ORIGINAL ARTICLE

A Model for Predicting Risk of Serious Bacterial Infection in Febrile Infants Younger Than 3 Months of Age

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Background: The objective of this study was to construct a model for predicting the risk of serious bacterial infection (SBI) in febrile infants.

Methods: A total of 135 febrile infants younger than 3 months of age who met the inclusion criteria were assessed on the following: physical appearance, complete blood count, serum C-reactive protein (CRP), urinalysis, stool smears for white blood cell (WBC) count if diarrhea was apparent, and blood and urine cultures. Chest X-rays were performed if respiratory symptoms were evident. Cerebrospinal fluid was analyzed if central nervous system infection was suspected.

Results: Of the 135 infants, 34 were diagnosed with SBI. Data from 99 infants were used to construct a model for predicting SBI by multivariate logistic regression. Sex (male), spun urine WBC count (≥10 per high-powered field [400×]) and CRP (≥3.6 mg/L) were significantly related to SBI. A probability cut-off of 0.265 was selected, where values below and above the cut-off reflected low and high SBI risk respectively. Data from the remaining 36 infants were used to test model validity. Both sensitivity and specificity were 77.8% for predicting SBI using this model.

Conclusion: These findings suggest that sex, serum CRP concentration and spun urine WBC count can be used to accurately predict SBI in febrile infants aged less than 3 months of age. [*J Chin Med Assoc* 2009;72(10):521–526]

Key Words: C-reactive protein, febrile infants, neonatal sepsis, risk factors, serious bacterial infection

Introduction

It is not uncommon for infants to suffer from fever within the first 3 months of life. Although such fevers are typically self-limiting, it has been reported that 1–38% of afflicted infants also have serious bacterial infection (SBI).[1–8] Traditionally, febrile infants younger than 90 days of age were hospitalized, received a full sepsis workup, and were treated with intravenous antibiotics until definitive culture results became available.[1,9] There are obvious problems with such a treatment strategy in that the majority of young infants with fever do not have SBI. Therefore, large numbers of febrile infants continue to receive unnecessary treatment that is costly, stressful for both infant and parents, and that may be associated with iatrogenic complications and antibiotic resistance.[10,11] If correctly identified, such infants could be treated on an outpatient basis.

Numerous investigations have been carried out in an effort to identify readily assessable variables that predict a low or high risk of SBI in young febrile infants (for a review on this topic, see reference 12). Despite this, there currently exists no uniformly accepted assessment approach. Two popular methods for assessing SBI risk are the Rochester criteria[3] and the Philadelphia protocol.[13] Both include measures of current and historical physical status as well as several laboratory variables, including white blood cell (WBC) count. While these approaches appear to be of use in

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older infants, it is apparent that sensitivity is decreased in infants less than 1 month of age.[14] Other researchers have reported that levels of C-reactive protein (CRP), absolute neutrophil count and procalcitonin can be indicative of SBI risk.[10,15–17]

In our pediatric department, standard handling of young infants with fever comprises hospitalization, septic workup and intravenous antibiotics pending culture findings. There are no accepted standard criteria for evaluation of SBI risk in Taiwan. In this study, we retrospectively examined a cohort of febrile infants (< 3 months of age) to assess significant SBI risk factors and hence develop and validate a model for predicting SBI.

Methods

Consecutive infants younger than 3 months of age who were admitted with fever between August 2003 and August 2004 were included for analysis. Fever was indicated when rectal temperature was ≥ 38°C. Those who were premature (born before 36 weeks of gestation) or who had underlying diseases (such as congenital heart disease, bronchopulmonary dysplasia, chronic lung disease, immunodeficiency, chromosome anomalies or congenital gastrointestinal tract anomalies) were excluded. Infants with hyperbilirubinemia and those who exhibited an antenatal setup for sepsis (premature rupture of membranes, maternal fever or peripartum antibiotics) were also excluded.

After admission, septic workup included a complete blood count, serum CRP analysis, urinalysis collected by urine bag, urine culture that was collected by suprapubic puncture or urinary catheterization, and blood cultures. Physical appearance was also graded by the attending pediatrician as either well or poor. Poor physical appearance was indicated by any of the following: decreased oral feeding, irritability, or any sign of dehydration (skin turgor, depressed fontanel, decrease urine output). If patients had diarrhea, bedside stool smears were obtained and immediately examined for WBC count. Chest X-rays were performed and evaluated if respiratory symptoms were apparent. Lumbar puncture and cerebrospinal fluid (CSF) analysis were performed if there was suspicion of central nervous system infection (i.e. seizure, irritability or drowsiness, bulging fontanel, toxic appearance with no infection focus). Each infant was treated with intravenous antibiotics while awaiting culture results.

SBI included bacteremia, bacterial meningitis, osteomyelitis, bacterial gastroenterocolitis, lobar pneumonia, and urinary tract infection. Urinary tract infection was defined as a single pathogen with a colony count exceeding 10^5/mL.

An IMMAGE Immunochemistry System (Beckman Coulter, Fullerton, CA, USA) was used to measure CRP in serum samples. The sensitivity of the test was 0.1 mg/dL, and the measurable range was from 0.1 mg/dL to 96 mg/dL.

Statistical analysis

Data are expressed as mean ± standard deviation or median (range) for continuous variables, and as number (%) for categorical variables. Differences between infants who did and did not have SBI were compared using Student's t test or the Wilcoxon rank sum test for continuous data, and the χ^2 or Fisher's exact test for categorical data. To determine the criteria for predicting SBI, 70% of the patients ($n = 99$) were randomly selected by simple random sampling for multivariate logistic regression. The estimated probabilities of having an SBI were obtained from the fitted model, and a cut-off point was selected for determining whether patients had SBI or not. The fitted regression model and the cut-off probability were then applied to the remainder of the patients for validation. All analyses were performed using SAS version 8.0 (SAS Institute Inc., Cary, NC, USA). A p value < 0.05 was considered to be statistically significant.

Results

The demographics and clinical features of infants who did and did not have SBI are presented in Table 1. A total of 135 febrile infants younger than 3 months of age were enrolled in the study; 34 (25.2%) were subsequently found to have SBI. The incidence of SBI was significantly higher in male infants and those older than 29 days at admission ($p < 0.01$ and 0.04, respectively, for both), while there was a decreased occurrence of SBI in infants who appeared well ($p = 0.03$). Infants with WBC count < 5,000/mm^3 or > 15,000/mm^3 were more likely to have SBI than those with WBC count of 5,000–15,000/mm^3 ($p = 0.02$). Infants with SBI had significantly higher levels of CRP and spun urine WBC count ($p < 0.01$ for both). With regards to the positive cultures, 82% were *Escherichia coli*. *Klebsiella pneumoniae* was detected in 2 infants. The 2 positive CSF cultures were group B streptococcus and Coxsackievirus. No non-SBI infant had positive blood or urine cultures. The single non-SBI infant (CSF viral culture revealed Coxsackie virus) who exhibited a positive CSF finding was diagnosed with

Table 1. Comparison of the demographic and clinical features of non-SBI and SBI patients

	Total ($n=135$)	Non-SBI ($n=101$)	SBI ($n=34$)	p
Age (d)*				0.04‖
<29	60 (44.44%)	50 (49.50%)	10 (29.41%)	
≥29	75 (55.56%)	51 (50.50%)	24 (70.59%)	
Sex†				<0.01‖
Male	90 (66.67%)	60 (59.41%)	30 (88.24%)	
Female	45 (33.33%)	41 (40.59%)	4 (11.76%)	
Appearance*				0.03‖
Well	105 (77.78%)	83 (82.18%)	22 (64.71%)	
Poor	30 (22.22%)	18 (17.82%)	12 (35.29%)	
Previously healthy				–
Yes	135 (100.00%)	101 (100.00%)	34 (100.00%)	
No	0	0	0	
Focal lesion†				0.17
Yes	108 (80.00%)	78 (77.23%)	30 (88.24%)	
No	27 (20.00%)	23 (22.77%)	4 (11.76%)	
WBC (count/mm^3)*				
5,000–15,000	97 (71.85%)	78 (77.23%)	19 (55.88%)	0.02‖
<5,000 or >15,000	38 (28.15%)	23 (22.77%)	15 (44.12%)	
Bands (%)‡	0 (0, 6)	0 (0, 5)	0 (0, 6)	0.13
Segments (%)§	47.80±18.34	46.44±16.91	51.85±21.83	0.14
Lymphocytes (%)§	40.28±16.64	41.32±15.79	37.20±18.87	0.21
Monocytes (%)‡	9 (1, 30)	10.0 (1.9, 30.0)	8 (1, 21)	0.10
CRP (mg/dL)†				<0.01‖
<3.6	67 (49.63%)	61 (60.4%)	6 (17.65%)	
≥3.6	68 (50.37%)	40 (39.6%)	28 (82.35%)	
Urine routine WBC‡	2.0 (0.2, 25.0)	2.0 (0.2, 25.0)	2.5 (1.0, 16.0)	0.25
Spun urine WBC count†				<0.01‖
<10/HPF (400×)	109 (80.74%)	95 (94.06%)	14 (41.18%)	
≥10/HPF (400×)	26 (19.26%)	6 (5.94%)	20 (58.82%)	
Urine bacterial culture†				<0.01‖
Positive	27 (20.00%)	0 (0.00%)	27 (79.41%)	
Negative	108 (80.00%)	101 (100%)	7 (20.59%)	
Blood bacterial culture†				0.01‖
Positive	3 (2.22%)	0	3 (8.82%)	
Negative	132 (97.78%)	101 (100.00%)	31 (91.18%)	
CXR†				0.45
Positive	10 (7.41%)	9 (8.91%)	1 (2.94%)	
Negative	125 (92.59%)	92 (91.09%)	33 (97.06%)	
CSF bacterial/viral culture†				<0.01‖
Positive	6 (4.44%)	1 (0.99%)	5 (14.71%)	
Negative	129 (95.56%)	100 (99.01%)	29 (85.29%)	

χ^2 test or †Fisher's exact test for categorical variables; ‡Wilcoxon rank sum test or §Student's t test for continuous variables; ‖$p<0.05$. SBI = serious bacterial infection; WBC = white blood cell; CRP = C-reactive protein; HPF = high-powered field; CXR = chest X-ray; CSF = cerebrospinal fluid.

aseptic meningitis (indicated if any of the following 4 findings was present: elevated CSF cell counts, increased intracranial pressure, positive CSF viral culture or positive electroencephalogram finding).

Sex, spun urine WBC count, and CRP were found to be significantly related to SBI (Table 2). Male infants, those with spun urine WBC count >10 per high-powered field (HPF; 400×), and CRP levels >3.6 mg/L had significantly increased risk of SBI ($p<0.05$ for all).

An estimated probability of SBI of 0.265 was selected as the cut-off point for predicting SBI as the

Table 2. Association between risk factors and SBI for 99 randomly selected patients (training sample) by multivariate logistic regression*

	OR	95% CI	*p*
Age (d)			0.41
≥29	0.52	(0.11–2.41)	
<29	Reference	–	
Sex			0.04†
Male	5.53	(1.06–28.82)	
Female	Reference	–	
Appearance			0.63
Poor	0.69	(0.15–3.11)	
Well	Reference	–	
WBC (count/mm^3)			0.89
<5,000 or >15,000	0.90	(0.20–4.09)	
5,000–15,000	Reference	–	
CRP (mg/dL)			<0.01†
≥3.6	9.54	(1.81–50.31)	
<3.6	Reference	–	
Spun urine WBC count			<0.01†
≥10/HPF (400×)	26.20	(5.35–128.25)	
<10/HPF (400×)	Reference	–	

**Positive likelihood ratio was 4.23, and negative likelihood ratio was 0.25; †significantly related to SBI, p < 0.05. SBI = serious bacterial infection; OR = odds ratio; CI = confidence interval; WBC = white blood cell; CRP = C-reactive protein.*

Table 3. Variations of probability for several cutoffs

Probability	Sensitivity	1 – Specificity
0.1169951	0.853	0.277
0.1865525	0.853	0.248
0.2550711	0.853	0.238
0.2649594	0.800	0.189
0.2739782	0.765	0.119
0.2897805	0.765	0.109
0.3308014	0.706	0.069

specificity was approximately equal to the sensitivity at this point. Infants with a probability ≥0.265 were considered to be at high risk for SBI. Those with probabilities below this value were considered to have low risk of SBI. Sensitivity and specificity were 80% and 81.1%, respectively (Table 3). To validate the criteria for predicting SBI, the fitted model and cut-off probabilities were applied to the 36 other patients not used for construction of the model. Both sensitivity and specificity were 77.8%.

Discussion

There have been many studies published that report low risk factors for SBI in young febrile infants. Despite this, there exists no uniformly accepted strategy for identifying such infants. In this study, we retrospectively examined infants younger than 3 months of age who were admitted with fever for SBI risk factors. We determined that sex, spun urine WBC count and serum CRP concentration were predictive of SBI. We further utilized these variables to construct and validate a model for predicting SBI.

As already noted, numerous studies have reported risk factors for SBI in infants. The Rochester criteria and the Philadelphia protocol are 2 popular assessment methods for predicting low risk of SBI. These methods include a range of variables including physical appearance, age, previous health and WBC counts in serum, spun urine, CSF and stool for assessment. A recent study by Garra and colleagues utilized both assessment techniques to determine low SBI risk in a cohort of infants aged ≤56 days.[18] It was found that the negative predictive values (NPV) for SBI in these infants were 97.1% and 97.3% for the Philadelphia protocol and Rochester criteria, respectively. A study conducted by Bachur and Harper incorporated urinalysis, WBC count, temperature and age as risk factors for SBI in infants younger than 90 days of age and found an NPV of 98.3%.[6] Another large study conducted in Taiwan yielded an NPV of 99.2% for SBI, where risk parameters included physical examination results, WBC count, differential count, urinalysis, stool exam and CRP levels.[5] While all of these

studies indicate that it is possible to achieve high rates of selectivity with respect to identifying infants at low risk for SBI, none could discriminate with 100% certainty.

Approximately one quarter of the infants included in our study were found to have SBI. Although at the upper end, this level of occurrence falls within the range of values reported in the general literature.[1–8] We determined that the incidence of SBI was higher in infants who were male, in those older than 29 days, with poor appearance, WBC count outside of the range 5,000–15,000 counts/mm^3, and those with higher CRP levels and spun urine WBC counts ≥10/HPF (400×). On further multivariate regression analysis, it was determined that sex, spun urine WBC count and serum CRP concentration were significantly related to SBI. Other studies have also found/utilized these measures to indicate SBI risk. The CRP cut-off of 3.6 mg/L utilized in our study is significantly lower than those reported in a number of other studies.[10,15,19] However, we have found that the normal CRP range is 0–5 mg/L. The spun urine WBC count cut-off of ≥10/HPF (400×) is the same as used in both the Rochester criteria and Philadelphia protocol.[3,13] To our knowledge, no other study has found sex to be a significant risk factor for SBI. This may simply be a reflection of the relatively small study sample size or the fact that urinary tract infections are more common in uncircumcised male infants.

Using the 3 significant risk factors of sex, CRP and spun urine WBC count, a cut-off probability for SBI was selected where infants with values below this probability were considered to have a low risk of SBI, and those above a high risk. This model was employed to assess SBI risk in a small cohort of febrile infants and found to be accurate in predicting SBI status. Hence, it would appear that sex, serum CRP concentrations and spun urine WBC count can be successfully employed to classify infants younger than 3 months of age as being at high or low risk for SBI.

Several studies have reported on the treatment of febrile infants at low risk for SBI as determined by various criteria. Baker et al reported that it is safe for low risk infants, aged 29–56 days, to be treated as outpatients and without antibiotics.[13] A study by Baskin and colleagues suggested that close outpatient monitoring with intramuscular ceftriaxone treatment is a successful alternative to hospital admission for infants aged 28–89 days.[2] Several other studies have suggested that low-risk infants should be hospitalized either without antibiotic treatment[5] or without antibiotic treatment until culture findings are available.[4,20] The latter treatment paradigm was not associated with any increase in morbidity when compared to infants in whom antibiotic treatment was initiated on admission. Hence, there is no consensus as to how low-risk SBI infants with fever should be treated assuming immediate antibiotic therapy is not instigated. Home care with vigilant parental supervision would appear to be the ideal option, but further study is needed to determine the optimal balance between infant and parental comfort and infant health.

Certainly, a major limitation of this study is the small sample size. With this in mind, we suggest that larger-scale, multicenter, randomized, controlled studies are warranted to further validate the criteria utilized in this study for predicting SBI status. It is also necessary to determine whether or not these criteria can be successfully applied in infants within a specific, less broad age range, i.e. <1 month old, >3 months old, and so on.

In conclusion, we have studied a group of febrile infants less than 3 months old, and found that sex, serum CRP concentration and spun urine WBC count could be utilized to predict SBI with a high degree of sensitivity and specificity. As our study population was relatively small, additional studies are warranted to further validate this assessment model.

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