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RESEARCH ARTICLE

NEONATAL SEPSIS–CULTURE POSITIVE SEPSIS VS. CLINICAL SEPSIS

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ABSTRACT

The incidence of sepsis is increasing globally, with high morbidity and mortality. Diagnosis of neonatal sepsis is still a clinical and laboratory challenge. Though blood culture is gold standard, it sometimes gives false negative result. So, judgement of clinical condition along with various investigations is important.
Methodology: Blood culture, sepsis screen, biochemical markers, cerebrospinal fluid (CSF) study, radiology, MRSA (methicillin resistance *Staphylococcus aureus*) surveillance were carried out in this study.
Results: One seventy (65.9%) were culture positive and 88 (34.1%) were culture negative out of 258 clinically suspected cases. Methicillin sensitive *Staphylococcus aureus* (MSSA) 66 (38.82%) was the commonest organism. Among 88 culture negative cases, 38(43.2%) babies were two or more sepsis screen tests positive, 40(45.5%) culture negative babies were with risk factors and 5 (5.7%) had radiological evidence of pneumonia.
Conclusion: The clinical diagnosis of it remains difficult as the symptoms are non-specific. So, blood culture is mandatory. Other diagnostic tests also help in this situation.

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INTRODUCTION

Neonatal sepsis is a socio-economic threat to every nation as it is the major cause of neonatal deaths globally. Current neonatal mortality rate (NMR) in India is 32.30/1000 live births (United Nation Children's Fund, 2011). Hence, early diagnosis and management of neonatal sepsis are essential to reduce the neonatal mortality (Kumar *et al*., 2007). According to National Neonatal Forum (NNF) of India, Probable (Clinical) Sepsis is based on existence of risk factors or positive sepsis screen or radiology findings of pneumonia, whereas culture positive sepsis denotes isolation of pathogen from blood in a baby having clinical picture suggestive of septicaemia (http://www.newbornwhocc.org/pdf/nnpd_report_2002_03).
Early diagnosis of neonatal sepsis is difficult as manifestations are ill-defined (Tripathi and Malik, 2010). On the other hand, multidrug resistant (MDR) strains are emerging (De *et al*., 2013). In this perspective, the purpose of the study is to evaluate the results of different diagnostic tests in the presence of risk factors and/or clinical picture. Blood culture, sepsis screen, biochemical markers, cerebrospinal fluid (CSF) study, radiology were included in this study.

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MATERIALS AND METHODS

This prospective study was carried out from October 2010 to June 2012 at a teaching institution cum tertiary care centre hospital in Pune, Maharashtra. Ethical clearance was obtained for the research project. Two fifty eight clinically suspected neonates admitted in neonatal intensive care unit (NICU) were studied. Clinical history, symptoms and signs were recorded. For blood culture, about 1-2 ml of blood was collected aseptically prior to administration of empirical antibiotics from each baby and inoculated into a McCartney bottle containing 10 ml of brain heart infusion broth and incubated aerobically at 37 c for 24 hr. Subcultures were done on Blood agar and MacConkey's agar and incubated overnight at 37 c.The growth was identified by colony characteristics, Gram's stain and standard biochemical tests (Koneman *et al*., 1997). Eighty samples were processed in BacT/ALERT-3D system (BioMerieux) and 11 samples were identified by VITEK-2 (BioMerieux). Antibiotic susceptibility testing including detection of methicillin resistance Staphylococcus aureus (MRSA), D test (inducible clindamycin resistance) and screening tests for extended spectrum beta lactamase (ESBL), metallo-beta lactamase (MBL) among Gram negative bacilli were carried out as per CLSI guidelines (Clinical and Laboratory Standard Institute, 2010).

A panel of sepsis screen tests were performed from the blood samples of all the neonates. Radiological tests and CSF study were done wherever indicated. MRSA surveillance was also carried out to prevent carrier state. Nasal swab of every staff of NICU and nasal, umbilical, perineal swabs of all neonates admitted in NICU were inoculated into mannitol salt semi-solid (MSA) agar with 0.6 µg cloxacillin and incubated at 37 C for 24 hrs. Epi Info Software system was used to calculate statistics.

RESULTS

During this study period, 258 suspected neonates were admitted to the NICU. Most of the babies had more than one clinical findings (Table-1). Low birth weight (LBW) and prematurity were the prevalent risk factors. Other risk factors are depicted in (Table-2). Out of 258 cases 170 (65.9%) were culture positive and 88 (34.1%) were culture negative. Majority of the isolates were Gram negative 86 (50.58%).

Methicillin sensitive *Staphylococcus aureus* (MSSA) 66 (38.82%) was the commonest organism followed by *Klebsiella pneumonia*e 41(24.11%). Two *Candida parasilopsis* (1.17%) were also isolated (Fig 1). Males (52%) are more affected as compared to female (47%). Sepsis screen parameter are shown in (Table-3 & Fig 2) MSSA showing 100% susceptibility to oxacillin, cefoxitin and vancomycin, while 60- 80% were susceptible to amoxycillin and cefuroxime, 25-40% susceptible to erythromycin and clindamycin. Ten (12.19%) isolates among Gram positive organisms were positive for D test and 30 (45.5%) were MRSA. *Klebsiella sp.* was susceptible to imipenem (97.67%) followed by ciprofloxacin (93.02%). Forty (46.51%) isolates were ESBL producers and 3 (3.48%) were MBL producers. Among 88 culture negative cases, 38(43.2%) babies were two or more sepsis screen tests positive, 40(45.5%) culture negative babies were with risk factors and 5 (5.7%) had radiological evidence of pneumonia. Suggestive clinical diagnoses are mentioned in (Table-4). Ten of 258 neonates died of sepsis, mortality rate being 3.87 %. All dead neonates were culture positive.

Table 1. Distribution of clinical findings of NICU cases

Clinical findings	Culture positive (170)	Culture negative (88)
Hypothermia	164 (96.47%)	50 (56.81%)
Hyperthermia	6 (3.52%)	2 (2.27%)
Tachycardia	96 (56.47%)	72 (81.81%)
Tachypnoea	110 (64.70%)	70 (79.54%)
Chest retraction	106 (62.35%)	70 (79.54%)
Cyanosis	120 (70.58%)	12 (13.63%)
Poor feeding /Refusal	59 (34.70%)	10 (11.36%)
Lethargy	68 (40%)	4 (4.54%)
Convulsion	10 (5.88%)	2 (2.27%)
Abdominal distension	15 (8.82%)	0
Vomiting	8 (4.70%)	0
Diarrhoea	4 (2.35%)	0

Table 2. Distribution of risk factors of neonates

Risk factors	Culture positive(170)	Culture negative (88)	Chi-Square	p-value
LBW < 2.5kg	128 (75.29%)	34 (38.63%)	45.63	0.00001
Preterm	125 (73.52%)	40 (45.45%)	18.62	0.0001
Birth asphyxia	122 (71.76%)	30 (34.09%)	32.46	0.00001
MSL	68 (40%)	17 (19.31%)	10.31	0.001
Maternal disease	25 (14.70%)	4 (4.54%)	5.02	0.025
PROM	51 (30%)	12 (13.63%)	7.54	0.006

[MSL-Meconium stained liquor, PROM- Premature rupture of membrane]

Table 3. The sepsis screen parameters of NICU cases

Screening test	Culture positive (170)	Culture negative (88)	Sensitivity (%)	Specificity (%)	PPV(%)	NPV(%)
CRP+	163 (95.88%)	56 (63.63%)	95.90% (C.I- 91.40-98.21)	36.40% (C.I-26.62-47.40)	74.41%(C.I-68-80)	82.10%(C.I- 65.90-91.91)
Increased TLC	158 (92.94%)	52 (59.09%)	92.94% (C.I-87.71-96.10)	40.90% (C.I-30.72-51.93)	75.22% (C.I-68.70-80.82)	75% (C.I-60.10-85.91)
Neutropenia	15 (8.82%)	0	8.82%(C.I-5.20-14.41)	100% (C.I-94.80-100)	100% (C.I-74.70-100)	36.20% (C.I-30.21-42.63)
I/TN >0.2	153 (90%)	10 (11.36%)	90%(C.I-84.2-93.9)	88.63% (C.I-79.7-94.1)	93.86%(C.I-88.7-96.9)	82.10% (C.I-72.6-88.9)
Decreased Platelet	23 (13.52%)	2 (2.27%)	13.52% (C.I-8.90-19.82)	97.70% (C.I-91.33-99.64)	92% (C.I-72.50-98.62)	36.92% (C.I-30.80-43.52)
Two or more tests positive	165 (97.05%)	38(43.18%)	97.05% (C.I-92.9-98.9)	56.81% (C.I-45.8-67.2)	81.28%(C.I-75.1-86.3)	90.90%(C.I-79.3-96.6)

[CRP- C-reactive protein, I/TN-Immature to total neutrophil , PPV- Positive predictive value, NPV-Negative predictive value, CI-Confidence interval]

Table 4. Spectrum of clinical diagnosis of NICU cases

Clinical diagnosis	Culture positive(170) (170)	Culture negative (88)
Respiratory distress syndrome (RDS)	127 (74.70%)	49 (55.68%)
Hypoxic ischaemic encephalopathy (HIE)	15 (8.82%)	4 (4.54%)
Urinary Tract Infection	10 (5.88%)	2 (2.27%)
Necrotising enterocolitis	6 (3.52%)	0
Pustular thrombophlebitis	6 (3.52%)	0
Umbilical sepsis	5 (2.94%)	1 (1.13%)
Human immunodeficiency virus infection (HIV)	1 (0.58%)	0
Meningitis	0	10 (11.36%)

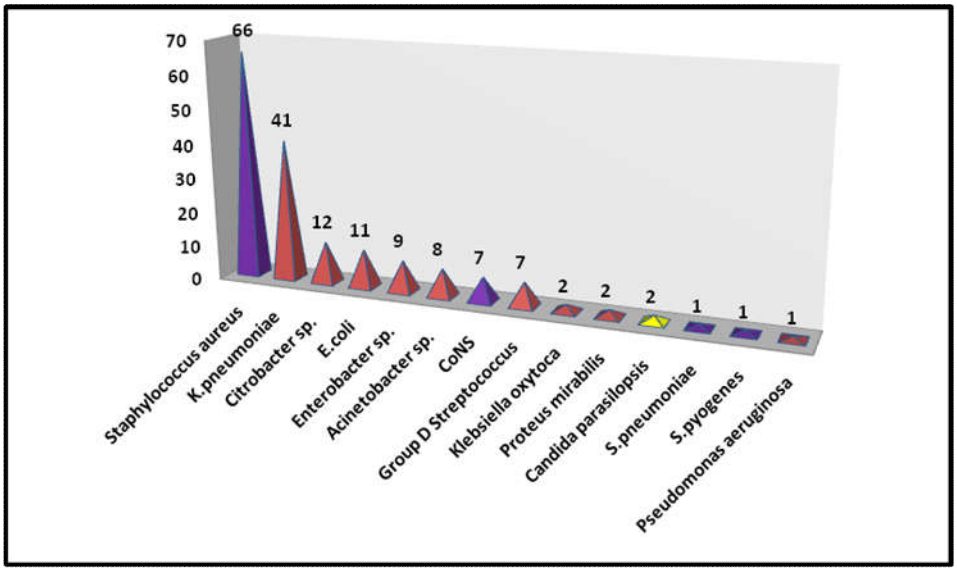

Fig. 1. Spectrum of isolates from blood cultures of NICU cases

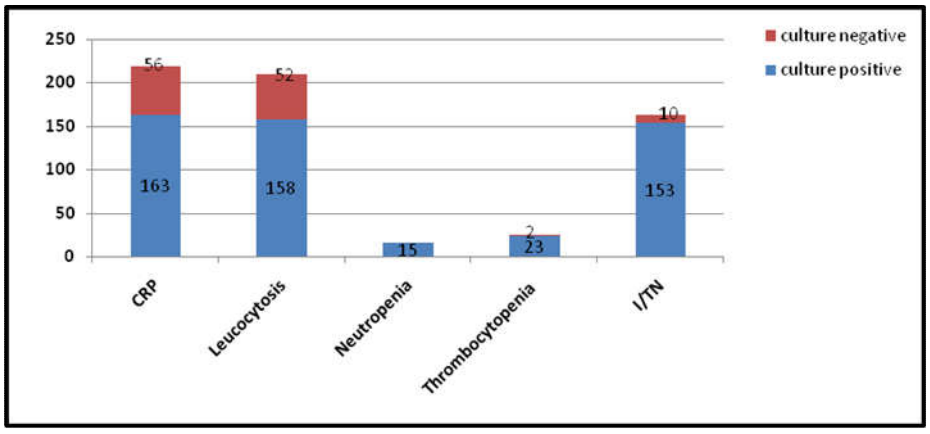

Fig. 2. The sepsis screen parameters of NICU cases

DISCUSSION

Neonates are uniquely susceptible to infection due to immature immune system. So early diagnosis and treatment are crucial (Sankar *et al*., 2008). The blood culture positivity rate (65.9%) was quite higher in this prospective study as some samples were processed in BacT/ALERT-3D system. It also reduced the turn around time. Blood culture is still the "Gold standard" for the diagnosis of septicaemia in neonates, but culture negativity cannot exclude the sepsis as a whole (Ntusi *et al*., 2010). There are many reasons behind blood culture negativity. The most important reason is that bacteraemia is often transitory or intermittent. So, timing of blood sampling is important. Two or three sets of blood can improve the chance of isolation. This is often due to the volume of blood inoculated into the blood culture bottle being insufficient or inadequate processing of the specimen. Blood sample should be collected before the institution of empirical therapy or at the "trough" *just before* the *next dose* is due (Betty *et al*., 2002). The ratio of culture positive neonatal septicaemia cases were higher among males (52.35%) than the females (47.64%).

The male preponderance in neonatal septicaemia may be due to the X- linked immune-regulatory gene factor which making the

host more susceptible to infection (Sriram, 2011). We observed that the respiratory distress (74.70%) was commonest symptom. In this study, 92.94% babies were with leucocytosis. No cases were found to be leucopenic. Absolute neutrophil count (ANC) was highly specific but very low sensitive test in our study. CRP and I/TN ratio showed high sensitivity but low specificity. When two or more sepsis screen tests were combined together, both sensitivity and specificity increased. *Staphylococcus aureus* was the predominant isolate may be from carriers as we got some carriers from NICU on MRSA surveillance. The results of the present study are comparable with the study conducted by Roy *et al*. (2002) and Shah *et al*. (2012).

Conclusion

Neonatal sepsis is a serious national health concern. MDR and fungal sepsis together worsen the situation. It can be managed by following proper antibiotic policy and standard treatment protocol. In addition, the preventive strategies including good antenatal care, hand washing, clean birth environment, clean cord care, exclusive breast feeding, well equipped and sterile nursery and neonatal intensive care unit (NICU), surveillance are promising to reduce the incidence of neonatal septicaemia.

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