Evaluation of neonatal candidemia: Emergence of non- albicans candida

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ABSTRACT

Introduction:

Candidemia is the most common blood stream infections in neonates with high mortality and morbidity, which have increased in its incidence over the last two decades. Recent studies have detected a significant shift from Candida albicans towards non-albicans Candida (NAC) species.

Objective:

The main aim of this study is to evaluate and establish this increase in incidence of candidemia in neonates mainly caused by non albicans species which has completely different spectrum of antifungal susceptibility and disease pattern.

Materials & Methods:

This prospective study was conducted for a period of one year from June 2015 to May 2016. Blood samples were collected aseptically from the neonates suspected of septicaemia. Blood culture was performed by automated Bact/ Alert 3D system [Biomerieux]. The identification was based on Gram stain showing Gram positive budding yeast cells, cultural characteristics and performing Germ tube test, for preliminary speciation of candida species. All the isolates showing negative for germ tube test were presumptively put all together as Non-albicans candida.

Results: Total number of neonatal candidemia cases were 94 out of whom 66 were males and 28 were females. Number of neonates with albicans candidemia were 20 and with non albicans candidemia were 74.

Conclusion: Neonatal candidemia is a potential health problem in our tertiary care health center which mainly covers the rural population. Especially the increasing cases of non albicans candida pose a serious threat and require strict control policies and proper prophylaxis to prevent the mortality and morbidity in the nenonates and infants.

Keywords: Candidemia, neonates, gram stain, germ tube.

INTRODUCTION

Candidemia is the most common blood stream infections in neonates with high mortality and morbidity, which have increased in its incidence over the last two decades. And recent studies have detected a significant shift from Candida albicans toward non-albicans Candida (NAC) species.[1,2] The genus Candida includes more than 150 species, but only few are known to be pathogenic to humans. Few of the human pathogens are *Candida albicans, Candida guilliermondii, Candida krusei, Candida parapsilosis, Candida tropicalis, Candida kefyr, Candida lusitaniae, Candida dubliniensis, and Candida glabrata.*[3]

These fungi inhabit the gastrointestinal tract including mouth and oropharynx, the female genital tract, and the skin of humans. They are also found ubiquitously on inanimate objects, in foods, and on animals.[4] Wide spread usage of antifungal agents accounts for the major shift of dominance of Candida albicans to non-albicans Candida species.[5,6] Currently NAC species causes approximately half of all the cases of candidemia and hematogenously disseminated candidiasis. And hence clinically identification of these plays an important role as they differ in susceptibility to the existing and newer antifungal agents. Other major risk factors includes preterm delivery with low birth weight <1500 g, prolonged endotracheal intubation, central venous catheters, parenteral nutrition, and the use of broad spectrum antibiotics.[7]

Candidemia in neonates is associated with high risk of neonatal mortality. Newborns that were identified positive for candidemia has significant risk for morbidity also. Most important risk factors for neonatal candidemia are vaginal delivery, low birth weight and also intrapartum administration of antibiotics.[8]

Antifungal susceptibility varies from species to species of candida significantly in non albicans candida species when compared with C.albicans. Among non albicans candida species like C.krusei, 75 % of the isolates are resistant to fluconazole. Even 35% isolates of C.glabrata and 10-25% isolates of C.tropicalis, C.lusitaniae are also resistant to fluconazole. Smaller proportions of non-albicans candida isolates also showed significant resistance to amphotericin- b.[5, 6, 9]

There had been increased incidence of neonatal candidemia cases in our institute. Hence the main aim of this study is to evaluate and establish this increase in incidence of candidemia in neonates in the neonatal and paediatric

intensive care units and also whether the candidemia is caused by non albicans species which has completely different spectrum of antifungal susceptibility and disease pattern.

MATERIALS AND METHODS

The sample size for the current study was calculated by using open-epi software.[10] With 95% confidence level the estimated sample size is 71 and with 99.99% confidence level are 91. This prospective study was conducted for a period of one year from June 2015 to May 2016 in the department of Microbiology, Prathima Institute of Medical Sciences (PIMS), Karimnagar. A total of 200 peripheral venous blood samples were collected aseptically from the neonates suspected of septicaemia during this one year period. Blood culture was performed by automated Bact/ Alert 3D system [Biomerieux]. The Bact/ Alert works on the principle of growth- based technology i.e. microorganisms produce Co2 with their growth, which is measured colorimetrically with these systems. This enhances recovery and helps in early detection of aerobic and facultative anaerobic microorganisms (bacteria and fungi) from blood and normally sterile body fluids.

Candidemia was defined as the presence of at least one positive blood culture containing pure growth of candida species in addition to supportive clinical features. The blood samples, approximately 2 ml, collected aseptically were inoculated into Bactec Peds plus/F culture bottles. All blood culture bottles that were indicated positive for growth were gram stained and were subcultured on 5 % sheep blood agar, Mac Conkey's agar and Sabouraud's dextrose agar at 37ºC.

The identification was based on Gram stain showing Gram positive budding yeast cells, cultural characteristics and performing Germ tube test, for preliminary speciation of candida species. All the isolates showing negative for germ tube test were presumptively put all together as Non- albicans candida.

All these isolates were tested for antifungal susceptibility to amphotericin-b, fluconazole, nystatin and cotrimoxazole discs by Kirby- Bauer disk diffusion method on muller- hinton agar. Zone diameters were interpreted according to National Committee for Clinical laboratory standards (NCCLS) guidelines. *C.parapsilosis* (ATCC 22019) was used as for quality control for AFS. Entire study period was carried following strict quality control. The statistical analysis was done by using SPSS 16 software and the results were tabulated.

RESULTS

The mean age of male neonates with candidemia were 8.78 ± 5.84 days and that of female neonates with candidemia is 5.53 ± 3.69 days. Mean age of neonates in days with albicans candidemia were 5.65 ± 4.05 and with non albicans candidemia were 8.40 ± 5.69. Mean age of females with non albicans candidemia were 5.86 ± 3.96 days and males with non albicans candidemia were 9.54 ± 6.01 days.[Table 1]

Table 1: Age and Sex of neonates with candidemia (both albicans and non- albicans)

Sex	N	Age in Days Mean ± SD	t	P
Females	28	5.53 ± 3.69	28	0.007**
Males	66	8.78 ± 5.84	66	
Albicans candidemia	20	5.65 ± 4.05	20	0.02*
Non albicans candidemia	74	8.40 ± 5.69	74	
Females with non albicans candidemia	23	5.86 ± 3.96	23	0.009**
Males with non albicans candidemia	51	9.54 ± 6.01	51	
N=sample size, p<0.05*- statistically significant, p<0.01** statistically highly significant				

Total numbers of neonatal candidemia cases were 94 out of whom 66 were males and 28 were females. Numbers of neonates with albicans candidemia were 20 and with non albicans candidemia were 74. [Table 2]

Table 2: Number of neonatal albicans and non albicans candidemia cases

Type of candidemia	Males	Females	Total number of cases
Neonates with Candidemia	66	28	94
Neonates with Albicans candidemia	15	5	20
Neonates with Non albicans candidemia	51	23	74
Percentage of neonates with non albicans candidemia	77%	82%	79%

DISCUSSION

In our current study the percentage of the neonates with non albicans candidemia is 79 % and with albicans candidemia is 21 %. 77 % of male neonates have non albicans candidemia and 82 % of female neonates have non albicans candidemia. When compared with early neonates the late neonates showed increased incidence of non albicans candidemia which can attribute prolonged hospital stay as potential risk factor. Similar results were seen in the studies conducted in other parts of India.[1, 2, 3, 4]

There is statistically significant difference in the mean age of neonates with albicans and non albicans candidemia ($p<0.05$*). There is statistically highly significant difference between mean ages of females and males with candidemia and also there is statistically highly significant difference between mean ages of females and males with non albicans candidemia ($p<0.01$**).

Studies showed that non albicans neonatal candidemia is associated with high mortality rates. Multiple risk factors are known to be responsible for development of this candidemia. The important risk factors were premature labor, low birth weight, catheterization and broad spectrum antibiotic therapy. Use of invasive devices damages the skin and mucosal integrity, which renders these procedural sites potential spaces for the colonization and infection by various non- albicans candida species. Antibiotics damage the natural bacterial flora of skin and predispose it for promotion of fungal overgrowth. TPN causes gastrointestinal tract mucosal atrophy and reduces the immunity which again increases the risk of infection. Most of the non- albicans candida species have high affinity for TPN and catheterization mode of entry and can cause outbreaks in ICU. Even there is increase is nosocomial infections caused by non- albicans candida.[1, 3]

Antifungal therapy for the neonates with candidemia should be species directed approach. Fluconazole is the primary drug of choice for both albicans and parapsilosis species of candida infection, whereas fluconazole resistance is seen in isolates of *C.galbrata and C.krusei*.[5,7] Amphoterecin- B lipid preparations are also highly effective against Candida spp with less renal toxicity even though few isolates of non- albicans candida showed resistance to it. Early treatment should be attempted especially for invasive non- albicans candidemia to prevent mortality and morbidity. [6, 7]

Prevention should mainly target the non- albicans candida horizontal transmission in the neonatal ICU. Strategies should be laid mainly to prevent TPN and central venous catheter associated infections and also awareness of hand hygiene should be promoted in the entire hospital care. Neonates identified with positive candidemia should be isolated to prevent the horizontal transmission especially in the ICU setup. Infection control policy directed towards the education of health care handlers and also hygiene maintenance of neonatal ICU staff to avoid the nosocomial infections should be developed. Encouraging breast milk feeding and avoiding TPN should be encouraged. Proper sterilization of the equipment and ICU reduces the risk of horizontal transmission. Strategies regarding antifungal prophylaxis reduces the invasive candida infections and also reduce the colonization by isolates. Use of intrapartum antibiotics, steroids and also broad spectrum antibiotics for neonates should be discouraged when the risk of infection/ colonization is predicted.

CONCLUSION

Neonatal candidemia is a potential health problem in our tertiary care health center which mainly covers the rural population. Especially the increasing cases of non- albicans candida poses a serious threat and require strict control policies and proper prophylaxis to prevent the mortality and morbidity in the nenonates and infants. To reduce this mortality and morbidity effects of candidemia, proper handling of parenteral administrations, restrictive usage of intrapartum antibiotics and the prophylactic usage of antifungals should be encouraged. The epidemiological data of this study should be used for developing guidelines to prevent and also to administer appropriate treatment for the non albicans candidemia. Mainly in the ICU cases of neonates, the speciation and fungal BSI should be reported and species targeted treatment should be initiated for achieving better treatment goals. As the study is conducted only in our center, the results cannot be generalized for the entire population of our area which can be the main limitation. The speciation, their sensitivity patterns, modes of transmission and species targeted treatment should be researched further; additionally it should include various other health institutions to cover most of the local population.

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