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Changing clinical and microbiological profile of Candidiasis in VLBW babies in NICU of a tertiary care Hospital

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Abstract

Introduction: Candida infection is a severe complication during the neonatal period among VLBW. The aim of this prospective observational study was to find the incidence, clinical and microbiological profile of candidiasis in VLBWs admitted in NICU.

Material and methods: This study was conducted in NICU, Department of Pediatrics, Government Medical College Amritsar (Punjab) India over one year and included all VLBW babies admitted in NICU. The baseline variables, treatment and interventions done were recorded. In babies having clinical deterioration after one week of stay blood and urine specimens were sent to microbiology lab for Candida species identification and sensitivity pattern. The incidence per 1000 patient and per 1000 device days was calculated.

Results : Out of 131 VLBW neonates, 91 completed the study. Incidence of Candida sepsis was 8.04/1000 patient day. We found oral thrush, poor perfusion, hypotension, abdominal distension, tachycardia and temperature instability as clinical manifestations of Candidiasis. Non albicans Candida species (61%) were predominant out of which 48% were *Candida tropicalis* followed by *Candida albicans* (39%). Most of the Candida species were sensitive to Amphotericin B (95%), Itraconazole (95%) and Voriconazole (95%) followed by Nystatin (82%), Fluconazole (74%). Mortality related to Candida infection was 23%.

Conclusion : In our study non albicans were more prevalent and fluconazole has shown increasing resistance for Candidiasis.

Keywords: Candidiasis, VLBW, Clinical features

Introduction

Neonatal sepsis is the commonest cause of mortality and is probably responsible for 30-50% of the total neonatal deaths each year in developing countries.[1] Invasive fungal infections are now emerging as a major cause (9-13%) of all blood stream infections in neonatal intensive care units.[2] Candidiasis in neonates is a serious and common cause of LOS (late onset sepsis) and has high mortality (25-35%). The incidence of such fungal infection has increased 11 fold over past 15 years. Candida species are the 3rd most frequent organism (after CONS) isolated in LOS in VLBW neonates.[3] More than 90 %of systemic Candida infections are caused by *C .albicans, C .parapsilosis, C .guilliermondii, C .glabrata, C .dubliniensis, C .tropicalis* and *C .krusei.*[4] The incidence has been increasing in neonates weighing less than 1000 g with the resuscitation and survival of more and more neonates.[5,6] There is upsurge in the frequency of non-albicans Candida species isolated from clinical specimens . C.parapsilosis is the most common non-albicans Candida species recovered from blood cultures.[7] In one of the studies results showed that, *C.tropicalis*)43.54 (%was the major isolate among different clinical specimens. [8]The clinical manifestation of neonatal candidiasis can be similar to invasive bacterial infection but symptoms are often subtle and indolent. The clinical features are: fever, apnea, lethargy, temperature instability, feeding intolerance, poor perfusion, hypotension, respiratory distress, need for increased ventilator support, abdominal distension, hyperglycemia and thrombocytopenia in blood stream infections (BSIs).[9] The commonest manifestation of Candidiasis is blood stream infection (BSIs) but the spectrum of illness includes pneumonia, septicemia with or without endocarditis, septic arthritis, meningitis, encephalitis, brain abscess, endophthalmitis, liver abscess, splenic abscess, cutaneous abscess and renal tract infection.[10] In NICUs using fluconazole prophylaxis, *C albicans* colonization and infection is prevented and these NICUs have fewer infections but they are often non-albicans.

Fluconazole is the most widely used drug for candidiasis. As resistance to azoles has been found in many studies so there is increasing use of Echinocandins .But resistance to Echinocandins is also increasing in many studies.[9,11]Kothari et al, Oberoi JK et al and Juyal D et al have found preponderance of non albican Candidiasis and also found increasing resistance to Fluconazole[12,13,14]. Basu S et al observed commonly isolated Candida species were *C. tropicalis* (39%), *C. albicans* (35.4%) and *C. parapsilosis* (12.2%). Susceptibility for Fluconazole and Amphotericin B was 86.6% and 68.3%, respectively.[15] Increase in detection of Candida albicans and non-albicans candida species are related to the widespread and inappropriate use of antifungal treatment)self-medication, topical use, long-term treatments and repeated Candida infection.(Species identification and determination of antifungal sensitivity patterns has the utmost importance for proper management of systemic candidiasis and to prevent resistance. The increased isolation rates of non-albicans Candida species and a gradual shift in the antifungal susceptibility profile reported in literature have underlined the need of this study.

Materials and Methods

This study included VLBW neonates (≤1.5 kg) admitted in NICU, over a period of 1 year, in the Department of Pediatrics, Government Medical College Amritsar. We assessed neonates from day 1 of admission and recorded the baseline variables, treatment given, interventions done and patient days and device days on a predesigned proforma after obtaining written informed consent. Neonates who remained sick or became sick/sicker after 7 days of stay, or who became sick within 48 hours of follow up after being

shifted out/discharged from the NICU were evaluated for clinical signs and symptoms of Candida infection and their samples of blood and urine were collected and transported to the Department of Microbiology for culture, detection of fungal hyphae in urine and urine culture respectively. Blood samples were collected in culture bottles containing Brain Heart Infusion media (BHI) under all aseptic conditions and transported to microbiology laboratory for further processing. Urine samples were collected in sterile container and transported to microbiology lab within 2 hours for detection of fungal hyphae and urine culture.

Processing of samples was done in microbiology laboratory, blood cultures were performed on blood agar and Sabouraud Dextrose Agar media. The culture plates were incubated at 37^{o}C.If cream colored, smooth, pasty colonies appeared in 24-48 hours, it was suggestive of Candida infection. Confirmation of the culture was done as per standard protocol. Urine culture was performed on both blood agar and Sabouraud Dextrose Agar media and urine for fungal hyphae was seen by KOH mount preparation. Species level identification of Candida Isolates was done by various methods like conventional methods which includes germ tube formation, chlamydospore formation on cornmeal agar, sugar assimilation, sugar fermentation and newer methods like colony characteristics on CHROM agar. A battery of tests was performed because not a single method is 100% sensitive for Candida species identification. The susceptibility of Candida species to antifungal drugs was performed by disc diffusion method as per CLSI M44-A2 protocol.[16] Other investigations done were Hb, TLC, DLC, platelet counts, blood sugar, blood urea, serum creatinine, CSF for cytology and biochemistry, CSF culture if suspecting meningitis in VLBW neonates since CSF cell counts and chemistry may be normal. The incidence per 1000 patient days and device days was calculated as per NNIS methods.[17]

Results

This prospective observational study was conducted in NICU, Pediatric Department of Govt. Medical College, Amritsar from 1st April 2016 to 31st March 2017. Out of a total 133 VLBW neonates admitted to NICU during the study period, 80 were inborn and 53 outborn. Out of these, 28 neonates expired before day 7 of life, 2 parents refused consent, 2 neonates left against medical advice (LAMA) and 10 neonates were discharged or shifted out from NICU at or before 5 days of life and were excluded from study. Thus 91 neonates completed the study. Neonates were followed till death or 48 hours after discharge/ being shifted out from NICU. Out of 91 neonates 26 VLBW neonates developed Candida infection. The incidence of Candida infection per 1000 patient days was 13.15 for ≤1000g, 6.27 for 1001-1500g and for whole population it was 8.04/1000 patient days. Incidence of Candida infection percentage wise was 42.30% for <1000g, 23.07% for 1001-1500g and 28.57% in overall population.

Out of study population, 26 (28.57%) neonates were of birth weight ≤1000 g (ELBW), 65 (71.42%) were of 1001-1500 g (VLBW). The mean birth weight of whole population was 1102.84±189.27g. The mean gestation age of whole population was 30.10±2.15 weeks. Most neonates were AGA 60 (65.95%), followed by SGA 30(32.96%) and least belonged to LGA 1(1.09%). The mean duration of stay in NICU was 33.09±18.08 days. Table 1 shows the clinical manifestations of babies who developed candidiasis during Nicu stay. Table 2 shows the distribution of candida species isolated from babies with candidiasis.

Table 1: Clinical features of Candidiasis in study population (n=26)

Sr. No.	Clinical features	No.	%	p-value
1	Oral thrush	9	34.62	0.001
2	Fever	4	15.38	0.728
3	Apnea	19	73.08	0.042
4	Lethargy	10	38.46	0.448
5	Respiratory distress	14	53.85	0.691
6	Feeding intolerance	16	61.54	0.009
7	Poor perfusion	12	46.15	0.002
8	Hypotension	9	34.62	0.003
9	Temperature instability	11	42.31	0.067
10	Abdominal distension	11	42.31	0.064
11	Tachycardia	14	53.85	0.004
12	Bradycardia	12	46.15	0.237

Table 2: Candida species Isolated in study population(n=23)

S. No	Candida species (n= 23)	%age
1	*Candida albicans* (n=9)	39.13%
2	*Candida tropicalis* (n=11)	47.82%
3	*Candida parapsilosis* (n=2)	8.69%
3	*Candida glabrata* (n=1)	4.34%
Total	Total (n=23)	100.0

Table 3: Drug sensitivity pattern of candida species isolated during study period.

Organism found	KET		FLU		ITRA		AB		NYS		VC	
	S	%	S	%	S	%	S	%	S	%	S	%
Candida albicans (n=9)	6	66.66	8	88.88	9	100.0	9	100.0	7	77.78	9	100.0
Candida tropicalis (n=11)	6	54.54	7	63.63	10	90.91	10	90.91	9	81.82	10	90.91
Candida parapsilosis (n=2)	1	50.0	1	50.0	2	100.0	2	100.0	2	100.0	2	100.0
Candida glabrata (n=1)	-	-	1	100.0	1	100.0	1	100.0	1	100.0	1	100.0
Total (n=23)	13	56.52	17	73.91	22	95.66	22	95.66	19	82.61	22	95.66

*KET=Ketoconazole, FLU=Fluconazole, ITRA=Itraconazole, AB=Amphotericin-B, NYS= Nystatin, VC=Voriconazole

Most of the Candida species were sensitive to Itraconazole (95.66%), Amphotericin B (95.66%) and Voriconazole (95.66%) followed by Nystatin (82.62%) and Fluconazole (73.91%), Candida species were least sensitive (56.52%) to Ketoconazole. Among Non albicans Candida species *Candida tropicalis* were found least sensitive to antifungal drugs as compared to others. Resistance to Ketoconazole (43.47%) and Fluconazole (26.08%) was most common followed by Nystatin (17.40%). *Candida tropicalis* was most common species found to be resistant to above antifungal drugs.

In our study population, 65(71.4%) out of 91 neonates were discharged, 17 (18.6%) died, 7(7.6%) left against medical advice and 2 (2.1%) were referred. Out of 26 positive for Candida, 18(69%) were discharged and among candida negative group, 47(72%) were discharged. Mortality in Candida positive was 6(23%) vs 11(17%) in negative. There was significant difference in mean duration of stay in NICU (41.5±20.8 vs 29.72±15.94 days) in Candida positive and Candida negative cases.

Discussion

This study was conducted to assess the incidence, clinical profile, species identification and sensitivity pattern of neonatal Candida infection in VLBW neonates in our NICU. During the study period out of 131 VLBW neonates admitted to NICU, 91 were included in the final analysis. In the study group, 26 VLBW neonates were positive for Candida infection, with an incidence of 28.57%. On stratifying according to weight, incidence in ELBW neonates was 11(42.30%) and in 1001-1500g it was 15(23.07%) . In terms of per 1000 patient days, incidence in ELBW neonates was 13.15, in 1001-1500gm neonates it was 6.27 and overall in VLBW it was 8.04. The incidence was found to be inversely related to birth weight.

VLBW neonates with Candida infection can present with many nonspecific signs and symptoms which are often subtle and indolent. In our study population oral thrush, feeding intolerance, apnea, poor perfusion, hypotension and tachycardia were found to be statistically significant at p value <0.05 (table no. 1). Most of the clinical characteristics of Candida infection found in this study were similar to previous publications.[18] We also found the relation of thrombocytopenia and hyperglycemia with the Candida infection to be statistical significant at p value = 0.001, similar to a study by Jonathan et al (2014).[18] In our study *Candida tropicalis* was major isolate (47.82%) among most samples, whereas *Candida albicans* was 39.13% and *Candida parapsilosis* was 8.69% (table no. 2). Similar results were obtained in a study done by Sardana V et al[19]. The results of present study were not in concordance with studies conducted by Jonathan et al[18], Waldie et al[20] and Kumar et al.[21] This change in pattern has been partly attributed to increase in immunocompromised patients, prolonged hospitalization, placement of CVCs and prophylactic use of antifungal agents in critically ill patients.[22] The widespread use of broad-spectrum antimicrobials also encourages the proliferation of drug-resistant non albicans Candida species. Kumar et al (2016) found all *Candida albicans* isolates were sensitive to Amphotericin B (100%) followed by Voriconazole (80.95%) and Fluconazole (76.19%). Non albicans Candida were sensitive to Amphotericin-B (100%), Voriconazole (78.57%) and Fluconazole (57.14%). C. kruzi was sensitive to only Amphotericin B.[21] The results are similar to our study as far as resistance to various antifungal drugs is concerned. Basu et al (2017) in their study found the commonly isolated Candida species were *C. tropicalis* (39%), *C. albicans* (35.4%) and *C. parapsilosis* (12.2%). Susceptibility for ampjhotericin B and fluconazole was 86.6% and 68.3%, respectively, similar to our study.[15] VLBW neonates have low immunity, their impaired host response to Candida infection may contribute to mortality. The mortality rate associated with Candida infection in the neonatal period ranges from 20%-50%. In our study the mortality was 23.07% vs 16.92%, in two groups with or without Candida infection.

Conclusion

In this study, there was a clear shift in prevalence of infection from *Candida albicans* to non albicans Candida species. Widely used antifungal drugs like Fluconazole had shown moderate resistance for non albicans Candida species and mild resistance to *Candida albicans*. Amphotericin B, Voriconazole and Itraconazole were found to be promising drugs for all type of Candida infections. A restrictive policy of antibiotic use, avoiding indiscriminate use of antifungal drugs and minimum possible duration of invasive procedures and IV fluids to reduce Candida infection rates should be implemented.

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Conflict of interest: None declared

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