

Original Research Article

Non albicans Candidemia: an emerging menace in neonatal intensive care unit

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Received: 08 December 2017

Accepted: 08 January 2018

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ABSTRACT

Background: Candidemia has become an increasingly major problem in neonatal intensive care unit (NICU) which is associated with high mortality and morbidity. In this study we evaluated the epidemiology of Candidemia in neonates who were admitted to NICU and their in vitro susceptibility to commonly used antifungal drugs.

Methods: This was a retrospective study of candidemia in NICU from October 2014 to September 2017. The isolates were identified as per standard mycological techniques and antifungal susceptibility was determined by disk diffusion method.

Results: Out of 563 blood culture analyzed, 54(9.59%) culture yielded Candida in their blood. The non albicans Candida (NAC) species were the predominant organism for candidemia in neonates, accounting for 35 (64.81%) and the remaining 19 (35.18%) isolates were of *C. albicans*. Among the NAC species, the maximum isolates were of *C. krusei* (31.48%) followed by *C. glabrata* (22.22%). Non albican Candida were more resistant to azole group of antifungal, especially commonly used antifungal like fluconazole (51.43%). Among NAC species, *C. glabrata* was most resistant and *C. tropicalis* was least resistant organism. Prematurity <34 weeks, very low birth weight (<1500gm), prolonged use of broad spectrum antibiotic therapy, prolonged use of central venous catheter, mechanical ventilation, parenteral nutrition, prolonged NICU stays and concomitant bacterial sepsis were significantly associated with Candida infection in blood stream. NAC species were also associated with high mortality rate.

Conclusions: Increased incidences of candidemia along with emergence of NAC species have become an important health care issue. Therefore, knowledge of local epidemiological data on candidemia is essential which will guide on therapeutic decision making.

Keywords: Antifungal, Candidemia, Neonates, Non albican candida

INTRODUCTION

Candida infection is the third most common cause of late onset sepsis in NICU patients and accounts for 9-13% of blood stream infection (BSI) in neonates.¹ Mortality associated with candidemia in newborn was as high as 20-34%.^{1,2} Any amount of sepsis introduced during NICU stay would essentially increase the hospital days and cause socio economic burden on the parents. Early antifungal therapy can improve intact survival. Hence, it

is very important for us to recognize these babies early, who are at risk of developing candidemia. Neonates are more vulnerable to develop candidemia due to their critical underlying conditions, immature immune system and invasive procedure during the stay in NICU. These neonates in would have one or two umbilical catheter or central line for prolonged period which helps in breaching the protective barrier of skin flora. Thus, the skin colonizer can gain entry into the circulation and establish fungaemia gradually. Other predisposing factors

like prematurity, very low birth weight, prolonged mechanical ventilation, total parenteral nutrition, use of broad spectrum antibiotic therapy and prolonged hospitalization can further worsen the existing risk for candidemia.^{3,4} Although *Candida albicans* has long been the most common cause of *Candida* infections isolated, NAC species such as *C. glabrata*, *C. krusei*, *C. tropicalis*, *C. parapsilosis* and *C. guilliermondii* have emerged as predominant isolates from blood streams of neonates in NICU.⁵⁻⁷ It was also associated with higher risk for mortality.^{4,5} Another serious problem associated with NAC is increased resistance to antifungal drugs commonly used in clinical practice.⁶

We are observing an increase in the isolation of NAC species over last few months from our NICU which was also associated with difficulty in treatment, as most of these species are resistant to commonly used antifungal. In view of this, we undertook this study to know the epidemiology of neonatal candidemia including risk factors with special reference to NAC species.

METHODS

The present study was conducted in NICU of tertiary care teaching hospital at Mangalore. All episodes of fungemia that occurred between October 2014 and September 2017 were identified. Patient data were obtained from NICU medical records and hospital infection committee. Approval of the study was obtained by the institution ethical committee.

All hospitalized neonates with culture proven *Candida spp.* infection were included in the study. We retrospectively reviewed demographic data, risk factors, clinical manifestations and outcomes of neonatal candidemia. Choice and duration of antifungal therapy was documented.

Initial culture was sent if infection was suspected at any time after admission to NICU. In addition, surveillance culture was sent for all patients with candidemia one week after starting antifungal therapy.

An episode of candidemia was defined as an isolation of any pathogenic species of *Candida* from at least one blood culture specimen from a patient with signs and symptoms of infection.

Recovery from candidemia was defined as the resolution of all clinical manifestations and negative blood culture within one week of initiating therapy. Failure to respond was defined as the persistence of clinical signs and symptoms or persistent candidemia caused by same *Candida* species after the onset of therapy.⁸

Identification of organism and susceptibility testing

Nearly, 1-3ml of blood was collected from neonates suspected of septicemia from peripheral vein under

aseptic precaution. It was inoculated into pediatric blood culture bottle (BACTEC Peds Plus/F) and introduced into an automated Blood culture system (BACTEC 9050). After the system signaled for positive cultures, samples were subjected to gram stain to confirm the presence of yeast cells. Subcultures were done on Sabouraud dextrose agar and blood agar.

Species identification was done with the help of CHROM agar, germ tube test, sugar fermentation and assimilation tests. Antifungal susceptibility was carried out by disk diffusion method as per Clinical Laboratory Standard Institute (CLSI) guidelines for Amphotericin-B, Fluconazole, Itraconazole and Voriconazole.⁹

Statistical analysis

The data analysis was done by using the SPSS version 17 and MS excel sheet. Relationships between categorical variables were analyzed by using chi-square test. Descriptive data was expressed as number and percentage. The p value of <0.05 was considered statistically significant.

RESULTS

During three year of study period, a total number of 563 blood cultures of the newborns admitted in NICU were included in the final analysis.

Table 1: Demographic characteristic of patients with candidemia.

Characteristics	No. of cases with Candidemia	Percent
Gender		
Male	29	53.70
Female	25	46.30
Gestational age (weeks)		
<28	26	48.14
28-37	20	37.04
>37	8	14.81
Birth weight (gm)		
<1000	24	44.44
1000-1499	21	38.89
1500-2500	7	12.96
>2500	2	3.70
Weight for gestation		
SGA*	10	18.52
AGA*	41	75.93
LGA*	3	5.56
Mode of delivery		
Vaginal	31	57.41
Caesarean	23	42.60
Mural status		
Inborn	38	70.37
Outborn	16	29.63

*SGA- Small for gestational age, AGA- Appropriate for gestational age, LGA- Large for gestational age

Of these, 257 (45.64%) cases of blood culture yielded positive growth and 54 (9.59%) blood culture had grown *Candida* species. The Table 1 shows the baseline characteristics of neonates with culture positive *Candida*.

Table 2: Risk factors for candidemia.

Characteristics	No. of cases with Candidemia	Percent
Prolonged antibiotic therapy (>14 days)	32	59.26
Central venous catheter (>7 days)	36	66.67
Mechanical Ventilation (>5 days)	29	53.70
Prolonged hospitalization (>14 days)	42	77.78
Parenteral nutrition	20	37.03
Abdominal surgery	3	5.56
Candiduria	7	12.96
Concomitant bacterial sepsis	22	40.74
Necrotizing enterocolitis	6	11.11
H2 blocker use	4	7.41
Postnatal steroid use	5	9.26
Maternal genitourinary fungal infection	4	7.41
Gestational diabetes mellitus	6	11.11
Premature rupture of membrane	7	12.96

There was no significant difference between genders, mode of delivery, mural status and weight for gestational age babies ($p>0.05$). Some of the parameter looks apparently high due to more number of neonates were involved in these study groups. However, candidemia was significantly seen in premature neonates especially <28 weeks of gestation and very low birth weight (<1500gm) and extremely low birth weight (<1000gm) babies ($p<0.05$). The mean gestational age of onset of candidemia was 29.1 ± 1.3 weeks and the mean birth weight 1125 ± 423 gm. The risk factors associated with candidemia had shown in Table 2.

Among the risk factors observed, prolonged use of broad spectrum antibiotic therapy, prolonged use of central venous catheter, mechanical ventilation, parenteral nutrition, prolonged NICU stays and concomitant bacterial sepsis were significantly associated with *Candida* infection in blood stream ($p<0.05$). Feed intolerance, abdomen distension, lethargy were prominent clinical symptoms and thrombocytopenia was most common abnormal laboratory finding in neonates with candidemia (Table 3). There was no significant

difference in clinical presentation in infants with *Candida albicans* and NAC infection.

Table 3: Clinical presentations observed in cases of neonatal candidemia.

Clinical features	No. of cases	Percent
Feed intolerance	42	77.78
Abdomen distension	35	64.81
Lethargy	33	61.11
Failure to gain weight	18	33.33
Hypothermia	16	29.63
Apnea	15	27.78
Poor perfusion	10	18.52
Convulsion	6	11.11
Respiratory distress	7	12.96
Thrombocytopenia <100,000/cumm	38	70.37
Leucopenia <4000/cumm	26	48.15
Hypoglycemia	15	27.78
Hyperglycemia	5	9.26

Out of the 54 isolates of various *Candida* species, the non albicans *Candida* species were the predominant organism for candidemia in neonates, accounting for 35 (64.81%) and the remaining 19 (35.18%) isolates were of *C. albicans* (Table 4). Among the NAC species, the maximum isolates were of *C. krusei* (31.48%) followed by *C. glabrata* (22.22%).

Table 4: Distribution of *Candida* species.

<i>Candida</i> Species	Number of isolates (Percent)
<i>Candida albicans</i>	19 (35.18%)
<i>Candida krusei</i>	17 (31.48%)
<i>Candida glabrata</i>	12 (22.22%)
<i>Candida tropicalis</i>	6 (11.11%)
Total	54 (100%)

Candida species were maximally resistant to Itraconazole (55.56%) whereas least resistant to Amphotericin-B (16.67%). Non albicans *Candida* were more resistant to azole group of antifungal, especially commonly used antifungal like fluconazole (51.43%). Among non albicans *Candida*, *C. glabrata* was the most resistant and *C. tropicalis* was least resistant organism. Again Amphotericin-B was better choice for initial treatment of non albicans candidemia.

In all, 37 of the patients (68.51%) survived and 17 (31.48%) died. During the study period the mortality rate of whole NICU was 10.45%. Out of 17 neonates, 2 (11.76%) babies were died due to *C. albicans* who also had concomitant sepsis and multi organ failure. Remaining 15 (88.24%) babies were died due to NAC species, of which *C. glabrata* was most common organism 10 (66.66%), followed by *C. krusei* 5 (33.33%). No deaths were directly attributed to *C. tropicalis* infection. Most of the neonates were treated

successfully with Amphotericin-B or Fluconazole/Voriconazole. Six patients had received liposomal Amphotericin-B due abnormal renal function. Only two neonates with *C. glabrata* and one patient with *C. krusei*

were not responded to above antifungal therapy. However, they were responded to treatment with Caspofungin.

Table 5: Antifungal sensitive pattern among Candida isolates.

Candida species	Antifungal sensitivity (percentage)			
	Amphotericin-B	Fluconazole	Itraconazole	Voriconazole
<i>Candida albicans</i> (n=19)	18 (94.74%)	13 (68.42%)	10 (52.63%)	17 (89.47%)
<i>Candida krusei</i> (n=17)	15 (88.24%)	8 (47.06%)	10 (58.82%)	15 (82.35%)
<i>Candida glabrata</i> (n=12)	6 (50.0%)	5 (41.67%)	4 (33.33%)	5 (41.67%)
<i>Candida tropicalis</i> (n=6)	6 (100%)	4 (66.67%)	4 (66.67%)	4 (66.67%)
Total (n=54)	45 (83.33%)	30 (55.56%)	24 (44.44%)	41 (75.93%)

DISCUSSION

Infection by *Candida* is one of the common causes of blood stream infections among newborn in NICU. Although, *Candida albicans* remains the most common fungal isolate responsible for neonatal candidemia, however recent studies suggest a shift towards non albicans *Candida* species.^{6,7} These NAC species are increasingly resistant to most commonly used azole group of antifungal therapy and also associated with higher mortality. Wide spread use of azole antifungal drugs especially fluconazole may be one of the reasons contributing to the increased isolation rate of NAC species.

In the present study, the non albicans *Candida* species were the predominant organism responsible for candidemia in neonates, accounting for 35 (64.81%) and the remaining 19 (35.18%) isolates were of *C. albicans*. A study from Meerut city, north India, suggests changing trends of *Candida* species, with predominance of NAC (86.4%) from cases of neonatal septicemia.¹⁰ They also reported *C. glabrata* (39%) as the predominant NAC species isolated followed by *C. tropicalis* (26.4%), *C. parapsilosis* (14.5%), *C. guilliermondii* (2.7%), *C. krusei* (1.8%), *C. dubliniensis* (0.9%) and *C. lusitaniae* (0.9%). Further they revealed, NAC species, especially *C. tropicalis*, *C. krusei*, *C. glabrata* and *C. parapsilosis*, tend to be less-susceptible to azoles, particularly fluconazole, than *C. albicans*.

In another study from Hyderabad, south India, Srinivas Rao MS et al had reported, *C. tropicalis* was the most common cause of candidemia in neonates (36.53%) followed by *C. albicans* (26.92%), *C. glabrata* (19.23%), *C. parapsilosis* (7.69%), *C. guilliermondii* (3.84%) and *C. krusei* (1.92%). In their study, *C. tropicalis* was highly susceptible to fluconazole (91%), whereas *C. parapsilosis* and *C. glabrata* showed lower sensitivity rates of 67.8% and 62.5% respectively.¹¹ Similar observations of change in trend of candidemia in NICU were also made by many western authors.^{5,12,13} In NICU, authors isolated only *C.*

albicans, *C. glabrata*, *C. krusei* and *C. tropicalis* unlike other authors from India, who also reported other NAC species like *C. parapsilosis*, *C. guilliermondii*, *C. dubliniensis*, *C. lusitaniae* etc.^{10,14} In fact, Juyal et al reported an outbreak of neonatal candidemia due to NAC species from a resource constrained setting of Uttarakhand state of India.¹⁵ Their case report describes the outbreak of six cases of NAC species within in a short period of 11 days which showed complete resistance to azole group of antifungal drugs. In present study, we also found non albicans *Candida* were more resistant to azole group of antifungals, especially commonly used antifungal drug like fluconazole (51.43%). Among non albicans *Candida*, *C. glabrata* was most resistant and *C. tropicalis* is least resistant organism. We found that the Amphotericin-B was better choice for initial treatment of non albicans candidemia.

Among the risk factors observed, prematurity <34 weeks, very low birth weight (<1500gm), prolonged use of broad spectrum antibiotic therapy, prolonged use of central venous catheter, mechanical ventilation, parenteral nutrition, prolonged NICU stays and concomitant bacterial sepsis were significantly associated with *Candida* infection in blood stream ($p < 0.05$) which was similar to observation made by others.^{3,4} Gopichand WR et al reported additional risk factors like intrapartum use of antibiotics and vaginal delivery in culture positive neonates.¹⁶

Clinical presentation of candidemia resembles sepsis syndrome and to establish a clinical diagnosis is difficult. In our study, feed intolerance, abdomen distension, lethargy was prominent clinical symptoms and thrombocytopenia was most common abnormal laboratory finding in neonates with candidemia. Avila-Auero ML et al had noticed significant difference in clinical features like axillary-inguinal lesion, apnea and seizures among those who survived and died.¹⁷ They were also identified skin lesion (60%), mucositis (57%), abdominal distention (57%), cyanosis (50%) and fever (45%) as a prominent clinical manifestation. Other

authors also reported respiratory distress and failure to thrive as a most common clinical presentation.^{6,10}

Candida blood stream infections are associated with very high crude mortality of over 60%, while attributable mortality may be as high as 49%.^{18,19} The incidence and associated mortality due to candidemia can be influenced by several factors including the population at risk, healthcare facility standards, *Candida spp.* involved, and antifungal resistance. In the present study, out of 54 neonates with candidemia, 37 of the patients (68.51%) survived and 17 (31.48%) died. Two (11.76%) babies were died due to *C. albicans* who also had concomitant sepsis and multi organ failure. Remaining 15 (88.24%) babies were died due to NAC species, of which *C. glabrata* was most common organism 10 (66.66%), followed by *C. krusei* 5 (33.333%). Most of literature also suggests NAC species associated with high mortality rate.^{4,5} Femitha P et al reported presence of candiduria was a significant risk factor for death (OR 5.14, 95% CI 1.17,22.49 P=0.04). They also noticed isolation of fungus from two normally sterile body sites is associated with higher risk for mortality.⁴ Hence the local epidemiological knowledge is essential in terms of prevention and better management of candidemia in NICU.

CONCLUSION

There was an increase in incidence of non albicans *Candida* infection in neonates admitted to NICU which is associated with increase in resistance to commonly used azole group of antifungal therapy. Therefore, it is important to know the correct identification of *Candida* species so that we can initiate appropriate antifungal treatment. Strict hospital infection control measures like restrictive use of multiple broad-spectrum antibiotic, prophylactic antifungal use, timely removal of unnecessary indwelling catheter and use of filters for parenteral nutrition should be implemented to reduce the morbidity and mortality associated with these infections.

ACKNOWLEDGEMENTS

Authors would like to thank Mrs. Manjula, Lecturer of Biostatistics, A.J. Institute of Medical Sciences, Mangalore, Karnataka, India for analysis of data.

Funding: No funding sources

Conflict of interest: None declared

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

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Cite this article as: Shettigar CG, Shettigar S. Non albicans Candidemia: an emerging menace in neonatal intensive care unit. *Int J Contemp Pediatr* 2018;5:436-41.