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ORIGINAL ARTICLE

Case Fatality Rate and Neurological Morbidity in Neonates with Sepsis in a Tertiary Care Neonatal Intensive Care Unit in a Developing Country

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Abstract

Background: The case fatality rate (CFR) for neonatal sepsis and its determinants vary from unit to unit. Sepsis may have a detrimental impact on neurodevelopment too. **Materials and Methods:** It is a descriptive observational study of neonates with culture-proven sepsis to determine the CFR, prevalence, predictors of mortality, and neurological morbidity. A neurological examination (Hammersmith neonatal neurological examination) was done at discharge. **Results**: The prevalence and CFR of proven sepsis were 24.5% (314/1282) and 24%, respectively. The greatest CFR was seen in neonates with Acinetobacter sepsis. On logistic regression, decreased movements (OR-5.48; 95% CI-2.17–13.83), convulsions at admission (OR-2.42; 95% CI-1.19–4.92), and Acinetobacter in blood culture (OR-1.42; 95% CI-0.65-3.10) were the significant predictors of mortality. Twenty-four (11%) neonates had abnormal neurological examination at discharge and convulsions at admission (OR 3.12; 95% CI 1.04–9.35), and Acinetobacter in blood culture (OR 4.87; 95% CI 1.51–5.66) were the significant predictors of neurological morbidity. **Conclusion:** A quarter of neonates with sepsis die, and more than a tenth have neurological morbidity.

Keywords: Culture proven neonatal sepsis; case fatality rates; neurological morbidity; developing country

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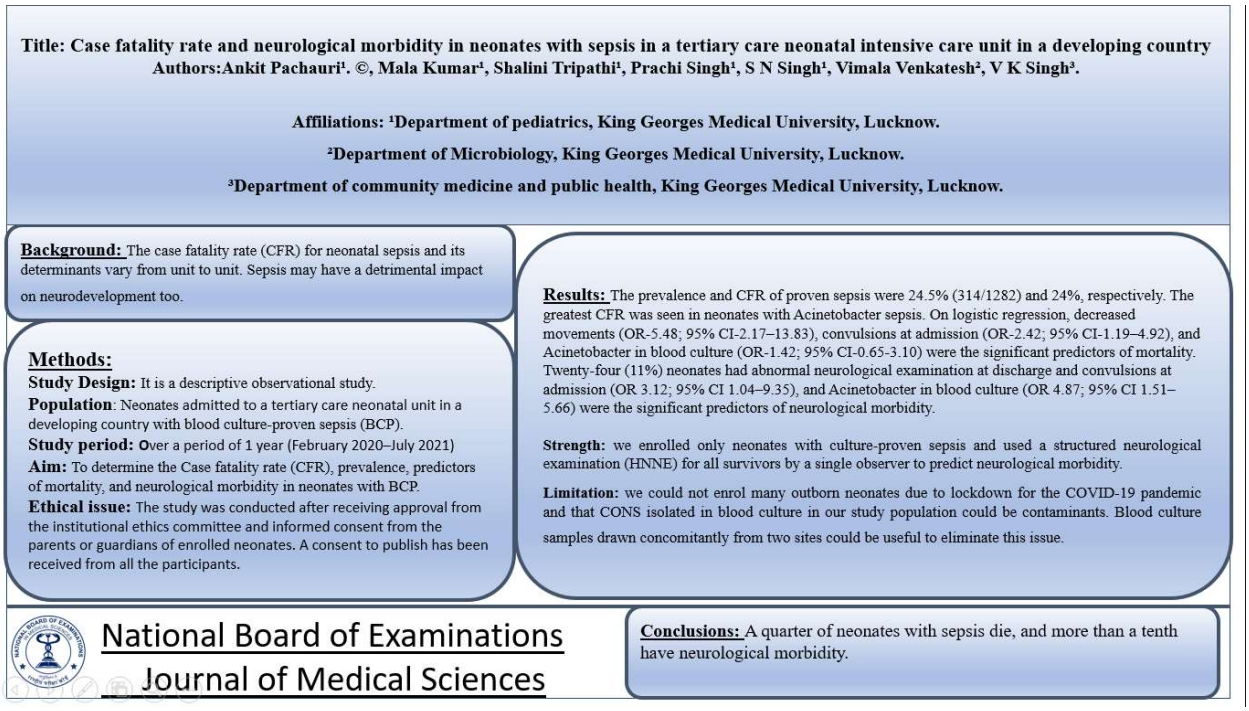
Graphical Abstract



Background

Sepsis is the third-most common cause of neonatal death globally [1]. Out of 5.2 million under-5-year-old deaths from preventable and treatable causes, neonates accounted for 2.4 million deaths [2].

India has made a significant contribution to the reduction of global newborn mortality, with its share of the global newborn mortality burden coming down to less than a quarter today from one third of total newborn deaths in 1990 [3,4]. Still, the burden of neonatal sepsis is huge in our country. Nearly one-fifth of neonates with sepsis die in the hospital, which rises to 50% for those with culture-proven sepsis [5].

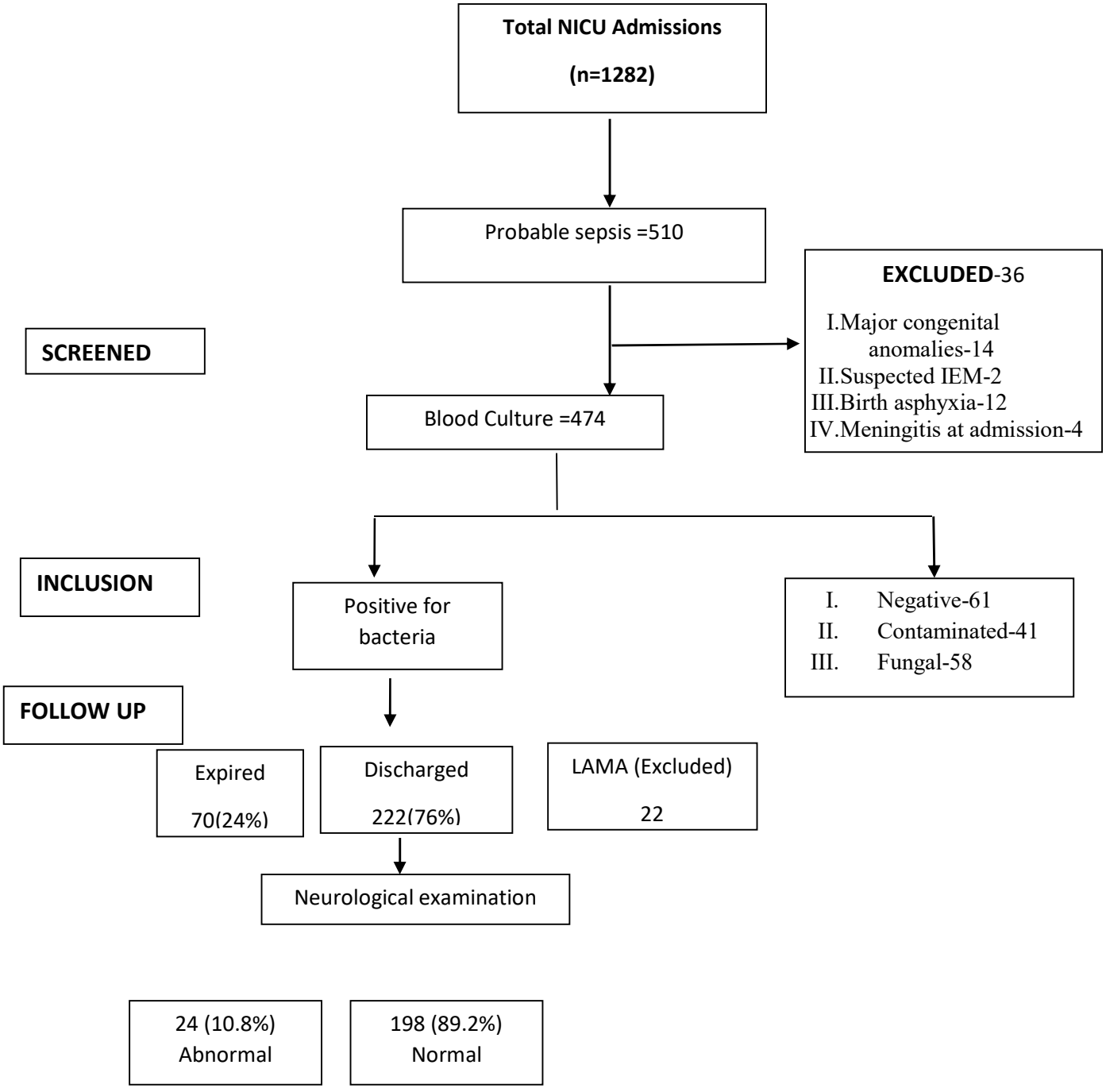
Case fatality rates for neonatal sepsis are different in different countries and even in different units of the same country. These rates depend on a number of factors, like level of care, human resources, and infrastructure. It also depends on the type of patients being admitted to the unit, whether inborn or outborn, term or preterm, and demographic characteristics like socioeconomic status. Therefore, it is essential to know the case fatality rate (CFR) in a unit, keeping in mind the determinants of mortality and morbidity in a unit.

Sepsis may have a detrimental impact on the neurodevelopment of neonates. Bacteremia-related neurological complications (BNC) are quite prevalent. The major BNCs consist of seizures, hydrocephalus, encephalomalacia, cerebral infarction, subdural empyema, ventriculitis, and abscess [6]. Since not only neonates with clinical signs of CNS involvement and proven meningitis have neurological sequelae, it becomes important to evaluate all neonates with sepsis for neurological outcome. We have conducted this study to

determine the CFR, neurological outcome of neonates with blood culture-positive (BCP) sepsis, and common determinants of mortality and morbidity in our unit.

Methods

Study Flow:



Study design

It was a prospective observational study conducted on neonates with sepsis admitted to a tertiary care neonatal unit in a developing country over a period of 1 year (February 2020–July 2021). Consecutive neonates with blood culture-positive sepsis (BCP) were enrolled. A neurological examination (NE) by Hammersmith Neonatal Neurological Examination (HNNE) was done at discharge for those who survived sepsis.

Population

Inclusion criteria: Neonates admitted in NICU with probable sepsis and growing a bacterial pathogen in blood culture.

Exclusion criteria: Major congenital malformations, suspected inborn errors of metabolism, not giving consent, meningitis on admission, birth asphyxia.

The primary objective of the study was to determine the CFR for neonates with sepsis. Secondary objectives were to study the prevalence, predictors of mortality, and neurological morbidity of these neonates. Those with a positive blood culture were included in the study. Neonates with major congenital malformations, suspected inborn errors of metabolism, birth asphyxia, meningitis at admission, or leaving against medical advice were excluded. Their baseline characteristics were noted from their records, and they were followed up prospectively till they were discharged, died, or left the hospital against medical advice. Neonates were managed according to the standard protocols of the unit. Relevant investigations were done, and the neonates were examined at the time of discharge or term equivalent age for any neurological morbidity by HNNE. The expired or discharged neonates and those with abnormal or normal NE were compared for the predictors.

Hammersmith Neonatal Neurological Examination (HNNE): A short HNNE proforma was used to do neurological examinations of neonates with sepsis at discharge. It consists of 12 items, of which 11 are set out in 3 columns, with 2 lateral columns reported as warning signs. The last item includes five abnormal neurological signs to be scored as yes or no. The babies in whom neurological findings were falling in the central grey column were within the reference range (90%) and taken as normal, and those falling in any of the warning sign lateral columns were labelled abnormal. In addition to this, the last row “abnormal signs” has to be circled as Yes or No for each sign [7].

Statistics

Sample size: Taking a mortality rate of 25%, as the developing countries have 2.7–50% mortality in neonates (8, 9, 10, 11) and the western world has a mortality rate of 4–18% (8, 9, 12) with sepsis, a sample size of 300 was calculated using the formula:

$= \{Z_{(\alpha/2)}\}^2 pq/e^2$
$= (1.96)^2\ (0.25)\ (0.75)\ 0.5x0.5 = 288 \sim 300$
Z = 1.96 for 95%
p= proportion of neonates dying (mortality) - 25%
q = (1-p)
e = allowable error- 5%

Statistical Analysis

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean ± SD and median. Odds ratios with 95% confidence intervals were calculated for selected variables as needed. Quantitative variables were compared using an unpaired t test between the two groups. Qualitative variables were compared using the chi-square or Fischer's exact test as appropriate. A p-value of <0.05 was considered statistically significant. The logistic regression analysis was done to find the independent factors associated with CFR and abnormal NE at discharge. The data was entered in an MS Excel spreadsheet, and analysis was done using the Statistical Package for Social Sciences (SPSS) Version 24.0.

Results

During the study period, 1282 neonates were admitted to our neonatal unit, of whom 314 had blood culture-positive sepsis and were enrolled. Of 314 enrolled neonates, 70 (24%) expired, 222 (76%) were discharged, and 22 were left against medical advice (LAMA). Neonates who went to LAMA were excluded from the study. So, the study comprised 292 neonates with blood culture-positive sepsis.

Table 1 shows a comparison of the baseline characteristics of expired and discharged neonates. The two groups were different for birth weight (p<0.001), gestational age (<0.001), and type of delivery (0.005).

Table 1. Baseline characteristics of expired and discharged neonates with sepsis

Baseline characteristics		**Expired neonates (n=70) No (%)**	**Discharged neonates (n=222) No (%)**	**p-value**
Birth weight	< 1000 g	8 (11.4%)	8 (3.6%)	**<0.001**
	1000-1499 g	24 (34.3%)	27 (12.1%)	
	1500-2499 g	20 (28.6%)	105 (47.3%)	
	>=2500 g	18 (25.7%)	82 (37%)	
Gestational Age	Preterm	46 (65.7%)	97 (43.7%)	**0.001**
	Term	24 (34.3%)	125 (56.3%)	
Onset of sepsis	EOS	57 (81.4%)	194 (87.4%)	0.211
	LOS	13 (18.6%)	28 (12.6%)	

Sex	Female	27 (38.6%)	97 (43.7%)	0.450
	Male	43 (61.4%)	125 (56.3%)	
Type of delivery	Cesarian section (LSCS)	25 (35.7%)	126 (56.75%)	**0.005**
	NA	0 (0.0%)	2 (0.9%)	
	Vaginal	45 (64.3%)	94 (42.35%)	
Place of delivery	Inborn	43 (61.4%)	139 (62.6%)	0.859
	Outborn	27 (38.6%)	83 (37.4%)	

NA-Not applicable as destitute neonate; EOS- Early onset sepsis; LOS- Late onset sepsis.

Table 2 shows predictors of mortality based on univariate analysis. The predictors were CONS and Acinetobacter in blood culture, tachycardia (HR>160/min.), bradycardia (HR-<100/min), temp >37.5 deg C, temp <35.5 deg C, decreased cry, decreased movements, RR>60/min, apnea, grunting, Spo2<90%, capillary refill time >3sec, hypotension, mottling, sclerema, abdominal distension, vomiting, hypoglycemia, convulsion, bulging AF, infiltrates on chest x-ray (p value<0.05). Also, during hospital stays, neonates requiring ventilation >48 hours, convulsions requiring AED, meningitis, and shock requiring vasopressors were more likely to die (p values <0.001, 0.011, <0.001, and <0.001, respectively).

Table 2. Predictors of case fatality rate in neonates with sepsis

Predictors	**Expired neonates (n=70)**	**Discharged neonates (n=222)**	**p-value**
	No (%)	No (%)	
Tachycardia (>160/min)	47 (67.1%)	92 (41.4%)	**<0.001**
Bradycardia (<100/min)	44 (68.5%)	86 (38.7%)	**<0.001**
Temp > 37.5°C	29 (41.4%)	43 (19.4%)	**<0.001**
Temp < 35.5°C	40 (57.1%)	70 (31.5%)	**<0.001**
Decreased movements	64 (91.4%)	144 (64.8%)	**<0.001**
RR> 60/min	63 (90%)	175 (78.8%)	**0.036**
Apnoea	31 (44.3%)	57 (25.7%)	**0.003**

Grunting	47 (67.1%)	95 (42.8%)	**<0.001**
Mottling	32 (45.7%)	10 (45%)	**<0.001**
Sclerema	32 (45.7%)	6 (2.7%)	**<0.001**
Abdominal distension	47 (67.1%)	75 (33.8%)	**<0.001**
Vomiting	62 (88.6%)	129 (58.1%)	**<0.001**
Hypoglycemia	60 (85.7%)	115 (51.8%)	**<0.001**
Hyperglycemia	15 (21.4%)	44 (19.8%)	0.770
Convulsion	23 (32.8%)	39 (17.6%)	**0.006**
Bulging AF	19 (27.1%)	6 (2.7%)	**<0.001**
Shock requiring vasopressors	63 (90%)	69 (31.1%)	**<0.001**
Infiltrates on chest x-ray	59 (84.3%)	143 (64.4%)	**0.002**
Ventilation for>48hrs	53 (75.7%)	51 (22.9%)	**<0.001**
Meningitis on admission	27 (38.5%)	7 (3.2%)	**<0.001**
CONS	23 (16.1%)	120 (83.9%)	**0.002**
Acinetobacter spp.	22 (37.9%)	36 (62.1%)	**0.005**
K.pneumoniae	13 (35.1%)	24 (64.9%)	0.089
S.aureus	3 (15.8%)	16 (84.2%)	0.388

AED-antiepileptic drugs; RR >60/min- respiratory rate >60/minute; Temp- Temperature; CONS-coagulase negative staphylococcus

Table 3 shows the factors associated with mortality in logistic regression. They were decreased movement (OR-5.48; 95% CI-2.17–13.83), convulsions at admission (OR-2.42; 95% CI-1.19–4.92), and CONS in blood culture (OR-0.43; 95% CI-0.21-0.86).

Table 3. Logistic regression analysis for prediction of mortality in neonates with sepsis

Parameters	**B**	**SE**	**p-value**	**OR**	**95% C.I.for OR**	
					Lower	**Upper**
Temp > 37.5°C	0.57	0.37	0.117	1.78	0.87	3.65
Temp < 35.5°C	0.50	0.36	0.160	1.65	0.82	3.31
Decreased movement	1.70	0.47	**<.001**	5.48	2.17	13.83
RR>60/min	0.48	0.48	0.317	1.61	0.63	4.10

Convulsion	0.89	0.36	**0.014**	2.42	1.19	4.92
CONS	-0.84	0.36	**0.018**	0.43	0.21	0.86
Acinetobacter	0.35	0.40	0.377	1.42	0.65	3.10
Constant	-0.41	0.55	0.459	0.66		

B- beta coefficient; SE -standard error; OR- Odds ratio; C.I- confidence interval; RR >60/min-respiratory rate >60/minute; Temp- Temperature; CONS- coagulase negative staphylococcus.

Table 4 shows the factors associated with abnormal neurological examinations based on logistic regression. Convulsions at admission (0.042; 1.04–9.35) and Acinetobacter in blood culture (0.008; 1.52-15.66)

Table 4. Logistic regression analysis for prediction of abnormal neurological outcome in neonates with sepsis

Parameters	**B**	**SE**	**p-value**	**OR**	**95% C.I. for OR**	
					Lower	**Upper**
Temp > 37.5°C	1.11	0.57	0.054	3.03	0.98	9.33
Temp < 35.5°C	0.79	0.53	0.141	2.20	0.77	6.26
convulsion	1.14	0.56	**0.042**	3.12	1.04	9.35
CONS	-0.80	0.62	0.195	0.45	0.13	1.51
Acinetobacter	1.58	0.60	**0.008**	4.87	1.52	15.66
Constant	-0.74	0.87	0.393	0.48		

B- beta coefficient; SE -standard error; OR- Odds ratio; C.I- confidence interval; RR >60/min-respiratory rate >60/minute; Temp- Temperature; CONS- coagulase negative staphylococcus

Discussion

In our study, the fatality rate for neonatal sepsis was 24%. Decreased movements and convulsions at admission and Acinetobacter in blood culture were the significant predictors of mortality.

Studies done in other tertiary care centres have found similar rates. CFR in different countries in South Asia ranged from 19.1% to 64.7% [8], and that for Indian neonates was 34.4% [8].

In another study from six developing countries (India, Pakistan, Bangladesh, Bolivia, Ghana, and South Africa), a lower CFR for culture-positive and culture-negative sepsis was suspected at 7% and 7.5%, respectively, but the setting was community-acquired sepsis [9].

The prevalence of BCP sepsis in our NICU was 24.5%. It was less as compared to other studies, like one from Karnataka with a prevalence of 28.8% [11] and 45.1% from Bhopal [13]. The incidence of culture-positive sepsis per 1000 live births in India was 16% [8], while according to other studies, it was 14.5% in Delhi [5] and 10.5% in a study conducted in six countries [9].

In our analysis, EOS (86%) was more common than LOS (14%). The most frequent pathogens (CONS, Acinetobacter, and Klebsiella pneumoniae) for both EOS and LOS were comparable in our study. While late-onset sepsis was more prevalent, these data were comparable to those of Ballot ED et al. (2012) [12]. Acinetobacter was shown to be the most common (22%) organism causing newborn sepsis with a significant incidence of multidrug-resistant infections in the Delhi newborn infection study (DeNIS) consortium (2016) [5].

The clinical characteristics of neonates with sepsis at admission were similar in our study to those of several other studies. Vomiting, increased respiratory rate, and lethargy were the most common and were found more frequently than in other studies [14,15]. Fever, convulsions, and sclerema were found in fewer patients as compared to other studies.

Sepsis may have a neurological morbidity, so we did a neurological exam of neonates with sepsis at discharge in an effort to estimate the proportion of bacteremia-related neurological morbidity. We found that more than 10% of neonates had abnormal HNNE at discharge, and it was mainly in the form of a tone abnormality. These neonates were in our follow-up, and out of these, five patients had an MRI brain at 6 months of age, and all were abnormal. Two had encephalomalacia, one had a cerebral infarction, and two had features suggestive of hypoxic ischemic encephalopathy; three had abnormal BERA and two abnormal EEGs, one of which was suggestive of hypsarrhythmia.

In another study, developmental delay was reported in 23.4% of neonates with sepsis when followed up for 6 months [16]. Another observational cohort study found that bloodstream infection-associated complications were reported in 10.4% of the patients with BSI, neurological complications comprised 33.7%, and persistent sequelae were seen in 18.3% [17].

In our study, 50% of abnormal NE was associated with Acinetobacter sepsis. Predictors of abnormal neurological examination at discharge were Acinetobacter (p value <0.001) in blood culture and convulsions (p value 0.039), bulging AF (p value <0.001), and hypoglycemia (p value 0.048) at admission. Morbidities like neonates requiring ventilation for >48 hours and developing shock during hospital stays were significantly more associated with abnormal neurological examinations, with p values <0.001 and 0.012, respectively. On logistic regression, convulsions and Acinetobacter in blood culture were the significant predictors of abnormal neurological outcomes. The OR for Acinetobacter was 4.87, and for convulsion, the OR was 3.12.

Strength

We enrolled only neonates with culture-proven sepsis and used a structured

neurological examination (HNNE) for all survivors by a single observer to predict neurological morbidity.

Limitation

We could not enrol many outborn neonates due to lockdown for the COVID-19 pandemic and that CONS isolated in blood culture in our study population could be contaminants. Blood culture samples drawn concomitantly from two sites could be useful to eliminate this issue.

Conclusion

Neonatal sepsis accounted for a quarter of total neonates admitted to our unit. CONS, Acinetobacter, and Klebsiella pneumoniae were the most common organisms isolated. Predictors of mortality were decreased movement, convulsions at admission, and Acinetobacter in blood culture. More than a tenth of neonates with BCP had abnormal neurological morbidity, and predictors of this were convulsions at admission and Acinetobacter in blood culture.

Ethical Approval

The study was conducted after receiving approval from the institutional ethics committee and informed consent from the parents or guardians of enrolled neonates. A consent to publish has been received from all the participants. No monetary or personal benefits from commercial bodies were provided to anybody involved in the study. Confidentiality of the data was maintained.

Conflicts of interest

The authors declares that they do not have conflict of interest.

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