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Original Article

Retrospective evaluation of candida infections in pediatric intensive care units

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ABSTRACT

Objective: *Candida* species are the most common infectious agents among the pathogens responsible for nosocomial fungal infections. Transmissions in intensive care units account for a significant proportion of the mortality and morbidity associated with candida infections. The present study evaluates the prevalence, type, treatment approach, underlying risk factors, and outcomes of candida infections in patients treated in a pediatric intensive care unit in Türkiye with a dense population of children who have fled the war in Syria.

Methods: The study was conducted in the 14-bed tertiary pediatric intensive care unit of a city hospital between March 2018 and March 2019.

Results: Candida species were reproduced in the studied samples of 28 (15.7%) of the 176 patients treated in the intensive care unit during the study period. Mortality occurred in six (21.4%) patients with invasive candidiasis of varying species, namely: *C. lusitaniae* (n=2); C. *parapsilosis* (n=2); *C. krusei* (n=1), and *C. albicans* (n=1), and candida was considered the cause of mortality in five of the six non-survivors. Resistance to liposomal amphotericin-B was observed in the *Candida* species isolated from the non-survivors.

Conclusion: In the present study, a prolonged stay in the intensive care unit, a higher number of indwelling medical devices, the use of broad-spectrum antibiotics, the presence of an underlying condition, and renal failure were observed to increase incidence of candida infection.

Keywords: Candida, pediatric, intensive care, mortality, evaluation

INTRODUCTION

Recently, there has been a significant increase in the incidence of nosocomial fungal infections in adults and children treated in intensive care units (ICUs). The advanced life support systems in ICUs, the increased number of invasive procedures, the prevalent use of cytotoxic therapies and broad-spectrum antibiotics, chronic diseases, and prolonged stays in ICUs are considered to be the main reasons for the increase in such infections.[1]

Candida infections are one of the most prevalent nosocomial fungal infections. The genus *Candida* includes around 150 species, the most commonly isolated of which are *C. albicans*, *C. glabrata*, *C. parapsilosis, C. tropicalis* and *C. krusei,* in descending

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order.[2] These species can cause infections in human at different ages, with, for example, *C. parapsilosis* being identified more commonly in newborns than other species.[3] *Candida* infections are considered a significant problem in ICUs worldwide, and their prevalence is increasing. Candidiasis is associated with high mortality and morbidity in which the sources of transmission in the ICU play an important role.

A study in Switzerland reported that one-third of *Candida* cases picked up the infection during treatment in the ICU. Compared to other therapeutic hospitalizations, patients are 5-10 times more likely to become infected with *Candida* species during intensive care treatment.[4] In the United States, C*andida species are* mostly isolated from the blood and result in bloodstream infections, accounting for 8-10% of cases, while *Candida* infections are the 6-10th most common infection in Europe, accounting for 2-3% of the transmissions through the bloodstream.

The present study evaluated the prevalence of various C*andida* species and investigated the treatment approaches, underlying risk factors, and outcomes in pediatric ICU patients in Hatay, a city in Türkiye that is host to many children who have fled the war in Syria.

MATERIALS AND METHOD

The study was conducted in a 14-bed public hospital with a tertiary pediatric ICU between March 2018 and March 2019. *Candida* growths in the blood, urine, and tracheal aspirate cultures of patients treated in the unit were analyzed retrospectively, as well as the agents (species), treatment approaches, time to negativity (days), and the effect on mortality. The study was approved by the Hatay Mustafa Kemal University ethics committee (approval number: 10/13, date: 8/9/2022). Informed consent was not required due to the retrospective study design.

Statistical analysis

Microsoft Excel 2010 was used for the analysis of the descriptive statistics of the study data.

RESULTS

A total of 176 patients treated in the ICU in the specified one-year study period, *Candida* growth was detected in 28 (15.7%). In the data analysis of the 28 patients, the mean age was 24.9±26.1 months and the female-to-male ratio was 11/17 (Table 1). The mean pediatric logistic organ dysfunction (PELOD II) score was 32.8±4.68, the mean pediatric risk of mortality (PRISM III) score was 27.3±7.38, and the mean MODS score was 18±6. Of the

Table 1. Demographic and clinical data of patients with positive cultures for *Candida*

	n (%)
Gender	
Female	11 (39.3%)
Male	17 (60.7%)
Age	24.9 ± 26.1 months
Growth distribution by anatomic region	
Blood	10 (35.7%)
Urine	6 (21.4%)
TAC	3 (10.7%)
Blood-urine	3 (10.7%)
Urine-TAC	3 (10.7%)
Blood-TAC	3 (10.7%)
Central Venous Catheter	
Yes	21 (75.0%)
No	7 (25.0%)
Intubation	
Yes	21 (75.0%)
No	7 (25.0%)
Uriner Catheter	
Yes	22 (78.6%)
No	6 (21.4%)
Systemic findings	
Yes	21 (75.0%)
No	7 (25.0%)
Prevalence of risk factors in patients (%)	
Chronic disease	20 (71.4%)
Neutropenia	-
Renal failure	20 (71.4%)
Postoperative surgery	5 (17.9%)
Immunosuppressive therapy	-
Broad spectrum antibiotics	28 (100%)
Parenteral nutrition	16 (57.1%)
Hemodialysis	17 (60.7%)
Mechanical ventilation	21 (75.0%)
Central venous catheter	22 (78.6%)
Urinary catheter	23 (82.1%)

patients, three were Turkish and 25 were Syrian. The Syrian patients had been under treatment in the war zone in Syria and were transferred to our hospital to continue with the therapy, or due to a deterioration of their clinical condition. All patients had underlying chronic conditions and at least one had chronic organ failure. The chronic conditions included respiratory failure related to hypotonicity secondary to genetic disorders, multi-drug resistant epilepsy, congestive heart failure secondary to complex cardiac anomalies, chronic kidney disease, sepsis, and acute liver failure.

Antifungal therapy was not initiated in five patients with positive cultures due to the absence of systemic findings, while 20 patients with suspected *candida* infections were initiated on empirical fluconazole therapy. The treatments were modified based on the results of susceptibility tests, and appropriate antifungal therapies were initiated targeting the pathogens identified in antibiotic susceptibility tests.

Of the 28 patients with candidemia, 20 had used inotropic agents. All of the non-survivors had been on inotropic therapy. After the identification of underlying chronic conditions, three patients were placed on continuous venovenous hemodiafiltration (CVVH) and one on therapeutic plasmapheresis (TPE). No patient received CVVT or TPE due to candida sepsis.

The length of stay of the sample in the ICU was 39.6±21.8 days. Of the patients with positive cultures for *Candida* (n=28), the organism was recovered from the blood, urine, and tracheal aspirate cultures in 16 (57.1%), 12 (42.8%), and nine (32.1%) patients, respectively, and the same agent was isolated from samples obtained from two different anatomical regions in nine patients (Tables 1 and 2).

The cultures did not become negative until death in three patients who died during their stay in the ICU, while the mean time to culture negativity was 11.37±6.80 (3–30) days for the other patients. Systemic findings were identified in 21 (75%) of the patients (Table 3, 4).

Table 2. Distribution of *Candida* species by infection localization

	Blood	Urine	TAC
C. peliculosa	1 (6.3%)	-	-
C. albicans	4 (25.0%)	5 (41.7%)	7 (87.5%)
C. lusitanie	2 (12.5%)	1 (8.3%)	-
C. parapsilosis	3 (18.8%)	-	-
C. spp	2 (12.5%)	-	-
C. tropicalis	4 (25.0%)	3 (25.0%)	1 (12.5%)
C. glabrata	-	1 (8.3%)	-
C. krusei	-	2 (16.7%)	-

In the present study, C. *albicans* was the most frequently (35.7%) isolated agent causing candidemia. Among the *non-albicans* species, C. *tropicalis* was the most commonly (25%) isolated species, followed by C. *parapsilosis* (10.7%). The proportion of *candida* species that could not be identified to a species level was 10.7%.

C. *lusitaniae* (n = 2), C. *parapsilosis* (n = 2), C. *krusei* (n = 1), and C. *albicans* (n = 1) were identified in the six (21.4%) non-survivors with a *candida*-positive culture result. Of those who died of *candidemia,* the pathogens were resistant to fluconazole and liposomal amphotericin B. In these patients, the *Candida* species were isolated from the blood, and five of the six exitus patients died due to *candida* sepsis. The same candida species were reproduced in both the blood and urine or the tracheal aspiration fluid culture of four of the six non-survivors. Hospital-acquired bacterial pathogens had previously been reproduced in the cultures of these patients, although candida species were only reproduced in the final culture tests. The candida species were either resistant to the antifungal therapies, or the therapy was initiated too late. It was seen that one candida species had no effect on mortality. Because the patient had a metabolic disorder, which was thought to be a mitochondrial disease and the main cause of death in this patient.

Table 3. Duration of antifungal therapy (days)

	n	Mean ± SD (days)	Min–max (days)	Candida species
Fluconazole	20	13.3 ± 7.6	1–26	*C. albicans/ krusei/ parapislosis/ tropicalis/ pelluculosis*
Micafungin	2	10.5 ± 9.2	4–17	*C. krusei/ albicans/ tropicalis*
Amphotericin B	1	17	-	*C. parapsilosis*
Caspofungin	2	6	-	*C. lusitania*
No agent administered	5	-	-	*C. krusei/ albicans/ spp.*

Table 4. Rates of antifungal agents according to patients	
Antifungal agents	**n**
Micafungin	2 (7.14%)
No agent	5 (17.85%)
Liposomal Amphotericin B	1 (3.5%)
Fluconazole	18 (64%)
Fluconazole + Caspofungin	2 (7.14%)

Of the other non-survivors, two had inoperable complex cardiac arrhythmia; one had hemolytic uremic syndrome and suffered a sustained cerebral infarction; one had neurogenic bladder, malnutrition, and external ventricular drainage, and had previously been fitted with a ventriculoperitoneal shunt; and one presented with acute hepatic failure of unknown origin and developed multiorgan failure after hospitalization.

DISCUSSION

A multicenter point-prevalence study conducted in adult intensive care units (ICUs) in Türkiye reported a rate of 4.7% for *Candida* species identified in sepsis cases in which the cause of sepsis could be identified.[5] In the present study, a total of 176 patients were treated in the ICU over the course of one year, and *Candida* growth was detected in 28 (15.7%). Broad-spectrum antibiotics, central venous catheters, parenteral nutrition, renal replacement therapies, neutropenia, and malignancy are the major risk factors for candidemia.[1] In the present study, high rates of central venous catheters, broad-spectrum antibiotic therapy, and renal failure were identified, and so the rate of candida growth was found to be higher than reported in the literature.

In Türkiye, the rate of *Candida* infection was reported to be 42% in blood cultures and 57% in urine cultures among pediatric patients treated in a tertiary pediatric ICU over an 11-year period.[6] In the present study, the rate of growth in blood and urine cultures was 57.1% and 42.8%, respectively, and this higher rate in the blood and urine cultures compared to other anatomical regions supports the findings of previous studies.

A study conducted in adult ICU patients identified C. *albicans* as the dominant species (47.9%), while the species most commonly associated with sepsis was identified as *C. parapsilosis*.[7] Other studies have reported *C. albicans* as the most common pathogen, followed by C. *parapsilosis*.[6,8,9] The present study also identified *C. albicans* (35.7%) as the dominant species, while the second most commonly isolated species was *C. tropicalis* (25%) and the third was *C. parapsilosis* (10.7%). The study by Omrani et al. reported C. albicans as the most common species followed by *C. tropicalis*.[10] A review of the literature reveals that there has been an increase in *non-candida albicans* species, although *C. albicans* is still the most common. Among the *non-albicans* species, the second most common species varies in different studies, with *C. parapsilosis, C. glabrata, C. krusei* and *C. tropicalis* all having been reported.[3,4,11,12]

In Türkiye, the mortality rate of adult ICU patients with candidemia has been reported to be 83%, and invasive *Candida* infections in the ICU setting have been identified as an independent risk factor for mortality.[13] The reported mortality rate associated with candidemia in pediatric ICU patients ranges from 7% to 26% in different studies.[12,14,15] One study reported a mortality rate of 13.7% in pediatric ICU patients[6], while the present study found a mortality rate of 21% in patients with candidemia. The difference in mortality rates associated with candidemia may be attributed to several factors, such as patient age, the presence of underlying diseases, the candida species, and the patient's physiological condition.

Based on moderate-quality evidence, IDSA strongly recommends empirical therapy for the treatment of invasive candidiasis in ICU patients with the presence of a high clinical index of suspicion.[16] In the present study, patients with underlying chronic conditions who were unresponsive to broad-spectrum antibiotherapy and with accompanying thrombocytopenia were initiated on prophylactic antifungal therapy.

The *Candida* species associated with mortality were different, although all species that led to mortality were resistant to liposomal amphotericin B and fluconazole. These species have been reported to be susceptible to micafungin, although recent guidelines recommend echinocandins or L amphotericin B as the first-line therapy for patients with suspected candidemia/invasive candidiasis.[17] A recent study supports the use of micafungin due to the fewer side effects, the safety of the drug, and the resistance to fluconazole and amphotericin B among *Candida* species.[6]

In the present study, the analyses conducted during the infection period revealed some pathogens to be resistant to fluconazole, flucytosine, caspofungin, and liposomal amphotericin B, and the infections in the non-surviving patients were all caused by the antifungal-resistant strains. Nevertheless, all *candida* species were found to be susceptible to micafungin. As the number of patients in our study was very small, the information is provided solely to contribute to the literature.

In conclusion, based on the findings of the present study, micafungin may be considered a promising antifungal agent against the increasing resistance to amphotericin B and

fluconazole. However, due to the small number of patients in the present study, this finding cannot be generalized and requires careful consideration.

Ethical approval

This study has been approved by the Hatay Mustafa Kemal University Non-Invasive Clinical Research Ethics Committee (approval date 08/09/2022, number 10/13). Informed consent was not required due to the retrospective study design.

Author contribution

Surgical and Medical Practices: GOT, TTK; Concept: YÇ, AK, TTK; Design: GOT, YA, SA, TTK; Data Collection or Processing: YÇ, AK, GOT, YA, SA, TTK; Analysis or Interpretation: YÇ, AK; Literature Search: YÇ, AK, TTK; Writing: YÇ.

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Conflict of interest

The authors declare that there is no conflict of interest.

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