RESEARCH PAPER

# Candida Blood Stream Infection in Neonates: Experience from A Tertiary Care Teaching Hospital of Central India

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**Objective:** To assess the epidemiology of neonatal Candida blood stream infection. **Methods:** Medical records of neonates with Candida blood stream infection over 5 years (September 2010 to August 2015) were reviewed. Clinical details, species distribution and antifungal susceptibility were noted. **Results:** 114 neonates developed Candida blood stream infection. Commonly isolated Candida species were *C. tropicalis*, *C. albicans* and *C. parapsilosis*. Susceptibility for fluconazole and amphotericin B was 86.6% and 68.3%, respectively. Central line >7 days and hospital stay >28 days were independent risk factors associated with non-albicans Candida infection. **Conclusions:** Early removal of central line, timely fungal culture and antifungal susceptibility are necessary for early and appropriate treatment and better outcome.

**Key words:** *Blood stream infection, Neonate, Outcome*, *Risk factors.*

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Candida blood stream infection (BSI) is an important cause of neonatal sepsis and sepsis-related mortality [1]. Common risk factors for Candida BSI include prematurity and very low birth weight (VLBW), central vascular catheterization, parenteral nutrition, use of broad-spectrum antibiotics, $H_2$ blockers and corticosteroids, endotracheal intubation, and prolonged hospital stay [1,2]. Although *C. albicans* accounts for 45–55% of Candida BSI among infants [1,3,4], recent studies have detected a shift towards non-albicans Candida (NAC) species [3-5], which are often associated with high mortality and poor antifungal susceptibility [5-7]. To evaluate the disease burden and plan for an early and effective intervention, a thorough knowledge of the local epidemiology of Candida infection is critical. The present study was undertaken to assess the species distribution, susceptibility pattern, risk factors and outcome of neonates developing Candida BSI during hospital stay.

## Methods

Medical records of all inborn neonates who developed Candida BSI over a period of 5 years (September 2010 to August 2015) were reviewed. Candida BSI was defined as at least one pure growth of *Candida* species in blood culture [8] within 72 hours of inoculation, in presence of clinical features suggestive of sepsis such as respiratory distress/apnea, tachycardia/bradycardia, poor perfusion, feeding intolerance, temperature instability, lethargy, or seizures [9]. Culture positivity within 14 days, with the same *Candida* species was considered to be the same infection episode [2]. The study protocol was approved by the Institute Ethics Committee.

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Clinical and investigation details, treatments received, response to therapy and outcome were noted. For blood culture, paired samples were inoculated in sheep brain heart infusion broth (Himedia, Mumbai, India) in 1:10 dilution and incubated at 37°C for 48 h. Any growth observed was subcultured on 5% sheep blood agar, MacConkey's agar, and Sabouraud's dextrose agar (SDA) with chloramphenicol (0.05%). Species was identified by colony morphology on SDA, color production on chromogenic media, growth at 45°C, germ tube test, chlamydospore formation, and carbohydrate fermentation and assimilation tests. Antifungal susceptibility was determined by the Clinical Laboratory Standards Institute disk diffusion testing [10]. Statistical analysis was done using SPSS 16. Risk factors were analyzed by univariate and stepwise multivariate logistic regression analysis.

## Results

During the period of review, 13346 neonates were

delivered and 3128 were admitted in the Neonatal Unit. Candida species was isolated in blood culture of 114 neonates (0.9% of total deliveries and 3.6% of total admissions); 4.9% of VLBW and 11.2% of extremely-low birth weight neonates developed candidemia. Speciation could be done in 82 isolates, *C. Tropicalis*, 32 (39%), *C. albicans*, 29 (35.4%), *C. parapsilosis*, 10 (12.2%), *C. glabrata*, 5 (6.1%), *C. krusei*, 4 (4.8%) and *C. guilliermondii*, 2 (2.4%).

NAC BSI was associated with lower mean gestational age. Common presentations of Candida BSI were lethargy, bleeding manifestations, intraventricular hemorrhage, feeding intolerance and pneumonia or apnea. Overall, the combined incidence of multi-system involvement including meningitis, renal candidiasis/ urinary tract infection, septic arthritis, endocarditis, endophthalmitis and Fournier's gangrene was higher with NAC than *C. albicans*, though no difference was observed in the incidence of individual morbidity. Mortality and mean duration of hospital stay were significantly higher in NAC (***Table* I**). Positive sepsis screen was documented in only 18 (15.8%), but the incidence of raised C-reactive protein (>10 mg/L) and

**TABLE I** DETAILS OF NEONATES WITH CANDIDA BLOODSTREAM INECTION

| *Parameter* | *All neonates with Candida BSI (n = 114)* | *Neonates with Candida albicans BSI (n = 29)* | *Neonates with Candida non-albicans BSI (n = 53)* | *P value** |
|---|---|---|---|---|
| Chorioamnionitis, *n* (%) | 17 (14.9) | 5 (17.2) | 9 (17.0) | 1.0 |
| *Mode of delivery* | | | | |
| SVD, *n* (%) | 71 (62.3) | 18 (62.1) | 33 (62.3) | 1.0 |
| Cesarean section, *n* (%) | 43 (37.7) | 11 (37.9) | 20 (37.7) | |
| Birth weight (g), mean (SD) | 1235 (485) | 1280 (520) | 1125 (482) | 0.18 |
| Gestational age (wk), mean (SD) | 30.6 (1.4) | 30.8 (2.1) | 29.7 (2.0) | 0.02 |
| Male: Female | 1:1 | 1.1:1 | 1:1 | 0.90 |
| *Apgar score* | | | | |
| 1 min, median (IQR) | 6 (5-7) | 6 (5-7) | 6 (5-7) | 1.0 |
| 5 min, median (IQR) | 8 (7 - 9) | 8 (7 - 9) | 8 (7 - 9) | |
| Late-onset sepsis, *n* (%) | 94 (82.5) | 23 (79.3) | 52 (98.1) | 0.007 |
| *Clinical presentations* | | | | |
| Lethargy, *n* (%) | 41 (36.0) | 16 (55.2) | 22 (41.5) | 0.26 |
| Bleeding manifestations, *n* (%) | 39 (34.2) | 10 (34.5) | 24 (45.3) | 0.36 |
| IVH, Grade I-II, *n* (%) | 38 (33.3) | 12 (41.4) | 21(41.5) | 0.49 |
| IVH, Grade III-IV, *n* (%) | 10 (5.3) | 2 (6.9) | 6 (11.3) | 0.71 |
| Feed intolerance, *n* (%) | 38 (33.3) | 10 (34.5) | 17 (32.1) | 1.0 |
| Pneumonia/apnea, *n* (%) | 34 (29.8) | 8 (27.6) | 21(39.6) | 0.34 |
| Multi-system involvement, *n* (%) | 40 (35.1) | 6 (20.7) | 27 (50.9) | 0.009 |
| Duration of hospital stay (d), mean (SD) | 24.8 (10.4) | 18.7 (14.2) | 32.4 (15.3) | <0.001 |
| Death, *n* (%) | 17 (14.9) | 2 (6.9) | 14 (26.4) | 0.041 |
| *Follow up* | | | | |
| PVL, *n* (%) | 13 (11.4) | 4 (13.8) | 8 (15.1) | 0.10 |
| ROP, *n* (%) | 11 (9.6) | 3 (10.3) | 7 (13.2) | 0.10 |
| Abnormal BERA, *n* (%) | 2 (1.8) | 0 (0.0) | 2 (3.8) | 0.54 |
| Abnormal DDST, *n* (%) | 8 (7.0) | 1 (3.4) | 6 (11.3) | 0.41 |

**Comparison was made between neonates with Candida albicans BSI and neonates with Candida non-albicans BSI, BSI – Blood stream infection, SVD – Spontaneous vaginal delivery, SD – Standard deviation, IQR – Inter Quartile Range, PVL - Periventricular leucomalacia, ROP - Retinopathy of prematurity, BERA - brainstem evoked response audiometry, DDST - Denever Developmental Screening test; IVH: Intraventricular hemorrhage.*

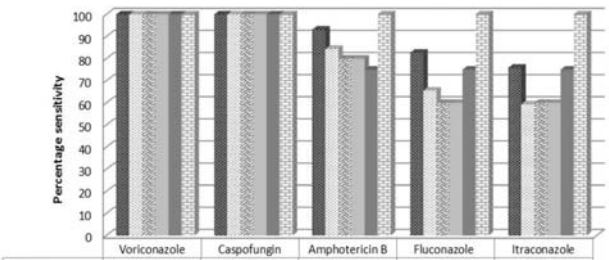
severe thrombocytopenia (<50000/µL) was high, 92 (80.7%) and 68 (59.6%), respectively.

On univariate analysis, risk factors significantly associated with NAC BSI were nil orally >5 days (OR 0.224, 95% CI 0.059, 0.842], mechanical ventilation >5 days (OR 0.187, 95% CI 0.039, 0.889), central line >7 days (OR 0.166, 95% CI 0.050, 0.543), intralipid infusion >7 days (OR 0.225, 95% CI 0.068, 0.740), and hospital stay >28 days (OR 0.217, 95% CI 0.079, 0.591). On step-wise logistic regression analysis, central line >7 days and hospital stay >28 days were independent predictors of NAC BSI (***Table* II**).

Intravenous fluconazole was the first empirical antifungal used on clinical suspicion of fungal sepsis and liposomal amphotericin B was the second line. Change of antifungal chemotherapy was based on clinical deterioration or susceptibility testing. No antifungal chemoprophylaxis was given. Voriconazole and caspofungin demonstrated 100% susceptibility, whereas overall sensitivity for amphotericin B, fluconazole and itraconazole were 86.6%, 68.3% and 67.1%, respectively. *C. parapsilosis* and *C. tropicalis* demonstrated least susceptibility to fluconazole and amphotericin B (***Fig.* 1**). 41.2% of Candida isolates from the neonates who expired were resistant to both fluconazole and amphotericin-B.

## DISCUSSION

In the present study the incidence of Candida BSI was 0.9% of total deliveries and 3.6% of total admissions. *C. tropicalis* was the most commonly isolated *Candida* species, followed by *C. albicans* and *C. parapsilosis.* The incidence of mortality and duration of hospital stay were significantly higher in NAC BSI. Central line >7 days and hospital stay >28 days were independent predictors of NAC BSI. *C. parapsilosis* and *C. tropicalis* demonstrated higher resistance to fluconazole and amphotericin-B.




| | Voriconazole | Caspofungin | Amphotericin B | Fluconazole | Itraconazole |
|---|---|---|---|---|---|
| C. albicans | 100 | 100 | 93.1 | 82.7 | 75.9 |
| C. tropicalis | 100 | 100 | 84.4 | 65.6 | 59.4 |
| C. parapsilosis | 100 | 100 | 80 | 60 | 60 |
| C. glabrata | 100 | 100 | 80 | 60 | 60 |
| C. krusei | 100 | 100 | 75 | 75 | 75 |
| C. guilliermondi | 100 | 100 | 100 | 100 | 100 |

**Fig. 1** *Percentage sensitivity of Candida spp. to antifungal drugs.*

**TABLE II** STEP-WISE MULTIPLE LOGISTIC REGRESSION ANALYSIS OF RISK FACTORS FOR CANDIDA NON-ALBICANS (NAC) BLOOD STREAM INFECTIONS

| *Risk factor* | *Adjusted Odds Ratio (95% CI)* |
|---|---|
| Nil orally >5 d | 1.0 (0.18-5.30) |
| Mechanical ventilation >5 d | 4.4 (0.81-24.75) |
| Central line >7 d | 4.3 (1.07-17.32) |
| 20% intralipid infusion >7 d | 1.8 (0.47-4.43) |
| Use of >2 broad spectrum antibiotics | 1.1 (0.32-3.80) |
| Prolonged stay in hospital (>28 d) | 3.1 (1.05-9.74) |

**The model was statistically significant, and explained 32.6% (Nagelkerke $R^2$) of the total variance in NAC BSI and correctly classified 76.8% of cases.*

The major limitations of our study are its retrospective design, and failure to perform species identification in all cases. We observed a wide spectrum of multi-system involvement, long-term complications and species distribution. Emergence of NAC as a common cause of candidemia has been reported by previous Indian studies [8,11-13]. *C. parapsilosis* was identified as the most common fungal species in neonates in earlier reports, which is in contrast to our observation [8]. *C. tropicalis* is virulent and is the second leading cause of candidemia in adults, but is quite infrequent among neonates [14]. Overall, resistance to fluconazole and amphotericin B was similar to previous studies [8]. Compared to other Indian studies [8], mortality was less in our study, but high incidence of resistance to both fluconazole and amphotericin B amongst infants who died was noted.

To conclude, emergence of NAC species and their association with higher mortality and longer duration of hospital stay is a cause for concern. Higher resistance of *C. tropicalis* and *C. parapsilosis* to fluconazole and amphotericin B is alarming. Prevention of risk factors in susceptible neonates with early removal of central line, timely fungal culture, Candida speciation and susceptibility testing are necessary for appropriate institution of treatment and better outcome. Frequent empirical use of fluconazole and amphotericin B may be avoided as it may lead to a shift in species distribution and higher antifungal resistance.

*Contributors:* SB: was involved in study planning, design and writing of the manuscript. RK: was involved with the data collection, analysis and writing of the manuscript. RT: was involved with the microbiological analysis and writing of the manuscript. AK: was involved with the study planning and writing of the manuscript. All authors approved the final version of the manuscript. SB will act as the guarantor of the paper.
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**WHAT THIS STUDY ADDS?**

- Non-albicans Candida infection was associated with higher mortality and increased duration of hospital stay.
- Both *C. parapsilosis* and *C. tropicalis* demonstrated higher resistance to fluconazole and amphotericin B.

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