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Original Research Article

Clinical features and septic screen in neonatal sepsis in a teaching hospital in India

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ABSTRACT

Background: Sepsis remains a leading cause of mortality and morbidity, especially during the first five days of life and in low and middle-income countries. The purpose of this study was to note the clinical features and analyze the relationship between the septic screen and blood culture positive sepsis in the neonatal unit.
Methods: A one-year descriptive cross-sectional study was carried out at the NICU of a teaching hospital in India.
Results: The incidence of clinically suspected septicemia was 19.3 per 1000 live births and the incidence of blood culture positive septicemia was 2.9 per 1000 live births among the inborn of the hospital. The most common clinical features were poor suck and lethargy in culture positive sepsis. The most common organisms causing sepsis were Coagulase negative *staphylococci* and *Klebsiella*. In the septic screen CRP was found to have a statistically significant association with blood culture positive sepsis. CRP also had the highest sensitivity and negative predictive value among the studied parameters.
Conclusions: Incidence of blood culture positive sepsis was 2.9 per 1000 live births among the inborn of the hospital. The most common clinical features were poor suck and lethargy in culture positive sepsis. The most common organism isolated in neonatal sepsis in the NICU was Coagulase negative *staphylococcus*. In resource poor settings, CRP continues to be an important tool in diagnosis and treatment of neonatal sepsis.

Keywords: Blood culture, C-reactive protein, Neonatal sepsis, Septic screen

INTRODUCTION

Sepsis remains a leading cause of mortality and morbidity, especially during the first five days of life and in low and middle-income countries.[1] In developing countries, clinically diagnosed sepsis is present in 49-170 per 1000 live births, culture-proven sepsis in 16 per 1000 live births and neonatal meningitis in 0.8-6.1 per 1000 live births.[2] According to the National Neonatal Perinatal Database (NNPD 2002-2003) the incidence of neonatal sepsis in India is around 30 per 1000 live births.[3]

According to the report on the expert meeting on neonatal and pediatric sepsis of EMA (2010), neonatal sepsis can be defined by the presence of at least two clinical symptoms and at least two laboratory signs in the presence of or as a result of suspected or proven infection (positive culture, microscopy or polymerase chain reaction).[1]

A positive blood culture result is the gold standard for detection of bacteremia in newborns with suspected sepsis. But results may be delayed for 72 hours. The yield of blood culture is between 30%-70%. Hence, some neonates with sepsis may go undetected. Inability to adequately exclude the diagnosis of neonatal sepsis early results in prolonged and unnecessary exposure to antibiotics.[4] Blood culture is affected by blood volume

inoculated, prenatal antibiotic use, level of bacteremia and laboratory facilities.

According to the All India Institute of Medical Sciences (AIIMS) protocols 2014, all neonates suspected to have sepsis should have a septic screen to corroborate the diagnosis. However, the decision to start antibiotics need not be conditional to the sepsis screen result, if there is a strong clinical suspicion of sepsis. The screen is positive if 2 parameters are positive (Table 1).[5]

Table 1: A practical sepsis screen.

Components	Abnormal value
Total Leukocyte Count (TLC)	<5000 / mm^3
Absolute Neutrophil Count (ANC)	Low counts as per Manroe chart for term and Mouzinho's chart for VLBW infants
Immature/Total neutrophil (IT)	>0.2
Micro-ESR	>15 mm in 1st hour
C Reactive Protein (CRP)	>1 mg/dl

Low White Blood Cell (WBC) count, low Absolute Neutrophil Count (ANC), as well as high immature-to-total (IT) neutrophil ratio are associated with an increased risk of infection. However, the sensitivity for detection of sepsis is low. Components of the white cell count, including absolute neutrophil count and immature to total neutrophil ratio have also been shown to be more useful for excluding infants without infection rather than identifying newborns who are infected.[6]

A number of acute phase proteins serve as indicators of acute infection in neonates. CRP levels rise following any inflammation. When CRP is negative at the onset it must be repeated after 12 hours. A semi quantitative bedside latex agglutination technique gives results within 15 minutes. CRP has a sensitivity and specificity of 87 and 83% respectively. Procalcitonin (PCT) is a more reliable marker of sepsis compared to CRP with sensitivity and specificity of nearly 100%. A broad-based PCR with amplification of DNA i.e. 16 Sr DNA has been used for identification of bacteria, but its cost is prohibitive.[7]

Newer markers are however not practical in developing countries because of their non-availability and high cost.[8-10]

The purpose of this study was to note the clinical features and analyze the relationship between the septic screen and blood culture positive sepsis in the neonatal unit.

METHODS

Study design was descriptive cross-sectional study. Setting and duration was the study was done at the Neonatal Intensive Care Unit (NICU), Government Medical College, Calicut, a teaching hospital in Kerala, India for a period from September 2003 to August 2004 (one year).

Inclusion criteria

- Neonates having a clinical picture of sepsis with isolation of organisms from blood (proven sepsis) were included in final analysis.

Exclusion criteria

- Neonates with blood culture showing growth of two or more organisms were excluded from the final analysis as they were considered contaminants. Neonates with gross congenital anomalies were excluded from the study. Babies 'at risk for sepsis' were not included unless they developed features of sepsis.

All neonates admitted in the NICU with clinical features of sepsis were considered for the study. Early Onset Sepsis (EOS) was defined as occurring in the first 7 days of life and Late Onset Sepsis (LOS) that occurring after 7 days of life. A pro forma was used to record details under the following headings: basic data, mother's details, details of delivery, neonate's data, clinical profile-symptoms and signs, investigations, treatment, complications, outcome. A detailed history was taken regarding the presenting complaints and with due importance to the risk factors for sepsis in antenatal, natal and postnatal periods. Babies were examined in detail. Neonates having a clinical picture of sepsis with isolation of pathogens from blood (proven sepsis) were included in the final analysis.

Investigations done in all cases were, septic work up - total White Blood Cell (WBC) count, C Reactive Protein (CRP), platelet count which was sent at the time of clinical presentation. I/T ratio and micro ESR could not be done for all cases due to technical issues hence were not included in final analysis. CRP was done by rapid slide latex agglutination method. Blood culture and sensitivity - Under strict aseptic precautions (after cleaning area with alcohol - povidone iodine - alcohol) 0.5 ml of blood collected in brain heart infusion broth 5 ml was sent in all cases before starting antibiotics. Antibiotic sensitivity was tested by disc diffusion method. Lumbar puncture was done in all cases of suspected meningitis and blood culture positive cases. Urine culture and sensitivity and swabs taken from sites of superficial infection were sent if needed. Repeat blood culture and sensitivity was sent if there was no response to treatment. Other investigations were sent as needed (Chest X-ray, bilirubin, electrolytes, ultrasonogram, renal function tests etc.).

All neonates with clinically suspected sepsis were treated with intravenous antibiotics as per Unit protocols. The antibiotic dose was adjusted according to the gestational age and weight of the neonate. Antibiotics were changed

according to the blood culture and sensitivity reports and if no clinical improvement occurred. Antibiotics were given for at least 14 days in proven sepsis and 21 days in meningitis. Maintenance of euthermia, seizure control, fluid and electrolyte balance, correction of hypoglycemia, blood transfusion, phototherapy, exchange transfusion and other supportive measures were provided. The babies were followed up in the hospital for improvement and for development of complications. Analysis was done using Chi-Square test in Epi Info software. The difference was considered significant if probability p value was less than 0.05.

Using blood culture as the gold standard in diagnosing neonatal sepsis, the sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for septic screen parameters was calculated.

RESULTS

Total number of live births during the period was 22371. Incidence of clinically suspected sepsis was 19.3 per thousand live births among inborn (432 inborn neonates). Incidence of blood culture positive sepsis was 2.9 per thousand live births among inborn (65 inborn neonates).

There was a total of 671 babies admitted for clinically suspected sepsis. Of these micro-organisms was isolated by blood culture in 100 cases (14.9%). Of the 100 cases 65 babies were born at the same hospital (inborn) and 35 born elsewhere (out born). Affected males (69) outnumbered females (31). Symptoms started within 72 hours of life in 58 babies and from 72 hours to 1 week in 22 babies. 20 babies were symptomatic after one week of life. The most common clinical features in both EOS and LOS were poor suck (66%) and lethargy (58%) (Table 2).

Table 2: Clinical features in blood culture positive sepsis.

Clinical features	EOS (n=80)	LOS (n=20)	Total % (n=100)
Poor suck	52	14	66
Lethargy	46	12	58
Fast breathing	27	6	33
Seizures	23	7	30
Fever	12	8	20
Jaundice	15	3	18
Apnoea	10	1	11
Umbilical sepsis	5	1	6
Bleeding manifestations	2	4	6
Incessant cry	3	2	5
Abdominal distension	4	1	5
Loose stools	4	1	5
Skin pustules	3	0	3
Vomiting	2	0	2
Infected cephal hematoma	2	0	2
Sclerema	0	1	1

The most common organism isolated in EOS, LOS and overall was CONS (27%). This was followed by *Klebsiella* (24%) and *Staphylococcus aureus* (18%). Group B streptococcus was not isolated in any of the cases (Figure 1).

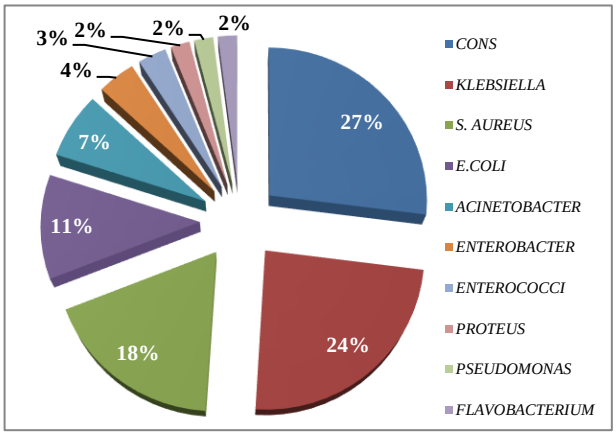

Figure 1: Microorganisms isolated in neonatal septicemia.

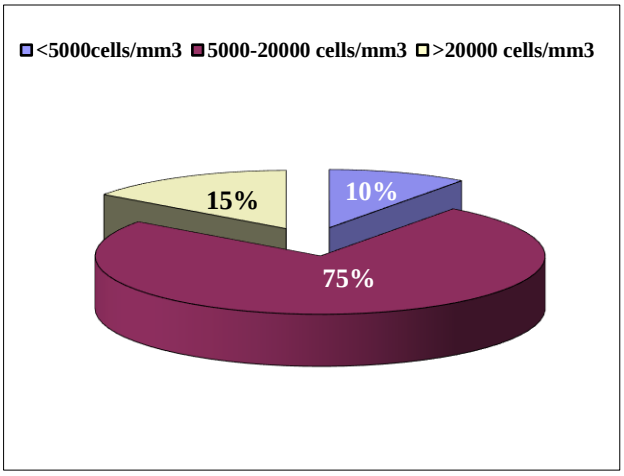

Figure 2: Total white blood cell (WBC) count and septicemia (n=100).

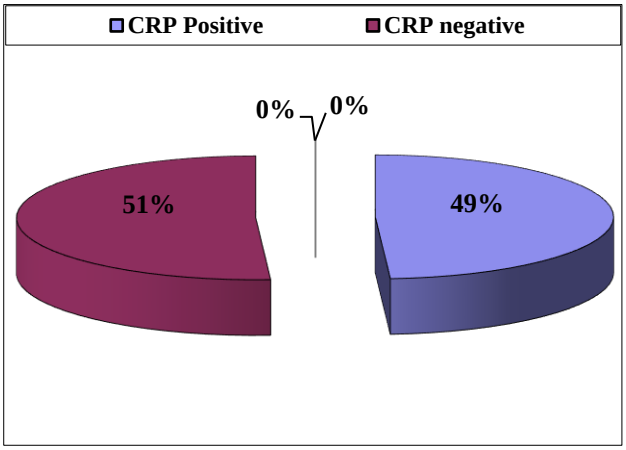

Figure 3: C-reactive protein and septicemia (n=100).

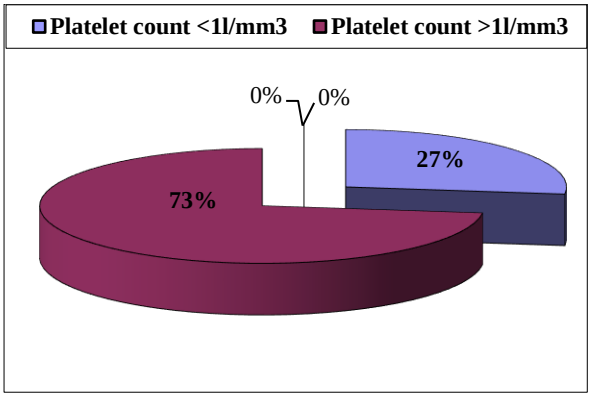

Figure 4: Platelet count and septicemia (n=100).

Septic screen in blood culture positive septicemia: Total White Blood Cell count (WBC) count <5000 cells/mm^3 was seen in 10% and >20000 cells/mm^3 in 15%. Majority of the cases (75%) had a total WBC count between 5000-20000 cells/mm^3 (Figure 2), 49% of the cases were found to be CRP positive and 51% of the cases were CRP negative (Figure 3). Platelet count <1 lakh/mm^3 was seen in 27% of cases (Figure 4), 30% of the cases had hypoglycemia.

Table 3 shows the comparison of investigations in blood culture positive septicemia and clinically suspected blood culture negative septicemia. Table 4 shows predictive accuracy of septic screen parameters using blood culture positive sepsis as the standard.

Table 3: Septic screen parameters.

Investigation	Blood culture positive septicemia (n=100)	Blood culture negative clinical sepsis (n=571)	Total (N=671)	Chi square	df	p
TC<5000cells/mm^3	10	64	74	0.132	1	0.7
TC>20000cells/mm^3	15	110	125	1.025	1	0.3
Platelet count <1 lakh /mm^3	27	122	149	1.54	1	0.2
CRP positive	49	179	228	11.83	1	0.0005

Table 4: Predictive accuracy of septic screen parameters.

Parameters	Sensitivity%	Specificity %	PPV%	NPV%
TC<5000cells/mm^3	10	88.79	13.51	84.92
TC>20000cells/mm^3	15	80.74	12	84.43
Platelet count <1 lakh/mm^3	27	78.63	18.12	86.02
CRP	49	68.65	21.49	88.49

DISCUSSION

During the one-year observation period, the incidence of clinically suspected sepsis among in borns was 19.3 per thousand live births (432 inborn neonates). Incidence of blood culture positive sepsis was 2.9 per thousand live births among in borns (65 inborn neonates).

In 14.9% of the clinically suspected cases, organism was isolated by blood culture. Another study done in South India showed similar blood culture positivity of 19.2% .[11] Higher rate of culture positivity of 47.47% was seen in a study from North India and another from South India 80 %.[12,13]

The low blood culture positivity here was possibly due to early use of maternal antibiotics. The use of maternal antibiotics has reduced the rate of positive blood culture in early onset sepsis.[14] 65% were inborn and 35% were out born among the blood culture positive cases. Males (69%) outnumbered females (31%).

The most common clinical features in both EOS and LOS were poor suck (66%), lethargy (58%) and fast breathing (33%). A study done by Lakhey et al, in Nepal found respiratory distress (56%), fever (26%) and feeding problems (12.6%) the most common clinical features.[15] EOS generally presents itself with respiratory distress, apnea, lethargy or irritability, temperature instability, and feeding difficulties.[16]

Overall the most common organism isolated was CONS (27%) followed by *Klebsiella* (24%) and *Staphylococcus aureus* (18%). According to the NNPD 2002-2003 *Klebsiella* is the most common cause of neonatal sepsis in India.[3] A study from North India found *Klebsiella* (31.9%) and Staphylococcus aureus (28.7 %) the most common organisms.[12]

Total WBC count <5000/mm^3 was seen in 10% and >15000/mm^3 in 15% cases. Hence 75% had a WBC count within the normal range. CRP was positive >1 mg/dl in

49% of cases. Thrombocytopenia was noted in 27%. Hypoglycemia was noted in 30% of patients.

Only CRP was found to have a statistically significant association with blood culture positive septicemia (p value 0.0005) (Table 1). CRP showed the highest sensitivity (49%). TC <5000 cells/mm^3 showed highest specificity (88.79%). All parameters had a high NPV, highest for CRP (88.49%) (Table 2).

In the study by Bhale et al, Absolute neutrophil count showed highest specificity (99%) and positive predictive value (97.5%) among all the other parameters of sepsis screen. CRP showed highest sensitivity (84.62%) and negative predictive value (84.78%) similar to this study. All the parameters of septic screen showed a relation with blood culture report which was statistically very significant (p<0.001).[12]

In the study by Vinay BS et al, CRP individually had better sensitivity (81.2%), specificity (50%), PPV (86.6%) and NPV (40%) than a positive septic screen. TLC < 10 × 109/L had a sensitivity of 58%, an NPV of 28%, with a PPV of 87%. The platelet count was not found to have good sensitivity (41.6%) and specificity (41.6%).[13]

A study from Gujarat in India showed CRP, thrombocytopenia and I/T ratio were positive in a higher proportion of culture-positive cases. CRP, m-ESR, and two or more tests positive were statistically significant with respect to culture-proven sepsis.[17] C-reactive protein (positive >1 mg/dl) had high sensitivity 95.24%, specificity 67.6%, PPV 83.3%, NPV 89.3%. Leukopenia had sensitivity 12.7%, specificity 97.3%, PPV 88.9%, NPV 39.6%. Thrombocytopenia had sensitivity 55.6%, specificity 59.5%, PPV 70.0% and NPV 44.0%. Two or more tests positive in the screen had sensitivity 81.0%, specificity 94.6%, PPV 96.2%, NPV 74.5%.

In a study from Nepal, leucopenia had sensitivity 62%, specificity 55%, PPV 56.2%, NPV 61.4%, p value >0.001. CRP Positive (>1 mg/dl) had sensitivity 77.8%, specificity 66.7%, PPV 68.2%, NPV 76.5%, p value <0.001.[15]

A study by Mittal et al, showed that thrombocytopenia, increased Mean Platelet Volume (MPV) and increased PDW (platelet differential width) were associated with sepsis.[18]

However non-infectious disorders (birth asphyxia, meconium aspiration, maternal pregnancy induced hypertension) may produce hematological changes similar to those seen with infection, thereby affecting the specificity and PPV of the hematological screening tests.

As seen above many authors have tried to find out the usefulness of septic screen with blood culture as gold standard to detect neonatal sepsis.[12,13] However blood culture negativity does not always rule out neonatal sepsis. As no single individual hematological parameter is better than another in predicting neonatal sepsis, a combination of these parameters in the form of septic screen has been recommended. Though several new expensive markers are available for neonatal sepsis, in developing countries CRP continues to be useful due to its easy availability and lesser cost.

The limitation of this study was that ANC, I/T ratio, Micro ESR, could not be done in all cases and hence could not be included in the analysis. A repeat value of CRP was also not sent in all cases and hence change in CRP could not be analyzed.

CONCLUSION

The incidence of clinically suspected septicaemia was 19.3 per 1000 live births and the incidence of blood culture positive septicaemia was 2.9 per 1000 live births among the inborn of the hospital. The most common clinical features were poor suck and lethargy in culture positive sepsis. The most common organism causing sepsis in the NICU was Coagulase negative *staphylococci* (27%). In resource poor settings, CRP continues to be an important tool in diagnosis and treatment of neonatal sepsis.

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REFERENCES

1. WHO reviews. Antibiotic use for sepsis in neonates and children:2016 evidence update. Available at: https://www.who.int/selection_medicines/committees/expert/21/applications/s6_paed_antibiotics_appendix4_sepsis.pdf. Accessed on 10 September 2019.
2. Thaver D, Zaidi AK. Burden of neonatal infections in developing countries: a review of evidence from community-based studies. Pediatr Infect Dis J. 2009 Jan 1;28(1):S3-9.
3. National Neonatal Perinatal Database - WHO newborn CC. Available at: http://www.newbornwhocc.org/pdf/nnpd_report_2002-03.PDF. Accessed on 1 September 2019.
4. Kumar CSV, Neelagaud YF. Incubation period for culture positivity to detect septicaemia in neonates. Indian J Medica Microbiol. 2005; 23(4): 270-5.
5. AIIMS protocols 2014- Sepsis in the new-born. Available at: https://www.newbornwhocc.org. Accessed on 30 August 2019.

6. Shah BA, Padbury JF. Neonatal sepsis: an old problem with new insights. Virulence. 2014 Jan 1;5(1):170-8.
7. Singh M. Perinatal infections. In: Singh M, ed. Care of the Newborn. Revised 8th ed. New Delhi: CBS publishers and distributors pvt. Ltd; 2017:285-294.
8. Buch AC, Shrivastava V, Kumar H, Jadhav PS. Evaluation of hematological profile in early diagnosis of clinically suspected cases of neonatal sepsis. Int J BAMS. 2011;1(1):01-6.
9. Bhat YR, Rao A. The performance of haematological screening parameters and CRP in early onset neonatal infections. J Clini Diagnostic Res. 2010 Dec 30;4(6):3331-6.
10. Swarnkar K, Swarnkar M. A study of early onset neonatal sepsis with special reference to sepsis screening parameters in a tertiary care centre of rural India. Intern J Infect Dis. 2012;10(1):36-42.
11. Jyothi P, Basavaraj MC, Basavaraj PV. Bacteriological profile of neonatal septicemia and antibiotic susceptibility pattern of the isolates. J Natural Sci, Biol, Med. 2013 Jul;4(2):306.
12. Bhale CP, Kale AV, Kale SS, Mahajan M, Mulay SS. Utility of Sepsis Screen in the Early Diagnosis of Neonatal Sepsis. Ind J Neonatal Med Res. 2016 July;4(3):1001-7.
13. Vinay BS, Girish GN, Adhikari S, Hugara S, Vinay BS. Evaluation of Septic Screen as a Diagnostic Tool for Neonatal Sepsis in a Tertiary Hospital at Mysore. Sch J App Me Sci. 2015;3(2G):1005-10.
14. Gerdes JS. Diagnosis and management of bacterial infections in the neonate. Pediatr Clini. 2004 Aug 1;51(4):939-59.
15. Lakhey A, Shakya H. Role of sepsis screening in early diagnosis of neonatal sepsis. J Pathol Nepal. 2017 Mar 30;7(1):1103-10.
16. Klingenberg CA, Kornelisse R, Buonocore G, Maier RF, Stocker M. Culture-negative neonatal sepsis at the crossroad between efficient sepsis care and antimicrobial stewardship. Frontiers Pediatr. 2018;6:285.
17. Hassan HR, Gohil JR, Desai R, Mehta RR, Chaudhary VP. Correlation of blood culture results with the sepsis score and sepsis screen in the diagnosis of early-onset neonatal septicaemia. J Clini Neonatol. 2016 Jul 1;5(3):193-8.
18. Mittal A, Arya S, Charan LS, Saluja S, Chellani H. Evaluation of platelet indices as additional diagnostic tool for neonatal sepsis. Astrocyte. 2018 Oct 1;4(4):205-9.

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