since oral thrush was already present before admission to the ICU. Due to obvious ethical reasons, we evaluated our patients for esophageal candidiasis with endoscopy only once. Thus, we do not know if the esophagus was involved before or after the ICU admission. Second, it is unclear if the esophageal candidiasis resulted from hematogenous spread of the fungi in the esophagus, or if the bloodstream involvement was directly related to the oral thrush or the esophageal candidiasis. Third, we did not focus on the treatment administered to patients with candidemia, although we did report that patients with *C. albicans* and non-*albicans* candidemia received fluconazole and liposomal amphotericin B intravenously, respectively. Fourth, we do not have readily available data on the length of stay of all patients who received care in the ICU or the total number of cases of candidemia in the ICU, including those excluded, to know how common candidemia is among ICU patients. Fifth, there are no readily available data regarding the type of therapy and the removal of CVCs and the influence of either factor on outcome in the two patient groups studied. Sixth, the sample of our study population is relatively small (study population from a single center) and thus does not permit a powerful statistical analysis; unfortunately, various practical reasons prevented us from incorporating data from other large ICUs into our study. Finally, we do not have readily available data on MICs because the laboratory usually reported the results for an isolate as either "susceptible" or "not susceptible" to fluconazole.

In conclusion, we compared various characteristics, including risk factors, manifestations, and outcome of IC and NIC ICU patients with candidemia. We found that oropharyngeal and esophageal candidiasis frequently coexisted with candidemia in IC patients. Prospective, clinical studies are needed to better define the value of avoiding colonization and/or of treating oropharyngeal and esophageal candidiasis for the prevention of systemic disease in selected critically ill patients.

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