Original research:

Role of Hs CRP in sepsis spectrum-birth to 2 months

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Abstract: *C-reactive protein (CRP) is an acute-phase reactant protein of hepatic origin1 that increases following interleukin-6 secretion by macrophages and T cells. Its levels in the body rise or fall in response to various pathological and physiological conditions. CRP is used mainly as a marker of inflammation and infection. Measuring and charting CRP values can prove useful in determining disease progress or the effectiveness of treatments.* ***Aims and Objectives: 1.****To estimate of CRP in suspected infections at the time of admission and after 48hrs 2. Correlate CRP values with respect to suspected infection among children reporting in the Paediatrics/NICU; OPD and IPD.3.To find association of CRP levels with possible neonatal sepsis.* ***Material and Methods, Study Design****: It was a descriptive, prospective, observational, clinical, correlative study. STUDY SITE:*

The study was conducted at MGM Hospital, Kamothe and Kalamboli, Navi Mumbai. It's a tertiary care hospital situated at 50 kms from the city of Mumbai. ***Methodology:*** *Each paediatric patient who came to MGM Hospital was initially categorized according to age till 2 months of age. Neonates were graded according to the signs and symptoms of FIMNCI. FIMNCI considers bacterial infections in young infants when signs or symptoms of sepsis, pneumonia or meningitis are present.* ***Results:*** *A total 59 cases were enrolled in the study in which infection was suspected at the time of admission based on the category in IMNCI/FIMNCI for suspicion of infection. Out of these, 50 cases were successfully followed up to 48 hours as was aimed at the beginning of the study and 9cases failed to complete a 48 hour study period due to various reasons. Majority of babies had shown positivity in HS-CRP at admission (43/50) as well as after 48 hours (46/50). Neonates were further categorised in 3 groups depending on clinical improvement and fall or rise of Hs CRP level was studied. It was seen that Hs CRP levels have decreased in group which had shown clinical improvement, however in both other groups it was showing rise. We have calculated independent t-value also for each group and it was seen that* change *in Hs CRP values after 48* hours *was significant.* ***Conclusion:*** *The study revealed that Hs CRP levels were increased in all cases of suspected neonatal sepsis. They remained high in neonates who had deteriorated or remained same clinically at 48 hours of follow-up. However, they significantly reduced in neonates showing clinical improvement.*

Keywords: *C-reactive protein (CRP), Hs CRP, IMNCI, Neonatal sepsis,*

Introduction: C-reactive protein (CRP) is an acute-phase reactant protein of hepatic origin1 that increases following interleukin-6 secretion by macrophages and T cells. CRP is synthesized by the liver additionally in response to factors released by macrophages and fat cells (adipocytes). (1) Its levels in the body rise or fall in response to various pathological and physiological conditions. CRP is used mainly as a marker of inflammation and infection. Its production and corresponding levels in the body maybe seen abnormally low in certain cases like liver failure. There are only a few known factors that interfere with CRP production.(1) Interferon alpha inhibits CRP production from liver cells which may explain the relatively low levels of CRP found during viral infections compared to bacterial infections. CRP is the most sensitive of the acute-phase proteins, with levels rising as much as 1,000-fold during the acute inflammatory processes.1

Levels begin to rise within 4 to 6 hours of the onset of signs of infection or tissue injury and peak 24 to 48 hours later. They rapidly disappear as the infection or inflammatory process starts resolving.(2,3) CRP is a useful serum marker to assess and monitor the presence, severity, and course of the inflammatory response in infectious and non-infectious disorders, including acute myocardial infarction, angina, malignancies, rheumatoid arthritis, inflammatory bowel disease, burns and trauma, cancer and after surgical procedures.(4) Measuring and charting CRP values can prove useful in determining disease progress or the effectiveness of treatments. ELISA, immunoturbidimetry, nephelometry, rapid immunodiffusion, and visual agglutination are all methods used to measure CRP. A high-sensitivity CRP (Hs CRP) test measures low levels of CRP using laser nephelometry.(3)

Many researchers have evaluated serum CRP for its predictive value in identifying infants with suspected sepsis. A CRP level measured at the onset of signs of infection has an overall sensitivity between 35% to 94% and specificity between 60% and 96% in diagnosing sepsis. (5,6,7) These broad ranges reflect variations in the population studied and the definition of sepsis, as well as different evaluation strategies, differences in defining abnormal serum cut-off levels, various methods of measuring CRP, and the number and timing of samples collected. Each variation in approach can influence the sensitivity and specificity of CRP levels in identifying sepsis. The timing of CRP measurement(s) is critical to achieve the highest sensitivity. A single CRP level drawn early in the course of disease has a low sensitivity between 35% and 96% in detecting the presence or absence of infection because the sampling time may precede a measurable rise in CRP levels; this rise may lag 12 to 24 hours after the onset of symptoms. (8, 9, 10) A single CRP level, obtained at the onset of illness, lacks sufficient sensitivity to be useful in prospectively excluding the diagnosis of sepsis. (10) Russel compared serial band cell with CRP (11), Frank, has shown that there is significant reduction in use of antibiotics with use of CRP and Laborda has studied usefulness of cytokines and CRP in first 24 hours of life (12).

The present study is carried to ascertain usefulness of estimation of CRP with technologically better method called **High Sensitivity C-Reactive Protein** (Hs CRP) estimation, in the spectrum of infection, ranging from infection to septic shock. The age group included is from birth to 2 months of age. An effort has been made to correlate values of Hs CRP with respect to severity of infection. **Aims and**

Objectives: 1. estimate of CRP in suspected infections at the time of admission and after 48hrs 2. Correlate CRP values with respect to suspected infection among children reporting in the Paediatrics OPD and IPD.3.To find association of CRP levels with possible neonatal sepsis **Material and Methods Study Design**: It was a descriptive, prospective, observational, clinical, correlative study. **Study population**: All the children in this age group with suspected infection who came to M.G.M. Hospital Kamothe and Kalamboli including OPD and IPD, NICU were the source of data during period of February 2017-November 2017. **Inclusion criteria**: 1. Newborns and children upto 2 months of completed age and admitted in paediatric department. 2. Suspicion of possible infections in newborns as per IMNCI/FIMNCI criteria in children based on IMNCI and clinical judgment of infection (localized or without infection). 3. Admission to NICU/PICU/WARD for further evaluation. 4. weight of babies above 50 th percentile **Exclusion criteria:** 1. Newborns and children with definitive viral and fungal infections at admission. 2. Newborns and children with MODS at admission. 3. Children with known immunodeficiency, autoimmune disorders, trauma at admission or during 48 hours period. **Sample size:** A convenient sample size of 227 patients was enrolled in the study, based on admission rate in paediatric department with an expected dropout rate of 10% of the patients. STUDY PERIOD: The period of this study lasted from 1st May 2016 to 25th October 2017 i.e. over a period of approximately 18 months.

Study procedure: Institutional Ethical Committee clearance was obtained before starting the study. **Methodology:** Each paediatric patient who came to MGM Hospital was initially categorized according to age till 2 months of age. Neonates were graded according to the signs and symptoms of FIMNCI. FIMNCI considers bacterial infections in young infants when signs or symptoms of sepsis, pneumonia or meningitis are present.

For our study, following signs and symptoms were considered for possible infections in neonates to enrol patients:

- unable to feed
- fast breathing (RR >60/min) severe retractions
- lethargic or unconsciousness
- bulging fontanelle
- convulsions

- nasal flaring
- Grunting
- less than normal movements
- axillary temperatre 37.5 C or above; or less than 35.5 C
- Painful joints, joint swelling, reduced movements around a particular joint and irritability
- many skin pustules/ big boils
- Umbilical redness extending to the periumbilical skin or umbilicus draining pus
- Meningitis is considered in neonates if one or more of the following signs are present: drowsiness, lethargy or unconsciousness• persistent irritability• high pitched cry• convulsions• bulging fontanelle•apnoeic episodes

HS-CRP kit used: The following high sensitivity application was used for hsCRP testing. Highly Sensitive Application – Beckman Coulter AU400/400e /480, AU600/640/640e /680 (0.2 - 160 mg/L), AU2700/5400 (0.2 – 80 mg/L): The main ingredients of the machine were the 2 reagents (R1-Glycine buffer 100 mmol/L & R2-Latex coated with anti-CRP Antibodies < 0.5 %) and the other ingredients being preservative and normal saline. The R1 and R2 reagents used in the analyzer increase the accuracy of the system and helps in detecting extremely low quantities of CRP making it high sensitive CRP (Hs CRP) and making it superior to the conventional CRP. The CRP antibodies present in the serum of the patient's blood react with the antiserum-antibodies present in the reagents R1 and R2 to form immune complexes. These Immune complexes formed in solution scatter light in proportion to their size, shape, and concentration. Turbidimeters in the system measure the reduction of incidence light due to reflection, absorption, or scatter. In this procedure, the measurement of the rate of decrease in light intensity transmitted (increase in absorbance) through particles suspended in solution is the result of complexes formed during the immunological reaction between the CRP of the patient serum and rabbit anti-CRP-antibodies coated on latex particles.

- C-reactive protein specimens are stable for 11 days at 20 - 25°C and 2 months at 4 - 8°C in serum and plasma. For longer storage, freeze serum to -20°C. A total of 80 samples could be run simultaneously with a run-time of 30 minutes making it as competitive as the conventional CRP but being more sensitive at the same time. The dynamic range of the beckman coulter

helped us attain broad and more specific values of Hs CRP. This value was noted.

Work up done :• Patients were then managed according to the protocols of the NICU, PICU and ward.• Patients who failed to stay hospitalized for 48 hours (for various reasons like death, discharge against medical advice or discharged on request) were considered as dropout cases. • 48 hours after admission, the patient's clinical condition was reassessed and each patient was then graded again according to his/her then grade of sepsis. • 2 ml of blood was again collected from the corresponding patient in a plain bulb under all aseptic precautions. • The sample was then sent again to MGM Hospital, Kamothe central pathology laboratory in a collection boxes for CRP testing. This sample was labelled as the 2 nd Hs CRP sample. • It was run on the same machine to avoid technological bias. • The 2nd Hs CRP value was noted too. • Their details are discussed further under statistical analysis. • Correlation of the data of CRP quantitative values with respect to severity of sepsis was done

Statistical analysis: Data were entered in Microsoft Excel. We calculated the means and standard deviations (SDs) for continuous variables. We also estimated the proportions for the categorical variables. The means between three groups were compared using the unpaired t-test. We estimated the various SDs of the Hs CRP values at the time of admission and after 48 hours.

Study variables: There were certain factors which would affect the hsCRP value and the clinical condition of the patient. They were as follows: Type of infection: bacterial, viral, fungal, parasitic infections, grade of severity of sepsis, laboratory errors, associated immunodeficiencies, associated inflammatory conditions eg. thrombophlebitis, meconium aspiration in neonates, presence of CRP gene mutation.Study sample was considered for possible bacterial infection on basis of criteria by FIMNCI /IMNCI evaluation, so these variables were not important from statistical point of view.

Results: A total 59 cases were enrolled in the study in which infection was suspected at the time of admission based on the category in IMNCI/FIMNCI for suspicion of infection. Out of these, 50 cases were successfully followed up to 48 hours as was aimed at the beginning of the study and 9cases failed to complete a 48 hour study period due to various reasons. Reasons being death, transfer to other

hospital and change in consent. Out of 50 newborns studied, 27 were male and 23 were female babies. Clinical improvement was assessed by hemodynamic profile, absence of presenting complaint/s and ability to tolerate feed and absence of blood culture positivity of first culture.15 babies improved clinically, whereas 18 babies had almost similar clinical profile.17 babies showed clinical downward status in spite of starting empirical antibiotics and supportive treatment.

Surprisingly, majority of babies had shown positivity in HS-CRP at admission (43/50) as well as after 48 hours (46/50).Mean and median of all babies as shown in Table 2 was not conclusive about severity of infection and CRP values. It seems that Hs CRP is very sensitive indicator for neonatal sepsis.

Neonates were further categorised in 3 groups depending on clinical improvement and fall or rise of Hs CRP level was studied. It was seen that Hs CRP levels have decreased in group which had shown clinical improvement, however in both other groups it was showing rise.

We have calculated independent t-value also for each group and it was seen *that* change *in Hs CRP values after 48* hours *was significant.*

Discussion: In our study, we enrolled 59 cases out of which 205 cases were successfully followed up to 48 hours to find the correlation of Hs CRP with clinical condition of the patient.

Prior studies have associated acute increase in CRP (on the order of 10–200 mg/dL) as a marker of sepsis illness severity as well as predicted of sepsis outcomes.(3-12) For example, in a series of 50 critically ill sepsis patients, Schmit, et al. observed that CRP on admission was 16.7±10.6 mg/dL and that the magnitude of CRP decrease was associated with response to antimicrobial therapy (12) .

Povoa ,Schmit and colleagues continued their longstanding work on C-reactive protein (CRP) kinetics by evaluating the patterns of evolution of CRP in patients with severe community-acquired pneumonia (CAP).(13,14)

In a study conducted by LOBO SM et al., CRP is an acute-phase protein synthesized by the liver after stimulus by cytokines and its serum levels increase markedly within hours after the onset of infection, inflammation or tissue injury.

Decreasing plasma concentrations of this biomarker have been used as an indicator for resolution of infection or sepsis. (15)

Coelho et al. studied 891 intensive care unit patients with community-acquired sepsis, observing a mean hospital admission CRP level of 20.1±13.9 mg/dL and finding association between rates of CRP decline and hospital survival.(16)

A time-dependent analysis was performed and CRP ratios were calculated daily in relation to the CRP concentration on day 0, considered equal to 1. They showed that survivors of CAP had a continuous decrease of the CRP ratio during the first week of antibiotic therapy.(14)

Along with cases showing a clinical improvement in our study, 15 cases showed a fall in Hs CRP values after 48 hours. Hence a decreasing trend of Hs CRP was seen in majority of cases from admission to 48 hours of admission. *Only patients with severe sepsis failed to show a significant change in Hs CRP values i.e. 37.5%.*

The secretion of CRP begins within 4–6 h of the stimulus, doubling every 8 h and peaking at 36–50 h. With a very intense stimulus, the CRP concentration can rise above 500 mg/l, i.e. more than 1000 times the reference value (17,18). After disappearance or removal of the stimulus, CRP falls rapidly, as it has a half-life of 19 h . However, CRP can remain elevated, even for very long periods, if the underlying cause of the elevation persists. With the exception of severe hepatic failure, CRP rises whenever an inflammatory process is present; its serum concentration only depends on the intensity of the stimulus and on the rate of synthesis. The CRP level is independent of the underlying pathology and is not modified by any therapy or intervention such as renal replacement therapy . Only those interventions affecting the inflammatory process responsible for the acute phase reaction can change the CRP level.

In a study by Suprin et. al., mean values were 70 mg/l in systemic inflammatory response syndrome (SIRS) patients, 98 mg/l in sepsis, 145 mg/l in severe sepsis and 173 mg/l in septic shock, probably reflecting different degrees of inflammatory response .(17)

Our study also is similar values at admission, but as shown in above discussion it can be deduced that fall or rise documentation was not important in all groups and clinical acumen is more important. In fact, it is not worthy to prick the child frequently to show that child has deteriorated or improved.

Recent study by Nagwan I. Rashwan et al states that CRP could be a helpful prognostic marker in late onset neonatal sepsis. Hs CRP and PCT have higher

diagnostic accuracy in neonatal sepsis in comparison to other studied markers. Both IL-6 and presepsin have equal diagnostic utility in neonatal sepsis, but presepsin could be helpful diagnostic marker in early onset neonatal sepsis.(19)

In a study for Evaluation of IL-6, CRP and Hs-CRP as Early Markers of Neonatal Sepsis by Purushothaman Ganesan et al in India it was concluded that IL-6 is a highly sensitive marker and CRP is a more specific marker for the diagnosis of neonatal sepsis. Hs-CRP is a less reliable marker. So, the combination of IL-6 and CRP are the better predictors of neonatal sepsis. However, the sample size of this study was only 40, so may have biased reporting. However, it is noteworthy that in this study, Hs CRP showed sensitivity of 90% and specificity of 32.86%.(20)

In extensive work done by William E. Benitz et al Serial Serum C-Reactive Protein Levels in the Diagnosis of Neonatal Infection, it was observed that Serial CRP levels are useful in the diagnostic evaluation of neonates with suspected infection. Two CRP levels < 1 mg/dL obtained 24 hours apart, 8 to 48 hours after presentation, indicate that bacterial infection is unlikely. The sensitivity of a normal CRP at the initial evaluation is not sufficient to justify withholding antibiotic therapy. The positive predictive value of elevated CRP levels is low, especially for culture-proven early-onset infections. This was very old study of 1998 and since now Hs CRP has altered the values but principle remains same. (21)

In our study also similar results are found and it can be concluded that serial Hs CRP may not be helpful if it is already high initially.

Conclusion: The study revealed that HS CRP levels were increased in all cases of suspected neonatal sepsis. They remained high in neonates who had deteriorated or remained same clinically at 48 hours of follow-up. However, they significantly reduced in neonates showing clinical improvement.

Tables:

Table 1: Clinical characteristics and values of HSCRP

Parameter		
Sex	27/23	
Clinical condition after 48 hr	Improved	15

	Same Deteriorated	18 17
Positive /neg on admission	43/7	
POSITIVE /NEG after 48 hr	46/4	
At admission / 48hrs(n=50)	 Mean Mode median	 59.80/63.9 37.7/73.3 55.2/60.1
Standard deviation (admission /48hours)		36.36/25.02
hsCRP comparison against age Paired t-test value (p-value)		1.364 (0.179)

Table 2: Comparison of HSCRP in Same, Deteriorated &Improved group

	Mean At admission/48hours	Median At admission/48hours	
Same **Deteriorated** **Improved**	29.43/43.30 51.01/73.62 78.32/52.92	25.4/40.35 48.9/72 73.5/49.2	
Standard deviation (admission /48hours)	29.12/38.32	27.23/33.45	
Independent t value			
	Same	Deteriorated	Improved
Mean (rise/ fall)	Rise	Rise	Fall
Median (rise/ fall)	Rise	Rise	Fall
Standard deviation (rise/ fall)	Rise	Rise	Fall
Average fall /rise	Rise	Rise	Fall
change in hsCRP values after 48 hours	p- value 0.002	Significant	

Declaration:

Contribution of Authors: YY-Collection of data, **PR-** statistical analysis, VK-Concept of study, writing manuscript **-, RT-** revising manuscript**.**

Conflict of Interest: None

Ethical Approval: The study approved by the Institutional Ethics Committee

Funding: Self

What this study adds: *Hs CRP is really sensitive indicator of possible neonatal infection and average values are higher than CRP. Clinical condition based on IMNCI and values of Hs CRP correlate well. The degree of fall of Hs CRP also correlates well with clinical condition of improved. Possible there is no need to repeat Hs CRP at 48 hours.*

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Original Research:
High Risk Score for early referral of Newborns

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Abstract:

The delay in identification of seriously sick newborns is mostly