

Thrombocytosis as a Potential Diagnostic Tool for Serious Bacterial Infection in Febrile Infants; Srinagar, India

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Abstract

Introduction

To estimate the incidence of Reactive Thrombocytosis among febrile young infants and to assess the utility of platelet count as a potential predictor and diagnostic tool of Serious bacterial infection (SBI).

Methods and Materials

This study was conducted a prospective non randomized study conducted between April 2011 to March 2012 at the tertiary care pediatric unit, Srinagar, India. Inclusion criteria were all infants 30 to 89 days of age, admitted with rectal temperature $>38^{\circ}\text{C}/100.4^{\circ}\text{F}$ without apparent focus of an infection on history and clinical examination. Exclusion criteria were infants having fever more than 72 hours and who had received antibiotics or vaccination within 48 hours of presentation. Also the results of the sepsis evaluation on admission were recorded. SBI included all cases of occult bacteremia, urinary tract infection, bacterial meningitis, pneumonia, bacterial gastroenteritis and infections of the soft tissues and bones.

Results

Of the 149 infants studied, 39 (26.2%) had SBI. Platelet count was significantly higher in infants with SBI compared to those without {Platelet count ≥ 4 lakhs /mm³ in SBI (84.6%) vs. Non SBI (54.4%). Mean platelet count 5.1 ± 1.1 in SBI vs. 3.9 ± 1.6 in non SBI which was statistically significant ($P < 0.05$). Thrombocytosis had moderate ability in predicting SBI [Area under curve area under the curve: 0.760]. The combination of platelet count $\geq 450,000/\text{mm}^3$, WBC $\geq 15,000/\text{mm}^3$, C-reactive protein ≥ 2 mg/dl and pyuria ≥ 5 White blood cells (WBC) per High power field (HPF) resulted in misclassification of only 2 infants with SBI (5.1% of SBIs).

Conclusions

Reactive thrombocytosis was a frequent finding in young infants with SBI. Thrombocytosis $\geq 450,000$ cells/mm³, in combination with leukocytosis, elevated C-reactive protein (CRP) and pyuria, may help in early recognition of febrile young infants at risk for SBI.

Key words: Diagnosis, Fever, Infants, Serious bacterial infection, Thrombocytosis.

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Received date: Nov 11, 2014 ; Accepted date: Nov 25, 2014

Introduction

Thrombocytosis an elevation in the peripheral blood platelet count to values more than 4 lakh/mm³ is common in infancy and childhood occurring in 3 to 13% of children. Thrombocytosis is of two types primary and secondary.

Primary is again divided into familial and essential. Familial has been described in number of families and appears to be heterogeneous as to underlying pathophysiological mechanism. Essential thrombocytosis is a chronic clonal myeloproliferative disease. Secondary thrombocytosis also known as reactive thrombocytosis in childhood results from increased thrombopoiesis as a reactive process due to underlying cause.

Reactive thrombocytosis seems to affect up to 15% of hospitalized children. It's more common in neonates, particularly premature ones and up to 2 years of age. Febrile infants less than 3 months of age present a management challenge, as many of these have no identifiable source of fever, and the prevalence of serious bacterial infection (SBI) in this age group is high. The most commonly suggested strategy is for the febrile neonates to be admitted to a hospital and undergo full sepsis work up.

In the past decade, several management strategies based on the combination of physical and laboratory findings have been proposed, but no protocol has been universally adopted. Furthermore, a series of laboratory parameters such as White blood cell (WBC) count, absolute neutrophil count, pyuria, C-reactive protein (CRP), and more recently, interleukin-6 and procalcitonin, have been extensively evaluated and compared as potential predictors of SBI. However these laboratory tests lack adequate predictive ability and the idea of a

simple, rapid and inexpensive diagnostic test that could accurately identify bacterial infections among febrile infants remains unattainable (1-32).

Methods and Materials

We followed the cases of all infants aged 30 to 89 days, admitted to G.B Pant Hospital associated with Government Medical College, Srinagar a tertiary care pediatric hospital in Srinagar district, northern India (Figure.1), from April 2011 to March 2012 for investigation of fever (defined as rectal temperature $>38^{\circ}\text{C}$) without a focus of infection. Infants who had fever for more than 72 hours, and had received antibiotics or vaccination were excluded.

All patients who fulfilled the inclusion criteria underwent sepsis evaluation including WBC count, platelet count, blood culture, urine microscopy and culture and serum CRP levels. Lumbar puncture for Cerebrospinal fluid (CSF) analysis and culture, pleural tap for pleural fluid analysis as well as stool culture and chest radiographs, were obtained at the discretion of the attending pediatrician.

The WBC count with differential and the platelet count were quantified using 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 or >10 leucocytes/mm³ in uncentrifuged sample (17). The urine, CSF , pleural and stool cultures were monitored using standard laboratory techniques.

Serious bacterial infection was defined as occult bacteremia, Urinary tract infection (UTI) pneumonia, bacterial enteritis and infection of soft tissue or bones. Isolates such as *Staphylococcus epidermidis* in the blood culture were considered contaminants unless they were isolated from more than two consecutive cultures.

Urinary tract infection was defined as a single known pathogen on urine culture with ≥ 1000 Colony-forming units (CFU) /ml of urine obtained by urethral catheterization. The diagnosis of UTI is based on culture of properly collected specimen Urinalysis is helpful in providing immediate information to suspect UTI and enable initiation of treatment.

Confirmation of the diagnosis on urine culture is necessary pneumonia was defined as the presence of a focal infiltrate on chest radiographs plus any of the following signs; a positive blood culture for a pathogenic organism or culture of a pathogenic organism from pleural fluid sample. Occult bacteremia was defined as pure growth of a single pathogenic micro-organism on blood culture of a febrile young infant without any apparent focus of infection on history and clinical examination.

Probable bacteremia was defined as the growth of two or more types of bacteria (19). Definite bacterial meningitis was defined as isolation of organism on Cerebrospinal fluid (CSF) culture. Probable bacterial meningitis was defined as abnormal CSF on analysis with sterile CSF culture. Only patient with definite bacterial infection was taken as serious bacterial infection.



Fig.1: Study area

Results

This study was conducted in the Department of Pediatrics, GB Pant Hospital a tertiary care hospital for a period of one year from April 2011 to March 2012, Srinagar, India. Total number of admissions of patients with fever without apparent source of infection admitted to hospital was 180. Total number of patients fulfilling the inclusion criteria was 149. 31 patients were excluded out of 180 as 12 of these had fever for more than 72 hours, 3 had recent vaccination history, and 16 were treated with antibiotics within 48 hours of presentation.

Results showed out of the 149 infants which fulfilled the inclusion criteria, SBI was documented in 39 (26.2%). Of these, 16 (41.0%) had UTI (11 with *Escherichia coli*), 8 occult bacteremia (2 with *klebsiella*, 3 with Methicillin resistant *staphylococcus aureus*, 3 with *Staphylococcus aureus*), 9 infants had pneumonia, and 6 were diagnosed with bacterial meningitis (2 with *E.Coli*, 2 with *Group B Streptococcus* and 2 with *methicillin resistant Staphylococcus Aureus*). One infants had positive blood as well as urine cultures for *Escherichia coli*. None of the infants had a positive stool culture there was no case of bacterial pneumonia positive for blood culture.

The remaining 110 infants (.73.8%) with negative sepsis evaluation were categorized in the Non SBI group (Table.1).

Table 1: Depicting Serious Bacterial Infection Across Diagnosis

Serious Bacterial Infection across diagnosis	Percentage
Pneumonia	23.1
Meningitis	15.4
Occult Bacteremia	20.5
Urinary Tract Infection	41.0

Age, gender and residence were non-significant across both SBI and Non SBI groups. P-value non-significant ($P > 0.05$). Thrombocytosis (Platelet count more than 4 lakh/mm³) was significantly higher in SBI, 33 out of 39 vs. Non SBI 60 out of 110 ($P < 0.05$), CRP and Total leucocyte count

(TLC) was significantly high on SBI than Non SBI ($P < 0.05$).

Blood culture was positive in 9 SBI patients, Urine culture 16, Cerebrospinal fluid (CSF) culture in 6, Chest x ray (CXR) for pneumonia and pleural fluid analysis /culture for isolation of pathogen for pneumonia in 9 patients (Tables.2-5).

Table 2: Comparing various variables across SBI and non SBI

Variables	SBI	Non SBI	P-value
Temperature(°F)	103 ±1.3 (101,105)	102 ±1.1 (101,105)	0.000
Hemoglobin	11.8±2.7 (9.2, 19.2)	12.0 ±2.3 (8.6, 19)	0.72
Total Leukocyte count (000's/mm ³)	14,915±4998 (5900,24500)	10,948±4586 (5200,29000)	0.000
Total Platelet Count (lakh/mm ³)	5.1± 1.1 (1.5 ,7.2)	3.9±1.6 (0.4,7.4)	0.000

Temperature, TLC and total platelet count was higher in SBI group than in Non SBI ($P < 0.05$) (Table.3) Shows the Mean ±1 SD (lowest and highest variable across each investigation).

Table 3: The mean platelet count in lakhs/mm³ across SBI and Non SBI

Pneumonia	4.7 lakh/m33
Bacterial meningitis	5.2 lakh/mm3
Occult bacteremia	4.9 lakh/mm3
UTI (urinary tract infection)	5.3 lakh/mm3
Non -SBI	3.9 lakh/mm3

Table 4: Depicting investigations across SBI And Non SBI

Investigation	SBI%	Non SBI%
Thrombocytosis >4 lakh/mm ³	84.6	54.5
CRP(≥2mg/dl)	51.3	13.6
Total Leukocyte Count(≥15,000/mm ³)	51.3	21.8
Urine examination for pus cells(>5/HPF)	64.1	5.5
Platelet count≥ 4.5 lakh/mm ³	82.1	30.0

Table 5: Test characteristics for differential platelet count threshold

Platelets in lakh/mm ³	N(39)	Sensitivity %	Specificity %	PPV%	NPV%	Accuracy %	OR %
≥4.0 lakh/mm ³	33	84.6	45.5	35.5	89.3	55.7	4.6
≥4.5 Lakh/mm ³	32	82.1	70	49.2	91.7	73.2	10.7
≥5.0 lakh/mm ³	20	53.8	70.0	38.9	81.1	65.8	2.7
≥6.0 lakh/mm ³	8	20.5	90.0	42.1	76.2	71.8	2.3

SBI: Serious bacterial infection; PPV: Positive predictive value; NPV: Negative predictive value.

According to test characteristics for different platelet count thresholds we came to know that platelet count of ≥ 4.5 lakh/mm³ carried best accuracy of 73.2 %, odds ratio of 10.7, sensitivity 82.1%, specificity 70%, Negative predictive value (NPV) 91.7% and Positive

predictive value PPV) 49.2% 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 (Table.6).

Table 6: Depicting combined high risk criterion of TLC, Pyuria, CRP and Platelet count in early prediction of patients of SBI

Variables	N (39)	Sensitivity %	Specificity %	PPV %	NPV%	OR
TLC	20	51.3	78.2	45.5	81.9	3.8
Pyuria ≥ 5 wbc/hpf	25	64.1	94.5	80.6	8.1	30.9
CRP	20	51.3	86.4	57.1	83.3	6.7
Plt Count(≥ 4.5 lakh/mm ³)	32	82.1	70.0	49.2	91.7	10.7
TLC+Pyuria	32	82.1	76.4	55.2	92.3	14.8
TLC+Pyuria+CRP	35	89.7	68.2	50.0	94.9	18.7
TLC+Pyuria+CRP+Platelet (≥ 4.5 lakh/mm ³)	37	94.9	53.6	42.0	96.7	21.4

PLT: Platelet count; CRP: C-reactive protein; HPF: High power field, PPV: Positive predictive value; NPV: Negative predictive value.

A combined high-risk criterion of two tests (15,000/mm³ for WBC and ≥ 5 WBC/HPF of pyuria, led the misclassification of 17.9 % of the SBIs (7 infants), while 26 infants were falsely classified as high-risk out of non SBI.

Further combination of WBC ≥ 15000 /mm³, pyuria ≥ 10 WBC /HPF, and CRP ≥ 2 mg/dl, led to the misclassification of 4 infants with SBI (10.2% of SBI), whereas 35 infants without bacterial infection were falsely classified as high-risk.

The addition of platelet count of ≥ 4.5 lakh/mm³ to the above combination of three tests resulted in misclassification of only 2 SBI infants (5.1%) with improvement of picking up 2 more patients with SBI over the combination of three tests, with final pick up of 37 out of 39 SBI patients thus the combination of four tests may help in early prediction of serious bacterial infection in febrile young patients (Figure.2).

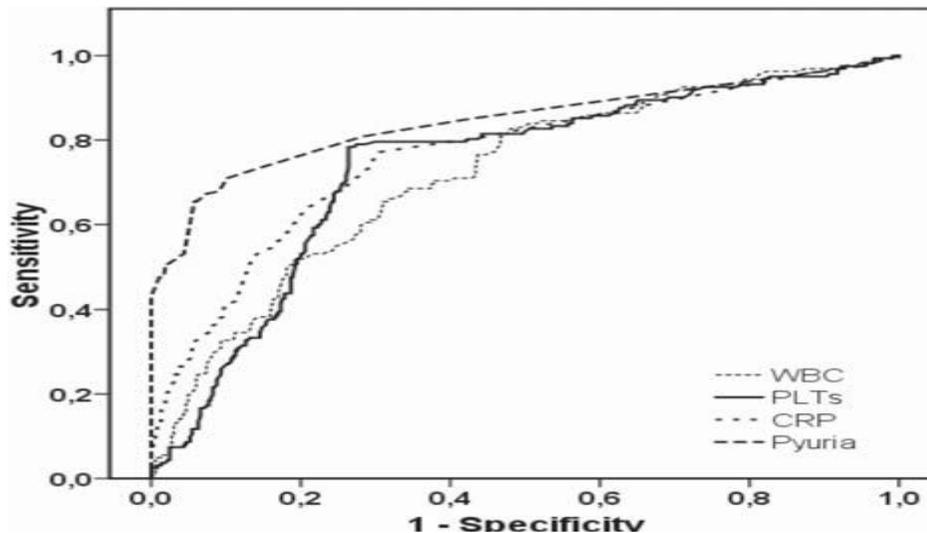


Fig.2: Depicting Receiver Operating characteristics curves (ROC) for plotted for platelet (PLT),WBC,CRP, and Pyuria predicting serious bacterial infection in febrile young infants

Receiver operating characteristics curve (ROC) was plotted for platelet (PLT), WBC, C- reactive protein (CRP) and pyuria predicting serious bacterial infection in febrile young infants.

Area under the curve (AUC) for PLT was 0.760 ; for WBC 0.64; for CRP 0.688 and for pyuria was 0.793. The AUC for WBC was significantly lower compared to the AUC for pyuria (P< 0.05). No statistically significant differences were found between the AUCs

of the other parameters, thus PLT with 0.760 AUC carry moderate ability in predicting patients with SBI.

Discussion

This study was conducted in Department of Pediatrics, G.B Pant Hospital, a referral tertiary care hospital associated with Government Medical College, for children of Kashmir valley. The study was conducted from April 2011 to March 2012. Total number of

admissions during period was 25640. Total number of patients with fever without apparent focus of infection on history and clinical examination, admitted during this period was 180. Finally total number of patients fulfilling the inclusion criteria was 149.

The purpose of this study was, to estimate the incidence of reactive thrombocytosis among febrile young patients and to assess the utility of platelet count as a potential predictor of serious bacterial infection. The prevalence of SBI in our population was 26.2% (39 out of 149 patients were positive for SBI). Since the study was conducted in a tertiary care hospital, to which more sick patients are referred, it can be the reason for high prevalence of SBI in our study.

In this study, platelet count was significantly higher in febrile infants with documented bacterial infection, particularly in those with UTI, occult bacteremia and pneumonia. However, due to a substantial overlap, it was difficult to identify threshold value that could clearly differentiate infants with SBI from other febrile infants. Platelet counts of $\geq 450,000/\text{mm}^3$ had the highest accuracy (73.2%) in differentiating infants with SBI, with less false negative and false positive results. The overall ability of platelet count to identify infants with SBI was moderate (AUC 0.76), but comparable to the other parameters.

The fact that platelets can behave like an acute phase reactant is well recognized. Stimulation of platelet production is triggered by interleukin-6 which enhances megakaryopoiesis directly and indirectly by stimulating hepatic thrombopoietin production.

In this study, platelet count was significantly higher in infants with SBI compared to those without, and this was so, reactive thrombocytosis in combination with WBC, CRP and pyuria seems to be a useful tool in predicting early the risk of SBI in young febrile patients. Hence, thrombocytosis in febrile young infants could be used as a quick inexpensive diagnostic tool for predicting SBI.

Conflict of interests: None

Acknowledgment

The authors is grateful to the colleagues and staffs for their help and cooperation during the study period.

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