

## Incidence of invasive candidal infection in very low birth weight neonates over a period of 5-year: A single institutional study

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Received – 16 June 2016

Initial Review – 27 June 2016

Published Online – 19 July 2016

### ABSTRACT

**Background:** Fungal infection is one of the important causes of bloodstream infection in very low birth weight (VLBW) and extremely low birth weight (ELBW) infants. **Objective:** To find out the incidence, mortality rate, and clinical spectrum of infants with invasive candidal infection (ICI) among VLBW infants. **Materials and Methods:** A retrospective descriptive study was conducted over a period of 5-year at a tertiary care hospital. VLBW infants admitted within 24 h of birth were included. The clinical characteristics and the outcome of the infants who developed fungal infection were studied. The end point was either discharge from the unit or death of the infants who developed fungal sepsis. **Results:** During the study period, there were a total of 641 VLBW infants admitted and 18 neonates had invasive fungal infections (ICI), which accounted to an incidence of 2.8%. The mean birth weight was 1010±289 g, and the mean gestational age (GA) was 28.6±2.93 weeks. End organ involvement was found in 9 (50%) infants with the eye being the most commonly involved organ (39%) followed by renal involvement (22%). Stratified analysis revealed that lower GA and lower birth weight were associated with higher incidence of ICI ( $p < 0.01$ ). Out of 18 isolates that were identified, *Candida albicans* was the most common organism isolated in 13 (72%) infants. More than ¼ of the cultures (28%) isolated were non-*albicans Candida* species. The mortality rate among infants with ICI was 11% (2/18). The two infants who died had septicemia caused by *C. albicans* and multiple (renal and eye) end organ involvement. All-cause mortality in the study group was also 11% (73/641). **Conclusion:** The incidence of ICI without systemic antifungal prophylaxis was 2.8% and 5.3% in VLBW and ELBW infants, respectively. *C. albicans* was more common, but the emergence of *Candida* non-*albicans* is seen as a growing threat with some of them displaying resistance to azole group of antifungals.

**Key words:** *Candida*, Fungal, Incidence, Neonates, Very low birth weight

Neonatal care has progressed tremendously leading to increasing number of survivors among very low birth weight (VLBW) neonates. Neonates, especially premature infants, are well known to have impaired innate immunity making them susceptible to systemic infection and fungal colonization [1,2]. The incidence of systemic fungal infection in preterm infants is reported to vary widely between 2% and 22% [3-9]. Specifically, invasive fungal infection is associated with end-organ involvement in 22-34% [10,11].

Blood culture remains the gold standard for diagnosing fungal infection. Approximately 90% of fungal infections in VLBW neonates are caused by *Candida* species [12], and most of them are caused by *Candida albicans* and *Candida parapsilosis* with increasing recognition of infection by *Candida tropicalis* [13,14]. The risk factors associated with invasive candidal infection (ICI) are extreme prematurity, broad-spectrum antibiotic use, prolonged antibiotic therapy for more than 7 days, central catheter use, ventilation, vaginal

delivery, use of H<sub>2</sub> blockers and steroids, and abdominal surgery [4,15-19].

As ICI is associated with high mortality and morbidity, prophylactic systemic antifungal therapy has been advocated, especially in units with a high incidence of ICI [5]. Studies on incidence of ICI in India being sparse, it was felt that investigating the incidence of ICI would help to define protocol on starting prophylactic systemic antifungal therapy and also to implement quality improvement initiatives to reduce neonatal fungal infections. Although candidal species are sensitive to amphotericin B and azoles, there are concerns on the emergence of resistant organism. Knowing antifungal susceptibility pattern would help physicians to decide on starting empirical antifungal therapy.

The present study was conducted to find out the incidence of ICI among VLBW infants. Further, the study identified the mortality rate and clinical spectrum of VLBW infants with ICI observed over a period of 5-year.

## MATERIALS AND METHODS

A retrospective descriptive study was conducted among VLBW infants admitted to Neonatal Intensive Care Unit (NICU) of a tertiary care hospital, between January 2010 and December 2014. The neonatal unit is a 60 bedded level III-B accredited unit with 24 intensive care beds. It has an average annual admission of 1100 neonates. Institutional Ethical Approval (IEC-NI/16/APR/52/23) was obtained for conducting the study.

Neonates with birth weight <1500 g (VLBW) admitted within 24 h of birth were included. The clinical characteristics and the outcome of the infants who developed fungal infection were studied. The end point was either discharge from the unit or death of the infants who developed fungal sepsis. Data were retrieved from the medical records department using inpatient database classified according to the International Code of Diseases (ICD) 10. The codes used were ICD code "P 07.3" (for preterm) and ICD code "P 37.5" (neonatal candidiasis). Neonatal admission records were also verified. The data were cross-checked with laboratory registry of the microbiology department. The following clinical parameters were collected: Gestational age (GA), birth weight, sex, mode of delivery, intramural delivery or outborn, ventilation, the length of stay, the day of occurrence of ICI, end organ involvement, and the outcome. Data were stratified into groups based on birth weight (<800 g, 800-1000 g, and 1001-1499 g) and GA (<26 weeks, 26-28 weeks, and >28 weeks) of the infants.

We defined the presence of ICI if *Candida* was isolated from sterile site (blood, cerebrospinal fluid [CSF], or urine) in the presence of systemic signs of infection. The day of obtaining positive blood culture was considered as day of acquiring the candidal infection. Species identification was made, and its antifungal susceptibility pattern was documented. End organ involvement was considered when there was any evidence of organ involvement following ICI.

During the study period, the unit protocol in the management of VLBW infants was as follows: All VLBW infants were started on total parenteral nutrition (TPN) with minimal enteral feed started within 24 h of birth with expressed breast milk. The feed was increased by 10-20 ml/kg/day until a target feeding volume of 150 ml/kg/day was achieved. To administer TPN, all the infants were started on central line (umbilical venous line or peripherally inserted central cannula) within 24 h of birth. All infants received 2 drops of clotrimazole swabbed over oral cavity while either on orogastric feeds or on antibiotics. Prophylactic systemic fluconazole was not used during the study period. Piperacillin with tazobactam and amikacin were used for late onset bacterial sepsis, and antibiotics were changed depending on the sensitivity and clinical response.

Infants with suspected sepsis underwent septic workup including blood culture, total blood count, differential count, absolute neutrophil count, and quantitative C-reactive protein (CRP). 1 ml of blood was obtained by venipuncture from a peripheral vein under aseptic precautions and was inoculated into Bactec Pediatric blood culture vial. Blood culture was considered

sterile if there was no growth detected after 7 days of incubation. If the blood culture grew fungus or when clinician suspected fungal sepsis, amphotericin B was started. Urine culture was obtained by suprapubic aspiration done under aseptic precautions before starting on amphotericin B. The infants were screened for end organ involvement within 72 h following isolation of *Candida* from the blood stream. Criteria for end organ involvement were as follows: CNS infection-if there was CSF pleocytosis or isolation of *Candida* from CSF or cranial ultrasound showing cerebral abscess, eye infection in presence of chorioretinitis as opined by ophthalmologist, cardiac infection in presence of vegetation detected by two-dimensional echocardiography; hepatic and/or renal infection-if ultrasonography showed evidence of fungal balls or abscess. Either voriconazole or flucytosine was added if there had been evidence of eye or CNS involvement, respectively. Blood culture was repeated every 48 h till culture became sterile.

Blood culture vials were incubated for 5 days in a continuous monitoring blood culture system, the Bactec 9120 (BD, USA), in the Department of Microbiology. Urine or CSF samples were inoculated into cystine lactose electrolyte deficient agar/blood agar/MacConkey agar. Once the candidal growth is identified, the samples were further processed using VITEK 2 Compact (bioMérieux, France) for species identification and susceptibility pattern.

## Statistical Analysis

Continuous variables were expressed in mean and standard deviation for normal distribution and median and interquartile range for non-normal distribution. Categorical variables were expressed as number and percentage. Categorical variables were analyzed using Chi-square test. All the analyses were done using SPSS version 18.0 software.

## RESULTS

During the study period, there were a total of 641 VLBW infants admitted to the NICU. Of them, 18 neonates had ICI, which accounted to an incidence of 2.8%. Baseline characteristics are depicted in Table 1. None of the infants had early onset (<72 h of life) ICI. All the infants who developed ICI had prior use of antibiotics. Mean antibiotic duration before ICI was 12.3±5.2 days. 11% of infants received antibiotics for <7 days. Half of the infants had prior bacterial sepsis. None of the infants received H<sub>2</sub> blockers. Candidal growth was reported as early as 2 days and latest by 5 days of sending blood cultures in all infants with fungal infection. After initiation of antifungal therapy, in the majority of infants (77%), fungal clearance occurred within 4 days.

End organ involvement was found in 9 (50%) infants. Eye and renal involvement was detected in 7 (39%) and 4 (22%), respectively. One infant had a hepatic granuloma. None of the infants with ICI had infective endocarditis, candidal meningitis, or cerebral abscess.

The incidence of ICI is depicted in the Fig. 1 and Table 2. Incidence of ICI among extremely low birth weight (ELBW) and VLBW infants were 5.3% (10/187) and 2.8% (18/641), respectively. Stratified analysis revealed that lower GA and lower birth weight were associated with higher incidence of ICI (p<0.01).

The hematological parameters are depicted in Table 3. None of the infants with ICI had absolute neutrophil count <1700 cells/mm<sup>3</sup>. 15 out of 18 (83%) had a positive qualitative CRP. Two-third of infants (12/18) had thrombocytopenia. Among the infants with thrombocytopenia, 9 (75%) had platelet count of <100,000 cells/mm<sup>3</sup>, and 4 (33%) had platelet count <50,000 cells/mm<sup>3</sup> (severe thrombocytopenia).

Out of the total 18 isolates, *C. albicans* was the most common organism isolated in 13 (72%) infants followed by *C. tropicalis* in 4 (22%) and *C. parapsilosis* in 1 (5%) (Fig. 2). More than ¼ of cultures (28%) isolated were non-albicans *Candida* species. All the *C. albicans* were sensitive to azoles whereas out of the 5 non-albicans *Candida* species, 2 were resistant to fluconazole, itraconazole, ketoconazole, and voriconazole. Both albicans and non-albicans were sensitive to amphotericin B.

The mortality rate among infants with ICI was 11% (2/18). The two infants who died had septicemia caused by *C. albicans*

and multiple (renal and eye) end organ involvement. In addition, the infants had bacterial sepsis before the development of fungal infection and received broad-spectrum antibiotics. All-cause mortality in the study group was also 11% (73/641).

**DISCUSSION**

*Candida* species is the third most common organism causing nosocomial sepsis in neonates [5]. The incidence of ICI among VLBW infants was 2.8% in the present study. Incidence reported in previous studies widely varies depending on the unit ranging from 2% to 12% [6,7,8,20]. Studies on incidence in developing countries are sparse. In a study by Singh et al., from India, invasive candidiasis occurred in 22.8% of preterm infants who stayed in NICU for more than 7 days [9].

The incidence of ICI in ELBW infants in our study was 5.3% when compared to the reported incidence of 5-16% [4,6,7,20]. The observed low incidence could be attributed to the use of prophylactic topical antifungal therapy in the unit, avoidance of use of cephalosporin group of antibiotics, and avoidance of the use of H<sub>2</sub> blockers. The incidence was inversely proportional to the birth weight. In the present study, ICI in infants <800 g and in infants between 800 and 1000 g, occurred 2.5 times and 1.5 times more frequently, compared to VLBW infants, respectively. There

**Table 1: Baseline characteristics**

General characteristics	N (%) (n=18)
Birth weight (g)	1010±289 g*
Gestational Age (weeks)	28.6±2.93*
Male	12 (67)
Vaginal delivery (n%)	12 (67)
Outborn (n, %)	5 (28)
ICU stay before ICI (in days)	17.5 (13, 38.25)#
Mechanical ventilation	10 (56)

\*Mean (±SD), #Median and interquartile range. All percentage rounded to whole number. ICU: Intensive care unit, ICI: Invasive candidal infection, GA: Gestational age

**Table 2: Incidence of ICI according to the GA and birth weight**

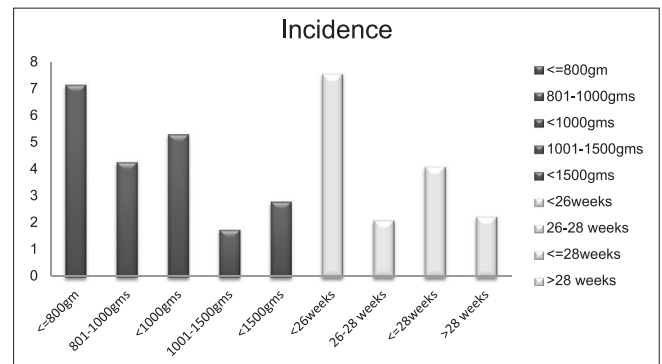
Birth weight/ GA at birth	Candidal infection (n)	Total infants (n)	Incidence (%)	p value*
≤800 g	5	70	7.14	0.009
801-1000 g	5	117	4.27	
1001-1500 g	8	454	1.76	
<26 wks	5	53	7.54	0.023
26-28 wks	3	142	2.11	
>28 wks	10	446	2.24	

\*Using Chi-square test. ICI: Invasive candidal infection, GA: Gestational age

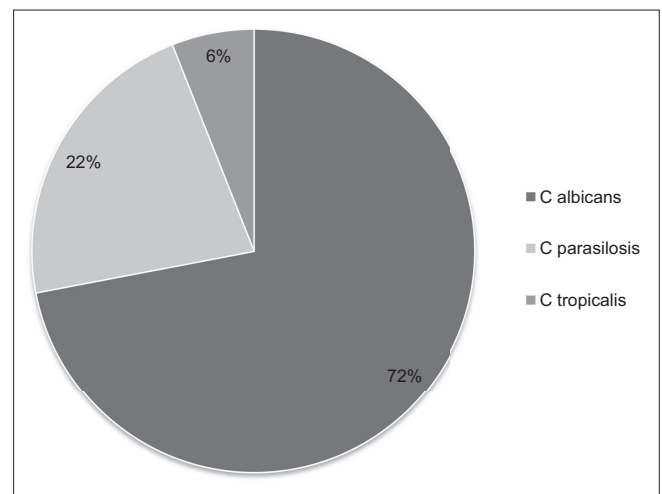
**Table 3: Hematological parameters**

Hematological variables	Median (IQR)
Hemoglobin (g%)	9 (10-11)
Total count (cells/mm <sup>3</sup> )	13550 (10847-18040)
ANC (cells/mm <sup>3</sup> )	6940 (5521-10231)
Quantitative CRP (mg/dL)	2 (1.32-4.2)
Platelet count (cells/mm <sup>3</sup> )	1.01 (0.6-3.26)

IQR: Interquartile range, ANC: Absolute neutrophil count



**Figure 1: Incidence of invasive candidal infection (%) according to the gestational age and birth weight**



**Figure 2: Distribution of organism**

was a significant increased incidence of ICI in lower birth weight ( $p=0.023$ ). Peak incidence was observed in infants <26 weeks after which the incidence plateaued. There was a significant increased incidence of ICI in lower GA ( $p<0.01$ ). Previous studies have also shown strong inverse relationship for both GA and birth weight with ICI [4,6,21,22]. Nearly, 90% of infants received antibiotics for more than 7 days. Among infants with ICI, two-third were born by vaginal delivery and two-third were male infants, both of which have been described as known risk factors for developing fungal infection [17].

In the present study, the median day of onset of ICI was 17.5 days ranging from 9 to 95 days. The review of the literature shows a predominant occurrence of systemic candidiasis between 2<sup>nd</sup> and 4<sup>th</sup> week of life [17,11] with longer duration of stay contributing to the development of fungal sepsis.

Quantitative CRP (cutoff of 1 mg/dL) was positive in 83% of infants with fungal infection. Absolute neutrophil count and total white cell count were not contributory. We observed that two-third of the infants with ICI had thrombocytopenia with only 22% showing severe thrombocytopenia (count <50,000/mm<sup>3</sup>). Severe thrombocytopenia has been reported to be one of the predictive markers for the diagnosis of candidemia [21].

As clinical presentations and markers of infection are non-specific, the diagnosis of ICI was predominantly based on the culture positivity. In the present study, culture reports were obtained in 48 h, but none of them had positive fungal culture after 5 days of sending blood culture. This will help the treating physician to stop empirical antifungal therapy in 5 days if culture is sterile.

ICI has been associated with end organ involvement in 22-34% in various studies [10,11]. We observed end organ involvement secondary to dissemination in 50% of the cases. In our study, both the infants who died were ELBW infants, with GA of <28 weeks; had prior bacterial infection; were on broad-spectrum antibiotics at the time of fungal sepsis; had candiduria, multiple end organ involvement, and *C. albicans* infection susceptible to amphotericin B. We could not study the risk factors associated with mortality as the sample size was small. The study recommends that all infants developing ICI should be screened for end organ involvement for assessing the severity of the infection. This would also help to decide the duration of treatment and to prognosticate. Mortality rate among infants with ICI in our center was in the lower limit of the reported mortality rate, which ranged from 11% to 30% in the literature [7,10,17,18,23-25].

The predominant organism isolated was *C. albicans* (72%), which is in agreement with previous studies [7,17,20]. In our study, more than 25% of the total fungal isolates were non-albicans *Candida* species, which is in concordance with various published reports [16,26]. However, in a study by Chaurasia et al., non-albicans *Candida* species were isolated in 80% of the neonates studied [14]. In our study, out of 5 non-albicans *Candida* species, 2 were resistant to fluconazole, itraconazole, ketoconazole, and voriconazole. Hence, emergence of non-albicans *Candida* species has been a threat to neonatal units [27,28]. This makes it

imperative to find both the species and antifungal susceptibility for all the fungal isolates. In our unit, amphotericin B should remain as drug of choice with the emergence of non-albicans, as all the isolates were susceptible to amphotericin B.

Evidence from a meta-analysis of 10 clinical trials involving 1371 infants has shown a significant reduction in the incidence of ICI among infants on fluconazole prophylaxis [19]. Red book of infectious diseases (2012) recommends the use of fluconazole prophylaxis in institutes with 5-10% of fungal infection incidence among ELBW infants [29]. Before implementation of fluconazole prophylaxis, individual units should have their own data on the incidence of fungal infection. The ICI incidence rate of 5.7%, observed in the current study, has helped us to plan on starting fluconazole prophylaxis for ELBW infants. It also substantiates the importance of epidemiological data to implement appropriate preventive and therapeutic strategies in all neonatal units and thereby decreasing morbidity and mortality.

## CONCLUSION

The incidence of ICI without systemic antifungal prophylaxis was 2.8% and 5.3% in VLBW and ELBW infants, respectively. Incidence increases significantly with decreasing GA and birth weight. *C. albicans* were more common, but the emergence of *Candida* non-albicans is seen as a growing threat with some of them displaying resistance to azoles group of antifungals. Epidemiological data such as incidence of fungal sepsis are important to implement appropriate preventive and therapeutic strategies in all neonatal units.

## ACKNOWLEDGMENTS

The authors would like to thank Cynthia for critically analyzing the manuscript.

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*Funding: None; Conflict of Interest: None Stated.*

**How to cite this article:** Amboiram P, Umamaheswari B, Ninan B, Saravanan R, Ashok C, Kumar KS. Incidence of invasive candidal infection in very low birth weight neonates over a period of 5-year: A single institutional study. *Indian J Child Health*. 2016; 3(3):191-195.