ORIGINAL ARTICLE

Fungal Sepsis in a Tertiary Neonatal Intensive Care Unit: A Cross-sectional Study

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Abstract

Aim and 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 Indian population is scarce. 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.

Materials and methods: This is a retrospective observational study conducted in the NICU of a pediatric tertiary care hospital in Kolkata from January 2018 to December 2020. All the neonates who had a blood culture positive for *Candida* were included in the study. The type of organisms and susceptibility pattern to antifungal agents were noted. The clinical details like the age and sex of the neonate, gestational age at delivery, birth weight, and other predisposing risk factors like intravascular devices, mechanical ventilation, parenteral nutrition, and the laboratory parameters were noted.

Results: Seventy-nine neonates whose blood culture was positive for *Candida* species were included in the study. Out of them, 65% were preterm ($n = 52$) and 67% were low birth weight (LBW). The chief presenting feature of the neonates was abdominal distension (39%), lethargy, refusal to feed (34%), respiratory distress (36%), convulsion (20%), and low-grade fever (5%). Sixty-one percent of the neonates required mechanical ventilation. Seventy-six percent ($n = 60$) of the babies were receiving parenteral nutrition with either peripheral or central line on the day blood culture was sent. Sixty-seven percent ($n = 53$) of the patients were diagnosed with fungal sepsis based on first blood culture on the day of admission (group I), whereas 33% ($n = 26$) were diagnosed after a few days of admission to NICU (group II). All the babies in group I were outborn and the average age of referral was day 7. In group II, 61.5% ($n = 16$) were outborn and 38.5% ($n = 10$) were inborn and the average age of positive fungal culture was day 12. Among the isolates, 43% were *Candida pelliculosa*, 31% were *Candida parapsilosis*, 8% were *Candida famata*, 7% were *Candida tropicalis*, 2.9% were *Candida krusei*, 5.7% *Candida guilliermondii*, and only 2.3% were *Candida albicans*. As per the culture sensitivity report, 13% ($n = 10$) of the *Candida* species were resistant to antifungal agent fluconazole but 100% were sensitive to voriconazole; 11% ($n = 9$) resistant to amphotericin B; 2.5% ($n = 2$) were intermediate sensitive, and 5% ($n = 4$) resistant to both caspofungin and micafungin. The general mortality rate was 32.9% ($n = 26$). The babies in group I had a higher mortality rate (37.7%) compared with the babies in group II (23%). Infection with *C. tropicalis* has the highest mortality (42.3%), followed by *C. parapsilosis* (30.7%) and *C. pelliculosa* (27%).

Interpretation: Our study revealed that fungal infection in neonates is mostly due to non-*albicans Candida* species (97.3%), *C. pelliculosa* was found to be the commonest organism accounting for 43% of infection. Infection with *C. tropicalis* was associated with maximum mortality. Thirteen percent of the *Candida* species were resistant to the drug fluconazole, 11% were resistant to amphotericin B, 5% were resistant to caspofungin and micafungin, whereas all of the organisms were sensitive to voriconazole. Preterm, LBW, need for mechanical ventilation, parenteral nutrition, and broad-spectrum antibiotics play a significant role in fungal sepsis-related morbidity and mortality.

Keywords: Antifungal resistance, *Candida albicans*, *Candida* non-*albicans*, Fungal sepsis, Neonatal, Risk factors.

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Introduction

Sepsis is one of the major causes of neonatal mortality globally, with India having the highest incidence rate of neonatal sepsis. Annually, >1 million neonates succumb to sepsis in the world. Globally, of the 3 million annual neonatal sepsis cases (2,202/100,000 live births), India has the highest incidence of clinical sepsis (17,000/100,000 live births).[1] The case fertility rate of sepsis among neonates ranges between 25% and 65% in India. Fungal infections have emerged as a significant cause of neonatal late-onset sepsis in the last two decades. Although bloodstream infections by bacteria are still more frequent, the frequency of fungal sepsis caused by the *Candida* species is on the rise.[2] There are plenty of literature on the bacteriological profile and the antibiotic sensitivity in neonatal early-onset sepsis as well as late-onset sepsis. But studies on the epidemiology of fungal sepsis in NICU are scarce. In the USA, *Candida* accounts for 8–10% of nosocomial infections. The risk factors associated with the development of candidemia in neonates like prematurity, very low birth weight (LBW), and extremely LBW neonates are increasing in number.[1,3] Advanced neonatal care with a prolonged hospital stay, central venous catheterization, intubation with mechanical ventilation, parenteral nutrition, and abdominal surgeries have increased the incidence of invasive candidiasis.[2] Although *Candida albicans* was the most prevalent species,[4] the incidence of BSI caused by *Candida* non-*albicans* has

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increased in the past decade.[5,6] In India, non-*albicans Candida* species are identified in 30–90% of cases of invasive candidiasis. There are a very limited number of studies published on the epidemiology of fungal sepsis in infants hospitalized in NICUs in the Indian subcontext. This study aims to determine the epidemiological trend of fungal infections, the organisms, and their susceptibility pattern to the different antifungal agents, clinical features, laboratory values, and the contribution of the various risk factors associated with the causation of fungal sepsis in neonates.

Objective

The objective of the study is to determine the epidemiology and clinicopathological features of fungal sepsis in neonates, the organisms involved, the culture sensitivity pattern to the antifungal agents, clinical features, laboratory values, and analysis of the various risk factors involved in the causation of fungal sepsis.

Materials and Methods

This is a retrospective observational study conducted in the NICU of a pediatric tertiary care hospital in Kolkata. The data for this study were taken from NICU records from January 2018 to December 2020. As per the NICU protocol, blood culture is sent to all babies with features of sepsis on the day of admission and also whenever there is deterioration and suspicion of hospital-acquired infection. All the neonates who had a blood culture positive for *Candida* were included in the study. Candidemia was diagnosed based on the *Candida* positivity in the culture report of a blood sample drawn from a peripheral or central vein. The clinical details like the age and sex of the neonate, gestational age at delivery, birth weight, and other predisposing risk factors like intravascular devices, mechanical ventilation, parenteral nutrition, and the laboratory parameters were noted. Blood cultures were done using the Bactec system. Identification of species and antimicrobial sensitivity including MIC were done using standard protocol along with the VITEK2 system. The type of organisms and susceptibility pattern to antifungal agents were noted. The different *Candida* species isolated were labeled as sensitive or resistant based on the species-specific MIC cut-off levels of the antifungal agents. Prematurity was defined as a gestational age <37 weeks. Birth weight <2,500 g was defined as the LBW, VLBW as birth weight of <1,500 g. All these neonates were initially started empirically on antibacterial agents after sending blood samples for culture and subsequently, antifungal drugs were added according to the culture sensitivity. The study was conducted after taking clearance from the institutional ethics committee.

Results

A total of 1,546 blood cultures were sent during the study period. Seventy-nine neonates showing fungal growth in blood culture were included in the study. The presenting features of the neonates were lethargy, refusal to feed (34%), respiratory distress (36%), abdominal distension (39%), convulsion (20%), and low-grade fever (5%). Among the 79 cases, 66% were preterm ($n = 52$) out of these 75% ($n = 39$) were LBW and 25% ($n = 13$) were VLBW. The total number of LBW neonates was 53 (67%). The sex ratio indicates males were more affected with the male:female ratio being 3:1. Most of the neonates (87.3%, $n = 69$) who developed fungal sepsis were outborn. Sixty-one percent ($n = 48$) of the neonates required mechanical ventilation. Seventy-six percent ($n = 60$) were receiving parenteral nutrition by either a peripheral or central venous catheter. All these risk factors are summarized in Table 1 and Figure 1. The cases were divided into two groups based on the day of positive blood culture after admission to NICU. Those neonates, who showed candidemia on day 1 of admission were put into group I and they accounted for 67% ($n = 53$) of the patients. The neonates who developed candidemia a few days after admission in NICU were put into group II and they accounted for 33% ($n = 26$). All the babies in group I were outborn and the average age of referral to our hospital was day 7. All the babies in group I were receiving broad-spectrum antibiotic combination therapy with carbapenem as one of the components. In group II, 61.5% were outborn and 38.5% were inborn and the average age of positive fungal culture was day 12. Most of the babies (84.6%) in this group were receiving aminoglycoside and cefotaxime combination therapy. The routine blood investigations showed leukocytosis in 22.2% (average 28,310/mm^3) and leukopenia in 27.8% (average 2,354/mm^3) of cases. Anemia requiring packed red cells transfusion was present in 50.3% (average hemoglobin–7.1 g/dL). 44.4% presented with thrombocytopenia requiring platelet transfusion (average platelet count–27,415/mm^3). CRP, a potent sepsis marker was increased in 68.6% of the neonates (normal value of CRP—<5, mean CRP level 42.8). Table 2 summarizes the basic blood count values. CSF study revealed meningitis in 13% of cases ($n = 10$) but CSF culture

Table 1: The prevalence of risk factors for fungal sepsis

Risk factor	*Percentage*
Preterm	66
Low birth weight	67
Male newborn	75
Outborn patient	87.3
Mechanical ventilation	61
Broad-spectrum antibiotics	100
Parenteral nutrition	76

Table 2: Mean value of basic blood counts

Parameter	*Mean value (per mm^3)*	*Percentage of patients*
Leukocytosis	28,310	22.2
Leukopenia	2,354	27.8
Anemia	7.1	50.3
Thrombocytopenia	27,415	44.4
CRP (cut-off <5)	42.8	68.6

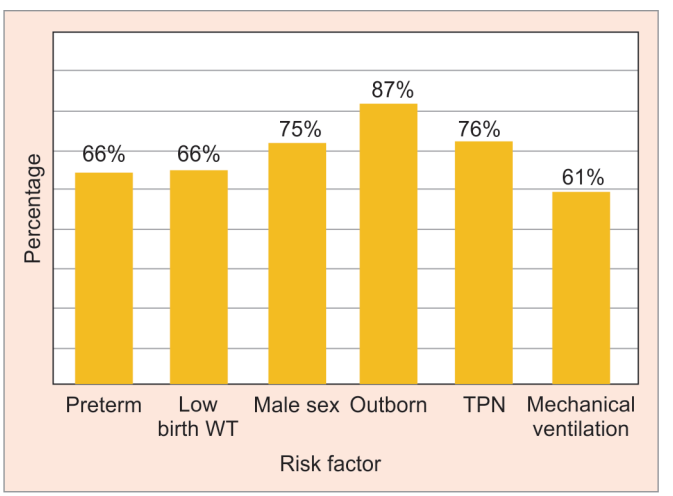


Fig. 1: Percentage of risk factors associated with neonatal fungal sepsis

was sterile in all the 10 neonates. Urine culture was negative in all 79 cases. Among the isolates, 43% (*n* = 34) were *Candida pelliculosa*, 31% (*n* = 25) were *Candida parapsilosis*, 8% (*n* = 7) were *Candida famata*, 7% (*n* = 5) were *Candida tropicalis*, 2.9% (*n* = 2) were *Candida krusei*, 5.7% (*n* = 4) *Candida guilliermondii*, and 2.3% (*n* = 2) were *C. albicans*. Figure 2 summarizes the percentage of each of the organism isolated. As per the culture sensitivity report, 87% of the *Candida* species were sensitive to antifungal agent fluconazole whereas 13% (*n* = 10) were resistant; 100% were sensitive to voriconazole; 89% sensitive to amphotericin B, whereas 11% (*n* = 9) resistant to the same; 93% were sensitive, 2.5% (*n* = 2) were intermediate sensitive, and 5% (*n* = 4) resistant to caspofungin and micafungin. Figure 3 summarizes the sensitivity percentage of the various antifungal agents. Table 3 summarizes the antifungal resistance of various species of *Candida*. The general mortality rate was 32.9% (*n* = 26). The babies belonging to group I had a mortality rate of 37.7% (*n* = 20) and the babies belonging to group II had a mortality rate of 23% (*n* = 6). Flowchart 1 summarizes the mortality rate of outborn and inborn neonates. The organism specific mortality percentage was—*C. tropicalis* (42.3%; *n* = 11), *C. parapsilosis* (30.7%; *n* = 8), and *C. pelliculosa* (27%; *n* = 7). None of the babies showed signs of disseminated infection like endocarditis, renal or visceral abscess, or endophthalmitis.

Discussion

Fungal sepsis contributes to a substantial number of cases of neonatal sepsis. Although *C. albicans* was the most common *Candida* species[4] associated with neonatal fungal sepsis in the past, the epidemiological trend has changed quite a lot in the last decade.[3] Many studies done in the United States and the UK have revealed non-*albicans Candida* species as the more common causative organism.[5–7] Even in India, non-*albicans* species are identified in 30–90% of cases of invasive candidiasis. Our study revealed that non-*albicans Candida* accounts for 97.7% of cases of invasive candidiasis in the neonate. In our study, *C. pelliculosa* was the most common organism causing fungal sepsis followed by *C. parapsilosis*, whereas *C. tropicalis* was responsible for maximum morbidity and mortality. These findings are inconsistent with other studies.[8–11]

Earlier almost all the *Candida* species were susceptible to fluconazole. 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 has increased fluconazole resistance. Many studies, similar to us have shown that many *Candida* species are presently resistant to the drug fluconazole.[12,13] In our study, even amphotericin B resistance was high (11.3%) and echinocandin resistance appears to be an emerging problem especially with *C. guilliermondii* and *C. tropicalis* isolates. However, in our study, all of the organisms were sensitive to voriconazole.

The study reveals outborn neonates have a higher risk of acquiring fungal sepsis due to the use of the broadest spectrum of antibiotics and the result is supported by a recent study done in North India.[14] The study also showed that group I had a significantly higher mortality rate than group II. It was also noted that group I neonates, had an early acquisition of candidemia than group II.

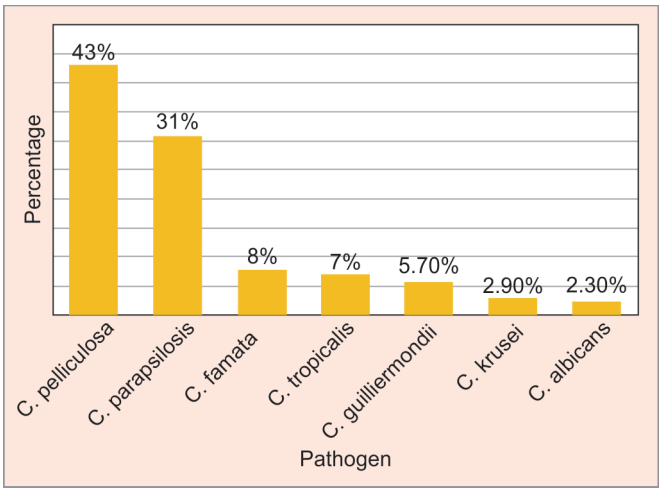


Fig. 2: Percentage of different isolates of *Candida* species

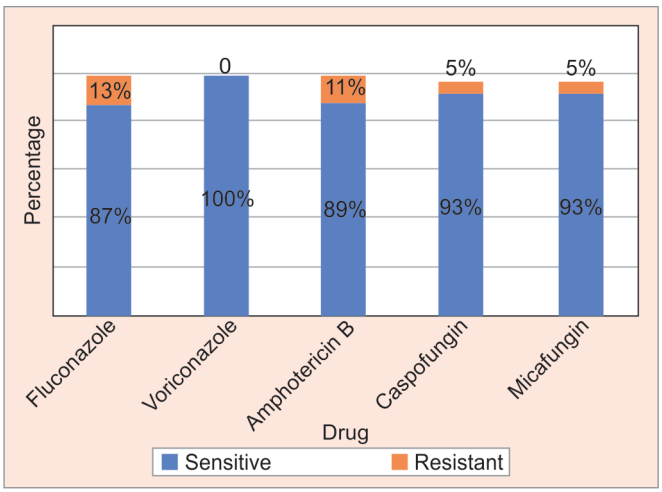
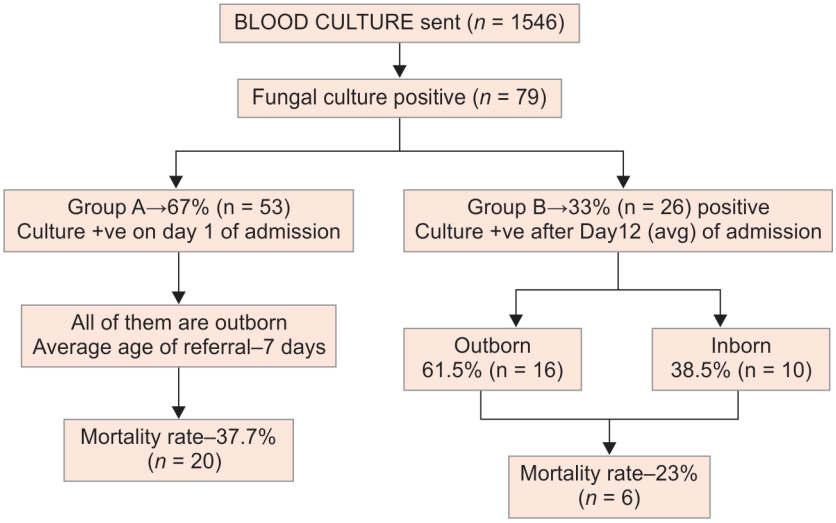


Fig. 3: Sensitivity percentage of different antifungal agents

Table 3: Species-specific antifungal resistance

Organism	*Resistance to fluconazole*	*Resistance to voriconazole*	*Resistance to amphotericin B*	*Resistance to caspofungin*	*Resistance to micafungin*
C. pelliculosa	12%	0	12%	0	0
C. parapsilosis	8%	0	8%	0	0
C. tropicalis	40%	0	20%	20%	0
C. famata	0	0	0	Intermediate sensitive-28%	Intermediate sensitive-28%
C. guilliermondii	25%	0	25%	50%	50%
C. krusei	50%	0	0	0	0
C. albicans	0	0	0	0	0

Flowchart 1: Distribution of outborn and inborn neonates and their mortality percentage



The difference may be due to the fact that they were receiving a relatively broader spectrum and multiple antibiotics like a combination of meropenem, colistin or meropenem, vancomycin, and sometimes irrational combination like meropenem, piperacillin tazobactam, or meropenem along with cefoperazone–sulbactam. In contrast, neonates in group II received a rational broad-spectrum antimicrobial combination of cefotaxime and amikacin as an empirical therapy and they were either escalated or de-escalated according to the blood culture report. This signifies that the use of a broader spectrum and irrational combination of antibiotics is a risk factor in fungal sepsis-related mortality.[15] Thus, there is a need for a stronger infection control strategy, rational use of antimicrobials, and implementation of quality control measures in the NICUs all over the country.[15,16] However, neonates referred from other hospitals were typically very sick and thus it is difficult to determine the proportion of death directly attributable to *Candida* infection.

Low birth weight and VLBW neonates always remain at higher risk of fungal sepsis because of prolonged hospital stay, higher rate of intubation and mechanical ventilation, and administration of parental nutrition.[17–19]

Conclusion

In this study, we are reporting the spectrum of fungal sepsis in the NICU of tertiary care set up in eastern India. We hereby report a high burden of neonatal fungal sepsis due to non-*albicans Candida* species (97.7%) as well as an alarming rate of antifungal resistance to fluconazole (13%) and change in the trend of the causative organisms and their antimicrobial sensitivity pattern. More studies are required to explore fungal sepsis and its contribution to neonatal morbidity and mortality.

References

1. Pana ZD, Roilides E, Warris A, et al. Epidemiology of invasive fungal disease in children. J Pediatric Infect Dis Soc 2017;6(Suppl 1):S3–S11. DOI: 10.1093/jpids/pix046
2. Ballot DE, Bosman N, Nana T, et al. Background changing patterns of neonatal fungal sepsis in a developing country. J Trop Peditr 2013;59(6):460–464. DOI: 10.1093/tropej/fmt053
3. Zaoutis TE, Prasad PA, Localio AR, et al. Risk factors and predictors for candidemia in pediatric intensive care unit patients: implications for prevention. Clin Infect Dis 2010;51(5):38–45. DOI: 10.1086/655698
4. Oeser C, Lamgni T, Heath PT, et al. The epidemiology of neonatal and paediatric candidemia in England and Wales, 2000–2009. Pediatr Infect Dis J 2013;32(1):23–26. DOI: 10.1097/INF.0b013e318275612e
5. Juyal D, Sharma M, Pal S, et al. Emergence of non-albicans Candida species in neonatal candidemia. N Am J Med Sci 2013;5(9):541–545. DOI: 10.4103/1947-2714.118919
6. Kaur R, Dhakad MS, Goyal R, et al. Emergence of non-albicans Candida species and antifungal resistance in intensive care unit patients. Asian Pacif J Trop Biomed 2016;6(Issue 5):455–460. DOI: 10.1016/j.apjtb.2015.12.019
7. Lausch KR, Schultz Dungu KH, Dungu MT, et al. Pediatric candidemia epidemiology and morbidities A nationwide cohort. Pediat Infect Dis J 2019;38(5):464–469. DOI: 10.1097/INF.0000000000002207
8. da Silva CM, de Carvalho Parahym AMR, Leão MPC, et al. Fungemia by *Candida pelliculosa* in a neonatal intensive care unit: a possible clonal origin. Mycopathologia 2013;175(1–2):175–179. DOI: 10.1007/s11046-012-9605-0
9. Lin H-C, Lin H-Y, Su B-H, et al. Reporting an outbreak of *Candida pelliculosa* fungemia in a neonatal intensive care unit. J Microbiol Immunol Infect 2013;46(6):456–462. DOI: 10.1016/j.jmii.2012.07.013
10. Ishiwada N, Kitajima H, Morioka I, et al. Nationwide survey of neonatal invasive fungal infection in Japan. Med Mycol 2018;56(Issue 6):679–686. DOI: 10.1093/mmy/myx096
11. Weinberger M, Leibovici L, Perez S, et al. Characteristics of candidemia with *Candida albicans* compared with non-albicans Candida species and predictors of mortality. J Hospital Infect 2005;61(2):146–154. DOI: 10.1016/j.jhin.2005.02.009
12. Orasch C, Mertz D, Garbino J, et al. Flucoazole non-susceptible breakthrough candidemia after prolonged low-dose prophylaxix: a prospective FUNGINOS study. J Infect 2018;76(5):489–495. DOI: 10.1016/j.jinf.2017.12.018
13. Magobo RE, Lockhart SR, Govender NP, et al. Fluconazole – resistant *Candida parapsilosis* strains with a Y132F substitution in the ERG11 gene causing invasive infections in a neonatal unit, South Africa. Mycoses 2020;63(5):471–477. DOI: 10.1111/myc.13070.
14. Jajoo M, Manchanda V, Chaurasia S, et al. Alarming rates of antimicrobial resistance and fungal sepsis in outborn neonates in North India. PLoS ONE 2018;13(6):e0180705. DOI: 10.1371/journal.pone.0180705
15. Laura F-A, Mike S, Adilia W. Management of invasive fungal disease in neonates and children. Pediat Infect Dis J 2019;38(6S):S2–S6. DOI: 10.1097/INF.0000000000002317

16. Cipolla D, Giuffre M, Mammina C, et al. Prevention of nosocomial infections and surveillance of emerging resistances in NICU. J Matern Fetal Neonatal Med 2011;24(sup1):23–26. DOI: 10.3109/14767058.2011.607567
17. Zhang X, Ru XF, Wang Y, et al. Clinical characteristics of neonatal fungal sepsis in neonatal intensive care unit. J Pek Univers (Health Sci) 2017;49(5):789–793.
18. Oeser C, Vergnano S, Naidoo R, et al. Neonatal invasive fungal infection in England 2004–2010. Orig Article Mycol 2014;20(9): 936–941. DOI: 10.1111/1469-0691.12578
19. Garland JS, Uhing MR. Strategies to prevent bacterial and fungal infection in the neonatal intensive care unit. Clin Perinatol 2009;36(1):1–13. DOI: 10.1016/j.clp.2008.09.005