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Candida Emergence in Adult Critically Ill Patients and the Administration of Systemic Antifungal Treatment

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Abstract

Background: *Candida* is the third most common pathogen in Intensive Care Units (ICUs) with an infection rate 17% and invasive candidiasis has been associated with poor clinical outcomes.

Methods: We sought to investigate possible risk factors for *Candida* emergence in adult critically ill patients, along with the characteristics of patients with *Candida* isolation according to the administration of systemic antifungal treatment (SAT) or not and the distribution of *Candida* species according to the time spent in ICU. We prospectively studied 161 patients who stayed in a general ICU above 72 hours and were not *Candida* infected at admission.

Results: *Candida* spp. were isolated in 63 patients (Group A), representing colonization in 56 (88.9%). Patients with *Candida* isolation had significantly longer prior hospitalization in the ward, higher *Candida* score, medical cause of admission and received more frequently SAT. Patients received SAT, either before (Group A2), or after *Candida* isolation (Group A3) had higher crude ICU mortality compared with patients who did not (Group A1) (17.2% vs 47.3% vs 53.3%, p=0.023). SAT duration was significantly longer for Group A2, while type of SAT did not differ. Prevalence of candidiasic infection was significantly higher in Group A2. Colonization preceded infection in 4/7 patients. Ratio of non-albicans species to *C. albicans* was similar either early or later during ICU stay.

Conclusions: Our critically ill patients, while on SAT, did not avoid candidiasic infections. Medical patients with high *Candida* score and already long prior hospitalization were at increased risk for *Candida* emergence during ICU stay.

Key words

Candida emergence; ICU-acquired *Candida* infection; adult critically ill patients; systemic antifungal treatment; risk factors; ICU mortality

Introduction

Candida is the third most common pathogen in Intensive Care Unit (ICU) with an infection rate 17% and account for 70% to 90% of all invasive mycoses [1,2]. Invasive candidiasis has been associated with poor clinical outcomes, with crude and attributable mortality ranging from 40-70% and 10-40% respectively [3]. Additionally, a shift toward non- albicans *Candida* species (NCA) has been observed recently [4,5].

In this prospective, observational study, we sought to investigate possible risk factors for *Candida* emergence in adult critically ill patients, along with the distribution of *Candida* species according to the time spent in ICU. Moreover, we assessed the characteristics of patients with *Candida* isolation according to the administration of systemic antifungal treatment (SAT) or not.

Material and Methods

Patient recruitment - definitions

The study was prospectively conducted at the multidisciplinary 9-bed ICU of Konstantopouleio - Patission General Hospital in Athens. The study was approved by the institutional review board of the hospital.

Patients older than 18 years admitted to the ICU were considered. Exclusion criteria included length of stay (LOS) in the ICU < 72 hours and ongoing systemic *Candida* infection at ICU admission (Figure 1). During an 18-month study period demographic and microbiological data were collected anonymously for each patient. Patients were divided in 2 Groups according to *Candida* isolation: Group A consisted of patients with *Candida* isolation (n=63) and Group B without *Candida* isolation (n=98). Group A was further

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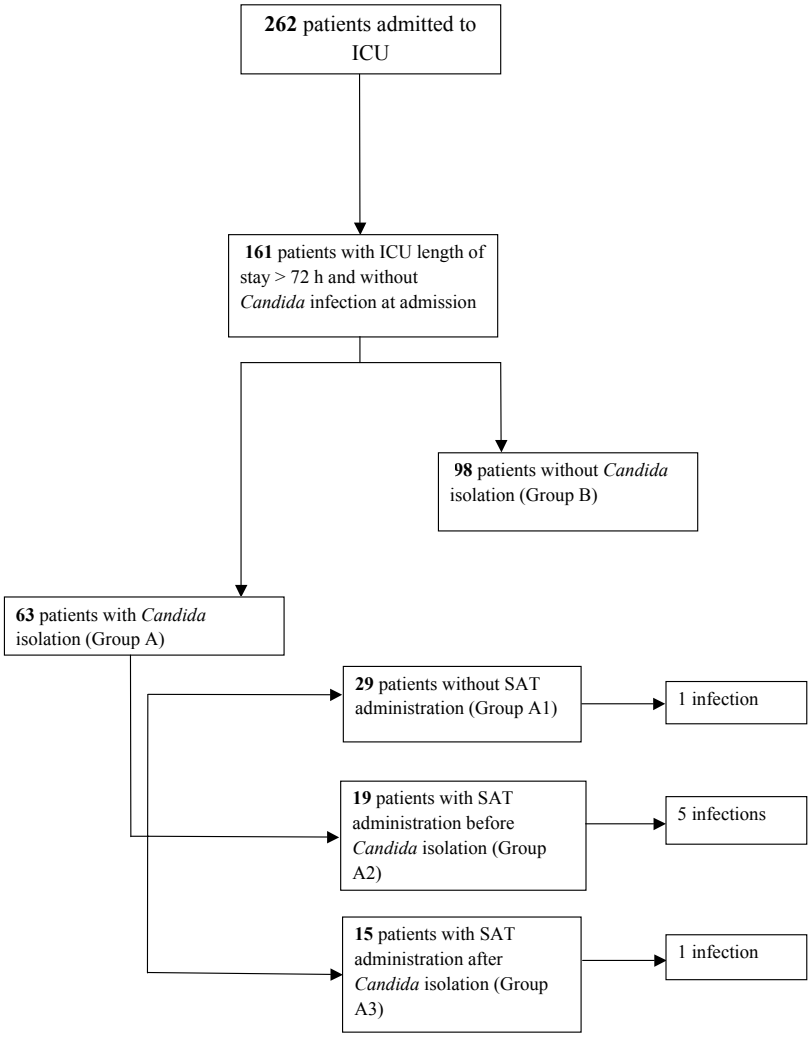

Figure 1: Flow chart of study population

divided in subgroups according to SAT administration. Group A1 included patients that did not received SAT (n=29), Group A2 those who received SAT before *Candida* isolation (n=19) and Group A3 those who received SAT after *Candida* isolation (n=15).

Fungal surveillance cultures of urine and tracheal aspirates were collected upon ICU admission and then twice weekly until death or ICU discharge [6]. The *Candida* species colonization index (CCI) was calculated by the ratio of the number of highly culture-positive (> 10^5 CFU/ml) surveillance sites to the total number of body sites cultured [7]. *Candida* score (CS) was calculated by adding the relevant points for each parameter [8]. Patients that met the clinical prediction rule by Ostrowsky-Zeichner were recorded [9].

Empirical therapy was defined as an early antifungal treatment instituted in patients with clinical signs suggestive of ongoing invasive infection [10]. The decision to start empirical therapy was left to the discretion of patient's attending physicians.

Proven invasive candidiasis was defined according to the Modified European Organization for Research and Treatment of Cancer/ Diseases Mycoses Study Group criteria [11].

Species identification and antifungal susceptibility testing

Yeast isolates were identified using AuxaColor 2 kit (BIORAD) and growth on CHROM-agar Candida medium (CHROMagar, France). Antifungal susceptibility testing for amphotericin B, fluconazole and echinocandins (caspofungin, micafungin, anidulafungin) was performed by the E-test method Liofilchem® MIC Test Strips (Liofilchem s.r.l., Italy), according to the instructions and the interpretive criteria of the Clinical and Laboratory Standards Institute (CLSI) [12]. The concentrations of strips were: amphotericin B 0.002-32 mg/L, caspofungin 0.002-32 mg/L, micafungin 0.002-32 mg/L, anidulafungin 0.002-32 mg/L, fluconazole 0.016-256 mg/L. Antifungal susceptibility tests performed with E-test method are not always fully compatible with other methods. Nevertheless, the adequacy of this method to evaluate amphotericin B and fluconazole and echinocandins susceptibility, has been demonstrated [13,14].

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range). Categorical variables were evaluated with the Chi-square test or Fisher's exact test. Student's t-test was used to compare normally distributed continuous variables and the Mann-Whitney U test was used to analyze variables not normally distributed. One-way analysis of variance (ANOVA) was used for comparisons among the 3 patient groups. When ANOVA revealed a statistical difference, all pair wise multiple comparison procedures were performed using Dunn's method or Bonferroni t-test, as appropriate. All tests were two-tailed, and a p-value of < 0.05 was considered to indicate statistical significance.

Results

Patients' characteristics

During the 18-month study period a total of 262 patients were admitted to the ICU. The study population consisted of 161 patients

(95 males, 114 medical cases) with mean age 68 ± 15 years old. At ICU admission, mean APACHE II (Acute Physiology and Chronic Health Evaluation) and SOFA (Sequential Organ Failure Assessment) scores were 20.7 ± 6.4 and 8.8 ± 3.1 respectively, and mean CS was 1.31 ± 1.18. *Candida* species were isolated in 63 patients, representing colonization in 56 (88.9%). Crude ICU mortality of the study population was 29.8%.

Risk factors for Candida emergence (Table 1)

The patients in whom *Candida* was isolated during their ICU stay had a longer prior hospitalization in the ward (median days 3 vs 1, p = 0.006) and higher *Candida* score (median, 2.038 vs 0.997, p < 0.001) compared with patients with no yeast isolation. The cause of ICU admission was mainly medical (80.9% vs 64.3%, p=0.036). No differences regarding co morbidities were identified. Patients with *Candida* isolation stayed in the ICU for a longer period of time (median days 22 vs 10, p < 0.001), spent longer period of time on mechanical ventilation (median days 19 vs 7, p < 0.001) and with central venous catheterization (median days 25 vs 11, p < 0.001) and they received more frequently SAT (57.1% vs 23.4%, p < 0.001). Crude mortality rate was higher in *Candida* isolation group (38.1% vs 24.5%). However, the difference did not reach statistical significance (p=0.096).

Analysis of patient subgroups with Candida isolation (Table 2)

Regarding patient-related factors, patients received SAT after *Candida* isolation (Group A3) had significantly higher disease severity at ICU admission, compared to patients did not receive SAT (Group A1). Duration of prior hospitalization on isolation day did not differ among the 3 subgroups. However, Group A3 stayed in the ICU for significantly longer period after *Candida* isolation compared to patients that received SAT before *Candida* isolation (Group A2) (median days 19 vs 11, p=0.024). Group A2 patients had significantly fewer medical admissions compared to A1 and A3.

Regarding the use of invasive interventions and medical devices, use of mechanical ventilation, CVC and arterial catheter did not differ among the 3 subgroups. However, institution of Continuous Renal Replacement Treatment (CRRT) was significantly more frequent in subgroups A2 and A3 (3.4% vs 36.8% vs 20%, p=0.011). Group A2 patients revealed significantly higher rates of parenteral nutrition (10.3% vs 36.8% vs 6.6%, p=0.028) and lower rates of enteral feeding

Characteristics	Group A	Group B	p-value
	Patients with *Candida* isolation (n=63)	Patients without *Candida* isolation (n=98)	
Patient characteristics at ICU admission			
Age (years) (mean ± S.D.)	69 ± 14	67 ± 22	0.529
Male sex	36 (57.1)	59 (60.2)	0.825
APACHE II score (mean ± S.D.)	22.2 ± 5.9	19.7 ± 6.4	**0.013**
SOFA score (mean ± S.D.)	9.4 ±3.1	8.3 ± 2.9	**0.03**
Candida score [median (IQR)]	2.038 (0.997-2.038)	0.997 (0-2.038)	**< 0.001**
Prior LOS in ward (days) [median (IQR)]	3 (1-9)	1 (1-4)	**0.006**
Medical admission	51 (80.9)	63 (64.3)	**0.036**
Co-morbidities			
Diabetes mellitus	23 (36.5)	33 (33.6)	0.842
Chronic lung disease	23 (36.5)	24 (24.5)	0.144
Chronic renal failure	15 (23.8)	13 (13.2)	0.131
Chronic neuro-psychiatric disorders	17 (26.9)	19 (19.3)	0.35
Chronic heart failure	21 (33.3)	23 (23.4)	0.234
Neoplasia	7 (11.1)	16 (16.3)	0.489
Immunosuppression[b]	3 (4.7)	7 (7.1)	0.782
Pancreatitis	2 (3.1)	1 (1.02)	0.697
ICU hospitalization			
ICU LOS (days) [median (IQR)]	22 (17-39)	10 (6-18)	**< 0.001**
Days on mechanical ventilation [median (IQR)]	19 (11-31)	7 (4-12)	**< 0.001**
Days of central venous catheterization [median (IQR)]	25 (18-40)	11 (6-18)	**< 0.001**
ICU mortality	24 (38.1)	24 (24.5)	0.096
SAT	36 (57.1)	23 (23.4)	**< 0.001**

S.D: Standard Deviation; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sepsis-related Organ Failure Assessment; LOS: Length of Stay; IQR interquartile range; SAT: Systemic Antifungal Treatment

[a] Data are no. (%) of patients unless otherwise stated

[b] Neutropenia (neutrophil count < 1000 / mm^3), immunosuppressant medication, splenectomy

Table 1: Comparison of demographic data, risk factors and mortality among patients with and without *Candida* isolation during ICU hospitalization[a]

	Group A1	Group A2	Group A3	p-value
	Patients who did not receive SAT (n=29)	Patients who received SAT before *Candida* isolation (n=19)	Patients who received SAT after *Candida* isolation (n=15)	
Age (years) (mean ± S.D.)	71 ± 11	66 ± 17	69 ± 14	0.429
APACHE II score (mean ± S.D.)[b]	20.4 ± 5.6	23.2 ± 6.7	25.1 ± 4.1*	**0.03**
Prior hospitalization (on isolation day[c])	12 (8-20)	17 (11-54)	11 (8-22)	0.182
ICU LOS after isolation (days) [median (IQR)]	10 (4-16)	11 (5-23)	19 (12-34)*	**0.024**
Medical admission	26 (89.6)	11 (57.9)	14 (93.3)	**0.009**
Broad-spectrum antibiotics[d]	24 (82.7)	18 (94.7)	15 (100)	0.136
Day on antibiotics[median (IQR)][d]	10 (5-14)	12 (8-51)	8 (6-12)	0.074
CVC[d]	29 (100)	19 (100)	15 (100)	NA
Mechanical ventilation[d]	25 (86.2)	16 (84.2)	14 (93.3)	0.709
Arterial catheter[d]	29 (100)	18 (94.7)	15 (100)	0.308
Enteral nutrition[d]	26 (89.6)	11 (57.9)	13 (86.6)	**0.021**
Parenteral nutrition[d]	3 (10.3)	7 (36.8)	1 (6.6)	**0.028**
Corticosteroids[d]	11 (37.9)	3 (15.8)	5 (33.3)	0.251
CRRT[d]	1 (3.4)	7 (36.8)	3 (20)	**0.011**
***Candida* score** [median (IQR)][d]	2.038 (0-2.038)	2.109 (1.938-3.121)	2.038 (2.038-3.035)	0.052
***Candida* colonization index** (mean ± S.D.)[d]	0.53 ± 0.14	0.45 ± 0.28	0.52 ± 0.31	0.434
SOFA score[d]	7.6 ± 3.7	8.8 ± 4.9	9.6 ± 3.3	0.289
NCA isolates	12 / 32 (37.5)	12 / 21 (57.1)	7 / 17 (41.1)	0.355
Duration of SAT (days) [median (IQR)]	NA	14 (10-18)	8 (4-14)	**0.031**
Type of SAT (fluconazole)	NA	9 (47.3)	9 (60)	0.699
Candidiasic infection	1 (3.4)	5 (26.3)	1 (6.6)	**0.039**
ICU mortality	5 (17.2)	9 (47.3)	8 (53.3)	**0.023**

*Significantly compared to Group A

S.D: Standard Deviation; APACHE: Acute Physiology and Chronic Health Evaluation; LOS: Length of Stay; IQR: interquartile range; CVC: Central Venous Catheter; CRRT: Continuous Renal Replacement Treatment; SOFA Sepsis-related Organ Failure Assessment; NCA: non-*candida albicans*; SAT: Systemic Antifungal Treatment; NA: Not Applicable.

[a] Data are no. (%) of patients unless otherwise stated

[b] At ICU admission

[c] Duration of prior ward plus prior ICU hospitalization

[d] On isolation day

Table 2: Characteristics of patient's subgroups with *Candida* isolation during ICU stay, according to administration of SAT or not[a]

(89.6% vs 57.9% vs 86.6%, p=0.021). Concerning medications, administration of broad-spectrum antibiotics and corticosteroids prior *Candida* isolation did not differ among the 3 subgroups.

Group A1 patients revealed marginally lower CS on isolation day. Ratio NCA to *Candida albicans* strains was similar in the 3 groups. Type of SAT (fluconazole or echinocandins) also did not differ among the corresponding groups. Nevertheless, SAT duration was significantly longer for Group A2 compared to Group A3 (median days 14 vs 8, p=0.031). Prevalence of candidiasic infections was significantly higher in Group A2. Crude ICU mortality was also significantly higher in the subgroups A2 and A3 that received SAT (17.2% vs 47.3% vs 53.3%, p=0.023).

Patients with documented invasive candidiasis

Seven patients (3 males) with mean age 63 ± 14 years and mean APACHE II and CS scores at ICU admission 23.8 ± 9.2 and 2.75 ±

Candida species	ICU length of stay (days)			
	4-6	7-10	11-30	>30
C. albicans	14	8	11	6
C. glabrata	6	2	2	0
C. tropicalis	2	2	1	0
C. parapsillosis	0	2	2	3
C. krusei	0	0	1	0
C. kefyr	0	0	1	0
NCA (not specified)	3	3	0	1
Total NCA	11	9	7	4

ICU: Intensive Care Unit; NCA: non-*Candida albicans*

[a] among 70 isolates which were identificated

Table 3: Distribution of *Candida* species[a] according to ICU length of stay

1.24 respectively, developed proven candidiasis (4 peritonitis, 3 candidaemias). Mean time from ICU admission to the development of ICU acquired invasive candidiasis was 7 ± 3 days. *Candida* colonization was detected in 4 (57.1%) prior to infection. Mean time for the first positive surveillance specimen to the documentation of infection was 3.5 ± 3 days. All patients met the criteria for Ostrowsky-Zeichner prediction rule.

On the day of infection, 5 patients were already on antifungal therapy for 4 (range; 3 to10) days (3 patients on fluconazole and 2 on echinocandins). A total of 8 candida isolates were isolated; 3 *Candida albicans*, 2 *Candida glabrata*, 1 *Candida tropicalis*, 1 *Candida kefyr* and 1 non-albicans (no identification). In 1 out of 5 patients with prior antifungal therapy, fluconazole-resistant *C. glabrata* was isolated while the patient was receiving fluconazole. Time elapsed between onset of *Candida* infection and ICU discharge was 19 ± 13 days. Crude mortality of infected patients was 71.4%, while attributed mortality was 14.3% (1/7 patients).

Distribution of yeast species accordingly to ICU length of stay

Among the 63 patients with *Candida* isolation, a total of 70 isolates were isolated. *Candida albicans* accounted for almost half of the isolates (39/70, 55.7%), followed by *C. glabrata* (10/70, 14.3%), *C. parapsillosis* (7/70, 10%), *C. tropicalis* (5/70, 7.1%), *C. krusei* (1/70, 1.4%), *C. kefyr* (1/70, 1.4%), while for 7 isolates no species identification was made (classified as non-albicans).

Distribution of *Candida* isolates according to the isolation time is shown in Table 3. The comparison between the occurrence of *C. albicans* and non-albicans isolates according to the isolation time did not reveal significant differences. Notably, all *C. parapsillosis* strains isolated after the first 10 days of ICU hospitalization.

Discussion

The continuum between *Candida* colonization and invasive candidiasis has been established in the recent years [15,16]. Similarly to previous workers, we determined that patients who became *Candida* colonized/infected had already a significantly longer prior hospitalization in a clinical ward [3,7,17], along with higher severity disease at ICU admission.

Risk factors for invasive candidiasis may be classified into host-related and health-care associated factors. For the first group, the leading factors include immunosuppressive diseases, neutropenia, age and deteriorating clinical condition [4]. For the latter group, long hospital or ICU stay is encountered as the most common risk factor. More specifically, factors associated with invasive candidiasis in critically ill patients are surgery, multiple-site *Candida* spp. colonization, severe sepsis and parenteral nutrition. [18] Accordingly, our patients who administered SAT before *Candida* isolation presented with significantly higher rates of parenteral nutrition and lower rates of enteral nutrition, renal replacement therapy and surgical admissions. Moreover, they presented with a marginally higher CS on isolation day. However, this strategy of early administered SAT did not prevent invasive candidiasis in our study population, since this patient subgroup demonstrated the highest incidence of candidiasic infections.

The efficacy of empirical or preemptive treatment has been evoked in many studies. Early administration of fluconazole in surgical ICU patients revealed contrasting results [19,20]. In a recent large prospective cohort of patients who received empirical SAT, only 21% developed a documented invasive candidiasis [21]. The researchers concluded that conventional risk factors such as parenteral nutrition, severe sepsis or previous antibacterial therapy were unable to identify patients at risk for invasive candidiasis. On the contrary, intra-abdominal surgery was identified as the sole risk factor for developing candidiasic infection. Similarly, in our cohort, almost two thirds of patients (5/7) were already on antifungal treatment on the day of infection diagnosis, probably reflecting attending physician's high suspicion about infection. All patients who developed candidiasic peritonitis were already on antifungal treatment for 4-10 days, indicating insufficiency of early antifungal treatment to prevent the occurrence of intra abdominal candidiasic infection. Likewise, a recent randomized, placebo-controlled trial of preemptive administration of echinocandin in high-risk surgical ICU patients with intra-abdominal infections was unable to prove efficacy in preventing invasive candidiasis [22]. Regarding the effect of empirical antifungal treatment on mortality, a recent observational study has questioned its beneficial effect, even in patients in septic shock with high colonization index [23]. Moreover, Empiricus study, a randomized controlled study, did not demonstrate any benefit on mortality [24]. Crude ICU mortality was significantly higher in the groups of treated patients (17.2% vs 47.3% vs 53.3%), accordingly to previous workers [23]. Concerning the crude (71.4%) and the attributed (14.3%) mortality of our infected patients were comparable with previous studies [3,25].

The influence of previous treatment with fluconazole still remains controversial. In a large multicenter, prospective study in France there was a trend toward higher rate of fluconazole resistant or susceptible dose dependant isolates in case of previous exposure to azole agents (30%) than in patients virgin for azole agents (16%) [4]. Based on the study of Lortholary et al. patients who exposed to azole derivatives and candins, were at increased risk for fungemia due to species with higher Minimum Inhibitory Concentrations (MICs) to the corresponding antifungal agents [26]. Nevertheless, in our infected patients who received empirical therapy only one fluconazole-resistant strain was isolated during treatment with fluconazole. The percentage of NCA strains was higher in the subgroup that received SAT before *Candida* isolation. However, the difference was not statistically significant. Moreover, the SAT duration was significantly longer in this subgroup which is associated with increase in cost and may contribute to modification in fungal species distribution and susceptibilities [27].

Regarding the distribution of *Candida* strains, *C. albicans* accounted for 55.7% of them, whereas *C. glabrata* was the most common (14.3%) non-albicans isolate. Similarly, Leroy et al. concluded that 42.6% of infections were caused by non-albicans *Candida*, with *C. glabrata* being the second most frequent pathogen isolated [4]. In a prospective and more recent study, non-albicans *Candida* was responsible for 42% of the infections [5]. The changes in fungal ecology are attributed to the widespread use of antifungal

agents, along with patient's distinctive characteristics [28]. *C. krusei* especially affects immunocompromised patients, whereas *C. glabrata* especially affects elderly patients with underlying diseases. Other species, such as *C. parapsillosis*, show a predilection to colonize and infect implantable or semi-implantable synthetic materials, including indwelling CVCs [29]. Consequently, an increased length of stay in the ICU might lead to a time-dependent pattern of *Candida* species distribution. Interestingly, in the present study, the ratio of NCA species to *C. albicans* is similar either early or later during ICU stay, probably reflecting local ecology and patient's demographic features. However, we observed a delayed isolation of *C. parapsillosis* in our patients which might be associated with the duration of CVC use [30].

There are several limitations of our study. This is a single-center study and local fungal ecology, along with management practices and susceptibility patterns might have influenced our conclusions. The absence of data on biological markers was a study limitation. The small number of infections may have underestimated the causal role of certain risk factors and the protective role of early antifungal treatment. Nevertheless, due to the sparity of randomized clinical trials, observational studies may represent an alternative approach to assess the effect of SAT on candidiasic infections and their related mortality.

Conclusions

In the present study, medical patients, who present with high *Candida* score and have already long prior hospitalization were at increased risk for *Candida* emergence during their ICU stay. *Candida* colonization preceded infection in more than half of our infected patients. Early pharmacological intervention to prevent fungal infection is desirable. Nevertheless, our critically ill patients, while being on empirical treatment did not avoid candidiasic infections. Local ecology and susceptibility patterns, along with each patient's characteristics should be taken into account when selecting empirically an antifungal agent, since NCA species accounted for a large amount of yeast isolates, even early during ICU stay.

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