



ROLE OF C-REACTIVE PROTEIN IN CHILDREN WITH ACUTE FEBRILE ILLNESS

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ABSTRACT

A convenient definition of fever without source is the occurrence of fever for 1 week or less in a child where history and physical examination fail to reveal a probable cause of the fever. 70% of infection agent are of viral etiology, however the rest suggest the possibility of severe bacterial disease. CRP is the fastest reacting and most effective indication of an acute inflammatory reaction. 215 children between the age group 1 month to 12 yrs with acute febrile illness, admitted in our institute between 2017- 2018 were taken. The study was mainly aimed to determine the diagnostic value of quantitative C-reactive protein in children with acute febrile illness. Comparison of C-reactive protein with other clinical and laboratory predictors of infection.

KEYWORDS : Acute Febrile Illness, C Reactive Protein

INTRODUCTION

Fever is a common cause of childhood visits to the emergency department and pediatric opd¹⁻². Approximately 20% of febrile children have identifiable source of fever after history and physical examination^{3,4}. 2%-3% children have occult bacterial infection^{5,12}. Streptococcus pneumoniae, Listeria meningitis and salmonella occur in approximately 1.5% of relatively well appearing children between 3 - 36 months. Common infections in children include otitis media, upper respiratory tract infection, pneumonia, enteritis, Urinary tract infection, osteomyelitis and meningitis. Risk factors indicating occult bacterial infections are temperature 39°C or WBC count 15,000 ul or elevated ANC, blood count, ESR or CRP. Palpable conjunctivitis in a febrile patient may be a common sign of mumps, Tuberculosis, Infectious mononucleosis, Cat Scratch Disease, leptospirosis. Cytomegalovirus, Toxoplasmosis, syphilis presents with rash along with systemic symptoms. A complete blood cell count with differential WBC count and a urine analysis should be part of usual laboratory evaluation. It is an useful aid in preliminary differentiation between acute bacterial and viral infection with sensitivity and specificity ratio of 100% and 95%⁶. An ESR value of 30 mm/hr indicate the bacterial infection and need evaluation. CRP is the fastest reacting and most sensitive indicator of acute inflammatory reaction. However because of its low predictive value as per treatment based on WBC 15000, results in needing treatment in 85%-95% cases^{5,7}. Although antibiotic treatment is necessary for children with serious bacterial infection, it is also important to limit therapy to those children at greatest risk. Recent data suggestion that are ANC is a more accurate test in detecting occult factors^{8,9}, however the over all percentage of ANC in similar to that of WBC⁹.

MATERIALS & METHODS

- A prospective study was conducted between 1/6/2017- 31/8/2018. 215 children between the age group 1 month to 12 yrs with history of admitted to the pediatric ward of SREE GOKULAM MEDICAL COLLEGE and HOSPITAL were enrolled for the study. Detailed case sheet was written along with laboratory investigation which consists of Total WBC count, differential count, peripheral smear, ANC, serum CRP and CHEST X-RAY. CRP – 6mg/L was baseline. The children were divided in to 2 group having CRP positive and CRP negative. Statistical analysis was computed with SPSS software under the guidance of a statistician. For data analysis, Chi Square test, Mann-Whitney U tests and multiple Regression analysis were used. P value <0.05 was interpreted as significant statistical correlation. CRP ≤6 mg/L was considered as 6 mg/L for statistical feasibility
- Children were first divided in to 2 groups: **CRP positive** and **CRP negative**
- They were then divided in to the following groups and compared with positive CRP values.

Duration of fever: ≥7days <7days
Grade of fever: high low
Chills: present absent

Focus at admission:
 1) present 2) absent

Antibiotics received prior to admission:
 1) Received 2) Not received

Duration of antibiotics received prior to admission:
 1) ≥7days 2) <7days

Laboratory indicators of infection

Total leucocyte count:	Abnormal	Normal
Band count :	≥10%	<10%
Absolute Neutrophils :	≥10,000/mm ³	<10,000/mm ³
Cytoplasmic vacuoles :	Present	absent
Toxic granules:	Present	absent
Culture:	positive	Negative
Positive cultures :	Deep sites	Superficial sites
ESR:	≥30 mm	<30 mm
Duration of antimicrobial:	≥14days	<14days
Hospital stay:	≥14days	<14days

HEMATOLOGICAL ASSAY:

Total leucocyte count was measured using EDTA blood sample in an automated cell counter. Peripheral smear was studied by the hematologist for differential count and features suggestive of infection – toxic granules and cytoplasmic vacuoles. Band count and Absolute neutrophil count were obtained.

URINE ANALYSIS:

Freshly collected mid stream clean catch urine sample after >1 hr bladder stay was determined for protein and nitrites by Dipstick method. Urine was centrifuged and the smear was examined under microscope for WBC and quantified per high power field.

SERUM C-REACTIVE PROTEIN:

Was done using CRP Turbilatex of Agappe diagnostics and levels >6mg/dl were considered positive. Turbilatex method has high sensitivity and specificity.

PRINCIPLE OF TURBILATEX:

The reagent CRP-Turbilatex agglutination assay is a quantitative turbidimetric assay for measurement of CRP in human serum. Latex particles coated with specific human anti-CRP are agglutinated when mixed with sample containing CRP. The agglutination causes an

absorbance change, depending upon the CRP contents of the patient sample, that can be quantified by comparison from a calibrator of known CRP concentration. Value up to 6 mg/dl in serum is given a guide line as normal. ≤6 mg/L was negative CRP and >6mg/L was positive CRP.

CULTURES:

Cultures were sent when indicated. The various samples sent in this study were blood, urine, bone marrow, throat swab, stool, pus, skin scrapings, CSF, pleural fluid and sputum. All samples were collected and sent to the microbiology department under aseptic precautions.

BLOOD CULTURE:

Blood culture was collected by strict aseptic technique using freshly opened 2 ml disposable plastic syringe and fresh IV catheter after cleaning the overlying skin with spirit and povidone iodine. 1 ml of blood was inoculated into 10 ml of brain heart infusion biphasic media supplied in a screw capped bottle. Inoculated blood culture bottles were kept at the room temperature and sent to microbiology laboratory at the earliest.

URINE CULTURE:

Urine culture and sensitivity was sent when WBC >5 cells/hpf with or without the presence of nitrites. Mid stream clean catch urine was collected in a sterile container and sent for culture at the earliest. Contamination growth reported by the microbiologist was considered culture negative. As individual cultures were too small for statistical analysis, cultures were collectively classified as positive and negative and compared to the serum CRP values.

ESR:

Calculated by Westergren method and reported at the end of 1 hr.

CHEST RADIOGRAPHY:

Chest X-Ray was done when indicated. Findings were reported by the radiologist. Abnormal CXR finding was considered in the presence of infiltrates, consolidation, collapse, effusion, pneumothorax.

STATISTICAL ANALYSIS:

Statistical analysis was computed with SPSS software under the guidance of a statistician. For the data analysis, Chi Square test, Mann-Whitney 'U' tests and Multiple Regression Analysis were used. P value <0.05 was interpreted as significant statistical correlation.

RESULTS AND DISCUSSION

By Arranging the various patient characteristics at the time of admission the following had strategically significant correlation to positive CRP which include occult bacterial infections with fever greater than 7 days, presence of chills and systemic signs. These 3 components correlated well with CRP probably because they are associated with severe bacterial infection maximum sensitivity was observed with presence of chills (84.9%) with focus of fever at admission (55.1%).

215 cases were enrolled in the study.

TABLE-1: SHOWING AGE DISTRIBUTION (n=215)

AGE	NUMBER (n=215)	PERCENTAGE
1 month - ≤1 year	51	23.7
>1 - ≤3 years	63	29.3
>3 - ≤6 years	42	19.5
>6 - 12 years	59	27.5
Total	215	100

Mean Decimal Age: 4.9 years

Minimum: 0.2 years, Maximum: 11.7 years

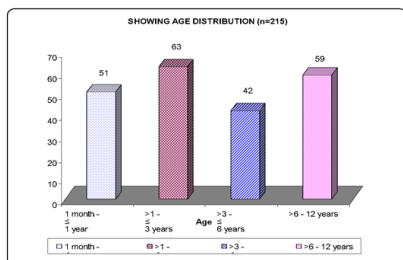


TABLE-2: SHOWING SEX DISTRIBUTION (n=215)

SEX	NUMBER (n=215)	PERCENTAGE
MALE	129	60
FEMALE	86	40

Ratio of males to females: 3:2

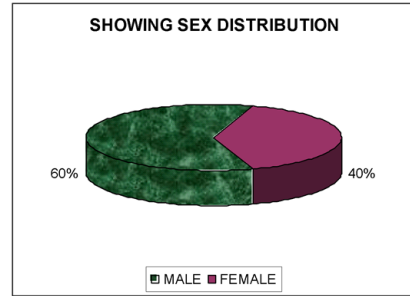


TABLE-3a: DISTRIBUTION OF CRP (n=215)

CRP	NUMBER (n=215)	PERCENTAGE
≤6.00 mg/L	89	41.3%
12.00 mg/L	28	13.0%
18.00 mg/L	47	19.1%
24.00 mg/L	18	8.3%
30.00 mg/L	02	0.9%
36.00 mg/L	31	14.4%

Median CRP value: 12 mg/L

Minimum: 6 mg/L, Maximum: 36 mg/L

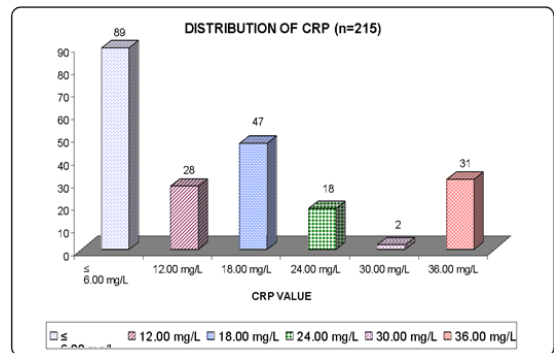


TABLE-3b: DISTRIBUTION OF CRP (n=215)

CRP	NUMBER (n=215)	PERCENTAGE
≤6.00 mg/L	89	41.3%
>6.00 mg/L	126	58.7%

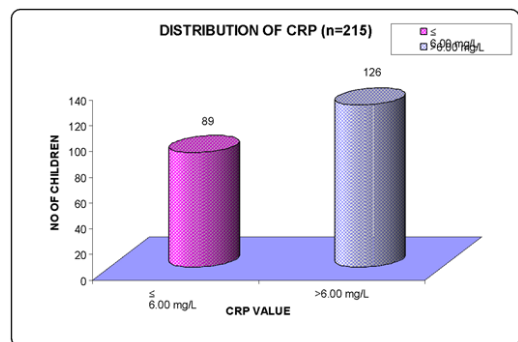


Table-4 Showing Correlation Of Different Patient Characteristics At Admission With Serum Crp

Patient Characteristics	Crp Positive (%)	Chi - square Value	P Value	Odds Ratio (95% Ci)	
Duration Of Fever (n=215)	≥7 days (n=105)	80 (76.2)	5.561	<0.05	4.45 (2.015-6.784)
	<7 days (n=110)	46 (41.8)			

Grade Of Fever (n=215)	High (n=132)	89 (67.4)	10.525	<0.01	
	Low (n=83)	37 (44.5)			
Chills (n=215)	Present (n=126)	106 (84.9)	18.657	<0.01	3.81
	Absent (n=89)	53 (59.5)			(2.112-8.015)
Focus Of Fever At Admission (n=215)	Present (n=167)	92 (55.1)	7.489	0.115	0.56
	Absent (n=48)	34 (70.8)			(0.309-1.139)
Antibiotics Received Prior To Admission (n=215)	Not received (n=130)	86 (66.2)	9.262	<0.05	2.24
	Received (n=85)	40 (47.1)			(1.221-3.625)
	≥7 days (n=19)	07 (36.8)			

Amongst the various patient characteristics at the time of admission, the following had statistically significant correlation to positive CRP:

1. Duration of fever ≥7 days
2. High grade fever
3. Presence of chills
4. No prior antibiotics

The first three correlated well with CRP probably because they were all associated with serious bacterial infections.

Maximum sensitivity was observed with presence of chills (84.9%) and least with focus of fever at admission (55.1%).

Amongst those who had received antibiotics, positive CRP was found in 60.7% with duration <7 days and 36.8% with duration ≥7days. The Odds ratio for the same was 2.63.

Those who had received antibiotics ≥7days had lower CRP probably because antibiotics tend to lower the CRP by controlling the infection. Amongst the parameters that correlated well with CRP, highest risk ratio (4.45) was observed with duration of fever ≥7 days and lowest risk (2.24) was found with treatment with antibiotics prior to admission.

Focus of fever at the time of admission did not show any statistical significance with CRP.

Table-5 Showing Correlation Of Different Laboratory Indicators Of Infection With Serum CRP

Laboratory Indicators Of Infection	Crp Positive (%)	Chi - square Value	P Value	Odds Ratio (95% Ci)	
Total Leucocyte Count (/mm ³)(n=215)	Abnormal (n=124)	84 (67.7)	4.661	<0.05	3.87 (1.054-5.288)
	Normal (n=91)	32 (35.2)			
Absolute Neutrophil Count (/mm ³) (n=215)	≥10,000 (n=120)	89 (74.2)	2.648	<0.05	4.50 (3.472-9.246)
	<10000 (n=95)	37 (38.9)			
BANDS (%) (n=215)	≥10 (n=128)	116 (90.6)	11.322	<0.01	9.54 (6.785-14.918)
	<10 (n=87)	29 (33.3)			
Toxic Granules (n=215)	Present (n=126)	86 (68.2)	17.359	<0.01	6.5 (1.902-8.957)
	Absent (n=89)	22 (24.7)			
Cytoplasmic Vacuoles (n=215)	Present (n=104)	75 (72.1)	14.661	<0.01	3.04 (1.727-5.245)
	Absent (n=111)	51 (45.9)			
Esr (mm/1 st Hr) (n=129)	≥30 (n=65)	46 (70.7)	3.920	<0.05	2.92 (1.345-6.129)
	<30 (n=64)	29 (45.3)			

All the laboratory parameters suggestive of infection listed below had statistically significant correlation to positive CRP:

1. Abnormal Total Leucocyte count
2. Absolute Neutrophil count ≥10000/mm³
3. Band count ≥10%
4. Presence of Toxic Granules in the peripheral smear
5. Presence of Cytoplasmic Vacuolations in the peripheral smear
6. ESR ≥30mm in the 1st hr
Band count ≥10% was observed to have highest risk ratio (9.54) as well highest sensitivity (90.6%) amongst all the other parameters.

ESR ≥30mm/1st hr had the least risk ratio (2.92) when compared with positive CRP. Least sensitivity (67.7%) was observed for abnormal total leucocyte count.

Our study found a sensitivity of 68.2% with toxic granules and 72.1% with cytoplasmic vacuolations. In a similar study done by [Seebach et al \(1997\)](#)¹⁰, morphological changes in neutrophils like toxic granules and cytoplasmic vacuolations had high sensitivity (80%) with CRP as comparable to our study.

In the same study band count cut off was taken as ≥20% and sensitivity (53%) found was low. In contrast the present study had a high sensitivity (90%) when compared to the present study (90%) when band count cut off was take as ≥10%

Table-6: Showing The Sensitivities Of Urine Analysis And Chest X-ray With Positive Crp

	Crp Positive	Sensitivity (%)	Odds Ratio (95% Ci)
Urine Analysis Significant For Infection (suspect Uti) (n=15)	11	73.3	2.34 (1.987- 5.490)
Abnormal Chest X-ray (n=171)	131	76.7	1.89 (1.005-2.667)

Table-7: Showing Correlation Of Culture With Crp

	Crp Positive (%)	Chi - square Value	P Value	Odds Ratio (95% Ci)	
Culture (n=181)	Positive (n=49)	38 (77.5)	0.999	>0.05	2.62 (0.429-8.113)
	Negative (n=132)	75 (56.8)			
Culture Positive Cases	Deep sites* (n=29)	24 (82.7)	4.469	<0.05	3.9 (2.625-5.466)
	Superficial sites** (n=20)	11 (55.0)			

Deep sites: blood, urine, stool, bone marrow aspirate, pleural fluid, CSF, pus from joints and bone, abscesses.

Superficial sites: pus from skin and subcutaneous tissue, throat swab, skin scrapings, sputum.

Though Positive CRP was found in a larger percentage of children who were culture positive compared to the culture negative group, this difference was statistically not significant. However, the difference between those who were culture positive for samples from deep sites and cultures from superficial sites was statistically significant.

Table-8 Showing Correlation Of Course Of Illness With Serum Crp

	Time Taken For Defervescence		Duration Of Antimicrobial Therapy		Hospital Stay	
	≥7 days (n=116)	<7 Days (n=99)	≥14 Days (n=108)	<14 Days (n=107)	≥14 Days (n=97)	<14 Days (n=118)
Crp positive	101 (87.1)	36 (36.3)	94(87.1)	32 (29.9)	76 (78.3)	50 (42.4)
Chi Square Value	17.546		19.368		15.542	

P value	<0.01	<0.01	<0.01
Odds Ratio (95% Ci)	15.7 (7.624 -18.312)	11.78 (4.155- 14.318)	4.92 (1.014- 7.593)

All the parameters listed below during the course of illness when studied, had statistically significant correlation with positive CRP:

1. Duration of therapy ≥14 days
2. Time taken for defervescence ≥7 days
3. Hospital stay ≥14 days

This implies that children with the above parameters probably had significant infections and hence had greater incidence of positive CRP results.

Table-9 Showing Outcome Of Patients With Crp Values

	OUTCOME	
	Recovered (n=207)	EXPIRED (n=8)
CRP POSITIVE	118 (57.0)	08 (100)
CHI-SQUARE VALUE	7.333	
p VALUE	<0.05	

Table-10 Showing Comparison Of Different Values Of Crp Versus Mortality

CRP VALUES (mg/L)	SENSITIVITY	SPECIFICITY
6	100%	0
12	100%	0
18	100%	58.9%
24	50%	79.7%
30	25%	87.0%
36	25%	87.9%

Mortality had a statistically significant correlation with positive CRP. CRP value with 100% sensitivity and highest specificity (58.9%) was seen at 18mg/L. Hence ≥18mg/L can be taken as a probable predictor of mortality.

Table-11: showing Various Laboratory Parameters With Cases Of Multiorgan Dysfunction Syndrome (mods) (n=18)

(n=18)	n	Sensitivity	Odds Ratio (95% Ci)	Odds Ratio (95% Ci) Combination Of Crp With Other Parameters
Crp Positive	17	94.4	6.15 (1.564-8.423)	-
Abnormal Total Leukocyte Count	14	77.7	4.31 (1.786-5.699)	9.42 (4.554-12.009)
Absolute Neutrophil Count ≥10000/mm ³	11	61.1	3.25 (2.338-4.564)	7.46 (3.444- 8.523)
Bands ≥10%	16	88.8	5.39 (2.456-8.768)	12.88 (9.076-15.786)
Toxic Granules Present	15	83.3	4.95 (3.451-7.653)	11.72 (9.543 -17.675)
Cytoplasmic Vacuolations Present	14	77.7	4.50 (1.093-7.774)	9.67 (4.532- 10.877)
ESR ≥30mm/1st hr	13	72.2	2.94 (2.087-8.630)	6.86 (2.336- 8.510)

18 cases had Multi Organ Dysfunction Syndrome (MODS). In this subgroup various laboratory parameters were compared and maximum sensitivity (94.4%) of was observed with CRP.

However in a similar study conducted by Flores et al (2003), CRP levels correlated neither with patient's survival nor with MODS⁴⁸ Band Count ≥10% and Toxic granules in the peripheral smear were

also good indicators with sensitivities of 88.8% and 83.3% respectively.

Risk ratios for each of them were computed and maximum risk (6.15) was found to be with positive CRP. Minimum risk (2.94) was with ESR ≥30mm/1st hr.

When the positive CRP was combined with other parameters and the risk ratio for each of these combinations were studied, maximum risk (12.88) was observed with a combination of positive CRP and Band count ≥10%. The next highest risk (11.72) was seen with combination of CRP and the presence of Toxic Granules.

Both these combinations are important an indicator of MODS and combination of two parameters has better risk predictability than a single parameter.

Median neutrophil count of 10,800/mm³ (Interquartile range of 4500-15,000/mm³) was found in our study. This was not comparable to the study conducted by Flores et al where median neutrophil count of 2100/mm³ (interquartile range: 891-6836/mm³) for patients with MODS.¹¹

Table-12 Comparison Of Fever With Convulsions Versus Crp ≥12mg/l (n=20)

	MENINGITIS POSITIVE	FEBRILE SEIZURES
CRP ≥12 mg/L	13 (100%)	1 (14.3%)
CRP <12mg/L	0	6 (85.7%)

Sensitivity: 100%, Specificity: 85.7%
20 cases of fever with convulsions in whom lumbar punctures had been performed were studied and analysed. CRP ≥12 mg/L at admission had a sensitivity of 100% and specificity of 85.7% and hence failed to miss any case of meningitis.

CONCLUSIONS

1. Serum CRP was estimated in 215 febrile children with male: female ratio of 3:2.
2. Amongst the patient characteristics at admission, duration of fever >7 days, high grade fever, presence of chills and those who had no prior antibiotics received had statistical significance with positive CRP (p<0.05).
3. Amongst the laboratory indicators of infection, abnormal total leucocyte count, absolute neutrophil count ≥10,000/mm³ and ESR ≥ 30mm in the 1st hr had statistically significant correlation with positive CRP (p<0.05).
4. When the peripheral smears were studied, band count ≥10%, presence of toxic granules and cytoplasmic vacuolations had statistically significant correlation with positive CRP (p<0.05).
5. All the parameters in the patients' course of illness: duration of antimicrobial therapy ≥14 days, time taken for defervescence ≥7 days, and hospital stay ≥14 days had statistically significant correlation with positive CRP (p<0.05).
6. Positive CRP was found to be having statistically significant correlation with the culture positive cases sampled from deep sites of the body and not for culture positive cases sampled from superficial sites.
7. CRP of 18mg/L is an important indicator of mortality with sensitivity of 100% and specificity of 58.9%.
8. Amongst the children with Multi Organ Dysfunction Syndrome (MODS) positive CRP had the maximum sensitivity (89.8%) and a maximum risk ratio (6.15) when compared to other laboratory indicators of infection.
9. The combination of Band Count >10% and positive CRP showed the maximum risk of MODS.
10. In cases of fever with convulsions CRP ≥12 mg/L did not miss any case of meningitis.

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