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Original Research

Candidal Infections in the Neonatal Intensive Care Unit: A Retrospective Observational Study

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Abstract

Objectives: The aims of this study were to evaluate the demographic characteristics, risk factors, mortality rates, and laboratory findings of infants with fungal sepsis in the Neonatal Intensive Care Unit (NICU).

Methods: This retrospective multicenter study included patients in NICU with *Candida* spp isolated in blood cultures between November 01, 2019, and September 01, 2022. The patients were evaluated in two groups as Group 1 infants with *Candida albicans* and Group 2 infants with *Candida non-albicans* positive blood cultures.

Results: Candida infection was detected in blood cultures in 57 of 3450 patients admitted to the NICU. A total of 57 infants included in the study. Candida infection was determined 1.6% of infants in the study population, and 57% of them were extremely pre-term infants. There was no significant difference between the two groups in terms of laboratory data. Normal vaginal birth was determined at a higher rate in Group 1. In Group 2, length of hospital stay, duration of total parenteral nutrition (TPN), and mechanical ventilation (MV) were determined to be longer. The mortality due to Candida fungemia was determined as 35%, and of these patients, 65% had an additional medical condition.

Conclusion: In accordance with the literature, this study showed that prolonged MV and longer TPN increased the incidence of fungal sepsis. Therefore, to decrease the fungal sepsis rate of NICU, shortening the hospital stay and effective screening programs are recommended.

Keywords: Candida spp., candidemia, fungal sepsis, neonatal intensive care unit, nosocomial infection

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Invasive Candida infections are less common than Gram-positive and Gram-negative bacterial infections in neonatal intensive care units (NICU); however, they have high rates of morbidity and mortality.[1] The rate of candidemia has been reported as 28%, especially in extremely low birth weight (ELBW) babies, and this rate rises to 43% in babies weighing <750 g.[2] These infants are more exposed to invasive procedures such as central venous catheterization and intubation, and the use of broad-spectrum antibiotics, total parenteral nutrition (TPN), antacids, and corticosteroids. All these clinical applications cause an increase in the frequency of invasive fungal infections, particularly Candida infections.[3]

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Mortality due to invasive Candida infections has been reported at rates ranging from 21% to 30%. This rate can reach up to 50% in ELBW infants.[4] Surviving ELBW infants from fungal sepsis have long-term neurological disorders such as cerebral palsy, blindness, hearing impairment, cognitive deficits, and periventricular leukomalacia.[5] Therefore, prevention and treatment of fungal infections are very important to improve the prognosis of premature babies.

The risk factors for invasive candidiasis have been defined as prematurity, central venous catheterization, endotracheal tube administration, TPN, broad-spectrum antibiotics (especially 3rd generation cephalosporin), prolonged hospital stay, abdominal surgery, exposure to H2 blockers, and Candida colonization.[1] Although *Candida albicans* is the most common invasive fungal pathogen, in recent years, there has been an increase in invasive candida infections caused by *Candida non-albicans* strains, primarily *Candida parapsilosis* and *Candida glabrata*.[5]

The aim of this study is to evaluate the demographic characteristics, risk factors, laboratory findings, and mortality rates of infants who had *Candida* sepsis in the NICU.

Methods

Study Design and Participants

The study was conducted in accordance with the principles of the Declaration of Delsinki. Ethical approval was obtained from the Local Ethical Committee, before the study commenced (Date: September 23, 2020, Decision no: 2020-09/08). This retrospective multicenter study included all the infants diagnosed with nosocomial Candida infection between November 2019 and September 2022. Neonatal intensive cares included in the study had a total of 56 beds at level 2 and level 3. One out of every three hospitalized patients was a pre-term baby. Most of the inpatients were the infants of refugees. Surgical patients and cases admitted from an external center were approximately 10% of the study population. Demographic and clinical data of the all infants who had Candidemia within the specified time period were recorded and evaluated. Isolation of Candida spp. in blood culture together with clinical symptoms and findings was defined as candidemia.[6] Fluconazole prophylaxis is administered as 3 mg/kg dose for 2 days a week to infants who are born under 28 weeks and/or below 1250 g and/or long-term intubated (more than 2 weeks) and/or long-term TPN patients, and those with central catheters in the study center.

The study exclusion criteria were defined as congenital and/or choromosomal abnormalities, no growth in blood culture, infants with fetal/neonatal alloimmune thrombocytopenia, cases diagnosed with maternal immune thrombocytopenic purpura, suspected immunodeficiency, and cases followed-up with thrombocytopenia who underwent blood exchange. For all the infants included in the study, a record was made of sociodemographic data, including gender, gestational week, birth weight, type of delivery, length of stay in hospital, length of stay before Candida infection, the presence of a central catheter, the use of TPN, duration of mechanical ventilation (MV), duration of antibiotherapy, laboratory findings, blood culture results, the postnatal day on which infection developed, and the clinical findings.

Collection and Analysis of Blood Culture Samples

Blood samples for culture were taken from peripheral veins using sterile technique. Blood and cerebrospinal fluid samples were inoculated into culture bottles of BACTEC Peds Plus/F (Becton-Dickinson, Sparks, MD, and USA). All the cultures were observed using an automatic culture system. Passages were made to blood agar and Sabouraud dextrose agar. Isolated yeasts (*C. albicans* and *Candida non-albicans*) were determined using molecular criteria (germ tube and chlamydospore formation) and definitive identification was made using the API ID 32 C system (BioMerieux Diagnostic System, Grenoble, France). The minimum inhibitory concentration (MIC) values obtained in *in vitro* antifungal susceptibility tests for Candida strains were evaluated according to the Clinical and Laboratory Standards Institute reference methods.[7]

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS version 22 software (IBM SPSS, and USA). The conformity of the data to normal distribution was assessed with the Shapiro–Wilk test. According to those results, analyses were made using the Mann–Whitney U-test and Pearson Chi-squared analysis. Continuous variables were stated as median, minimum-maximum values, and categorical variables were stated as number (n) and percentage (%). A $p<0.05$ was accepted as the level of statistical significance.

Results

Flow diagram of the study is presented in Fig. 1. Retrospective evaluation was made of 3450 newborn infants admitted to two NICUs with an initial diagnosis of sepsis between November, 1, 2019, and September, 1, 2022. The study included 57 (1.6%) newborns with Candida infection, comprising 25 (44%) males and 32 (56%) females, at median gestation week 31 (26–35), and with a median birth weight of 2050 g (1180–2750). Candida infection was determined in 33 (57%) extremely pre-term infants. The median length of hospital stay was 29 days (20–40 days). All the Candida infections were classified as late-onset sepsis.

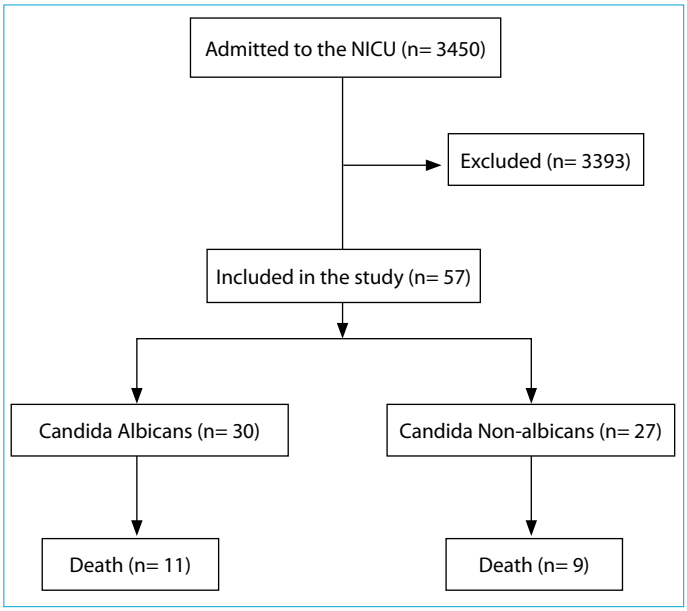

Figure 1. Flow diagram of the study is presented in Figure 1.

The clinical characteristics of the newborns according to the *Candida* strain produced are shown in Table 1. In this study, 30 of the cases were *C. albicans*, while 27 were non-albicans Candida. No significant difference was determined between the two groups in respect of gender, gestational week, birth weight, length of stay before candidemia, duration of umbilical catheter, duration of antibiotherapy, and mortality. The rate of normal vaginal delivery (NVD) was determined to be statistically significantly higher in Group 1 (*C. albicans*) ($p<0.05$). The length of hospital stay, duration of TPN, and duration of MV were determined to be statistically significantly longer in Group 2 (*Candida non-albicans*) ($p<0.05$) (Table 1).

A total of 20 (35%) of the newborn infants with candidemia demised, of which 4 (20%) were born at term and 16 (80%) pre-term. These were determined as 4 infants at >37 weeks, 5 at 34–37 weeks, 5 at 29–33 weeks, and 6 at <28 weeks. In the infants that demised, the combination of prematurity and necrotizing enterocolitis was determined in 1, perinatal asphyxia in 1, intestinal atresia in 3, intracranial hemorrhage in 2, large artery transposition in 2, Down's syndrome in 1, hydrocephaly in 1, Di George Syndrome in 1, and no accompanying pathology was determined in eight patients.

The distribution of Candida infections is shown in Table 2. The most common agents were determined to be *C. albicans* (52%), *Candida parapsilosis* (14%), *Candida glabrata* (14%), *Candida* species (8.8%), *Candida tropicalis* (3.5%), *Candida pelliculosa* (3.5%), *Candida krusei* (1.8%), and *Candida utilis* (1.8%) (Table 2).

The laboratory data of the newborn infants according to types of Candida isolation are shown in Table 3. No statistically significant difference was determined between the

Table 2. Distribution of the agents of candida infections produced in blood cultures

***Candida* spp. identified**	**n (%)**
Candida albicans	30 (52)
Candida parapsilosis	8 (14)
Candida glabrata	8 (14)
Candida species	5 (8.8)
Candida tropicalis	2 (3.5)
Candida pelliculosa	2 (3.5)
Candida krusei	1 (1.8)
Candida utilis	1 (1.8)

Table 1. The clinical characteristics of the newborns according to the *Candida* strain produced

Clinical characteristics	***Candida albicans* (n=30)**	***Candida non-albicans* (n=27)**	**p**
Gender M/F, n (%)	10 (33)/20 (67)	15 (56)/12 (44)	0.077
Gestational week*	31 (25–36)	31 (26–35)	0.974
Birthweight*	2135 (1886–2962)	1600 (890–2200)	0.052
Delivery Mode (NVD-C/S), n (%)	20 (67) /10 (33)	10 (37) /17 (63)	**0.024**
Length of stay in hospital (days)*	23 (15–36)	37 (25–45)	**0.037**
Length of stay before candidemia (days)*	13.5 (8.75–26.5)	16 (10–37.5)	0.205
Umbilical catheter present-duration (days)*	12 (0–14)	13 (10–15)	0.244
TPN duration (days)*	24 (14–30.5)	40 (25.5–57)	**0.002**
Mechanical ventilation duration (days)*	16 (5.2–27.5)	30 (11.25–44.25)	**0.027**
Antibiotherapy duration (days)*	21.5 (16.25–30)	28 (14–40)	0.585
Mortality, n (%)	11 (36)	9 (33)	0.965

*Median (minimum-maximum). M: Male; F: Female; NVD: Normal vaginal delivery; C/S: Cesarean section delivery; TPN: Total parenteral nutrition.

Table 3. Laboratory characteristics of the two groups producing *Candida albicans* and *Candida non-albicans*

Laboratory parameters	*Candida albicans* (n=30)	*Candida non-albicans* (n=27)	p
Leukocyte count (/mm^3)	10500 (8050-18000)	11000 (7097-19325)	0.960
Hemoglobin (g)	13.8 (10.45-17.4)	13.4 (9.1-19.1)	0.813
Thrombocyte count (/mm^3)	163000 (80500-283500)	152000 (42750-224750)	0.495
C-reactive protein (mg/dL)	40.9 (10.1-88.4)	33.65 (6.2-88.2)	0.698

Laboratory parameter values are stated as median (minimum- maximum) values.

Table 4. The antifungal minimal inhibitor concentration (MIC) values (µg/ml) of the *Candida* strains produced in blood cultures

Candida species	Flukonazol	İtrakanozol	Vorikanozol	Flusitozin	Ketokanazol	Caspofungin	Mikafungin	Amfoterisin B
Candida albicans	<0.5 (S)	<0.12 (S)	≥1 (R)	<1 (S)	≤0.25 (S)	<0.12 (S)	<0.06 (S)	≤0.5 (S)
Candida parapsilosis	<0.5 (S)	-	<0.12 (S)	<1 (S)	-	≤0.25 (S)	≤0.5 (S)	≤0.5 (S)
Candida glabrata	4 (SDD)	-	>1 (R)	<1 (S)	≥1 (R)	≥1 (R)	<0.06 (S)	≤0.5 (S)
Candida species	<0.5 (S)	-	<0.12 (S)	<1 (S)	-	≥1 (R)	≥1 (R)	≤0.5 (S)
Candida tropikalis	≥9 (R)	≥2 (R)	>4 (R)	≥9 (R)	≥1 (R)	≥1 (R)	≥1 (R)	>4 (R)
Candida pelliculosa	≤2 (S)	-	-	≤1 (S)	≤0.25 (S)	<0.25 (S)	<0.06 (S)	≤0.5 (S)
Candida krusei	≥9 (R)	-	-	-	-	-	-	<2 (S)
Candida utilis	<0.5 (S)	≤0.12 (S)	-	≤1 (S)	≤0.25 (S)	-	≤0.5 (S)	≤0.5 (S)

MIC: Minimal inhibitory concentration; R: Resistant; S: Susceptible; SDD: Susceptible-dose dependent. not tested.

groups in respect of leukocyte count, hemoglobin, thrombocyte count, and C-reactive protein (p>0.05) (Table 3).

The antifungal sensitivity values examined with MIC of the Candida strains produced in sterile samples are shown in Table 4.

Discussion

This study revealed that Candida infection was more common in extremely pre-term infants. Besides, while the NVD rate was found to be significantly higher in Group 1 (*C. albicans*), the length of hospital stay, TPN duration, and MV duration were found to be higher in Group 2 (*Candida non-albicans*).

Candida infections are the most common fungal infections in the neonatal period, especially in very low birth weight infants, with high morbidity and mortality rates.[8] It has been reported that Candida infections are responsible for 1.4% of the early neonatal sepsis and 2.6%–16.7% of late-onset sepsis in very low birth weight infants.[8] In a study examining single-center nosocomial infections, they found 61.9% Gram-positive bacteria, 30.9% Gram-negative bacteria, and 7.2% fungi.[9] This rate has been reported to vary between 1.1% and 1.3% in studies in Europe[1], and 4–7.7% in Asia.[10] Similarly current study, reported the frequency of Candida-related sepsis as 1.6%. The differences in the frequencies of candida infections can be attributed to differences in patient characteristics in the study groups, study design, and health-care practices.

Very low birth weight infants are known to be vulnerable to Candida infections due to prolonged hospital stay, exposure to invasive treatment procedures, the placement of a central catheter, MV, and TPN application.[1,5] Öncü et al.[11] found parenteral nutrition, intensive care unit (ICU) stay and MV as major risk factors in newborns in a study conducted by them. It has been reported that most newborns infected with Candida are ≤30 gestational weeks and have a birth weight of ≤1500 g.[5] In the present study, Candida infections were determined at the rate of 57% in extremely pre-term infants. The previous studies have shown that catheter application is a factor that increases the risk of *Candida* infection, especially in these newborn babies. In a study by Caggiano et al.[1], the frequency of catheter-related candidemia was determined to be 57%. This has been explained as *Candida* strains adhering to the biofilm surface of the catheter formed with thrombocytes and fibrinogen, thereby acting as a reservoir causing spread.

Invasive candidiasis is a serious infection among infants with underlying medical conditions. Transmission from *C. albicans* to *Candida non-albicans* has been observed worldwide. In the current study, seven different strains of candida were determined (*C. albicans, C. parapsilosis, C. tropicalis, C. glabrata, C.pelliculosa, C. krusei, C.utilis, and C.species (unspecified)*). In another study, the distribution of 71 Candida strains isolated in hospitalized patients was 28 (39%) *C. albicans,* 13 (18.3%) *C. parapsilosis*, 11 (15.5%) *C. glabrata*, 10 (14.1%) *C. tropicalis*, 4 (5.6%) *C. krusei*, 3 (4.2%) *C. lusitaniae*, and one (1.4%) as *C. kefyr* and *C. dubliniensis*.[12] The frequency of candida strains varies, with *C. albicans* reported to be the most predominant agent in Europe, and North and South America.[1,13,14] However, in Asian countries, *Candida non-albicans* strains are seen more frequently.[15,16] In addition, there has been a shift toward the reproduction of *Candida non-albicans* strains since the introduction of routine fluconazole prophylaxis in NICUs.[17] A previous study in Turkey showed the production of candida non-albicans strains at the high rate of 60.8% in the period when fluconazole prophylaxis was not widely used.[18] In the current study, *C. albicans* was determined to be produced more, at the rate of 52.6%, which was consistent with the production rates reported from some hospitals in Europe and the USA.[1]

In the current study, it was determined that *C. albicans* was significantly more common particularly in infants born with NVD. Auriti et al.[19] showed an increase of approximately 70% in *C. albicans* in vaginal candida colonization during pregnancy. This increased colonization is thought to play a role in obstetric tears. The onset of fungal infection is formed with adherence to vaginal epithelial cells, which then attempt to limit the infection by producing cytokines and inflammatory mediators. The binding of *C. albicans* occurs by inducing endocytosis and active penetration. Hyphal formation plays a role in the process of active penetration between vaginal epithelial cells, and protease production helps the vaginal epithelial deterioration by impairing the tight epithelial protein bonds. As a result of both endocytosis and penetration, the vaginal epithelium is damaged and undergoes necrosis and apoptosis.[20]

The presence of a vascular catheter and long TPN treatment has been reported as risk factors for *C. parapisilosis*, a non-albicans type.[1] The formation of a biofilm is important for *C. parapisilosis* to pass from yeast cells to pseudohyphae formation. The amino acids in TPN cause this conversion and this may explain the frequency of fungal infections in catheterized newborns.[21] In the present study, the frequency of *Candida non-albicans* strains was determined to be significantly higher in the group that received TPN. This can be explained by the higher frequency of C. parapisolisis. The probability of the development of *C. parapisolisis* in NICU patients is higher than for other non-albicans strains, which can be attributed to the greater capacity of *C. parapisolisis* to adhere to catheter lines than other fungal species.[22]

Consistent with the findings of previous studies, resistance to fluconazole, and amphotericin B in *C. albicans* infections was not determined in the present study.[1,23] These drugs are the preferred antifungal drugs in the prophylaxis and treatment of systemic *Candida* infection in newborn infants.[24] In the present study, fluconazole resistance was determined in *C. tropicalis* and *C. crusei* in the non-albicans group. The previous studies have shown that long-term fluconazole prophylaxis is responsible for the development of resistance to azole groups.[17,25]

This study had some limitations. As the study was retrospective, some of the data obtained from the patient records may have been missing, and data of non-infected patients in the NICU were not available, so comparison with uninfected neonates was not possible. Besides, since most of the pregnant women were immigrants and the retrospective design of the study, it could not be possible to obtain vaginal cultures for all women included in the study.

Conclusion

This study showed that *C. albicans* fungemia is more common in infants born by vaginal route; therefore, prenatal vaginal culture is recommended as well as being aware of vaginal candidiasis risk in pregnant women. Besides, further studies are needed to develop novel modalities in preventing the pre-term birth, reducing the duration of TPN, MV, and the hospital stay of those babies under risk.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Sivas Cumhuriyet University (No: 2020-09/08, dated 23.09.2020).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – G.T, F.K.; Design – F.K., A.T.; Supervision – G.T, F.K., A.T.; Materials – F.K., A.T.; Data collection &/or processing – G.T, F.K., A.T.; Analysis and/ or interpretation – G.T, F.K., A.T.; Literature search – G.T, F.K.; Writing – G.T, F.K.; Critical review – G.T, A.T.

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