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CANDIDA KRUSEI AN EMERGING PATHOGEN IN LATE ONSET NEONATAL SEPTICEMIA- AN EXPERIENCE FROM A TEACHING INSTITUTE.

Clinical Microbiology

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ABSTRACT

Background: Candidemia is an important cause of morbidity and mortality in Neonatal Intensive Care Unit. Incidence of neonatal candidemia is progressively increasing due to a marked improvement in survival of sick neonates. **Aim :** To identify the predominant organisms causing late onset septicemia in neonates. **Methods:** A prospective study conducted, over a period of 18 months. Samples for blood culture received in Department of Microbiology SKIMS were processed on Bac T Alert 3D and VITEK 2 Compact system for identification and antimicrobial susceptibility testing. **Results:** Out of 1200 samples received, Candida species N=52(29%)[EOS=20 (20.4%); LOS= 32 (52.5%)] were isolated from 178 blood culture positive samples . All of them were Non Albicans Candida(NAC), most found isolate was Candida krusei ,(N=38;21.34%) [LOS=36;EOS=2]. Candida parapsilosis (N=6) [EOS=6(3.37%)] , Candida tropicalis , (N=3) [EOS=1;LOS=2],Candida pelliculosa(N=2) [EOS=1;LOS=1].Candida dublinansis, (N=1)[LOS=1] and Candida lipolytica, (N=2)[LOS=2]. The Chi-squared test ($\chi 2$) was 4.02 and the two-tailed p-value was less than 0.05 indicating strong association of Candida krusei with late onset of sepsis. **Conclusions:** Candida krusei has emerged as important cause of neonatal septicemia, being more drug resistant strengthens need of antifungal stewardship policies to minimize acquisition of resistance. Moreover measures should be taken to reduce risk factors wherever possible to reduce morbidity, mortality, and antifungal drug pressure in neonates.

KEYWORDS

Neonatal septicemia, late onset sepsis, Non Albican Candida, C krusei

INTRODUCTION

The incidence and prevalence of candidemia are on rise in many countries worldwide. According to National Nosocomial Infection Surveillance, USA in the 1990s, *Candida* species are the fourth most common bloodstream pathogen accounting for 8% of all hospital-acquired bloodstream infections.[1] The Asian scenario is not very clear however a long study, for 13 years from Thailand demonstrated a prevalence of 6.14% for *Candida* species among blood culture isolates.[2] In India, there are few studies indicating increasing trend of candidemia in some tertiary care hospitals.[3] Candida species account for 9-13% of all blood isolates in neonatal intensive care units (NICUs).[4] Although C. albicans has historically been the most frequently isolated species, infections caused by the non-albicans Candida have been diagnosed with increasing frequency in recent years. Neonatal septicemia is the second leading cause of death in this population in our country and is responsible for almost a quarter of total neonatal deaths.[5] Inherent factors like immature innate immune system, poorly developed skin barrier, mucosal defense mechanisms and blood brain barrier contribute to the increased susceptibility of the neonates to infection. Most of the neonatal deaths are preventable by adopting standard aseptic precautions and rational use of antibiotics. Neonatal septicemia may be categorized as early onset septicemia (EOS) (<72 h of life) or late onset septicemia(LOS) (>72 h of life). LOS is commonly acquired from care giving environment.[6] Candidemia lead more frequently to end-organ damage than other newborn infections and can involve kidneys, brain, lungs, eyes, liver spleen, bones, and joints.[7] Over the past year, an increase in the isolation rate of nonalbicans *Candida* species from cases of neonatal septicemia have been noticed, the present study was hence designed; to analyze and evaluate the change in the species distribution of *Candida* species in neonatal septicemia and determine their *in vitro* antifungal susceptibility.

AIM

To identify the predominant organisms causing late onset septicemia in neonates.

MATERIALS AND METHODS

This prospective study was conducted, over a period of 18months, included 1200 blood samples from neonates received routinely in the Department of Microbiology SKIMS. This study was approved by the Ethical Committees of the institution.

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 were used. The culture bottles were loaded into the BacT/ALERT microbial detection system based on the 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, MacConkey agar plates, and Sabouraud dextrose agar(SDA) slant with antibiotics but without cycloheximide (Hi-Media Pvt. Ltd., Mumbai, India) in aerobic atmosphere. The preliminary identification was done by colony morphology on SDA, chromogenic media (HiChrome, Himedia, Pvt., Ltd.), growth at 45°C and germ tube test. A suspension was prepared from pure culture and processed for Vitek-2 compact system for identification of the organism using Vitek 2 ID and AST cards, chosen according to the results of the Gram staining results and used as per manufacturer's instructions. The Vitek-2 system reported the results after 8-10 hours, automatically with software release.

RESULTS

Out of 1200 samples processed with provisional diagnosis of neonatal septicemia, Candida species, N=52(29%)[EOS=20 (11.23%);LOS= 32 (17.9%)] were isolated from positive blood culture samples(N=178), all of them were Non Albicans Candida(NAC) and were significantly responsible for LOS. Gram positive isolates(N=73)[EOS=63(35.39%);LOS=10(5.61%)] showed preponderance towards EOS and Gram negative organisms(N=53)[EOS=25(14.04%);LOS=28(15.73%)] were uniformly associated with either onset sepsis. Most found NAC isolate was Candida krusei (N=38) [EOS=2(1.1%);LOS=36(20.22%)] followed by Candida parapsilosis(N=6) ,[EOS=6(3.3%)], Candida tropicalis(N=3) [EOS=1(0.56%);LOS=2(1.1%)],Candida pelliculosa(N=2) [EOS=1(0.56%);LOS=1(0.56%)], Candida lipolytica, (N=2)[LOS=2(1.1%)] and Candida dublinansis, (N=1)[LOS=1(0.56%) . The Chi-squared test ($\chi 2$) was 4.02 and the two-tailed p-value was less than 0.05 indicating that Candida krusei has strong association with late onset of sepsis.

All *C. krusei* isolates exhibited similar pattern of antifungal susceptibility. They were resistant to fluconazole but susceptible to amphotericin B, caspofungin, and micafungin. However some isolates of *C krusei* were resistant to Amphoteracin B. 70% C.tropicalis were sensitive to fluconazole, voriconazole, caspofungin, micafungin and

92% were sensitive to Amphoteracin B and Flucytocine. C dublinences showed good sensitivity to all antifungals.

DISCUSSION:

The prevalence of blood culture proven neonatal sepsis was 14.83% (n= 178) among the provisionally diagnosed NNS (n=1200) in our study ,similar to the observations from national and international studies, by Dr. Gargi Pathak et al. (17%).[8] However higher prevalence has been observed in studies conducted by Shah *et al* (31.57%).[9] The low culture positivity in our study could be due to inadequate sampling, over emphasis on sending blood culture of neonates (as the clinical presentations are subtle)and prior use of antibiotics.

In our study 29.21%,(n=52) of yeast was isolated out of 178 isolates. All of the isolates were yeast like, moreover the non-*albicans Candida* (NAC) and presented predominantly in LOS. This finding was similar to the study by Koppad et al who noticed 39.39% isolates of yeast responsible for NNS.[10] Among the NAC , *Candida krusei* was the most found isolate in our study and has emerged as a notable pathogen, especially in compromised patient groups in nosocomial settings. Widespread use of triazoles in these patients has contributed to a selective increase in *C. krusei* infection as evident from the study of S.R.Rongpharpi et al.[11]

This increasing incidence of candidemia is associated with some risk factors like use of medical catheters as evidenced by the study of Liu M et al,use of high-level antibiotics and prolonged antibiotic use, prior surgeries, preterm birth with low birth weight and frequent use of advance life support in such cohart.[12][13]

Candidemia is a disease of modern neonatal intensive care. It deserves urgent attention for its prevention as well as effective treatment in order to minimize neonatal morbidity and mortality. Outbreaks of candidemia due to *C. Krusei* have been linked with caregiving environment. Contaminated milk bottles, perenteral nutrition, glycerin suppositories, contaminated intravenous fluids, health care worker hand-colonization, and long term indwelling vascular devices. It has been recognized as a difficult to treat fungal pathogen due to Fluconazole resistance and decreased susceptibility to Flucytosine and Amphotericin B.

In our study the most commonly isolated yeast, C krusei was resistant(100%) to Fluconazole. However good sensitivity (80- 90%) was observed in all three other species of NAC isolates recovered in our study to whole panel of antifungal, similar observations were perceived by kaur et al.[14]

Table 1: Associations of isolates with onset NNS

Isolates	EOS	LOS	TOTAL
	Frequency N(%)	Frequency N(%)	
C.*krusei*	02(1.1%)	36(20.22%)	38
C.*parapsilosis*	06(3.3%)	0	06
C.*tropicalis*	01(0.56%)	02(1.1%)	03
C. *pelliculosa*	01(0.56%)	01(0.56%)	02
C.*lipolytica*	0	02(1.1%)	02
C. *dublinansis*	0	01(0.56%)	01
Gram positive isolates	63(35.39%)	10 (5.61%)	73
Gram negative isolates	25(14.04%)	28(15.73%)	53
Total	98	80	178
Chi .square = 4.02 ; *p* value = 0.045*			

CONCLUSION:

Non-albicans Candida, particularly Candida krusei has emerged as an important cause of neonatal septicemia. Fluconazole is generally used as empirical therapy. NAC are notorious of being multi drug resistant and some being intrinsically resistant (*C. krusei*) to fluconazole strengthens the need of antifungal susceptibility testing on priority basis. There is a need to know the regional epidemiology of *Candida* in septicemia patients and to strengthen antifungal stewardship policies to minimize acquisition of acquired resistance. Prior knowledge of species distribution in clinical isolates and drug sensitivity pattern among species help the clinician to choose early empirical therapy. Delay in the initiation of antifungal drug may contribute to elevated mortality rate. Association of candidemia with late onset sepsis in neonates also press upon, infection control in NICU, hand hygiene along with regular surveillance of neonatal septicemia is required to reduce the risk of change in antibiotic susceptibility patterns.

Limitation of our study was that it was single center study done for a short duration of time. However, a nationwide study is the need of the hour to formulate policies and strategies for risk identification and management (i.e., prophylaxis, empirical therapy) for candidemia.

Ethical Approval:

The study was approved by ethical committee of the institution.

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