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Original Research Article

Profile of fungal septicaemia in new born at a tertiary care hospital in North India

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ABSTRACT

Background: Advances in neonatal management have led to considerable improvement in new-born survival. The objective of this study was to determine the predominant organisms, antifungal sensitivity patterns and clinical risk factors in neonatal fungal blood stream infection cases (BSI) admitted to our hospital.
Methods: This is a retrospective study of all neonatal fungal BSI cases between January 2015 to December 2015.
Results: Fungal sepsis was found in 50/360 (13.6%) of cases. Non *Albicans candida* (NAC)species were responsible for 88% of cases with *Candida*. glabrata (54%)as the most predominant species. Other species isolated were *C. tropicalis* 9 (18%). *C. albicans* 6 (12%). *C. paraspinolosis* 5 (10%), *C. Krusei* 2 (4%) and *C. Kodo1* (2%). Antifungal sensitivity results revealed that most of the NAC isolates especially candida glabrata,candida paraspinolosis were resistant to flucanazole, than *Candida albicans*. Amphoterician B had greater sensitivity than FLK over NAC species Among the risk factor observed for candidemia were low birth weight (62%), prematurity (60%,), broad spectrum antibiotic use (60%), ventilater support (56%) and total parentral nutrition (50%).
Conclusions: The increase in neonatal fungal BSI and resistant organisms highlights the need to review use of strict infection control strategies, appropriate preventive and therapeutic measures such as prophylactic antifungal use and a restrictive policy of antibiotic use.

Keywords: Candida, Fungal sepsis, Fungal blood stream infection, Neonates

INTRODUCTION

Advances in neonatal management have led to considerable improvement in newborn survival. However, early (<72 hours) and late (>72 hours) onset systemic infections, both bacterial and fungal remain a devastating complication and an important cause of morbidity in these babies. 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 to 13% of blood sream infections (BSI) in neonates.[1] Fungal sepsis should be suspected in a critically ill neonate with negative blood culture.[2] 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*.[3,4] This changing trend is a matter of concern due to the emerging resistance of the non-albicans species to azoles. There is growing evidence suggesting a role of increasing use of azole agents in this epidemiological shift. Several of these NAC species exhibit intrinsic resistance to traditional triazoles like fluconazole (FLK) and may also demonstrate cross resistance to newer triazoles.[5] This makes it imperative to perform both speciation and

antifungal susceptibility (AFS) of all the yeast isolates from blood or otherwise.

The sources of candidiasis in NICU are often endogenous following colonization of babies with fungi. About 10% of these babies get colonized in the first week of life and up to 64% babies get colonized by 4 weeks of hospital stay.[6] Administration of contaminated intravenous solutions, notably the solution for total parental nutrition (especially the intra-lipid) may result in NICU outbreaks. Spread may also occur from patient to patient or through a colonized health care worker.[7-9]

Apart from these a number of other factors including the use of indwelling devices, broad spectrum antibiotics, low birth weight (LBW), prematurity, gastrointestinal surgery, artificial ventilation, and/or history of fungal colonization contribute to the risk.[10]

Clinical presentation of candidemia resembles sepsis syndrome and to establish a clinical diagnosis is difficult.[11,12] Signs of fungal sepsis include thrombocytopenia, lethargy, glucose instability, increasing ventilation requirement and apnoea. End organ damage is more common and severe in systemic fungal infections and can involve the kidneys, joint, brain, lung, eyes, liver, spleen and bones.[13] Widespread infection despite negative culture is common.[14] The renal manifestations can be in the form of acute renal failure, hypertension or flank masses. Endopthalmitis is a complication of invasive disease and needs urgent intervention.[15]

Candida BSIs are associated with very high crude mortality of over 60%, while attributable mortality may be as high as 49% 4.[16] The incidence and associated mortality due to candidemia can be influenced by several factors including the population at risk, healthcare facility standards, *Candida spp.* involved, and antifungal resistance.[3] Due to considerable regional variability, the local epidemiological knowledge is critical in terms of prevention and management of invasive Candida infections.

The objective of this study was to determine the different fungal pathogens, review their sensitivity patterns and clinical risk factors in fungal BSI.

METHODS

This retrospective study was conducted between January 2015 and December 2015 in a tertiary care NICU in our hospital. All new-born aged 0 to 28 days admitted in neonatal intensive care unit (NICU) from January 2015 to December 2015 in whom fungal organism was isolated in blood culture were recruited in the study. Empirical antibiotic used was retrieved from the study. Candidemia was defined as the presence of at least one positive blood culture containing pure growth of *Candida spp.* with supportive clinical features.

Any growth indicated was sub-cultured on 5% sheep blood agar and Sabouraud's dextrose agar (SDA) with chloramphenicol (0.05%) and incubated at 37°C for a minimum of 48 hours up to two weeks. The Candida spp. isolated was identified as per standard mycological techniques.[17] Preliminary identification was done by colony morphology on SDA, chromogenic media (Hichrome, Himedia Pvt. Ltd.), grown at 45°C, germ tube test, chlamydospore formation, and was confirmed by carbohydrate fermentation and assimilation tests.[17]

Anti-Fungal sensitivity was performed for FLK (25 mg), and amphotericin B (AMB, 100 units) using disc diffusion method on Muller-Hinton agar supplemented with 2% glucose and methylene blue (5 mg/ml).[18,19] Zone diameters were interpreted as per the approved Clinical Laboratory Standards (CLSI) guidelines. Quality control for AFS was performed using C. albicans-ATCC 90028 and C. parapsilosis-ATCC 22019.[20]

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.

RESULTS

Of the total 360 neonates included in the study fungal sepsis was found in (50/360)13.8% of cases. NAC species were responsible for 88% of cases with *C. glabrata* (54%)as the most predominant species. Other species isolated were *C. tropicalis* 9 (18%), *C. albicans* 6 (12%), *C. paraspinolosis* 5 (10%), *C. krusei* 2 (4%) and *C. kodo* 1 (2%) (Table 1).

Table 1: Characterization of various candida species isolated from blood (n = 50).

Organism	No of isolates	%
Candida glabrata	27	54
Candida tropicalis	9	18
Candida albicans	6	12
Candida parapselosis	5	10
Candida Krusei	2	4
Candida Kodo	1	2

Antifungal sensitivity results revealed that most of the NAC isolates especially Candida glabrata, Candida paraspinolosis were resistant to fluconazole than Candida albicans. AMP had greater sensitivity than FLK over NAC species (Table 2).

Table 2: Anti-fungal susceptibility profile of Candida isolates (n = 50).

Organism	FLK* n	(%)	AMB** n	(%)	Total no. of isolates
Candida glabrata	6	22	21	80	27
Candida tropicalis	6	70	9	100	9
Candida albicans	5	90	6	100	6
Candida paraspinolosis	4	80	5	100	5
Candida krusei	0	0	1	50	2
Candida kodo	1	100	1	100	1

FLK* - Fluconazole; AMB** - Amphotericin B.

Among the risk factor observed for candidemia (Table 3) were LBW, prematurity, prolonged antibiotic use, ventilator support and TPN as described below in Tables 3-7.

Table 3: Potential risk factor for candidemia among neonates (n = 50).

	Frequency	%	Valid %	Cumulative %
<1 kg	10	20	20	20
1-1.5 kg	11	22	22	42
1.6-2.5 kg	10	20	20	62
>2.5 kg	19	38	38	100
Total	**50**	**100**	**100**	

Table 4: Gestational age.

	Frequency	%	Valid %	Cumulative %
<32 weeks	19	38	38	38
33-36 week	11	22	22	60
>36 weeks	20	40	40	100
Total	**50**	**100**	**100**	

Table 5: Antibiotic use.

	Frequency	%	Valid %	Cumulative %
<7 days	5	10	10	10
7-14 days	8	16	16	26
>14 days	17	34	34	60
Not used	20	40	40	100
Total	**50**	**100**	**100**	

Table 6: Ventilator support.

	Frequency	%	Valid %	Cumulative %
<7days	4	8	8	8
7-14 days	10	20	20	28
>14 days	14	28	28	56
Not used	22	44	44	100
Total	**50**	**100**	**100**	

Table 7: TPN (total parental nutrition use).

Days	Frequency	%	Valid %	Cumulative %
<7	10	20	20	20
>7	15	30	30	50
Not used	25	50	50	100
Total	**50**	**100**	**100**	

DISCUSSION

Fungal BSI is an important cause of morbidity and mortality in sick newborn infants. In the present study, isolation rate observed was 13.8%. This was comparable with study conducted by Agarwal et al showing isolation rate 13.6% and another study conducted by Rani et al where isolation rate was 11%.[21,22]

Of the total cases of neonatal candidemia, NAC species accounted for 88% of the cases, whereas *C. albicans* was responsible for 12% of cases. This corroborates well with the results of other authors23.Striking feature of the present study was isolation of *C. glabrata* (54%) as the most predominant NAC species followed by *C. tropicalis* (18%).

In recent years, there is marked shift in isolation rates of non-albicans Candida species compared to *Candida albicans* in cases of neonatal sepsis. Kossoff et al.[24] showed significant shift from Candida albicans to non-albicans, i.e. *Candida parapsilosis* over 15 years. Rani et al observed candida tropicalis as predominant pathogen (92%), followed by *Candida albicans* and *Candida kefyr* (4% each).[24] All these findings are in contrast to present study which showed that Candida glabrata is emerging as predominant cause of neonatal sepsis. This is in accordance with Karen et al which showed *Candida glabrata* as emerging pathogen.[25]

Historically, *Candida glabrata* has been considered to be relatively non-pathogenic saprophyte of normal flora of healthy individuals rarely causing serious infections.[26] 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.[22,27] Though *Candida glabrata* has emerged as important nosocomial pathogen, yet little is known about its epidemiology.[26] Infection with this species is associated with high-mortality rate.[25,26] *Candida glabrata* is of special importance because of its innately increased resistance to antifungal drugs, especially azoles.[25,26] The reasons behind emergence of the species as predominant pathogen could be because of selection of lesser susceptible species due to frequent use of fluconazole as prophylaxis.[27]

C. tropicalis causes infections with high mortality in adults and children with hematological malignancies or in immune-compromised individuals.[28] Ability of this organism to produce clusters is one of its major virulence factors. Once introduced into the immune-compromised host, *C. tropicalis* may be more virulent than *C. albicans* and can rapidly progress from colonization to invasion. It is the second leading cause of candidemia in adults, but is quite infrequent among neonates.[28] In the present study, *C. glabrata* and *C. tropicalis* have emerged as predominant species accounting for 72% of infected neonates.

AFS results showed that 22% of *C. glabrata* species were sensitive to FLK. High degree of resistence to azole compounds among *C. glabrata* species has been seen in many reports and can vary from 3.6% to 64%.[29,30] Resistence to AMB noted to be 12% is a matter of concern as emergence of such isolates may pose serious therapeutic challenges and also increases risk of nosocomial infection.

Combination of various risk factors is known to be strongly associated with development of candidemia. The major risk factors identified in our study were prematurity (60%), low birth weight (60%), prolonged antibiotic use (60%), ventilator support (56%) and total parentral nutrition (50%).

Most of the neonates positive for candidemia were premature or low birth weight. This is in close agreement with many other reports.[23]

Mechanical ventilation has well been described as a risk factor for the development of neonatal fungal blood stream infection.[23]

Broad spectrum antibiotics were being administered to most of the neonates in the present study. They promote fungal overgrowth at the expense of normal bacterial flora and encourage translocation of yeast across the intact mucosa. The risk of candidemia is known to increase exponentially with each class of antimicrobial used. Long term use of these broad-spectrum antibiotics must have created a negative pressure and favorable environment for Candida spp. to flourish. This substantiates the need of prophylactic antifungal to be used in a set up where continuous upsurge in the incidence of candidemia is seen.

CONCLUSION

Fungal BSI is an important problem in neonates with a high mortality rate and significant incidence of resistant organisms. 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. Preventive measures such as use of filters for TPN, prophylactic antifungal use, and a restrictive policy of antibiotic use to decrease Candida colonization infection rates should be implemented to decrease mortality and morbidity associated with these infections. Also, previously ignored, NAC species esp *Candida glabrata* received little attention; therefore, not surprisingly our knowledge regarding them is not only incomplete, but also significantly lacking. So, we now need to have more studies and more tools; specially molecular tools to study the epidemiology of this emerging problem. Understanding the mechanisms of innate and acquired resistance may facilitate development of new targets for antifungal agents.

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