

Original Research Article

Clinical spectrum and outcomes of fungal sepsis in neonates in the two neonatal intensive care unit of Bangladesh: a prospective observational study

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ABSTRACT

Background: Fungal infections have emerged as a significant cause of late-onset neonatal sepsis in the last two decades. Epidemiological data on fungal sepsis in neonates especially in the Bangladesh population is scarce. Fungal infections are frequent and major causes of septicemia in neonatal intensive care units and are associated with high morbidity and mortality. Objective of the study: This study aims to determine the epidemiological trend of neonatal fungal infection, the organisms, and their susceptibility pattern to the different antifungal agents and additionally to look for the various risk factors, clinical features, and laboratory manifestation of fungal sepsis in neonates.

Method: This Prospective observational study was carried in Neonatal Intensive Care Unit (NICU) of Bangabandhu Sheikh Mujib Medical University (BSMMU) & Neonatal Intensive Care Unit (NICU) of Central hospital, Dhaka after approval from IRB. A total of 106 admitted neonates during the study period who were eligible for this study were included. On the basis of exclusion criteria 12 neonates were excluded. Blood culture was tested in the department of Microbiology of participating institutes.

Results: After meeting all inclusion criteria 94 patients were included in the study. Most of the neonates (62.8%) were male and 67% were outborn. Around 34% Birth weight was between 2500gm to 3999gm followed by 31.9% in between 1000 gm to 1499 gm. Preterm were 69.2% and delivery by LUCS was 75.5%. Death occurred in 12.8% cases. Fungal growth were isolated in 69.1% cases. All were *Candida* species. There was no statically significant difference in between Culture positive and no growth group in terms of risk factors and laboratory findings except temperature instability. In culture positive group 82.4% cases had temperature instability compared to no growth group. All *Candida* species were sensitive to most of the antifungal agents except *Candida ciferrii* which was only sensitive to flucytosine.

Conclusion: *Candida* is the most prevalent fungus in NICU. *Candida ciferrii* is an emerging fungus which is resistant to classical antifungal agents.

Keywords: Fungal sepsis, NICU, *Candida ciferrii*

INTRODUCTION

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia, fungus and virus in the first month of life.¹ It is one of the major contributors of neonatal mortality and morbidity worldwide.² Neonates are vulnerable for developing sepsis which estimates around 3 million global incidence with a mortality of 22.2% and significant long-term neurological defects. Neonatal sepsis has been classified into early and late onset sepsis. Early sepsis occurs within the first 72 hours of birth and late neonatal sepsis occurs after 72 hours of birth. Neonatal invasive candidiasis is a serious and common cause of late onset sepsis and has a high mortality (25 to 35%) Over the past 15 years, the incidence of such fungal infections has increased 11-fold. Preterm infants are predisposed to Candida infections because of immaturity of their immune system and invasive interventions. Vertical (from maternal vaginal infection) or nosocomial transmission of Candida are common. Candida infections are frequent and major causes of septicemia in neonatal ICUs, and are associated with high morbidity and mortality rates. The sources of candidiasis are mostly endogenous, and the frequency of the disease is influenced by the patient population and by various treatment regimens, antibiotics, and other supportive care procedures. Clinical presentation of candidemia resembles sepsis, hence its clinical diagnosis is difficult. Signs of fungal sepsis include thrombocytopenia, lethargy, glucose instability, increasing ventilation requirement and apnoea. End organ damage is more common and severe in systemic fungal infections and the kidneys, joint, brain, lung, eyes, liver, spleen and bones can be involved. Widespread infection despite negative culture is common. So, this study aims to determine the epidemiological trend of neonatal fungal infection, the organisms, and their susceptibility pattern to the different antifungal agents and additionally to look for the various risk factors, clinical features, and laboratory manifestation of fungal sepsis in neonates.

METHODS

This prospective observational study was done in the Department of Neonatology, Bangabandhu Sheikh Mujib Medical University (BSMMU) and NICU of Central Hospital, Dhaka from January 2022 to December 2022, after getting the approval from the Institutional Review Board (IRB). A total of 106 admitted neonates during the study period who were eligible for this study were included. On the basis of exclusion criteria 12 neonates were excluded).

Inclusion criteria

All NICU admitted neonates with suspected fungal sepsis whose blood culture was sent on admission or during clinical deterioration or not improving with antibiotics or

departmental protocol for repeat culture after 72 hours of antibiotic therapy were included in the study.

Exclusion criteria

Neonates with multiple congenital anomalies were excluded.

Study procedure

This prospective observational study was conducted in the Department of Neonatology, BSMMU and NICU of Central hospital after approval by Institutional Review Board (IRB) over a period of one-year from January 2022 to December 2022. These centres had well established Neonatal Intensive Care Unit (NICU) with standard laboratory facilities.

Neonates after meeting the eligibility criteria were included. Collection of blood for blood culture was obtained before other blood specimen. Before procedure washing hands with soap and water and then sterile gloves were used. At first all the necessary equipments like sharps disposal container within easy access, a dressing pack containing sterile gauze, sterile sheet and cover sheet, sterile gloves, Chlorhexidine Gluconate (0.5% Biotaine in 70% alcohol, Blood culture media(s) (BacT/Alert Paediatric or BacT/Alert Standard Aerobic boCles), appropriate size syringe, butterfly or straight needle (24 gauge in a neonate) were assembled. An assistant helped the procedure and created a sterile field using the dressing-pack, emptied the syringe and needle onto the field and cleaning solution into the holding vessel.

Then the dust cap from the blood culture bottle was removed, the septum of the blood culture bottle was disinfected with a chlorhexidine-soaked gauze and then allowed to dry. Optimal skin decontaminant was ensured by cleaning the phlebotomy site with gauze soaked in chlorhexidine in a circular motion inward to outwards and allowing the site to dry for at least 30 seconds. A sterile sheet with the opening over the site for the blood culture was placed. An appropriate volume of blood (1-2ml) for inoculation into the blood culture medium was withdrawn. Then pressure with dry gauze to the phlebotomy site was applied to prevent further bleeding and the blood drawn into the blood culture bottle was inserted without changing the needle. The needle in the sharps container was disposed after procedure. The blood culture to mix the blood with the culture medium was rotated not shaken. Adequate information on the laboratory request form, including diagnosis, site of venepuncture and previously administered antibiotics was provided. Then specimens were transported as soon as possible to specimen reception and specimens were not refrigerated while awaiting transport.

In this study information was obtained in the form of Basic information including gestational age, birth weight

of the patient, sex, place and mode of delivery, Patients having any risk factors for sepsis such as prolonged rupture of membrane (>18 hours), foul smelling liquor, maternal fever, perinatal asphyxia, prematurity, poor cord care, pre lacteal feeding, bottle feeding, prolonged NICU stay in other hospital etc, Clinical presentation of patient related to sepsis and Blood culture related variables like time of sending blood culture, site of sample collection, method of blood culture and type of organisms isolated with sensitivity pattern.

All these information were taken from maternal history, direct examination of the patient and from laboratory as well as from blood culture reports. Then data was entered in the pre-designed structured data collected sheet. All enrolled neonates were followed up during the period of hospital stay and outcome was assessed as Discharge/Discharge on Request (DOR)/Left Against Medical Advice (LAMA)/Death.

Data analysis

After collection, data were entered into a personal computer then edited, analyzed, plotted and were presented in graphs and tables. Qualitative data were expressed in proportion or percentage and statistical test were done by chi-square test and quantitative data were expressed as mean and SD and statistical test were done by student t test. All data were analyzed by SPSS software for windows, version 20. P value <0.05 was considered as level of significance.

RESULTS

A total of 106 admitted neonates during the study period who were eligible for this study were included. On the basis of exclusion criteria 12 neonates were excluded.

Most of the neonates (62.8%) were male, birth weight was mostly between 2500gm to 3999gm (34.0%), followed by in between 1000 gm to 1499 gm. Most of the babies were preterm and were delivered by LUCS. Fungal growth were found in 69.1% cases. Total 87.2% were discharged and 12.8% expired (Table 1).

Candida species were the predominant fungus. Only 11 species could be identified among which Candida parapsilosis was the commonest (Table 2).

Antifungal sensitivity and resistance pattern of organisms were shown in Figure 1 and 2 which reveal all Candida species were sensitive to most of the antifungal agents except Candida ciferrii which was only sensitive to flucytosine.

Comparison of risk factors in between culture positive and no growth group is shown in Among risk factors, the incidence of prolonged hospital stay, prolong use of antibiotics, multiple antibiotic use, lack of enteral

feedings, complicated gastrointestinal disease, umbilical catheterization, use of postnatal steroids, H2 blockers, trauma were more in culture positive group than the no growth group but not statically significant (Table 3).

Table 1: Baseline characteristics of neonates (n=94).

Characteristics	N (%)
Sex	
Male	59 (62.8)
Female	35 (37.2)
Place of delivery	
Inborn	31 (33.0)
Out born	63 (67.0)
Birth weight	
<1000 gm	5 (5.3)
1000-<1500 gm	30 (31.9)
1500-<2500 gm	27 (28.7)
2500-<4000 gm	32 (34.0)
4000 gm or more	0
Gestational age	
Term	29 (30.9)
Preterm	65 (69.2)
Mode of delivery	
VD	23 (24.5)
LUCS	71 (75.5)
Blood culture profile	
Organism found isolated	65 (69.1)
No growth	29 (30.9)
Outcome	
Discharge	82 (87.2)
DOR	0
LAMA	0
Death	12 (12.8)

LUCS: Lower uterine cesarean section, VD: Vaginal delivery, DOR: Discharge on request, LAMA: Left against medical advice.

Thermal instability, Frequent apnea, Lethargy, Convulsions, GI symptoms, Respiratory distress, Hypoglycemia, Hypotension, Renal Failure were more in Culture positive group than the no growth group where temperature instability had only statically significant difference (Table 4).

Table 2: Organism isolated from blood culture (n=94).

Organisms	N (%)
<i>Candida albicans</i>	2 (2.1)
<i>Candida ciferrii</i>	3 (3.2)
<i>Candida guillermi</i>	1 (1.1)
<i>Candida parapsilosis</i>	4 (4.3)
<i>Candida tropicalis</i>	1 (1.1)
<i>Candida species</i>	54 (57.4)
No growth	29 (30.9)

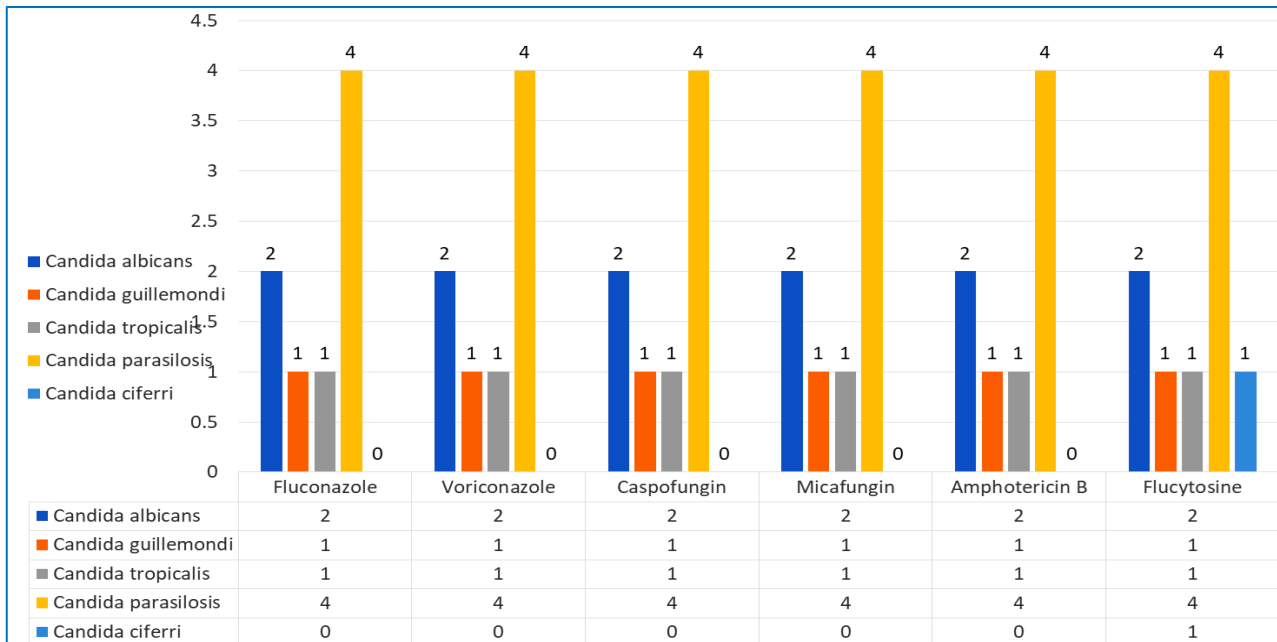


Figure 1: Antifungal sensitivity pattern of different organisms.

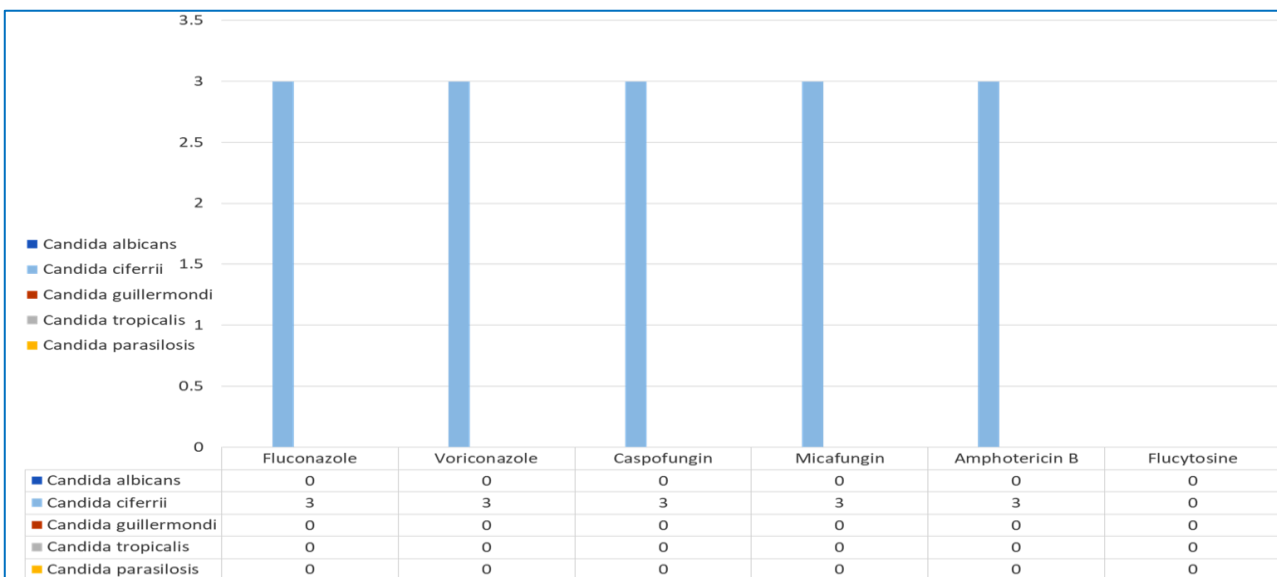


Figure 2: Antifungal resistance pattern of different organisms.

Table 3: Comparison of risk factors in between culture positive and no growth group.

Risk factors	Culture positive group (n=65) N (%)	No growth group (n=29) N (%)	P value
Hospital stay >7 days	62 (68.9)	28 (31.1)	0.268
Prolong use of antibiotics	61 (65.5)	28 (31.5)	0.148
2 or more antibiotic use	64 (69.6)	28 (30.4)	0.509
Lack of enteral feedings	14 (82.4)	3 (17.6)	0.204
Complicated gastrointestinal disease	14 (70.0)	6 (30.0)	0.991
Use of postnatal corticosteroids	1 (100)	0	0.499
Mechanical ventilation	25 (71.4)	10 (28.6)	0.584
Duration on mechanical ventilation, mean±SD	12.31±13.04	6.70±1.83	0.188

Continued.

Risk factors	Culture positive group (n=65) N (%)	No growth group (n=29) N (%)	P value
Umbilical catheterization	20 (74.1)	7 (25.9)	0.516
Use of postnatal steroids	5 (62.5)	3 (37.5)	0.666
H ₂ blockers	28 (66.7)	14 (33.3)	0.624
Trauma	12 (85.7)	2 (14.3)	0.139

Table 4: Comparison of symptoms in between culture positive and no growth group.

Symptoms	Culture positive group (n=65) N (%)	No growth group (n=65) N (%)	P value
Thermal instability	28 (82.4)	6 (17.6)	0.047 ^s
Frequent apnea	28 (70.0)	12 (30.0)	0.984
Lethargy	51 (73.9)	18 (26.1)	0.152
Convulsions	10 (83.3)	2 (16.7)	0.277
GI symptoms	20 (64.5)	11 (35.5)	0.424
Respiratory distress	46 (70.8)	19 (29.2)	0.779
Hypoglycemia	3 (60)	2 (40)	0.620
Hypotension	3 (100)	0	0.240
Renal failure	4 (80.0)	1 (20.0)	0.591

Table 5: Comparison of alboratory findings in between culture positive and no growth group.

Symptoms	Culture positive group, N (%)	No growth group, N (%)	P value
Leucopenia	9 (75.0)	3 (25.0)	0.172
Leucocytosis	1 (33.3)	2 (66.7)	0.698
Thrombocytopenia	28 (73.7)	10 (26.3)	0.367

Regarding Comparison of Laboratory findings in between Culture positive and no growth group there was no statically significant difference in between Culture positive and no growth group in terms of leucopenia or leucocytosis and thrombocytopenia (Table 5).

DISCUSSION

Fungal sepsis is an important cause of morbidity and mortality in sick newborns. In the present study, *Candida* was isolated in 69.1%. This was higher than the study conducted by Pandita et al, (13.8%) as ours was a prospective observational study of suspected fungal sepsis.³ Although *C. albicans* was the most common *Candida* species associated with neonatal fungal sepsis in the past, the epidemiological trend has changed quite a lot in the last decade.⁴ Many studies done in the United States and the UK have revealed non-*albicans* *Candida* species as the more common causative organism.⁵

Our study revealed that non-*albicans* *Candida* also cause invasive candidiasis in the neonate. Earlier almost all the *Candida* species were susceptible to fluconazole. But recently few *Candida* species found to be resistant to fluconazole. In our study *Candida ciferrii* was such species which is only sensitive to flucytosine. The reason behind fluconazole resistance may be its widespread use as a prophylactic antifungal agent in many NICUs to

prevent fungal infection and empirical use of the drug in suspected fungal sepsis and continuing the drug even when a culture shows a bacterial growth. Study done by Magobo et al had similar finding as us that many *Candida* species are presently resistant to the drug fluconazole.⁶ Different risk factors responsible for fungal sepsis were also observed.

Prolonged hospital stay, prolong use of antibiotics, multiple antibiotic use, lack of enteral feedings, complicated gastrointestinal disease, umbilical catheterization, use of steroids, use of H₂ blockers, trauma, thermal instability, frequent apnea, lethargy, convulsions, GI symptoms, respiratory distress, hypoglycemia, hypotension, renal failure were found important risk factors in our study where in different studies found low birth weight, prematurity, use of broad spectrum antibiotics, mechanical ventilation and prolonged hospital stay as important risk factors associated with neonatal candidiasis.^{3,7,9,1}

Tasneem et al also found thrombocytopenia, feed intolerance, increased requirement for ventilator support, temperature instability, apnea were significant clinical parameters which were also more in culture positive group in our study.⁷ Thrombocytopenia can be specific marker of fungal sepsis. But in the study, there was no significant difference between culture positive and no

growth of suspected fungal sepsis comparison done between suspected fungal sepsis. But Yunus et al, found a higher rate of thrombocytopenia.⁸

CONCLUSION

Candida is the most prevalent fungus in NICU. *Candida ciferrii* is an emerging fungus which is resistant to classical antifungal agents. There is no statistically significant difference in between culture positive and no growth group in terms of risk factors and laboratory findings except temperature instability.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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