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Candidemia in neonatal ICU- experience from a tertiary care hospital

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Abstract:

We studied the clinical and microbiological parameters associated with candidal sepsis in neonates and identified possible predictors of poor outcome. Observational study of all cases admitted to NICU between October 2009 and July 2011, proven to have candidal growth in blood culture. Thirty six cases were identified during the study period. Odds of very low birth weight babies (3.1% vs 0.43%; OR 7.41; 95%CI 3.82, 14.39; p<0.0001) and preterm neonates (1.4% vs 0.32%; OR 4.56, 95%CI 2.08, 10.03; p<0.0001) admitted to NICU to acquire fungal sepsis were significantly more. Candida glabrata was the offending agent in 16 (44.4%) cases. Non albicans species was associated with higher mortality. Presence of candiduria was a significant risk factor for death (OR 5.14, 95% CI 1.17,22.49 P=0.04). Candida glabrata caused the most number of cases of fungal septicemia. Non albicans species and isolation of fungus from two normally sterile body sites are associated with higher risk for mortality.

Keywords: Fungal sepsis, Candidemia, Newborn babies, Mortality

Accepted

Introduction

Modern day neonatal care has improved survival of extremely low birth weight babies but increased the need for multiple invasive procedures. The scourge of hospital acquired infections has only been rising due to multiple factors. Increasing rates of fungal sepsis is one of the prices paid (1-4). Improvement of outcome depends on prompt suspicion, commencement of antifungal therapy, recognition of end organ damage and close follow-up. It is imperative for pediatricians involved in neonatal care to recognize babies at risk for fungemia since early antifungal therapy is vital for improving chances for intact survival. The risk factors for acquiring fungal sepsis have been extensively studied (5,6). Mortality associated is distressingly high and it is important to recognize risk factors for poor outcome. Reports from developing countries are sparse. We thus conducted this study in our hospital to study the clinical and microbiological parameters associated with candidal sepsis in neonates and identify possible predictors of mortality.

Material and Methods

This observational study was undertaken during the period from October 2009 to July 2011 after approval from the Institute Ethics Committee in the Level 3 NICU of our hospital. The neonates having fungal blood culture positive were identified. Candidemia was defined as *Candida* species growth from at least 1 blood culture from a peripheral or central venous sample. We obtain fungal blood cultures along with bacterial culture specimens in a case of late onset sepsis in preterm or very low birth weight babies, and in term neonates with other risk factors like severe asphyxia, need for central line, prolonged ventilation, prolonged use of broad spectrum antibiotic. Babies with positive blood culture for Candida are subjected to tests for detection of end organ involvement including lumbar puncture unless contraindicated in individual cases, head USG, ophthalmological evaluation, urological system imaging and echocardiogram. Cultures were done using Saborauds dextrose agar and sensitivity testing using Kirby Bauer method. Species identification was conducted using lactophenol cotton blue wet mount microscopy of the fungus grown followed by biochemical confirmation. All maternal, perinatal and neonatal details were recorded. Risk factors, clinical findings, management undertaken and outcome were studied. All descriptive data were compiled and analyzed using SPSS statistical software 13.0. Epical 2000 program was used to compute Odds ratio and 95% confidence interval for individual risk factors. P value of <0.05 was taken as significant.

Results

There were 27076 live births during the study period. The number of admissions to NICU were 4342 of which 2445 (56.3%) were term and 1897 (43.7%) were preterm. Thirty six neonates had blood culture positive for fungal growth. Overall incidence was 1.3 cases per 1000 live

births, and incidence among NICU admissions was 0.82%. Three fourths of these were premature. Mean birth weight was 1622.7±577.2 g. Median gestational age was 32 weeks (range 26 to 40 weeks). Very low birth weight babies had significantly higher risk of developing fungal sepsis than larger babies (3.1% vs 0.43%; OR 7.41; 95%CI 3.82, 14.39; p<0.0001). Similarly preterm neonates admitted to NICU were more prone to acquire fungal sepsis (1.4% vs 0.32%; OR 4.56, 95%CI 2.08, 10.03; p<0.0001). Fungal sepsis was first suspected at a mean age of 8.3±5.8 days of life. The presence of risk factors for fungal sepsis have been enumerated in Table 1. More than half the babies required intubation, 80.6% required prolonged antibiotic therapy, 97.2% had at least one change to higher antibiotics and H2 blockers were used in 69.4%.

Analysis of clinical features revealed shock (94.4%), bleeding (69.4%), NNEC(30.6%) to be the commonest major morbidities. There was only one neonate with fungal meningitis and he succumbed to disease on day 11 of life. Two babies had hemodynamically significant PDA, but no cases of fungal endocarditis or endophthalmitis were identified. Although there was candiduria in 13 neonates, there were only 3 cases of renal pelvic dilatation. Two of these resolved spontaneously on repeat radiological examination, but one neonate succumbed before a second scan could be obtained. Fungal ball in the urinary bladder was detected in one infant. Severe thrombocytopenia (as defined by counts <50 000/cu mm) was the most prevalent laboratory finding (77.8%). All babies with severe thrombocytopenia had overt bleeding manifestations. Intraventricular hemorrhage was detected in 4 neonates. (Table 1). The mean duration of hospital stay was 19±8.9 days.

Candida glabrata was the offending agent in 16 (44.4%) cases followed by C. albicans in 9(25%). There was higher mortality associated with non albicans species. All the organisms were sensitive to fluconazole and amphotericin B. There was associated bacterial growth (Klebsiella pneumoniae) in 3 babies obtained at the same time as fungal culture when late onset sepsis was suspected. Amphotericin B was used in 41.6% of affected neonates, 3 of them required Liposomal Amphotericin B in view of abnormal renal function. The remaining responded well to fluconazole given parenterally.

Overall mortality was 44.4%, of which 4 were term and 12 were preterm. Neonates who had fungal growth from two sterile body fluids- urine and blood were found to be significantly more at risk of mortality than those who had only blood culture positivity (69% vs 43%, OR 5.14, 95% CI 1.17,22.49 P=0.04). Need for ventilation (OR 1.16; 95% CI 0.3-4.42, P=1.0), diagnosis of necrotising enterocolitis (OR 1.8;95% CI 0.43-7.53; P=0.48), presence of

Table 1. *Presence of specific risk factors and characteristics among cases (total=36)*

Characteristic	Number of cases	Percentage
Maternal		
GDM	5	13.9
PIH	12	33.3
Genitourinary fungal infection	6	16.7
PROM>18 hours	20	55.6
Neonatal		
Clinical		
Asphyxia	4	11.1
Need for intubation	21	58.3
Need for ventilation>7 days	6	16.7
Central venous catheter	15	41.7
H2 Blocker therapy	25	69.4
Antibiotic >7 days	29	80.6
Parenteral nutrition	8	22.2
Need for inotropes	35	97.2
Postnatal steroids	4	11.1
Mucocutaneous candidiasis	5	13.9
Skin discoloration	25	69.4
Shock	34	94.4
Bleeding manifestations	25	69.4
NNEC	11	30.6
Surgery	2	5.6
ROP	8	22.2
Hemodynamically sig. PDA	2	5.6
Laboratory		
Thrombocytopenia<50 000/cu mm	28	77.8
Hypoglycemia	7	19.4
Hyperglycemia	8	22.2
Radiological		
Abnormal neurosonogram- IVH	4	11.1
Microbiological		
Concomitant bacterial sepsis	3	8.3
Candiduria	13	36.1

Table 2. *Risk factors for mortality*

Risk factor(n)	Deaths (%)	OR (95% CI)	P value
Gestational age			
<34 weeks(26)	12	1.28(0.29-5.66)	1.0
≥34 weeks(10)	4		
Birth weight			
<2500 g(31)	14	1.23(0.18-8.46)	1.0
≥2500 g(5)	2		
Central venous catheter	12(41.3)	0.53(0.09-2.81)	0.7
Present(29)	4(57.1)		
Absent(7)			
Need for ventilation			
Yes(15)	7(46.6)	1.16(0.3-4.42)	1.0
No(21)	9(42.8)		
Concomitant bacterial sepsis	2(66.7)	2.71(0.22-33.01)	0.57
Yes(3)	14(42.4)		
No(33)			
NNEC			
Present(11)	6(54.5)	1.8(0.43-7.53)	0.48
Absent(25)	10(40)		
Hypoxia ischemic encephalopathy	5(45.4)	1.06(0.25-4.41)	1.0
Yes(11)	11(44)		
No(25)			
Candiduria			
Yes(13)	9(69.2)	5.14,	0.038
No(23)	7(30.4)	(1.17,22.49)	
Species			
Non albicans(27)	15(55.5%)	10.0(1.09-91.49)	0.026
Albicans(9)	1(11.1%)		

concomitant bacterial sepsis(OR 2.71;95% CI 0.22-33.01;P=0.57) and hypoxic ischemic encephalopathy (OR 1.06; 95% CI 0.25-4.41;p=1.0) were associated with higher mortality, but the risks were not statistically significant. (Table 2).

Discussion

There is a wide variation in the reported incidence of fungal septicemia in NICU admissions, ranging from 2.6% to 16.7% among VLBW and still higher in extremely low birth weight infants (7). A recent study from a developing country reported a frequency of 0.9% in the NICU which is similar to our finding of 0.82%.(8) But, their incidence was as high as 46% in VLBW. Our hospital incidence was much lower at 3.1% for these infants. Fungal colonization of skin, respiratory and gastrointestinal tracts are considered an initial step in the pathogenesis of invasive disease (9,10). This is further strengthened by the evidence which proves that fluconazole prophylaxis prevents colonization and invasive disease (11). We did not give fluconozole prophyaxis during the study period. To make the study of colonization meaningful it is important to take surveillance cultures for all neonates admitted to the intensive care unit. The high case load and large number of preterm and VLBW admissions made it impractical to obtain surface and mucosal interface cultures from all admissions.

Mean age at onset of infection ranged from 15 to 33 days in earlier reports (10,12). In our study, it was as early as 8.3±5.8 days of life. Clinical features are mostly non specific and overlap with those of bacterial infections in neonates (13). Of special significance is the occurrence of hyperglycemia in these infants in spite of constant glucose infusion rates (12,14). In our study, this finding was detected in 8(22.2%) neonates. Although temperature instability is common to bacterial and fungal infections, hyperthermia is considered an important indicator of invasive fungal infection in neonates, reported in as many as 42.8%.(2)

Of the 36 neonates, 28 (77.8%) developed severe thrombocytopenia defined as <50000/cumm. Guida et al reported nearly 85% incidence of thrombocytopenia in patients with invasive fungal sepsis, their cut off count being 100 000/cu mm (15). Candidemia is known to cause invasion of the eyes, meningitis and brain abscesses, fungal endocarditis and renal abcesses (16). Benjamin et al reviewed literature on end organ damage in 2003 and concluded that due to heterogeneity of reporting, precise estimates of the frequencies of end organ damage was not possible (17). There was low occurrence of these problems in the survivors in our study, probably due to empiric antifungal therapy initiated at suspicion itself. Some cases could however have been missed, as autopsy was not done in those who expired. Involvement of these organs have been found to be associated with prolonged fungemia (16) and failure to remove central catheters promptly after identification (18).

Classically C.albicans has been reported to cause about half of the burden (10). Ariff et al also found it to be the leading causative organism (55%) in an NICU in Pakistan (8). Over the years, non-albicans *Candida* infections have become more frequent (2). Candida parapsilosis was reported to be most common isolate in one study from Spain (19). Our data shows C.glabrata to be the main agent. C. glabrata was considered to be less pathogenic but studies have shown no significant differences in morbidity among species (20). Azole treatment of maternal genital infection has been postulated to contribute to C. glabrata infection in preterm neonates due to relatively azole-resistant C. glabrata among neonates (10). Documented clinical diagnosis of genital candidiasis was present in 6 mothers in our study; however culture and species identification had not been done.

Guidelines in adult medicine recommend empiric antifungal therapy in patients with fever and neutropenia. Newborns with normal WBC counts may still be immunocompromised due to inherent and developmental defects in the immune system. The authors of a multicen-

tric, retrospective, cohort study in 2003 suggested empiric therapy for who are <25 weeks' estimated gestational age and to neonates who have thrombocytopenia at the time of blood culture, also to consider therapy in those between 25 to 27 weeks gestational who received third-generation cephalosporin or carbapenem 7 days before the culture (21). Early and empiric antifungal therapy has been shown to improve outcome (2,21). Contrary to this, Benjamin et al found that of 40 infants who received empirical therapy, 38% died, and of the 97 who did not receive empirical therapy 33% died (5). Since the benefits of empirical therapy have not been conclusively proven, its use in premature neonates based on bedside judgment alone is still not routinely recommended (22).

All-cause mortality among VLBW infants who experienced fungal sepsis has been reported in several multicenter studies to range from 28 to 32%, though it is higher for ELBW (10). The crude mortality in our study was 44.4%. Previous reports suggest more severe disease with albicans (3,4). We however found higher mortality with non albicans species. NNEC, asphyxia and ventilation were associated with higher mortality, but were not statistically significant. Neonates who had fungal growth from two sterile body fluids- urine and blood were found to be significantly more at risk of mortality than those who had only blood culture positivity. Our sample size is small and the confidence intervals are wide so no definite conclusion can be obtained at this stage from this result.

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Conclusions

Fungal sepsis is more common among preterm and very low birth weight infants. It causes high mortality and prolonged hospital stay. Candida glabrata caused the most number of cases of fungal septicemia. Non albicans species and isolation of fungus from two normally sterile body sites are associated with higher risk for mortality.

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