Predictors of serious bacterial infection in children aged 3 to 36 months with fever without source

Goh P L, Lee S W, Wong E H

ABSTRACT

Introduction: Children commonly present with fever without source yet there is no reliable and consistent method of identifying those at risk of serious bacterial infection. In this study, we sought to identify predictors of serious bacterial infection in children aged between three to 36 months with fever without source.

Methods: Inpatient records of all children aged three to 36 months admitted from the Emergency Department of Singapore's main paediatric hospital between October 2001 to February 2002 with International Classification of Diseases (ninth revision) diagnosis codes 038 (septicaemia), 079 (viral fever), or 780 (pyrexia of unknown origin), were retrieved and reviewed. Patients identified as having fever without source were enrolled.

Results: Of 86 enrolled children, 17 (19.8 percent) had serious bacterial infection. Duration of fever and white blood cell count were found to be significant predictors. Children with white blood cell count equal to or greater than 16,000/mm³ had 6.9 times (95 percent confidence interval [CI] is 1.7 to 28.4) increased risk of serious bacterial infection, while children with fever of duration exceeding three days before presentation had 3.8 times (95 percent CI is 1.1 to 13.1) increased risk of serious bacterial infection. A combination of white blood cell count less than 16,000/mm³ and duration of fever three days or less had a negative predictive value of 1.0 (95 percent CI is 0.88 to 1.0) and a sensitivity of 1.0 (95 percent CI is 0.82 to 1.0).

Conclusion: The two identified predictors offer an estimate of the risk of serious bacterial infection in children aged three to 36 months with fever without source.

Accident & Emergency Department
Changi General Hospital
2 Simei Street 3
Singapore 529889

Goh P L, FRCSE
Associate Consultant

Lee S W, FRCSE
Associate Consultant

Clinical Trials and Epidemiological Sciences
National Cancer Centre
11 Hospital Drive
Singapore 169610

Wong E H, MSc
Biostatistician

Correspondence to:
Dr. Goh Pak Liang
Tel: (65) 6850 1687
Fax: (65) 6260 3756
Email: pak_liang_goh@cgh.com.sg

Key Words: bacteraemia, children, fever of unknown diagnosis, fever without source, white blood cells

Singapore Med J 2006; 47(4):276-280

INTRODUCTION

Fever without source (FWS) is a commonly encountered condition in paediatric patients presenting to the Emergency Department (ED). The vast majority of these children will have a benign illness and appear clinically well, and are therefore managed on an outpatient basis. Some children however, may appear clinically unwell or have abnormal screening investigations, and are often then admitted for inpatient investigation and management. A small percentage of these children will eventually be found to have a clinically undetectable serious bacterial infection (SBI).

In a child with FWS, estimating the risk of SBI remains a diagnostic challenge. Although various protocols have been suggested using a variety of demographical, clinical and laboratory predictors such as age, appearance of the child, amplitude of fever, total white blood cell (WBC) count, absolute neutrophil count (ANC), C-reactive protein (CRP) and erythrocyte sedimentation rate, none have been universally adopted or accepted. Furthermore, these protocols are often targeted only at those <three months of age[1-5]. In this study, we sought to identify predictors that could help the Emergency Physician to estimate the risk of SBI in children aged three to 36 months with FWS.

METHODS

The study was conducted at the ED of KK Women's and Children's Hospital in Singapore. For a five-month period from October 2001 to February 2002, inpatient records of all children aged three to 36 months admitted with International Classification of Diseases, ninth revision (ICD-9) diagnosis codes 038 (septicaemia), 079 (viral fever), or 780 (pyrexia of unknown origin), were retrieved. A single

unblinded emergency physician (the first author) reviewed these records to exclude patients who did not fulfil the criteria of having FWS (defined as fever with no apparent focus of infection after a complete history and examination). Patients with fever of more than one week's duration were also excluded as these patients are often managed differently as pyrexia of unknown origin. The remaining patients were considered to have FWS and were enrolled. Fever was defined as a rectal, oral or axillary temperature of more than 38°C. Duration of fever was based on anecdotal history reported by the parents or caregiver.

Data collected included patient demographics (age, gender, ethnicity), duration and amplitude of fever, vital signs, abnormal physical examination (presence of dehydration, lethargy, grunting, poor peripheral circulation/cyanosis, or toxic-looking child), various basic initial investigations (such as WBC count, ANC, CRP, urinalysis and chest radiograph), as well as various further inpatient investigations. The study group was dichotomised into those eventually diagnosed as having "SBI" and those having "No SBI". For purposes of this study, SBI was based on the eventual hospital discharge diagnosis of occult bacteraemia, urinary tract infection (UTI), meningitis, septic arthritis, osteomyelitis, or pneumonia.

The various demographical and clinical data and investigative findings that could potentially predict the risk of SBI were investigated for their association with the presence of SBI using logistic regression. These include age, gender, heart rate, respiratory rate, temperature at presentation, duration of fever before presentation at ED (≤three days versus >three days), the presence or absence of abnormal examination, and WBC count (≤16,000/mm^3 versus >16,000/mm^3). A univariate logistic regression was performed for each independent variable. Variables with p-value <0.25 were then included in a multiple logistic regression using a backward elimination procedure. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 11.0 (Chicago, IL, USA).

RESULTS

During the study period, the records of 144 children were retrieved and reviewed. 33 cases did not fulfil the criteria of having FWS and 24 cases had fever of more than one week duration. These children were excluded. The remaining 86 children were included in the study. The median age was 10.8 months (range 3.1 months to 33.3 months). The patients' demographics and clinical characteristics are presented in Table I and Table II, respectively, while their haematological and laboratory findings are presented in Table III.

17 children (19.8%) were eventually diagnosed to have SBI. This comprised UTI in 11 patients

Table I. Patient demographics.

	SBI† n=17		No SBI† n=69		Total n=86	
	n	%	n	%	n	%
Ethnic group						
Chinese	12	70.6	47	68.1	59	68.6
Malay	4	23.5	15	21.7	19	22.1
Indian	0	0	4	5.8	4	4.7
Others	1	5.9	3	4.3	4	4.7
Gender						
Male	10	58.8	36	52.2	46	53.5
Female	7	41.2	33	47.8	40	46.5
Age (months)						
Median (IQR‡)	10.7 (23.52)		10.8 (15.42)		10.8 (17.84)	
5th, 75th quartile	4.93, 28.45		6.45, 21.87		5.93, 23.78	
Range	3.6, 33.3		3.1, 30.3		3.1, 33.3	
SBI† type						
Urinary tract infection	11	64.7	0	0	11	12.8
Chest infection	6	35.3	0	0	6	7.0

†SBI: Serious bacterial infection; ‡IQR: Inter-quartile range.

Table II. Clinical characteristics.

	SBI†		No SBI†		Total	
	n	%	n	%	n	%
Temperature at presentation (in degrees Celsius)	n=15		n=69		n=84	
Median (IQR‡)	39.2 (1.40)		38.8 (1.65)		38.9 (1.58)	
25th, 75th quartile	38.40, 39.80		37.85, 39.50		37.93, 39.50	
Range	38, 41		35, 41		35, 41	
Heart rate (per minute)	n=15		n=69		n=84	
Mean (SD)	178.3 (27.11)		168.4 (21.85)		170.2 (23.01)	
Range	134, 220		104, 219		104, 220	
Respiratory rate (per minute)	n=15		n=69		n=84	
Mean (SD)	34.8 (3.76)		34.6 (5.52)		34.6 (5.23)	
Range	28, 40		24, 48		24, 48	
Duration of fever (days)	n=17		n=66		n=83	
Median (IQR‡)	4.0 (4.5)		3.0 (3.0)		3.0 (3.0)	
25th, 75th quartile	2.5, 7.0		2.0, 5.0		2.0, 5.0	
Range	1, 7		1,7		1, 7	
Duration of fever						
≤3 days	7	41.2	45	68.2	52	62.7
>3 days	10	58.8	21	31.8	31	37.3

†SBI: Serious bacterial infection; ‡IQR: Inter-quartile range.

Table III. Haematological and laboratory investigations.

	SBI†	No SBI†	Total
Urine leukocytosis (cells/μL)	n=15	n=57	n=72
Median (IQR‡)	100.0 (1005.0)	0.0 (14.50)	0.0 (28.0)
25th, 75th quartile	0, 1005.0	0, 14.50	0, 28.0
Range	0, 2000	0, 1270	0, 2000
White blood cell count ($1,000/mm^3$)	n=17	n=69	n=86
Median (IQR‡)	21.4 (11.0)	12.7 (13.45)	14.4 (14.02)
25th, 75th quartile	14.4, 25.4	7.7, 21.1	8.4, 22.4
Range	8.2, 39.2	2.6, 42.8	2.6, 42.8
Absolute neutrophil count ($1,000/mm^3$)	n=17	n=69	n=85
Median (IQR‡)	15.0 (9.41)	6.9 (10.23)	9.2 (10.92)
25th, 75th quartile	8.96, 18.37	3.76, 13.99	4.07, 14.99
Range	3.57, 27.83	0.15, 40.66	0.15, 40.66
C-reactive protein (mg/L)	n=14	n=26	n=40
Median (IQR‡)	116.5 (97.88)	42.9 (91.70)	77.8 (104.85)
25th, 75th quartile	63.93, 161.80	15.75, 107.45	20.20, 125.05
Range	11.3, 251.6	5.0, 229.6	5.0, 251.6

†SBI: Serious bacterial infection; ‡IQR: Inter-quartile range.

Table IV. Univariate logistic regression.

Variable	Regression coefficient (SE)	Unadjusted odds-ratio	95% confidence interval	p-value
White blood cell count ($1,000/mm^3$)				0.009
≥16 (n=40)	1.62 (0.62)	5.06	1.49, 17.13	
<16 (n=46)	–	1	–	
Duration of fever (days)				0.045
>3 (n=31)	1.12 (0.56)	3.06	1.02, 9.16	
≤3 (n=52)	–	1	–	
Heart rate (per minute) (n=84)	0.02 (0.01)	1.02	0.99, 1.05	0.137
Temperature (in degrees Celsius) (n=84)	0.37 (0.27)	1.45	0.86, 2.46	0.162
Abnormal examination				
Yes (n=15)	-1.40 (1.07)	0.25	0.03, 2.01	0.191
No (n=71)	–	1	–	
Age (months) (n=86)	0.02 (0.03)	1.02	0.97, 1.08	0.420
Gender				
Male (n=46)	0.27 (0.55)	1.31	0.45, 3.84	0.623
Female (n=40)	–	1	–	
Respiratory rate (per minute) (n=84)	0.01 (0.05)	1.01	0.91, 1.12	0.882

SE: Standard error.

and chest infection in six patients. *Escherichia coli (E. coli)* was the causative agent in nine of the eleven children with UTI. One child with *E. coli* UTI also had *E. coli* bacteraemia. Urine leukocytosis and chest radiograph findings were not included in the analysis for their association with SBI, since these variables are directly predictive of UTI and chest infection, the two main causes of SBI in this cohort of patients.

The unadjusted odds ratios for age, gender, heart rate, respiratory rate, temperature at presentation, duration of fever before presentation at ED, presence or absence of abnormal examination and WBC count are shown in Table IV. Children with WBC count of at least $16,000/mm^3$ had a five times higher risk of having SBI compared to those with WBC count $<16,000/mm^3$, and those with fever duration >three days had a three times higher risk of SBI compared to those with fever ≤three days. When these two variables, together with heart rate, temperature at presentation and abnormal examination, were included in a multiple logistic regression model using backward elimination, WBC count and duration of fever were found to be statistically significant (Table V).

Children with WBC count ($\geq 16,000/mm^3$ were found to have almost seven times (95% CI = 1.7 to 28.4) increased risk of SBI compared to those with WBC count $<16,000/mm^3$, adjusting for duration of fever. Children with >three days of fever before presentation at ED had an increased risk of SBI 3.8 times (95% CI = 1.1 to 13.1) that of children with fever of duration ≤three days, adjusting for WBC count. The diagnostic value using a combination of WBC count and duration of fever was also investigated (Table VI). The test is defined as negative when a child has WBC count $<16,000/mm^3$ and fever duration of ≤three days, and positive when otherwise. This test yielded a negative predictive value of 1.0 (95% CI = 0.88 to 1.0) and a sensitivity of 1.0 (95% CI = 0.82 to 1.0). No child with a combination of WBC count $<16,000/mm^3$ and duration of fever ≤three days was found to have SBI eventually. However, the test had low specificity and positive predictive values of 0.41 (95% CI = 0.30 to 0.53) and 0.30 (95% CI = 0.20 to 0.43), respectively.

DISCUSSION

Children with FWS commonly present to hospital emergency departments, yet there is little uniformity on their management. This is not unexpected, since different regions have differing patient populations, incidences of FWS and SBI (due in

part to different rates of *Haemophilus influenza B* (Hib) and pneumococcal vaccination), thresholds for performing investigations, definitions of the high and low risk febrile child, and admission guidelines. For example, in Singapore (as compared to the United States), the Hib vaccination rate is generally much lower, whereas the admission policy is generally more liberal, due to differing payment structures between inpatient and outpatient care.

Any study on this topic will therefore have to be taken in the context of local practice variations. KK Women's and Children's Hospital is the main and largest children's hospital in Singapore, with its children's ED seeing an average of 95,000 patients annually. Here, febrile children with an identifiable source of fever are managed accordingly. Those with FWS but who appear clinically well are managed expectantly on an outpatient basis. The remaining small subset of children with FWS is often admitted for inpatient management. A proportion of these admitted children will be eventually diagnosed to have a SBI, most often from UTI, pneumonia or bacteraemia. The many studies on this topic have yielded a wide variety of predictors and clinical prediction rules[6-12]. However, as many of these protocols have been developed specifically for infants aged <three months of age, their usefulness is limited in older children. In this study, the authors sought to identify predictors of SBI in children aged three to 36 months with FWS. The incidence of SBI in this study group was found to be 19.8%. This is consistent with figures (18%-24%) quoted in some previous studies[13,14]. The causes of SBI in this study consisted exclusively of UTI and pneumonia. No cases of bacterial meningitis, septic arthritis or osteomyelitis were found.

This study has identified duration of fever and WBC count as significant predictors of SBI in children aged three to 36 months admitted for FWS. Duration of fever of >three days had a 3.8 times increased risk of SBI compared to a fever of ≤three days duration, adjusting for WBC count; while a WBC count of ≥16,000/mm^3 carried 6.9 times as much risk of SBI as a WBC count <16,000/mm^3, adjusting for duration of fever. A combination of fever ≤three days duration and a WBC count of <16,000/mm^3 had a negative predictive value of 1.0 in our study, thus a child with this combination of negative results effectively has minimal risk of SBI. These results need to be prospectively validated on a separate cohort of patients.

Table V. Multiple logistic regression.

Variable	Regression coefficient (SE)	odds-ratio	95% CI	p-value
Duration of fever (days)				
>3 (n=30)	1.33 (0.64)	3.78	1.09, 13.13	0.036
≤3 (n=51)	–	1	–	
WBC count (1,000/mm^3)				
≥16 (n=38)	1.94 (0.72)	6.94	1.70, 28.35	0.007
<16 (n=43)	–	1	–	
Constant	-3.3 (0.73)	0.04	–	<0.001

SE: Standard error.

Nagelkerke R-square = 0.24

NB: 81 cases were included in the analysis. Five cases had missing values on at least one of the variables.

Table VI. Combination of white blood cell count <16† and fever ≤3 days.

	No SBI	SBI	Total
WBC count <16† AND fever ≤3 days	27	0	27
All other combinations	39	17	56
Total	66	17	83

†(1000/mm^3)

NB: Three patients had missing number of days of fever.

These results have useful implications in the ED, as the risk of SBI in a child with FWS after a complete history and examination can be estimated by knowing the duration of fever and WBC count, two easily-obtained variables. Based on these estimates, emergency physicians as well as parents can then be more objective in coming to an informed decision regarding a child's eventual disposal from the ED. A FWS child thus stratified to a low risk group (duration of fever ≤three days and WBC count <16,000/mm^3) may be a candidate for discharge from the ED, thus potentially reducing the need for inpatient admission. These results do not reduce or replace the utility of chest radiographs and urinalysis as screens for chest infection and UTI, the commonest two causes of SBI.

The use of WBC count and duration of fever in estimating the risk of SBI should supplement, rather than substitute, chest radiographs and urinalysis in the management of the child with FWS. Regardless of historical information, laboratory or radiological findings, the authors stress to qualify that the clinical skill in recognising a sick child remains paramount, especially in the

setting of a busy ED. For a sick or toxic-appearing child, the use of a raised WBC to predict SBI becomes irrelevant and unnecessary. On a secondary note, this study found that age, gender, vital parameters, amplitude of fever and abnormal physical signs were not useful in indicating the presence of SBI. This is in contrast to some previous studies where the identified predictors of SBI in febrile children included gender, temperature and a number of adverse symptoms and signs[15,16].

This study has some limitations. The study data is gathered from a cohort of patients admitted from the ED, a population slightly different from the actual cohort of patients presenting to the ED. The retrospective nature of the study meant that the management, extent of investigations and disposal of children presenting with FWS to the ED was not standardised by a formal study protocol, and was left to the discretion of the attending doctor. The five-month period of the study was also arbitrarily assigned. As there was no specific ICD diagnosis code for FWS, the authors used the ICD diagnosis codes for septicaemia, viral fever and pyrexia of unknown origin as a proxy to identify cases of FWS, but this method is not entirely accurate, as the study population is thus "limited" by these three ICD codes.

In this study, no attempt was made to gather information on those children with FWS who were discharged from the ED because they were judged to be clinically well. A small proportion of these children may have SBI that would have been "missed" unless they re-attended the ED. This can perhaps be the focus of future research on this topic. By limiting the definition of SBI as such (excluding conditions such as otitis media, bacterial enteritis and aseptic meningitis), the true prevalence of SBI may be underestimated.

In conclusion, children with FWS commonly present to the Emergency Department, yet there is no reliable and consistent method of identifying those at risk of serious bacterial infection. The findings of this study offer the emergency physician an estimate, based on duration of fever and white blood cell count, of the risk of serious bacterial infection in children aged three to 36 months with fever without source.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Goh Siang Hiong of Changi General Hospital and Dr Angelina Ang of KK Women's and Children's Hospital for their critical review of the manuscript and their kind advice and encouragement; and Ms Shen Liang of Clinical Trials and Epidemiology Research Unit for her assistance in the initial statistical analysis.

REFERENCES

1. Singer JI, Vest J, Prints A. Occult bacteremia and septicemia in the febrile child younger than two years. Emerg Med Clin North Am 1995; 13:381-411.
2. 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.
3. Baraff LJ. Management of fever without source in infants and children. Ann Emerg Med 2000; 36:602-14.
4. Avner JR, Baker MD. Management of fever in infants and children. Emerg Med Clin North Am 2002; 20:49-67.
5. King C. Evaluation and management of febrile infants in the emergency department. Emerg Med Clin North Am 2003; 21:89-99.
6. Jaskiewicz JA, McCarthy CA, Richardson AC, et al. Febrile infants at low risk for serious bacterial infection – an appraisal of the Rochester criteria and implications for management. Pediatrics 1994; 94:390-6.
7. Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. N Engl J Med 1993; 329:1437-41.
8. Baker MD, Bell LM, Avner JR. The efficacy of routine outpatient management without antibiotics of fever in selected infants. Pediatrics 1999; 103:627-31.
9. Dagan R, Powell KR, Hall CB, Menegus MA. Identification of infants unlikely to have serious bacterial infection although hospitalized for suspected sepsis. J Pediatr 1985; 107:855-60.
10. Kupperman N, Fleisher GR, Jaffe DM. Predictors of occult pneumococcal bacteremia in young febrile children. Ann Emerg Med 1998; 31:679-87.
11. Bonsu BK, Harper MB. Identifying febrile young infants with bacteremia: is the peripheral white blood cell count an accurate screen? Ann Emerg Med 2003; 42:216-25.
12. Pantell RH, Bergman DA, Takayama JI, et al. Detecting serious bacterial illness in febrile infants: do guidelines help? In: American Academy of Pediatrics [online]. Available at: www.aap.org/research/00pas6.htm. Accessed November 8, 2003.
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; 108:1275-9.
14. Berger RM, Berger MY, van Steensel-Moll HA, Dzoljic-Danilovic G, Derksen-Lubsen G. A predictive model to estimate the risk of serious bacterial infection in febrile infants. Eur J Pediatr 1996; 155:468-73.
15. Issacman DJ, Shults J, Gross TK, Davis PH, Harper M. Predictors of bacteremia in febrile children 3 to 36 months of age. Pediatrics. 2000; 106:977-82.
16. Bleeker Se, Moons KGM, Derksen-Lubsen G, Grobbee DE, Moll HA. Predicting serious bacterial infection in young children with fever without apparent source. Acta Paediatr 2001; 90:1226-32.