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**Original Research Article**

# Persisting non-albicans candidemia in low birth weight neonates in a tertiary care hospital, Jammu and Kashmir

**Tabindah Jahan[1], Anjum Farhana[1]*, Sabah Nargis[2]**

[1]Department of Microbiology, [2]Department of Physiology, Government Medical College, Srinagar, Jammu and Kashmir, India

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***Correspondence:**
Dr. Anjum Farhana,
E-mail: tabindah.farooq@gmail.com

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## ABSTRACT

**Background:** Neonatal candidemia is among the leading causes of mortality in neonatal intensive care units of the developing countries like India. This work aimed at determining the prevalence of candidemia, spectrum of disease, risk factors and the antifungal susceptibility in low birth weight neonates in neonatal intensive care unit (NICU)'s at a tertiary care level.
**Methods:** This was a prospective cross-sectional study of blood culture positive candidemia cases in neonates admitted to the neonatal intensive care unit of tertiary care hospital, SMHS, Jammu and Kashmir, India, between July 2021 to December 2022. All neonates with a clinical suspicion of candidemia with a positive blood culture (BacT alert) were identified. Patient demographics, clinical details, neonatal risk factors, and laboratory data and antifungal susceptibilities (using VITEK 2 compact system) were recorded and analyzed.
**Results:** A total of 680 neonatal blood culture samples were collected from NICU's, out of which 88 (12.94%) developed candidemia. Low birth weight (33.33%), indwelling catheters (31.52%), prematurity (31.31%) and prolonged use of antibiotics were important risk factors. The commonest clinical manifestation was feed intolerance 66.1% and respiratory distress 62.2%. Non-albicans candida was seen in majority cases 86.36% with *Candida krusei* 77.27%. All the *Candida spp.* showed 100% sensitivity to voriconazole and caspofugin followed by amphotericin B, fluconazole and micafugin.
**Conclusions:** In this study, we focussed on determining the prevalence of candidemia in low birth weight neonates. The persistently emerging non-albicans *Candida* particularly *Candida krusei* has emerged as a big concern and needs attention for its prevention and treatment to minimize the morbidity and mortality rate.

**Keywords:** Candidiasis, Azoles, *C. krusei*

## INTRODUCTION

Neonatal sepsis is the second most leading cause of death in India and is responsible for almost a quarter of total neonatal deaths.[1] Significance of *Candida* spp. among low birth weight neonates is increasingly being recognized. It accounts for 9-13% of blood stream infections (BSI) in neonates.[2] Invasive candidiasis is a leading cause of infection related morbidity and mortality in very low birth weight (<1000 gms). *Candida* infections are frequent and major causes of septicemia in neonatal intensive care units (ICUs), and are associated with high morbidity and mortality rates. The sources of candidiasis are mostly endogenous, their frequency of the disease is influenced by various treatment regimens, antibiotics, and other supportive care procedures.[3,4] Invasive candidiasis in neonates is a serious and common cause of late onset sepsis and has a high mortality (25 to 35%).[5]

*Candida albicans* has been the most frequently isolated species, but recently non-albicans *Candida* (NAC) have emerged as important opportunistic pathogen, most

frequently isolated non-albicans *Candida* include *Candida tropicalis, C. parapsilosis, C. krusei, and C. glabrata.*[6,7] There is growing evidence suggesting a role of increasing use of azole agents in this epidemiological shift. Several of these NAC species exhibit intrinsic resistance to traditional triazoles like fluconazole and may also demonstrate cross resistance to newer triazoles.[8] Number of factors including the use of indwelling devices, broad spectrum antibiotics, low birth weight (LBW), prematurity, gastrointestinal surgery, artificial ventilation, and history of fungal colonization contribute to the risk.[9] Preterm, very low birth weight (VLBW): ≤1,500 g; extremely low birth weight (ELBW): ≤1,000 g; and critically ill infants are at highest risk of invasive *Candida* infections.[10] Candidial infections can also spread through vertical transmission from maternal flora or via horizontal transmission from hands of healthcare workers (HCW).[11,12] Infants less than 1 year of age have one of the highest rates of candidemia of any age group.[13] We have noticed an increase in the isolation rate of Non albicans *candida* species specially *C.krusei* over last few years from cases of neonatal septicaemia in our hospital . Earlier, two *C. krusei* candidemia outbreaks have been reported from India in neonatal ICU (NICU) with seven and six cases.[14,15] The rise of *C. krusei* is of concern due to its intrinsic resistance to fluconazole. Therefore, our aim was to examine the prevalence of neonatal candidemia at our hospital and its correlation with the associated risk factors and it's in vitro antifungal susceptibility.

### *Aims and objective*

Aims and objectives of the study were: to determine the prevalence, risk factors, clinical spectrum, organism profile of *Candida* species among very low birth weight neonates, and to determine the antifungal susceptibility of different *Candida* species.

## METHODS

### *Study type*

This was a prospective cross sectional study. The study involved low birth weight babies admitted in NICU'S and their blood samples were referred to our laboratory for further investigations. Study participants included low birth weight (LBW) <1500 gms neonates, who presented with neonatal sepsis in NICU.

### *Study period and place*

A study period of one and half year was conducted between July 2021 and December 2022 in the department of microbiology in Government Medical College, SMHS, Srinagar, Jammu and Kashmir, India.

### *Sample collection*

Prior to the sample collection a written informed consent from patient's guardian/ parents were obtained from a total of 680 neonates (<32 weeks of gestation, admitted to NICU with clinical suspicion of septicaemia). Under all aseptic standard precautions, 1–2 ml of blood was drawn from the neonates.

One milliliter of blood was inoculated into ready to use BacT/ALERT PF and culture bottles (yellow color coded) for pediatric use with all the required precautions and shaken well. The culture bottles were loaded into the instrument after scanning the barcode of the bottle and incubated. Blood culture samples were incubated in BacTAlert 3D (Biomerieux, India®) machine-driven blood culture system. Positive or negative culture bottles were determined by BacT/ALERT microorganism detection system. The *Candida* spp. isolated were identified as per the standard mycological techniques.[14] Blood cultures were considered negative only after it showed no growth after seven days of incubation.

### *Preliminary identification*

Positive samples were examined by microscopy through gram staining and sub-cultured on Blood agar plate, Mac Conkey agar plates, and Sabouraud dextrose agar (SDA) slant with antibiotics without cyclo-heximide (Hi-Media Pvt. Ltd., Mumbai India) in aerobic atmosphere. The preliminary identification was done by colony morphology on SDA, chromogenic media (HiChrome, Himedia, Pvt. Ltd.) growth at 45°C, germ tube test, and by carbohydrate fermentation and assimilation tests.[16]

### *Identification of the organism and its antifungal susceptibility testing*

This was confirmed with automated Vitek 2 compact sixty system (BioMerieux India®) usingVitek-2 ID and AST yeast cards. These were loaded into the Vitek-2 Compact system. Antifungal sensitivity of the samples was performed against voriconazole, 5 flucytosine, fluconazole, caspofungin, amphotericin B and micafungin. According to the interpretative criteria provided by the automated systems' recommendations by (CLSI) guidelines the MICs obtained were grouped into the three clinical categories susceptible (S), intermediate (I), and resistant (R).

### *Inclusion criteria*

Infants with birth weight <1500 gms were included. These infants were not followed beyond discharge to determine long term outcome. Patients who had candidemia (a positive *Candida* culture from a sterile body site -blood). Candidemia was defined as the presence of atleast one positive blood culture containing pure growth of *Candida* spp, with supportive clinical features.

### *Exclusion criteria*

Neonates with bacterial septicaemia were excluded from this study.

***Birth weight***

Very low birth weight (VLBW) infants were those with a birth weight <1500 g. Low birth weight infants were those with a birth weight < 2500 g.

Prolonged antibiotic use was defined as >14 days of continuous administration.

***Statistical analysis***

JASP 0.14 for data analysis and p value of <0.05 was taken.

## RESULTS

680 samples were collected from low birth weight neonates admitted in the NICU. Among them, blood cultures were positive for 442 (65%). Out of 442 samples, 88 (12.94%) neonates developed candidemia, remaining 354 (52.05%) had other bacterial infections and were excluded from this study.

***Candida spp. colonization***

A total of 88 (12.94%) neonates were colonized by *Candida spp*. on both day 1 and day 7.

A total of 39 (44.31%) and 49 (55.68%) neonates were colonized by *Candida spp*. on first day and seventh day of life, respectively.

***Gender distribution in the study group***

Out of 88 candidemia culture positive newborns admitted in the NICU, 46 (20.44%) were male babies and 42 (19.35) were female babies respectively (Table 1).

***Hospital duration***

Out of 88 culture positive (candidemia) newborns admitted in the NICU, majority of the babies had a hospital stay duration of more than one week. 65 out of 88 (20.12%) babies had a prolonged hospital stay before developing candidial sepsis (Table 1).

***Associated risk factors and clinical presentations***

In this study low birth weight was the most common risk factor accounting for 33.33% (p=0.0001). This was followed by indwelling catheters 31.52% (p=0.0001) and prematurity 31.31% (p=0.0001). The neonates who underwent mechanical ventilation accounted for 29.25% (p=0.0006). Use of broad spectrum antibiotics for more than a week with 24.49% (p=0.09) and steroid use (24.24%) were also associated risk factors (Table 1).

**Table 1: Detailed parameters of neonates with candida blood stream infections.**

| Parameters | Total samples (N) | No. of culture positive cases for candidemia (N) (%) | Odds ratio (95% CI) versus reference category | P value |
|---|---|---|---|---|
| **Total** | 442 | 88 (19.91) | | |
| **Demography/prevalence** | | | | |
| **Gender** | | | | |
| Male neonates | 225 | 46 (20.44) | 1.07 | 0.774 |
| Female neonates | 217 | 42 (19.35) | Ref | |
| **Mode of delivery** | | | | |
| Vaginal | 153 | 53 (34.64) | 3.84 | 0.0001 |
| C-section | 289 | 35 (12.11) | | |
| **Admission duration (days)** | | | | |
| <7 | 119 | 23 (19.33) | 0.95 | 0.852 |
| >7 | 323 | 65 (20.12) | | |
| **Risk factors** | | | | |
| **Birth weight (gm)** | | | | |
| <1000 | 153 | 51 (33.33) | 3.4 | 0.0001 |
| 1000-1500 | 289 | 37 (12.80) | | |
| **Central line** | | | | |
| Yes | 184 | 58 (31.52) | 3.32 | 0.0001 |
| No | 258 | 32 (12.40) | | |
| **Prematurity** | | | | |
| Yes | 198 | 62 (31.31) | 3.71 | 0.0001 |
| No | 244 | 26 (10.66) | | |
| **Mechanical ventilation** | | | | |
| Yes | 147 | 43 (29.25) | 2.29 | 0.006 |
| No | 295 | 45 (15.25) | | |

Continued.

| Parameters | Total samples (N) | No. of culture positive cases for candidemia (N) (%) | Odds ratio (95% CI) versus reference category | P value |
|---|---|---|---|---|
| **Antibiotics durations (days)** | | | | |
| <7 | 295 | 52 (17.63) | 0.65 | 0.09 |
| >7 | 147 | 36 (24.49) | | |
| **Steroid use** | | | | |
| Yes | 132 | 32 (24.24) | 1.45 | 0.137 |
| No | 310 | 56 (18.06) | | |

***Comparison between C. albicans and non-Candida albicans neonatal candidemia***

Neonates with non-*Candida albicans* showed more number of low gestational age of <32 weeks in neonates (p=0.088). Length of hospital stay of >1 week and low birth weight was seen more in non-albicans candidemia neonates (n=44). Various risk factors involved were comparatively more in non-albicans candidemia which are mentioned in Table 3.

***Comparison of different variables: C. albicans versus non-Candida albicans***

Comparison of different variables in given in Table 3.

**Table 3: Comparison of different variables: *C. albicans* versus non-*Candida albicans*.**

| Characteristics | *C. albicans* (n=12) | C. non-albicans (n=76) | P value |
|---|---|---|---|
| **Low gestational age ≤32 weeks** | 10 | 74 | 0.088 |
| **Low birth weight (less than 1500 gms)** | 07 | 44 | 1 |
| **Length of hospital stay (days)** | | | |
| ≤7 | 08 | 15 | 0.001 |
| ≥7 | 04 | 61 | 0.082 |
| **Presence of CVC** | 07 | 51 | 0.533 |
| **Mechanical ventilation** | 09 | 17 | 0.008 |
| **Prolonged antibiotic therapy** | 06 | 30 | 0.92 |
| **Steroid therapy** | 05 | 27 | 0.2 |

***Candida isolates recovered from low birth weight babies***

Among the positive samples for candidemia, non-albicans *Candida* were responsible for 86.36 % cases, whereas 13.63 % cases were due to *Candida albicans*. A total of four species of *Candida* were isolated from the study population, which included *C. krusei (68), C. albicans* (12), *C. tropicalis* (05) and *C. parapsilosis* (03) respectively (Table 4).

***Distribution of Candida species isolated from low birth weight neonates with candidemia***

Distribution of *Candida* species isolated from low birth weight neonates with candidemia is given in Table 4.

**Table 4: Distribution of *Candida* species isolated from low birth weight neonates with candidemia.**

| S. no | *Candida* species isolated (n=88) | No. of isolates (%) |
|---|---|---|
| **1** | *Candida krusei* | 68 (77.27) |
| **2** | *Candida albicans* | 12 (13.63) |
| **3** | *Candida tropicalis* | 05 (5.68) |
| **4** | *Candida parasilopsis* | 03 (5.40) |

***Antifungal susceptibility testing of various candida isolates***

The activities of amphotericin B, flucytosine, and the echinocandins against bloodstream isolates of *Candida spp.* was done using VITEK 2 system (Table 5).

Out of 68 isolates of *Candida krusei*, it showed sensitivity to voriconazole, caspofungin, micafungin and amphotericin B. Voriconazole showed 100% (68/68) sensitivity whereas Amphotericin B with MIC's of ≥0.5 mg/l was noted in 70.58% (48/68) isolates. Only 8.8% (6/68) and 4.41% (3/68) of the isolates tested had the MIC of >1 mg/l against caspofungin and micafungin.

Out of 12 isolates, *Candida albicans* showed sensitivity to voriconazole and caspofugin 100%, amphotericin B, micafungin and flucytosine were 91.66%, fluconazole showed 83.3% sensitivity.

Out of 5 isolates, *Candida tropicalis* showed sensitivity to voriconazole were 100%, amphotericin B were 80%, flucytosine were 80%, micafungin were 100%, fluconazole was 60%, and caspofungin were 100%.

03 isolates of *C. parapsilosis* showed 100% sensitivity to caspofungin, micafungin and voriconazole. Other antifungals like amphotericin B, flucytosine, and fluconazole showed 66% sensitivity.

**Table 5: Antifungal susceptibility testing in neonatal candidemia.**

| Species | Antifungal agents | Test method | MIC (mg/l) range | MIC | Number and percentage | | |
|---|---|---|---|---|---|---|---|
| | | | | | S | SDD (I) | R |
| ***Candida krusei*** | Fluconazole | Vitek 2 | ≤0.5 | 2 | - | - | 68 (100) |
| | Voriconazole | Vitek 2 | ≤0.12 | 0.12 | 68 (100) | - | - |
| | Flucytosine | Vitek 2 | ≤1 | 8 | - | - | 68 (100) |
| | Amphotericin B | Vitek 2 | ≤0.25-2 | 0.5 | 48 (70.58) | 18 (26.47) | 2 (2.94) |
| | Caspofugin | Vitek 2 | 0.12-2 | 0.5 | 6 (8.8) | 4 (5.88) | 58 (85.29) |
| | Micafugin | Vitek 2 | 0.06-12 | 0.12 | 3 (4.41) | 6 (8.82) | 59 (86.7) |
| ***Candida albicans*** | Fluconazole | Vitek 2 | ≤0.5 | 2 | 10 (83.3) | - | 02 (16.66) |
| | Voriconazole | Vitek 2 | ≤0.12 | 0.12 | 12 (100) | - | - |
| | Flucytosine | Vitek 2 | ≤1 | 8 | 11 (91.66) | | |
| | Amphotericin B | Vitek 2 | ≤0.25-2 | 0.5 | 11 (91.66) | - | 01 (8.33) |
| | Caspofugin | Vitek 2 | 0.12-2 | 0.5 | 12 (100) | - | - |
| | Micafugin | Vitek 2 | 0.06-12 | 0.12 | 11 (91.66) | 01 (8.33) | - |
| ***Candida tropicalis*** | Fluconazole | Vitek 2 | ≤0.5 | 2 | 03 (60) | - | 02 (40) |
| | Voriconazole | Vitek 2 | ≤0.12 | 0.12 | 05 (100) | - | - |
| | Flucytosine | Vitek 2 | ≤1 | 8 | 04 (80) | - | - |
| | Amphotericin B | Vitek 2 | ≤0.25-2 | 0.5 | 04 (80) | 01 (20) | - |
| | Caspofugin | Vitek 2 | 0.12-2 | 0.5 | 05 (100) | - | - |
| | Micafugin | Vitek 2 | 0.06-12 | 0.12 | 05 (100) | - | - |
| ***Candida parasilopsis*** | Fluconazole | Vitek 2 | ≤0.5 | 2 | 02 (66) | - | 01 (33.33) |
| | Voriconazole | Vitek 2 | ≤0.12 | 0.10.12 | 03 (100) | - | - |
| | Flucytosine | Vitek 2 | ≤1 | 8 | 02 (66) | - | 01 (33.33) |
| | Amphotericin B | Vitek 2 | ≤0.25-2 | 0.5 | 02 (66) | - | 01 (33.33) |
| | Caspofugin | Vitek 2 | 0.12-2 | 0.5 | 03 (100) | - | - |
| | Micafugin | Vitek 2 | 0.06-12 | 0.12 | 03 (100) | - | - |

## DISCUSSION

We conducted 1 and half year (18 months) retrospective study to find the incidence of candidemia among high-risk low birth weight neonates in a tertiary care neonatal ICU, the clinical spectrum of the disease, the risk factors, organism profile, and the antifungal susceptibility was seen.

The prevalence of fungal candidemia in neonatal isolates in this study was 12.94%. Out of 88 candidemia culture positive newborns admitted in the NICU, male and female showed almost equal distribution 46 male and 42 female babies.

67 out of 88 babies who developed neonatal candidiasis had a hospital stay of more than 1 week. The incidence of duration of hospital stay of more than a week were significantly higher (20.12%) in neonatal candidemia blood stream infections, which is similar to the study done by James et al.[17] Invasive fungal sepsis is a common cause of late-onset sepsis, especially in preterm neonates due to their weak immune system and fragile skin/gut barrier.[18]

Candida colonization in neonates has been documented as a major predisposing factor to invasive candidiasis.[14] Majority of the candidemia episodes occurred in babies with low birth weight and premature babies which accounted for more than 60% of our cases highlighting the significant burden of this disease in infants. Use of multiple invasive devices (central line 31.52%, endo tracheal tubes 29.25%) causes break in the skin/mucosal lining, which predisposes these sites for colonization/ infection by *Candida* spp. This was similar to a study done by Juyal et al.[19] The high incidence of disease among the most premature neonates has been described in other studies also.[16] It is because of the immaturity of immune system, prolonged NICU stay, and greater requirement of invasive procedures such as central venous lines, invasive ventilation, and frequent use of broad-spectrum antibiotics in this population. All these factors place them at high risk for fungal infection. Extensive and unnecessary use of antibiotics promote fungal overgrowth at the expense of normal bacterial flora and encourage yeast to translocate across the intact mucosal membranes. Based on high perinatal risk factors for early onset sepsis the long-term use of broad spectrum antibiotics must have created a favorable environment for *Candida spp*. to flourish and thus caused a negative impact on the immunity. This validates the need of prophylactic antifungals to be used in a set up where persistent upsurge in the incidence of neonatal candidemia is seen.

The major clinical presentation in our study was feed intolerance 66.1% and respiratory distress 62.2%. which is similar to the study done by Juyal et al.[19]

In the present study non-*Candida albicans* 86.36% were isolated more in numbers than *C. albicans* 13.63%. This correlates well with the results of other authors.[18-20]

*Candida krusei* was the predominant isolate (77.27%) in current study which was also seen by other researchers in same geographical area who have documented the predominance of non-albicans *Candida* over other *Candida* in neonatal candidemia.[20] Niranjan et al also demonstrated *Candida krusei* to be the predominant non-albicans species followed by *Candida tropicalis.*[21] In this study we isolated *C. parasilopsis* and *C. tropicalis* amongst the second and third commonest species of non-albicans *Candida* similar to studies done by Koppad et al.[22] Although *C. parasilopsis* is less virulent, but because of indwelling catheters and high IV glucose infusion, the virulence may increase and is thus difficult to eradicate this organism.[23]

All neonates with candidemia received antifungal treatment. Very few suspected neonates were started with antifungal drugs on the clinical presentation before blood cultures yielded positive fungal growth.

All the *Candida* spp. showed 100% sensitivity to voriconazole amd caspofugin followed by amphotericin B, fluconazole and micafugin. Among non-albicans *Candida spp, C. krusei* isolates were more resistant to azoles, particularly fluconazole, than *C. albicans* which was similar to study done by Juyal et al.[19] Overall, resistance to fluconazole and amphotericin B was similar to previous studies.[19]

The use of fluconazole prophylaxis is reported as a risk factor for the majority of *C. krusei* outbreaks though this practice is not prevalent in our hospital.[18]

A shift towards persistent non-albicans candidemia in neonates is associated with high mortality and poor antifungal susceptibility pattern. Thus making it a big concern.

The limitation of our study was that it was a prospective study for only a period of one and half year hence less no of babies with candidemia were reported. Also, other body fluids were not sent, only blood cultures were sent for culture and reported accordingly.

## CONCLUSION

The present data demonstrates the high incidence of persistent candidemia in LBW infants in NICU. Mechanical ventilation and intubation appeared to be the major factors for the development of persistent candidemia. Prevention of risk factors in susceptible neonates can be achieved with early removal of central line, stop unnecessary use of antibiotics, timely fungal culture, *Candida* speciation and susceptibility testing are necessary for appropriate treatment and better outcome. Frequent irrational use of fluconazole and amphotericin B may be avoided as it leads to a shift in species distribution and higher antifungal resistance.

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