RESEARCH PAPER

Reactive Thrombocytosis in Febrile Young Infants with Serious Bacterial Infection

S FOUZAS, L MANTAGOU, E SKYLOGIANNI AND A VARVARIGOU

From the Department of Pediatrics, University Hospital of Patras, Patras, Greece.
Correspondence to: Fouzas Sotirios, Department of Pediatrics, University Hospital of Patras, Rio, Patras, 265 04, Greece.
sfouzas@gmail.com

Objective: To estimate the incidence of reactive thrombocytosis among febrile young infants and to asses the utility of platelet count as a potential predictor of serious bacterial infection (SBI).

Design: Retrospective study between January 2005 and December 2008.

Setting: Tertiary care pediatric unit.

Participants: All infants 29 to 89 days of age, admitted with rectal temperature >38^{o}C without a focus of infection.

Main Outcome Measures: 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 408 infants studied, 103 (25.2%) had SBI. Platelet count was significantly higher in infants with SBI compared to those without (median 513000 /mm^3 [interquartile range 455,000–598,000/mm^3] *vs* median 398000/mm^3; [interquartile range 313,000–463,000/ mm^3]; *P*<0.001). Thrombocytosis had only moderate ability in predicting SBI (area under the curve: 0.74, 95%CI 0.70-0.79). The combination of platelet count ≥450,000/ mm^3, WBC ≥15,000/mm^3, C-reactive protein ≥2 mg/dL, and pyuria ≥10 WBC/hpf would lead to misclassification of 4 infants with SBI (3.9% of SBIs; negative likelihood ratio 0.08).

Conclusions: Reactive thrombocytosis was a frequent finding in young infants with SBI. Thrombocytosis ≥450,000 cells/mm^3, in combination with leucocytosis, elevated 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.*

Published online 2010 March 15. PII: S097475590900522-1

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(1-7). The most commonly suggested strategy is for the febrile neonates to be admitted to a hospital and undergo full sepsis workup(5-7). 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(8-11). 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(8-16). 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(3,4,6, 13,15,17).

Accompanying Editorial: Pages: 923-924

Reactive thrombocytosis is a common finding in infants that occurs in the preponderance of cases secondary to an infection(18-25). To our knowledge, no study has previously focused on the incidence and characteristics of reactive thrombocytosis in young infants with SBI. Moreover, the platelet count has

neither been considered nor evaluated as a potential predictor of SBI among young febrile infants.

The objective of our study was to estimate the incidence of reactive thrombocytosis in febrile young infants, especially in those with bacterial infections, and assess the value of platelet count as a potential predictor of SBI.

METHODS

We retrospectively reviewed the case-records of infants aged 29 to 89 days, admitted to our tertiary care pediatric unit between 1 January 2005 and 31 December 2008 for investigation of fever (defined as rectal temperature >38ºC) without a focus of infection. Infants who had fever for more than 72 hours, and had received antibiotics or vaccination within 48 hours of presentation, were excluded.

All patients had sepsis evaluation including WBC count, platelet count, blood culture, urine microscopy and culture and CRP. Lumbar puncture for cerebrospinal fluid (CSF) analysis and culture, 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 SE 9500, GMI, Inc). Blood cultures were monitored by an automated system (BacT/ALERT 3D, bioMérieux, Inc). Urine was obtained by suprapubic needle aspiration or by urethral catheterization using a sterile technique. The WBC in the urine were quantified by standard microscopic examination and expressed as WBC per high power field (hpf)(28). The urine, CSF and stool cultures were monitored using standard laboratory techniques.

Serious bacterial infection (discharge diagnosis) was defined as occult bacteremia, urinary tract infection (UTI), bacterial meningitis, pneumonia, bacterial enteritis and infection of soft tissue or bones. Isolates such as *Staphylococcus epidermidis* or *Streptococcus viridans* 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 growth ≥1000 colony-forming units (cfu) / mL of urine obtained by suprapubic needle aspiration or ≥100,000 cfu /mL of urine obtained by urethral catheterization. Pneumonia was defined as the presence of a focal infiltrate on chest radiograph as interpreted by the attending radiologist(29).

The data were analyzed using the SPSS 15.0 for Windows (SPSS, Inc). Non parametric data are presented as medians with interquartile ranges (IQR). Differences between the groups were assessed for statistical significance using either the Mann Whitney U or chi-squared test, as appropriate. Individual differences between nonparametric variables were evaluated by the Kruskal-Wallis multiple-comparison z-value test with Bonferroni correction (alpha=0.05; medians significantly different if z-value >2.93), using the statistical package NCSS 2004 (Number Cruncher Statistical Systems, Kaysville, UT, USA). The overall performance of individual parameters in predicting SBI was assessed by receiver operating characteristic (ROC) curve analyses and area under the curve (AUC) comparisons, using the statistical software MedCalc 8.1 (MedCalc, Mariakerke, Belgium). The study was approved by the ethics committee of the University Hospital of Patras, Greece.

RESULTS

During the study period, 464 infants 29 to 89 days of age, were admitted for investigation of fever >38ºC without a source. Of these, 12 had fever for more than 72 hours, 9 had received vaccination, 23 were treated with antibiotics within 48 hours of presentation, and 12 had incomplete medical records.

Of the remaining 408 infants, SBI was documented in 103 (25.2%). Of these, 88 (85.4%) had UTI (74 with *Escherichia coli*), 9 occult bacteremia (2 with *Streptococcus pneumoniae*, 3 with *Group B Streptococcus*, 2 with *Staphylococcus aureus* and 2 with *Escherichia coli*), 6 infants had pneumonia, and 2 were diagnosed with bacterial meningitis (1 with *Neisseria meningitidis* and 1 with *Group B Streptococcus*). Two infants had concurrent positive blood and urine cultures for *Escherichia coli*. None of the infants with pneumonia had documented

bacteremia. The remaining 305 infants (74.8%) with negative sepsis evaluation were categorized in the non–SBI group.

Clinical and laboratory characteristics of the non–SBI and SBI groups are presented in ***Table* I**. A comparison of platelet counts between the non–SBI and SBI groups is shown in ***Table* II**. We also noted a substantial overlap between the two groups (***Fig.* 1**).

The ROC curve depicting the ability of platelet count in identifying infants with SBI was also compared with WBC, CRP and pyuria (***Fig.* 2**).

To explore further the utility of platelet count in identifying SBI, test characteristics were calculated for different decision thresholds (***Table* III**). A platelet count of ≥450,000/mm^3 had the highest accuracy for identifying high-risk infants. At this decision threshold, 18 infants with SBI (17.4% of SBIs) were falsely classified as low-risk and 90 infants without SBI (22.0% of the study population) were falsely classified as high risk (negative LR 0.25; positive LR 2.8).

A combined high-risk criterion of ≥15,000 /mm^3 for WBC and ≥10 WBC/hpf for pyuria, led to the misclassification of 17.5% of the SBIs (18 infants; negative LR 0.24), while 20.8% were falsely classified as high-risk (85 infants; positive LR 3.0). Further combination of WBC ≥15000 /mm^3, pyuria ≥10 WBC /hpf, and CRP ≥2 mg/dl, led to the misclassification of 9 infants with SBI (8.7% of SBIs; negative LR 0.16), whereas 135 infants without bacterial infection (33.1% of the population) were falsely classified as high-risk (positive LR 2.1). This 12.3% increase in the percentage of the falsely classified high-risk infants was significant (P<0.001). The addition to the above criteria of a platelet count of ≥450,000/mm^3, resulted in a decrease of the percentage of the misclassified SBIs

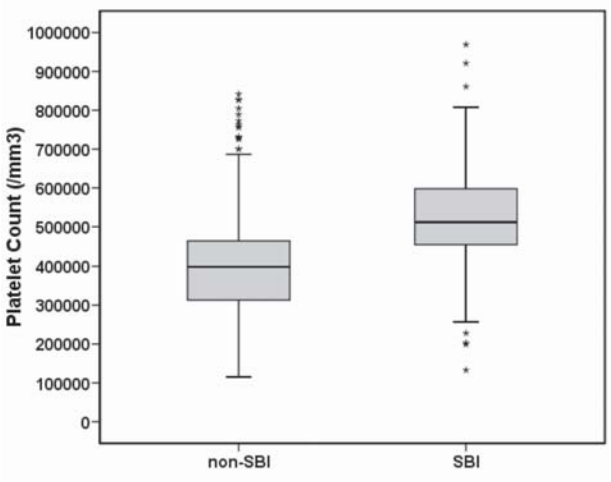

FIG. 1 *Box plots presenting the distribution of platelet counts in the non–SBI and SBI group. The central box represents the values from the lower to upper quartile (25th to 75th percentile). The middle line represents the median. A line extends from the minimum to the maximum value, excluding "outside" values or "outliers" which are displayed as separate points.*

TABLE I CLINICAL AND LABORATORY CHARACTERISTICS OF THE NON-SBI AND SBI GROUPS

	Non-SBI (*n*=305)	SBI (*n*=103)	*P* Value
Age (d)	57 (42-72)	60 (44–75)	0.10
Sex (male/female)	162/143	57/46	0.78
Duration of fever (h)	14 (6–27)	14 (6–29)	0.49
Fever on admission (^{o}C)	38.5 (38.1–38.8)	38.5 (38.1-39.0)	0.22
Hemoglobin (g/dL)	10.5 (9.7–11.0)	10.4 (9.6–11.0)	0.30
WBC (10^3/mm^3)	9.65 (7.15–14.20)	16.0 (11.1–20.2)	<0.0001
PLT (10^3/mm^3)	398 (313–463)	513 (455–598)	<0.0001
CRP (mg/dL)	0.2 (0.0–1.2)	1.6 (0.1-–4.2)	<0.0001
Pyuria (WBC/hpf)	1 (1–3)	10 (3–45)	<0.0001

Data are expressed as median (interquartile range); All comparisons by Mann-Whitney U test except sex difference by x^2 test; SBI: serious bacterial infection; WBC: white blood count; PLT: platelet count; CRP: C-reactive protein; hpf: high power field.

TABLE II PLATELET COUNTS IN THE NON–SBI GROUP AND SBI SUBGROUPS

Group*	N	Platelet count (10^3/mm^3)		Significant to: ‡
		Median	IQR	(z-value)
non–SBI	305	398	313–463	UTI (7.85) OB (3.95) PN (3.23)
UTI	88†	513	453–597	non–SBI (7.85)
OB	9†	523	500–611	non–SBI (3.95)
PN	6	490	477–541	non–SBI (3.23)

IQR, interquartile range; SBI: serious bacterial infection; UTI: urinary tract infection; OB: occult bacteremia; PN: pneumonia Infants with Bacterial meningitis (n=2) were not included in comparison; † four UTIs with concomitant bacteremia considered as OB; ‡ Kruskal-Wallis multiple-comparison z-value test with Bonferroni correction (for alpha=0.05 medians are considered significantly different if z-value >2.93).*

TABLE III TEST CHARACTERISTICS FOR DIFFERENT PLATELET COUNT THRESHOLDS

Platelet threshold (10^3/mm^3)	*n*	SBI (*n*)	Sensitivity (%)	Specificity (%)	PPV* (%)	NPV* (%)	LR +	LR –
≥400	253	88	85.4	45.9	34.8	90.3	1.6	0.32
≥450	175	85	82.5	70.5	48.6	92.3	2.8	0.25
≥500	122	54	52.4	77.7	44.3	82.9	2.4	0.61
≥600	53	23	22.3	90.2	43.4	77.5	2.3	0.86

* *The prevalence of SBI was 25.2% (103/408 infants)*; *SBI: serious bacterial infection; PPV: positive predictive value; NPV: negative predictive value; LR + likelihood ratio for positive test; LR – likelihood ratio for negative test.*

to 3.9% (4 infants; negative LR 0.08), and an insignificant increase (3.6%; *P*=0.31) of the infants falsely classified as high-risk to approximately 36.7% (150 infants; positive LR 2.0) (***Table* IV**).

DISCUSSION

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 a threshold value that could clearly differentiate infants with SBI from other febrile infants. Platelet counts of ≥450,000/mm^3 had the highest accuracy 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 0.74), but comparable to the other parameters.

The prevalence of SBI in our population (25.2%) was quite high. This study was conducted in a tertiary care pediatric unit that represents the referral center for south-western Greece. Thus, only infants who were more ill appearing or presumably more likely to have SBI may have been referred to our unit. In fact, an appreciable percentage of well-appearing febrile infants are evaluated in primary and secondary pediatric care facilities of our region. A larger, prospective and multicenter study would yield an unbiased prevalence of SBI among young febrile infants without a source of infection and would allow for a more reliable evaluation of the predictive ability of reactive thrombocytosis.

The fact that platelets can behave like an acute phase reactant is well recognized(18-25). Stimulation of platelet production is triggered by interleukin-6 which enhances megakaryopoiesis directly and indirectly by stimulating hepatic

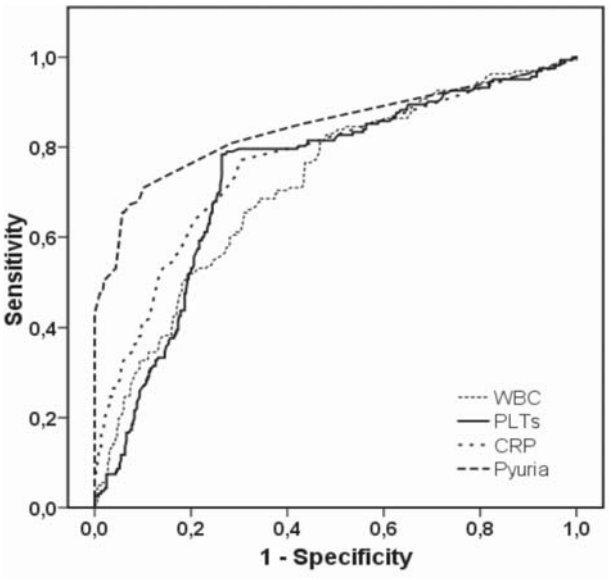

FIG. 2 *Receiver operating characteristics curve for PLT, WBC, CRP and pyuria predicting serious bacterial infection in febrile young infants. Area under the curve (AUC) for PLT 0.74 (95%CI: 0.70–0.79); for WBC 0.72 (95%CI: 0.67–0.76); for CRP 0.75 (95%CI: 0.71–0.80); and for pyuria 0.82 (95%CI: 0.78–0.86). The AUC for WBC was significantly lower compared to the AUC for pyuria (P=0.02). No statistically significant differences were found between the AUCs of the other parameters. WBC white blood count; PLT platelets count; CRP C-reactive protein.*

thrombopoietin production(18,23). Yet, the role of reactive thrombocytosis, especially in the sphere of the immature immune system of young infants, needs to be further elucidated. In addition, thrombocytosis secondary to anemia is a matter of concern in this age group(18-21). In this study, platelet count was significantly higher in infants with SBI compared to those without, and this was independent to the incidence of anemia in the two groups. 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.

Contributors: SF developed the concept, helped in data collection, performed data analysis, and prepared the manuscript. LM and ES performed data collection and helped in the preparation and correction of the manuscript. AV developed the concept, interpreted the results and revised the manuscript for important intellectual content. She will act as guarantor of the study. The final manuscript was approved by all authors.

Funding: None.

Competing interest: None stated.

REFERENCES

1. Slater M, Krug SE. Evaluation of the infant with fever without source: an evidence based approach. Emerg Med Clin North Am 1999; 17: 97-126.
2. Baraff LJ, Oslund SA, Schriger DL, Stephen ML. Probability of bacterial infections in febrile infants less than three months of age: a metaanalysis. Pediatr Infect Dis J 1992; 11: 257-264
3. Isaacman DJ, Shults J, Gross TK, Davis PH, Harper M. Predictors of bacteremia in febrile children 3 to 36 months of age. Pediatrics 2000; 106: 977-982.
4. Hsiao AL, Chen L, Baker MD. Incidence and

TABLE IV TEST CHARACTERISTICS FOR DIFFERENT DECISION THRESHOLDS

Decision threshold	Sensitivity (%)	Specificity (%)	PPV* (%)	NPV* (%)	LR+	LR–
WBC >15×10^3/mm^3	52.4	78.7	45.4	83.0	2.5	0.6
Pyuria ≥10 WBC/hpf	65.0	94.1	78.8	88.9	11.0	0.37
PLT ≥450×10^3/mm^3	82.5	70.5	48.6	92.3	2.8	0.25
CRP ≥2 mg/dL	51.5	86.6	56.4	84.1	3.8	0.56
WBC + pyuria	82.5	72.1	50.0	92.4	3.0	0.24
WBC + pyuria + CRP	91.3	55.7	41.0	95.0	2.1	0.16
WBC + pyuria + CRP + PLT	96.1	50.8	39.8	97.5	2.0	0.08

** The prevalence of SBI was 25.2% (103/408 infants) PPV: positive predictive value; NPV: negative predictive value; LR+: likelihood ratio for positive test; LR–: likelihood ratio for negative test; SBI serious bacterial infection; WBC white blood count; PLT platelets count; CRP C-reactive protein; hpf high power field .*

WHAT IS ALREADY KNOWN?

- Reactive thrombocytosis is common in infants with bacterial infections.

WHAT THIS STUDY ADDS?

- Thrombocytosis ≥450,000 cells/mm^3 may help in assessing the risk for serious bacterial infection in febrile young infants.

predictors of serious bacterial infection among 57- to 180-day-old infants. Pediatrics 2006; 117: 1695-1701.

5. Baker MD, Avner JR, Bell LM. Failure of infant observation scales in detecting serious illness in febrile, 4- to 8- week-old infants. Pediatrics 1990; 85: 1040-1043.
6. Steere M, Sharieff GQ, Stenklyft PH. Fever in children less than 36 months of age – Questions and strategies for management in the emergency department. J Emerg Med 2003; 25: 149-157.
7. Ishimine P. Fever without source in Children 0 to 36 months of age. Pediatr Clin North Am 2006; 53: 167-194.
8. Baraff LJ, Bass JW, Fleisher GR, Klein JO, McCracken GH Jr, Powell KR, *et al*. Practice guideline for the management of infants and children 0 to 36 months of age with fever without a source. Pediatrics 1993; 92: 1-12.
9. Baskin MN, O'Rourke EJ, Fleisher GR. Outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone. J Pediatr 1992; 120: 22-27.
10. Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. N Engl J Med 1993; 329: 1437-1441.
11. Jaskiewicz JA, McCarthy CA, Richardson AC, White KC, Fisher DJ, Dagan R, *et al*. Febrile Infant Collaborative Study Group. Febrile infants at low risk for serious bacterial infection – an appraisal of the Rochester criteria and implications for management. Pediatrics 1994; 94: 390-396.
12. Bachur RG, Harper MB. Predictive model for serious bacterial infections among infants younger than 3 months of age. Pediatrics 2001; 108: 311-316.
13. Pulliam PN, Attia MW, Cronan KM. C-reactive protein in febrile children 1 to 36 months of age with clinically undetectable serious bacterial infection. Pediatrics 2001; 108; 1275-1279.
14. Galetto-Lacour A, Zamora SA, Gervaix A. Bedside procalcitonin and C-reactive protein tests in children with fever without localizing signs of infection seen in a referral center. Pediatrics 2003; 112; 1054-1060.
15. Mathew JL. Can CRP predict bacterial infection in children with fever? Indian Pediatr 2008; 45:129-133.
16. Olaciregui I, Hernández U, Muñoz JA, Emparanza JI, Landa JJ. Markers that predict serious bacterial infection in infants under 3 months of age presenting with fever of unknown origin. Arch Dis Child 2009; 94: 501-505.
17. Hsiao AL, Baker MD. Fever in the new millennium: a review of recent studies of markers of serious bacterial infection in febrile children. Curr Opin Pediatr 2005; 17: 56-61.
18. Mantadakis E, Tsalkidis A, Chatzimichael A. Thrombocytosis in childhood. Indian Pediatr 2008; 45: 669-677.
19. Matsubara K, Fukaya T, Nigami H, Harigaya H, Hirata T, Nozaki H, *et al*. Age-dependent changes in the incidence and etiology of childhood thrombocytosis. Acta Haematol 2004; 111:132-137.
20. Dame C, Sutor AH. Primary and secondary thrombocytosis in childhood. Br J Haematol 2005; 129: 165-177.
21. O'Shea J, Sherlock M, Philip R. Thrombocytosis in childhood. Acta Haematol 2005; 113: 212.
22. Vlacha V, Feketea G. Thrombocytosis in pediatric patients is associated with severe lower respiratory tract inflammation. Arch Med Res 2006; 37: 755-759.
23. Dodig S, Raos M, Kovac K, Nogalo B, Benko B, Glojnaric I, *et al*. Thrombopoietin and interleukin-6

in children with pneumonia-associated thrombocytosis. Arch Med Res 2005; 36: 124-128.

24. Thomas GA, O'Brien RT. Thrombocytosis in children with *Hemophilus influenzae* meningitis. Clin Pediatr (Phila) 1986; 25: 610-611.

25. Garoufi A, Voutsioti K, Tsapra H, Karpathios T, Zeis PM. Reactive thrombocytosis in children with upper urinary tract infections. Acta Paediatr 2001; 90: 448-449.

26. Dharnidharka VR, Kandoth PW. Prevalence of bacteriuria in febrile infants. Indian Pediatr 1993; 30: 987-990.

27. Srivaths PR, Rath B, Prakash SK, Talukdar B. Usefulness of screening febrile infants for urinary tract infection. Indian Pediatr 1996; 33: 218-220.

28. Hoberman A, Wald ER. Urinary tract infections in young febrile children. Pediatr Infect Dis J 1997; 16: 11-17.

29. Bachur R, Perry H, Harper M. Occult pneumonias: empiric chest radiographs in febrile children with leukocytosis. Ann Emerg Med 1999; 33: 166-173.