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Candidemia in Neonatal Intensive Care Units: Magnitude, Species Identification And Antifungal Susceptibility Pattern

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Background:*-Invasive fungal sepsis contributing significant neonatal mortality and in last two decade changed in growing species and sensitivity pattern, this hospital base prospective observational study with aims to find magnitude of candidemia and drug susceptibility pattern of candida species in neonatal intensive care units at tertiary level center.*
Methods*: All Preterm and full term infants with risk factors for fungal infection admitted in neonatal intensive care unit (167) of Zenana and Mahila chikitsalaya during the study period (May 2014- April 2015) were included. The candida isolates were identified with automated Vitek-2 compact system of Biomeriux, Germoney using the YST ID cards and their antifungal susceptibility was performed using AST YS 06 Cards.*
Results: *A total of 20 (11.97%) Candida isolates were found among 167 NICU patients. Candida albicans (35%) was the most common isolate followed by Candida parapsilosis (30%), Candida tropicalis (15%), Candida krusei (15%), and Candida glabrata (5%). Among the 20 Candida isolates, resistance to the Fluconazole was 35%, to Ketoconazole 25%, to Miconazole 20%, to Amphotericin-B 15%, and to Caspofungin 5%.*
Conclusion: *Increased incidences of candidemia along with emergence of Non-albicans Candida species are become an important healthcare issue worldwide. Therefore, the early and accurate identification of Candida spp along with susceptibility testing is very important.*
Keywords: *Antifungal susceptibility, Candidemia, Candida albicans, Non albicans candida*

I. Introduction

Neonatal deaths account for 40% of deaths under the age of 5 years worldwide. Therefore, efforts to achieve the UN Millennium Development Goal 4 of reducing childhood mortality by two-thirds by 2015 are focused on reducing neonatal deaths in high-mortality countries[1]. Sepsis is the commonest cause of neonatal mortality; it is responsible for about 30-50% of the total neonatal deaths in developing countries[2]. The pathogens most often implicated in neonatal sepsis are bacteria, although with increasing survival of smaller, more immune-compromised preterm infants, the incidence of invasive fungal infection is increasing among Neonatal Intensive Care Unit (NICU) patients. After gram positive and gram negative bacteria, *Candida* species are the third most frequent cause of septicemia after 72 hours of life in neonates with estimated incidence of 1.6 to 9% among very low birth weight (VLBW) and 10 to 12% among extremely low birth weight (ELBW) neonates in neonatal intensive care units. Infections due to invasive fungal infections account for 15% of all blood stream infections (BSI) in the NICU[3]. *Candida albicans*is the most frequently recovered fungus, but in the last two decades the trend has changed with *C. parapsilosis* as the more prevalent organism. *Aspergillus*is second only to *Candida* as a cause of invasive fungal infections in neonates. Invasive candidemia is associated with a mortality of 38% and a crude mortality of 30%-75%[4]. This study is designed with primary objective to identify specific candida species and their drug sensitivity pattern that helps in diagnosis and effective management of candidiasis in neonatal intensive care unit.

II. Material And Methods

This is a hospital based prospective observational study carried out in neonatal intensive care units of Zenana and Mahila Chikitsalaya attached to SMS Medical College and Hospital, Jaipur after obtaining clearance from institute ethical committee. After obtaining written informed consent, 167 neonates admitted in NICU from May 2014 to April 2015 with inclusion criteria prematurity, lower birth weight, selected term neonates with risk factors like clinical evidence of sepsis, history of premature rupture of membrane, maternal history of symptoms of lower genital tract infection, maternal fever, gestational diabetes and requiring parenteral nutrition,

mechanical ventilation more than 7 days, central venous catheter, H2 blocker therapy, and antibiotics more than 7 days were included. Full term neonates admitted in NICU with indication other than sepsis like metabolic disease, neonatal jaundice, congenital malformations were excluded. A thorough history, physical examination and routine investigations were done in every case and recorded in the pre–designed performa. Sample for blood cultures was taken in Brain Heart Infusion (BHI) bottle at the time of admission to NICU and weekly thereafter till discharge or death. The BHI bottle was incubated at 37^0C in the laboratory and observed daily for visible growth. Subculture was performed after 48 hours and on 7th day before being reported negative. If visible growth was observed earlier, they were sub cultured on primary inoculation media i.e. Blood agar (BA), MacConkey agar (MCA). Colonies of yeast on blood agar were identified by their smooth creamy colored appearance and Gram's staining. All isolates of candida were characterized and subjected to antifungal susceptibility testing using the Vitek-2 yeast YST ID and antimicrobial susceptibility test (AST) YS 06 cards as per to manufacturers (Biomeriux) instructions and results were evaluated[5].

The Vitek-2 is an automated microbial identification system that provides highly accurate and reproducible results. Fresh subcultures of all the *Candida* isolates were obtained on sabouraud's dextrose agar (SDA) plates for identification and antifungal susceptibility testing using the Vitek 2 Compact, YST ID card, and AST YS 06 cards as per manufacturer's instructions. In AST YS 06 cards, antifungal susceptibility results based on interpretative guidelines recommended by Clinical Laboratory Standards Institute (CLSI) 2012 were obtained for fluconazole, ketoconazole, miconazole, amphotericin-B, and caspofungin.

III. Statistical analysis

Med Calc 12.2.1.0 version software was used for statistical calculation. Nominal and categorical data were summarized as proportion (%). Chi-square test was used for analysis of nominal and categorical data. Odds ratio was calculated and 95% confidence interval was estimated. P-value < 0.05 was taken as significant.

IV. Results

In our study, out of 167 neonate enrolled, 43 (25.74%) showed microbial growth in their blood culture. Among these 23 (13.77%) and 20 (11.97%) showed bacterial and *candida* blood stream colonization respectively in blood culture. Male preponderance was seen with male to female ratio 1.2:1. Majority of newborns was preterm 140 (83.8%) {Table I}. Out of the 20 isolates of various *candida* species, the *non albicans candida* species were the predominant accounting for 13 (65%) and the remaining 7 (35%) isolate were of *C. albicans* {Table II}. Maximum isolates were of *C. albicans* (n=7, 35%), followed by *C. parapsilosis* (n=6, 30%), *C.* k*rusei* (n=3, 15%), *C. tropicalis* (n=3, 15%) and *C.* glabrata *(n=1. 5%)* {Table III}. *Candida* species are maximally resistant to fluconazole (35%) whereas least to newer antifungal capsofungin (5%) {Table IV}.

Table I: Baseline characteristics of the study participants

Variables		**Number (n=167)**
Sex wise distribution	Male	92
	Female	75
Gestational age wise distribution	<28 week	14
	28 to <32 week	68
	32 to <37 week	58
	37 to 42 week	26
	>42 week	1
Weight wise distribution	ELBW	12
	VLBW	64
	LBW	60
	Normal	30

Table II: Distribution of candida albicans and Non albicans Species

Species	**Number**	**Percentage (%)**
Candida albicans	07	35%
Non albicans candida	13	65%
Total	20	100%

Table III: Distribution of Candida according to species by Vitek-2 yeast identification

Candida species	Number of isolates	Percent
Candida albicans	07	35%
Candida parapsilosis	*06*	30%
Candida krusei	03	15%
Candida tropicalis	03	15%
Candida glabrata	01	05%
Total	20	100%

Table IV: Antifungal Resistance pattern among candida isolates

Candida species (n)	Resistance			
	Fluconazole	Ketoconazole	Miconazole	Amphotericin-B
C. albicans(7)	14.2%	20.56%	28.57%	14.2%
C.parapsilosis(6)	33.33%	16.66%	0%	16.66%
C. tropicalis(3)	33.33%	33.33%	0%	0%
C. krusei(3)	66.66%	0%	33.33%	0%
C. glabrata(1)	100%	100%	100%	100%
Total (20)	35%	25%	20%	15%

V. Discussion

Fungal septicaemia is a common occurrence in Neonatal Intensive Care Unit patients. Prolonged hospital stay of premature babies, intense therapy, invasive procedures, central venous catheters, total parenteral nutrition, and various other risk factors leads to blood stream infection (BSI) leading to sepsis with various bacterial and fungal agents. Since various species differ in their antifungal susceptibility pattern, antibiotic susceptibility testing also done.

There is wide variation in the reported prevalence and incidence of fungal septicaemia in neonates admitted in NICU, ranging from 2.6 to16.7%. The incidence of candidemia in our study were 11.97% that is similar to study conducted by Agrawal et al and Rani et al showing isolation rate of 13.6% and 11% respectively[5,6]. Prevalence of candida species in blood stream infection has increased worldwide in the last decades. In the last few years occurrence of non albicans candida species are steadily increasing. In our study candida species other than C. Albicans were found to be leading cause of candida, BSI in neonates admitted in NICU accounted 13 (65%) of total 20 candida isolates cases. Maria et al (1994)[7] in his study also reported that C. Albicans was isolated in 90% of positive culture and remaining 10% isolate were of C. Tropicalis. C. Albicans was the leading causative organism isolated in 7 (35%) of all cases diagnosed (n = 20 isolates), followed by C. parapsilosis 6 (30%), C. tropicalis 3 (15%), C. krusei 3 (15%) and C. Glabrata 1 (05%). ShabinaAriff et al (1996)[8] reported 55% of all cases diagnosed (n = 49 isolates) were of C. albicans, followed by C. tropicalis (21%), and C. glabrata (9%). Although fluconazole still remain a safe and effective choice for the treatment of candidemia, there are increasing trends of fluconazole resistance has been reported in many studies as 37.5% by Gupta et al[9], 36% by Kothari et al[10], 25% by Adhikari et al[11] and 11.7% by Xess et al[12]. In the present study 35% of candida was resistance to fluconazole. Non albicans candida species, especially C. glabrata and C. krusei were found more resistant to azoles, particularly fluconazole, than C. albicans. 92.31% Candida albicans isolates were susceptible to fluconazole and itraconazole, while only 21.43% of C. krusei and 26.32% of C.glabrata isolates were susceptible to fluconazole. These two species were also only 21.43% and 36.84% susceptible to itraconazole respectively. The changing spectrum of candida species causing candidemia from C. albicans to Non albicans candida esp. C. glabrata and C. krusei is responsible for fluconazole resistance. In present study resistance to Amphotericin-B among all candida isolates was 15%. Similar results were reported by Jaswinder K Oberoi et al[13] 10.4% and M Bhatt et al[14] 8%.

Although Amphotericin-B has a rapid cidal action against most strains of candida species (esp. C.albicans), it is not the first choice due to associated nephrotoxicity and the newer lipid formulation having a better cidal effect profile. However in the developing country like India, fluconazole is the most widely drug of choice for treatment of candidemia due to its low cost, higher bioavailability along with intravenous (IV) formulation. In present study 5% isolates were resistant to caspofungin which correlated with the study of Michael A.P faller et al[15] and Maria Teresa Montagna et al[16] found 1.9% and 3.8% resistance respectively. Jaswinder K O et al[13] reported 100% sensitivity to caspofungin in his study. There was only one isolate of C. glabrata which is resistant to fluconazole, ketokonazole, miconazole and amphotericin B while sensitive to caspofungin.

VI. Conclusion

Increased incidences of candidemia along with emergence of Non-albicans Candida species are become an important healthcare issue worldwide. This study therefore emphasizes the need for a continuous surveillance of candidemia in the newborns admitted to intensive care units. Identification of *candida* up to

species level and determination of their antifungal resistance pattern will help the clinician in the management of candidemia and to reduce the morbidity and mortality in these neonates.

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