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Original Research Article

Clinical and microbiological profile of fungal sepsis in neonates: a retrospective observational study in an out-born unit

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ABSTRACT

Background: Infections due to non-*Candida* species though uncommon is emerging as an important cause of neonatal sepsis in neonatal intensive care unit (NICUs). The aim of this study was to determine the etiology, clinical profile, outcome and predictors of mortality in neonates with fungal sepsis.
Methods: Neonates with the diagnosis of blood culture proven fungal sepsis from January 2018 to December 2019 were analysed. Relevant data was collected in a proforma from case records which included demographic information, clinical symptoms and signs, investigations, treatment and outcome. Data was analysed using IBM SPSS 25 software.
Results: During the study period, 618 (13.8%) babies out of the 4461 admitted developed culture positive sepsis. Culture positive fungal sepsis were 66 (10.6%) out of total sepsis. *Candida non albicans* constituted 60 (90.9%) and *Candida albicans* was six (9.1%). The most common non-albicans species was *Candida parapsilosis* (25.8%). Lethargy, respiratory distress, hypothermia and apnea were common symptoms. Elevated C-reactive protein and thrombocytopenia were common laboratory findings. The mortality rate was 59.1 percentage. Delayed initiation of antifungal treatment, need for inotropes and mechanical ventilation were significant factors associated with mortality.
Conclusions: *Candida non-albicans* was the predominant organism causing fungal sepsis. Fungal sepsis over all was associated with high mortality. Need for inotropes, mechanical ventilation and delay in initiating antifungal treatment were the significant factors associated with mortality.

Keywords: Candida non-albicans, Fugal sepsis, Inotropes, Thrombocytopenia, Ventilation

INTRODUCTION

Infections due to Candida has emerged as an important cause of neonatal sepsis and is associated with significant morbidity and mortality.[1-3] Fungal infections in neonates, other than those caused by Candida species, are uncommon. These are often overlooked because neonatal infections due to bacteria and virus are more prevalent.[2] The incidence of candida blood stream infection varies in different parts of the world from 1.1-1.3% in Europe, 0.5-1.6% in North and South America, to 4-7.7% in Asia.[4]

Although *Candida albicans* has historically been the most frequently isolated species in neonatal late onset sepsis, recently non-albicans Candida have emerged as important opportunistic pathogen, notably *Candida parapsilosis, Candida tropicalis, Cadida krusei, and Cadida glabrata*.[5,6] The aim of this study was to determine the etiology, clinical profile, outcome and predictors of mortality in neonates with fungal sepsis in a tertiary care neonatal unit.

METHODS

Study design and period

It was a retrospective observational study conducted in our out born unit. All neonates≤28 days of life admitted to the in the newborn ward/NICU (neonatal intensive care unit) from January 2018 to December 2019 (2 years) with clinical features of sepsis along with culture proven fungal isolates were included in the study.

Study measures

Neonates with the diagnosis of fungal sepsis were identified from blood cultures records. Culture positivity within 14 days, with the same fungal species were considered as being the same infectious episode. Blood culture was taken by either NEC (non-enteric culture) or BACTEC method and 1ml blood was used for this purpose. All fungal growths were isolated from blood cultures in sabouraud dextrose agar. The fungal species were identified by chrome agar method. Weight was recorded by electronic weighing scale and gestational age estimated by first trimester ultrasound scan. Data noted in the proforma from the case records included; demographic information, clinical symptoms and signs, anthropometry, vitals investigations, treatment and outcome.

Statistical analysis

Data were analyzed with IBM SPSS 25 software. Categorical variables were compared with the chi square test. Predictors of mortality of fungal sepsis in neonates analyzed by bivariate analysis. A p value<0.05 has considered significant.

RESULTS

During the study period 4461 neonates were admitted in our unit. Out of which 618 (13.8%) developed culture positive proven sepsis. Sixty-six neonates (10.6%) out of 618 had culture positive fungal sepsis. Mean birth weight was 2103 g (range: 760-3960 g) and mean gestational age was 34.81 weeks (range 26-40 weeks) (Table 1).

Candida non albicans (90.9%) predominated over albicans (9.1%). Most common non-albicans was Candida parapsilosis (25.8%) (Figure 1).

The common symptoms noticed were lethargy (72.7%), respiratory distress (57.6%), hypothermia (40.4%), and apnea (31.8%). Common laboratory findings were, elevated CRP (96.9%), thrombocytopenia (90.9%), and hyponatremia (37.9%). Common complication was shock (89.4%), coagulopathy (30.3%). Clinical profile of fungal sepsis is shown in (Table 2).

Out of 13 factors analyzed by bivariate analysis for predicting mortality, only three factors were noted to be significant i.e. Delay in initiating antifungal treatment, need for inotropes and mechanical ventilation (Table 3).

Table 1: Baseline characteristics of neonates included in the study.

Parameters	Survivors n (%)	Non-survivors n (%)	P value
Total (N-66)	**n-27**	**n-39**	
Parity			
Primi gravida	13 (48.1)	16 (41.0)	0.566
Multi gravida	14 (51.9)	23 (58.9)	
Mode of delivery			
Normal delivery	14 (51.9)	21 (53.8)	0.873
Caesarean	13 (48.1)	18 (46.2)	
Sex			
Male	14 (51.9)	22 (56.4)	0.715
Female	13 (48.1)	17 (43.6)	
Gestational age			
37-42 weeks	13 (48.1)	16 (41.0)	0.745
34-36 weeks	5 (18.5)	8 (20.5)	
32-33 weeks	4 (14.8)	4 (10.3)	
28-31 weeks	4 (14.8)	6 (15.4)	
<28 weeks	1 (3.7)	5 (12.8)	
Birth weight			
>2.5 kg	7 (25.9)	15 (38.5)	0.242
1.5-2.499 kg	14 (51.9)	13 (33.3)	
1-1.499 kg	6 (22.2)	8 (20.5)	
<1 kg	0 (0)	3 (7.7)	

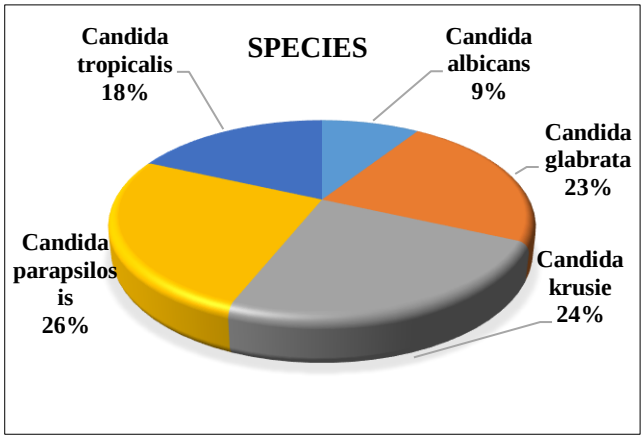

Figure 1: Species distribution.

Out 66 neonates, 27 (40.9%) survived and 39 (59.1%) expired. Mean birth weight, gestational age and platelet count in survived group were 2333 grams, 36.26 (±3.21) weeks and 88,592 (±59816) per cu mm respectively. Mean birth weight, gestational age and platelet count in non-survivor group was 1533(±608) grams, 31.10 (±3.42) weeks and 27,179 (±36291) per cu mm respectively. The mortality rate was 83.3 % in <28 weeks and 56.6% in >28 weeks neonates. Out of 39 neonates who expired, 17

(43.5%) died before culture confirmation and antifungal treatment was not initiated (Table 4).

Table 2: Clinical profile of fungal sepsis.

Parameters	Total cases (N=66) n (%)
Hypothermia	27 (40.4)
Hyperthermia	4 (6.1)
Respiratory distress	38 (57.6)
Apnea	21 (31.8)
Tachycardia	17 (25.8)
Bradycardia	1 (1.5)
Feed intolerance	16 (24.2)
Lethargy	48 (72.7)
Seizure	16 (24.2)
Bleeding	8 (12.1)
Thrombocytopenia (Platelet count <150000 mm^3)	60 (90.9)
Leukopenia (Leukocyte count <5000 mm^3)	21 (31.8)
Leukocytosis (Leukocyte count >20000 mm^3)	24 (36.4)
Elevated C-reactive protein (>6 mg/dl)	64 (96.9)
Abnormal RFT (Serum Creatinine >1 mg/dl or Blood Urea >40 mg/dl)	24 (36.4)
Abnormal LFT (Serum Aspartate or Alanine amino transferase >50 IU/L)	13 (19.7)
Hyponatremia (Serum sodium <130 mEq/L)	25 (37.9)
Hypernatremia (Serum sodium >150 mEq/L)	2 (3.0)
Coagulopathy (PT >20 or APTT >60 or INR >2)	20 (30.3)
Shock	59 (89.4)

APTT: Activated partial thromboplastin time, INR: International normalized ratio, LFT: Liver function test, PT: Prothrombin time, RFT: Renal function test.

Table 3: Predictors of mortality.

Predictive factor	Non-survivors n (%)	Pearson Chi-square value	P value (p<0.05 significant)
Gestational age	39 (59.1)	1.952	0.745
Birth weight	39 (59.1)	4.188	0.242
Sex	39 (59.1)	0.134	0.715
Species	39 (59.1)	5.457	0.243
Hypothermia	19 (28.7)	2.421	0.490
Seizure	6 (9.0)	1.937	0.164
Thrombocytopenia	37 (56.0)	3.482	0.323
Hyponatremia	17 (25.7)	1.333	0.513
Coagulopathy	12 (18.1)	2.277	0.320
Inotropes	39 (59.1)	11.311	**0.001**
Transfusion	32 (48.5)	0.580	0.446
Ventilation	39 (59.1)	9.533	**0.002**
Delayed antifungal treatment	39 (59.1)	16.589	**0.001**

Table 4: Candida species pattern& Outcome distribution.

Organism	Total n (%)	Survivors n (%)	Non-survivors n (%)
Candida albicans	6 (9.1)	0 (0)	6 (100)
Candida glabrata	15 (22.7)	7 (46.6)	8 (53.3)
Candida krusie	16 (24.2)	6 (37.5)	10 (62.5)
Candida parapsilosis	17 (25.8)	9 (52.9)	8 (47)
Candida tropicalis	12 (18.2)	5 (41)	7 (58.3)
Total	66 (100)	27 (40.9)	39 (59.1)

DISCUSSION

Incidence of candidemia in neonates was 1.5% among all admissions during the study period, which was similar to that (1%) reported by Femitha et al.[7] Candida was isolated from 66/618 (10.6%) of neonatal sepsis almost comparable to 15.7% in Yunus et al and 13.6% reported by Agarwal et al.[8,9] A change in the distribution of Candida species causing candidemia has been noted in several institutions with increasing isolation of non-albicans species in neonates.[1] *Candida non-albicans* (90.9%) predominate over albicans (9.1%) in our study. Neonatal infections caused by non-albicans species, occur at a later age and are more likely to be acquired from the hospital environment than *C. albicans*.[10]

The most common non- albicans identified in our study was *Candida parapsilosis* (25.8%) similar to *G Caggiano* et al, but common non-candida species isolated in studies of Basu et al, Yunus et al and Femitha et al were *Candida tropicalis* (39%), *Candida krusie* (63.8%) and *Candida glabrata* (44.4%) respectively.[4,7,8,11] The common sympt oms noticed were lethargy (72.7%), respiratory distress

(57.6%), hypothermia (40.4%), apnea (31.8%), and feed intolerance (24.2%). In James et al study feed intolerance (58%) was the most common presentation followed by increased need for ventilator support (52.5%), temperature instability (52.5%) and apnoea (50%).[12] In our study 60/66 (90.9%) developed thrombocytopenia (<150000/mm3) which was similar to studies of Guida et al and Yunus et al.[8,13] Most common complication noted was shock (89.4%) which is similar (94.4%) to that found in Femitha et al's study.[7]

Predictive factors of mortality in our study were delay in initiation of antifungal treatment, need for inotropes and mechanical ventilation as compared to very low birth weight, need of ventilation and NEC in Yunus et al study.[8] Reported mortality rates vary from 3 to 50 percent.[3] Our study revealed a high mortality rate of 59.1% similar to Agrawal study (51%).[8,9] Increased mortality in our unit could be attributed to delay in initiating anti-fungal therapy due to late referral and non-availability of antifungal sensitivity pattern in the fungal isolates. The strengths of our study were, we included only neonates with culture proven fungal sepsis. Limitations of our study were, it was a retrospective study and it was not compared with control groups.

CONCLUSION

Candida non-albicans was the predominant organism causing fungal sepsis and need for inotropes and mechanical ventilation and delay in initiation of anti-fungal therapy were the significant factors associated with mortality. The commonest *non-albicans Candida* detected in the present study was *Candida parapsilosis*. Early suspicion and initiation of broadspectrum antifungal treatment may help in reducing the high mortality in neonates with sepsis who fail to respond to higher antibiotics and have elevated CRP with persistent thrombocytopenia.

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