ISSN No:-2456-2165

Prevalence of Candidemia in High-Risk Neonates of Neonatal Intensive Care Unit – A One-Year Cross Sectional Study

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Abstract:-

- ***Background:***

Fungal sepsis in neonates is third most common blood stream infections in ICUs. The changing epidemiology to non-albicans *Candida* is grossly evident. Azole resistance is on rise, next alternative are Echinocandins.

- ***Objective:***

To study the prevalence of Candidemia in high-risk neonates of NICU and to study Caspofungin (Echinocandin) antifungal susceptibility in Fluconazole resistant *Candida* isolates by E test / MIC test strip method.

- ***Material and Methods:***

The blood sample collected from all high-risk neonates admitted during the study period in NICU of Dr. Prabhakar kore charitable hospital, Belagavi during study period, were included in the study. All the samples were processed according to the standard operating procedures of Mycology, conventionally.

- ***Results:***

A total of 230 Blood samples collected from NICU from the high-risk neonates with suspected sepsis, who were admitted in the study period and were processed and were evaluated. Of which total of 63 were Fungal isolates (27.39%), *Candida albicans* were 25.4% (n=16) and NAC species (n=47), predominant being *C. glabrata* 46.03% (n=29). 53.97 (n= 34) isolates are resistant to Fluconazole and 76.19 (n=48) are resistant to Voriconazole. By E-strip method 20.63 (n=13) were resistant to Caspofungin.

- ***Conclusion:***

Prophylactic usage of Fluconazole as an antifungal drug is now questionable as Fluconazole resistance is on rise. Echinocandins are the only next alternative. Strict infection control strategies, appropriate preventive, and therapeutic measures should be implemented.

Keywords:- *Fungal Sepsis, Candida, NAC Species, Critically Ill High-Risk Neonates.*

I. INTRODUCTION

Candida species are the source for many clinical manifestations ranging from mucocutaneous to life threatening disseminated infections mainly including blood stream infection notoriously known to cause fungal sepsis[(1,2,19)].Candidemia is now showing its increasing prevalence in all age groups more considerably in high-risk neonates. Incidence of invasive fungal sepsis due to *Candida* species in neonates is the 3rd most common cause for BSI in NICU accounting for 9-13% [(2.14)].Neonates such as Preterm, extremely/ very/ low birth weight, on TPN, mechanical ventilator, on broad spectrum antibiotics, prolonged stay in hospital are at high-risk for *Candida* infections [(1,2,3)].Epidemiological shift of increased prevalence of NAC species infection and their emerging resistance to azole group of drugs represents a major challenge for empirical, therapeutical, and prophylactic strategies[(24).] Echinocandins have become the savior for azole resistant *Candida* species. Hence identification and isolation of *Candida species* in blood stream of critically ill neonates has become mandatory [(2,17)] along with study the efficacy of Echinocandins in the treatment of invasive Candidiasis is the need of the hour. [(32)]

II. MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Microbiology, J. N. Med. College, KAHER, Belagavi after collecting the blood sample collected from all high-risk neonates admitted during the study period in NICU of Dr. Prabhakar kore charitable hospital, Belagavi from January 2021 to December 2021. All the other clinical samples of high-risk neonates and non-high-risk neonates admitted during the study period in NICU were excluded. Based on inclusion and exclusion criteria a total of 230 critically ill neonate blood samples were collected and processed according to the standard operating procedures using conventional techniques. Under aseptic condition 0.5 - 1ml of blood of high-risk neonates is collected and immediately is inoculated into the color cult aerobic blood culture vial provided on bedside, these culture vials contain Resins/ adsorbent polymeric beads help in neutralizing many antibiotics along with β-lactam antibiotics, sodium polyanethol sulphonate inhibits the compliments and also inhibits the phagocytosis in turn enhances the growth of pathogens. 30ml of highly nutritive media is present in the vial to support the growth of both fastidious and non-

fastidious organisms. After sample was inoculated overnight incubation was done and next day subculture onto chocolate agar and SDA was done, colony characteristics, Gram staining, Germ tube test and inoculation onto Corn meal agar (Dalmau method) and Chrom-agar (Hi-media, India) for speciation and Antifungal susceptibility (both by Kirby-Bauer Disc diffusion and E-strip of Himedia, India) on SDA was done simultaneously. Data obtained was statistically analyzed with respect to the variables like Preterm, extremely/ very/ low birth weight, on total parenteral nutrition, on mechanical ventilator, on broad spectrum antibiotics, prolonged stay in hospital for p-values and their correlation with *C.albicans* and Non-albicans *Candida* isolates.

III. RESULTS

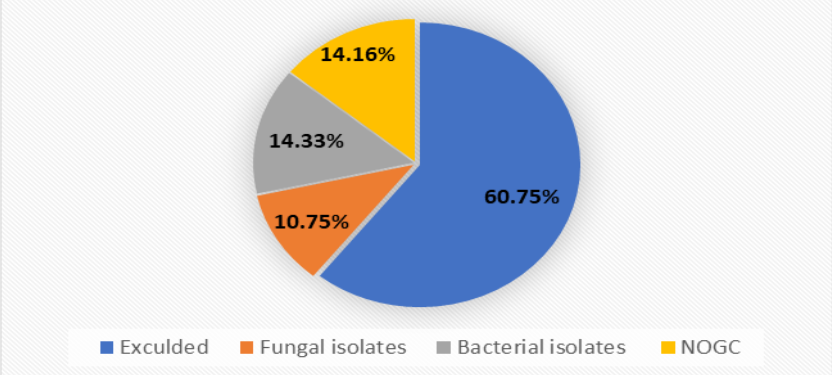
Among total of 586 NICU admission 356 neonates were excluded, 230 blood samples were collected and further processed of which 63 are pure isolates of fungal sepsis. *Candida albicans* (n=16) constitutes to 25.4% and Non-albicans *Candida* (n=47) are 74.6% of total isolates and resistance to Fluconazole is seen in 53.38% and sensitivity to Echinocandins (Caspofungin) is seen in 79.36% of fungal isolates done by E- strip test.

Neonatal candidemia accounts to 10.75% of total neonate admitted in NICU during study period, constituting to third most common blood stream infection. The most common isolate in *Candida glabrata* (46.03%) followed by *Candida albicans* (25.40%). Ratio of Non-albicans to *Candida albicans* is 3:1. There were 31 male patients and 32 female patients. The total Male to Female ratio is approximately 1:1. Here in 37 (59%) neonates were born through LSCS and 26 (41%) through NVD. The ratio LSCS: NVD is 1.5: 1. According the data p value is 0.0962 indicates that candidemia is not significant with respect to gender and p value is 0.0962 indicates that candidemia is not significant with respect to mode of delivery.

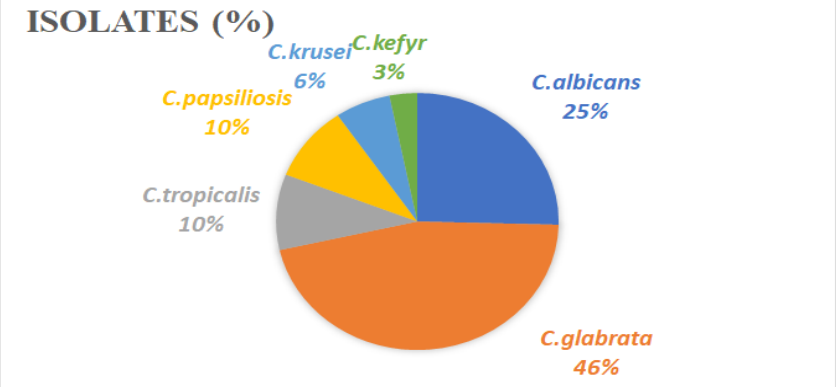
Table 1 Number of Fugal Isolates in 1st Subculture

	1st SUBCULUTRE								
	C.albicans	***C.krusei***	***C. parapsilosis***	***C. tropicalis***	***C.glabrata***	***C.kefyr***	**TOTAL**	**p VALUE**	**INFERENCE**
ALBICANS	16	0	0	0	0	0	16	< 0.0001	HS
NON ALBICANS	0	4	6	6	29	2	47		
TOTAL	16	4	6	6	29	2	63		

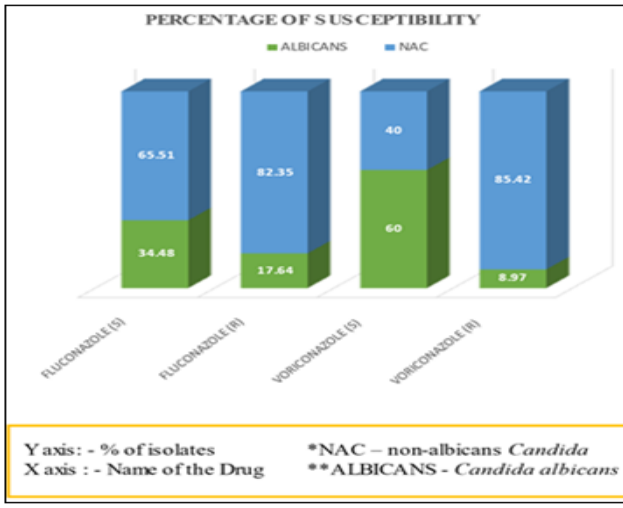
According the table 1 p value is < 0.0001 indicates that candidemia is significant with respect to 1st sub culture, indicating that the fungal isolates correlate with day of inclusion and isolation.



Graph 1 Showing Percentage of Isolated from NICU During Study Period.



Graph 2 Showing Total Number of Fungal Isolates in Percentage

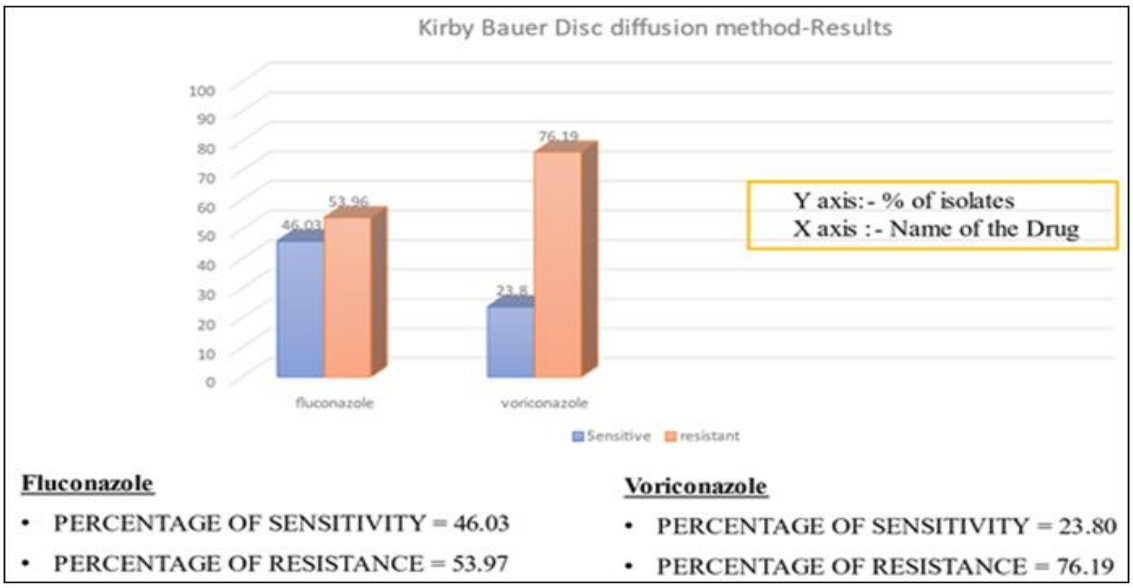


FUNGAL ISOLATE	DISC DIFFUSION METHOD FLUCONAZOLE		
	R	S	TOTAL
ALBICANS	6 (17.64%)	10(34.48%)	16
NON ALBICANS	28(82.35%)	19(65.51%)	47
TOTAL	34	29	63

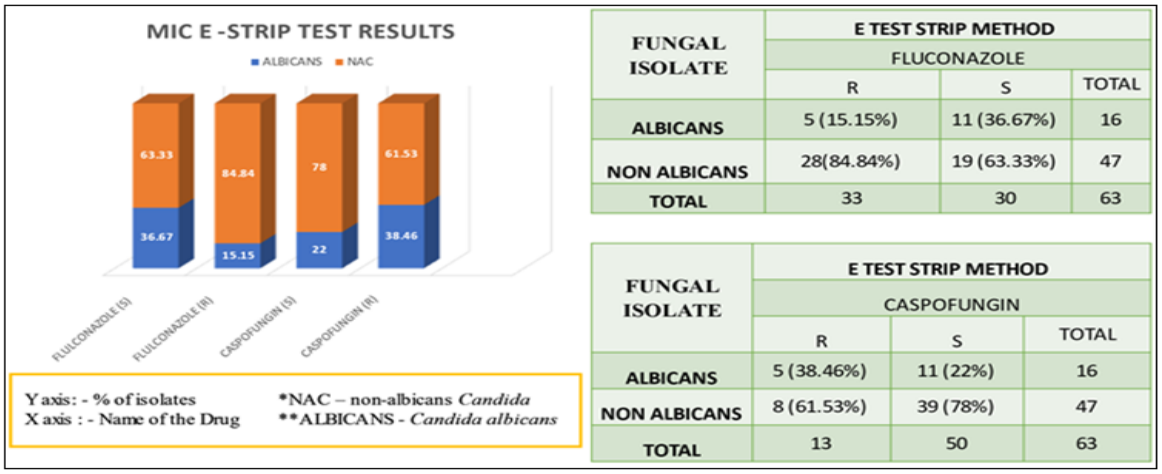
FUNGAL ISOLATE	DISC DIFFUSION METHOD VORICONAZOLE		
	R	S	TOTAL
ALBICANS	7(8.97%)	9(60%)	16
NON ALBICANS	41(85.42%)	6(40%)	47
TOTAL	48	15	63

Graph 3 (On Left) Shows Graphical Representation % Susceptibility to Fluconazole & Voriconazole

Table 2 (On Right Top) & Table 3 (Right Bottom) Shows % of Isolates Susceptibility to Fluconazole & Voriconazole Respectively.



Graph 4 showing drug susceptibility to Fluconazole and Voriconazole



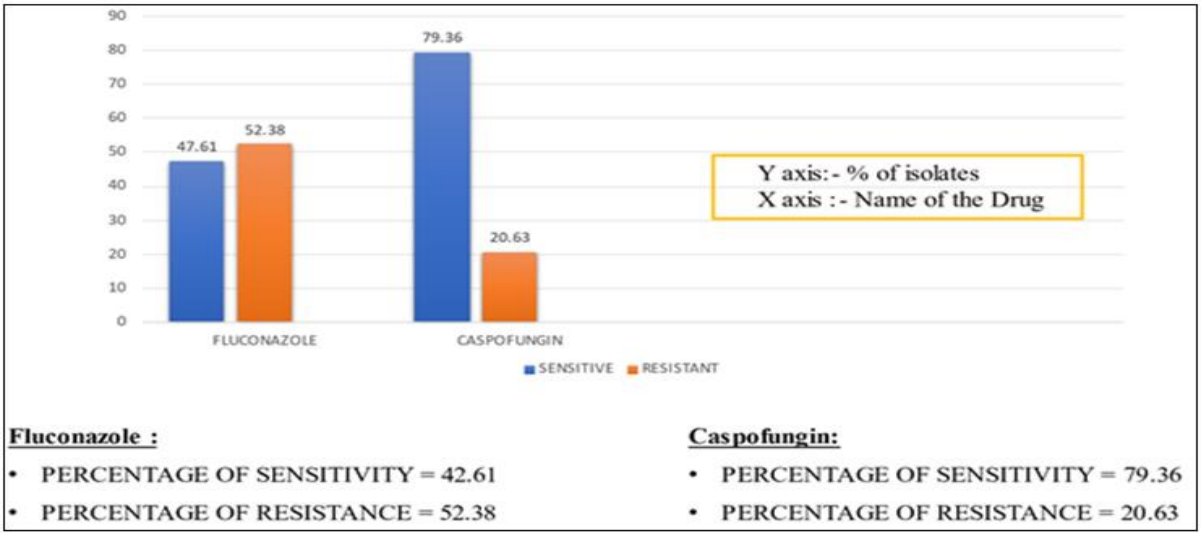
FUNGAL ISOLATE	E TEST STRIP METHOD FLUCONAZOLE		
	R	S	TOTAL
ALBICANS	5 (15.15%)	11 (36.67%)	16
NON ALBICANS	28(84.84%)	19 (63.33%)	47
TOTAL	33	30	63

FUNGAL ISOLATE	E TEST STRIP METHOD CASPOFUNGIN		
	R	S	TOTAL
ALBICANS	5 (38.46%)	11 (22%)	16
NON ALBICANS	8 (61.53%)	39 (78%)	47
TOTAL	13	50	63

Graph 5 (On Left) Shows Graphical Representation % Susceptibility to Fluconazole & Voriconazole

Table 4 (On Right Top) & Table 5 (Right Bottom) Shows % of Isolates Susceptibility to Fluconazole & Caspofungin Respectively.

ISSN No:-2456-2165



Graph 6 Showing Drug Susceptibility to Fluconazole and Caspofungin

Table 6 Risk Factors in Association with *Candida albicans* & NAC Species

Risk factor		No of neonates	*C. albicans*	Non-albicans *Candida*	Percentage
Gender	Male	32	11	21	50.79
	Female	31	5	26	49.20
Mode of delivery	LSCS	37	7	31	58.73
	NVD	26	9	16	41.26
Gestational age	Term (>36 wks.)	17	6	11	26.98
	Preterm (32-36 wks.)	19	4	15	30.15
	Very preterm (<32wks)	22	5	17	34.92
	Extremely preterm (26-28wks)	5	1	5	7.93
Birth weight	Normal (≥2500 gms)	10	4	6	15.87
	LBW (< 2500 gms)	25	6	19	39.68
	VLBW (<1500 gms)	25	6	19	39.68
	ELBW (<1000 gms)	3	--	3	4.76

Table 7 Risk Factors in Association with *Candida albicans* & NAC Specie

Risk factor		No of neonates	*C. albicans*	Non-albicans *Candida*	Percentage
Antibiotic usage		63	16	47	100
Total parenteral nutrition		62	15	47	98.41
Mechanical ventilation		17	6	11	26.98
Respiratory depression		54	15	38	85.71
Thrombocytopenia		57	15	42	90.47
Neonatal seizures		16	6	10	25.39
Long-line insertion		49	9	40	77.78
Duration of stay in NICU	1st week (0-7days)	6	2	4	9.52
	2nd week (8-14days)	12	5	7	19.04
	3rd week (15-21 days)	17	4	13	26.98
	4th week (22-28days)	24	4	20	38.09
	>28days	4	1	3	6.34
Mortality		10	3	7	1.7

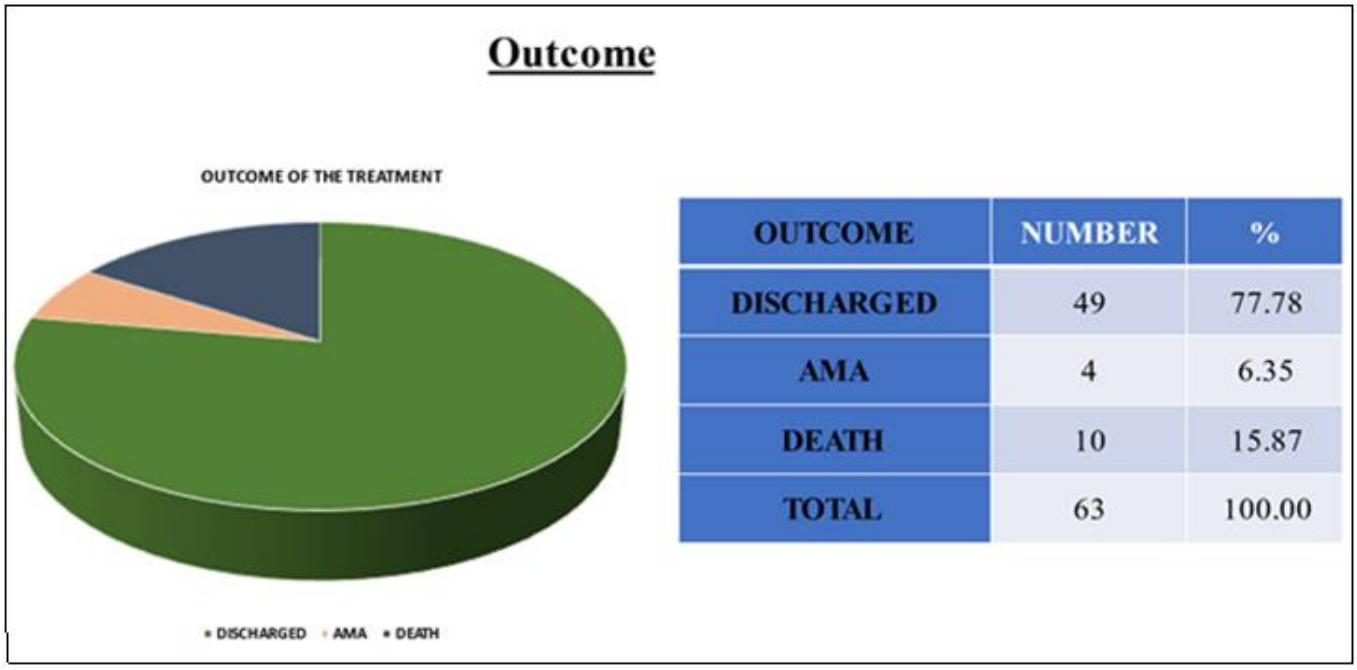
ISSN No:-2456-2165

Table 8 In the Following Table to Find the Agreement between Disc Diffusion Method and E Test Strip Method for Fluconazole Kappa Statistic is Calculated

	E TEST STRIP METHOD		
DISC DIFFUSION METHOD	**R**	S	**TOTAL**
R	33	1	34
S	0	29	29
TOTAL	33	30	63

p < 0.0001 (HS) KAPPA = 0.9681

- There is almost perfect agreement between the two procedures.



OUTCOME	NUMBER	%
DISCHARGED	49	77.78
AMA	4	6.35
DEATH	10	15.87
TOTAL	63	100.00

Graph 7(On Left): Shows Outcome Obtained with the Study

Table 8 (on right) Shows the Number of Outcome

IV. DISCUSSION

Our study reports 63 fungal isolates of 230 blood samples collected. Thus, we report a prevalence of 27.39 % of Candidemia in high-risk neonates. In our present study 63 Fungal isolates were reported with age group from Day 3 to day 28 of birth in critically ill neonates. Male to female ratio is 1:1 and mode of delivery ration between LSCS and NVD being 1.5:1. Ratio of Non-albicans *Candida to Candida albicans* being 3:1 indicating the rise in Non-albicans *Candida* and is risk factors associated with the development of candidemia in high-risk neonates like prematurity, LBW, VLBW, prolonged stay in hospitals, neonates on mechanical ventilation and external devices used. And rising resistance to Fluconazole used as empirical treatment is also recorded. In our study male to female ratio is 1:1 and has no significance with fungal sepsis, when compared to *Uttam KG et al*[(1)] showed male to female ratio is 3:1, whereas *Anataiah et al*[(2)], *Sundaram et al*[(3)] also showed male to female ratio 1:1 and says that gender has no significance with fungal sepsis, indicating both the genders are at equal risk. Same is with the mode of delivery, our study and other studies conducted by *Anataiah et al*[(2)] , *Shettiger et al*[(14)] says that no significance for fungal sepsis with mode of delivery . According the above statistics, invasive candidiasis in premature preterm infants from our study is 65% and low birth weight 39.68% and very low birth weight 39.68% which is in close agreement with *Uttam et al*[(1)] from Kolkatta west Bengal, *Anantaiah et al*[(2)] Dharward Karnataka, *Shettigar et al*[(14)] from Mangalore, *Fu et al*[(4)], China, M.S. *Hammoud et al*[(34)], Kuwait. Pre mature neonate who are less to their gestation age are at high risk when compared to term babies. Apart from preterm LBW, VLBW the other risk factors as explained such as neonates on mechanical ventilators, on TPN, and on devices like central lines, UVC and UAC, long line tips, neonates admitted in NICU with increased duration of hospital stay and prolonged usage of antibiotics are at potentially higher risk for fungal sepsis or late onset sepsis. Almost all the studies show similar association with the Risk factors as mentioned in neonates such as TPN, mechanical ventilation, prolonged usage of antibiotics, neonates on external devices like long line insertion, UAC/UVC and signs and symptoms of sepsis like respiratory distress. Comparison of our study with the other studies and data with respect to susceptibility to azole group of drugs and echinocandins, basing on our tertiary care center antifungal prophylaxis, test was done for Fluconazole and Voriconazole by Kirby Bauer disc

diffusion method and for Fluconazole and Caspofungin by E-strip test method. And all the studies focused on the increasing trends of NAC species followed by decreased susceptibility to empirically used drugs such as Fluconazole. Our study showed of all isolates 53.97% resistance to fluconazole and 76.19 % resistance to Voriconazole by Disc diffusion method and resistance to Caspofungin is shown by 20.63% by E-strip method, which is in contrast with *Uttam et al*[1], *and Ananthaiah et al*[2], showing 0% resistance to voriconazole, 5% resistance to Caspofungin where as our study showed 79.36% sensitivity for Caspofungin. *Sandu et al* [27] showed 70% sensitive to Fluconazole and voriconazole, but 60% resistance showed by Non-albicans *Candida.*In the other study done by *Shettigar et al*[14] in 2018 from Mangalore showed Fluconazole sensitivity 55.56%. Similar study from Uttarakhand conducted by *Juyal et al* [28] in 2013 showed 65.91% sensitivity to Fluconazole. From Varanasi in 2017 Basu et al [21] did a similar study in their tertiary care center which shows 100% sensitivity to Caspofungin and Voriconazole with increased resistance of Fluconazole *Jain et al* [17] study done at Bundelkhand Medical College, Madhya Pradesh, India in the year 2017 showed that among all isolates of *Candida* species including albicans and non-Albicans 53.21% resistance to Fluconazole with shows a close agreement with our study which also showed 53.97% resistance to Fluconazole. Similarly, a study from Kolkata in 2016 done by *Bhattacharjee P et al* [26] showed increased resistance to Fluconazole in fungal isolates constituting to 61.11% which is in close agreement with our study. Out of 33 Azole resistant *Candida* isolates of 20 were sensitive to Caspofungin and 10 isolates were resistant is recorded in our study, which infers that *Candida* species are slowly developing resistance to Echinocandins also. *Whaley et al* [23] from Memphis, TN, USA had studied about the gene responsible for increased resistance shown by *Candida* isolates especially NAC species, also concluded that *C. glabrata* has highest incidence of azole resistance, which has an inherently property of less susceptibility to Azole drugs. Another similar study done in India done by *Goel et al*[36], in 2009, PGIMS, Rohtak recorded that of total 67 isolates, antifungal susceptibility testing was done by two different methods i.e., disc diffusion method and broth micro dilution method in which they concluded saying small percentage of discrepancy was seen between the two methods used for detection of antifungal susceptibility. In contrast to this study our study has shown almost perfect agreement between the two procedures used i.e., Disc diffusion method and E-strip test method. All though there are many recent advances to decrease the morbidity and mortality of neonates there is increasing rates of fungal sepsis in neonates admitted to NICU, and they are showing increased resistance to empirically used Azole drugs. Mortality rate in our study recorded is 10 deaths out of 586 admitted in NICU during the study period which is around 1.7%. Tough above all studies used automation for rapid identification and to study antifungal susceptibility our study totally was relied on conventional standard mycological techniques for identification isolation and antifungal susceptibility reporting. Overall results and outcome are in very close similarity and agreement with the results of other studies who used automation.

V. CONCLUSION

In this present study we are reporting the spectrum of *Candida* infection in high-risk neonates of NICU in our tertiary care hospital. We hereby report high burden of neonatal Candidemia, prevalence being 27.39% and predominantly due to non-albicans *Candida* species (74.60%) as well as an alarming increase resistance to azole group of drugs, Fluconazole resistance (53.97%) Voriconazole resistance (76.19%). And 79.36% sensitivity to Caspofungin. Prophylactic usage of Fluconazole as an antifungal drug is now questionable. Suggested for increased dose of fluconazole according to body weight. Echinocandins are the available group of drugs as life saviour. There is no significant association of fungal isolates with respect to gender and mode of delivery indicates low or no risk for vertical transmission. Persistent Invasive Candidemia is most associated with prematurity, LBW and VLBW, TPN, prolonged stay in NICU, mechanical ventilation and usage of broad-spectrum antibiotics are the risk factors for fungal sepsis. Utmost care should be taken by all health care personnel (along with mother) to prevent horizontal transmission and cross contamination with the help of strict infection control protocols, appropriate hand hygiene, periodic environmental surveillance of air, water and NICU and change of indwelling devices as and when required can be suggested basing on our data analysis. Mother to child transmission while breast feeding in NICU should also be monitored to avoid horizontal transmission. Timely check on local epidemiology and antibiogram of NICU is needed for changing the protocol empirical or prophylactic antifungals along with antibiotics. Limitations of the study are Turnaround time was more when compared to automation. Follow up with the patient was not done. More study is needed for Echinocandins susceptibility. Repeat blood sample was not done, discharge of the neonate was done based on the improvement symptomatically (clinical based). Sample size should be more to comment on significant p- values and to calculate odds ratio. All neonates were taken in consideration without segregation of inborn and out born neonates. Polymicrobial causes of death and along with other comorbidities, though less number were seen but was not included in our study. Multiple gestation, Birth asphyxia, Respiratory distress, Neonatal seizures in association of Candidemia were not commented. Though many other parameters were noted still did not comment due to less sample size.

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