Candida Species Causing Neonatal Septicaemia - Experience in a Tertiary Care Centre

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ABSTRACT

BACKGROUND

Candida species is one of the most common causes of bloodstream infections among neonates and accounts for 9-13% of such infections. Non-albicans *Candida* have emerged as important opportunistic pathogens, notably *C. tropicalis*, *C. glabrata*, *C. parapsilosis* and *C. krusei*. With the introduction of antifungal agents, the causes of *Candida* infections shifted from an almost complete dominance of *Candida albicans* to the common involvement of *Candida glabrata* and other non-albicans *Candida* species.

METHODS

This prospective, microbiological observational study was conducted in a tertiary care hospital for one and a half years from July 2016 to December 2017. Blood samples of neonates collected into Bactec Peds Plus/F Culture vials of an automated blood culture system (Bactec 9120, Becton Dikinson, USA) from clinically suspected cases of neonatal septicaemia were subjected to culture. Detailed clinical history such as presence of respiratory distress, abdominal distension, lethargy, feed intolerance, failure to thrive, poor perfusion, history of convulsions, duration of NICU stay and antibiotic use was taken from the medical records. The *Candida* species isolated were identified using standard mycological techniques.

RESULTS

Out of the total 250 clinically suspected cases of neonatal septicaemia, fungal growth was positive in 30 (12%) cases. *Candida albicans* accounted for 10% and non albicans *Candida* accounted for 90% of the fungal isolates. *Candida glabrata* (73.33%) was the commonest species followed by *Candida tropicalis* (16.67%) and *Candida albicans* (10%). Failure to thrive (60%), lethargy (50%) and respiratory distress (30%) were the most common clinical presentations seen, followed by feed intolerance (26.67%), abdominal distension (13.33%) and fever (10%). Among the risk factors observed for neonatal candidemia, low birth weight (76.67%) and prematurity (73.33%) were commonest followed by broad spectrum antibiotic use (66.67%), total parenteral nutrition (53.3%), ventilator support (36.67%) and indwelling catheters (26.67%).

CONCLUSIONS

Non-albicans *Candida* has emerged as an important pathogen causing neonatal septicaemia. Fungal sepsis is more common among preterm, low birth weight infants, those with prolonged antibiotic use and those on total parenteral nutrition. *Candida glabrata* caused the highest number of cases of fungal septicaemia.

KEY WORDS

Neonatal Candidemia, Non-Albicans *Candida*, *Candida Glabrata*

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BACKGROUND

Significance of *Candida* species in neonatal intensive care unit (NICU) is increasingly being recognized. *Candida* species is one of the most common causes of bloodstream infections among neonates and accounts for 9-13% of such infections.[1] Historically *Candida albicans* has been the most frequently isolated species worldwide. Recently non- albicans *Candida* have emerged as important opportunistic pathogen, notably *C. tropicalis*, *C. glabrata*, *C. parapsilosis* and *C. krusei*.[2,3,4] Candidemia is a significant cause of mortality and morbidity in neonates.[5] Previous studies have suggested that possible risk factors such as very low birth weight (LBW), prematurity, prolonged antibiotic therapy, prolonged use of fat emulsions in total parenteral nutrition (TPN), use of artificial ventilation, presence of indwelling central venous catheters (CVC), and intensive care unit (ICU) stay have made neonates prone to candidemia. Preterm, very low birth weight (VLBW): ≤1500 g; extremely LBW: ≤1000 g; and critically ill infants are at highest risk of invasive *Candida* infections. The clinical manifestations are respiratory insufficiency, apnoea, bradycardia, feeding intolerance, temperature instability and abdominal distension.[5] Colonization of skin and gastrointestinal tract is the first step in the pathogenesis of invasive candidiasis.[6] Delay in recognition of *Candida* infections and in the initiation of appropriate antifungal therapy often leads to significant morbidity and mortality rates among high‐risk infants.

The genus *Candida* encompasses more than 150 species, only a few of which cause disease in humans. With rare exceptions, the human pathogens are *Candida albicans*, *Candida guilliermondii*, *Candida krusei*, *Candida parapsilosis*, *Candida tropicalis*, *Candida kefyr*, *Candida lusitaniae*, *Candida dubliniensis*, and *Candida glabrata*.[7,8] These organisms are found on inanimate objects, in foods, and on animals, and are normal commensals of humans. They inhabit the gastrointestinal tract (including the mouth and oropharynx), the female genital tract, and the skin in humans with introduction of antifungal agents, the causes of *Candida* infections shifted from an almost complete dominance of *Candida albicans* to the common involvement of *Candida glabrata* and the other species listed above.[9] The NAC species now account for approximately half of all cases of candidemia and hematogenously disseminated candidiasis. Recognition of this change is clinically important, since the various species differ in susceptibility to the newer antifungal agents. In developed countries, where medical therapeutics are commonly used, *Candida* species are now among the most common nosocomial pathogens.[9] There are multiple risk factors that are responsible for neonatal candidemia like preterm such as low birth weight <1500 g and infection through vertical transmission from maternal flora or via horizontal transmission from hands of health care workers. The incidence and associated mortality due to candidemia can be influenced by several factors including characteristic of population at risk, standard of the health care facilities available, distribution of *Candida* species and prevalence of antifungal resistance. Systemic candidiasis in neonates is increasing in frequency especially since the survival of babies with low birth weight (LBW) has increased.[6] Considering all these facts, the present study was conducted to find out the percentage of isolation of *Candida* species from clinically suspected cases of neonatal septicaemia; the underlying co-morbid conditions in culture proven cases of candidemia and identify *Candida* species causing septicaemia in neonates.

METHODS

The study was a cross-sectional microbiological observational study carried out for one and a half year duration from July 2016 to December 2017. The study was conducted after approval from the Institutional Ethics Committee. Informed consent was taken from the parent (Of neonate) prior to the patient enrolment.

Blood samples of neonates collected into Bactec Peds plus/F culture vials of an automated blood culture system (Bactec 9120, Becton Dikinson, USA) from clinically suspected cases of neonatal septicaemia was subjected to culture. Detailed clinical history such as presence of respiratory distress, abdominal distension, lethargy, feed intolerance, failure to thrive, poor perfusion, history of convulsions, duration of NICU stay and antibiotic use was taken from the medical records. When pathogenic bacteria gain access into the bloodstream, they may cause overwhelming infection without much localization (septicaemia). Candidemia is defined as the presence of at least one positive blood culture containing pure growth of *Candida* species with supportive clinical features.[10]

Smears were prepared of the samples that flashed positive in the automated blood culture system. The positive samples were subcultured on 5% sheep blood agar plate and were kept for overnight incubation at 37^0C. *Candida*l growth was confirmed by gram staining of the smears prepared from growth on blood agar plate. Any growth indicated was subcultured on Sabouraud dextrose agar with chloramphenicol (0.05%) and cycloheximide and incubated at 37^0C and at room temperature.[11] All the *Candida* isolates were subjected to germ tube test using normal human serum. Colonies were identified up to the species level on the basis of morphology on Corn meal agar (Dalmau method) and sugar assimilation pattern.

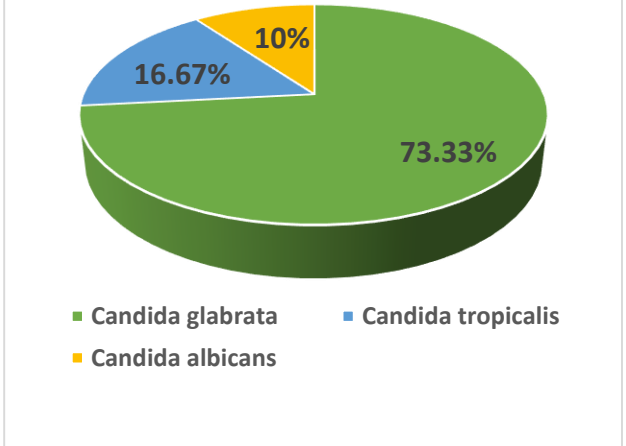
Statistical Analysis

For data analysis, frequency and percentages were calculated. The percentage of isolation of *Candida* species from the total number of clinically suspected cases of neonatal septicaemia was calculated. The underlying co-morbid conditions in the culture proven cases of candidemia were enlisted and frequency table was formulated. *Candida* species causing neonatal septicaemia were identified and frequency tables were formulated.

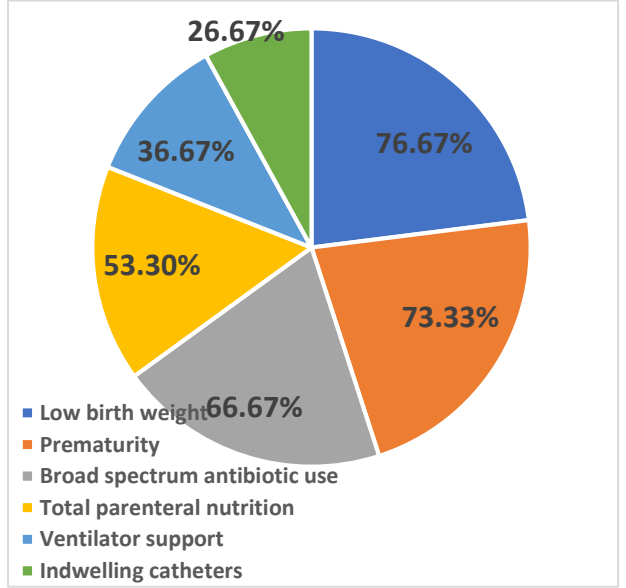
RESULTS

Out of the total 250 clinically suspected cases of neonatal septicaemia, growth was seen in 40 (16%) of cases. Fungal growth was positive in 30 (12%) cases, bacterial growth was seen in 10 (4%) cases, 11 (4.4%) showed contamination and 199 (79.6%) did not show any growth. *Candida albicans* accounted for 10% and non albicans *Candida* accounted for

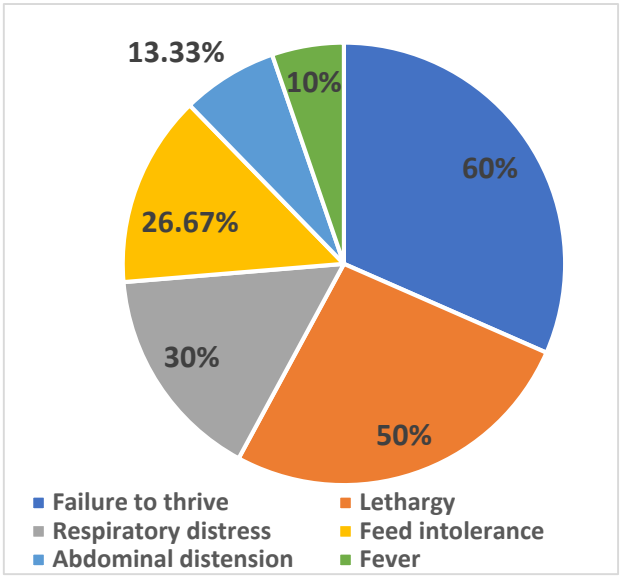
90% of the fungal isolates. *Candida glabrata* (73.33%) was the commonest species followed by *Candida tropicalis* (16.67%) among the fungal isolates. The bacterial growth constituted of *Klebsiella pneumoniae* 4 (1.6%), methicillin resistant *Staphylococcus aureus* (MRSA) 3 (1.2%), *Enterococcus sp.* 1 (0.4%), *Streptococcus sp.* 1 (0.4%) and *Enterobacter sp.* 1 (0.4%). *Candida sp.* were isolated from 30/40 (75%) of positive cases while bacteria were isolated from 10/40 (25%) of positive cases. *Candida glabrata* (73.33%) was the commonest isolate followed by *Candida tropicalis* (16.67%) and *Candida albicans* (10%). The average gestational age was 32 weeks (30-39 weeks) and average birth weight was 1.77± 0.615 kg (0.82 – 3 kg). Among the risk factors observed for neonatal candidemia, low birth weight (76.67%) and prematurity (73.33%) were commonest followed by broad spectrum antibiotic use (66.67%), total parenteral nutrition (53.3%), ventilator support (36.67%) and indwelling catheters (26.67%). Failure to thrive (60%), lethargy (50%) and respiratory distress (30%) were the most common clinical presentations seen, followed by feed intolerance (26.67%), abdominal distension (13.33%) and fever (10%).



Distribution of Candida spp. in NICU



Potential Risk Factors Observed for Candidemia among Fungal Culture Positive Cases (n=30)



Various Clinical Presentations Observed in Cases of Neonatal Candidemia from NICU

Total	250	Percentage
Growth	40	16%
Fungal Growth	30	12%
Bacterial Growth	10	4%
Contamination	11	4.4%
No Growth	199	79.6%

Culture Results

Growth	Number	Percentage
Candida glabrata	22	73.33%
Candida tropicalis	5	16.67%
Candida albicans	3	10%

Distribution of Candida Species in NICU

Risk Factors	Number of Cases	Percentage
Low birth weight	23	76.67%
Prematurity	22	73.33%
Broad spectrum antibiotic use	20	66.67%
Total parenteral nutrition	16	53.3%
Ventilator support	11	36.67%
Indwelling catheters	8	26.67%

Potential Risk Factors Observed for Candidemia among the Fungal Culture Positive Cases (n=30)

Sign/Symptoms	Number of Cases	Percentage
Failure to thrive	18	60%
Lethargy	15	50%
Respiratory distress	9	30%
Feed intolerance	8	26.67%
Abdominal distension	4	13.33%
Fever	3	10%

Various Clinical Presentations Observed in Cases of Neonatal Candidemia (n=30)

DISCUSSION

The rate of isolation of *Candida* species from fungal culture positive isolates in our study is 12% which is comparable to the study done by Kumar et al[12] in 2011, in which the rate of isolation was 14.9%. Various studies have been carried out over the last decade which showed the rate of isolation of *Candida* species as 19.14% (Baradkar et al, 2008),[1] 30.1% (Sardana et al, 2012),[13] 20.39% (Srinivas Rao et al, 2014),[14] 32.26% (Wadile et al, 2015).[6]

Several studies have demonstrated the association of various risk factors with candidemia like low birth weight, preterm delivery, prolonged use of higher antibiotics like third generation cephalosporins and carbapenems, use of intravenous catheters, parenteral nutrition etc.[15,6] These risk factors increase the susceptibility to infections because of the immaturity of the immune system and invasive medical equipment needed for improvement of the survival rate of the neonates. LBW, prematurity and use of broad spectrum antibiotics were the major risk factors implicated followed by total parenteral nutrition, ventilator support and indwelling catheters in the present study. This was in consistence with other studies done by Sardana et al, Juyal et al, Srinivas Rao et al and Wadile et al.[13,6, 14,16]

Failure to thrive (60%), lethargy (50%) and respiratory distress (30%) were the most common clinical presentations seen, followed by feed intolerance (26.67%), abdominal distension (13.33%) and fever (10%). Failure to thrive (18/30) and lethargy (15/30) were consistent clinical findings in our neonatal cases, similar to other studies.[17,18,6,19] Respiratory distress (74.55%) followed by failure to thrive and lethargy were most common clinical findings in a study by Sardana et al whereas Juyal et al showed failure to thrive (74.42%) followed by abdominal distension and feed intolerance.[13,16]

Candida species are an increasingly common cause of neonatal sepsis and are responsible for considerable morbidity and mortality.[20,21,17] Modern day neonatal care has definitely improved the survival rate of neonates but also increased the use of multiple invasive medical equipment, which has further enhanced the acquired sepsis among the newborns. Over the last two decades, non-albicans *Candida* (NAC) are accounting for a large burden of neonatal septicaemia.[18,22,13] Agarwal and co-authors reported that 76 out of the 90 isolates were NAC. Yadav et al also observed 88.46% of the isolates belonged to non albicans group.[20,23] In our study, non-albicans *Candida* bloodstream infections were commonest (90%). This finding is consistent with other studies where non-albicans *Candida* spp. predominate in Asia, South Europe, South America and also in the subcontinent of India.[17,24]

C. glabrata was the commonest species isolated in 73.33% cases of candidemia followed by *C. tropicalis* (16.67%) and C. albicans (10%) in the present study. Whereas in a study by Yadav et al,[20] the commonest species isolated was *C. tropicalis* (26.92%). The rate of isolation of *Candida glabrata* (73.33%) in the present study is quite high in comparison to other studies done over the last ten years. According to previous studies the rate of isolation of *C. glabrata* has been 61.22% (Baradkar et al, 2008),[1] 19.69% (Kumar et al, 2011),[2] 39% (Sardana et al, 2012),[13] 13.50% (Juyal et al, 2014),[16] 19.23% (Srinivas Rao et al, 2014),[14] 6.7% (Shrivastava et al, 2015),[9] 10% (Wadile et al, 2015),[6] 15.8% (Sil et al, 2017)[25] and 33.3% (Fu et al, 2017).[26] Non-albicans *Candida* spp. are of special concern, due to their high virulence and low azole susceptibility characteristics, augmenting the high mortality rates. This rise is suggested to be a result of fluconazole prophylaxis given as a practice in many tertiary care centers.

In the present study, out of the total 250 clinically suspected cases of neonatal septicaemia, fungal growth was positive in 12% cases and bacterial growth was seen in 4% cases. The clinical manifestations of neonatal sepsis are indistinguishable in bacterial and fungal septicaemia. Thus it is important to identify the etiological agent in order to start appropriate treatment. 4.4% showed contamination which included micrococci and diphtheroids.

Probably infections due to *Candida* species are endogenous. It has been studied that about 10% of babies in the NICU get colonized in the first week of life and 64% babies get colonized by 4 weeks of hospital stay. The gastrointestinal tract is the first to become colonized though multiple sites may be involved.[1,27] There is some evidence showing correlation between fungal colonization and invasive disease in very low birth weight, premature babies.[1,27,28] Microorganisms including *Candida* spp. causing pneumonia acquired during labour and delivery may also act as source of candidemia.[29] Various fungal agents colonize hospitalized infants, healthcare workers and visitors. Pathogenic organisms can be transmitted by direct contact or indirectly via contaminated instruments and intravenous fluids.[27] This endogenous source, together with other predisposing factors as long-term antibiotics, catheterization, patients on ventilator, respiratory distress syndrome lead to candida septicaemia in NICU.[1]

Historically, *Candida glabrata* has been considered to be relatively nonpathogenic saprophyte of normal flora of healthy individuals rarely causing serious infections.[30] However, following widespread and increased use of immunosuppressive therapy, broad spectrum antibiotic therapy, increased conditions causing compromise of the immune system, the frequency of mucosal as well as systemic infections caused by *Candida glabrata* has increased significantly.[1,31,32,33,30] It is the only species of *Candida* that does not form pseudohyphae, it is found as blastoconidia (1-4 µm), both as commensal and as pathogenic states. On Sabouraud's Dextrose agar, it forms glistening smooth, cream colored colonies, indistinguishable from *Candida albicans* but on Cornmeal agar it does not form pseudohyphae. It assimilates only glucose and trehalose. [30] Karen et al,[29] compared *Candida glabrata* sepsis with other. According to this significant study, *Candida glabrata* sepsis occurred in infants with higher gestational periods (29.7 weeks as against 26.6 weeks in case of *Candida albicans*) and birth weight (*Candida glabrata* 1442 g, *Candida albicans* 931 g), but no such difference was observed in the present study.

The reasons behind the emergence of the species as predominant pathogen could be because of selection of lesser susceptible species due to frequent use of fluconazole as prophylaxis.[4] The changing epidemiology of candidaemia, therefore, highlights the need for close monitoring of *Candida* species distribution and susceptibility in order to optimise therapy and outcome. We should also develop guidelines for empiric therapy based on the epidemiology of India.[34] Understanding the mechanisms of innate and acquired resistance may facilitate the development of new targets for antifungal agents. More and more comprehensive studies of its epidemiology, pathogenesis, and resistance are needed to control the infections by *Candida glabrata* properly.[1]

CONCLUSIONS

In our study, among the two hundred and fifty (250) clinically suspected cases of neonatal septicaemia, 12% were fungal culture positive. Amongst these, *Candida glabrata* (73.33%) was the commonest pathogen isolated, followed by *Candida tropicalis* (16.67%) and *Candida albicans* (10%). Non-albicans *Candida* has emerged as an important pathogen causing neonatal septicaemia. Fungal sepsis is more common among preterm, low birth weight infants, those with prolonged antibiotic use and in those on total parenteral nutrition. *Candida glabrata* caused the highest number of cases of fungal septicaemia.

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