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Research Paper

A Study of the Incidence and Outcome of Fungal Infections in the Neonatal Intensive Care Units; A Seven-year Surveillance

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ABSTRACT

Background and Aim: *Candida* infections are rare in the neonatal period, but they are an important cause of morbidity and mortality in neonatal intensive care units. Invasive fungal infections are extremely difficult to diagnose. It is suggested to start empirical treatment with antifungal therapy in high-risk, low-birth-weight infants who do not respond rapidly to antibacterial therapy or in those who are in a septic state due to an unknown source, based on regional guidelines. The aim of this study was to facilitate the earlier detection of at-risk newborns to initiate antifungal therapy as soon as possible, thereby lowering mortality rates and serious permanent disabilities.

Methods: This is a retrospective cross-sectional observational study on newborns admitted to the neonatal intensive care unit (NICU) from March 2010 to February 2016. Risk factors, such as birth weight, sex, route of delivery, the timing of oral feeding, total parental nutrition (TPN), prescribed drugs (such as antibiotics, H_2 blockers, methylxanthine, vasopressors, and corticosteroids), underlying diseases, history of surgery, urinary catheter insertion, central venous catheterization, and mechanical ventilation were extracted from patients' files. Also, we analyzed the blood groups of patients to find any possible relation to fungal infections.

Results: During the seven-year period, 2927 newborns were admitted to the NICU, of whom 32 patients (1.1%) were infected by fungal microorganisms. All but one of these neonates were infected by *C. albicans*. Most of them had positive urine or blood cultures for *C. albicans* (48.8% and 27.9%, respectively). All of our patients received amphotericin B as standard therapy, resulting in a 75% recovery rate.

Conclusion: Surveillance of newborns with underlying risk factors aids in early decision-making to start treatment for fungal infections in high-risk groups, thereby decreasing mortality rates and long-term devastating complications.

Keywords: Blood culture, *Candida*, *Candida albicans,* Fungal infection, Neonate, Neonatal intensive care unit

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Introduction

Nowadays, with advances in neonatal care, the survival rates of preterm and low-birth-weight (LBW) babies have improved significantly. However, it should be kept in mind that systemic infections are still considered the main cause of mortality and morbidity in these patients [1, 2]. Studies on fungal infections have developed significantly in the last two decades, greatly improving the survival rate of infants. Yeast infections are still a common cause of late-onset infections in newborns [3]. Benjamin et al., in a prospective study of 4,579 newborns with extremely low birth weight (ELBW), identified several risk factors that increase susceptibility to candidiasis. These included exposure to third-generation cephalosporins, prematurity, low birth weight, and delayed initiation of oral feeding. In this study, infants with a birth weight of less than 750 g had a higher incidence of candidiasis compared to infants who weighed between 751 and 1,000 g (11.4% vs. 3.4%, respectively). Infants who began oral feeding by the third day of life developed candidiasis less frequently than those with delayed enteral feeding (3.4% vs. 8.7%, respectively) [4, 5].

There is a significant reduction in gastrointestinal colonization by *Candida* species among LBW and very-low-birth-weight (VLBW) preterm neonates receiving probiotics. It is suggested that probiotics can modify intestinal flora by competitively excluding pathogenic fungi and reducing their ability to colonize the intestinal mucosa by increasing mucosal IgA secretion [6]. Also, intestinal immaturity is generally associated with increased membrane permeability and may reduce the baby's ability to defend against pathogenic microorganisms in the bowel [3]. Admission to the neonatal ward itself and the administration of multiple drugs also appear to increase the risk of fungal infections in all neonates. Using H_2-blocking agents may allow more pathogens to enter the intestinal tract by lowering gastric acid activity.

On the other hand, the inability to tolerate breast milk and the need for parenteral nutrition means that the baby is deprived of maternal antibodies [3, 4]. A decrease in normal intestinal flora due to prolonged treatment with broad-spectrum antibiotics and late commencing of oral nutrition are important risk factors in these patients. Therefore, pathogenic and non-inhabitant species, such as *Candida* can more easily colonize the baby's intestine [3, 4]. Other known risk factors are the administration of corticosteroids, aminophylline, concomitant mucocutaneous candidiasis, perianal dermatitis or perineal *Candida* colonization, and endotracheal intubation [2-4]. Hence, such pathogens can find their way to the bloodstream from the intestine. Fungal colonization generally occurs very early in the hospitalization course. Approximately 10% of colonization happens during the first week, reaching as high as approximately 64% by the fourth week [5]. Interestingly, increasing the infant's age, starting breastfeeding earlier, and removing the central venous catheter significantly lower the incidence of fungal infections in infants with longer hospital stays [7]. Previous studies have demonstrated that *C. albicans* infection is more common in preterm infants, while *C. parapsilosis* generally causes infection in infants fed through a central venous catheter. *C. tropicalis* infection has also been reported in the neonatal period [2-4]. Although neonatal blood culture is the best way to diagnose invasive *Candida* infections, it is not as sensitive as bacterial cultures. It should be noted, however, that the clinical manifestations of fungal septicemias are not significantly different from those of bacterial septicemias.

On the other hand, due to the difficulty of cultivating fungal organisms in blood, cerebrospinal fluid, and urine, relying only on culture results may underestimate the incidence of fungal infections, resulting in a late initiation of appropriate treatment and leading to higher mortality and morbidity [8, 9]. *Candida* species are found in measurable amounts in urine (candiduria) in 1% of clean catch samples from healthy individuals, but they represent 5% of all urine cultures in general hospitals and 10% of urine isolates in tertiary care centers. All common *Candida* species are capable of causing urinary tract infections (UTIs), and non-*albicans Candida* species predominate in many centers around the world. Contrary to their rarity in adults, fungal bezoars are particularly common in UTIs among critically ill newborns, regardless of the route of infection [10, 11]. This study aimed to investigate the epidemiological aspects of neonatal fungal infections to assist clinicians in initiating appropriate empirical treatments even before culture and antibiogram results become available.

Materials and Methods

This is a retrospective cross-sectional observational study on newborns admitted to the NICU from March 2010 to February 2016 who developed fungal infections during hospitalization. Evaluation of the complete blood cell count and C-reactive protein levels, blood culture, cerebrospinal fluid evaluation, and culture of any suspected site, such as intubation tube, central venous line, or urine catheter, were performed routinely in suspected neonates. On a regular basis, neonates with documented fungal infections and those who were strongly sus-

pected based on the clinical grounds were treated with antifungal drugs. The data obtained from patient files were recorded in a manual questionnaire according to the proposed protocol. All data extracted manually from patients' files, along with the clinical response of the patients, were recorded carefully.

As all tests and assessment forms were totally within the routine ward program, there was no need to obtain any informed consent from patients or their parents. This study is a result of a fellowship project and was approved by the research committee of the Tehran University of Medical Sciences. Details of the study were completely discussed with the participants, and consent from the patients, their parents, or their relatives, when applicable, was obtained prior to enrollment in the study.

The collected data were analyzed using SPSS software version 22, with quantitative data expressed as Mean±standard deviation (SD) and qualitative data assessed using the chi-squared test. In all tests, $P<0.05$ were considered statistically significant.

Results

During the study period, a total of 2927 babies were admitted to the NICU of our center. Among these, there were 32 infants with fungal infections, resulting in a prevalence of fungal infections over seven years estimated at 1.1%. According to the culture results, there were 31 cases of *C. albicans* infection and one case of non-*albicans Candida* infection. Details and frequency of findings according to each variable are stated in Table 1.

The mean age of patients with fungal infection at the time of onset was 19.8±17.7 days, ranging from 1 to 73 days. Both sexes were affected equally. The lowest and highest gestational ages were 28 and 38 weeks, respectively (mean age: 37±1 weeks in term and 30±2.5 weeks in preterm infants). The frequency of systemic fungal infections in infants who received TPN was significantly higher, with infections generally occurring 3 to 30 days following the initiation of TPN. The average duration of the TPN until obtaining a positive culture was 15±9 days. All confirmed fungal-infected neonates had received some type of medication, including antibiotics, followed by H_2 blockers, methylxanthines, and corticosteroids. The least commonly used drugs were vasopressors and corticosteroids. The frequency of systemic fungal infections in infants receiving antibiotics was significantly higher than in other groups.

The mean duration of hospitalization and using antibiotics until obtaining a positive fungal culture was 26.8±19.1 days, ranging from 3 to 87 days. Receiving more than seven days of third-generation cephalosporins or vancomycin was associated with an increased risk of fungal infection. Twenty-two (69%) of the neonates with fungal infections required mechanical ventilation, indicating a significant relationship between mechanical ventilation and the frequency of fungal infections.

The mean duration of mechanical ventilation was 8.6±6.6 days, with a minimum of one to a maximum of 30 days. Regarding surgical procedures, the most common underlying problem in neonates requiring surgery was necrotizing enterocolitis, intestinal perforation, duodenal atresia, esophageal atresia, imperforate anus, and recto-vaginal fistula. Predisposing underlying non-surgical conditions included metabolic derangements, renal disorders, underlying heart and lung diseases, skin and gastrointestinal disorders, and central nervous system (CNS) problems, such as CNS infections, hydrocephalus with shunt placement, etc. However, there was no statistically significant difference in the incidence of systemic fungal infections according to the underlying disease ($P=0.073$). Twenty-four newborns (75%) with fungal infections had some type of catheterization, the most common being a central venous line, followed by urinary tract catheterization, with the least common being both types of catheterization simultaneously.

The most common sample positive for fungal elements was urine, followed by blood, tracheal secretions, intestinal secretions, wound site secretion, articular fluid, central venous catheter tips, and ascitic fluid ($P<0.001$). There was only one case with metastatic fungal foci (orbital) among our cases (3.1%). Positive bacterial cultures were found in blood (eight cases, 31%), urine (six cases, 24%), colostomy site, ascitic fluid, intravenous catheter (three cases, 11%), endotracheal secretions (two cases), and one wound sample. Klebsiella was the most common bacterial growth, detected in 9 cases (35%). Other microorganisms detected in cultures included *Staphylococcus aureus*, *Pseudomonas* spp., *Acinetobacter* , and *Enterococcus*, each detected in three cases (11%), *E. coli* in two cases, and *Enterobacter*, *Serratia* and *Staphylococcus epidermidis* each in one case.

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Table 1. Frequency of patients according to different variables

Variables		No. (%)	P
Gestational age (week)	Term	18(56)	0456
	Preterm	14(44)	
Birth weight (g)	>2500	14(44)	0.197
	1500-2499	12(37)	
	<1500	6(18)	
Delivery type	Cesarean section	19(61)	0.290
	Normal delivery	13(39)	
Catheterization state	Central Venous	19(59.3)	0.001
	Urinary Tract	1(3.1)	
	Central venous & urinary tract	2(2)	
	None	8(24)	
Mechanical ventilation	Yes	22(69)	0.034
	No	12(31)	
Feeding type	Breast milk	5(15.6)	0.002
	Formula	4(15.6)	
	Total parental nutrition (TPN)	15(12.5)	
	Breast milk and TPN	7(21.9)	
	Formula and TPN	1(3.1)	
Specimen positive for fungi	Urine	21(48.8)	0.001
	Blood	12(27.9)	
	Trachea	3(6.9)	
	Wound secretions	3(6.9)	
	Articular fluid	2(4.6)	
	Central venous catheter	2(4.6)	
	Ascites fluid	1(2.3)	
Underlying problems	Abdominal surgery	13(41)	0.73
	Metabolic disorder	4(13)	
	Renal diseases	4(13)	
	Cardiac diseases	3(9)	
	Pulmonary diseases	3(9)	
	Cutaneous disorders	2(6)	
	Gastrointestinal diseases	2(6)	
	Central nervous system diseases	1(3)	

Variables		No. (%)	P
Drugs	Antibiotics	32(100)	0.035
	H_2 blockers	22(66.7)	
	Methylxanthine	12(37.5)	
	Vasopressors	3(9.4)	
	Corticosteroids	2(6.3)	
Prognosis	Recovery	24(75)	0.005
	Death	8(25)	

Table 2. Frequency of systemic fungal infections according to the use of third-generation cephalosporins

Antibiotic type	Prescription	Patients, No. (%)	P	Duration, No. (%)		P
Cephalosporine	Yes	31(96.9)	0.034	>7 days	25(80)	0.001
	No	1(3)		<7 days	6(20)	

This study showed that *Candida* strains were responsible for almost all neonatal fungal infections, with only one case being non-*albicans*. All patients were treated with amphotericin B immediately and no resistance was reported. The average duration of treatment was 14.5±5.4 days, ranging from 6 to 27 days. Most infants responded well to treatment, with 24 cases (75%) recovering from fungal infections; unfortunately, eight (25%) patients died (P=0.0050). All newborns who died of fungal infection had a positive urine culture; two of them also had positive blood cultures, and one had a positive ileostomy site culture. The lowest and highest weights of dead neonates were 1860 and 4300 g, respectively.

The frequency of patients according to different variables is demonstrated in Table 1. Table 2 shows the frequency of systemic fungal infections in relation to the administration of third-generation cephalosporins. Table 3 represents the frequency of systemic fungal infections related to the use of vancomycin. Table 4 demonstrates systemic fungal infections according to the administration of third-generation carbapenems and aminoglycosides. Table 5 presents the frequency of systemic fungal infections according to different blood groups, and Table 6 demonstrates the frequency of systemic fungal infections in relation to underlying or concomitant non-fungal infections.

Table 3. Frequency of systemic fungal infections according to the use of vancomycin

Antibiotic type	Prescription	Patients, No. (%)	P	Duration, No. (%)		P
Vancomycin	Yes	27(84)	0.001	>7 days	20(62.5)	0.001
	No	5(16)		<7 days	7(218)	

Table 4. Frequency of systemic fungal infections according to the use of third-generation carbapenems and aminoglycosides

Antibiotic type	Prescription	Patients, No. (%)	P
Carbapenem	Yes	21(66)	0.077
	No	11(34)	
Aminoglycoside	Yes	20(60)	0.289
	No	12(40)	

Table 5. Frequency of systemic fungal infections according to blood group

Blood Group	Patients, No. (%)	P
O	15(46.9)	0.001
B	13(40.6)	
A	2(6.3)	
AB	2(6.3)	

Discussion

In this retrospective observation, we studied the prevalence of fungal infections, their risk factors, prognostic factors, and overall prognosis of fungal infections in newborns admitted over a seven-year period. The overall prevalence of fungal infections in this study was estimated at 1.1%, compared to 3.6% and 0.45% in the studies conducted by Basu et al. (India) and Baptista et al. (Portugal), respectively [12, 13]. This difference in prevalence could be attributed to better hospital care and more compliance with infection control rules in more developed countries. In the study by Garzillo et al. in Italy, the mean duration of hospitalization for infants at the time of infection with *C. parapsilosis* was 19.29 days, ranging from 5 to 75 days, which is consistent with our findings [14]. In the study by Basu et al., hospitalization for more than 28 days was considered an independent risk factor for non-*albicans* infections [12]. The results of this study showed that male and female infants have equal susceptibility to fungal infections, which aligns with the findings of Basu et al. and Garzillo et al. [12, 14]. However, according to Garzillo et al., the risk of *C. parapsilosis* infection in boys was more than three times greater than in girls [14]. This conclusion seems to lack precision and requires further investigation. In our study, 44% of preterm neonates and 56% of full-term infants had fungal infections. In the study by Almoosa et al., only about 29% of premature babies had fungal infections and approximately 33% of them weighed less than 2500 g at birth [15].

However, other studies have confirmed the greater incidence of fungal infections in preterm infants weighing less than 2500 g. For example, in the study by Baptista et al., about 66% of affected babies weighed less than 1000 g (extremely low birth weight) [13]. However, in Garzillo et al.'s study, 14 neonates weighed less than 1500 g, one weighed between 1500 and 2500 g, and two weighed more than 2500 g at birth, In this study, prophylactic fluconazole was prescribed for all newborns weighing below 1500 g at a dose of 6 mg/kg every 72 hours during the first two weeks after birth, and then continued every 48 hours [14]. In Basu et al.'s study, the average gestational age of newborns infected by *Can-*

Table 6. Frequency of systemic fungal infections according to underlying or concomitant non-fungal infections

Type of Bacteria	Type of Culture							
	Blood	Venous Catheter	Ascites Fluid	Trachea	Urine	Colostomy	Wound	Total
Klebsiella	3	2	1	0	2	1	0	9
Staphylococcus aureus	2	0	0	0	0	1	0	3
Enterobacter	0	0	1	0	0	0	0	1
Staphylococcus epidermidis	1	0	0	0	0	0	0	1
Pseudomonas spp.	1	0	0	2	0	0	0	3
Serratia	0	0	0	0	1	0	0	1
E. coli	0	0	0	0	1	1	0	2
Acinetobacter	0	2	0	0	0	0	1	3
Enterococcus	1	0	1	0	1	0	0	3

dida was 30.6±1.4 weeks. In Garzillo et al.'s study of 17 neonates with systemic C. parapsilosis infections, 16 were premature babies with an average gestational age of 26 weeks (ranging from 24 to 32 weeks), while only one case had a gestational age of 40 weeks [12, 14]. In the study by Leibovitz et al., there was an association between the route of delivery and the risk of colonization with fungal strains [16]. In our study, the incidence of systemic fungal infections in infants who received their metabolic needs through TPN was also significantly higher. Only 28% of these infants were fed orally, while approximately 47% required TPN. Thus, the feeding route may be an important risk factor. In addition to intravenous feeding, some of the newborns were fed breast milk, formula, or both.

Almirante et al. also found a 54% association between fungal infection and TPN [17]. Previous studies have shown that the *C. parapsilosis* strain grows well in intravenous feeding solutions [18]. Clark et al. also found that TPN increases the risk of fungal infections by 5.9 times [19]. In our study, fungal infections were observed 3 to 30 days after starting TPN, with the mean duration of TPN until detection of a positive fungal culture being 15±9 days. According to Horan et al., catheter insertion should be considered an important risk factor, especially if left in place for 48 hours or more (either umbilical vein or central venous catheter) [20]. In our patients, catheterization was done in 75% of cases (59.3% had central venous catheterization), and it was one of the main risk factors in our study as well. In the Almoosa et al.,' study, central venous catheters were used in approximately 46% of infants who had systemic fungal infections [15]. However, in studies by Baptista et al. and Garzillo et al., all infants with fungal infections had undergone central venous catheterization [13, 14]. Steinbach also showed that central venous catheterization was associated with a 9.6 times increased risk of developing fungal infections [21].

Antibiotics, H_2 blockers, and corticosteroids have also been identified as risk factors for fungal infections in several studies [17, 22]. In the Almoosa et al.' study, approximately 65% of patients had received antibiotics [15]. All of our patients received systemic broad-spectrum antibiotics (either prophylactic or therapeutic), making it one of the main risk factors in our study. The antibiotics used in our patients included third-generation cephalosporins in 97%, vancomycin in 84%, carbapenems in 66%, and aminoglycosides in 60%. Among these antibiotics, third-generation cephalosporins and vancomycin—especially when administered for more than 7 days—were associated with an increased likelihood of systemic fungal infections.

However, there was no statistically significant association between the use of carbapenems and aminoglycosides and fungal infections in our study y. Chen et al. also showed that the administration of vancomycin, carbapenem, multiple antibiotics, and third-generation cephalosporins increased the risk of fungal infections by 12.17, 9.47, 7.71, and 1.86 times, respectively. Interestingly, the data from Chen et al.'s study and ours show a significant difference in terms of the antibiotics used, with carbapenems being the most common antibiotic administered in 72.5% of cases in Chen et al.'s study, followed by third-generation cephalosporins in 57.4%, concomitant use of antibiotics in 53.6%, and vancomycin alone in only 14.5% [23]. The mean duration of antibiotic treatments in Chen et al.'s study was 33.5 days compared to 26.8 days in ours. In another study, Kaufman found that reduced use of carbapenems could decrease the incidence of fungal infections [24]. Prolonged use of broad-spectrum antibiotics appears to increase *Candida* colonization and, consequently, the risk of resistant *Candida* infections due to a decrease in the normal flora of the intestinal tract [25]. Saiman et al. also found that H_2 blockers are an important risk factor in neonatal fungal infections due to their effect on lowering gastric acid levels [5]. In our study, 30% of newborns received H_2 blockers. Other medications used included methylxanthines in 17%, vasopressor drugs in 5%, and corticosteroids in 3% of patients. In the study by Almoosa et al., corticosteroids were administered to approximately 15% of patients with systemic fungal infections [15].

However, Saiman et al. found that corticosteroids did not increase the risk of neonatal fungal infection [10]. About 70% of our patients experienced intubation and mechanical ventilation. The mean duration of mechanical ventilation was 8.6 days, with a minimum intubation period of one day and a maximum of 30 days. In studies by Ariff et al. and Chen et al., approximately 71% and 62% of newborns who underwent mechanical ventilation contracted systemic fungal infections, respectively [3, 23]. In Ariff et al.'s study, the average mechanical ventilation duration was 19 days, and the need for mechanical ventilation for more than one week increased the risk of fungal infections by 7.14 times [3]. However, according to Fu et al., mechanical ventilation generally increased the incidence of fungal infections with non-*albicans* species by up to 3.3 times compared to *C. albicans* infections [25]. This may be due to the ability of *Candida* strains to enter the circulation after injury to the respiratory mucosa during intubation [26]. The attachment of *Candida* to the surfaces of medical devices and the formation of a biofilm membrane can protect it against the immune system and antifungal medications [27]. In this study, 47% of infected neonates had blood group O. Also, the prevalence of *Candida* spp. infection in patients with blood

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group B was more than other blood groups, consistent with previous studies. Approximately 37.5% of the population had blood group O and approximately 24.7% had blood group B. There may be an association between blood group type and its secretory state, as well as the presence of *Candida* spp. in the gastrointestinal tract. Individuals with blood group O and those who do not secrete blood group antigens in body fluids (non-secretory) are more likely to carry *Candida* spp. than others [28, 29]. An explanation for the relatively high prevalence of fungal infections in patients with blood group B may be their non-secretory state.

According to Fu et al.'s study, approximately 43% of patients with *C. albicans* infections and 61% of patients without *C. albicans* infections have underlying disorders [25]. In our study, 41% of fungal-infected patients had some form of surgical intervention, such as necrotizing enterocolitis, esophageal atresia, imperforate anus, duodenal atresia, intestinal perforation; however, none of these underlying disorders was identified as an independent risk factor for systemic fungal infections. This contrasts with the findings of Baptista's study, [13] which found that surgery within the past 15 days increased the risk of developing systemic fungal infections by 2.73 times [13]. The different sample sizes in the two studies may account for this discrepancy. Urine cultures obtained routinely by suprapubic route in our cases were reported to be positive for *Candida* in approximately half of our patients, followed by blood cultures in approximately 28%. In Benjamin et al.'s study, blood cultures accounted for approximately 70%, urine cultures for 38%, cerebrospinal fluid cultures for 6.7%, and other body fluids for 7.3% of *Candida*-positive cultures [30]. In the Almoosa et al.'s study, blood, cerebrospinal fluid (CSF), peritoneal fluid, pleural tap, and synovial fluid cultures yielded microbial growth in 88%, 5.4%, 3.9%, 1.6%, and 0.8% of patients, respectively [15]. The reason for this difference could be attributable to sampling techniques, as Benjamin et al. [30] used the insertion of a suprapubic catheter to collect urine samples, and Almoosa et al. excluded patients who had positive tissue or urine cultures for candidiasis [15, 30]. In our study, simultaneous positive bacterial blood and urine cultures were detected in 30% and 26% of the *Candida*-positive samples, respectively. Also, 85% of these cases (26 neonates) had Gram-negative infections, while only 15% had Gram-positive bacterial infections.

In the Ariff et al.'s study, blood, endotracheal secretions, and urine cultures were positive for bacterial infection in 64%, 31%, and 18% of patients, respectively, and a positive bacterial culture was associated with an increased risk (up to 1.93 times) of candidiasis [3]. Other studies have shown that *Candida* spp. infections, followed by Gram-positive and Gram-negative bacterial infections, are the most common healthcare- and device-associated infections in NICUs [8, 30, 31] The mean duration of treatment for these infants was approximately 14.5 days, which is approximately comparable to that reported in Ariff et al.'s study [3]. In the study by Almoosa et al., 97.6% of cases of *Candida* strains were sensitive to amphotericin B [15]. Although this drug remains the gold standard of the empirical treatment of neonatal fungal infections, Basu et al. showed that amphotericin B treatment was effective in only 76% of patients with yeast infections, consistent with our results [12]. Basu et al. also found that resistance of *Candida* strains to this drug has increased over time, and today only about 68% of *Candida*-infected cases are sensitive to antifungals, which is concerning and necessitates careful judgment regarding its use [12].

Conclusion

This study demonstrates that fungal infections occur in both preterm and high-risk term neonates. Another interesting finding was the high incidence of Gram-negative bacterial infections in fungal-infected newborns, suggesting that these infections may share the same source or predispose one another. It is also important to keep in mind that amphotericin B-resistant strains may emerge if used as a routine practice.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Tehran University of Medical Sciences (Code: 98-02-30-43116).

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results, and manuscript drafting. Each author approved the submission of the final version of the manuscript.

Conflict of interest

The authors declared no conflict of interest.

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