Original Article

DOI: 10.7860/IJNMR/2023/57554.2372

Paediatrics Section

Neonatal Candidiasis: Clinical Spectrum and Epidemiology at a Tertiary Care Centre, Bhopal, India

MINHAJUDDIN AHMED[1], NITESH UPADHYAY[2], MOHAMMED IQBAL ANSARI[3], MANAL ASHRAF ALI[4]

ABSTRACT

Introduction: Neonatal candidiasis is one of the leading cause of sepsis amongst newborns admitted to newborn care unit, especially premature and Low Birth Weight (LBW) babies. It is one of the significant contributors to neonatal morbidity and mortality.

Aim: To describe the clinical spectrum and epidemiology of fungal sepsis in Neonatal Intensive Care Unit (NICU) at a tertiary care level.

Materials and Methods: A longitudinal study was conducted from January 2018 to December 2019 in NICU of Chirayu Medical College and Hospital, a tertiary level hospital in Bhopal, Central India. All neonates, who had positive fungal blood culture were included in the study, their demographic data was analysed (age, birth weight, predisposing factors etc.,), maternal history, their response to the antifungal treatment was documented and complications were noted. Statistical analysis was done using the Chi-square test with the help of Statistical Package for Social Sciences (SPSS) software version 2.0.

Results: A total of 409 neonates admitted in the NICU during the study period, were suspected clinically to have sepsis and their blood culture was done, of which 110 samples were culture positive. Amongst the 110 neonates, 41(37.2%) were positive for fungal infection {29 showed *Candida albicans*, 12 showed Non Albicans Candida (NAC)}. Total 25 neonates were preterm (60.97%). The mean age of admission was 3.02 days, 51.2% (21/41) of the neonates had a history of respiratory distress and related symptoms at birth. There was no significant maternal history. Among various risk factors only central line and invasive ventilation had significant association (p-value <0.05) with the poor outcome of diseases in neonates. Urine for candidial hyphae was positive in 12 out of 41 cases (29.27%). Incidence of candidal meningitis was seen in four neonates (13.33%). Thrombocytopenia was the most common laboratory finding amongst these cases (32/41). Among the different regimens used the combination regimen of Lipid based amphotericin B and voriconazole was associated with a better survival.

Conclusion: Candida sepsis was found to be the most common cause of septicaemia in the NICU. LBW and preterm babies are especially at greater risk of candida sepsis. Candida albicans still continues to be a dominant aetiology for fungal sepsis, as compared to non candida species.

Keywords: Antifungal regimen, Fungal septicaemia, Neonates

INTRODUCTION

Newborn babies are prone to systemic infections, either bacterial or fungal. This is more common in premature babies which further increases morbidity and rate of mortality. Fungal colonisation occurs in 10% of sick neonates within first week and 90% in 2-3 week of stay in hospital [1]. The incidence of systemic infections caused by candida accounts for about 9-13% of bloodstream infections in neonates [2]. Candidaemia in hospital NICU has been a recurring health problem. Use of multiple antibiotics, steroids, central catheters and ventilation alter ecology and facilitate colonisation of Candida [3].

Various studies have quoted the incidence of candida infections from 5-16.1% of LBW babies and even more in Very Low Birth Weight (VLBW) ranging from 1.6-9% and Extremely Low Birth Weight (ELBW) in 10-20%. [4]. The mortality rate due to Candida sepsis has been reported upto 44% [5]. All Candida species can cause disease in neonates, but *Candida albicans* remains the most frequently isolated yeast species followed by C *parapsilosis*, although some studies have reported *C tropicalis* also as a cause recently [6,7]. Recent reports suggested that, there has been a change in the distribution of candida species causing candidaemia from *Candida albicans* to candida non *albicans* species [5]. The selection of less susceptible species due to frequent use of antifungal agents like fluconazole [8]. The study was undertaken to describe the spectrum and epidemiology of fungal sepsis in NICU.

MATERIALS AND METHODS

This longitudinal study was conducted in the NICU amongst the neonates who were documented to have fungal sepsis by blood culture, and their response to various antifungal drugs were observed and analysed. This study was conducted from January 2018 to December 2019, after getting approval from the Institutional Ethics Committee (IEC/18/12) in the Paediatric Department of Chirayu Medical College and Hospital, a tertiary level hospital in Bhopal, Central India.

Inclusion criteria: All neonates having sepsis on the basis of clinical presentation and confirmed by fungal growth on blood culture and were admitted to the NICU during the period of study were included in the study.

Exclusion criteria: Cases in which blood culture was negative inspite of clinical suspicion and those found to have candida colonisation only were excluded from the study.

Study Procedure

Baseline investigations like Complete Blood Count (CBC), C-Reactive Protein (CRP), blood culture from peripheral vein and urine microscopic examination for fungal hyphae were performed for all neonates enrolled in the study. Those cases which were found to be culture positive were further screened for Central Nervous System (CNS), renal, cardiac, ophthalmic and hepatic dissemination. Appropriate

samples were taken in cases requiring invasive procedures e.g., tip of central venous catheters, endotracheal tubes in cases of invasive ventilation. Culture media used for plating was Bactec culture media which is appropriate for both bacterial as well as candida isolation. The candida species were further classified into *albicans* and Non albicans Candida (NAC) species after plating them on chrome agar culture plates. Both *Candida Albicans* as well as NAC species have distinct morphological colonies on chrome agar. *C.albicans* species characteristically shows blue colonies while NAC species have ash white coloured colonies on chrome agar plate.

Those neonates found to be positive on blood culture were treated as per the discretion of the consultant Paediatrician and the patient was followed clinically and via appropriate laboratory investigations. Treatment with antifungals were initiated as per institutional antibiotic policy. Prophylaxis therapy was not given. Empirical therapy was started with Intravenous (i.v.) Fluconazole in cases assumed to be at a higher risk of Candida sepsis (i.e., ELBW, longer duration of NICU stay, already on broad spectrum antibiotics). The average age of neonate on which antifungal was started was day 10 (range 7-20 days). Antifungal drugs used were fluconazole, amphotericin B, voriconazole independently and combination of two, if needed. Poor outcome was labeled in case of morbid illness.

STATISTICAL ANALYSIS

Data was analysed using SPSS software version 2.0. Test of significance used was Chi-square test and its value was calculated with 95% Confidence Interval (CI).

RESULTS

A total 633 neonates were admitted in the newborn care unit during the study period, of which blood culture was done in 409 because of clinical suspicion of sepsis. Majority of the admissions belonged to ≥2.5 kg category 219 (34.59%), there were 315 (49.76%) term babies, followed by preterm babies 209 (33.01%) and late preterm babies 109 (17.21%). Out of the 409 blood cultures, positive blood culture was found in 110 samples (26.89%) [Table/Fig-1]. The mean age of admission was 3.02 days, 51.2% (21/41) of the neonates had a history of respiratory distress and related symptoms at birth.

Organism	Number
Candida species	41
Bacterial	69

[Table/Fig-1]: Distribution of the pathogenic organisms (n=110).

Thus, fungal infection as represented by candida sp. was responsible for 41 (37.27%) of sepsis cases, followed by bacteraemia. Out of these 41 cases, culture-positive candidal sepsis cases, 29 (70.73%) were due to C.*albicans* species and 12 (12.27%) were NAC [Table/Fig-2].

Urine microscopy for candida pseudohyphae was done in all cases, of which 12 were positive (29.27% cases). Lumbar puncture was done in 30/41 cases, of which 4 were positive (13.33% cases). A 2D echocardiography was performed in 32/41 cases out of which one revealed fungal vegetation (3.12%). Necrotising enterocolitis was seen in 9/41 cases positive for candida sepsis (21.95% cases). There was no evidence of involvement of any other organ systems represented by liver abscess, splenic abscess, endophthalmitis, septic arthritis, renal abscess, cutaneous abscess or focal bowel perforation. A mortality rate of 29.26% was seen inspite of all care and support; 12 of the 41 neonates succumbed to sepsis. The average age of death was at 21 days of life (10 days to 32 days). Incidence of candidal meningitis was seen in four neonates (13.33%).

Risk factor	Variables	No. of neonates (N=41) (%)
Age	Preterm (<36 weeks)	25 (60.97%)
	Late preterm (>36 weeks)	5 (12.20%)
	Full term	11 (26.83%)
Gender	Male	30 (73.17%)
	Female	11 (26.83%)
Place of birth	Inborn	17 (41.46%)
	Outborn	24 (58.54%)
Mode of delivery	Vaginal	26 (63.41%)
	Caesarean	15 (36.59%)
Sepsis	Early onset (<3 days of birth)	26 (63.41%)
	Late onset (>3 days of birth)	15 (36.59%)
Birth weight	<1000 g	4 (9.75%)
	1000-1499 g	21 (51.22%)
	1500-2499 g	11 (26.83%)
	>2500 g	05 (12.2%)
Candida species	*C. albicans*	29 (70.73%)
	C. parapsilosis	4 (09.75%)
	C. krusei	5 (12.20%)
	C. tropicalis	3 (07.32%)
Outcome	Survived	29 (70.73%)
	Died	12 (29.27%)

[Table/Fig-2]: Demographic data of the candida positive blood culture samples.

In the present study, among various risk factors only central line and invasive ventilation had significant association (p-value <0.05) with the poor outcome of diseases in neonates. Other risk factors did not show any significant association with poor outcome among neonates [Table/Fig-3].

Risk factors	Present	Absent	In cases with poor outcome	Chi-square value, p-value
Previous NICU stay (among 24 outborn)	18	6	9	χ^2=1.4815, p-value=0.223
Previous antibiotic usage (among 24 outborn)	18	6	11	χ^2=2.74, p-value=0.097
Enteral feeding after 48 hour	34	7	10	χ^2=0.08, p-value=0.77
Central lines	9	32	4	χ^2=7.28, p-value=0.006
Invasive ventilation	13	28	5	χ^2=6.133, p-value=0.013
Hospital acquired septicaemia	26	15	10	χ^2=1.56, p-value=0.21
Platelet count ≤50000/μL	18	23	6	χ^2=1.47, p-value=0.22
CRP (>50 mg/dL)	28	13	7	χ^2=1.18, p-value=0.27
Candida albicans	29	12	10	χ^2=0.54, p-value=0.45
Low Birth Weight (LBW)	36	05	10	χ^2=0.13, p-value=0.71

[Table/Fig-3]: Association of various risk factors with disease outcome. *Poor outcome was labelled in patients who had morbid outcome. p-value <0.05 considered significant

Among the various treatment options available, this study found that the combination regimen of lipid based amphotericin B and voriconazole was associated with a better survival [Table/Fig-4].

Drugs	Number of cases	Number of cases survived	p-value
Fluconazole	9	6	0.70
Amphotericin B	16	10	0.30
Fluconazole+Amphotericin B	2	2	-
Amphotericin B+Voriconazole	11	9	0.30
Voriconazole	1	0	-
Fluconazole+Voriconazole	2	2	-

[Table/Fig-4]: Comparison of various treatment options on the basis of their effect on outcome.

Laboratory Features

Thrombocytopenia was the most common laboratory finding found among the cases of candida sepsis which was present in 32/41 (78.05%). Leucopenia was noted in 4 out of 41 cases (9.75%) and only one patient had leucocytosis (WBC count more than 30,000/cu mm). CRP was positive in 28 out of 41 cases (68.29%). Urine for candidal hyphae was positive in 12 out of 41 cases (29.27%). Mean creatinine value amongst the cases was 1.50 mg/dL with a SD of 0.936 [Table/Fig-5]. All the laboratory parameters were deranged in patients with poor outcome.

Laboratory parameter	Range in the study population	Mean±SD
Platelet count (per cu mm)	10,000-2,60,000	89,000±71,127
Total leucocyte count (per cu mm)	1900-38500	10,651±7346
Creatinine (mg/dL)	0.9-2.50	1.50±0.936

[Table/Fig-5]: Laboratory parameters of all neonates with candida sepsis (n=41).

DISCUSSION

Fungal infections are the emerging threat to the neonates in the tertiary care centres. Candida has been found to be the most common fungal pathogen especially in immunocompromised hosts such as neonates. Various studies conducted in western countries have shown candida sepsis as a major cause of neonatal morbidity and mortality. Improvements in perinatal care in last few decades in India lead to increase in incidence of candidal sepsis.

In the present study, Candida sepsis was found to be the most common cause of sepsis among neonates 41 (37.27%). As per the data collected by Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) national research network and published in 2002, Candida accounted for third most common cause (12.2% of cases) of late onset sepsis and mortality rates as high as 32% for candida sepsis and 36% for candida meningitis among late onset sepsis [9] though few studies have recently reported a decreasing trend, probably due to the use of prophylactic drugs [10]. A study done in Lucknow, India reported 13.6% cases of septicaemia due to candida in term newborns [11]. The incidence of *C. albicans species* noted in the present study was 6.48% as compared to 9-13% incidence reported by various studies amongst Indian and western population [2,12]. In the present study, amongst the patient with candida septicaemia 9.75% were ELBW, 51.22% were VLBW, 26.83% were LBW and 12.2% were of weight more than 2500 grams. Several studies have reported the incidence among VLBW infants from 2-4% and among ELBW infants from 10-16% [8,13-15]. LBW neonates accounted for 87.81% of total candida sepsis cases which was similar to the study by Agrawal J et al., (73.3%), Narain S (90%) and Noyola DE et al., 83.7% [11,13,16]. Similarly, premature neonates contributed 73.17% cases of candida sepsis which was similar to 89.8% reported by Gupta N et al., [17] and greater than 38.6% reported by Agrawal J et al., [11].

Most common candida species isolated was *Candida albicans* which was responsible for 70.73% of cases. Similarly isolation of candida species (albicans) has been reported by various authors from the western countries with a range from 13.6% to 42.8% [7,12,13,16,18-22]. Similarly, the incidence of candidal meningitis was 13.33% among neonates with Candida sepsis which was similar to 14.7% incidence reported by Noyola DE et al., [16]. In yet another prospective study the incidence of meningitis was 8% among neonates with candida sepsis; however, only 51% infants in his study had lumbar puncture as a part of sepsis evaluation [23]. Among the organs involved in candida sepsis, it was found that renal involvement was there in 29.27% of cases evidenced by demonstration candidal pseudohyphae in fresh urine samples. Renal involvement in candida sepsis was noted in 20% cases as reported by Baley J et al., [19], 26.6% as reported by Noyola DE et al., [16] and a much higher incidence of 49% reported by Benjamin DK Jr [2].

Candidial vegetation was present in only one out of 32 screened by 2D echocardiography the incidence of which has been reported to be around 5-15% [12,16]. Necrotising enterocolitis was seen in 9 out of 41 cases (21.95%) positive for candida sepsis which was lower than 60% (6 out of 10 cases) reported by Baley J et al., [19]. There was no evidence of liver abscess, splenic abscess, endophthalmitis, septic arthritis, renal abscess, cutaneous abscess or focal bowel perforation. High number of cases were found in VLBW and LBW cases. Also, it was found that newborns having birth weight >2.5 kg have a lesser risk of having candida sepsis. It was found that preterm babies born at ≤34 weeks of gestation have greater risk of candida sepsis while full term babies were found to have lesser chances of having candida sepsis.

Amongst the invasive procedures studied, i.e., central line and invasive ventilation, there was a significant association with poor outcome of diseases in neonates. Although there was no statistically significant risk of candida sepsis in those neonates who were ventilated in our newborn care unit (p-value >0.05). Several investigators have emphasised the particular importance of endotracheal intubation as a risk factor for candida sepsis in paediatric patients [23-25]; furthermore Rowen JL et al., demonstrated that endotracheal colonisation in neonates with a LBW was associated with the development of candida sepsis [26]. It was found through these factors were more common amongst newborn with poor outcome, the result were not statistically significant (p-value >0.05). Present study reported that the choice of antifungal used did not affected the outcome, although a combination of amphotericin B with voriconazole was associated with reduced risk of a poor outcome. This was similar to what has been stated in an RCT conducted by Pappas PG et al., [21]. Fluconazole and liposomal amphotericin B were used to some extent by 90% and 69% of respondents, respectively. Amphotericin B was the preferred therapy for candidemia (88%). If a cerebrospinal fluid culture is positive 25% would use amphotericin B alone whereas 62% would add flucytosine. It was observed that 28/41 cases developed candida sepsis inspite of being on fluconazole. Poor outcome in the form of death or discharge against medical advice was noted in 12/41 cases with candida sepsis i.e. 29.27% of the cases. Various western studies have reported mortality rate due to candida to be ranging from 13% to as high as 32% [7,26-28].

Limitation(s)

The limitations of the study were that it was a single centre study with limited number of participants.

CONCLUSION(S)

Candida sepsis was found to be the most common cause of septicaemia in the present study which is an alarming situation because of the increased morbidity and mortality associated with the candida sepsis. Corroborating with various other studies, *Candida albicans* was the most common species responsible but the presence of a significant number of cases due to NAC species also raises concerns as few of them were found to be inherently resistant to certain antifungals and also more virulent.

Various risk factors associated with increased risk of Candida sepsis were LBW, VLBW, prematurity and central line placement which are very common in any NICU, hence appropriate care and strict asepsis precaution are mandatory in order to prevent the development of sepsis. Further study in this area is required in order to find out effective management strategy to reduce the mortality associated with this disease. Especially in a country like India, where due to, substandard obstetric and neonatal care facilities, the risk of neonatal sepsis is very high at the same time the relevant Indian data is substantially lacking.

Acknowledgement

Special thanks to Dr. Manal Ashraf Ali for the help she rendered to prepare this manuscript.

REFERENCES

[1] Ballot DE, Bosman N, Nana T, Ramdin T, Cooper PA. Background changing pattern of fungal sepsis in a developing country. J Trop Pediatr. 2013;59(6):460-64.
[2] Benjamin DK Jr, Stoll BJ, Gantz MG, Walsh MC, Sánchez PJ, Das A, et al. Neonatal candidiasis: Epidemiology, risk factors, and clinical judgment. Pediatrics. 2010;126(4):865-73.
[3] Schellack N, Gous AGS. Amphotericin B in the management of fungal infections in a neonatal intensive care unit: Experiences in a teaching hospital. South Afr J Epidemiol Infect. 2012;27(1):24-29.
[4] Yunus M, Agarwal V, Tomar P, Gupta P, Upadhay A. Epidemiology, clinical spectrum and outcomes of fungal sepsis in neonates in a neonatal intensive care unit: A prospective observational study. Int J Contemp Med Res. 2018;59(1):01-05.
[5] Ariff S. Clinical spectrum and outcome of neonatal candidiasis in a tertiary care hospital in Karachi, Pakistan. J Infect Dev Ctries. 2011;5(3):216-23.
[6] Niranjan HS. An emerging threat of non albicans candida infection in tertiary care neonatal intensive care units. Sch J App Med Sci. 2015;3(7B):2583-85.
[7] Kapila S. Indentification of candida species in neonatal septicaemia. Int J Contemp Pediatr. 2016;3(2):601-05.
[8] Lee J, Kim HS, Shin SH, Choi CW, Kim EK, Choi EH, et al. Efficacy and safety of flucanazole prophylaxis in extremly low birth weight infants: Multicenter pre-post cohort study. BMC Pediatr. 2016;16:67.
[9] Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late onset sepsis in very low birth weight neonates: The experience of the NICHD Neonatal Research Network. Pediatrics. 2002;110:285-91.
[10] Carey AJ, Saiman L, Polin RA. Hospital-acquired infections in NICU: Epidemiology for the new millenium. Clin Perinatol. 2008;(35):223-49.
[11] Agrawal J, Bansal S, Malik GK, Jain A. Trends in neonatal septicemia: Emergence of non albicans candida. Indian Pediatr. 2004;(41):712-15.
[12] Rani R, Mohapatra NP, Mehta G, Randhawa VS. Changing trends of neonatal septicemia in a tertiary North Indian hospital. Ind J Med Micro. 2002;20(1):42-44.
[13] Narain S. Neonatal systemic candidiasis in a tertiary care centre. Ind J Med Microbiol. 2003;21:56-58.
[14] Manzoni P, Ariso R, Mostert M. Prophylactic fluconazole is effective in preventing fungal colonisation and fungal systemic infections in preterm neonates: A single-center, 6 year retrospective cohort study. Pediatrics. 2006;117:e22-32.
[15] Ganesan K, Harigopal H, Neal T. Prophylactic oral Nystatin for preterm babies under 33 weeks' gestation decreases fungal colonisation and invasive fungaemia. Archives diseases Child Fetal Neonatal Ed. 2009;94:F275-78.
[16] Noyola DE, Fernandez M, Moylett EH, Baker CJ. Ophthalmologic, visceral and cardiac involvement in neonates with candidemia. Clin Infect Dis. 2001;32:1018-23.
[17] Gupta N, Mittal N, Sood P, Kumar S, Kaur R, Mathur MD. Candidemia in neonatal intensive care unit. Ind J of Path Micro. 2001;44(1):45-48.
[18] Makhoul IR, Kassis I, Smolkin T, Tamir A, Sujov P. Review of 49 neonates with acquired fungal sepsis: Further characterization. Pediatrics. 2001;107:61-66.
[19] Baley JE, Kliegman RM, Pararoff AA. Disseminated fungal infections in very low-birth-weight infants: Clinical manifestations and epidemiology. Pediatrics. 1984;73:153-57.
[20] Pc Ng. Systemic fungal infection in neonates. Arch Dis Child. 1994;71:130-35.
[21] Pappas PG, Rex JH, Lee J, Hamill RJ, Larsen RA, Powderly W, et al. A prospective observational study of candidemia: Epidemiology, therapy and influences on mortality in hospitalized adult and pediatric patients. Clin Infect Dis. 2003;37:634-43.
[22] Cahan H, Deville JG. Outcomes of neonatal candidiasis: The impact of delayed initiation of antifungal therapy. Int J Pediatr. 2011;2011:813871.
[23] Benjamin DK Jr, Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins RD, et al. Neonatal candidiasis among extremely low birth weight: Risk factors mortality and neuro-developmental outcomes at 18-22 months. Pediatrics. 2006;117(1):84-92.
[24] MacDonald L, Baker C, Chenoweth C. Risk factors for candidemia in a children's hospital. Clin Infect Dis. 1998;26:642-45.
[25] Saiman L, Ludington E, Pfaller M. Risk factors for candidemia in neonatal intensive care unit patients. Pediatr Infect Dis J. 2000;19:319-24.
[26] Rowen JL, Rench MA, Kozinetz CA, Adams JM, Baker CJ. Endotracheal colonisation with Candida enhances risk of systemic candidiasis in very low birth weight neonates. Pediatrics. 1994;124:789-94.
[27] Fridkin SK. The changing face of fungal infections in health care settings. Clin Infect Dis. 2005;41:1455-60.
[28] Zaoutis TE, Heydon K, Localio R, Walsh TJ, Feudtner C. Outcomes attributable to neonatal candidiasis. Clin Infect Dis. 2007;44(9):1187-93.

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Paediatrics, Chirayu Medical College, Bhopal, Madhya Pradesh, India.
2. Associate Professor, Department of Paediatrics, Chirayu Medical College, Bhopal, Madhya Pradesh, India.
3. Assistant Professor, Department of Paediatrics, Chirayu Medical College and Hospital, Bhaisakhedi, Near Bairagarh, Bhopal, India.
4. Professor, Department of Pathology, Chirayu Medical College and Hospital, Bhaisakhedi, Near Bairagarh, Bhopal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Minhajuddin Ahmed,
Associate Professor, Department of Paediatrics, Chirayu Medical College, Bairagarh, Bhopal, Madhya Pradesh, India.
E-mail: minzahmad@yandex.ru

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 06, 2022
- Manual Googling: Feb 13, 2022
- iThenticate Software: Feb 16, 2022 (9%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **May 04, 2022**
Date of Peer Review: **Jul 07, 2022**
Date of Acceptance: **Feb 17, 2023**
Date of Publishing: **Mar 31, 2023**