

# Measurements of C-Reactive Protein for Successful Management and Follow-Up Treatment of Neonatal Sepsis and Nosocomial Infection

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## Abstract

**Objective:** To develop an optimal follow-up treatment for neonatal and nosocomial infections and to examine correlations between the C-reactive protein (C-RP) and platelets. **Methods:** A sample of 27 septic neonates and 14 non-septic neonates were selected for this study. The non-septic neonates served as a control group. Blood samples were collected from both groups and analyzed for bacterial contamination via blood culture, complete blood count (CBC), and C-RP, according to international laboratory standards. Blood collection and analysis were repeated every day during the follow-up treatments with antibiotics to evaluate the kinetics of C-RP. **Results:** Blood culture found *E. coli* and *Staphylococcus aureus* in the blood of the septic cases. Serum C-RP concentrations were at high levels (24 mg/dl) in the septic neonates and at normal levels (lower than 6 mg/dl) in the control group. Treatment with active antibiotics resulted in a drastic reduction of the C-RP values and helped to reach a normal level as in the control group. On the other hand, there were increases in the platelet levels as the C-RP levels decreased. This result indicates a strong negative association between C-RP and platelet levels in the septic group only. Statistical analysis shows significant differences between the mean C-RP serum concentrations of the sepsis and non-sepsis. **Conclusion:** blood culture, active antibiotics, and kinetic C-RP measurements during the medical follow-up treatment are strong driving parameters for the optimal and successful management of sepsis.

## Keywords

Blood Culture, Active Antibiotics, C-RP, Neonatal Sepsis

## 1. Introduction

Sepsis is a major cause of death in intensive care units [1]. Its early diagnosis and timely antimicrobial treatment are driving parameters for the improvement of nosocomial and neonatal septic cases [2]. Early diagnosis of sepsis may be a challenging element since inflammation may be caused by pathogenic microbes [3] and/or environmental factors [4] [5]. Currently, C-reactive protein (C-RP) is a widely used marker of inflammation. It is synthesized by liver cells in response to pro-inflammatory cytokines [6]. Concentrations of C-RP in blood are very low in healthy individuals but may rapidly be increased after induction of an inflammatory response associated with bacterial infections. This property makes C-RP an important marker to detect many inflammatory diseases. For instance, it has been used to predict human lung epithelial cells [7], impaired lung function [8], oxidative stress [9], bronchiolitis obliterans syndrome [10], pulmonary diseases [11], bronchial hyperresponsiveness [12], chronic obstructive pulmonary disease [13], lung cancer [14], asthma, [15] and neonatal sepsis [16].

Successful management of sepsis among neonates depends on the experience of the physicians, in many cases visual rating of patient features play a critical role in the medical treatment. In case of limited experience, physicians change the used antibiotics with different types to get successful management. This step may create antibiotic-microbial resistant species, or reduce patient immunity. Nevertheless, quantitative measures evaluating the optimal management of sepsis among neonates is not available. Furthermore, the abovementioned studies are limited for determining C-RP concentrations in the relationship with inflammation only without any follow-up and kinetic determinations during the medical treatment. Furthermore, a correlation between C-RP levels and CBC contents such as platelets and/or white blood cells (WBC) remains poorly investigated. The author of this study emphasized the importance of dynamic measurements of C-RP during medical treatment and follow-up of neonatal and nosocomial sepsis to some cases from the intensive baby care unit in the hospital of south Gaza and provided quantitative measures for the optimal managements.

## 2. Materials and Methods

### 2.1. Sample Size

The population of the sample size was calculated using Google sample size calculator (<http://www.raosoft.com/samplesize.html> 2018) in which the sample size are 41 septic neonates. All cases were recorded during seven months of the study period. The control group involved 14 sick neonates with physiological symptoms, such as jaundice who visited the hospital during the medical treatment of the groups. The septic cases were 14 nosocomial and 13 neonatal sepsis, in total 27 cases. Furthermore, the parents of the sepsis and non-sepsis cases were interviewed for data collection.

Cases of neonatal sepsis were characterized by signs and symptoms of infec-

tion with or without accompanying bacteremia in the first 72 hours of age. It encompasses various systemic infections of the newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis, and urinary tract infections.

On the other hands, case of nosocomial (hospital-acquired) or community-acquired and neonates usually present with septicemia, pneumonia or meningitis after 72 hours of age up to 28 days.

## **2.2. Observing Clinical Symptoms**

The clinical symptoms and signs of the cases were observed in accordance with international standards for septic cases [17]. The observed symptoms included baby skin color, baby activity, vomiting, urine, stool and feeding methods and amounts. These symptoms were recorded during 24 hours according to the internal method of the WHO [18].

## **2.3. Blood Collections and Analysis**

Five ml blood sample was collected every day from each case during the medical treatment which lasted in 8 days. The collected blood was used for complete blood count (CBC), C-RP, blood culture, and liver function test, in accordance with international laboratory measurements [19] using commercially available kits.

## **2.4. Antibiotic Microbial Response Tests**

Dose response relationships were conducted in the hospital laboratory in accordance with the international method [20].

## **2.5. Management and Medical Follow-Up of the Cases**

Three well qualified medical teams from the main hospital in Gaza were taking care of the medical requirements and follow up of the cases according to the international methods during 24 h.

Ethical issues: The study was approved by a local Ethical committee at ministry of health. Compliance with Ethical Standards was full filed and conflict of interest form was filled.

## **2.6. Statistical Analysis**

The study consisted of three groups. Nosocomial, neonatal and control group. Blood parameters such as HB, WBC, Platelets, and C-RP were measured every day. Means and standard deviation of blood parameters in each group were calculated using Excel program. The statistical analysis was conducted by the t-test to detect differences between C-RP and platelets of the sepsis and control groups. A p-value  $\leq 0.05$  indicates significant differences where further medical treatments and follow-up are necessary for the septic cases. In case of p-value  $> 0.05$ , no further medical treatment or follow-up is required, and patients can be released from the hospital.

The study was approved by the research committee of the Toxicology department at the Faculty of Science, the Islamic University-Gaza and by Helsinki Committee at the Ministry of Health. Consent form was obtained from the parents of the neonates.

### 3. Results

#### 3.1. Physical Feature of the Cases

The population size of the cases was 27 in which 14 of them are nosocomial infection cases and 13 neonatal sepsis cases. The control group was 14 non-septic neonates. The physical features of these cases are shown in **Table 1**. It is obvious that patients affected by nosocomial infection cases, neonate sepsis and the control group have different body weight, temperature, skin color, activity and different feeding modes. The gender distribution is not significantly different between the three groups.

**Table 1.** Physical features and clinical symptoms and signs. Values in brackets indicate % of the case under investigation.

Baby item	Nosocomial infection (n = 14)	Neonatal sepsis (n = 13)	Control group (n = 14)
Weight range (kg)	1.75 - 2.8	2.9 - 3.4	2.9 - 3.5
Temperature range (°C)	36 - 39	36 - 39	36.5 - 37.5
Gestational age (week)	32 - 35	33 - 36	38
Skin color	pink	cyanotic	normal
Male	8 (19.5)	7 (17.1)	9 (22)
Female	6 (14.6)	6 (14.6)	5 (12.2)
Baby activity	active	hypoactive	active
Nasogastric tube	+	+	-
Lung collapse	9 (22)	5 (12.2)	0
Cardiomegaly	3 (7.3)	1 (2.44)	0
Hepatomegaly	6 (14.6)	6 (14.6)	0
Heart beat	65 - 146	48 - 65	60 - 82
Jaundice	8 (19.5)	10 (24.4)	13 (31.7)
Blood culture	+	+	-
<i>Staphylococcus aureus</i>	00	13 (31.7)	0
<i>E. coli</i>	6 (14.63)	00	0
<i>Klebsiella spp.</i>	8 (19.5)	00	

### 3.2. Observed Clinical Symptoms

The observed clinical symptoms included a collapsed lung in which represents 22 and 12.2% in the nosocomial infections and neonate sepsis cases, respectively. On the other hand, the percentage of cardiomegaly was higher in the nosocomial infections than in neonate sepsis cases. Furthermore, the percentage of hepatomegaly is nearly equal in nosocomial infections and neonate sepsis cases. Additionally, the central nervous system does not show any abnormality in all cases. The heartbeats are in different ranges in the septic group and control group. The percentages of jaundice were 19.5%, 24.4% and 31.7% in nosocomial infections, neonate sepsis cases and the control group, respectively.

### 3.3. Kinetic Measurement of Blood Parameters during the Medical Treatment

Hemoglobin (HB), white blood cells (WBCs), platelets and C-RP concentrations in the nosocomial infections, neonate sepsis and control group are presented in **Tables 2(a)-(c)**. The nosocomial infection group showed normal blood parameters on the 1st day of medical treatment (on admission). On the 2nd day, HB and WBCs started to increase indicating microbial inflammation whereas platelets started to decrease. On the 3rd day, C-RP showed the highest measured value, 24, indicating extreme infection. Then, the medical treatment continued day by day until the C-RP value reached the lowest value suggesting the patient was free of the infection. Nonetheless, neonatal sepsis (**Table 2(b)**) shows high values of WBCs and C-RP and the lowest PLT value on the 1st day of hospital admission indicating early sepsis.

### 3.4. Antibiotic Microbial Response Tests

Blood culture detected three different microbes: *Staphylococcus aureus*, *E. coli*, and *Klebsiella spp.* The percentage of *Staphylococcus aureus* infection was zero and 31.7% in nosocomial infections and neonate sepsis cases, respectively. The percentage of *E. coli* and *Klebsiella spp.* infections was 14.63% and 19.5% in nosocomial infections, respectively, whereas none were found in neonatal sepsis cases.

### 3.5. Microbe Antibiotic Sensitivity Tests

Microbe antibiotic sensitivity tests showed that *E. coli* is sensitive to Amikacin, Ciprofloxacin and Gentamicin; *Klebsiella* is sensitive to Amikacin, Meropenem and Vancomycin; and *Staphylococcus aureus* is sensitive to Amikacin, Ciprofloxacin, Meropenem and Cefotaxime.

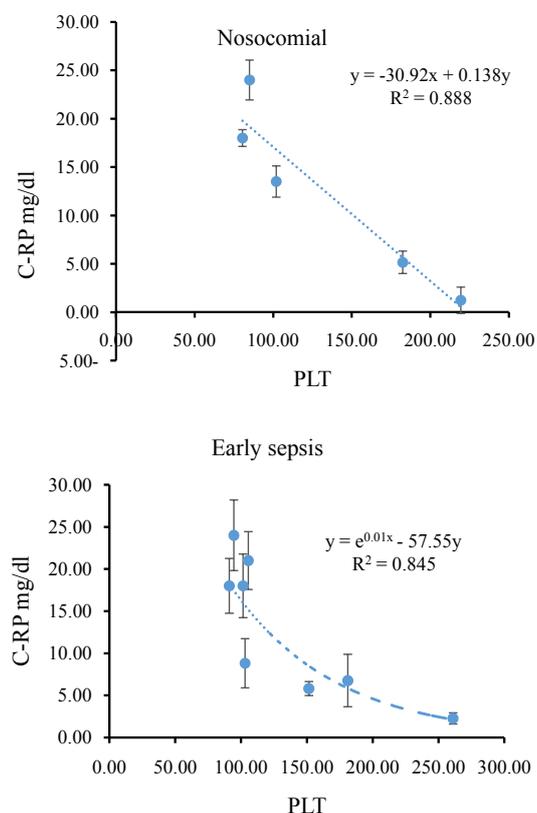
### 3.6. Management and Medical Follow-Up of the Cases

The medical treatment continued as mentioned above until the C-RP values were reduced to the lowest value using the antibiotics mentioned above. It is obvious by looking at **Table 2(b)** that the value of platelets is low at high C-RP values, and the value tend to increase at a low C-RP value. Comparing the data

in **Table 2(a)** and **Table 2(b)** with those in **Table 2(c)**, showing significant differences. This indicates that the blood parameters in **Table 2(a)** and **Table 2(b)** are higher than those in the control group (2C) indicating immediate medical treatments are required. Moreover, comparing blood parameters in **Table 2(a)** and **Table 2(b)** with those in **Table 2(c)** on the last day of medical treatment showing nearly similar parameters indicated effective follow-up and medical treatments. Statistical analysis showed significant differences between blood parameters in **Table 2(a)**, 1st day and those in **Table 2(c)**. Then, medical treatments continued until the statistical analysis showed a significant difference between the data in **Table 2(a)**, especially at the 5th day and the 8th day of **Table 2(b)**, and at the 5th day of **Table 2(c)**, indicated successful medical treatments. So far, a regression examining the values of C-RP and platelets reveals a strong negative association with the R2 values of nosocomial infections and neonate sepsis cases, which were in the range 0.846 - 0.889 (**Figure 1**).

**Table 2.** Blood parameters of nosocomial (2A), early sepsis (2B) and control group (2C).

(a)								
Parameter	Nosocomial							
	1st d	2nd d	3rd d	4th d	5th d			
HB (g/dl)	18.30 ± 0.57	18.65 ± 0.78	16.70 ± 0.28	14.85 ± 1.06	15.35 ± 0.78			
WBCs (k/ $\mu$ l)	13.40 ± 0.85	22.45 ± 17.75	17.30 ± 14.14	12.10 ± 8.34	12.95 ± 10.54			
Platelets (k/ $\mu$ l)	219.50 ± 5.59	85.00 ± 8.49	80.50 ± 3.61	102.00 ± 6.67	182.50 ± 4.75			
C-RP (mg/dl)	<6.00 ± 0.00	24.00 ± 0.00	18.00 ± 8.49	13.50 ± 6.36	5.15 ± 0.92			
(b)								
Parameter	Neonatal sepsis							
	1st d	2nd d	3rd d	4th d	5th d	6th d	7th d	8th d
HB (g/dl)	19.85 ± 4.31	17.05 ± 1.34	18.80 ± 0.28	19.25 ± 1.77	18.80 ± 0.42	19.25 ± 1.77	20.00 ± 1.41	19.30 ± 1.84
WBCs (k/ $\mu$ l)	37.15 ± 4.88	28.55 ± 9.12	27.85 ± 10.11	21.80 ± 1.27	18.45 ± 2.33	30.20 ± 6.79	23.70 ± 15.98	16.45 ± 6.29
Platelets (k/ $\mu$ l)	94.50 ± 17.28	105.50 ± 14.18	101.50 ± 15.59	103.00 ± 12.02	181.00 ± 12.87	91.00 ± 13.44	151.50 ± 3.44	261.00 ± 2.73
C-RP (mg/dl)	24.00 ± 0.00	21.00 ± 4.24	18.00 ± 8.49	8.80 ± 4.53	6.75 ± 7.42	18.00 ± 8.49	5.80 ± 0.28	2.25 ± 1.06
(c)								
Parameter	Control group							
	1st d	2nd d	3rd d	4th d	5th d			
HB (mg/dl)	16.12 ± 2.45	15.81 ± 1.51	16.73 ± 2.45	18.51 ± 0.45	16.63 ± 0.86			
WBC (k/ $\mu$ l)	18.23 ± 1.23	20.22 ± 3.34	23.12 ± 5.63	23.41 ± 6.42	21.00 ± 2.12			
Platelets (k/ $\mu$ l)	210.55 ± 21.64	250.60 ± 14.32	220.78 ± 8.94	197.98 ± 5.43	217.50 ± 21.65			
C-RP (mg/dl)	3.24 ± 0.11	2.80 ± 0.23	3.22 ± 0.87	2.11 ± 0.67	3.30 ± 0.44			



**Figure 1.** Dynamic relationship between C-RP and platelets concentrations in blood serum of sepsis cases.

#### 4. Discussions

The data in **Table 1** clearly show the physical and clinical features of nosocomial infections, neonatal sepsis cases and the control group on the 1st day of medical treatments. It is obvious that the body weight on patients with nosocomial infections ranged from 1.75 - 2.8 kg. The lowest body weight (1.75 kg) may be caused by the fact that the neonate was born at 32 weeks, several weeks before a normal gestational period (38 weeks). The body temperature of the groups ranged from 36°C - 39°C, suggesting the existence of hypothermia and hyperthermia among the groups. The skin color varied from pink to cyanotic. The activity was low in nosocomial infection cases and hypoactive in sepsis. Feeding was performed by nasogastric tube in all septic cases, whereas breastfeeding occurred within the control group. Furthermore, the chest suffered from lung collapse in nosocomial infections, whereas no wheezing was observed in cases of neonate sepsis or the control group. Additionally, cardiomegaly was observed in three cases, including one case in patients with nosocomial infections and two in patients with neonate sepsis. No cases were observed within the control group. Moreover, investigation of the abdomen showed a similar percentage of hepatomegaly in nosocomial infections and neonate sepsis. The heartbeats were in the range of 48 - 146 beats per minute. The quite low heartbeats may be due to the fact the sympathetic and parasympathetic nervous system are affected by the bacterial toxins in which

these two systems have tremendous effect on controlling the heart rate. It is well known in the literature that neonatal and nosocomial sepsis can decrease heart beats.

The percentage of jaundice in nosocomial infections was the lowest, whereas the highest percentage was found within the control group. In all cases, the central nervous system does not show any abnormal movement.

The explanation of these results is that patients with nosocomial infections and neonate sepsis were infected with *E. coli*, *Klebsiella* or *Staphylococcus aureus* (Table 1). These microbes produced toxins in the blood that disturbed the normal life of the baby. Moreover, the neonates were given antibiotics without performing a blood culture or C-RP measurement. It appears that *Staphylococcus aureus*, *E. coli*, and/or *Klebsiella* caused sepsis and septic shocks to many cases due to the toxins they produced on the hosting body. Our explanation agrees with Butt *et al.* [21] who found that *Staphylococcus aureus* and *E. coli* were a common causative agent of postoperative infections and puerperal sepsis. Nevertheless, gram negative bacilli were found in larger numbers in nosocomial indication than in neonatal sepsis probability due to the fact that *E. coli* can be found in contaminated drinking water and or food samples.

Furthermore, the mistaken medical treatment may result in antibiotic-resistant *Staphylococcus aureus*, which causes a major bloodstream infection with a high mortality rate among neonates. Additionally, a continuous high level of C-RP would have occurred (Table 2). Thus, C-RP values remain at high levels as long as the neonate receives ineffective antibiotics. This finding is in accordance with Jamsa *et al.* [22] who found high values of C-RP during sepsis. By performing blood cultures and microbial sensitivity tests, the neonates would have received effective antibiotics that reduced or stopped the growth of microbes. This would have caused the values of C-RP to be progressively reduced and platelets to increase. The right medical treatment helps the neonates and makes them active again where they are able to breastfeed instead of having a nasogastric tube for feeding. It is well known that neonatal sepsis remains an important cause of morbidity and mortality and requires prompt empiric treatment.

It can be suggested that neonatal septic cases should undergo blood culture for detecting the corresponding microbes, microbial-antibiotics sensitivity test and C-RP measurements during hospital admission time and the follow-up medical period. If the C-RP value is reduced during the follow-up treatment, the medical treatment goes in the right direction, and the neonate will successfully be saved. On the other hand, if the C-RP value remains higher than 6 mg/dl during the medical treatment, steps such as changing antibiotics and checking for multi-resistant microbes should be undertaken. During medical treatment, the blood parameters of the patients should be compared with the blood parameters in the control group (Table 2(c)) using statistical analysis to detect differences. If the p-value is above 0.05, this indicates that there are no significant differences between the control group and patients. If the p-value is equal or less than 0.05, this indicates that some blood parameter of the patient is still higher than in the

control group, and medical treatment is still required. Furthermore, the data in **Figure 1** show a strong negative association between C-RP and platelet values in the blood. Moreover, this figure supports the abovementioned discussion. So far, our discussion is in agreement with Kim *et al.* [23], who investigated the clinical and microbiological aspects associated with early patient mortality from methicillin-resistant *Staphylococcus aureus* bacteremia. Further support to our discussion comes from previous reports [24] [25] which investigated early recognition of methicillin-resistant *Staphylococcus aureus* surgical site infections, and revealed that there was positive consensus that sepsis, >2 weeks of hospitalization, was one of the major factors.

However, the presented results clearly demonstrate the effectiveness of blood culture, microbe-antibiotic sensitivity tests, and C-RP measurements as critical parameters for optimal and successful medical treatments.

## 5. Conclusion

Neonatal and nosocomial sepsis are extremely difficult cases. They need careful attention and a blood culture investigation to identify the microbes and its respective active antibiotics before any antibiotic is used in the septic cases. C-RP kinetic measurements show the effectiveness of medical treatments. It is strongly recommended to make a kinetic C-RP measurement during the follow-up treatment. In summary, blood culture identification, bacterial antibiotic activity and C-RP are important driving parameters in septic case treatments.

## Declarations

### Ethics Approval and Consent to Participate

Ethical approval of this study was obtained from the Research Committee of the Faculty of Science and Faculty of Medicine, The Islamic University Gaza.

### Consent Form

Consent forms were obtained from the father and mother of neonates.

### Availability of Data and Material

The datasets supporting the conclusions of this article are included within the article, can be available online after publication or under request to the authors.

### Author Contribution Statement

YZE designed the experiments and wrote the manuscript; ATA performed the experiments; MRA performed the statistical analysis. All authors reviewed the manuscript.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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### **Abbreviations**

HB: Hemoglobin;

WBC: White Blood Cells;

CBC: Complete Blood Count;

PLT: Platelets;

C-RP: C-Reactive Protein;

WHO: World Health Organization.