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C-REACTIVE PROTEIN AND ITS CORRELATION IN CHILDREN WITH ACUTE FEBRILE ILLNESS

Paediatrics

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ABSTRACT

BACKGROUND: Fever is a common cause of childhood visits to emergency departments (EDs) and pediatric offices. Approximately 20% of these children will have no identifiable source of fever after history and physical examination. children under 3 years of age are at increased risk of clinically undetectable serious bacterial infection (SBI). Approximately 2% to 3% of these children have occult bacteremia (OB). We sought to prospectively study the diagnostic properties of quantitative CRP in comparison with other clinical and laboratory predictors in children with febrile illness.

MATERIALS AND METHODS: 215 children of the ages of 1 month to 12 years with history of fever admitted to the Paediatric wards of Sri Venkateshwaraa Medical college Hospital and Research Centre [SVMCH] Puducherry were enrolled for the study.This is a hospital based prospective study,These children are subjected for the lab investigation along with the crp levels and correlation of crp with other lab parameters are tabulated

RESULTS: 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 ($p<0.05$).
CRP of 18mg/L is an important indicator of mortality with sensitivity of 100% and specificity of 58.9%.

CONCLUSION: 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 ($p<0.05$). When the peripheral smears were studied, band count ≥10%, presence of toxic granules and cytoplasmic vacuolations had statistically significant correlation with positive CRP ($p<0.05$). 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.

KEYWORDS

Acute febrile illness, Occult bacteremia, C-Reactive Protein and Blood culture

INTRODUCTION

Fever is a common cause of childhood visits to emergency departments (EDs) and pediatric offices.[1,2] children under 3 years of age are at increased risk of clinically undetectable serious bacterial infection (SBI). Approximately 2% to 3% of these children have occult bacteremia (OB).[5–7]

While 2% to 8% have urinary tract infection (UTI), depending on the age and gender.[8]

Other causes of serious bacterial infection include occult bacterial pneumonia (3%) [9], meningitis, or less commonly bone and joint infection, deep soft tissue abscess, or bacterial enteritis.

Although antibiotic treatment is necessary for children with serious bacterial infection, it is also important to limit therapy to those children at greatest risk.

Because the majority of febrile young children do not have serious bacterial infection, laboratory tests and expectant antibiotic therapy of these children adds to cost, time, discomfort, and parental anxiety and may contribute to antibiotic resistance.

Clinical observations alone lack the necessary sensitivity and specificity in detecting occult serious bacterial infection.[10]

Because it is clinically difficult to identify children with occult serious bacterial infection, a number of diagnostic and management strategies have been suggested, and the topic remains a source of considerable debate.

Some studies have suggested that acute phase reactants, including C-reactive protein (CRP) may be helpful in this clinical situation.[11–16]

We sought to prospectively study the diagnostic properties of quantitative CRP in comparison with other clinical and laboratory predictors in children with febrile illness.

However, Blood culture remains the gold standard in detecting occult bacteremia ; the average time for detection of positive cultures is 15 to 16 hours and may be as long as 24 to 48 hours[6,17] increasing the risk of complications.

AIMS AND OBJECTIVES

To determine

1. The diagnostic value of quantitative C-reactive protein (CRP) in children with acute febrile illness.
2. Comparison of C-reactive protein with other clinical and laboratory predictors of infection.
3. Correlation of C-reactive protein with grade of fever duration of illness and antibiotic usage.

MATERIALS AND METHODS

A Hospital based prospective study was conducted between 01.09. 2015 to 28. 02. 2017.

INCLUSION CRITERIA:

215 children of the ages of 1 month to 12 years with history of fever admitted to the Paediatric wards of Sri Venkateshwaraa Medical college Hospital and Research Centre [SVMCH] Puducherry were enrolled for the study.

EXCLUSION CRITERIA:

1) Children who were immunized within 2 days prior to admission
2) Children diagnosed to have autoimmune disorders
3) Children diagnosed to have immunodeficiency/ malignancies
4) Children already on steroids
5) Children discharged against medical advice during the course of treatment.

Details of the case were taken according to the proforma.

The following were obtained in all patients at admission:

1) Total WBC count and Differential WBC count
2) Peripheral smear for evidence of infection / sepsis

3) Band Count and Absolute Neutrophil Count.
4) Urine microscopy and nitrites.
5) Serum CRP, Cultures, Chest radiography and other investigations were obtained as per treating physician's discretion

DEFINITIONS[36]

1. **Fever**: Defined as ≥100.4°F (38°C) recorded in the axilla
2. **High grade fever**: ≥102.2°F
3. **Absent focus**: Fever with no detectable source.
4. **Normal WBC count:** 5000-11000/mm3
5. **Abnormal WBC count**: <5000 or >11000/mm3
6. **Band cells**: Young cells of neutrophil series belonging to Arneth Stage 1 having unlobed but deeply indented nucleus.
7. **Significant Band count** : ≥10%
8. **Absolute neutrophil count**: ([Neutrophil count + Band count] x Total leucocyte count) / 100
9. **Significant Absolute neutrophil count** : ≥10,000/mm3
10. **CRP Positive**: Values above 6 mg/L : 12, 18, 24, 30, 36 mg/L
11. **CRP Negative**: ≤6 mg/L
12. **Culture positive**: Microbiological growth of any organism in the culture medium under optimized conditions **(except Culture positive UTI : see below)**
13. **Suspect UTI**: ≥5 WBC/hpf in a centrifuged urine sample
14. **Culture positive UTI**: Growth of a single urinary tract pathogen > 10^5CFU/ml and/or nitrites positive
15. **High ESR** : ≥30 mm in the 1st hr by Westergren method
16. **Abnormal CXR**: Presence of infiltrates, consolidation, collapse, effusion, pneumothorax
17. **MODS (Multiorgan Dysfunction Syndrome):** Presence of altered organ unction that homeostasis cannot maintain without intervention.

ANALYSIS

- 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.

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.

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.

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

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

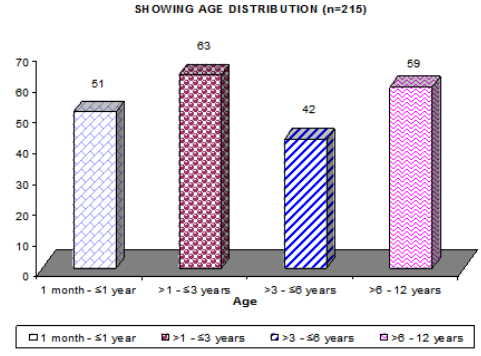

Table-2:showing Sex Distribution (n=215)

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

Ratio of males to females: 3:2

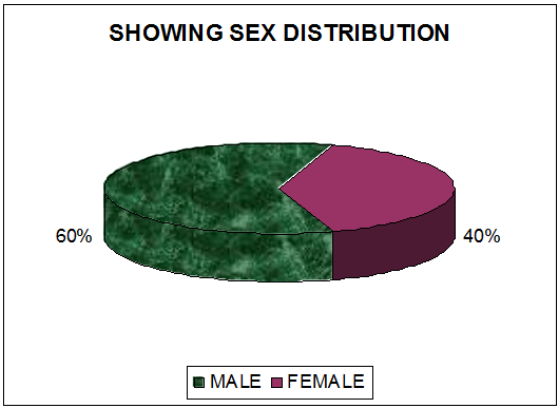

Table-3a: Distribution Of Crp (n=215)

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

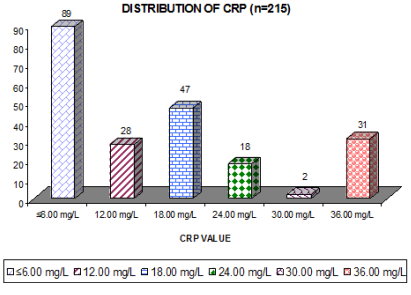

Table-3b: Distribution Of Crp (n=215)

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

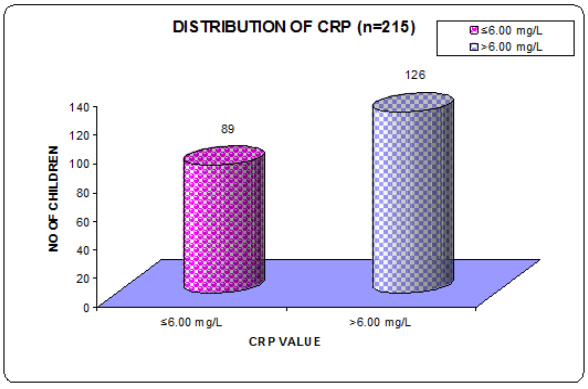

Table-4 Showing Correlation Of Different Patient Characteristics At Admission With Serum Crp

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	2.57 (1.426-4.335)
	Low (n=83)	37 (44.5)			
CHILLS (n=215)	Present (n=126)	106 (84.9)	18.657	<0.01	3.81 (2.112-8.015)
	Absent (n=89)	53 (59.5)			
FOCUS OF FEVER AT ADMISSION (n=215)	Present (n=167)	92 (55.1)	7.489	0.115	0.56 (0.309-1.139)
	Absent (n=48)	34 (70.8)			
ANTIBIOTICS RECEIVED PRIOR TO ADMISSION (n=215)	Not received (n=130)	86 (66.2)	9.262	<0.05	2.24 (1.221-3.625)
	Received (n=85)	40 (47.1)			
	≥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/1st 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.

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.

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.

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.
1. 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).

2. 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 ($p<0.05$).
3. When the peripheral smears were studied, band count ≥10%, presence of toxic granules and cytoplasmic vacuolations had statistically significant correlation with positive CRP ($p<0.05$).
4. 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 ($p<0.05$).
5. 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.
6. CRP of 18mg/L is an important indicator of mortality with sensitivity of 100% and specificity of 58.9%.
7. 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.
8. The combination of Band Count >10% and positive CRP showed the maximum risk of MODS.
9. In cases of fever with convulsions CRP ≥12 mg/L did not miss any case of meningitis.

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