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# Comparative Study between C-Reactive Protein and Other Hematological Parameters in the Diagnosis and Treatment of Neonatal Sepsis in Term Neonates

***Dr. Haider M. Hussein Kufi[1], Dr. Oday Abdullhussein Abbood[2], Dr. Hussein Neamah Ubaid[3] and Dr. Ali Qais Abdulkafi[4]***

*[1]M.B.Ch.B. \ F.I.B.M.S. \ D.CH. \ (Pediatrics), Iraqi Ministry of Health, Karbala Health Directorate, Karbala Teaching Hospital for Children, Karbala, Iraq*

*[2]M.B.Ch.B. \ F.I.B.M.S. \ D.CH. \ (Pediatrics), Iraqi Ministry of Health, Iraq, Karbala Health Directorate, Karbala Teaching Hospital for Children, Karbala, Iraq*

*[3]M.B.Ch.B. \ F.I.B.M.S. \ D.CH. \ (Pediatrics), Iraqi Ministry of Health, Karbala Health Directorate, Karbala Teaching Hospital for Children, Karbala, Iraq*

*[4]M.B.Ch.B. \ D.C.H. \ (Pediatrics), Iraqi Ministry of Health, Kirkuk Health Department, Kirkuk General Hospital, Kirkuk, Iraq*

**Abstract:** Neonatal sepsis N. S. is one of the major causes of morbidity and mortality in neonates. The management of the N. S., especially in developing countries, is problematic. There is no single reliable marker of infection available at present. There are many attempts to develop screening tests or scoring systems that can identify infected infants at the time of initial assessment, sparing others from invasive diagnostic procedures, intravenous antibiotics therapy, mother-infant separation, and parental anxiety. The objective of the study is to analyze hematological parameters and C-reactive protein (CRP) so as to evaluate their diagnostic value in neonatal sepsis (N. S.) and determine the duration of antibiotics treatment in suspected N. S. A prospective study was performed in the neonatal care unit and general wards at Karbala Teaching Hospital for Children during a period from the first of November 2019 to the end of September 2020. (166) neonates with a clinical diagnosis of neonatal sepsis (patients group) and (50) neonates admitted or visited the outpatient clinic of the hospital for causes other than neonatal sepsis (control group) were enrolled in this prospective study and evaluated for a set of investigations including blood culture, CRP, White Blood Cell count (WBC), Absolute Neutrophil count (ANC), Platelets count, and Immature to Total neutrophil ratio (I/T ratio) was done for all patients group while single CRP was done for the control group. One hundred sixty-six neonates (patients' group) and 82 neonates (49.4%) had positive blood cultures. CRP was positive on the first day in 114 neonates (68.7%) and negative in 52 neonates (31.3%), while it was positive in 3 neonates of the control group. CRP had a sensitivity of (69%), specificity (of 94%), positive predictive value (of 67.5%), and negative predictive value (of 47.5%). The sensitivity of Platelets count, I/T ratio, and WBC were (30%), (27%) and (24%) respectively. A single negative CRP value does not exclude N. S., and two negative CRP values, 24 hours apart, can exclude the probability of N. S. and allow the pediatrician to discontinue treatments. N. S. with documented pneumonia necessitates prolonged antibiotics therapy, just like meningitis. Total W. B. C. count, ANC, Platelets counts, and I/T ratio have the lowest sensitivity in both cultures positive and culture negative N. S.

**Keywords:** Neonatal Sepsis, C-Reactive Protein, Staphylococcus epidermidis, Escherichia coli, Pseudomonas.

## INTRODUCTION

Infection is a frequent and important cause of morbidity and mortality in newborns and infants. The incidence of serious neonatal sepsis is uncertain. In developing countries, rates of bacteremia range from 1.7 to 33 and rates of clinical sepsis from 6.5 to 38 per 1000 live births, these rates of bacteremia are 3 to 20 times higher than in developed countries. Mortality rates range from 9-15% in developed countries and 30-45% in developing countries (Behrman, R. *et al*., 2007).

Neonatal infection is unique (Adams-Chapman, I. *et al*., 2001) Infectious agents can be passed from mother to fetus or neonate through different patterns. (S`Aez-Llorens, X. *et al*., 1993) Newborns are less able to respond to infection due to one or more immunodeficiencies. (Jafari, H.S. *et al*., 1992) Coexisting conditions often complicate the diagnosis and treatment of neonatal infection. (iv) Clinical manifestations of neonatal infection are varied and include subclinical infection, mild to severe manifestations of focal or systemic infection, and rarely congenital syndromes due to uterine infection. Timing of exposure, inoculum size, immunological status, and pathogen virulence affect disease expression. (Buttery, J. P, 2002)

Maternal infection that is the source of transplacental infection of the fetus during pregnancy, is often not diagnosed because the mother was either asymptomatic or had nonspecific signs and symptoms at the time of acute infection. (Kirsten, E. *et al*., 2005) A variety of pathogens infect the newborn, including bacteria, viruses, fungi, protozoa, and mycoplasmas. (Behrman, R.E. *et al*., 2007) Immature, very low birth weight (VLBW) newborns have improved survival but prolonged hospitalization in an environment that puts them at constant risk of acquired infection. A number of factors may affect a newborn in the womb, during





*Corresponding Author: Dr. Haider M. Hussein Kufi

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childbirth, or after birth. Intrauterine infections across the placenta of significance to the fetus and/or neonate include syphilis, herpes simplex virus (HSV), cytomegalovirus (CMV), hepatitis B (HBV), C viruses, parvovirus B19, varicella, HIV, rubella, toxoplasmosis, and tuberculosis (TB) (Behrman, R.E. *et al*., 2007).

The most common way these agents are transmitted is during childbirth during labor and delivery with passage through an infected birth canal (HSV, HIV, HBV) or after birth from contact with an infected mother or caretaker (TB). Any microorganism that inhabits the genitourinary or lower gastrointestinal tract of the mother may cause infections during childbirth or after childbirth. The most common bacteria are group B streptococci (GBS), Enterobacteriaceae, Gram-negative enterobacteria (especially Escherichia coli), Listeria monocytogenes, other streptococci (enterococci), anaerobes, Haemophilus influenzae, gonococci, and chlamydia. (McIntosh, N. *et al*., 2008; Lee, N.C. *et al*., 2004)

Fungal infection, most commonly Candida albicans, is a rare cause of neonatal sepsis and the incidence of invasive fungal infection is more in VLBW with a higher mortality rate of 41% (McIntosh, N. *et al*., 2008). Recent evidence suggests that perinatal sepsis is also important in the pathogenesis of neurodevelopmental impairment, infants born at term after maternal infection are nine times more likely to develop cerebral palsy than the control group. In preterm infants, sepsis is also associated with an adverse neurodevelopmental outcome. Infections distant from the brain may damage the brain's white matter, resulting in impaired neurological development. This study is a comparative Study Between C-Reactive Protein and Other Hematological Parameters in the Diagnosis and Treatment of Neonatal Sepsis in Term Neonates.

## PATIENTS AND METHOD

The study was conducted at Karbala teaching hospital for children, Karbala, Iraq, over eleven months period from November 2019 to September 2020. The study subjects included 166 neonates admitted in the special care baby unit (SCBU) and general pediatric wards with a clinical diagnosis of NS having either non-specific signs and symptoms or focal signs of infection, and 50 neonates (control group) admitted or visited the outpatient clinic for causes other than NS.

The neonates who had a congenital malformation, birth asphyxia, inborn error of metabolism, hemolytic jaundice, meningitis, those who had undergone surgery, gestational age <37 weeks, and weight < 1500 gm were excluded.

N. S. was suspected according to the following septic score, which included the following signs and symptoms such as refusal to feed, lethargy, feable cry, vomiting, diarrhea, excessive crying, jaundice, hypothermia, fever, apnea, tachypnea, cyanosis, poor capillary refill, abdominal distension, seizure, omphalitis, conjunctivitis, sclerema, and petechiae or bleeding diathesis. If the neonate had three or more than three of the above signs and symptoms, NS was suspected.

All patients group underwent a detailed history, complete physical examination, and relevant hematological, microbiological, and biochemical investigations to explore all possible sources of infection. Under strict aseptic measures, blood samples for culture and sensitivity were collected. 0.5-1 ml of blood was added to a bottle containing 10 ml of BHI broth.

The samples of blood were collected for complete blood count (CBC), including total WBCs counts, ANC, and Plts. Counts and I/T were performed manually on Leishman-stained blood smear. Serial serum CRP was done for all patients in the studied group and once in control groups. CRP value was estimated by latex agglutination method with CRP kit manufactured by Bioconn Diagnostic, Heke 8,34516 Vohl / Marienhagen, Germeny.

Cerebrospinal fluid examination and culture were performed in selected cases who had symptoms suggestive of meningitis, and those with findings consistent with meningitis were excluded from the study.

Serum random blood sugar (RBS) was done for all patients. Other investigations such as chest x-ray and swabs for culture and sensitivity when required.

Every patient was administered intravenous antibiotics, generally a combination of ampicillin and aminoglycoside (gentamicin) or 3rd generation cephalosporin (cefotaxime).

The parameters studied for NS screening and their cut-off value for positive tests were; CRP > 6 mg/dl, thrombocytopenia-platelet count < 150,000/mm, leucocytes indices including total WBC count<5000/mm or >20,000/mm, ANC-an age-adjusted normal reference range was used and



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neutrophilia and neutropenia were considered abnormal and (I/T) ratio >0.2 considered abnormal.

Positive blood culture was taken as the gold standard for the diagnosis of NS and was performed on all 166 patients having a clinical diagnosis of NS. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPP) of CRP were calculated.

## RESULTS

In the present study, 166 (90 male, 76 female) neonates admitted in BSCU and general wards with clinical features of N. S. (patients' group) and 50 (28 male, 22 female) neonates admitted or visited the outpatient clinic for other causes (control group) were investigated. Out of 166 sick neonates (patients' group),78 neonates (47%) were less than seven days old, 88 neonates (53%) were more than seven days, 68 neonates (41%) weighed 1501-2500 gm, 81 neonates (49%) weighed 2501-3500 gm, 17 neonates (10%) weighed more than 3500 gm. Twenty-three neonates (14%) had a positive previous history of hospital admission more in late-onset N. S.

**Table 1:** Shows the presenting symptoms of N. S. (N=166)

| Symptoms | NO. | % |
|---|---|---|
| Reluctant to feed | 152 | 91.5 |
| Lethargy | 143 | 86.1 |
| Feeble cry | 119 | 71.7 |
| Vomiting | 34 | 20.5 |
| Excessive crying | 18 | 10.8 |
| Diarrhea | 7 | 4.2 |
| Cough | 5 | 3 |

**Table 2:** Shows presenting signs of N. S. (N=166)

| Signs | No. | % |
|---|---|---|
| Rectal temp.< 35 for > 1hour | 75 | 45.2 |
| Tachypnea | 60 | 36.1 |
| Apnea | 55 | 33.1 |
| Cyanosis | 35 | 21 |
| Peripheral capillary refill > 3 sec. | 35 | 21 |
| Rectal temp.> 38 for > 1hour. | 32 | 19.3 |
| Jaundice > 15mg/dl | 16 | 9.6 |
| Omphalitis | 13 | 7.8 |
| Sclerema | 12 | 7.2 |
| Abdominal distension (ileus) | 11 | 6.6 |
| Petechiae or bleeding diathesis | 9 | 5.4 |
| Conjunctivitis | 9 | 5.4 |
| Heart rate > 160/min. | 7 | 4.2 |
| Seizures | 4 | 2.4 |

Blood cultures were positive in 82/166 cases (49.4%), 48/82 (58.5%) were male, and 40/82 (41.5%) were female. Table (3) shows the organisms isolated.





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**Table 3:** The organisms isolated from 82 blood culture positive neonr. Rates

| Organisms | No. | % |
|---|---|---|
| Staphylococcus epidermidis | 42 | 51.21 |
| Escherichia coli | 25 | 30.48 |
| Klebsiella | 4 | 4.87 |
| Pseudomonas | 4 | 4.87 |
| Group B streptococci | 4 | 4.87 |
| Staphylococcus aureus | 3 | 3.65 |

Out of 166 cases of the patient's group, CRP was positive on the first day in 114 patients (68.7%) and negative in 52 patients (31.3%), from which 9/52 patients (17.3%). CRP became positive on the third day. CRP was positive in 3 neonates (6%) of the control group.

**Table 4**: Hematological indices: Total W. B. Cs count in the studied group

| W.B.C counts | No. | % |
|---|---|---|
| < 5000 | 20 | 12% |
| 5000-10000 | 101 | 61% |
| 10000-20000 | 41 | 25% |
| > 20000 | 4 | 2% |

**Table 5:** Hematological indices: ANC in the studied group

| ANC | No. | % |
|---|---|---|
| < 1000 | 28 | 17% |
| 1000-2000 | 79 | 48% |
| 2000-4000 | 45 | 27% |
| >4000 | 14 | 8% |

**Table 6:** Hematological indices: Plts. Count in the studied group.

| Plts. count | No. | % |
|---|---|---|
| >150000 | 136 | 82% |
| 100000-150000 | 10 | 6% |
| 50000-100000 | 7 | 4.25% |
| 20000-50000 | 7 | 4.25% |
| <20000 | 6 | 3.5% |

Out of 166 cases of the patients' group, CRP was negative on the first and third day of treatment in 52/166 patients (31.3%), in 9/52 patients (17.3%), CRP was negative on the first day and positive on the third day. In 19/166 patients (11.5%), CRP was positive in the first day and negative on the third day; in 45/166 patients (27%), CRP was positive in the first day and negative on the seventh day, in 31/166 patients (18.5%) CRP was positive on the seventh day and negative on the tenth day, in 12/166 patients (7.25%) CRP positive on the tenth day and negative on the fourteenth day, while only 7/166 patients (4.24%) CRP was positive up to the fourteenth day and became negative in 2 cases on the sixteenth day, 4 cases on eighteenth and 1 case on the twenty-first day, 5 of the last seven had pneumonia diagnosed by chest x-ray, and other two died.

**Table 7:** Duration of treatment in days according to the result of CRP (- or +)

| Days of treatment | | | | | | NO. | % |
|---|---|---|---|---|---|---|---|
| 1 | 3 | 7 | 10 | 14 | >14 | | |
| - | - | | | | | 43 | 26 |
| - | + | - | | | | 9 | 5.5 |
| + | - | | | | | 19 | 11.5 |
| + | + | - | | | | 45 | 27 |
| + | + | + | - | | | 31 | 18.5 |
| + | + | + | + | - | | 12 | 7.25 |
| + | + | + | + | + | + | 7 | 4.25 |



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**Table 8:** Results of blood culture, CRP, and I/T in died patients (N=31)

| Results | No. Of positive cases(+) | No. Of negative cases(-) |
|---|---|---|
| Blood culture | 18 (58%) | 13 (42%) |
| CRP | 27 (87%) | 4 (13%) |
| I/T | 12 (38.7%) | 19 (61.3%) |

Thirty-one neonates/166 (18.6%) died of N. S. out of them, 18/31 (58%) were blood culture positive and CRP positive, while I/T was > 0.2 in 12 out of 31. Thirteen/31 (42%) were blood culture negative, 9/13 (69.2%) were CRP positive, and I/T < 0.2, and 4/31 (30.8%) were CRP negative and I/T < 0.2.

## DISCUSSION

In the present study, the male: female ratio was 1.24: 1, which showed male preponderance, the high susceptibility of males to sepsis is uncertain, but some theories explain the difference, that the factors regulating immunoglobulin synthesis may be on X-chromosome. Therefore, the presence of two X-chromosomes produces greater genetic diversity of female immunologic defenses (Makkar, M. *et al*., 2013).

The incidence was more in late-onset sepsis 88/166 (53%), while early-onset sepsis 78/166 (47%) in contrast with reports from other developing countries (Narasimha, A. *et al*., 2011; Terrin, G. *et al*., 2011), this may be due to nosocomial infections (poor antiseptic measures in hospitals, poor home care, poor hand washing, overcrowding, bottle feeding, and infected contacts).

Higher incidence of N. S., 81/166 (49%) in neonates weighed (1501-2500 gm), 68/166 (41%) weighed (2501-3500 gm) and 17/166 (10%) weighed > 3500 gm, also higher M. R 15/31 (48.5%) in neonates weighed (1501-2500gm), 11/31 (35.5%) in neonates weighed (2501-3500 gm), 5/31 (16%) in neonates >3500 gm, which is often due to low immunity, prolonged hospitalization, use of invasive procedures during resuscitation, fetal distress, perinatal asphyxia, jaundice and that risks associated with maternal infections, amniotic fluid problems, drugs, e.g., corticosteroids and others, this rate were higher in comparison with other countries researches (Prashant, A. *et al*., 2013; Ayazi, P. *et al*., 2014; Al-Zahrani, A.K. *et al*., 2015).

The most common symptom in the present study was reluctance to feed in 152/166 (91.5%) of the patients, followed by lethargy 143/166 (86.2%) and poor cry 119/166 (71.7%), which is similar to other studies done in the Karbala teaching hospital for children Zuhair, *et al*. and Guha, *et al*. (Mkony, M.F. *et al*., 2014)

Fever was not a prominent feature in our study, as demonstrated by other workers (Yang, A.P. *et al*., 2016; Lv, B. *et al*., 2014), while hypothermia was more common 75/166 (45.2% vs.19.3%), followed by tachypnea 60/166 (36.1%) and apnea 55/166 (33.1%).

The incidence of blood culture positivity was 82/166 (49.4%) in the present study, which is similar to other studies, Anwer, *et al*., 2000 has documented 42% blood culture-positive cases of N. S. (Vouloumanou, E.K. *et al*., 2011). Also, Aurangzeb, *et al*., 2003, has reported 55.8% culture-positive N. S and higher than other studies, Zeeshan, *et al*., 2005 and Arshad, *et al*., 2003 with the positivity of 28% and 25%, respectively. This variation in the positivity of blood culture results may depend on the criteria of the studied group, sample volume, sampling site, and different study populations. Although essential for diagnosis and appropriate management, blood culture results are not immediately available, and their yield is low and depends on skin disinfection, sample volume, and sampling site. (Hisamuddin, E. *et al*., 2015; West, B.A. *et al*., 2012)

Staphylococcus epidermidis was the commonest bacterial pathogen isolated in blood culture, 42/82 (51.21%); this high incidence could be a true sepsis or contaminant, 36/42 (85.7%) revealed positive CRP, so we can use CRP to differentiate a true staphylococcus epidermidis sepsis from contamination.

The second most common pathogen was E. coli (30.48%). The other pathogens are pseudomonas, GBS, Klebsiella, and staph. Aureus was 4.87%,4.87%,4.87%, and 3.65%, respectively, while GBS and E. coli are the two most common bacterial pathogens in term infants in the first 28 days of life (Moorman, J.R . *et al*., 2011; Whiting, P.F . *et al*., 2011; Abdollahi, A . *et al*., 2012).

Hajiehe, B. *et al*., 2008, has reported that klebsiella, staphylococcus aureus, and CONS were the common causal organism of proven neonatal sepsis



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Gram-positive cocci in Zamora, *et al*. and klebsiella in Misallatie, *et al*., papers were reported as the commonest organisms in N. S.

Anwer, S.K, *et al*., have concluded from their etiological study that gram-positive organisms, such as enterococci, staphylococcus aureus, and staphylococcus epidermidis, were the main cause of neonatal sepsis and klebsiella spp. is the commonest organism causing early onset N. S (Delanghe, J.R. *et al*., 2015).

It seems the prevalence rates for specific bacterial pathogens vary from one NICU to another and may change with time. Thus, the data about most commonly isolated bacteria in NICU must be periodically reviewed and antibiotic policy revised according to the susceptibility of these organisms.

In this study, CRP had sensitivity, specificity, PPV, and NPV of 69%, 94%, 67.5%, and 47.5%; respectively, these figures were 79%, 85%, 36%, and 97% in Hajiehe, B. *et al*., 2008 study which shows a clear difference in PPV (67.5% vs. 36%), while Nuntnariamit, P. *et al*., who observed that sensitivity, specificity, PPV and NPV of CRP were 100%, 94%, 91.6%, and 100% respectively for detecting proven sepsis and localized infection.

Santana, *et al*., reported 80% sensitivity and 92% specificity for CRP, which is in the line with the present study, while an Australian study has documented 67% sensitivity and 86% NPV of CRP in the diagnosis of neonatal sepsis

The discrepancy in sensitivity, specificity, PPV, and NPV in different studies may be due to different methods of CRP estimation and/or variation in the criteria of the positivity of the test (cut-off value) with respect of the number and timing of sample collection.

CRP was negative in 52/166 (31.3%) neonates on the first day and became positive in 9/52 (17.3%) on the third day of admission, which means that single negative reading on the first day of admission does not exclude the diagnosis of N. S., which is similar to the suggestion of Chiesa, C. *et al*., [(62)] and the study of Garland, S.M. *et al*.

Antibiotics were stopped in 62/166 (37.5%) neonates by the third day, 54/166 (32.5%) neonates by the seventh day, 31/166 (18.5%) neonates by the tenth day, while 19/166 (11.5%) neonates required longer duration of treatment > 10 days, 16/19 (84%) had positive blood culture, suggesting that those with positive blood culture and positive CRP needed longer duration of antibiotics therapy which is in the line with the study of Jawsal, R. S. *et al*.

Five neonates were having pneumonia documented by chest x-ray, and their CRP remain positive > 14 days, which means that patients with pneumonia may have persistent CRP > 14 days which necessitates prolong treatment with antibiotics.

W.B.C. count was abnormal in 24/166 (14.5%) neonates with a sensitivity of 14.5%, which is not significant in predicting N. S.

Regarding ANC, after checking references of neutrophils count in neonates, the results were insignificant since the total W. B. C. count in the neonate is 5000-20000/$mm^3$ and neutrophils count is about 40%, i.e., 2000-8000/$mm^3$ and in this study, ANC was within this limit.

Platelet count was < 150000/mm in 30/166 (12%) neonates with clinical features of N. S. and sensitivity is (12%). Zeeshan, *et al*., 2005 has reported ANC, Platelets, and W.B. Cs with a sensitivity of 71.4%, 64.3%, and 39.3%, respectively, for proven sepsis.

The discrepancy in sensitivity of these parameters may be due to the severity of infection, age of the neonates, or criteria of the studied group, as thrombocytopenia is generally observed late in the N. S., and they were normal when the N. S. has been diagnosed.



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## CONCLUSIONS

Single negative CRP value does not exclude N. S. since false negative values can occur in preterm neonates, overwhelming sepsis, and the first 24 hours of N. S.

Two negative CRP values, 24 hours apart, can exclude the probability of N. S. allow clinicians to discontinue treatments, limiting unnecessary antibiotics exposure unless the baby is very sick.

Clinical sepsis with positive CRP can guide us not to miss any case of N. S. even with negative blood culture.

Serial CRP can have a role in the duration of antibiotics therapy in N. S.

N. S. with documented pneumonia necessitate prolonged antibiotics therapy, just like meningitis.

CRP has high sensitivity, specificity, and PPV in N. S.

Total W. B. C count, ANC, Platelets counts, and I/T ratio have low sensitivity in N. S.

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