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Methods: Through consecutive sampling, we got 94 cases and 188 controls. For comparison, chi-square test was used, and for strength association Odds ratio was used. Analysis was done using SPSS V18. Binary logistic regression has been used to identify independent risk factors.

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Neonatal Candidemia: Clinical Presentation, Laboratory Profile, Risk Factors and Immediate Outcome in a Tertiary Hospital in Kerala- A Case-Control Study

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Results: In our study the prevalence rate of neonatal candidemia was 3.89%. Silent hypoxemia (OR – 50.54, CI – 6.66, 383.41) and sub-threshold feed tolerance (OR – 3.38, CI – 2.81, 4.07) were found to be two symptoms of neonatal candidemia with high specificity. The mortality rate among neonates with candidemia was 18.1%, and in controls was 8.5% . The mean hospital stay of cases were 25.17 days, and of controls were 10.46 days.

Conclusion: Management of maternal vaginal candidiasis, judicious use of antibiotics, maintaining euglycemia, and early enteral feeding may reduce the risk for neonatal candidemia. Duration of hospital stay and mortality were high in neonates with candidemia. Silent hypoxemia and sub-threshold feed tolerance are two specific symptoms to suspect neonatal candidemia.

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I. Introduction

Neonatal sepsis is frequently due to organisms colonizing the skin and mucosal surfaces, such as Coagulase-negative Staphylococci and Candida (1). Blood stream infection (BSI) due to Candida species in the neonatal intensive care unit (NICU) is less frequent than that due to Gram-positive or Gram-negative bacteria, but it has higher morbidity and mortality rates (2). Candida is the third most common etiologic agent in late-onset neonatal sepsis and is responsible for 8 to 15% of hospital-acquired infections (3). Preterm infants have high Candida colonization rates compared to term infants, and it is well established that colonization with Candida is inversely proportional to gestational age (4, 5). Colonization precedes invasive Candida infection, and the number of colonization sites and density of skin colonization with Candida correlate with candidemia (6-8). Even though Candida albicans is the most prevalent yeast pathogen, BSIs caused by Candida non-albicans, particularly Candida parapsilosis complex and Candida glabrata complex has been increased in recent years (9, 10). Newborns who survived from invasive candidiasis frequently have a long-term neurological impairment, including cerebral palsy, blindness, hearing impairment, cognitive deficits, and periventricular leukomalacia (9). Candida infections are responsible for an 'attributable mortality' of 18–25%, significant morbidity, and healthcare costs (11). The incidence and associated mortality due to candidemia can be influenced by several factors, including the population at risk, healthcare facility standards, Candida spp. involved and anti-fungal resistance (12).

Clinical presentation of candidemia resembles sepsis syndrome and to establish a clinical diagnosis of candidemia is difficult. (13). Here, in this study, we are trying to identify the clinical and laboratory profile of neonatal candidemia and the risk factors associated with it.

Ethical consideration: Permission to conduct this study was obtained from the institutional research committee and ethical committee of Government T. D Medical College, Alappuzha.

II. Methods

This study was a retrospective case-control study. Sex matched cases and controls were selected through consecutive sampling by file review of newborns of NICU of Govt. T.D. Medical College from 1st January 2010 to 31ST December 2014.Cases were identified through the review of a meticulously maintained NICU logbook in which relevant details

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(including the IP number, name, age, sex, date of admission, discharge diagnosis, date of discharge/death, and status at discharge) of all admitted cases were entered. We also reviewed the blood culture record of all cases and controls for final case confirmation from Microbiology Laboratory. All babies in whom blood culture yielded candida were considered as cases. Two newborns of the same-sex as that of the case and admitted within one week prior or after the case but negative for candida blood culture were considered for controls. New born babies who were on antibiotics before sampling for blood culture and whose case books incomplete or not available were excluded.

Case records of all these newborns were retrieved from the medical record library. After applying exclusion criteria, cases and controls were finalized. Details of risk factors (maternal, neonatal, and nosocomial), clinical features, investigation results, and outcome of all cases and controls were recorded in the proforma and analyzed.

III. Definitions

Candidemia: The blood culture yields candida species organisms.

Silent hypoxemia: Low Spo2 with no tachypnea/ bradypnea/apnoea/ respiratory distress/ hypothermia and with no evidence of shock.

Feed intolerance: The enteral milk feeding has to be stopped due to presence of one or more of the following- gastric residuals >50% of previous feed, vomiting, abdominal distension, visible bowel loops, and blood in the stool (occult/ gross).

Sub-threshold feed tolerance: The gastric residue is 20-50% of previous feed consecutively for at least three times without features of feed intolerance.

For statistical analysis, continuous variables were summarized using mean and standard deviation and categorical variables using frequencies and percentages. To identify risk factors of candida infection, Chi-square test was used, and for the strength of association odds ratio was used. Binary logistic regression was performed using the enter method to identify independent predictors of neonatal candidemia and mortality associated with candidemia. All analysis was performed using SPSS V18.

IV. Results

From1st January 2000 to 31st December 2014, there were 2754 admissions to the newborn nursery. Out of this, 107(3.9%) had candidemia. Seven babies who were started on fluconazole before blood culture and 6 with incomplete case records were excluded from the study. Finally, 94 cases and 188 controls were included in this study. 92(97.9%) cases were Candida nonalbicans, and the rest were candida albicans. Cases and controls were comparable concerning sex, route of delivery, and gravidity. The frequency of Gestational diabetes mellitus, Gestational hypertension, PROM, and 3rdtrimester UTI was also comparable (Table-1).

Table-1: Baseline Characteristics of Cases and Controls

VARIABLE	CASE-94 (100%)	CONTROL-188 (100%)	P value
Sex (M)	57(60.6)	114(60.6)	.518
Route of delivery (vaginal)	42(44.7)	100(53.2)	.207
PrimiGravida	51(54.3)	114(60.6)	.309
GDM	3(3.2)	6(3.2)	1.000
GHT	14(14.9)	19(10.1)	.244
PROM	20(21.3)	23(12.2)	.054
3rd trimester UTI	4(4.3)	7(3.7)	1.000

There was a significant difference in the mean age of admission between cases and controls. Symptoms &signs such as lethargy (67%), respiratory distress (67%), apnoea (35.1%), silent hypoxia (21.3%), seizure(14.9%), feed intolerance (33%), sub-threshold feed tolerance(16%), weak cry (86.2%), prolonged CFT (48.9%), mucosal candida infection (5.3%), abdominal distension (54.3%) and hepato-splenomegaly (22.3%) was significantly higher in cases (table-2). Newborn babies with candida BSI showed a significantly higher proportion of thrombocytopenia (75.5%), positive C-reactive protein (47.9%), and abnormal CSF (9.6%). Urine fungal hyphae (14.9%) were isolated only from neonates with candidemia. The mean WBC count was significantly lower in cases (10858) compared to controls (14191) (table-2).

Table-2: Comparison of clinical and laboratory profile of cases and controls

VARIABLE	CASE-94 (100%)	CONTROL-188 (100%)	P value	OR	95% CI
Age on admission (Mean & SD)	1.10 (0.39)	1.74(1.19)	<0.001		
Lethargy	63(67)	37(19.7)	<0.001	8.29	4.74, 14.52
Resp distress	63(67)	75(39.9)	<0.001	3.06	1.82, 5.15

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Apnoea	33(35.1)	18(9.6)	<0.001	5.11	2.68, 9.73
Silent hypoxemia	20(21.3)	1(.5)	<0.001	50.54	6.66, 383.41
Seizures	14(14.9)	9(4.8)	0.005	3.418	1.44, 8.37
Feed intolerance	31(33)	2(1.1)	<0.001	45.76	10.65, 196.7
Sub threshold feed tolerance	15(16)	0(0)	<0.001	3.38	2.81, 4.07
Weak Cry & activity	81(86.2)	61(32.4)	<0.001	12.97	6.7, 25.1
Prolonged CFT	46(48.9)	23(12.2)	<0.001	6.88	3.8, 12.5
Mucosal candida	5(5.3)	0(0)	.004	3.1	2.6, 3.7
Abdominal distension	51(54.3)	13(6.9)	<0.001	15.97	7.98, 31.97
HSM	21(22.3)	6(3.2)	<0.001	8.73	3.39, 22.5
Thrombocytopenia	71(75.5)	31(16.5)	<0.001	15.6	8.5, 28.7
Positive CRP	45(47.9)	35(18.6)	<0.001	4.02	2.3, 6.9
Abnormal CSF	9(9.6)	2(1.1)	.001	9.85	2.08, 46.56
Urine fungal hyphae	14(14.9)	0(0)	<0.001	3.35	2.78, 4.03
Total WBC count (Mean & SD)	10858(7088)	14191(5444)	<0.001		

When the maternal risk factors associated with the development of candidiasis were analyzed, statistical significance was seen for maternal vaginal candidiasis at the time of labor and for mothers who had received antenatal steroids. Among the neonatal risk factors, prematurity, LBW, birth asphyxia, resuscitation which need bag and mask/ ET, delayed enteral feed >24 hours, and neonatal hyperglycemia was significantly associated with neonatal candidemia. Nosocomial risk factors significantly associated with neonatal candidemia were amino acid infusion, steroids, more than two antibiotics, central venous access, endo tracheal intubation, assisted ventilation, oxygen, intravenous immunoglobulin, aminophylline, caffeineand surfactant. (Table-3)

Table-3: Comparison of risk factors associated with systemic candidiasis among cases and controls

VARIABLES	CASES=94	CONTROLS= 188	P value	OR	95% C I
Preterm	80(81.5)	77(41)	<0.001	8.24	4.4, 15.6
LBW	84(89.4)	85(45.2)	<0.001	10.2	4.98, 20.8
Very preterm (<28wks)	34 (36.2)	19 (10.1)	<.001	5.04	2.7,9.5
Extremely LBW (<1.0kg)	12 (12.8)	5(2.7)	0.001	5.4	1.8,15.7
Ante natal steroid	33(35.1)	17(9.0)	<0.001	5.44	2.83, 10.47
Maternal vaginal candidiasis	18(19.1)	5(2.75)	<0.001	8.668	3.106, 24.2
Birth asphyxia	31(33)	31(16.5)	0.002	2.49	1.4, 4.44
Active Resuscitation	24(25.5)	23(12.2)	0.006	2.5	1.3, 4.6
Delayed enteral feed (>24hrs)	73(77.7)	57(30.3)	<0.001	7.99	4.49, 14.22
Neonatal Hyperglycemia before C&S	69(73.4)	30(16)	<0.001	14.5	8, 26.5
Amino acid infusion	78(83)	32(17)	<0.001	23.77	12.3, 45.93
Steroid for baby	12(12.8)	5(2.7)	0.002	5.36	1.83, 15.7
Ranitidine	7(7.4)	6(3.2)	0.134	2.44	.796, 7.48
More than 2 antibiotics used	78(83)	113(60.1)	<0.001	3.24	1.8, 5.97
CV catheter	13(13.8)	3(1.6)	<0.001	9.9	2.75, 35.7
Endo-tracheal intubation	33(35.1)	16(8.5)	<0.001	5.81	2.99, 11.3
Assisted ventilation	38(40.4)	26(13.8)	<0.001	4.23	2.36, 7.58
Oxygen	74(78.7)	69(36.7)	<0.001	6.4	3.6, 11.4
Abdominal surgery	3(3.2)	3(1.6)	0.404	2.03	0.4, 10.3
IVIG	11(11.7)	6(3.2)	0.007	4.02	1.44, 11.24
Aminophylline	6(6.4)	0(0)	0.001	3.14	2.64, 3.73
Caffeine	54(57.4)	20(10.6)	<0.001	11.34	6.1, 21.0
Surfactant	30(31.9)	15(8.0)	<0.001	5.41	2.7, 10.7

As many of these risk factors are interdependent, inorder to identify the independent risk factors of candidemia, we did binary logistic regression. The independent risk factors were; more than two antibiotics, amino acid infusion, neonatal hyperglycemia before blood culture, and maternal vaginal candidiasis (table-4).

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Table-4: Independent risk factors of neonatal candidiasis

Variable	Adjusted odds ratio (95% CI)	P value
Maternal candidiasis	12.7 (2.5, 65.5)	.002
Amino acid infusion	5.5 (1.6,18.7)	.006
More than 2 antibiotics used	5.05 (1.8, 13.9)	.002
Hyperglycemia	10.9 (4.2,28.1)	<.001

The mortality rate among admitted newborns with candidemia and without candidemia was 18.1% and 8.5%,respectively. This finding was statistically significant. The mean duration of hospital stay among cases was also significantly higher. (table-5)

Table-5: Comparison of immediate outcome between cases and controls

VARIABLE	CASE-94 (100%)	CONTROL-188 (100%)	P value	OR	95% CI
Death	17(18.1)	16(8.5)	.018	2.37	1.14, 4.94
Duration (days) of hospital stay (mean & SD)	25.17(12)	10.46(11.6)	<0.001		

On univariate analysis, we found that the following were predictors for mortality in neonatal candidiasis; vaginal delivery, preterm <32 weeks GA, birth weight <1.5 kg, lethargy, respiratory distress, apnoea, prolonged CFT, skin mottling, endo tracheal intubation, assisted ventilation, administration of caffeine or surfactant ,and abdominal surgery. (Table-6)

Table -6: Risk factors of mortality in neonatal candidemia

VARIABLES	Death=17(100%)	Discharged=77(100%)	P value	OR	95% C I
Route of delivery-vaginal	13(76.5)	29(37.7)	0.004	5.38	1.6, 18.1
<32 weeks gestation	12(70.6)	22 (28.6)	0.001	6.0	1.9, 19.0
ELBW & VLBW	14 (82.4)	31 (40.3)	0.002	6.9	1.8, 26.1
Lethargy	15(88.2)	48(62.3)	0.040	4.5	.97, 21.3
Respiratory distress	15(88.2)	48(62.3)	0.040	4.5	.97, 21.3
Apnoea	13 (76.5)	20 (26)	<0.001	9.3	2.7, 31.7
Prolonged CFT	13 (76.5)	33 (42.9)	0.012	4.33	1.3, 14.5
Skin mottling	6 (35.3)	5 (6.5)	0.001	7.86	2.0, 30.2
Endotracheal Intubation	14 (82.4)	19 (24.7)	<0.001	14.2	3.7, 55
Assisted ventilation/ CPAP	16 (94.1)	22(28.6)	<0.001	40	5, 320
Abdominal surgery	2 (11.8)	1 (1.3)	0.026	10.1	.86, 119
Caffeine	14 (82.4)	40 (51.9)	0.022	4.3	1.1, 16.2
Surfactant	10 (58.8)	20 (26)	0.009	4.1	1.37, 12.1
Active resuscitation	8 (47.1)	16 (20.8)	0.025	3.39	1.12, 10.1

Multivariate regression analysis found out only three independent predictors of mortality. These were apnoea, abdominal surgery, and active resuscitation.(Table-7)

Table-7: independent risk factors for mortality in neonatal candidemia

Variable	Adjusted odds ratio (95% CI)	P value
Apnoea	36.3(1.81, 74)	.020
Abdominal surgery	332 (1.3, 831)	.039
Active Resuscitation	14 (1.1, 186)	.041

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V. Discussion

We report a prevalence of 3.89%for neonatalcandidemia during the study period. This prevalence rate is comparable to the prevalence reported from developed countries.[14- 16]

Our study found a significant difference in the age of admission between cases and controls contrary to a study from China (17).This may be due to the difference in indications for admission among the hospitals.

The clinical features associated with neonatal candidemia reported in our study namely lethargy, respiratory distress, apnoea, silent hypoxia, seizure, feed intolerance, sub-threshold feed tolerance, weak cry, prolonged CFT, mucosal candida infection, abdominal distension, and hepatosplenomegaly were similar to that reported in the literature (18,19).The two new signs we identified were silent hypoxemia (specificity- 99.46% and sensitivity-21%) and sub-threshold feed tolerance (specificity- 100% and sensitivity-15.9%),which is not reported in other studies. In some of the cases, these early signs were the reason for suspecting candidiasis.

We found that neonatal candidemia was significantly associated with thrombocytopenia, positive CRP, a relatively low total WBC count, and abnormal CSF, which is consistent with reports elsewhere.

Most of the significant riskfactors for neonatal candidemia we obtained were documented in the literature (18, 19, 22, 23). Many of these factors are interdependent. Regression analysis revealed only four independent risk factors that are significantly associated with neonatal candidemia. Though the administration of ranitidine and abdominal surgery are reported to be significant risk factors, we could not find this association.

The death rate of neonates with candidemia was significantly higher than neonates without candidemia (18.1% vs. 8.5%). Other studies also report a higher death rate among systemic candidiasis compared to other inpatients of the NICU (24).The duration of hospitalization was also high for cases.

The independent risk factors of mortality in neonatal candidemia were apnoea, abdominal surgery, and invasive resuscitation. The increased mortality in the babies who underwent abdominal surgery may be linked to large inoculum size of candida organisms, which is already colonized in GIT and use of broad-spectrum antibiotics after surgery, which may facilitate its growth. The anaerobic environment during apnoea and before resuscitation may facilitate adhesion, tissue invasion, and disruption of host immune function by candida through increased production of secretory aspartyl proteinases (SAP), which may increase the severity of the infection.

Our study has few limitations. We could not perform species differentiation among the candida organisms and antifungal susceptibility. Assessments of complications using USG abdomen & CT of the head could not be performed in many cases because of logistic problems.

In conclusion, in developing countries, Candidemia is a common cause of BSI among neonates. Candida nonalbicansis the predominant type identified. Two new signs (silent hypoxemia and sub-threshold feed tolerance) identified were more specific for neonatal candidemia. Management of maternal vaginal candidiasis during pregnancy, judicious use of antibiotics in newborns, maintaining euglycemia in the newborn period, early enteral feed, and avoiding amino acid infusion may help in the reduction of neonatal candidiasis. Early identification of this problem, especially among babies who had apnoea, active resuscitation, and abdominal surgery and managing them, may help to reduce mortality.

What is already known: Clinical diagnosis of neonatal candidemia is difficult What this study adds: Silent hypoxemia and sub-threshold feed tolerance are two most specific features of neonatal candidiasis.

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