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Original Research Article

PREVALENCE AND ANTIFUNGAL SUSCEPTIBILITY PROFILE OF CANDIDA SPECIES ISOLATED FROM BLOOD STREAM INFECTIONS IN NEONATES IN A TERTIARY CARE HOSPITAL

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Abstract

Background: Fungi are achlorophyllous eukaryotic organisms which multiply sexually and asexually by production of spores. The fungi are widely found in environment and most of them are harmless commensals, contaminants or nonpathogenic agents. Neonates, elderly patients and those admitted to intensive care units (ICUs) are at greater risk of death than other categories of patients. Candida blood stream infection (BSI) is an important cause of neonatal sepsis and sepsis related mortality. Common 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, through vertical transmission from maternal flora or via horizontal transmission from hands of health care workers have made neonates prone to candidemia. **Materials and Methods:** This study was a hospital based cross sectional study conducted at Srirama Chandra Bhanja Medical College, Cuttack. The study group comprised of 1350 patients of neonatal age groups who were clinically suspected to have blood stream infection from neonatal ICU of Sardar Vallabhbhai Patel Post Graduate Institute of Pediatrics and Dept. of Pediatrics of SCB medical college. Newborns with above mentioned criteria were included in this study. Data like date and time of delivery, mode of delivery (normal, LSCS, outlet forceps and vacuum extraction), duration of labour, place of delivery (home, primary health centre (PHC), Government hospital (GH), private hospital and institutional delivery), transport details if any and admission time with date were recorded. All data were entered into Microsoft Excel spread sheet. **Result:** Majority of Candidemia cases were associated with Low Birth Weight followed by Broad spectrum antibiotics use, Respiratory distress and Preterm delivery. C.tropicalis (29.03%) was found to be the predominant species followed by C.parapsilosis (25%). All 124 isolates were identified using all four methods except Candida guillormondii which were not able to be identified using CHROM agar. And 2 isolates of Candida parapsilosis were failed to be identified using CHROM Agar. Thus, Dalmau, sugar fermentation and sugar assimilation shows 100% sensitivity whereas the sensitivity of CHROM is 81.4% (compared with Dalmau). **Conclusion:** Candidemia in hospitalized patients especially in NICU and SNCU patients is emerging as a significant problem worldwide. The change in epidemiology and pattern of antifungal susceptibility of Candida infection has made identification of aetiological agent compulsory along with its antifungal susceptibility. Various risk factors have attributed to this increase in Candidemia in the hospital settings.

INTRODUCTION

Fungi are achlorophyllous eukaryotic organisms which multiply sexually and asexually by production of spores. The fungi are widely found in environment and most of them are harmless commensals, contaminants or nonpathogenic agents.[1] They are found in the form of yeasts, molds, or dimorphic fungi2. The overall incidence and prevalence of mycotic infections is increasing particularly during last three decades due to growing number of immunocompromised and more susceptible individuals.[2] Yeasts of genus Candida are associated with a wide range of different clinical manifestations, including bloodstream infections (BSIs), intra-abdominal candidiasis, deep- seated candidiasis, and superficial infections like vaginitis, oral candidiasis and cutaneous candidiasis.[3]

Neonates, elderly patients and those admitted to intensive care units (ICUs) are at greater risk of death than other categories of patients.[4,5] Candida blood stream infection (BSI) is an important cause of neonatal sepsis and sepsis related mortality.[6] The clinical manifestations are respiratory insufficiency, apnoea, bradycardia, feeding intolerance, temperature instability and abdominal distension.[7] Colonization of skin and gastrointestinal tract is the first step in the pathogenesis of invasive candidiasis.[8] In addition, candidemia is associated with prolonged hospitalization, resulting in substantially increased health care costs.

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, type of Candida species causing the BSI and prevalence of antifungal resistance.[9] Systemic candidiasis in neonates is increasing in frequency especially since the survival of babies with low birth weight (LBW) has increased.[10]

An incidence rate of 1.61 per 1000 hospital admissions for candidemia has been reported. A prevalence rate of 18% for Candida species among blood culture isolates was found in New delhi.[11] An incidence rate of 5.7% for candidemia among children with onco-haematological malignancies was reported in South India.[12] An isolation rate of 8.1% for Candida species from cases of neonatal septicaemia was reported from North India.[13] A prevalence rate of 6% for Candida species was reported from AIIMS, New Delhi in a 5-year study (2001– 2005).[14] The mortality rate is unacceptably high, ranging from 29% to 76%.[15]

Common 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, through vertical transmission from maternal flora or via horizontal transmission from hands of health care workers have made neonates prone to candidemia.[16]

Clinicians now depend on identification of Candida to the species level in order to optimize the selection of antifungal agents allowing them to provide the best possible patient care.[17] Therefore there is a need for continuous surveillance to monitor trends in incidence, species distribution and antifungal drug susceptibility profiles of Candida BSI.[18]

The present work aimed to calculate the prevalence of candidaemia among neonatal patients, identify the risk factors, characterize the involved species and determine the susceptibility of the isolated strains to antifungal agents, specifically caspofungin, amphotericin B, itraconazole, miconazole, fluconazole and flucytocine using automated methods.

MATERIALS AND METHODS

This study was a hospital based cross sectional study conducted at Srirama Chandra Bhanja Medical College, Cuttack.

The study group comprised of 1350 patients of neonatal age groups who were clinically suspected to have blood stream infection from neonatal ICU of Sardar Vallabhbhai Patel Post Graduate Institute of Pediatrics and Dept. of Pediatrics of SCB medical college.

Inclusion Criteria

Babies admitted with suspected septicaemia along with :

a. Premature babies (37 weeks), low birth weight babies (<2500gms).
b. Babies on ventilator care.
c. H/O insertion umbilical line / Presence of central venous catheter
d. Use of surfactant / blood, blood products or exchange transfusion / on total parenteral nutrition (TPN).
e. Newborn with broad-spectrum antibiotics administration.
f. Neonates who underwent major surgeries.

Exclusion Criteria

1. Patients on prior antifungal treatment
2. Other healthy babies

Data Collection

Newborns with above mentioned criteria were included in this study. Data like date and time of delivery, mode of delivery (normal, LSCS, outlet forceps and vacuum extraction), duration of labour, place of delivery (home, primary health centre (PHC), Government hospital (GH), private hospital and institutional delivery), transport details if any and admission time with date were recorded. All data were entered into Microsoft Excel spread sheet.

Statistical Analysis: Statistical analysis was carried out using SPSS software version 16.0. Variables are analysed for frequencies and percentages. Chi-square test was used as test of association, for which p value was calculated. Significance level was set as p value of 0.05. Fisher's Exact was used as appropriate.

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RESULTS

Maximum cases selected from Inborn ward (institutional delivery babies admitting unit-NICU) was 74(59.68%), followed by cases from Special Newborn Care Units- SNCU (sick labour theatre delivered babies, was 31(25%) and from Advanced Care Research Centre (ACRC) was 19(15.32%) [Table 1].

On analyzing 124 cases of neonatal candidemia, the sex distribution of selected cases was found to be male 75 (60.48%) and female 49 (39.52%). There was a slight male preponderance in this study with a ratio 1.5:1 [Table 2].

Majority of Candidemia cases were associated with Low Birth Weight followed by Broad spectrum antibiotics use, Respiratory distress and Preterm delivery [Table 3].

C.tropicalis (29.03%) was found to be the predominant species followed by C.parapsilosis(25%) [Table 4].

All 124 isolates were identified using all four methods except Candida guillormondii which were not able to be identified using CHROM agar. And 2 isolates of Candida parapsilosis were failed to be identified using CHROM Agar. Thus, Dalmau, sugar fermentation and sugar assimilation shows 100% sensitivity whereas the sensitivity of CHROM is 81.4% (compared with Dalmau) [Table 5].

All the124 isolates were identified using both conventional methods and Vitek 2. Out of 124 isolates 102 isolates were identified using conventional methods and 22 isolates were not able to be identified which was identified by Vitek 2.In Vitek 2 101 isolates were identified and 23 isolates were not identified which was identified through conventional methods. Therefore the concordance between two methods is 79(63.71%). [Table 6]

Table 1: Distribution of cases in relation to ward

Ward	No. of cases	Percentage
NICU	74	59.68%
SNCU	31	25%
ACRC	19	15.32%
Total	124	100%

Table 2: Sex wise distribution of cases.

Sex	No. Of Candidemia Cases	Percentage
Male	75	60.48%
Female	49	39.52%
Total	124	100%

Table 3: Risk factors among selected cases

Risk Factor	No. of cases of candidemia	p value
Low birth wt.	102	0.001
Mechanical ventillation	81	0.002
Broad spectrum antibiotics >7days	95	0.04
Central line >7 days	53	_
Total parentral nutrition >7days	32	_
Preterm	73	0.001
Hospital stay >7days	46	0.008
Postnatal Steroid treatment	26	_

Table 4: Species level distribution of Candida

Name. Of Species	No. of Isolates	Percentage
C.tropicalis	36	29.03%
C.parapsilosis	31	25%
C.guilliermondii	17	13.71%
C.albicans	14	11.29%
C.krusei	2	1.61%
C.utilis	12	9.68%
C.famata	7	5.65%
C.lusitanaea	1	0.81%
C.glabrata	2	1.61%
C.kefyr	2	1.61%
Total	124	100%

Table 5: Speciation by Dalmau plating method, CHROM agar,Sugar fermentation and sugar assimilation tests.

Species (Total in no.)	Dalmau	CHROM	Sugar fermentation	Sugar assimilation
C.tropicalis	36	36	36	36
C.parapsilosis	31	29	31	30
C.guilliermondii	17	N/A	17	17
C.albicans	14	14	14	14
C.krusei	2	2	2	2

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Table 6: Comparison of candida spp identification by conventional and automated methods.

Manual identification	Vitek 2 Identification									
	C.albicans	C. tropicalis	C. parapsilosis	C. guillermondii	C. utilis	C. famata	C.krusei	C.lusitaneae	Unidentified	Total
C.albicans	14	0	0	0	0	0	0	0	0	14
C. tropicalis	0	27	0	0	0	0	0	0	9	36
C. parapsilosis	0	0	29	0	0	0	0	0	2	31
C. guillermondi	0	0	0	9	0	0	0	0	8	17
C.kefyr	0	0	0	0	0	0	0	0	2	2
C.glabrata	0	0	0	0	0	0	0	0	2	2
Candida species	0	0	0	0	12	7	2	1	0	22
Total	14	27	29	9	12	7	2	1	23	124

Table 7: MIC distribution of antifungal drugs against most common candida species.

Totals	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	≥8
Fluconazole										
C.albicans			6	1	1	1				5
C.parapsilosis			4	8	6	1	1	2		9
C.tropicalis			6	11	2	1				16
C.guilliermondii					6	3	2			6
C.utilis					3	1	2	1		5
Voriconazole										
C.albicans	10		2	1	1					
C.parapsilosis	13	5	5	8						
C.tropicalis	28		8							
C.guilliermondii	13	4								
C.utilis	10	1	1							
Micafungin										
C.albicans	11	2	1							
C.parapsilosis				11	8	6	4	1		1
C.tropicalis	23	4	5	4						
C.guilliermondii		2	3	6	5	1				
C.utilis										
Caspofungin										
C.albicans	11	1	1	1						
C.parapsilosis				13	8	5	4			1
C.tropicalis	27	4	3	2						
C.guilliermondii	5	8	4							
C.utilis										
Amphotericin B										
C.albicans			2	3	7					2
C.parapsilosis				8	21	2				
C.tropicalis				11	19	5				1
C.guilliermondii		5	4	6	1					1
C.utilis		5	6	1						
Flucytosine										
C.albicans		8	4	2						
C.parapsilosis			22	8	1					
C.tropicalis			12	6	5	4	7			2
C.guilliermondii			8	3	2			4		
C.utilis				2				8		2

Table 8: Antifungal susceptibility rate of various antifungals

Antifungal	No of isolates Tested	Sensitive	Percentage
Amphotericin B	124	120	96.77%
Caspofungin	112	111	99.19%
Fluconazole	124	83	66.94%
Flucytosine	124	116	93.55%
Micafungin	112	111	99.19%
Voriconazole	124	123	99.19%

Out of all the antifungal agents tested voriconazole, caspofungin and micafungin showed highest sensitivity of 99.19% followed by. Amphotericin B showing 96.77% sensitivity. A total of 83 (66.94%) isolates were sensitive to fluconazole.

Table 9: Antifungal resistance pattern of candida species

Candida species	No. of cases n=124	Resistance n(%)					
		FLU	VOR	MIC	CAS	AMB	FLY
C.albicans	14	5 (35.71%)	0(0%)	0(0%)	0(0%)	2(14.28%)	0(0%)
C.parapsilosis	31	9 (29.03%)	0(0%)	1(3.23%)	1(3.23%)	0(0%)	0(0%)
C.tropicalis	36	16(44.44%)	0(0%)	0(0%)	0(0%)	1(2.78%)	2(5.56%)
C.guilliermondii	17	6(35.29%)	0(0%)	0(0%)	0(0%)	1(5.88%)	4(23.52%)
C.utilis	12	3(25%)	0(0%)	0(0%)	0(0%)	0(0%)	2(16.67%)
C.famata	7	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
C.krusei	2	2(100%)	1(50%)	0(0%)	0(0%)	0(0%)	0(0%)
Others	5	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Total	124	41(33.06%)	1(0.81%)	1(0.81%)	1(0.81%)	4(3.23%)	8(6.45%)

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Note: FLU-fluconazole, VOR-voriconazole, MIC-micafungin, CAS- caspofungin, AMB-amphotericin b, FLY-flucytosine.

A total of 41 (33.06%) isolates were resistant to Fluconazole. Fluconazole resistance was more in C. tropicalis followed by C. parapsilosis. Voriconazole resistance was seen in 1 isolate (0.81%). Micafungin and caspofungin resistance were noted in 1 isolate (0.81%). Amphotericin B resistance was noted in 4 (3.23%) isolates more in C. albicans. Flucytosine resistance was noted in 8 (6.45%) isolates predominantly among C.guilliermondii.

Table 10: Comparison of antifungal susceptibility of C.albicans & non- albicans.(S. Tatte & R. Bhise, 2018)

Isolates	No. % N=124	Resistance %					
		FLU	VOR	MIC	CAS	AMB	FLY
C.albicans	14(11.29%)	14.28%	0%	0%	0%	14.28%	0%
Non albicanscandida	110(88.71%)	20%	0.91%	0.91%	0.91%	3.64%	7.27%

Fluconazole resistance was more among non albicans candida (20%) as compared to Candida albicans (14.28%). Amphotericin B resistance was noted more among Candida albicans (14.28%) as compared to 3.64% in Non albicans.

DISCUSSION

In this study, out of 124 candida isolates,75(60.48%) were from male patients and 49 (49%) from female patients. Male predominance was noted in our study (n=75/124) with a ratio 1.5:1. A study from Maharashtra by S. Tatte & R. Bhise,[19] 2018 is in concordance with our study showing a male preponderance (64.6%). This is also similar to another study by Caggiano et al,[20] 2017 reported male preponderance with a ratio of 1.6:1.

The species distribution in our study is as follows, C.tropicalis 36 (29.03%), C.parapsilosis 31 (25%), C.guilliermondii 17(13.71%), C.albicans 14 (11.29%), C.utilis 12(9.68%), C.famata 7(5.65%) C.krusei 2(1.61%), C.glabrata 2(1.61%), C.kefyr 2 (1.61%), and C.lusitanaea 1 (0.81%). This is in concordance with the study conducted by Basu et al,[21] 2017 who reported C.tropicalis as the predominant species contributing 39% of all.

In our study 14(11.29%) of isolates belonged to the Candida albicans and 110(88.71%) of isolates belonged to Non albicans Candida. This is in accordance with the study done by Lakra et al,[9] 2020 who reported 10% Candida albicans and 90% non albicans Candida. In last decade, several reports stated that non albicans Candida is an emerging pathogen. The C.gulliermondii was isolated in NICU by K. Sesu kumari et al(2014) in their study.[22]

Biochemical reactions like sugar fermentation and sugar assimilation are useful for further speciation of Candida. In identification of different species Dalmau technique, sugar fermentation and sugar assimilation were concordant in all cases in our study. Hence the sensitivity of CHROM agar was found to be 81.4% in comparison to the other three tests. This is concordant with the study done by Shymala et al.[23]

In our study resistance to fluconazole ranges between 35-45% .Resistance to Amphotericin B was noted in 4 Candida isolates (3.23%). This is in concordance with the study done by S. Tatte & R. Bhise,[19] 2018 who reported 6.25% amphotericin resistance. There are very few reports of Amphotericin B resistance in Candida isolates from cases of Candidemia in India (Adhikari and Joshi,2011).[24] Though only 2% of isolates of NAC spp. were resistant to amphotericin B, the high frequency of renal toxicity and several other adverse effects limits its use(Logu et al.,2005).[25]

The majority of enrolled cases 83(66.94%) died within 30 days of diagnosis, of whom 33.73% were resistant to fluconazole. This is in concordance with the study conducted by Khairat et al,[12] 2019 who reported 34.4% resistance to fluconazole among deceased. Crude mortality remained high for both non albicans and C.albicans groups with a slightly lower rate for later overtime.

CONCLUSION

Candidemia in hospitalized patients especially in NICU and SNCU patients is emerging as a significant problem worldwide. The change in epidemiology and pattern of antifungal susceptibility of Candida infection has made identification of aetiological agent compulsory along with its antifungal susceptibility. Various risk factors have attributed to this increase in Candidemia in the hospital settings. The increase in resistance to antifungal agents among Candida isolates has resulted in increased mortality and morbidity. Prevention of risk factors in Candidemia patients with early removal of central line, timely fungal culture, Candida speciation and antifungal susceptibility testing are necessary for appropriate treatment and better outcome.

Even though CHROMagar helps with identification at a lower cost as compared to automated methods like Vitek-2, which is useful in countries having low resources, but it takes longer duration for complete identification, which is the main drawback of this method. Vitek-2 is considered as a reliable technique for antifungal susceptibility of yeast species, it also has the added advantage of being more rapid and easier than the alternative procedure developed by CLSI like broth microdilution method which is cumbersome and expensive. So, a fast and accurate technique for yeast identification is very important for microbiological laboratories. Accordingly, Vitek-2 can be applied for early identification and antifungal susceptibility testing. Local epidemiological data and antifungal susceptibility

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profile should be taken into consideration when establishing antifungal treatment strategies. Infection control measures like hand and personal hygiene by healthcare workers, proper catheter care, frequent clinical examination of patients who are weaned off invasive device to be practiced to reduce nosocomial transmission as candidemia represents 10% of nosocomial infections in hospitalised patients and also antibiotic stewardship must be emphasised.

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