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RESEARCH ARTICLE

EPIDEMIOLOGY AND RISK FACTORS ASSOCIATED WITH RISE OF NON ALBICANS CANDIDEMIA AT NICU OF A TERTIARY CARE INSTITUTE

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Abstract

Background: Candidemia continue to be a critical challenge in neonatal intensive care units worldwide despite remarkable progress in diagnostic and therapeutic approaches. Over past few years, there has been a progressive mycological shift from*Candidaalbicans* to non *albicans Candida* species.

Objectives: To identify the epidemiology and riskfactors of neonatal candidemia in NICU of a tertiary care hospital.

Material Methods: Blood samples of neonates with provisional diagnosis of sepsis, routinely received in the Department of Microbiology of our institution were screened to highlight pattern of *candida* species recovered and their antifungal sensitivity. Possible risk factors associated were also analyzed.

Results: Candidemia was proven in 4.33%(N=52) and bacteremia in 10.50%(N=126)] among twelve hundred samples received from NICU. Clinically significant isolates(N=178), demonstrated41%(N=73) Gram positive isolates,29.8% (N=53) Gram negative isolates and 29.22%(N=52) non *albicans Candida* [*Candida krusei*(N=38, 21.34%); *Candida parapsilosis* (N=6, 3.37%); *Candida tropicalis*(N=3, 1.68%); *Candida pelliculosa*(N=2, 1.1%); *Candida lipolytica*(N=2, 1.12%); *Candida dublinansis*, (N=1, 0.56%), with preponderance towards late neonatal period(*p* value = 0.045*). 80-100% NAC isolates were sensitive to amphotericin B except for C. pelliculosa. *Ckrusei*was100% resistant to fluconazole. Preterm, low birth weight neonates, using antibiotics for longer duration, total parenteral nutrition and mechanical ventilation were significant risk factorsfor candidemia.

Conclusion: The advent of non albicans Candida species merits attention as they are highly resistant to most of the azoles. Therefore, speciation of Candida in septicemia is essential to institute appropriate antifungal therapy.

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Introduction:-

Infections are a major cause of morbidity and mortality in newborns.Advances in neonatal management have led to considerable improvement in newborn survival.Neonates with a low birth weight, preterm births, need advance life support systems and broad-spectrum antibiotics for longer time,4–8% acquire candidemia and account for 30% of mortalityin this group of patients.Although candidemia isless frequent than bacteremia, *Candida*sp. are the fourth most common bloodstream pathogens [1] Candidemia has become third most common cause of septicemia in late neonatal period.[2]Neonates who survive, frequentlyhave long-term neurological impairment, includingcerebral palsy, blindness, hearing impairment and cognitivedeficits. *Candida* species can spread through vertical or horizontal transmission. Prematurity, use of central venous lines, endotracheal tubes, parenteral nutrition, prolonged hospitalization and colonizers contribute as risk factors for candidemia.*C. albicans*has historically been the most frequently isolated *Candida*species, however non-*albicans Candida* species (NAC) have also been isolated with increasing frequency in recent years. As most published data on spectrum of *candida* species in neonatal septicemia is from developed countries and local epidemiological knowledge is critical in terms of prevention and management of such cases,so this study was undertaken to guide initiation of empirical anti fungal treatment. Neonatal period may be categorized as:[3]

Early neonatal period:
Age <3days of life.

Late neonatal period:
Age >3days of life.

Materials And Methods:-

This study was conducted, over a period of 18months.1200 blood samples from neonates received routinely in the Department of Microbiology SKIMS were screened prospectively and clinical data was collected retrospectively. Study was approved by the Ethical Committee of the institution.

Sample collection and processing:
One milliliter of blood was inoculated into ready to use BacT/ALERT® PF Plus Aerobic Pediatric Blood Culture Bottles (BioMerieux, Inc. Durham, NC 27712) specifically adapted to accommodate smaller volumes and containing additional growth factors and binding resins to enhance organism recovery. The culture bottles were loaded into the BacT/ALERT microbial detection system, based on colorimetric principle.Samples considered negative after five days of incubation by the system were discarded. Positive samples were examined by microscopy of Gram‑stained preparations and subcultured on blood agar plate,Sabouraud dextrose agar(SDA) slant with antibiotics but without cycloheximide and chromogenic media (Hi‑Media Pvt. Ltd., Mumbai, India) in aerobic atmosphere.The preliminary identification was done by colony morphology of growth on SDA and chromogenic media and results of germ tube test. A homogenous organism suspension with inoculum density 1.80 to 2.20 McFarland Standardwas prepared from pure culture of age 18 to 72 hours and processed on Vitek-2 compact system for identification of yeast to species level and its antimicrobial susceptibility testing(AST)using Vitek 2 YST ID and AST cards, chosen according to the results of Gram staining and used as per manufacturer's instructions and the results were generated after 8-10 hours, automatically with software release.

Results:-

There were 2731 admissions in NICU during study period of 18months and 1200 (43.90%) were with clinical suspicion of sepsis and blood samples from such neonates, with request for culture and AST were received routinely in the Department of Microbiology. There was culture positivity of 14.83%(N=178/1200), proving candidemia in 4.33%(N=52) and bacteremia in 10.50%(N=126)[Table 1]. Among bacterial isolates, 73 were Gram positive(GP) isolates and 53 Gram negative(GN) isolates. All *Candida* species, 29%(N=52/178) isolated were NAC[*C.krusei* (N=38) *C.parapsilosis* (N=6), *C.tropicalis* (N=3), *C.pelliculosa*(N=2), *C.lipolytica* (N=2), *C.dublinansis*(N=2)]. NAC species were significantly high in late neonatal period, with *C.krusei* being most found isolate[Table 2;Fig 1]. All *C.krusei*isolates exhibited similar pattern of antifungal susceptibility. They are (100%) resistant to fluconazole(FLU) but 80% to100% susceptible to amphotericin B(AB), caspofungin(CAS), and micafungin(MCF).*C.paripsolosis* shows goof sensitivity pattern (83% to 100% over whole anti fungal panel while 66.7% *C.tropicalis* were sensitive to FLU, voriconazole(VRC), CAS, MCF and 100% were sensitive to AMB and Flucytocine(FCT).*C.peliculosa* and *C.dublinences*showed good sensitivity pattern however *C.lipolytica* showed

more resistant pattern except to AB[Table 3]. The major risk associated are prematurity, LBW, total parenteral nutrition(TPN), mechanical ventilation, and broad spectrum antibiotic therapy[Table 4]

Table 1:	**Total Frequency,N(%)**
Total samples received	1200(43.90%)
Septicemia	178(14.83%)
Candidemia	52 (4.33%)
Bacteremia	126(10.50%)

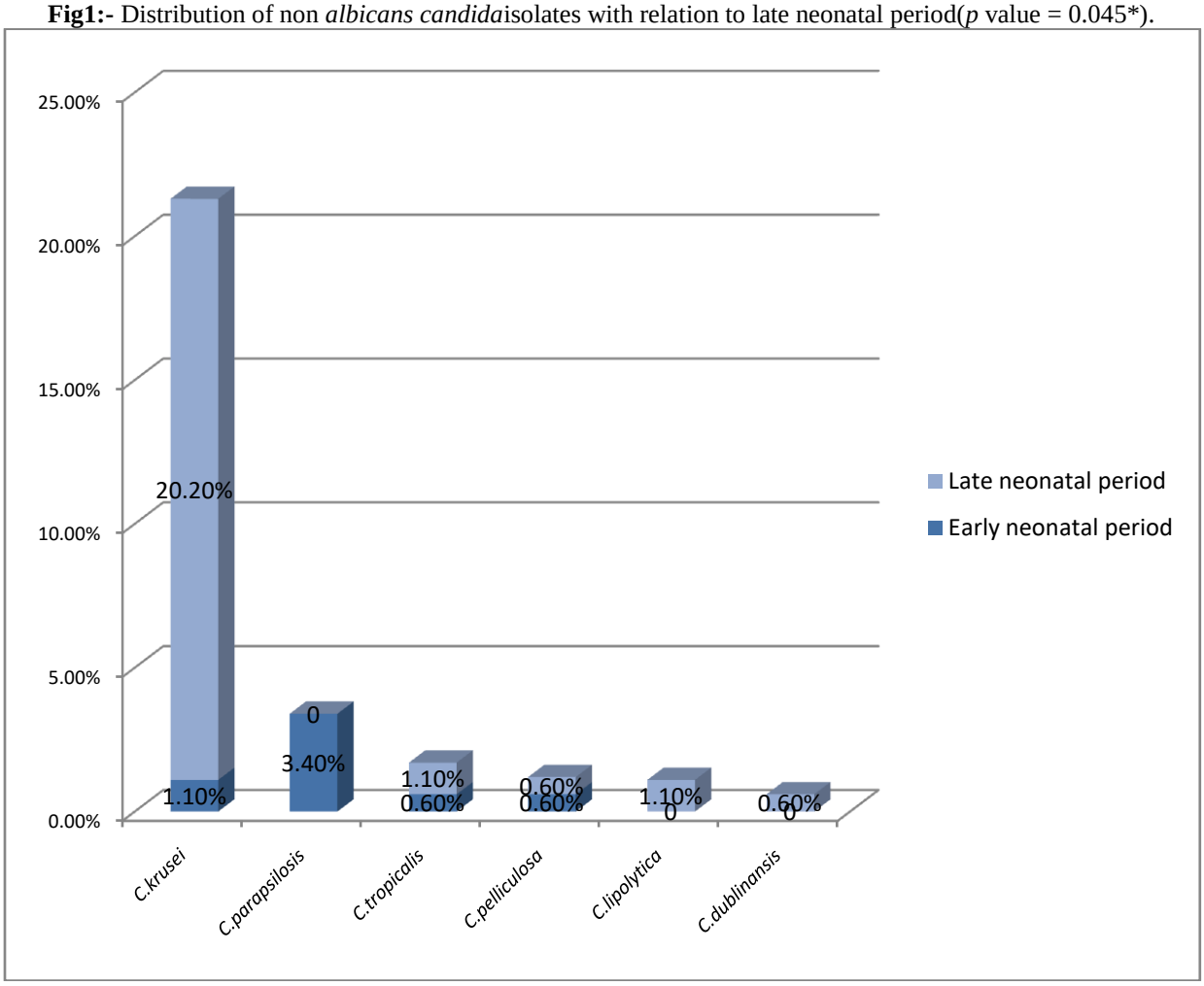
Table 2:- Distribution of total isolates.

Isolates	Early neonatal period	Late neonatal period	TOTAL
	Frequency N(%)	Frequency N(%)	
C.krusei	02(1.1%)	**36(20.2%)**	38(21.3%)
C.parapsilosis	06(3.4%)	0	06(3.4%)
C.tropicalis	01(0.6%)	02(1.1%)	03(1.7%)
C. pelliculosa	01(0.6%)	01(0.6%)	02(1.1%)
C.lipolytica	0	02(1.1%)	02(1.1%)
C. dublinansis	0	01(0.6%)	01(0.6%)
Gram positive isolates	63(35.3%)	10 (5.6%)	73(41%)
Gram negative isolates	25(14%)	28(15.7%)	53(29.7%)
Total	98	80	178
Chi .square = 4.02 ; *p* value = 0.045*			

Table 3:- Anti fungal sensitivity pattern of non *albicans Candida* isolates.

Yeast (N)	**FLU(%)**	**VRC(%)**	**CAS(%)**	**MCF(%)**	**AB(%)**	**FCT(%)**
C.krusei	S-0 I-0 R-100%	S-100% I-0 R-0	S-100% I-0 R-0	S-100% I-0 R-0	S-81.57% I-13.15% R-5.28%	S-18.42% I-23.67% R-57.91%
C.paripsolosis	S-83.3% I-0 R-16.7%	S-83.3% I-0 R-16.7%	S-83.3% I-0 R-16.7%	S-100% I-0 R-0	S-83.3% I-0 R-16.7%	S-100% I-0 R-0
C.tropicalis	S-66.7% I-0 R-33.3%	S-66.7% I-0 R-33.3%	S-66.7% I-0 R-33.3%	S-66.7% I-0 R-33.3%	S-100% I-0 R-0	S-100% I-0 R-0
C.peliculosa	S-100% I-0 R-0	S-50% I-0 R-50%	S-100% I-0 R-0	S-100% I-0 R-0	S-50% I-0 R-50%	S-50% I-0 R-50%
C.lipolytica	S-50% I-0 R-50%	S-50% I-0 R-50%	S-50% I-0 R-50%	S-50% I-0 R-50%	S-100% I-0 R-0	S-50% I-0 R-50%
C.dublinences	S-100% I-0 R-0	S-100% I-0 R-0	S-100% I-0 R-0	S-100% I-0 R-0	S-100% I-0 R-0	S-100% I-0 R-0
TOTAL NAC	**S-66.67% I-0 R-33.34%**	**S-75% I-0 R-25%**	**S-83.33% I-0 R-16.66%**	**S-86.1% I-0 R-13.9%**	**S-85.8% I-2.2% R-12%**	**S-69.7% I-4% R-26.3%**

Fig1:- Distribution of non *albicans candida*isolates with relation to late neonatal period(*p* value = 0.045*).



Discussion:-

Majority of admissions in NICU are with provisional diagnosis of sepsis amounting to 44% of total admissions, as also evidenced by study of EmanM.Rabie et al (45.9%).[4]The culture positivity in our setup is 14.83% (N= 178), similar to the observations of Segal J et al (18%)[5]However higher prevalence has been observed by Shah et al (31.57%)[6]The low culture positivity in our study could be due to inadequate sampling, over emphasis on sending samples for blood culture, as clinical presentations are subtle in this age group or prior use of antibiotics. Bacteremia was proven from 10.50% (N=126) samples with preponderance of Gram positive isolates 41%(N=73), similar to the observations of Fortress yayraaku et al (69%).[7]However Naher BS et al, reported predominance of Gram negative organisms (78%)[8].Candidemia was observed in 4.3% (N=52), similar to the study from Thailand (6.14%)[9], even higher number (39.4%) was reported by Koppad et al[10]The present study highlights changing trend of Candidasp from *albicans* to non *albicans* sp. consistent with the observations of Y.K.Tiwari et al(76.47%).[11]This epidemiological shift can be partly explained by increased intrinsic or acquired resistance of NAC species to antifungal agents, capacity to form biofilms which have reduced susceptibility to antifungal drugs as well as to host defense and improvements in diagnostic techniques.[12]Preponderance of NAC species towards late neonatal period,also observed byMehara et alcan attribute to prolonged hospital stay as also evidenced from other parts of India.[13]

Among NAC species, *C.krusei*, the most found isolatehas emerged as a notable pathogen and shows 100% resistance to FLU, being apotential multidrug-resistant yeast, intrinsically resistant to FLUandshows cross resistance to other antifungal drugs.[14]Also forms monospecies as well as polymicrobial biofilms where in antagonistic interaction inhibits growth of *C.glabrata* and *C.albicans* and being more hydrophobic, adheres to host cells and inert surfaces. A sensitivity of 70- 90%to FLU was observed in all other NAC isolates, 80-90% being sensitive to AB

except for *C.pelliculosa*, which shows, AB (S=11%) and VRC(S=52%) similar to the observationsof kaur et al.[15]Resistance to AB is very rare, may present increased sensitivity of mutants to host-relevant stresses. There are reports of increasing minimum inhibitory concentration (MIC) of AB in *C. krusei*.[16]In the present study, *C. parapsilosis* and *C. tropicalis* have emerged as pathogens as also reported internationally.[17] *C.parapsilosis*frequently colonizes hands of care givers, has high affinity for intravascular devices, and parenteral nutrition. Although less virulent, but under certain conditions (IV catheters, high IV glucose concentrations) virulence may increase many folds and it is relatively difficult to eradicate organism.*C. tropicalis* causes infections with high mortality in immunocompromised individuals as it has ability to produce clusters and to progress from colonization to invasion. It is the second leading cause of candidemia in immunocompromisedadults, infrequent among neonates, however premature and low birth weight (LBW) neonates have an immature immune system and behave like an immunocompromised adult patient in this regard.

More than 42% of our cases were either premature or LBW, highlighting significant burden of candidemia among such neonates, TPN induces gut mucosal atrophy and has immunosuppressive effects, use of multiple invasive devices (catheters, endotracheal tubes) causes break in skin/mucosal integrity, which predisposes these sites for colonization/infection by *Candidasp*and broad spectrum antibiotics promote fungal overgrowth at expense of normal bacterial flora and encourage translocation of yeast across intact mucosa.Moreover, certain *Candidasp.* like *C.parapsilosis*has higher affinity towards parenteral nutrition. Hands of HCW and environmental surfaces are newly appreciated potential reservoirs for nosocomial strains of *Candida sp.*

Conclusion:-

Reporting candidemia due to NACspecies is essential measure in any ICU in order to implement appropriate preventive and therapeutic strategies. Epidemiological data of our study can serve as a template for development of local guidelines for prevention and appropriate treatment of neonatal candidemia. Mainly in NICU, speciation andanti fungal susceptibility testing should be done and species targeted treatment should be initiated. Strategies should be laid to prevent TPN and central venous catheter associated infections, andto encourage breast milk feeding, use of filters for parenteral nutrition, awareness of hand hygiene and proper sterilization ofequipment/ICU to reduces risk of horizontal transmission. Also use of intrapartum antibiotics and steroids should be discouraged and a restrictive policy of antibiotic use should be implemented.Though powered to detect significant risk factors, species distribution and resistance pattern of non *albicans candida*sp, the main limitation of our study is that it is single center study done for short duration of time. A nationwide study is need of the hour to formulate policies and strategies for risk identification and management of non *albicans*candidemia.

Bibliography:-

1. D. Testoni, M.Hayashi, M. Cohen-Wolkowiez et al., “Late-onset bloodstream infections in hospitalized term infants,” PediatricInfectious Disease Journal, vol. 33, no. 9, pp. 920–923, 2014.
2. Montagna MT. Invasive fungal infections in neonatal intensive care units of Southern Italy: a multicentric regional active surveillance. J Prev Med Hyg. 2010;51:125-30.
3. Aggarwal R, Sarkar N, Deorari AK, Vinod K. Sepsis in the newborn. Indian J Pediatr 2001;68:1143‑51.
4. M. Rabie et al,Epidemiology of Neonatal Sepsis and Implicated Pathogens.BioMed Research International 2011; 1-11
5. Segal J, Hoxha M, Wien S, et al. The bacterial profile of neonatal sepsis and antibiotic use in the tertiary care NICU of Kosovo. J Pediatr Neonatal Care. 2018;8(2):105–108. DOI: 10.15406/jpnc.2018.08.00319
6. Shah,et al. 2012. Neonatal sepsis: high antibiotic resistance of the bacterial pathogens in a neonatal intensive care unit of a tertiary Care hospital. J. Clin. Neonatol.,1: 72–5.
7. AkuYet al. Maternal Health, Neonatology, and Perinatology (2018) 4:2 DOI 10.1186/s40748-017-0071-z
8. Naher BS, Afroza S, Roy S, Nahar N, Kundu TN. Neonatal Sepsis in A Tertiary Care Hospital: Evaluation of Causative Agents and Antimicrobial Susceptibilities. Bangladesh J. Child Health. 2013;37(1):14–17
9. Tritipwanit K, Chindamporn A, Suankratay C. Epidemiologyofcandidaemia at King Chulalongkorn Memorial Hospital, Thailand. J Infect Dis Antimicrob Agents 2005;22:59‑69.
10. Koppad B et al. Int J ContempPediatr. 2017 Mar;4(2):438-441
11. Yogendra.K.Tiwari et al To Study Prevalence of Organisms Causing Neonatal Septicemia in NICU in A Tertiary Care Hospital of Jhalawar JMSCR Volume 06 Issue 01 January 2018 .

12. Sadeghi G, Ebrahimi-Rad M, Mousavi SF, Shams-Ghahfarokhi M, RazzaghiAbyaneh M. Emergence of non-Candida albicans species: epidemiology, phylogeny and fluconazole susceptibility profile. J Mycol Med. 2018; 28: 51–58.
13. V. Mehara, D. Yadava, P. Somania, G. Bhatambareb, S. Mulyea and K. Singha, Neonatal sepsis in a tertiary care center in central India: Microbiological profile, antimicrobial sensitivity pattern and outcome. Journal of Neonatal-Perinatal Medicine 2013;(6)165–1.
14. Robbins N, Caplan T, Cowen LE. Molecular evolution of antifungal drug resistance. Annu Rev Microbiol. 2017; 71: 753–775.
15. Kaur R, Dhakad MS, Goyal R, Kumar R. Emergence of non-albicans Candida species and anti-fungal resistance in intensive care unit patients. Asian Pacific Journal of tropical Biomedicine, 2016, 6 (5), 455-460.
16. Vincent BM, Lancaster AK, Scherz-Shouval R, Whitesell L, Lindquist S. Fitness trade-offs restrict the evolution of resistance to amphotericin B. PLoS Biol. 2013; 11: e1001692.
17. Hartung de Capriles C, Mata-Essayag S, Azpiróz A, Ponente A, Magaldi S, Pérez C, et al. Neonatal candidiasis in Venezuela: Clinical and epidemiological aspects. Rev LatinoamMicrobiol 2005;47:11-20.