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PREVALENCE OF ALBICANS CANDIDA AND NON-ALBICANS CANDIDA IN NEONATES ADMITTED FOR SEPTICEMIA WITH ASSOCIATED RISK FACTORS

Dr. Deepak Gawali[1], Dr. Ashish Saraswat[2], Dr.Nidhi Sharma[3], Dr. Seema Sharma[4*]

[1] Demonstrator, Department of Microbiology, MGM Medical College, Indore,(M.P.)
[2] Demonstrator, Department of Microbiology, M.L.B. Medical College , Jhansi,(U.P.)
[3] Demonstrator, Department of Pathology , MGM Medical College, Indore,(M.P.)
[4*]Senior Resident, Department of Obstetrics & Gynecology, M.L.B. Medical College Jhansi,(U.P.)

***Corresponding Author:** Dr. Seema Sharma
*****Senior Resident, Department of Obstetrics & Gynecology, M.L.B. Medical College Jhansi,(U.P.)

Abstract

Aim: To know the prevalence and epidemiology of candidemia an uncommon infection among newborns admitted to our hospital.

-To summarize the clinical characteristics of candidemia in neonates, and determine whether specific risk factors may be identified to aid the selection of patients.

Materials and Methods: This prospective study was conducted between August 2018 and May 2019 in the Departments of Microbiology and Pediatrics of tertiary care hospital in central , India. From a total 244 neonates admitted to NICU with clinical suspicion of septicaemia. blood samples were collected in blood culture bottle and incubated at 37^0C followed by subculture done on blood agar and Mc conkey agar and Sabouraud's dextrose agar with chloramphenicol (0.05%) and incubated at 37^0C. Only those isolates which yielded pure growth of candida spp. Were included in the study. Preliminary identification was done by colony morphology on SDA , Chromogenic medium, growth at 45^0C , Germ Tube test , chlamydospore formation and was confirmed by carbohydrate fermentation test. Candidemia was defiend as the presence of at least one positive blood culture containing pure growth of candida spp. With supportive clinical feature.

Results- Total 244 neonates included in the study, 129(53%)were females and 115(47%) were males .Candida albicans responsible for 64% cases while NAC species responsible for 36% cases with14% cases by C. tropicalis, 08% cases by C. parapsillosis, 7% by C. gullermondii, 4% by C. krusei, 3% by C.kefyr. The risk factors observed for candedimia are prematurity and LBW , indwelling catheters are commonest followed by broad spectrum antibiotic use, TPN prolonged hyperalimentation. Various clinical presentations also seen in Candidemia.

Conclusion-Candidemia in neonates is an ominous prognostic sign and is an important entity in our hospital. Preventive measures such as use of filters for parenteral nutrition, prophylactic antifungal use, and a restrictive policy of antibiotic use to decrease Candida colonization/ infection rates should be implemented to reduce the morbidity and mortality associated with these infections.

Key words: Low birth weight, Prematurity, Colonization, Parentral nutrition, Horizontal transmission.

Introduction-

Candidal infections are a serious problem in neonatal intensive care units, increasing morbidity and mortality in low birth weight infants in addition to escalating health-care costs.

Invasive fungal infections are a considerable cause of morbidity, mortality, increased hospital stay durations, and high health care costs in critically ill or immunocompromised children (1–4). The majority of invasive fungal infections in children occur in a hospital setting, and the majority of infections are caused by Candida species (1,5). In addition to the presence of Candida species in the blood (candidemia), Candida infections can disseminate to each main organ, including the brain, lung, liver, heart, kidneys, eyes and spleen (2,3). Significance of Candida spp. in neonatal intensive care units (NICU) is increasingly being recognized. It is the third most common cause of late onset sepsis in NICU patients and accounts for 9-13% of blood stream infections (BSI) in neonates. (1). Although Candida albicans has historically been the most frequently isolated species, recently non-albicans Candida (NAC) have emerged as important opportunistic pathogen, notably Candida tropicalis, C. parapsilosis, C. krusei, and C. glabrata. Number of factors including the use of indwelling devices, broad spectrum antibiotics, low birth weight (LBW), prematurity, total parenteral nutrition (TPN), gastrointestinal surgery, artificial ventilation, and/or history of fungal colonization contribute to the risk.[5] 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[6] Candida spp. can also spread through vertical transmission from maternal flora or via horizontal transmission from hands of healthcare workers (HCW).[7,8] Clinical presentation of candidemia resembles sepsis syndrome and to establish a clinical diagnosis is difficult. The incidence of candidemia can be influenced by several factors including the population at risk, healthcare facility standards, Candida spp. involved, and antifungal resistance.[2] We were noticing an increase in the isolation rate of NAC species over last few months from cases of neonatal septicemia, which prompted us to undertake the present study, to examine the prevalence and epidemiology of neonatal candidemia at our hospital Candida species are the 4th leading cause of nosocomial blood stream infection in the united states and ranks 7th in Europe.although more than 17 different species of candida have been reported to be etiologic agents of invasive candidiasis in humans, only 5 species (candida albicans, candida glabrata, candida tropicalis, candida parapsillosis, and candida Krusei) accounted for 92% of cases of candidemia. An increase in the isolation of non-albicans Candida (NAC) species can be seen worldwide; however, C. albicans still remains the most common cause of candidemia.[1] The USA and northern Europe have reported a high number of cases by C. glabrata whereas in Brazil and Spain C. parapsilosis is the predominant species isolated from candidemia patients among the NAC species. Furthermore, globally, it is seen that the frequency of C. albicans is decreasing, while that of C. glabrata and C. krusei is stable, and C. parapsilosis and C. tropicalis are increasing.[7] Nationwide data are lacking from India, but from individual studies, 6%–8% of candidemia rates have been reported with increasing isolation of NAC species [8-10] Polyenes, allylamines, azoles, and echinocandins are the antifungal drugs available for the treatment of systemic and invasive candidiasis. Epidemiological shiftfrom C. albicans to NAC may be attributed to the increasing use of azoles giving rise to increased isolation of resistant species from candidemia patients such as C. glabrata and C. krusei (intrinsically resistant to fluconazole). They may also show cross resistance to newer triazoles.[13] The isolation of antifungal resistant Candida is on a rise from such group of patients. As morbidity and mortality are very high in such patients, selection of an effective empirical therapy for invasive candidiasis requires a critical knowledge of local epidemiology and regional variability of the concerned area. Therefore, following study was conducted to know the occurrence of candidemia in our region, among suspected septicemic patients.

Materials and Methods

This prospective study was conducted between August 2018 and May 2019 in the Departments of

Microbiology and Pediatrics of G.R. Medical College & JA group of Hospitals, Gwalior a tertiary care hospital in central , India. Premature infants comprise 15-20% of total number of deliveries in the hospital. From a total 244 neonates admitted to NICU with clinical suspicion of septicaemia. blood samples were collected in blood culture bottle and incubated at 37^0C .then subculture done on blood agar and Mc conkey agar and Sabouraud's dextrose agar with chloramphenicol (0.05%) and incubated at 37^0C. Only those which yielded pure growth of candida spp. Were included in the study. Preliminary identification was done by colony morphology on SDA, chromogenic medium, growth at 45^0C , germ tube test , chlamydospore formation and was confirmed by carbohydrate fermentation test. Candidemia was defined as the presence of at least one positive blood culture containing pure growth of candida spp. With supportive clinical feature. Patients with positive results of Candida species from two cultural samples were allocated to the candidemia group, while individuals with negative results were placed in the non-candidemia group. The clinical characteristics, prognosis and previously identified risk factors for the two groups were recorded. The risk factors included gastrointestinal dysfunctions, the administration of antibiotics prior to the occurrence of candidemia, the presence of a central venous cannula, parenteral nutrition, gastrointestinal and secondary gastrointestinal surgery, repeated tracheal intubation and the occurrence of maternal candidal vaginitis.

Statistical analysis

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 11 and the prevalence of organisms was determined and expressed in percentage

Result -

Total 244 neonates included in the study, 129(53%)were females and 115(47%) were males. Candida albicans responsible for 67% cases whileNAC species responsible for 33% cases .
Persant of CA and NAC species-

Table(1) Number of Isolated Candida albicans & Non-albicans species from Blood.

Organism	**Total no.**	**Percent**
Candida albicans	156	64%
Non albicans (i.e)	88	36%

NAC spp. were responsible for 36. %, whereas 64% of the cases were caused due to C. albicans. C. parapsilosis (25.0%), and C. tropicalis (21.97%) were the predominant NAC species isolated, followed by C. glabrata (14.39%) and C. krusei (10.61%) .The results revealed that the symptoms of fever, abdominal pain, vomit, edema, serous effusion, tetter, thrush, shock, gastrointestinal and pulmonary hemorrhage and multiple organ failure were significantly more common in the candidemia group when compared with the non-candidemia group. Among the accompanying examination results, the occurrence of procalcitonin (PCT) levels of >2 ng/ml, hemoglobin levels of 50 mg/l, thrombocytopenia, liver dysfunction, hypoproteinemia and pathogenic bloodstream infections other than Candida were significantly higher in the candidemia group compared with the non-candidemia group. In addition, the length of hospital stay and ICU stay in the candidemia group was significantly longer compared with the non-candidemia group (Fig. 1)
Potential risk factors for candidemia among neonates n=244
among the risk factors observed for candidemia prematurity and LBW , indwelling catheters are commonest followed by broad spectrum antibiotic use, TPN prolonged hyperalimentation.

Table(2). Potential risk factors for candidemia observed in neonates.

Factors	**Number of cases**	**Percentage**
Prematurity	73	30%

Low birth weight	49	20%
Risk Indwelling catheters	52	21%
Broad spectrum antibiotic use	39	16%
Total parentral nutrition(TPN)	17	7%
Ventilator support	8	3%
Prolonged hyperalimentation	8	3%

Various clinical presentations observed in cases of neonatal candidemia n==244
such as failure to thrive in 50% case, feed intolrence in 27% cases, respiratory distress etc

Table(3). Various clinical presentations observed in cases of neonatal candidemia.

Sign/symptom	**Number of cases**	**Percentage**
1. Failure to thrive	122	50%
2. Feed intolerance	66	27%
3. Respiratory distress	15	6.3%
4. Abdominal distention	11	4.5%
5. Lethargy	11	4.5%
6. Poor perfusion	10	4.5%
7 .Convulsions	6	2.7%

Characterization of various Candida species isolated from blood-12% cases by C. tropicalis, 10% cases by C.parapsillosis, 5% by C. gullermondii, 4% by C. krusei,2% by C.kefyr.

Table(4). Various Candida species isolated from blood

S.no	**Organism**	**Percentage**
1.	Candida albicans	156(64%)
2.	Candida tropicalis	(10%)24
3.	Candida parapsillosis	(08%)19
4.	Candida krusei	(8%)19
5.	Candida gullerimondii	(4%)9
6.	Cadida kefyr	(6%)14

Table(5.) shows CA and NAC in SNCU and PICU pateints-

	CANDIDA ALBICANS	NON ALBICANS CANDIDA	
SNCU	113(60%)	75(40%)	189
PICU	49(89%)	6(11%)	55

Discussion

In the present study NAC species accounted for 36 % of the cases of neonatal candidemia, whereas C. albicans was responsible for 64% of cases. This corroborates well with the results of other authors.[15-18] Striking feature of the present study was isolation of C. tropicalis (10%) 24cases as the most common NAC species and C. parapsilosis (08 %) 19 cases as the most second common NAC species similar to the study of Ankhi Dutta etal(27), , C. Krusei (08%) 19 cases and C. gullermondii(4%)9case C. kefyr (6%)4case. Although C. parapsilosis is less virulent, but under certain conditions (IV catheters, high IV glucose concentrations) virulence may increase many folds and it is relatively difficult to eradicate this organism.[19] This subsequently has pharmacotherapeutic and pharmacoeconomic implication as to treat such infections is quite difficult. C. parapsilosis is an

emerging fungal pathogen and the major threat for neonates in NICU as it frequently colonizes the hands of HCW, has high affinity for intravascular devices, and parenteral nutrition.[20,21] In the present study, 21% and 07% of patients were on indwelling catheters and TPN respectively, Higher affinity of C. parapsilosis to adhere on foreign material and ability to form biofilms are important factors for the development of fungemia.[22] C. Tropicalis causes infections with high mortality in adults and children with hematological malignancies or in immunocompromised individuals.[25] Ability of this organism to produce clusters is one of its major virulence factors. Once introduced into the immunocompromised host, C. tropicalis may be more virulent than C. albicans and can rapidly progress from colonization to invasion. In the present study, C. tropicalis and C. parapsillosis have emerged as predominant species. AFS results showed that 34.09% of Candida isolates were resistant to antifungal drugs. High degree of resistance to azoles was seen among C. krusei (78.57%) and C. glabrata (63.16%). Previous studies have reported that resistance to azole compounds among C. glabrata species can range from 3.6 to 64%.[26,27] A significant proportion of C. tropicalis isolates were resistant to azoles especially FLK. Although resistance to AMB was quite low (3.79%), but is a matter of concern as emergence of such isolates may pose serious therapeutic challenges and also increases risk of nosocomial infection. A noteworthy feature observed was that 3/46 neonates who died were infected with these AMB resistant strains) . The major risk factors identified in our study were prematurity, LBW, indwelling catheters, and broad spectrum antibiotic therapy. 27% of our cases were premature and 18% LBW, highlighting the significant burden of this disease among such infants. Use of multiple invasive devices (catheters, endotracheal tubes) or surgery causes break in the skin/mucosal integrity, which predisposes these sites for colonization/infection by Candida spp..and leading to 18% of total candidemia.. Broad spectrum antibiotics ranging two to four in number were being administered to most of the neonates in the present study leading 13.6% cases. Antibiotics promote fungal overgrowth at the a translocation of yeast across the intact mucosa. The risk of candidemia is known to increase exponentially with each class of antimicrobial used. Ventilator support associated candidemia seen in 4.5% of cases. Prolonged hyperalimentation associated candedimia also seen in 4.5% cases. TPN induces gut mucosal atrophy and has immunosuppressive effects which again predisposes individual for infection. Moreover, certain Candida spp. like C. parapsilosis has higher affinity towards parenteral nutrition, and can be responsible for outbreaks in NICUs.13.6% cases of TPN have candidemia. The hands of HCW and environmental surfaces are newly appreciated potential reservoirs for nosocomial strains of Candida spp. Neonatal candidemia is generally associated with high mortality.

Conclusion-

Candidemia in neonates is an ominous prognostic sign and is an important entity in our hospital. Preventive measures such as use of filters for parenteral nutrition, prophylactic antifungal use, and a restrictive policy of antibiotic use to decrease Candida colonization/ infection rates should be implemented to reduce the morbidity and mortality associated with these infections. Reporting of fungal BSI and the spectrum of species involved are essential measures in any ICU in order to implement appropriate preventive and therapeutic strategies. Though powered to detect significant risk factors for fungal sepsis, this is a single center study and our findings may not be generalizable to other institutions. Additional studies are necessary to validate our findings and define more accurately the reservoirs, mode of transmission, emergence of new species, and their sensitivity patterns. Epidemiological data of our study can serve as a template for the development of local guidelines for prevention and appropriate treatment of neonatal candidemia. Based on high perinatal risk factors for early onset sepsis, the current hospital antibiotic policy recommends empiric use of ampicillin- gentamicin for neonates born within the facility and cefotaxime-amikacin for neonates reffered from elsewhere. Long-term use of these broad spectrum antibiotics must have +c +reated a negative pressure and favorable environment for Candida spp. to flourish. This substantiates the need of prophylactic antifungals to be used in a set up where continuous upsurge in the incidence of

candidemia is seen. colonization/ infection rates should be implemented to reduce the morbidity and mortality associated with these infections. Prior knowledge of species distribution in clinical isolates and drug sensitivity pattern among species help the clinician to choose early empirical therapy. Delay in the initiation of antifungal drug may contribute to elevated mortality rate, in spite of low antifungal resistance. There should be strengthening of antifungal stewardship policies to minimize acquisition of acquired resistance. However, a nationwide study is the need of the hour to formulate policies and strategies for risk identification and management (i.e., prophylaxis, preemptive therapy, or empirical therapy) for invasive candidiasis.

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Conflict of interest
The authors declare no conflict of interest.

Ethical approval
Not required

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