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REACTIVE THROMBOCYTOSIS IN FEBRILE CHILDREN WITH SERIOUS BACTERIAL INFECTION

Amita Jane D'Souza[1], Anil Shetty[2], Divya Krishnan K[3]

ABSTRACT: BACKGROUND: Fever is a common presenting symptom in paediatric outpatient practices and emergency rooms, particularly in children <3 years of age. Approximately 20% of these children will have no identifiable source of fever after history and physical examination. 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 serious bacterial infection (SBI). These laboratory tests lack adequate predictive ability and hence the idea of a simple, rapid and inexpensive diagnostic test that could accurately identify bacterial infections among febrile infants, remains unattainable. **AIMS AND OBJECTIVES:** To assess the utility of platelet count as a potential predictor of serious bacterial infection (SBI) and to estimate the incidence of reactive thrombocytosis among febrile children. **MATERIALS AND METHODS:** A retrospective study was done on febrile children up to 2 years admitted during Jan- June 2014. Fever was defined for the study as axillary temperature >99°F. Neonates with a clinical suspicion of sepsis were included in the study. A thorough history and physical examination and laboratory investigations – complete blood count, urine routine, C-reactive protein were retrieved from records. Cultures were obtained where indicated. **OBSERVATIONS:** A total of 44 children (18.3%) were diagnosed to have serious bacterial infection (SBI) out of the 240 febrile children studied during the 6 month period from Jan-June 2014. The incidence of reactive thrombocytosis was 20.7% and of these 28.6% was due to serious bacterial infection. The sensitivity and specificity of CRP in predicting SBI was 68.2% and 60.4% respectively considering a cut off value of >7mg/dl. Thrombocytosis i.e. platelet count >4lakh was more specific in diagnosing SBI with a sensitivity and specificity of 31.8% and 82.9% respectively. Leucocytosis ie total count >15000/mm^{3} also showed a higher specificity i.e., 63.9% than sensitivity i.e., 45.5%. Duration of pyrexia (>7days) had the maximum specificity of 91.7% thus having the best diagnostic accuracy among the variables studied i.e. 76.6%. Among the investigative methods platelet count had the best diagnostic accuracy i.e., 72.57%. **CONCLUSION**: Thrombocytosis was found to have the best diagnostic accuracy, among the investigative methods studied, in predicting serious bacterial infection (SBI).
KEYWORDS: Reactive thrombocytosis, febrile infants, serious bacterial infection (SBI).

INTRODUCTION: Thrombocytosis refers to a platelet count above the normal value. Today with the widespread use of electronic cell counters and the subsequent availability of a platelet count as part of a routine blood count, thrombocytosis is more often observed as an unexpected finding. Thus, an elevated platelet count has become an important clinical problem for differential diagnosis.[1,2]

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The definition of normal platelet count in the range of 150 X 10^9/l and 450 X 10^9/l is generally accepted for healthy neonates, infants, children and adolescents. However, the definition of thrombocytosis varies between platelet counts of >400 X 10^9/l and >1000 X 10^9/l. To consider the characteristics and clinical implication of thrombocytosis and to compare published data, the following arbitrary classification of thrombocytosis has been chosen in current textbooks: mild thrombocytosis, if the platelet count is >500 and <700 X 10^9/l; moderate thrombocytosis, if the platelet count ranges between >700 and <900 X 10^9/l; severe thrombocytosis, if the platelet count is >900 X 10^9/l; and extreme thrombocytosis, if the platelet count is >1000 X 10^9/l.[3]

Thrombocytosis during infancy and childhood occurs following infection, trauma, hypoxaemia and autoimmune diseases. These phenomena have been called reactive thrombocytosis (RT), occurring in 6–13% of hospitalized children[4].Bacterial or viral infections (acute or chronic) are the most common cause for RT (37–78%) at any age during childhood. Within this group, infections of the respiratory tract account for 60–80% of RT, followed by infections of the gastrointestinal and urinary tract.[5]

Fever is a very common cause of paediatric consultation. Physical examination cannot identify the focus of the infection in many patients, and this problem becomes more accentuated the younger the child. Although the majority of children present minor infections, it is important to identify those with serious bacterial infection (SBI) in order to start antibiotic treatment early.[6]

The risk of SBI varies with age; in infants who present with fever, it develops in 8% to 14% of those under 1 month of age, in 5% to 9% of those between 1 and 3 months of age, and in 3% to 15% of those over 3 months of age.[7-9] The most commonly suggested strategy is for the febrile neonates to be admitted to a hospital and undergo full sepsis workup.[6,10-12]

Later, the tendency was to select patients with a low risk of SBI by using evaluation scales – Rochester criteria and to manage them as outpatients.[9] The Rochester scale includes a good general appearance in a previously healthy child, the absence of focal infection, and certain laboratory values (leucocyte count of 5000–15 000/mm^3, 1500 band neutrophils, urinalysis with 10 leucocytes per high power field, and 5000 leucocytes per high power field in faeces in patients with diarrhoea) as indicators of good prognosis; the negative predictive value of this scale was 98.9% for SBI and 99.5% for bacteraemia.[13]

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.[14-16] 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.[6,9,10]

OBJECTIVES:
1. To assess the utility of platelet count as a potential predictor of serious bacterial infection (SBI).
2. To estimate the incidence of reactive thrombocytosis among febrile children.

MATERIALS AND METHODS: This is a retrospective study and the study subjects included were febrile children up to 2 years of age admitted in our hospital during the study period Jan 2014 – June 2014. Fever was defined for the study as axillary temperature > 99°F or a history of fever. Neonates with a clinical suspicion of sepsis were also included in the study.

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Any child who had received antibiotics 48 hours prior to evaluation was not included in the study. A thorough history and physical examination details were obtained from case records in all children included in the study. Lab investigations: WBC count- total and differential count, platelet count, urine microscopy and CRP were retrieved. Blood culture, urine culture, lumbar puncture for cerebrospinal fluid (CSF) analysis and culture, as well as stool culture and chest radiographs, was done at the discretion of the attending pediatrician.

The WBC count with differential and the platelet count was quantified using automated laboratory equipment. Blood cultures were monitored by an automated system (BacT/ALERT 3D). Urine was obtained by clean catch midstream sample or urine bag. The WBC in the urine was quantified by standard microscopic examination and expressed as WBC per high power field. The blood, urine, CSF and stool cultures were monitored using standard laboratory techniques. The data was analyzed using Chi-Square test and Karl Pearson correlation coefficient.

RESULTS: Out of the 240 children included in the study, 2.7 % were neonates, 5.4% were 1-3months, 45.7% were 3-12months and 46.2% were > 1yr of age. Females formed 45% and males were 55 % of the study group. A total of 44 children (18.3%) were diagnosed to have serious bacterial infection (SBI) out of the 240 febrile children studied during the 6 month period from Jan 2014-June 2014 (Figure 1). Causes of SBI included pneumonia,[9] urinary tract infection,[8] meningitis,[3] sepsis,[13] bronchopneumonia[11] (Figure 2).

The incidence of reactive thrombocytosis was 20.7% and of these 28.6% was due to serious bacterial infection. The sensitivity and specificity of CRP in predicting SBI was 68.2% and 60.4% respectively considering a cut off value of >7mg/dl (Table 1). The area under the curve for CRP was 0.694 which was the maximum among the other variables (Figure 3).

Thrombocytosis i.e. platelet count >4lakh was more specific in diagnosing SBI with a sensitivity and specificity of 31.8% and 82.9% respectively. Leucocytosis i.e. total count >15000/mm^3 also showed a higher specificity (63.9%) than sensitivity (45.5%). Duration of pyrexia (>7days) had the maximum specificity of 91.7% thus having the best diagnostic accuracy among the variables studied i.e. 76.6%. Among the investigative methods, platelet count had the best diagnostic accuracy (72.57%) (Table 1).

DISCUSSION: Olaciregui et al[17] found that 23.63% of the study group had SBI, while the incidence of SBI in our study was 18.3%. The sensitivity and specificity of CRP in diagnosing SBI was 64% and 84% in comparison to 68.2% and 60.4% in our study. Our study had a higher sensitivity since we took a lower cut off of 7 compared to 20 in the Olaciregui study. The sensitivity and specificity of leucocytosis, 38% and 84% respectively was comparable to that seen in our study taking a cut off of ≥15000/mm.^{3}

Pulliam P. et al[18] studied 77 febrile children age 1-36months and found 18% had SBI. Causes of SBI included UTI,[6] pneumonia[4] and occult bacteria,[4] however sepsis was the most common cause in our study. CRP with a cut off 7mg/dl had a sensitivity of 79.1% and specificity of 91% and a post-test probability of 60%, comparable to the diagnostic accuracy of CRP found in our study i.e. 61.86%. WBC count of ≥ 15000/mm^3 had a sensitivity and specificity of 64% and 67% respectively, however our study showed leucocytosis as a less sensitive parameter. In conclusion they found that CRP was a better predictor than WBC of serious bacterial infection.

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The causes of reactive or secondary thrombocytosis have been studied on several occasions.

Hang and Teu[19] found that 78% cases of reactive thrombocytosis may be due to infections. Similar estimates were shown by Matsubara et al[20] where 68% of thrombocytosis was on account of infection. In our study, the incidence of reactive thrombocytosis was 20.7% and that due to infection was 28.6%. In 72.86% of children with reactive thrombocytosis, platelet count ranges between 500 and 700 x 10^9/L (mild thrombocytosis).

Moderate thrombocytosis i.e. 700 -900 x $10^{9/L}$ has been found in approximately 6-8% of children with reactive thrombocytosis and only 0.5 – 3% have platelet count > 1000x10^9/L.[19,20] Fouzas S et al[21] studied 408 infants and found 25.2% had SBI. Platelet count was significantly higher in infants with SBI compared to those without. Thrombocytosis had only moderate ability in predicting SBI (area under the curve 0.74). In our study the area under the curve for platelet count was 0.524. They found that a combination of thrombocytosis, leucocytosis, elevated CRP and pyrexia, may help in early recognition of febrile young infants.

Amanda P et al[22] studied 128 children in the age group1-36 months. They found 62% of the children in the > 12 hours of fever group had SBI. The sensitivity of CRP at a cut off 7mg/dl was 73% and specificity 81%. The sensitivity of WBC in predicting SBI was 82% and specificity 69% with a cut off of 15000/mm^3. These values were better than those in our study. Our study found that fever duration had a 91.7% specificity for predicting SBI. Amanda P et al concluded that CRP had a better sensitivity and specificity, WBC regardless of the fever duration is a useful lab screening tool in infants without a source of infection.[22]

CONCLUSION: Diagnostic accuracy of C-reactive protein and total count was 60-61% which was fairly good. Thrombocytosis was found to have the best diagnostic accuracy, among the investigative methods studied, in predicting serious bacterial infection (SBI).

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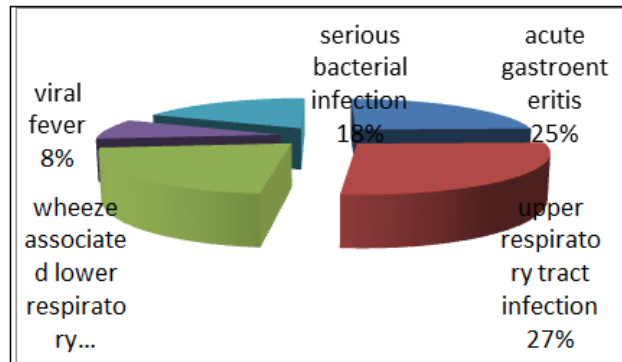Figure 1: Causes of fever: Serious bacterial inection contributed 18.3% of cases.

Figure 1

Figure 2: Causes of serious bacterial infection: Sepsis contributed 30% cases of SBI.
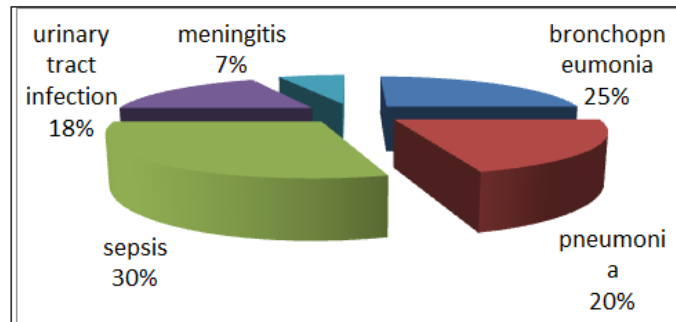

Figure 2

Figure 3: Receiver Operator Curve comparing the four variables.

  Area under the curve for CRP was maximum i.e.0.694, closely followed by fever duration 0.610, total count 0.548 and platelet count 0.524.
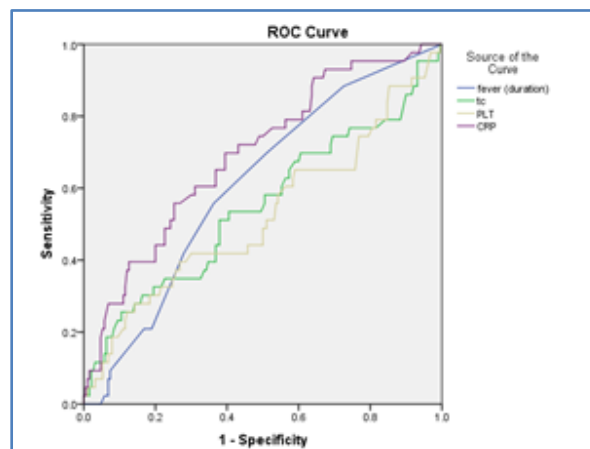

Figure 3

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Diagnostic accuracy was maximum for fever duration ie 76.69%. Among the laboratory investigations studied platelet count had maximum diagnostic accuracy 72.57%.

PARAMETER	SENSITIVITY	SPECIFICITY	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE	DIAGNOSTIC ACCURACY
CRP	68.20%	60.40%	28.30%	89.20%	61.86%
PLATELET	31.80%	81.90%	28.60%	84.00%	72.57%
FEVER	9.30%	91.70%	20.00%	81.90%	76.69%
TOTAL COUNT	45.50%	63.90%	22.20%	83.80%	60.50%
Table 1: Validity indicators					

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