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A Study On Thrombocytosis As A Predictor Of Serious Bacterial Infection In Young Infants.

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ABSTRACT

Fever without focus in young infant is often a management challenge. The percentage of serious bacterial infection in this age group estimated around 20 – 25 %. The diagnosis of this SBI group often by blood culture. We hypothesize that the utility of platelet as a potential predictor of serious bacterial infection in young infants. To evaluate the ability of the platelet count as a predictor of serious bacterial infection in infants aged between 1month to 3 months of age. This is a hospital based prospective study done infant between 29 days to 89 days of life who are admitted in pediatric ward of Madurai Medical College with the fever axillary temperature of 100.4^0c. After getting informed consent history, examination, investigations like complete blood count, CRP, urine routine, blood culture were done. Depending on the clinical features CSF analysis, chest x-ray was done. Serious bacterial infection was defined as occult bacteremia, urinary tract infection, bacterial meningitis, pneumonia, bacterial gastroenteritis and bone, soft tissue, skin infections. Total study population taken was 140. Out of which 44 (31 %) diagnosed as a SBI. Thrombocytosis found in SBI population 65.9% VS non-SBI population 25%. The mean platelet count in SBI population was 5.4±1.3 and the non-SBI population was 3.7±0.5. The difference was statistically significant. ($p<0.05$). The combination of thrombocytosis (>4.5 lakh/mm^3), WBC count> 15,000/mm^3, CRP positivity, urine pus cells helps in identification of infants with SBI. Thrombocytosis in combination with other laboratory parameters like WBC count, CRP, presence of urine pus cells helps in detection febrile infants at risk of SBI.

Keywords: Thrombocytosis, Young Infants, Serious Bacterial Infection, fever.

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INTRODUCTION

The most frequent clinical condition that requiring medical attention by the pediatrician is fever. Febrile infants without localizing signs are challenge to evaluate because they display limited signs of infection making it difficult to clinically distinguish between a serious bacterial and self –limited viral illness [1]. The etiology and evaluation of fever without localizing signs depends on the age of the child. It is classified into the age group less than a month1month to 3 months and beyond 3 months to 36 months old. Fever without a focus-refers to a rectal temperature of 38°C (100.4°F) or higher as the sole presenting feature. The viral infections are more common than the bacterial infections [2]. The prevalence of bacterial infection said to be 20 percent to 25 percent of total febrile infants less than 90 days old [3]. Serious bacterial infection including bacteremia, urinary tract infection, meningitis, pneumonia and bone and soft tissue infections. Urinary tract infection is the most common serious bacterial infection [4]. E. coli is the most common pathogen identified. Other organisms are group B streptococcus, L.monocytogens, Salmonella enteritidis. Those infants who are suspected to have a serious bacterial infection should undergo detailed evaluation [5]. It is very difficult to define the serious bacterial infection by the single test. Laboratory markers which have been used to predict Serious bacterial infection include raised white blood cell (WBC) counts, C-reactive protein (CRP), procalcitonin (PCT) and even interleukin-6 levels [6]. WBC count, though easily available and used widely as a predictor of SBI, but it does not comparable with the markers of recent ones like PCT. Because of the widely available automated hematology analyzers the platelet count become more accurate now. Thrombocytosis is an elevation in the peripheral blood platelet count to values more than 4.5 lakh/mm3 [7]. Thrombocytosis percentage in pediatric population is 3% to 15%. 8Thrombocytosis in this age group most commonly due to infective etiology. The next most common cause of thrombocytosis in Indian pediatric population is iron deficiency anemia [8]. Chronic hemolytic state also associated with thrombocytosis. Primary thrombocytosis is young pediatric population is extremely rare. Infections of the respiratory, urinary and gastrointestinal tract and the bones and meninges are the most common causes of reactive thrombocytosis. Higher counts are more common in neonates and infants [9]. Platelets act like an acute phase reactant. During infections, release of interleukin-6 enhances megakaryopoiesis directly and indirectly by stimulating hepatic thrombopoietin [10]. However, the platelet count has not been evaluated as a predictor of SBI among febrile infants Hence the present study proposed to identify the simple test-presence of thrombocytosis which detect the serious bacterial infection in young infants with high predictive value and cost effectiveness.

MATERIALS AND METHODS

This Hospital based prospective study was done at paediatric ward of Institute of child health and research centre, Madurai medical college, Madurai in the year 2022.

Inclusion Criteria

Infants with 1 month to 3 months of life .Admitted with fever, (Axillary temperature > 38.5 degree C /101.4 degree F)

Exclusion Criteria

Infants who are treated with antibiotics prior to presentation. H/O recent vaccination. Infants with anemia. Infants on corticosteroid therapy and iron supplements.

All patients who fulfilled the inclusion criteria undergo sepsis evaluation including WBC count, platelet count, blood culture, urine microscopy and culture and serum CRP levels. Chest xray and CSF analysis based on clinical conditions. The WBC count with differential and the platelet count were done with hematology automated laboratory equipment (Sysmex KX 21). Blood cultures were monitored by an automated system (BacT/ALERT 3D). Urine was obtained by urethral catheterization using a sterile technique. The WBC in the urine were quantified by standard microscopic examination and expressed as WBC >5 per high power field (HPF) in centrifuged sample. The urine, CSF, Blood cultures were monitored using standard laboratory techniques. UTI was the diagnosis if a single known pathogen growth ≥1000 colony forming units (cfu)/ml of urine obtained by supra pubic needle aspiration or≥100,000cfu/ml of urine obtained by urethral catheterization. The presence of a focal infiltrate on chest radiograph with clinical findings diagnosed as pneumonia.[10]Bacterial meningitis was diagnosed by CSF analysis if a positive gram stain or culture, or all of WBC >100/mm3, polymorphonuclear lymphocytes >80, protein >200mg/dl,

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glucose <40mg/dl or ratio of CSF/blood glucose<0.4 [11]. Those getting diagnosed as serious bacterial infection were one group and those without were categorized as non SBI group.

Statistical Analysis

MS excel was used for data entry and was analyzed using computer software, Statistical Package for Social Sciences (SPSS) version 16. Non-parametric data are expressed as mean with standard deviation. For all statistical evaluations, a two-tailed probability of value <0.05 was considered significant.

RESULTS

Table 1: Profile Of Study Population (Age Wise)

AGE (days)	SBI	Non SBI	Total
29 - 60	16	31	47
61 - 89	28	65	93
Total	44	96	140
p value	0.779 Not significant		
chi square value	0.078		

Table 1: Of 140 infants 47 were in the age group of 29 days to 60 days old.(33%) , 93 were in the age group 61 days to 89 days old. (66%). Age determinant is not significant among SBI and non – SBI groups.(p value 0.078). Out of 140 infants, the number of male infants were 87(67%), and the female were 53 (37%). Sex determinant was not significant among SBI and non SBI groups (p value 0.0498).

Table 2: Symptomology Analysis

Symptoms	No Of Cases	Percentage
Respiratory symptoms	98	70%
Gastrointestinal symptoms	7	5%
No focus of infection	28	20%
Respiratory symptoms & CNS symptoms	7	5%

Table 2: Out of 140 infants, 98 of them were present with respiratory symptoms (70%). 28 cases were presented without focus of infection.(20%).7 cases were presented with gastrointestinal symptoms.(5%)

Table 3: WBC Count Vs Outcome

WBC	SBI	Non SBI	Total
<15000	24	93	117
>15000	20	3	23
Total	44	96	140
p value	< 0.001 Significant		

Table 3: Among the study population 16% showed the WBC count more than 15, 000.Out of 44 SBI cases, 20 cases had a WBC count > 15,000.(45%).In non-SBI population 3 cases were showed the WBC count >15,000(3%).The difference is found to be statistically significant (p value is <0.001)

Table 4: Platelet Count And Outcome

Platelet	SBI	Non SBI	Total
4.5 - 5Lakhs	7	24	31
5 - 8Lakhs	17	0	17
8 – 10 Lakhs	5	0	5
Normal count	15	72	87
Total	44	96	140
p value	< 0.001 Significant		

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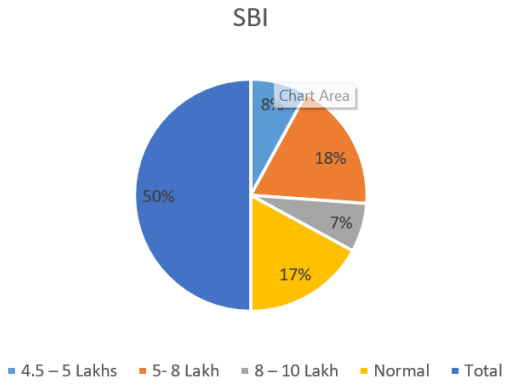
Table 4: Out 140 case 53 cases had a Thrombocytosis. In SBI population, out of 44 cases 29 were platelet count above 4.5lakh/mm^3. The occurrence of thrombocytosis among SBI group was 65.9 %. In non-SBI group 24 out of 96 had a thrombocytosis (25 %). The SBI group with normal platelet count was 34%. The non-SBI group with normal platelet count was 77%. The probability of occurrence of thrombocytosis was significant. p valve (<0.05)

Graph 1: The mean platelet count in lakh/mm^3 in SBI subgroups and NON SBI



The mean platelet count in SBI was 5.4±1.3 lakh/mm^{3}and the mean platelet count among non-SBI group was 3.7±0.5.The mean platelet count of each in each SBI subgroup given in table 6.The highest mean platelet count was noted in infants with pneumonia. Thrombocytosis was present in 71.4% of UTI cases and 87.5% of bacterial pneumonia and 50 % cases of meningitis.

Table 5: Urine Microscopy Vs Outcome

Urine R/E	SBI	Non SBI	Total
Normal	39	83	131
Abnormal	5	13	9
Total	44	96	140
p value	0.049 Significant		

Out of 140 cases , abnormal urine microscopy was found in 18 cases. Urine microscopy examination in predicting the SBI was statistically significant. (p value is < 0.05).

Table 6: CRP Results Vs Outcome

CRP	SBI	Non SBI	Total
Positive	24	38	62
Negative	20	58	78
Total	44	96	140
p value	< 0.001 Significant		

Table 6: Of 44 cases with SBI 24 cases had a positive CRP.The percentage of CRP positivity among the SBI group was 54% and non SBI group was 39 %. The difference is statistically significant. (p value is <0.001)

Table 7: Chest X-Ray Examination

Chest x-ray diagnosis	No of cases
Bronchopneumonia	27
Bronchiolitis	65
Normal Chest X-Ray	25

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The percentage of patients present with respiratory symptoms as already mentioned was 68.9% . chest x ray done for 117 cases . Among 117 cases 27 cases were showed the features of bronchopneumonia . 65 cases were showed the features of bronchiolitis. 25 cases had a normal chest x-ray.

Table 8: Blood Culture Results

BLOOD CULTURE	SBI	Non SBI	Total
Growth Present	13	0	13
No Growth	31	96	131
Total	44	96	140
p value	< 0.001 Significant		

Table 8: Of 13 cases with culture positive sepsis,3 cases were positive for enterococci,2 cases were positive for non fermentative gram negative bacilli, 4 cases were positive for klebsiella growth,3 cases positive for citrobacter,1 case was positive for staphylococci.

Graph 2: Blood culture results

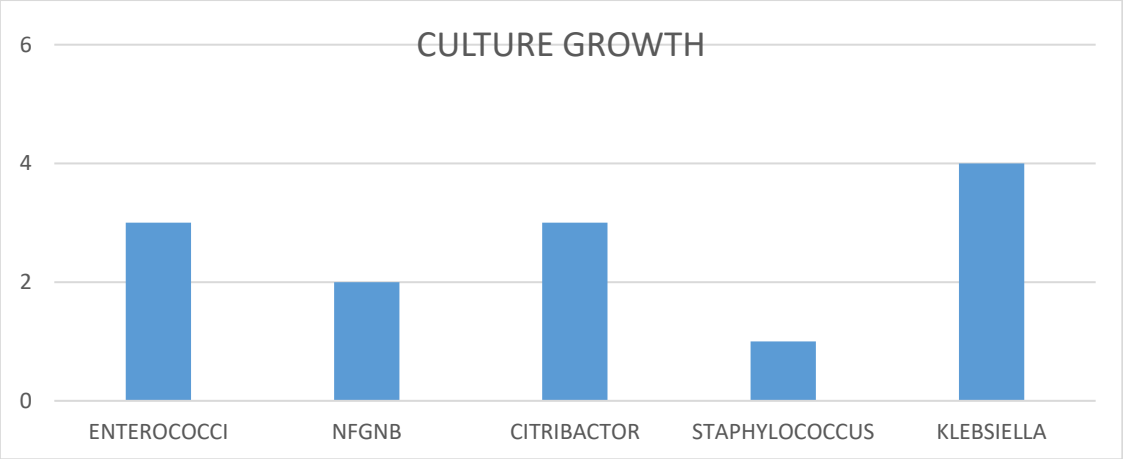

Table 9: Urine Culture Results

Urine Culture	Results
Growth Present	4
No Growth	17

Table 9: Among the 4 cases were diagnosed as urinary tract infection out of which 2 of them was positive for E. coli growth other 2 was positive for klebsiella .

Table 10: Lumbar Puncture Results

Lumbar Puncture	Sbi	Non Sbi
Growth Present	5	0
No Growth	0	1

Table 10: Lumber puncture done in patients with CNS symptoms .Out of 6 cases were presented with CNS symptoms out of that 5 cases were culture positivite .1 case were positive for Igm antibody for chikungunya virus .

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Table 11: Spectrum Of Diseases In A SBI Population

SBI	No of cases	Percentage
Pneumonia	27	19.2
Sepsis	7	5
Meningitis	5	3.5
UTI	4	2.8
Bone & Soft Tissue Infections	1	0.7
NON SBI	96	69
Total	140	100

Table 11: Among the SBI subgroups the most frequently occurred infection in my study population was pneumonia and second most common infection was culture positive sepsis. The percentage of pneumonia in study population was 19.2 % .

Table 12: Test Characteristics Of Different Platelet Threshold

Platelet count	SBI N=44	Sensitivity	Specificity	PPV	NPV	Accuracy
Platelet > 4.5	29	65.91	62.5	44.62	87.91	80
> 6	22	75.86	82.08	32.35	87.72	67.6
> 8	5	17.24	95.5	42.2	91.43	62

According to test characteristics for different platelet count thresholds, we came to know that platelet count of ≥4.5 lakh/mm3 carried an accuracy of 80 %, sensitivity 65.91 %, specificity 44.62%, Negative predictive value (NPV) 87.72% and Positive predictive value (PPV) 44.62% than any other platelet threshold. So, the platelet count of ≥4.5 lakh/mm3 had a differential tendency to pick up the maximum patients out of SBI and lesser patients out of Non SBI. At the decision threshold of >4.5 lakh/mm^3 , in the SBI population only 15 infants out of 44 misclassified as a low risk group. The percentage was 34 % . If the higher platelet count threshold was taken into an account , the sensitivity of the test was so low to recommend as a cut off.

Table 13: The Tesh Characteristics For Different Decision Theshold

Investigation	SBI	Non SBI	Sensitivity	Specificity	PPV	NPV	Accuracy
	n=44	n=96					
Platelet > 4.5 lakhs	29	36	65.91	62.5	44.62	80	63.57
WBC > 15000	20	87	45.45	29.38	18.69	27.27	72.71
CRP	24	83	54.55	13.54	22.43	39.39	76.43
Urine R/E	41	86	43.18	40.91	29.93	50	79.29

The platelet count of ≥4.5 lakhs alone identified 29 out of 44 infants with SBI; while total count ≥15,000/mm3 identified 20 of them and CRP Positivity 24 of them. A combined high-risk criterion of two tests (≥15,000/mm3 for WBC and ≥4.5 lakhs for platelet), did not pick up more SBI than platelet count alone did; while 80 infants were falsely classified as high-risk out of non SBI. Further combination of platelet count ≥4.5 lakhs, WBC ≥15000/mm3, pyuria ≥5 WBC /HPF, and CRP positivity led to the identification of all 44 infants with SBI. Thus, the combination of five tests may help in early prediction of serious bacterial infection in febrile young patients.

DISCUSSION

Fever in infants is the most common presenting problem in peadiatric outpatient department. Most of these infants have self- limiting illnesses. Only few of them have serious bacterial infections. Because of vague clinical presentation these infants are often overlooked. Sometimes, these infants under 2 to 3 months of age undergo full diagnostic work up for sepsis including blood, urine ,spinal fluid cultures and many

infants are hospitalized and started with empiric antibiotic therapy pending negative culture results [11]. In the process of finding newer and cost effective diagnostic modality in diagnosing infants with fever, platelet count could play a significant role by acting as an acute phase reactant . During an infection Interleukin-6 , Interleukin- 8,Tumour Necrosis Factor –A stimulate megakaryopoiesis in bone marrow both directly and by stimulating hepatic thrombopoietin .Thrombocytosis or elevation peripheral blood platelet > 4,50,000/mm is common during infection infancy and childhood, occurring in 3 to 13% of cases [12]. In healthy pediatric subjects normal count platelet ranges between 250,000/muL and 450,000/muL. An elevated platelet count greater than 2 SD defines a condition of thrombocytosis. The prevalence of SBI in the study population was 29.3%.15In their study, Fouzas found a very large proportion of children (74%) having SBI. A considerable amount of evidence points to the finding that platelets can act like acute phase reactants and that their production is triggered by interleukin-6 by directly enhancing megakaryopoiesis or indirectly by stimulating hepatic thrombocytosis secondary to anemia [13]. The odds of having thrombocytosis was 6.37 (95% CI 2.87-14.13, p<0.001) times higher in children with a serious bacterial infection, which was statistically significant [14]. In line with this finding Brown LST said that reactive thrombocytosis had the highest accuracy in differentiating infants with SBI with less false positive or false negative results and that it can be a useful tool that could help the clinician to look for further investigations in infants with SBI.On the contrary, several studies opined that clinical impression and routine laboratory tests were unable to accurately identify the presence of SBI. However, certain markers have been consistently identifiedwith SBI like leucocytosis, elevated CRP, pyuria and thrombocytosis [15]. Apart from the common indicators of SBI like CRP and WBC even cytokines like interleukin-6 are also useful. Though among the various makers, raised serum CRP level is a better indicator of SBI, however, no marker, either alone or in combination, has demonstrated adequate sensitivity or specificity for the diagnosis of SBI in febrile infants [16]. In addition, thrombocytosis secondary to anemia is a matter of concern in this age group.Reactive thrombocytosis in combination with WBC, CRP and pyuria seems to be a useful tool that could help clinician to target further investigation and follow-up strategy [17-20].

CONCLUSION

Estimation of platelet count in infants with fever can predict serious bacterial infection and also it is a cost effective investigation. The sensitivity of reactive thrombocytosis in predicting SBI was 65.91%, specificity was 62.5%. positive predictive value 44.62%, negative predictive value was 80%, accuracy 63.57 %. The sensitivity was very high reaching100 % in association with other parameter like WBC count., CRP, Urine pus cells were used to diagnose the serious bacterial infection.

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