

# Emerging threat of candida resistance among neonates at a teaching institute of Jharkhand

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## ABSTRACT

**Purpose:** In the past few decades, candidemia has escalated to worrisome levels, leading to substantial morbidity and mortality in neonates. The rise in anti-fungal drug resistance demands prompt diagnosis and treatment. This study aimed to determine the speciation and susceptibility pattern of *Candida species* recovered from special care new-born units and identify risk factors for developing candidemia in neonates. **Method:** A total of 580 blood samples from clinically suspected septicemic neonates were collected and subjected to culture. Cultures positive for yeasts were sub-cultured on Sabouraud dextrose agar. Identification of a suspected purified colony of *Candida* was confirmed to the species level by both conventional and automated techniques matrix-assisted laser desorption and ionization time-of-flight mass spectrometry. Anti-fungal susceptibility of isolates was performed by an automated method (VITEK 2 system) using VITEK 2 cards. Multi-variate logistic regression analysis was used to identify risk factors associated with candidemia. **Result:** A total of 56 (9.66%) isolates of *Candida species* were recovered from 580 blood cultures. Non-albicans *Candida* species predominated with 82.14% of cases, whereas 17.86% of cases were caused by *Candida albicans*. *Candida tropicalis* (46.42%) was the most common isolate recovered, followed by *Candida albicans* (17.8%). Risk factor analyses identified a very low birth weight [odds ratio (OR) =4.05, 95% confidence interval (CI) =2.03-8.08] and prolonged antibiotic therapy (OR = 3.79, 95% CI = 1.7-8.7) among others as significant predictors of candidemia. All the *Candida* isolates showed 100% sensitivity to voriconazole and micafungin, whereas the overall sensitivities for fluconazole, amphotericin B, caspofungin, and flucytosine were 85.71%, 96.43%, 96.43%, and 91.07%, respectively. **Conclusion:** Candidemia is a life-threatening condition in neonates. Identification of *Candida species* and routine anti-fungal susceptibility is a must to select a suitable and effective anti-fungal therapy to revoke emerging resistance to anti-fungals.

**Keywords:** Anti-fungal susceptibility tests, candida tropicalis, candidemia, very low birth weight

## Introduction

*Candida* species have emerged as major blood stream infection pathogens associated with pronounced mortality and morbidity in very-low-birth-weight neonates (defined as birth

weights <1500 g).<sup>[1,2]</sup> Successful management of neonatal candidemia includes appropriate anti-fungal therapy and supportive care as well as preventive measures to reduce the risk of systemic *Candida* infections.

At present, *Candida* is the fourth most common cause of bloodstream infections in the United States, causing invasive life-threatening fungal infections among hospitalized patients.<sup>[3,4]</sup> The global incidence of candidemia has increased more than fivefold in the past decade.<sup>[5]</sup> The incidence of candidemia is

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about 6.51 cases per 1000 intensive care unit (ICU) admissions in India.<sup>[6]</sup>

Importance of *Candida* species in neonatal sepsis and sepsis-related mortality is increasingly being recognized.<sup>[7]</sup> In particular, among new-borns with a birth weight <1000 g, 4–8% will develop candidemia, with a mortality rate of 30%.<sup>[8]</sup> Common risk factors for neonatal candidemia include prematurity and a very low birth weight [VLBW <1500 g; low birth weight (LBW) <2500 g], central vascular catheterization, parenteral nutrition, use of broad-spectrum antibiotics, H2 blockers and corticosteroids, endotracheal intubation, and prolonged hospital stay.<sup>[7,9]</sup> New-borns who survive frequently have long-term neurological impairment, including cerebral palsy, blindness, hearing impairment, cognitive deficits, and periventricular leukomalacia.<sup>[10]</sup>

Furthermore, many regions of the world are witnessing a surge in non-*albicans* *Candida* species. *Candida tropicalis* is the most common non-*albicans* *Candida* (NAC) causing blood stream infection (BSI) in hospital settings. In India, it ranks first among all *Candida* species known to cause BSI.<sup>[11–13]</sup> A similar change in species distribution was also noted in other Asian countries.<sup>[14]</sup> Therefore, routine screening of *Candida* isolates to the species level is of crucial importance as this could assist clinicians in promoting adoption of important prophylactic and treatment guidelines for its improved management.

Although diagnostic competency for fungal infections has improved, the critical status and the non-specific presentation of the invasive disease in hospital settings often delay confirmation of etiology and appropriate management.<sup>[15]</sup> With the rise in anti-fungal resistance, susceptibility tests play an ever-increasing role in the selection of anti-fungal drugs. Knowledge on risk factors to consider when deciding to administer empirical anti-fungal therapy is essential for clinicians to prevent candidemia. Therefore, the present study aimed to assess changing trends of candidemia in neonates admitted to special new-born care units to examine *in vitro* susceptibility to common anti-fungal drugs and to assess risk factors for *Candida* septicaemia.

## Materials and Methods

This prospective study was performed in the Department of Microbiology, Rajendra Institute of Medical Sciences, Ranchi, from July 2020 to June 2021. A total of 580 blood samples were collected aseptically in blood culture bottles (BD BACTEC Peds Plus) from neonates admitted in special care new-born units (SCNUs) for clinically suspected neonatal sepsis before starting anti-microbial therapy and processed for culture using an automated blood culture system (BD BACTEC FX 100). If BACTEC flagged positive results, then sub-culture was performed on blood agar, Mac Conkey agar, and Sabouraud's dextrose agar (SDA) with antibiotics. The suspected *Candida* colonies were identified by Gram stain and further speciated

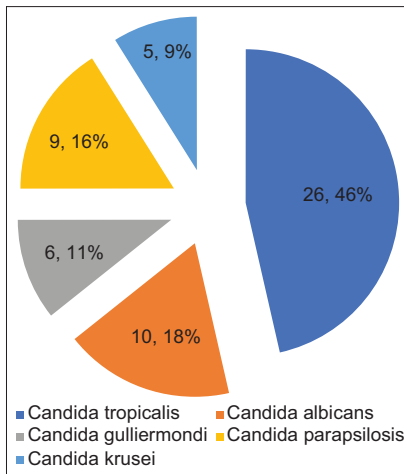
by a panel of tests like germ tube test, color on Hi Chrome *Candida* differential agar, growth morphology on corn meal agar (Dalmau's plate method), and sugar assimilation tests. It was further confirmed with an automated identification method using matrix-assisted laser desorption and ionization time-of-flight mass spectrometry (MALDI-TOF MS) (BioMeriux). Candidemia was diagnosed by isolation of *Candida* species from at least one positive blood culture containing pure growth of *Candida* species with supportive clinical features. The clinical and laboratory data on all eligible neonates were collected in a structured proforma. The anti-fungal susceptibility tests of the isolates were performed by an automated method (VITEK2 system) with anti-fungal drugs amphotericin B (AMB), caspofungin (CAS), fluconazole (FLU), flucytosine (FC), micafungin (MFG), and voriconazole (VRC) using AST-YS08 card. The drug concentration was in the range of 0.25–16 µg/ml for AMB, 0.25–4 µg/ml for CAS, 1–64 µg/ml for FLU and FC, 0.06–4 µg/ml for MFG, and 0.125–16 µg/ml for VRC. Results of MICs were obtained according to the interpretative criteria provided by the automated systems' recommendations (CLSI) guidelines.<sup>[16]</sup> Quality control was performed using the following strains as controls for the evaluation: *Candida albicans* (ATCC 90028), *Candida parapsilosis* (ATCC22019), and *Candida krusei* (ATCC 6258).

## Statistical analysis

Data were collected in a structured proforma and were classified, analyzed, and evaluated by using SPSS version 21 for Windows (SPSS Inc., Chicago, IL). We had performed uni-variate logistic regression of known risk factors for neonatal candidemia. All variables with  $P < 0.05$  were selected for inclusion in the multi-variate logistic regression model to identify predisposing risk factors associated with neonatal candidemia.

## Result

Out of 580 blood samples, 43.4% ( $n = 252$ ) were culture-positive. Among positive culture, 54.4% were Gram-negative bacilli, 23.4% were Gram-positive cocci, and 22.2% ( $n = 56$ ) were *Candida* isolates. The prevalence of candidemia was 9.66% of total clinically suspected cases of neonatal sepsis. Candidemia was more prevalent in male (62.5%) than in female (37.5%). The male-to-female ratio was 1.66:1. Among neonates with positive blood culture for candidemia, the gestational age ranged from 30 weeks to 40 weeks with a mean age of 34.12 weeks [95% confidence interval (CI) for the mean of 33.26 to 34.99] and the birth weight ranged from 930 g to 2760 g with a mean weight of 1588.30g (95% CI for the mean of 1456.87 to 1719.73). The majority of candidemia episodes occurred in VLBW (<1500 g) neonates (66.07%). The mean duration of the total hospital stay was 16.03 days (95% CI 14.76 to 17.31 days). *Candida* species were isolated mainly in late-onset sepsis (LOS), 35/56 (62.5%), when compared to early-onset sepsis (EOS), 21/56 (37.5%). Out of 56 isolates, non-*albicans* *Candida* (NAC) accounted for 46 isolates (82.14%), whereas *Candida albicans* were 10 (17.86%) isolates. The most common species isolated was *Candida tropicalis* 26 (46.42%), as shown in Figure 1.



**Figure 1:** Distribution of Candida species isolated from blood culture

All the Candida isolates showed 100% sensitivity to voriconazole and micafungin, and the overall sensitivity for fluconazole, amphotericin B, caspofungin, and flucytosine is summarized in Figure 2.

The baseline characteristics of the neonates with candidemia are summarized in Table 1.

The percentage anti-fungal susceptibility of *Candida albicans* and NAC is shown in Table 2.

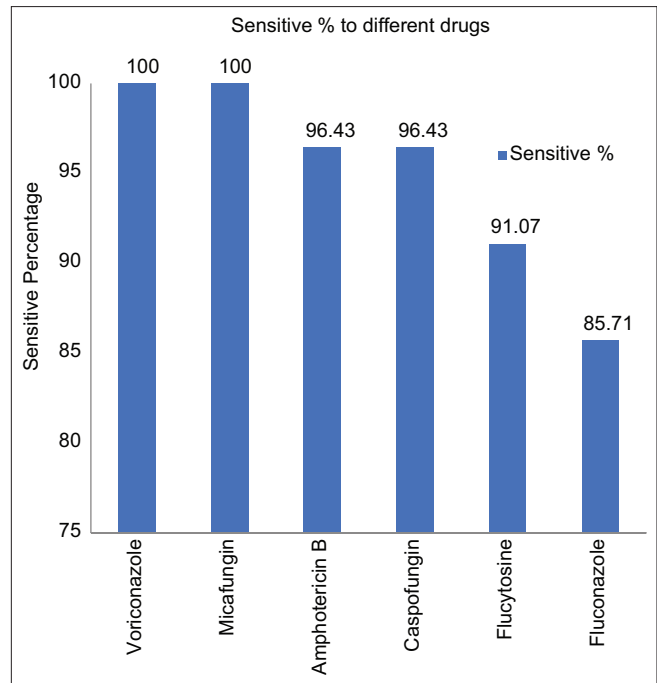
In the uni-variate analysis, the factors significantly associated with candidemia were total parenteral nutrition ( $P < 0.0001$ , 95% CI 0.077 to 0.14), VLBW ( $P < 0.0001$ , 95% CI 0.29 to 0.37), assisted ventilation ( $P < 0.0001$ , 95% CI 0.4337 to 0.5301), pre-term ( $P = 0.0001$ , 95% CI 0.40 to 0.49), central line ( $P < 0.0001$ , 95% CI 0.25 to 0.34), and prolonged antibiotic use ( $P < 0.0001$ , 95% CI 0.37 to 0.46).

Forward step-wise multi-variate logistic regression was used to evaluate the risk factors for candidemia identified as significant in the uni-variate analyses. The results of this analysis are detailed in Figure 3.

Fever was the most common presenting symptom in 92.85%, followed by tachypnea (80.35%), poor weight gain (69.6%), and lethargy (62.5%) observed in our study. The correlation coefficient of fever with tachypnea was 0.77 (CI 0.74 to 0.80,  $P < 0.001$ ). The central line was put in 58.93% for inotropic support and proper management of the neonates. Some of them developed multiple organ dysfunction syndrome (MODS), and the final outcome succumbed to death within 48 hours of candidemia diagnosis. The overall mortality rate in neonates with candidemia was 30.3%.

## Discussion

In the present study, candidemia was responsible for 9.65% cases of suspected neonatal sepsis, which is consistent with the observations of Lamba M *et al.*,<sup>[17]</sup> Goel *et al.*,<sup>[18]</sup> and Benjamin



**Figure 2:** Anti-fungal sensitivity pattern of Candida isolates in the study ( $n = 56$ )

**Table 1: Baseline characteristics of neonates with candidemia**

| Variables   | Value       | P       |
|---|-------------|---------|
| Mean birth weight (g) (mean)                      | 1921        | <0.0001 |
| Male, gender, n (%)                               | 35 (62.5%)  | -       |
| Low birth weight, n (%)                           | 37 (66.07)  | <0.0001 |
| Total parenteral nutrition, n (%)                 | 36 (64.29%) | 0.0031  |
| Normal vaginal delivery, n (%)                    | 36 (85.7%)  | NS      |
| Prolonged use of antibiotics, n (%)               | 46 (82.14%) | <0.0001 |
| Prematurity, n (%)                                | 40 (71.4%)  | 0.00013 |
| Ventilator support, n (%)                         | 26 (46.4%)  | <0.0001 |
| Prolonged rupture of membranes (>18 hours), n (%) | 11 (19.64%) | 0.0007  |
| Thrombocytopenia (<1,50,000 cells/mm)             | 45 (80.35%) | <0.0001 |
| Post-natal steroid treatment                      | 15 (26.78%) | 0.0091  |
| Fever, n (%)                                      | 52 (92.85%) | <0.0001 |
| Tachypnea, n (%)                                  | 46 (81.05%) | 0.32    |

*et al.*<sup>[7]</sup> In a study conducted by Chaudhury *et al.*,<sup>[19]</sup> from Eastern India, the total cases of neonatal candidemia were 10.4%, which is similar to our study, whereas some authors have observed higher rates (31%) of neonatal candidemia.<sup>[12]</sup> These variations in isolation rate of Candida could be because of variability in the various risk factors in the study population. Of the 56 neonates with candidemia in the present study, the majority presented with late onset sepsis and only had early sepsis, which is consistent with the findings of Caggiano *et al.*<sup>[20]</sup> and Benjamin *et al.*;<sup>[7]</sup> they also reported candidemia accounting for 9–13% of blood stream infections in neonates in neonatal ICUs (NICUs).

In our study, Candidemia was more commonly found to be due to NAC species (82.14%), followed by *Candida albicans* (17.8%),

which is similar to several other studies conducted from different regions of India.<sup>[17,18,21-23]</sup> In a 11-year prospective pediatric study in Turkey in 2020, Aslan N *et al.*<sup>[24]</sup> showed collective predominance for NAC species in parallel with our study.

As per the previous reports, most cases of neonatal and pediatric candidemia were caused by *Candida albicans*.<sup>[25]</sup> However, recent studies from different geographical areas of the world including India have shown changing trends of neonatal candidemia, with emergence of NAC species as an important cause of candidemia.<sup>[26-28]</sup>

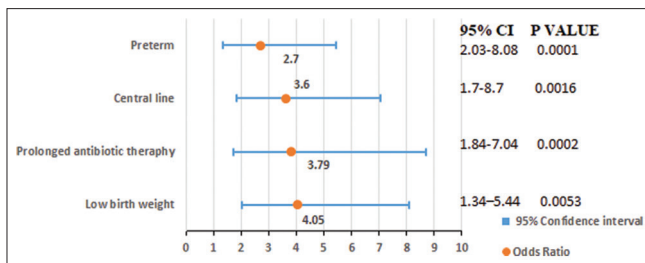
The increased incidence of NAC is probably due to the greater use of invasive devices, broadspectrum anti-bacterial agents,

more extensive surgical procedures, and selection of less susceptible species by the pressure of anti-fungal agents such as fluconazole.<sup>[26]</sup>

In our study, the most common species isolated was *Candida tropicalis* (46.42%), which is comparable to the epidemiological studies carried out in different parts of our country, indicating *Candida tropicalis* as the common cause of nosocomial candidemia.<sup>[6,17]</sup>

Increased incidence of *C. tropicalis* as a cause of candidemia in hospitalized settings may pertain to its presence on the hands of the hospital personnel. The major virulence factor of this organism is the ability to produce clusters. *C. tropicalis* may be more virulent than *C. albicans* when introduced in an immunocompromised host and thereby rapidly progress from colonization to invasion.

The multi-variate logistic regression model suggested that VLBW, prolonged use of antibiotics, and central line were the factors most highly associated with increased odds of candidemia. Similar findings have been reported by other studies that demonstrated the association of risk factors with candidemia in the neonates.<sup>[3,12,17,18,29-31]</sup>



**Figure 3:** Multi-variate logistic regression analysis to determine predisposing risk factors of neonatal candidemia

**Table 2: Anti-fungal susceptibility profile of Candida isolates by VITEK 2 system**

| Organism isolated           | Anti-fungals   | Susceptibility (%) | Intermediate | Resistance (%) |
|-----------------------------|----------------|--------------------|--------------|----------------|
| <i>C.tropicalis</i> (n=26)  | Amphotericin B | 26 (100%)          | -            | 0              |
|                             | Fluconazole    | 26 (100%)          | -            | 0              |
|                             | Voriconazole   | 26 (100%)          | -            | 0              |
|                             | Flucytosine    | 25 (96%)           | -            | 1 (4%)         |
|                             | Caspofungin    | 26 (100%)          | -            | 0              |
|                             | Micafungin     | 26 (100%)          | -            | 0              |
| <i>C.albicans</i> (n=10)    | Amphotericin B | 10 (100%)          | -            | 0              |
|                             | Fluconazole    | 10 (100%)          | -            | 0              |
|                             | Voriconazole   | 10 (100%)          | -            | 0              |
|                             | Flucytosine    | 10 (100%)          | -            | 0              |
|                             | Caspofungin    | 10 (100%)          | -            | 0              |
|                             | Micafungin     | 10 (100%)          | -            | 0              |
| <i>C.gullerimondi</i> (n=6) | Amphotericin B | 6 (100%)           | -            | 0              |
|                             | Fluconazole    | 6 (100%)           | -            | 0              |
|                             | Voriconazole   | 6 (100%)           | -            | 0              |
|                             | Flucytosine    | 6 (100%)           | -            | 0              |
|                             | Caspofungin    | 6 (100%)           | -            | 0              |
|                             | Micafungin     | 6 (100%)           | -            | 0              |
| <i>C.parapsilosis</i> (n=9) | Amphotericin B | 9 (100%)           | -            | 0              |
|                             | Fluconazole    | 6 (66.66%)         | -            | 3 (33.33%)     |
|                             | Voriconazole   | 9 (100%)           | -            | 0              |
|                             | Flucytosine    | 9 (100%)           | -            | 0              |
|                             | Caspofungin    | 9 (100%)           | -            | 0              |
|                             | Micafungin     | 9 (100%)           | -            | 0              |
| <i>C.krusei</i> (n=5)       | Amphotericin B | 3 (60%)            | -            | 2 (40%)        |
|                             | Fluconazole    | 0                  | -            | 5 (100%)       |
|                             | Voriconazole   | 5 (100%)           | -            | 0              |
|                             | Flucytosine    | 1 (20%)            | -            | 4 (80%)        |
|                             | Caspofungin    | 4 (80%)            | -            | 1 (20%)        |
|                             | Micafungin     | 5 (100%)           | -            | 0              |



In our study, the majority of candidemia episodes occurred in VLBW (<1500 g) neonates (66.07%). VLBW infants are known to be at a high risk of candidemia because of their immature immune system, which may lead to an inability to eliminate pathogens from the bloodstream at the initiation of the anti-fungal system.

Broad-spectrum antibiotic use poses a significant threat for candidemia.<sup>[29,10]</sup> A previous study conducted by Kaufman *et al.*<sup>[32]</sup> showed that decreased use of carbapenem may be associated with decreased incidence of invasive fungal infections. The widespread use of anti-bacterial agents may suppress bacterial flora and increase the *Candida* colonization density.<sup>[33]</sup> This finding highlights the need to evaluate the anti-microbial burden in local NICUs in India.

Use of various invasive devices, such as catheters and endotracheal tubes, may be to blame for the nosocomial spread of pathogens through the hands of health care workers (HCWs). In this study, we did not obtain samples from potentially colonized HCW in the unit. The hands of HCW and environmental surfaces are recently acknowledged as potential reservoirs for nosocomial strains of *Candida*. More importantly, prophylactic measures such as the use of filters for parenteral nutrition and implementing a restrictive policy toward antibiotic use to decrease *Candida* colonization/infection rates will further reduce the morbidity and mortality associated with these infections.

It was observed in the present study that fever was the most common presenting symptom (92.85%), followed by tachypnea (80.35%). Similar findings have been reported by other authors also.<sup>[34]</sup>

Thrombocytopenia can be a specific marker of fungal sepsis in NICU. In our study, 45 out of 56 neonates (80.35%) had thrombocytopenia, which is comparable to Yunus *et al.*,<sup>[33]</sup> who found 66/83 (80%) incidence of thrombocytopenia in patients with invasive fungal sepsis.

In the present study, we found an increase in the anti-fungal drug resistance, especially for the azole group of drugs in NAC species. Many authors have also found increasing trends of fluconazole resistance, reported as 37.5% by Gupta *et al.*,<sup>[35]</sup> 36% by Kotbari *et al.*,<sup>[36]</sup> and 11.7% by Xess *et al.*<sup>[29]</sup>

In the study reported by Narain *et al.*,<sup>[37]</sup> all fungal isolates were sensitive to amphotericin B, which is in contrast to our study as fungal resistance to amphotericin B was found to be 3.57% among all the *Candida* isolates. Similar results were reported by Bhatt *et al.*<sup>[38]</sup> with resistance to amphotericin B at 8%.

In other studies also, a variable range of resistance to flucytosine was reported, ranging from 37% by Bhatt *et al.*<sup>[38]</sup> to 0% by Pahwa *et al.*<sup>[39]</sup>

Our study showed increasing incidence of multi-drug-resistant species of *Candida krusei* (8.90%), which is comparatively higher than

findings (1–4%) in previous studies.<sup>[6,17,18]</sup> This high incidence of *Candida krusei* could be due to use of fluconazole in empirical treatment of suspected neonatal systemic candidiasis, which might have led to selection of innately resistant to it. Xess *et al.*<sup>[29]</sup> reported 3.3% incidence of *C. krusei* in North India. Only one Indian study by Shrivastava G, *et al.*<sup>[40]</sup> reported 38% incidence of *C. krusei* in Central India. The rise of resistant species is alarming and should be considered thoroughly. It shows the importance of keeping echinocandins as the second-line drugs at hand.

This study has limitations inherent to a single center and a lack of follow-up of neonates who were diagnosed to have candidemia to study the long-term consequence in neonates. More regional data from different hospital settings are needed in future to allow comparison of findings. Further studies on risk factors for candidemia and on newer anti-fungal drugs should be emphasized.

## Conclusion

*Candida* species are important bloodstream pathogens in neonates that are being isolated with increasing frequency. In this population, candidemia due to NAC has been increased dramatically in the past few decades and associated with a poor prognosis. To conclude, emergence of NAC species and their association with higher mortality and longer duration of hospital stay is a cause for concern. Increased incidence and occurrence of multi-drug resistance of *C. krusei* are 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. Adequate and accurate laboratory diagnosis with correct species identification can limit the mortality by initiation of timely and cost-effective anti-fungal treatment and will lead to containment of multi-fungal-resistant infection in the community.

## Ethical approval

Approved by Institutional Research Board (IRB) and Institutional Ethics Committee (IEC) wide memo no. 31, IEC, Rims, Ranchi, Dated 03-06-2020.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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