

# Comparative study of procalcitonin versus c-reactive protein in the diagnosis of sepsis in children below 16 years-a single centre observational study

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## Abstract

**Introduction:** Given the limitation of non-specific nature of signs, symptoms and physical examination in diagnosing sepsis; especially in young children, a diagnostic marker that will aid in an early diagnosis is needed. Procalcitonin satisfies most of the criteria for smart biomarker of sepsis. The present study is done to compare procalcitonin (PCT) with C-reactive protein (CRP) as a diagnostic marker of sepsis in children. **Materials & Methods:** A prospective observational study was done in the Department of Paediatrics, ASRAM Medical College and Hospital, Eluru from July 2015 to June 2016. Children admitted to PICU during the above tenure are included in the study. Specific inclusion and exclusion criteria are formulated with a sample size of 100. Procalcitonin level is analyzed by enzyme linked immunoluminometric assay using Elecsys Brahms PCT kit. CRP analysis is done using immunoturbidometry which is a quantitative method. **Results:** Out of 100 children 72 have sepsis. The mean procalcitonin level in children with sepsis is  $19.09 \pm 24.53$  ng/ml compared to  $0.34 \pm 0.49$  ng/ml in children without sepsis. In comparing sepsis with a sepsis, PCT (Cutoff value of 0.58ng/ml) have a better sensitivity (90.3%) and specificity (92.9%) than CRP (Cut off value of 0.7mg/dl) sensitivity of 87.5% and specificity of 57.1%. **Conclusion:** PCT offers better sensitivity and specificity than CRP, to differentiate sepsis from a sepsis. In febrile children PCT is a better diagnostic marker of sepsis than CRP.

**Keywords:** Biomarker, C-reactive protein, Procalcitonin, Sepsis.

## Introduction

Fever is the most common reason for visits to paediatrician. Given the limitation of non-specific nature of signs, symptoms and physical examination in diagnosing sepsis; especially in young children, a diagnostic marker that will aid in an early diagnosis is needed. The utility of a biomarker is enhanced if it reflects the severity of infection and progression of the disease as well as the effectiveness of therapy.

Blood culture is the gold standard but requires precious 48 hours and the positivity yield is low. PCT satisfies most of the criteria for smart biomarker of sepsis [1].

Procalcitonin, a polypeptide identical to prohormone of calcitonin is initially described as a potential marker of bacterial disease by Assicot et al[2]. When its elevated levels were reported in patients with bacterial infection, PCT became an important protein in the detection and differential diagnosis of inflammatory states [3].

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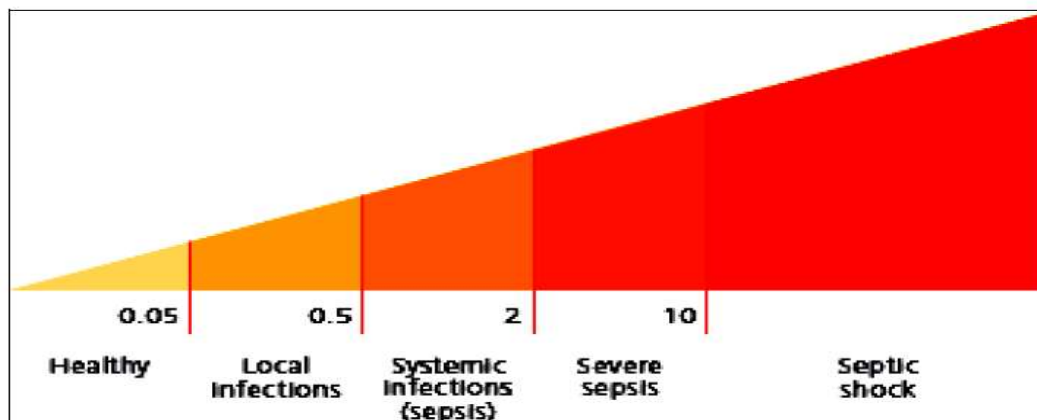
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### Cut off Values of Procalcitonin

Plasma PCT has a normal half-life of 25-30 hours and 30-45 hours in patients with severe renal dysfunction. PCT detectable in the plasma during inflammation is not produced by C-cells of the thyroid [3]. The probable sites of PCT production in inflammation are the neuroendocrine cells in the lungs or intestine. The expression of mRNA coding PCT



has been demonstrated in vitro in monocytes, stimulated by endotoxin or inflammatory cytokines [4]. PCT is not elevated by viral infections or autoimmune inflammation, or by the presence of neoplasm's [5]. Physiologically PCT can be raised in neonates up to 72 hours. Birth weight and gestation did not significantly affect normal PCT values [6].

Sequential measurements of procalcitonin have shown a rapid fall within 48 hours of antibiotic administration. An immunoluminometric procalcitonin assay is now commercially available (BRAHMS diagnostika) and values can be obtained within two hours of blood sampling.

Volanakis and Kaplan identified the specific ligand for CRP in the pneumococcal C polysaccharide as phosphocholine; part of the teichoic acid of pneumococcal cell wall. CRP, an acute phase protein involved in coagulation, acts as opsonin for gram positive bacteria to aid in phagocytosis. CRP is synthesized by the liver in response to and as a part of the inflammatory response. IL-6 is the major stimulus for production of CRP along with IL-1, TNF $\alpha$  [6]. CRP is synthesized within 6-8 hours of exposure to an infective process or tissue damage.

Its half-life is 19 hours and may show a thousand fold rise during an acute phase response. Serial measurements at 24 and 48 hours after the onset of illness considerably improve the sensitivity to 82% and 84% respectively [7]. Sequential measurements of CRP levels are helpful in determining the response to anti-microbial therapy and duration of treatment.

**Aims and objectives of the study:** To compare Procalcitonin (PCT) versus C-reactive protein (CRP) as a diagnostic marker of sepsis in children and to assess the utility of PCT as an early marker in diagnosis of sepsis.

### Materials and Methodology

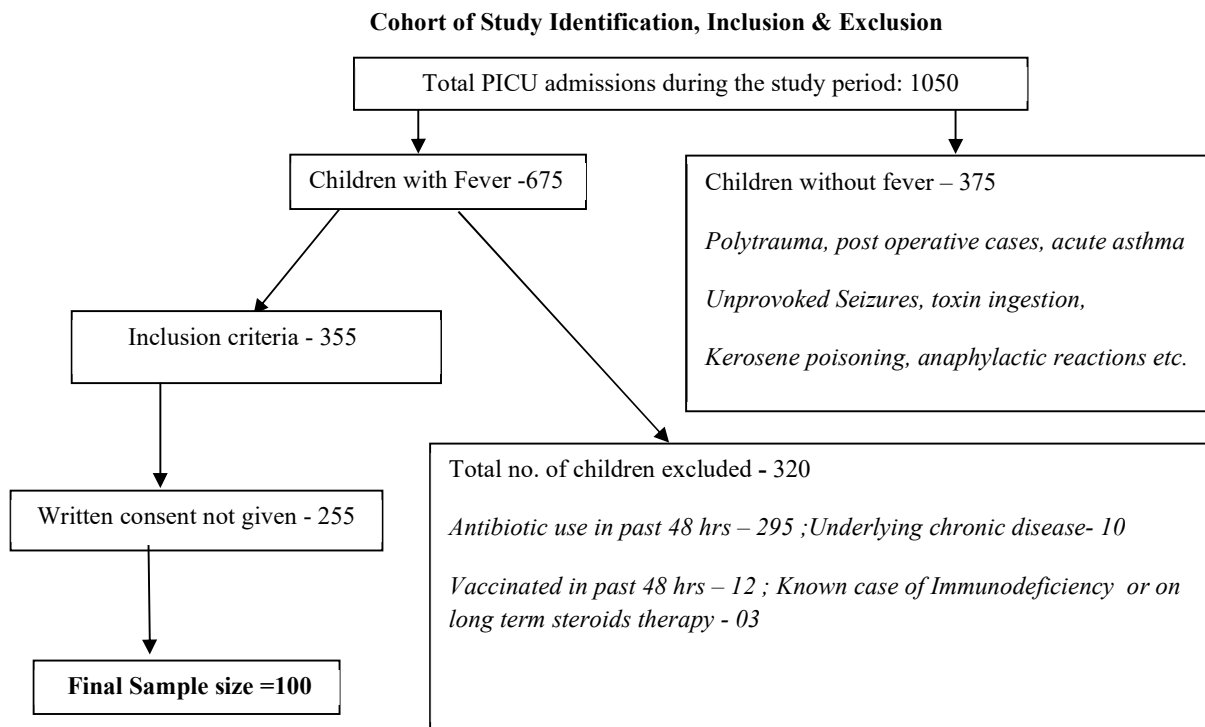
This is a prospective observational study done in the department of Pediatrics, ASRAM medical college and hospital, a tertiary care centre, Eluru, Andhra Pradesh. The study is conducted from August 2015 to September 2016 over a period of 13 months.

**Inclusion criteria:** Children less than 16 years of age admitted to PICU with rectal temperature of  $\geq 38^{\circ}\text{C}$ .

**Exclusion criteria:** Children treated with antibiotics and those who received vaccination in past 48 hrs. Known cases of chronic inflammatory disorder and immunodeficiency are also excluded.

**Sample size calculation:** Based on the mean and SD of previous studies [8,9] with an  $\alpha$  value of 0.05 and power  $(1-\alpha)$  of 0.8, a sample size of 100 is found to be adequate. Prospective cases were analyzed and data recorded. All children included in the study had fever. Those with symptoms and signs of sepsis are included in sepsis group and rest of the children with no signs and symptoms are included in a sepsis group.

Based on *International consensus definitions of paediatric sepsis* [10,11] children included in the study are divided into two groups - Asepsis and Sepsis. Children satisfying any of the criteria for definite or probable sepsis are included in the sepsis group and the rest are included in a sepsis group. After the Institutes ethical committee clearance and informed consent from the guardians, data collected is entered into a structured proforma.



Procalcitonin level analysis is done using enzyme linked immunoluminometric assay by using Elecsys BRAHMS PCT kit. Range: 0.02-100 ng/mL. CRP analysis is done using immunoturbidometry, with the minimal detectable concentration being 0.1mg/dl. Blood culture is done by Bactec-9050/Micro scan system. The data is analyzed using windostat version 8.6.

**Results**

**Age distribution:** In the present study around half of the study population is between 1-20 months of age and 72% of the subjects are under 5 years of age indicating that the most common age group with fever requiring PICU admission is < 5 years.

	Asepsis		Sepsis		P value
	Mean	SD	Mean	SD	
Age in months	35.82	+40.94	41.66	+47.02	0.564

**Frequency of age distribution among asepsis and sepsis**

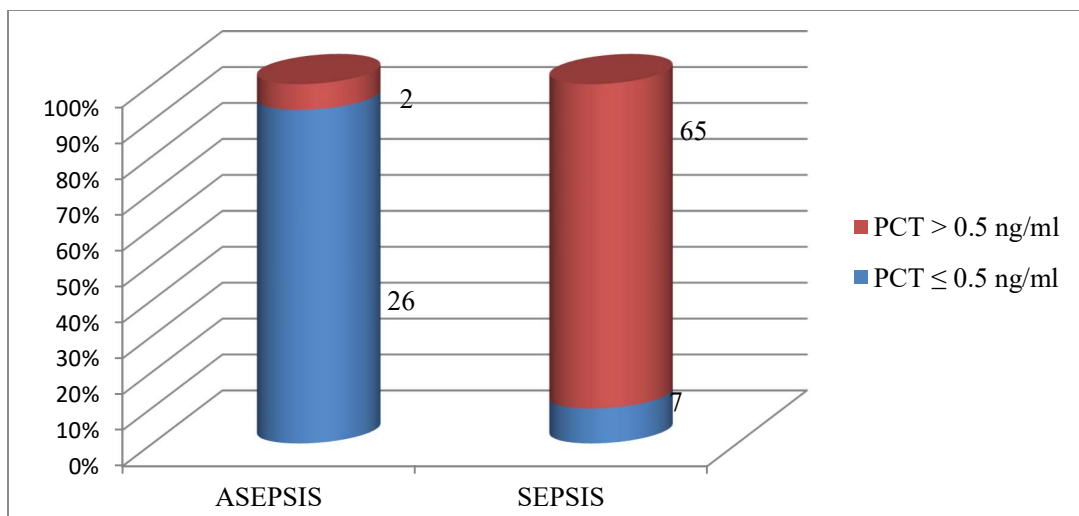
Using the student’s test for statistics, 95% confidence limits, it is found that there is no significant difference in the mean age distribution among two groups (sepsis and asepsis). (p = 0.564).

**Gender distribution:** Of the 100 children included in the study 57 are males and 43 females. The mean age in males is 32.5 ± 42.5 months. The mean age in females is 49.9 ± 47.2 months. In the present study significant difference does not exist in gender variation among two groups (p = 0.36)

**Procalcitonin:** According to our lab reference parameters, PCT ≤ 0.5 ng/ml is negative and PCT > 0.5 ng/ml is positive. Among 100 children in the study 33 are PCT negative and 67 are PCT positive. Range: 0.02 ng/ml - 100 ng/ml (mean 13.8 ± 2.8 ng/ml).

**Distribution of PCT among sepsis and asepsis:** Number of children with sepsis and asepsis are 72 and 28 respectively.

**Distribution of PCT among sepsis and asepsis.**



Among 28 patients with asepsis PCT is positive in 2 children (7%) and negative in 26 children (93%). Among 72 patients with sepsis PCT is positive in 65 children (90.3%) and negative in 7 children (9.7%).

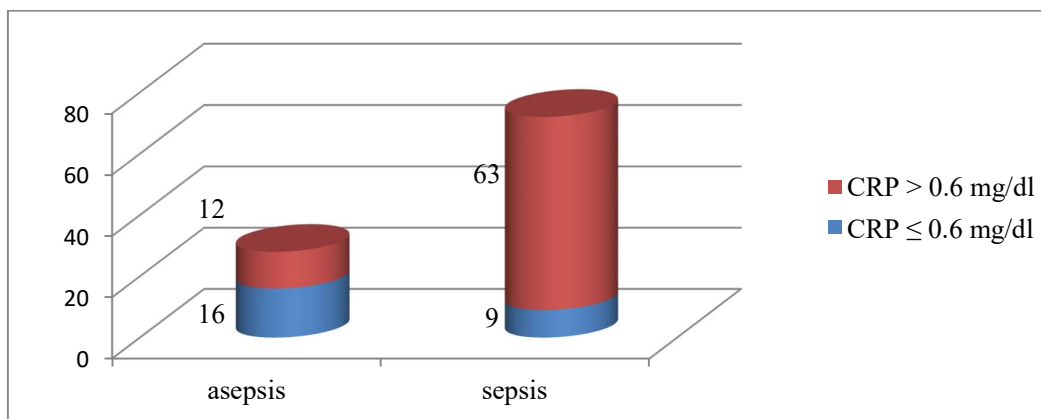
	Asepsis		Sepsis		P value
	Mean	SD	Mean	SD	
Procalcitonin	0.34	0.49	19.09	24.53	0.00011

The mean of PCT levels among asepsis patients is 0.34 ± 0.49 ng/ml and among sepsis patients it is 19.09 ± 24.53 ng/ml. Using the students test for correlation and 95% confidence interval, significant statistical difference is noted in levels of PCT measurements among two groups (p=0.00011).

**C- reactive protein:** According to our lab reference parameters, CRP ≤ 0.6 mg/dl -negative and CRP > 0.6 mg/dl-positive. Amongst 100 children 25 are CRP negative and 75 are CRP positive. Range: 0.2mg/dl -21.5mg/dl (mean-3.62mg/dl).

**Distribution of CRP among sepsis and asepsis:** Number of children with asepsis are 28 and sepsis are 72. Among 28 patients with asepsis CRP is positive in 12 children (42.8%) and negative in 16 children (57.1%). Among 72 patients with sepsis CRP is positive in 63 children (87.5%) and negative in 9 children (12.5%).

**Distribution of CRP among sepsis and asepsis.**



The mean ± SD CRP levels among asepsis patients are  $1.38 \pm 1.71$  mg/dl and among sepsis patients it was  $4.49 \pm 4.37$  mg/dl.

	Asepsis		Sepsis		P value
	Mean	SD	Mean	SD	
<b>C-Reactive Protein</b>	1.38	1.71	<b>4.49</b>	<b>4.37</b>	<b>0.00044</b>

Using the students’ t test for correlation and 95% confidence interval, significant statistical difference is noted in CRP measurements among two groups.(asepsis and sepsis) (p=0.00044)

**Relative sensitivity and specificity at different cut off values of PCT AND CRP:**

	Cut off value	Sensitivity (%)	Specificity (%)	PPV (%) Positive predictive value	NPV (%) Negative predictive value
PCT (ng/ml)	0.58	90.3	92.9	97.01	78.7
	1.2	75	92.9	96.4	59.09
CRP (mg/dl)	0.7	87.5	57.1	84	64
	0.9	80.6	60.7	84.05	54.8

ROC curve for PCT is constructed comparing children with asepsis and sepsis. These curves are used to identify cut off values and sensitivity and specificity. In comparing asepsis with sepsis the ROC area under the curve (AUC) for PCT is 0.92, a cut off value of 0.58ng/ml yielded.

ROC curve for CRP is constructed comparing children with asepsis and sepsis. These curves are used to identify cut off values and sensitivity and specificity. In comparing asepsis with sepsis the ROC area under the curve (AUC) for CRP is 0.75, a cut off value of 0.7 mg/dl yielded.

	Culture positive	Culture negative	p value
Mean PCT	$22.37 \pm 21.9$	$27.08 \pm 27.33$	0.61
Mean CRP	$5.10 \pm 3.52$	$5.33 \pm 5.37$	0.89

**Blood culture and sensitivity:** Of 72 patients with sepsis, blood culture is sent in 41 children, of which only 11 (26.8%) are positive.

As the blood cultures are sent in children with sepsis, mean values for PCT and CRP are high in both culture positive and culture negative cases. No significant difference in CRP and PCT values, in either culture positive or negative cases.

## Discussion

Interpretation of the literature dealing with Procalcitonin in children is complicated by the diverse age range and nature of the study population and variation in the choice of the cut off value of Procalcitonin.

**Age group:** Mean age of presentation in our study among asepsis and sepsis is 35.8 and 41.1 months; this age distribution corresponds to other study by Dominique Gendrel et al[12] with 2 subgroups with mean ages of 31.2 and 43.2 months. In a study by Corsino Rey et al [13] mean age was 43.2 months. In a study by Paolo Pecile et al.,[8] mean age was 19 months with 66% < 1 yr.

**Gender distribution:** In our study 57% are males and 43% are females. Study by Corsino Rey et al.,[13] included 59% males and 41% females. In the study by Paolo Pecile et al 69% are females and 31% are males.

**PCT and CRP measurements:** In the present study comparing asepsis with sepsis PCT had better sensitivity (90.3 vs. 87.5%), specificity (92.9 vs. 57.1%), PPV (97 vs.84%), NPV (78.7 vs. 64%) than CRP.

### Studies in children comparing PCT Versus CRP.

Reference	N	Age in months	Test	Sensitivity (%)	Specificity (%)	AUC(Area under the curve)
Fernandez Lopez[14]	445	1-36	PCT	91	94	0.95
			CRP	78	75	0.81
Andreola [15]	408	0-36	PCT	69	85	0.82
			CRP	84	75	0.85
Carrol et al[16]	108	1-192	PCT	94	93	0.96
			CRP	81	89	0.90
Vincenzo Maniaci et al[17]	234	0-3	PCT	96.7	30.3	0.82
			WBC			0.66
Paolo Pecile[8]	100	1-156	PCT	83.3	93.6	
			CRP	94.4	31.9	
Mark Hatherill [18]	175	0-193	PCT	100	62	0.96
			CRP	91	62	0.83

In a Meta analysis, Liliana Simon et al.,[19] evaluated the accuracy of determination of PCT and CRP levels for the diagnosis of bacterial infection. PCT level was more sensitive (88% vs. 75%) and more specific (81% vs. 67%) than CRP level for differentiating bacterial from non-infective causes of inflammation. On the basis of this analysis, the diagnostic accuracy of PCT markers was higher than that of CRP markers among patients hospitalized for suspected bacterial infections. In a study by Fernandez Lopez et al[14] the optimum cut off values suggested for detecting any bacterial infection was 0.53 ng/ml (sensitivity : 65% ; specificity: 94%; PPV : 96% ;NPV : 59% ). For detecting invasive bacterial infections was 0.59 ng/ml (sensitivity: 91.3%; specificity: 75 %; PPV: 69%; NPV: 81%).

A study by Mark Hatherill et al., [18]concluded that in critically ill children the admission procalcitonin concentration of 2ng/ml or more is a better diagnostic marker of infection than C reactive protein or leucocyte count. A study by Deis JN et al., [20] compared PCT with interleukin 6 and CRP, and found that IL-6 performed better than PCT which performed better than CRP.

## Conclusion

In febrile children admitted to paediatric intensive care unit the admission Procalcitonin concentration is a better diagnostic marker of sepsis than C - reactive protein. A PCT concentration of 0.58 ng/ml might be useful in differentiating sepsis in infants and children.

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