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A Retrospective Study on Importance of CRP as a Predictor and to Analyze the Effectiveness of Antibiotics in the Treatment of Neonatal Sepsis at Karpaga Vinayaga Institute of Medical Sciences and Research Centre

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Abstract

Aim: Early diagnosis of sepsis in a neonate is often difficult because symptoms and signs are usually non-specific. A study was conducted to evaluate C-reactive protein (CRP) as a screening tool and the effectiveness of anti-biotics in the treatment of neonatal sepsis. **Methods:** The retrospective study was conducted at Karpaga Vinayaga Institute of Medical & Research Centre, from June 2016 to December 2016, on total of 120 neonatal sepsis patients. Patients of Group I received Ampicillin + Gentamicin, Group II received Ampicillin + Gentamicin followed by Cefotaxime + Amikacin, Group III received Cefotaxime + Amikacin, Group IV received Ampicillin + Gentamicin followed by Piptaz followed by Amikacin + Ciprofloxacin and Group V received, Ampicillin+ Gentamicin followed by Piptaz then by Amikacin + Meropenem and then by Ciprofloxacin. Chi-square test two side p-value and ONE-WAY ANOVA followed by Tukey-Krammer Multiple Comparison Test is used for statistical analysis. **Results:** Among study subjects, 18 (15%) and 102 (85%) had negative and positive CRP respectively. According to blood culture studies, 15 cases were culture positive, with the following organisms, *Klebsiella pneumoniae* (53.33%), *Escherichia coli* (20%), *Staphylococcus aureus* (20%) and *Proteus marbilis* (6.66%). Group II is an appropriate choice for empirical therapy of neonatal sepsis and was 46.96% of 66 patients. Group I, which is considered as First Line treatment was 33.33% of 66 patients. **Conclusion:** CRP is a highly sensitive parameter in detection of cases with neonatal sepsis. The most effective treatment was found out as Group I and Group II.

Keywords
Anti-biotics, Blood culture, CRP, Neonatal sepsis.

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INTRODUCTION

The Third International Consensus Definitions Task Force (Sepsis-3) defined sepsis as "life-threatening organ dysfunction due to a dysregulated host response to infection [1]. Neonatal sepsis remains one of the main causes of mortality and morbidity despite the progress in hygiene, introduction of new and potent antimicrobial agents for treatment, and advanced measures for diagnosis [2]. So, it is responsible for 30- 50% of the total neonatal deaths in developing countries. It is estimated that up to 20% of the neonates develop sepsis and approximately 1% die of sepsis related causes [3].

Neonatal sepsis can be divided into two main classes depending on the onset of symptoms related to sepsis into Early Onset Sepsis (EOS) and Late Onset Sepsis (LOS). Early-onset sepsis is commonly caused by organisms acquired from the mother's genital tract around the time of delivery [4-6]. Late onset sepsis is usually caused by pathogens acquired during the course of hospitalization or during delivery [5 & 6]. The pathogens most often implicated in neonatal sepsis in developing countries differ from those seen in developed countries. Overall, Gram negative organisms are more common and are mainly represented by *Klebsiella, Escherichia coli, Pseudomonas* and Salmonella [7-11]. Of the Gram-positive organisms, *Staphylococcus aureus* [9, 10, 12, 13], *Coagulase negative staphylococci* (CONS) [14], *Streptococcus* pneumoniae [15] and *Streptococcus* pyogenes are most commonly isolated.

Irrespective of the etiological agent the sepsis in neonates usually present with similar features like lethargy, refusal to feed, respiratory distress in the form of tachypnea and intercostal and subcostal retractions, convulsions and renal failure [16]. C-reactive protein (CRP) is a good marker for diagnosis of NS. Elevated CRP levels are seen in infection, in autoimmune disease, in surgery, meconium aspiration and recent vaccination. Also, the CRP values do not rise significantly until almost 14-48 hr after the onset of infection [17]. Blood culture is the *gold standard* for the diagnosis of neonatal sepsis. However, its positivity rate is low and is affected by blood volume inoculated, prenatal anti-biotic use, level of bacteremia and laboratory capabilities [18].

Rubarth is among haematological scoring tool that are used for screening for neonatal sepsis. The scale takes into consideration the clinical presentation of the neonate and integrates it with FBP and blood pH results. The tool has two parts. The first part includes the physical examination findings namely skin colour, capillary refill time, muscle tone, response to pain, respiratory distress, respiratory rate, temperature and apnea. The second part has blood investigations results for pH, and components of FBP. The total score from both parameters is 55[19]. Complications of neonatal sepsis include respiratory failure, pulmonary hypertension, cardiac failure, shock, renal failure, liver dysfunction and cerebral oedema [20].

Sepsis originates from a breach of integrity of the host barrier, either physical or immunological, and direct penetration of the pathogen into the bloodstream, creating the septic state [21]. The fetus is protected by the membranes and placenta from bacterial exposure [22]. It has also been shown that the amniotic fluid has inhibitory properties against bacterial growth [22-24]. Foetal bacteremia may occur in preterm labor [25], and term neonates may have bacteremia or present symptoms at birth [26] suggesting that bacterial colonization may take place before birth.

The management consists of immediate supportive care. Empirical treatment with the common antibiotics to which the bacterial flora is susceptible should be started [27]. The antibiotics treatment can be changes depending upon the culture and sensitivity report. If nosocomial infections are suspected, then cephalosporin and Aminoglycoside combination should be empirically started [28]. The aim of our study is to find out the diagnostic importance of CRP and to analyze the effectiveness of anti-biotics in the treatment of neonatal sepsis.

MATERIAL AND METHODS

This was a retrospective study conducted over a period of 6 months between December 2016 and June 2017, at the Neonatal Intensive Care Unit Karpaga Vinayaga Institute of Medical Sciences & Research Centre, Maduranthagam, Tamil Nadu, India. During the study period, neonates born with the risk of neonatal sepsis were enrolled for the study. This study was approved by the Ethics Committee of Karpaga Vinayaga Institute of Medical Sciences & Research Centre, Maduranthagam, (Reference No: IHEC/KVIMSRC/2016-17/004)

The Inclusion Criteria were:

- Maternal fever >38˚c
- Meconium stained liquor
- Low birth weight < 2.5 kg
- Prematurity < 34 wks
- Maternal WBC> 15000 Cells/cu.mm
- PROM
- Amnionitis
- More than 3 per vaginal examinations during labour
- Active resuscitation required in the labour room.

The Exclusion Criteria were:

- Neonates with obvious malformation/ congenital anomalies
- Outside born babies
- Babies born to mothers who had received antenatal anti-biotic therapy

During the study period of 6 months, 120 consecutive neonates with risk factors of septicemia were studied. Collected data included demographics, gestational age, type of delivery, weight at birth, signs of sepsis at time of blood culture draw, comorbidities, laboratory values at time of sepsis, microbiology data (including type of organism and antimicrobial susceptibility), type of empiric treatment and final outcome. We compared clinical features, laboratory data and final outcome for patients with sepsis. Data were collected by using a case sheets, master chart was prepared in excel and statistical analysis was performed using Chi-square test two side p-value & ONE-WAY ANOVA followed by Tukey-Krammer Multiple Comparison Test.

RESULTS & DISCUSSION

Out of 322 screened patients, 202 were excluded and 120 were enrolled based on the inclusion and exclusion criteria. Out of 120; 65(54%) were males and 55(46%) were females; 60(50%) of the babies were in term, 26(21.6%) of the babies were in near term and 34(28.3%) of the babies were in pre term;56(46.6%) were of NBW, 60(50%) were of LBW and 4(3.33%) were of VLBW. The commonest signs and symptoms presented by the neonates has been described as reduced sucking 49(40.83%), respiratory distress 42(35%), fever 26(21.6%), yellowish discoloration of skin 9(7.5%), increased irritability 5(4.16%), lethargy 5(4.16%), convulsion 3 (2.5%) and vomiting 1(0.83%) encountered at admission (Table 1).

Out of 120 clinically suspected cases of neonatal sepsis, 15 had positive blood cultures, which indicate prevalence of 12.5%. The main isolates in blood culture were Gram positive organisms *K.pneumoniae* (53.33%) , *E.coli* (20%), *S.aureus* (20%) and *P.marbilis* (6.66%). (Figure 1)

CRP was done in 120 cases out of which cases were positive 102(85%) and 18(15%) cases were negative. CRP is taken as a predictive value and it was compared with the body weight, gestational age, platelet count and it is used as a parameter to check the effectiveness of antibiotics. CRP values of the blood culture-positive and -negative samples are shown in Table 2. Of the 15 positive blood cultures, 1(6.66%), 9(60%), 5(33.33%) had CRP 0-5 mg/dL, 6-20mg/dL and >20mg/dL respectively. whereas among the 105-blood culture-negative neonates, 17(16.19%), 65(61.90%), 23 (21.90%) had CRP CRP 0-5 mg/dL, 6-20mg/dL and >20 mg/dL respectively. The association between CRP and blood culture was statistically significant (Figure 2). In Table 3, 12 patients had CRP level between 0-5mg/dL with Rubarth's Scale score between 10-15, around 72 patients had CRP level between 6-20mg/dL with Rubarth's Scale score between >15.

The 120 recruited patients were allocated into 5 groups I, II, III, IV and V consisting of patients according to the treatment pattern they received. Patients of Group I received Ampicillin + Gentamicin, Group II received Ampicillin + Gentamicin followed by Cefotaxime + Amikacin, Group III received Cefotaxime + Amikacin, Group IV received Ampicillin + Gentamicin followed by Piptaz followed by Amikacin + Ciprofloxacin and Group V received, Ampicillin + Gentamicin followed by Piptaz then by Amikacin + Meropenem and then by Ciprofloxacin to check the effectiveness of antibiotics which is shown in Table 4.

The effectiveness of antibiotics was compared with the symptomatic relief of the babies and the most effective one was the one which reduced the symptom faster in Table 5 & Figure 3.

Neonatal sepsis is a systemic inflammatory response syndrome that is secondary to infection. It is a major cause of neonatal mortality in the world, very particularly in developing countries. In general, definitive diagnosis requires the isolation of pathogens from a normally sterile body site, including blood, cerebrospinal fluid and urine. Empirical anti-biotic therapy is based on the physician's knowledge of the anticipated bacterial species and their expected anti-biotic susceptibilities. Present retrospective study was conducted to identify the importance of CRP as a predictor and to analyse the effectiveness of anti-biotic treatment on Neonatal Sepsis at Maduranthagam.

In our study male babies were more prevalent than female babies (54% Vs 46%). From our study it was revealed that low birth weight babies were 60 in numbers and very low birth weight babies were 4 numbers, which is in agreement with previous reports[29]. It was observed that near term babies were 26 in numbers and preterm were 34 among 120 patients. There was a statistically significant ($p < 0.05$, near term Vs Preterm) difference was observed between gestational age groups. However, the opposite was documented in some other previous studies[30].

The clinical symptoms of our study subjects were distributed in the following categorize, reduced

sucking (40.83%), respiratory distress (35%), fever (21.67%), yellowish discoloration (7.5%), irritability (4.17%), lethargy (4.17%) and convulsion (2.5%). In general, the clinical symptoms of sepsis case in neonates are non-specific, the author Birju AS and James FP, 2014, reported the same class of clinical symptoms[31].

In our retrospective study, gram negative bacteria, specifically *klebsiella pneumoniae* was more common pathogenic organism (53.33%, 8 out of 15 patients) in culture sensitivities test. Gram negative bacteria, specifically *E. coli* and *S.aureus* were secondary pathogenic organism (20%, 8 out of 15 patients) in selected culture test report. Similar findings were obtained in other studies from different countries such as Egypt, China, Mexico, South Africa and Kenya[32,33]. From our study, it was revealed that 9 positive blood culture patients had CRP level between 6-20 mg/dL, which is a sign of that CRP level between 6-20 mg/dL patients to get some more special attention to monitor for further evaluation.

From our study, it was noted that 12 patients had CRP level between 0-5 mg/dL with Rubarth's Scale score between 10-15, around 72 patients had CRP level between 6-20 mg/dL with Rubarth's Scale score between >15, which is a sign to give more attention for the management of sepsis. The earlier studies reported that Rubarth's scale also a tool to validate sensitivity[31]. Similar findings have been shown by Manucha *et al*., in India [34] who found that absolute neutropenia and thrombocytopenia was highly associated with neonatal sepsis. In our study, a higher proportion of 37 number of patients with NBW were belongs to CRP level between 6-20 mg/dL. Similarly, a medium range of 33 numbers of patients with LBW were belongs to CRP level between 6-20 mg/dL.

From our study, it was observed that higher proportions of male patients were suffered with sepsis among 120 numbers. In which, very particularly the same male 38 sepsis patients were had CRP level between 6-20 mg/dL. In our study, it was found that 20 numbers of preterm babies with either sex having the CRP range between 6-20 mg/dL. Apart from these findings, 30 numbers of term babies also having the CRP ranges between 6-20 mg/dL. From our study, it was observed that mild and moderate levels of leucopenia restrain sepsis babies 43 and 29 respectively belongs to the CRP level between 6-20 mg/dL. Similarly, platelet count with normal and moderate range of sepsis 47 and 15 numbers respectively had the CRP level between 6-20 mg/dL.

Table 1: Baseline demographic characteristics of the neonates enrolled in the study

CHARACTERISTICS	NUMBER OF PATIENTS	PERCENTAGE (%)
SEX		
Male	65	54%
Female	55	46%
GESTATIONAL AGE		
Term	60	50%
Near-term	26	21.6%
Pre-term	34	28.3%
BODY WEIGHT		
NBW	56	46.6%
LBW	60	50%
VLBW	4	3.33%
CLINICAL FEATURES		
Reduced sucking	49	40.83%
Respiratory Distress	42	35%
Fever	26	21.6%
Yellowish discoloration	9	7.5%
Increased irritability	5	4.16
Lethargy	5	4.16
Convulsion	3	2.5%
Vomiting	1	0.83%

Figure 1: Distribution of Isolated Pathogens

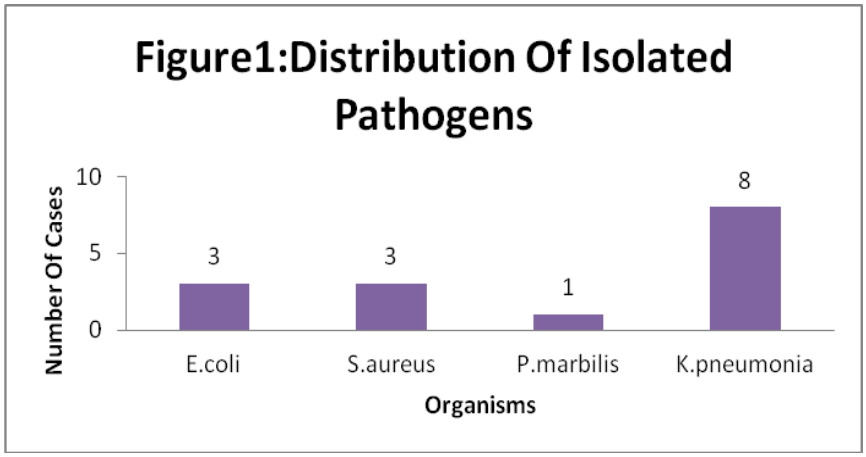


Table 2: Correlation of CRP with blood culture

BLOOD CULTURE	CRP (mg/dL)		
	0-5	6-20	>20
Positive	1	9	5
Negative	17	65	23

Figure 2: Anti-biotic Usage

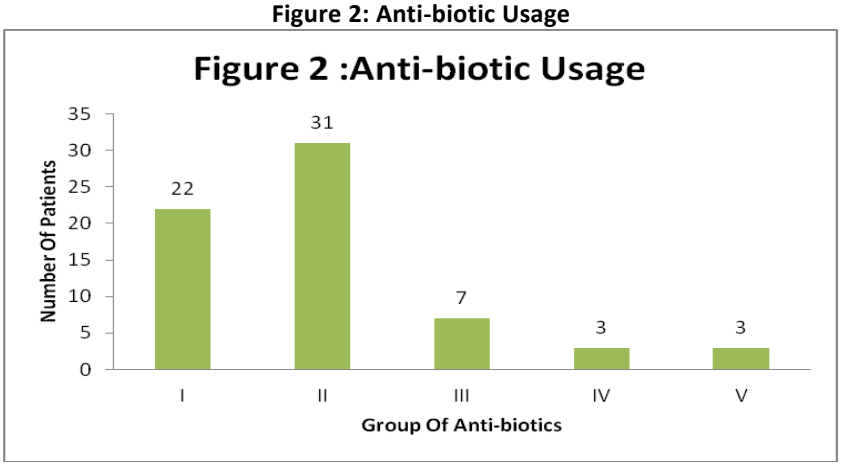


Table 3: Shows the Rubarth's scale score and CRP level.

Rubarth's scale score	CRP Level (mg/dL)		
	0-5	6-20	>20
10-15	12	2	0
>15	6	72	28
Chi-square test p- value	p< 0.001	p< 0.001	p< 0.001

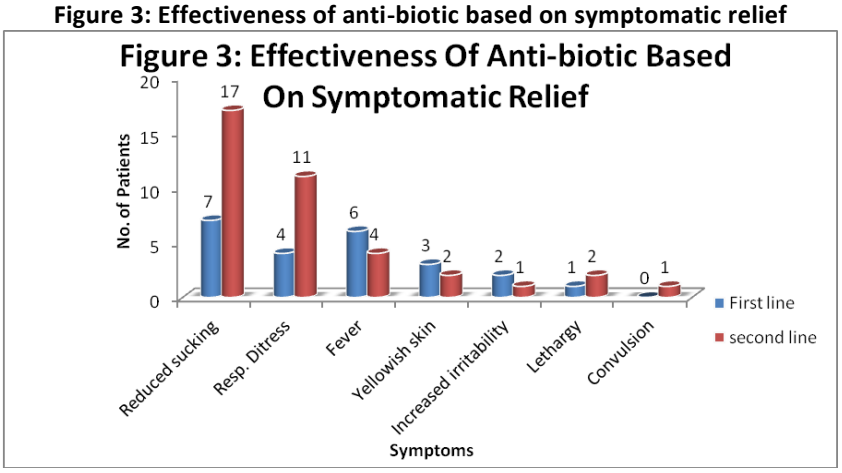
Table 4: Shows the Antibiotic Usage by The Patients

Anti-biotic	Number
Group I	22
Group II	31
Group III	7
Group IV	3
Group V	3

Table 5: Effectiveness of Antibiotic Based on Symptomatic Relief

Symptom	First Line	Second Line
Reduced Sucking	7	17
Respiratory Distress	4	11
Fever	6	4
Yellowish discoloration	3	2
Increased Irritability	2	1
Lethargy	1	2
Convulsion	0	1

Figure 3: Effectiveness of anti-biotic based on symptomatic relief



CONCLUSION

From our retrospective analysis, it was found that 31 numbers of sepsis cases (25.83%) were treated empirical therapy of Amipicillin + Gentamicin, followed by Cefotaxime + Amikacin. Secondly, 22 number of sepsis cases (18.3%) were treated empirical therapy of Ampicillin + Gentamicin combination alone. Around, 7 numbers of sepsis cases (5.8%) were treated empirical therapy of Cefotaxime + Amikacin combination alone. From our retrospective study, it was revealed that mostly second line empirical drug therapy like Ampicillin + Gentamicin followed by Cefotaxime + Amikacin were quickly decreased symptomatic relief comparably first line drug therapy (Ampicillin + Gentamicin).

Also 11 sepsis cases (9.16%) were decreased with complaint of respiratory distress. Only 7 sepsis cases (5.83%) were reduced with complaint of sucking while receiving first line drug therapy. Only 11 sepsis cases (9.16%) were reduced with complaint of respiratory distress while receiving second line drug therapy.

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