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Severe bacterial infection in young infants with pyrexia admitted to the emergency department

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Abstract

The objectives of this study were to understand the clinical presentations of febrile young infants with severe bacterial infection (SBI), and to investigate the pathogen variations throughout the vaccine era and after antenatal group B *Streptococcus* (GBS) screening.

All infants < 90 days old with a body temperature of ≥38.0°C and admitted to the emergency department were retrospectively enrolled in our study. SBI was defined as a positive culture of urine, blood, or cerebrospinal fluid. All clinical variables were analyzed and compared between the SBI group and the non-SBI group, to identify the relevant risk factors for SBI in infants with pyrexia.

A total of 498 infants were studied, 279 of whom (56%) had SBI. The body temperature at triage was higher in the SBI group, and the difference was highly obvious in the neonatal group. White blood cell count and C-reactive protein levels were both significantly higher in the SBI group ($P < .05$), whereas neutrophil percentage and band percentage demonstrated no significant differences. *Escherichia coli* was the most common pathogen and plasmid-mediated extended-spectrum lactamases were detected in up to 9.1%. GBS was detected in 16 cases of bacteremia (6 cases with concurrent meningitis).

The body temperature at triage may provide a clue for differentiating sick babies, especially in the neonatal group. Complete serum analysis is required for infection survey, especially white blood cell and C-reactive protein. *Escherichia coli* is the most common pathogen, and clinician should raise awareness of drug resistance in some patients. The prevalence of GBS infection in the young infant group remains high after routine antenatal GBS screening

Abbreviations: CRP = C-reactive protein, ED = emergency department, GBS = group B *Streptococcus*, SBI = severe bacterial infection, UTI = urinary tract infection, WBC = white blood cell.

Keywords: bacteremia, fever, infant, meningitis, urinary tract infection

1. Introduction

A core temperature of ≥ 38°C is considered fever and is the most common reason for infants to visit the emergency department (ED).[1] Although viral infection is the most common cause of fever in young infants, the literature reports severe bacterial infection (SBI) rates of up to 12% in infants aged < 28 days and up to 9% in infants aged 1 to 3 months.[2–7]

When evaluating febrile young infants, the goal is to identify infants who are at a high risk for SBI and therefore require hospitalization for empiric antimicrobial therapy. Several clinical prediction models are available to help guide the practitioner's medical decision-making about diagnostic evaluations and therapeutic interventions, such as the Yale Observation Scale,[8] Philadelphia protocol,[3,9] Boston criteria,[10] Milwaukee proto-

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col,[11] Rochester criteria,[7,12] and Young Infant Observation Scale.[13] However, these tools may not have sufficient power to identify serious illness in all febrile infants.[14–16] In addition, their sensitivities and specificities differ when they are applied to infants from different age groups.

In this study, we aimed to analyze febrile infants < 90 days old admitted from the ED to understand the clinical differences and initial presentations of febrile young infants with SBI, and to identify how the findings vary by age (from 0 to 3 months). Moreover, we also aimed to analyze the possible pathogen variations throughout the vaccine era and after antenatal group B *Streptococcus* (GBS) screening.

2. Materials and methods

2.1. Patient population

This was a retrospective cohort study conducted at China Medical University Children's Hospital, a tertiary care pediatric hospital in central Taiwan, between January 1, 2014 and December 31, 2017. All infants aged < 90 days who visited the ED with fever were included in our study. However, infants with a previously identified immunodeficiency, chronic disease, vesicoureteral reflux requiring antibiotic prophylaxis, immunizations in the 48 hours preceding the visit, or prematurity (gestational age < 35 weeks) were all excluded from further analysis. Our study was approved by the institutional review board of China Medical University Hospital in Taiwan. All methods were performed in accordance with the relevant guidelines and regulations. Data were collected, reviewed, de-identified, and anonymized before analysis, and the ethics committee waived the requirement for informed consent owing to the anonymized nature of the data and the scientific purpose of the study.

2.2. Study design

The following variables were recorded and analyzed: age, sex, gestational age, body weight, admission weight, delivery method (normal spontaneous delivery or cesarean section), vital signs at triage in the ED and during hospitalization, length of hospital stay, and activity of the infants. The laboratory test results at the time of admission and during hospitalization were also recorded. In this study, all included infants with pyrexia were divided into 2 groups: SBI group and non-SBI group. SBI was diagnosed according to the following criteria:

(1) urinary tract infection (UTI), defined as a urine culture (from catheterization) with > 50,000 colony-forming units/mL;
(2) bacteremia, defined as a positive blood culture result for a pathogen; and
(3) bacterial meningitis, defined as a positive cerebrospinal fluid culture result for a pathogen.

We further analyzed the patients based on different age groups, as follows: infants aged < 30 days (group 1), 30 to 59 days (group 2), and 60 to 89 days (group 3). All clinical variables were analyzed and compared between the SBI group and the non-SBI group to identify the relevant risk factors for SBI in infants with pyrexia.

2.3. Statistical analysis

Statistical analyses were performed using the *t*-test and chi-square test. The results of the descriptive analyses of independent variables are reported as percentages and mean ± standard deviation. Differences between the 2 groups are presented with their 95% confidence intervals. Statistical significance was defined at the $P < .05$ level, and all statistical analyses were conducted using IBM SPSS Statistics software (version 22.0; SPSS Inc., Chicago, IL).

3. Results

A total of 498 infants with pyrexia who were admitted to the ED during the 4-year study period were enrolled in this study (median age 54 days). The overall prevalence of SBI was 56%. Of the 279 infants with SBI, 10 (3.6%) had positive blood cultures, 245 (87.8%) had positive urine cultures, and only 2 (0.7%) had positive cerebrospinal fluid cultures. Among the infants with SBI, 12 (4.3%) had urosepsis (concurrent UTI and bacteremia) and 7 (2.5%) had concurrent bacteremia and bacterial meningitis.

The demographics and laboratory results are listed in Table 1. With respect to clinical parameters, no difference was observed between the non-SBI and SBI groups in age, gestational age at birth, birth weight, and admission weight. The logistic regression models to determine factors associated with SBI is listed in Table 2. The body temperature at triage tended to be higher in the SBI group (38.17°C vs 38.46°C, $P < 0.001$); however, the pulse rate at triage did not show a significant difference when we performed both multivariate analysis and a subgroup analysis of the patients based on age. Male sex percentage (53% vs 75.6%, $P < 0.001$) and length of hospital stay (4.1 vs 6.5 days, $P < 0.001$) were significantly higher in the SBI group than in the non-SBI group. With respect to blood laboratory studies, white blood cell (WBC) counts (10,519.3/μL vs 13,943.6/μL) and C-reactive protein (CRP) levels (13.7 vs 38.3 mg/L) were significantly higher in the SBI group than in the non-SBI group (both $P < 0.05$), whereas neutrophil percentage and band percentage demonstrated no significant differences between the 2 groups (Table 1).

Among the various age groups, group 1 infants with SBI presented with a higher body temperature at triage than group 1 infants without SBI (38.11°C vs 38.49°C, $P < .05$). However, no significant difference was observed in the maximal body temperature of pyrexia after admission and in the fever subsidence time. In blood laboratory data, CRP levels were significantly higher in infants with SBI than in infants without SBI in all the 3 age groups. However, WBC and total neutrophil counts were significantly higher in infants with SBI in group 2 and group 3 (both $P < .05$), but no significant difference was observed in group 1 (11,349/μL vs 13,391/μL, $P < .05$). Moreover, band percentage showed no significant difference between the SBI and non-SBI groups in all 3 age groups (Table 3). With respect to possible pathogens in infants with SBI, *Escherichia coli* (*E coli*) was the most common pathogen, responsible for 219 (86.2%) of the UTI cases (including 12 cases with bacteremia). In 30 cases of bacteremia, GBS was noted in 16 cases, including 6 cases of meningitis, and *E coli* was detected in 12 cases, including urosepsis in 11 cases. The prevalence of bacteremia was 9.01% (11/122) in group 1, 8.02% (13/162) in group 2, and 2.8% (6/214) in group 3 (Table 4).

4. Discussion

Hyperthermia in young infants is considered an alarming condition indicative of hidden systemic infections. It is important for emergency physicians to rapidly identify infants with

Table 1

Comparison of clinical characteristics, vital signs, and blood laboratory findings in febrile infants in the SBI and non-SBI groups.

Variables	Non-SBI (n = 219)	SBI (n = 279)	*P*-value
Age, mean ± SD (d)	50.4 ± 24.37	52.4 ± 23.54	.351
Male sex, n (%)	116 (53%)	211 (75.6%)	<.001
Duration of hospital stay, mean ± SD (days)	4.1 ± 2.9	6.5 ± 5.5	<.001
GA, mean ± SD (wk)	38.27 ± 1.37	38.34 ± 1.27	.150
Birth weight, mean ± SD (g)	3085.1 ± 413.2	3065.7 ± 389	.596
Admission weight, mean ± SD (g)	4713.7 ± 1105.6	4889.35 ± 1114.1	.081
BT at triage, mean ± SD (°C)	38.17 ± 0.71	38.46 ± 0.78	<.001
Highest BT after admission, mean ± SD (°C)	38.56 ± 0.48 (n = 85)*	38.63 ± 0.57 (n = 146)*	.361
Fever subsidence time, mean ± SD (d)†	2.16 ± 1.39	2.2 ± 1.46	.798
Pulse rates at triage, mean ± SD (/min)	168.47 ± 19.85	172.53 ± 21.33	.030
Laboratory data (blood)			
WBC, mean ± SD (/□L)	10,519.3 ± 5047.5	13,943.6 ± 6200.7	<.001
Neutrophils (%)	44.61	54.54	.004
Bands (%)	0.19	0.07	.146
CRP, mean ± SD (mg/L)	13.7 ± 31.3	38.3 ± 48.5	<.001

BT = body temperature, CRP = C-reactive protein, GA = gestational age, SBI = severe bacterial infection, SD = standard deviation, WBC = white blood cell.

* Data collected in patients who still had a body temperature of > 38°C after admission.

† Defined as the days during which no fever episode was detected for a consecutive 48-h period.

hyperthermia who require transfer for further investigations for SBI or immediate treatments. However, in pediatric EDs, it remains challenging to identify febrile infants who require transfer based on clinical histories and vital signs at triage without further relevant examinations. Previous studies reported that the highest body temperature of febrile young infants in the pediatric ED may be a risk factor for the rate of positive blood culture.[17,18] In our study, we noticed that the body temperature at triage may serve as an important clue to differentiate sick babies in the pediatric ED, especially in infants aged < 30 days and between 60 and 89 days. In these 2 age groups, infants with SBI had a higher body temperature than those without SBI. Another universal vital tool, heart rate, is routinely monitored in septic newborns as an early sign of potentially catastrophic illness.[19,20] However, some studies in febrile young infants demonstrated that heart rate could not satisfactorily predict serious infection.[21] In our study, we found that pulse rate at triage on admission to the ED had a significant difference between the non-SBI and SBI groups of febrile infants. Infants with SBI had higher heart rates at triage on admission to the pediatric ED than those without SBI. In addition, the duration of hospital stay in infants with SBI was longer than that in infants without SBI, especially in those aged < 60 days, indicating severe clinical courses in young infants < 60 days old with SBI.

In routine blood laboratory examinations, we found that the WBC counts, total neutrophil counts, and CRP levels were significantly higher in the SBI group than in the non-SBI group. However, when the data were further divided into different age groups, WBC counts and total neutrophil counts were not reliable predictors in infants aged < 30 days. A previous cohort study that focused on WBC counts in febrile neonates showed modest discriminatory power in identifying neonates with bacterial infections, with substantial overlap among groups, and suggested against the use of any WBC count threshold to identify bacterial infections.[22] In contrast, the CRP levels were all higher in the different age groups in infants with SBI than in those without SBI. Except for WBC count and CRP level, a wide variety of laboratory thresholds were applied alone or in combination across previous studies. Some studies have demonstrated that a single marker is not sufficient to serve as a stand-alone indicator for diagnosis.[23] Recent investigations have incorporated the use of laboratory tests, especially procalcitonin, CRP, and urine dipstick, into clinical algorithms to optimize the identification of SBI among febrile infants.[24] However, Bressan et al. still reported a high misdiagnosis rate when these biomarkers were used (30%).[25]

The rate of bacteremia (detection of pathogen in blood culture) in our study was 6.02% (30/498). A trend of decreasing prevalence has been demonstrated, from 9.01% in the neonate group, to 8.02% in infants aged 30 to 59 days, and to 2.8% in infants aged 60–89 days. Given that the overall prevalence of SBI has been reported to be higher in neonates, most experts recommend full sepsis evaluation and hospitalization.[4,26] In Taiwan, antenatal GBS screening and the use of intrapartum

Table 2

Logistic regression with univariate and multiple analysis to identify factors associated with SBI.

	Univariate analysis			Multivariate analysis (adjusted)		
	OR	95% C.I.	*P*-value	OR	95% C.I.	*P*-value
Gender	2.755	1.882–4.033	<.001	2.715	1.782–4.137	<.001
BT At triage	1.672	1.307–2.140	<.001	1.795	1.363–2.363	<.001
Pulse rates at triage	1.010	1.001–1.018	.031			
WBC/100	1.119	1.080–1.160	<.001	1.101	1.058–1.145	<.001
Neutrophil	1.038	1.025–1.051	<.001			
CRP	1.250	1.157–1.351	<.001	1.154	1.070–1.245	<.001

BT = body temperature, CRP = C-reactive protein, SBI = severe bacterial infection, WBC = white blood cell.

Table 3

Clinical findings and laboratory results among various age groups in young infants below 90 days of age with pyrexia.

	< 30 d (n = 122)			30–59 d (n = 162)			60–89 d (n = 214)		
Age	**Non-SBI**	**SBI**	***P*- value**	**Non-SBI**	**SBI**	***P*- value**	**Non-SBI**	**SBI**	***P*- value**
Male sex, n (%)	22 (39.3%)	55 (83.3%)	< .001	40 (54.1%)	68 (77.3%)	.002	54 (60.7%)	88 (70.4%)	.138
GA, mean ± SD (weeks)	38.71 ± 1.44	38.27 ± 1.3	.075	38.14 ± 1.35	38.40 ± 1.19	.194	38.08 ± 1.29	38.35 ± 1.31	*.352*
Birth weight, mean ± SD (g)	3214.9 ± 414.7	3062.8 ± 419.4	.052	3029.5 ± 401.5	3033.8 ± 384.0	.945	3053.2 ± 409.7	3090.2 ± 377.3	.503
Admission weight, mean ± SD (g)	3544.4 ± 589.1	3558.9 ± 706.4	.903	4588.6 ± 633.6	4735.5 ± 607.6	.903	5572.9 ± 925.7	5700.2 ± 800.2	.287
Clinical variables									
BT at triage, mean ± SD (°C)	38.11 ± 0.63	38.49 ± 0.69	.002	38.2 ± 0.67	38.43 ± 0.83	.067	38.18 ± 0.8	38.47 ± 0.8	.010
Pulse rate at triage, mean ± SD (/min)	164.64 ± 20.55	170.94 ± 17.38	.069	173.15 ± 21.2	172.19 ± 22.3	.544	168.72 ± 18.0	172.93 ± 22.6	.132
Highest BT after admission, mean ± SD (°C)	38.45 ± 0.32	38.52 ± 0.53	.618	38.56 ± 0.41	38.65 ± 0.59	.009	38.61 ± 0.57	38.67 ± 0.57	.642
Fever subsidence period, mean ± SD (date)*	1.89 ± 1.1	2.05 ± 1.2	.514	2.15 ± 1.54	2.48 ± 1.83	.292	2.33 ± 1.4	2.07 ± 1.25	.221
Duration of hospital stay, mean ± SD (d)	4.02 ± 2.49	7.86 ± 5.07	<.001	3.97 ± 2.76	7.91 ± 6.86	<.001	4.17 ± 3.27	4.87 ± 3.92	.168
Laboratory data (blood)									
WBC, mean ± SD (/μL)	11,349 ± 4964	13,391 ± 6758	.058	8628 ± 3695.7	12920 ± 6481.9	<.001	11578 ± 5639.4	14955 ± 5553.6	< .001
Neutrophils (%)	54.87	60.28	.633	39.4	49.25	<.001	42.60	55.23	.003
Bands (%)	0.47	0.22	.438	0.15	0.00	.081	0.06	0.04	.549
CRP, mean ± SD (mg/L)	18.0 ± 41.1	45.0 ± 62.6	.006	8.8 ± 15.8	36.1 ± 50.2	<.001	15.0 ± 33.8	36.4 ± 38.1	< .001

BT = body temperature, CRP = C-reactive protein, GA = gestational age, SBI = severe bacterial infection, SD = standard deviation, WBC = white blood cell.
* Defined as the date during which no fever episode was detected for a consecutive 48-h period.

chemoprophylaxis have been recommended since 2010 and have been widely implemented since 2012. However, in our data collected during 2014 to 2017, GBS still accounted for the majority of sepsis and meningitis cases. According to a study which was conducted in pre antenatal GBS screening era, pathogens isolated from 120 patients younger than 60-day-old, GBS accounts for 11.6%. Similar to our study, GBS is the second main pathogen reported in febrile young infant who diagnosed as SBI. The percentage and ranking did not change through the past 2 decades.[27] As reported in a Cochrane review,[28] these measures can reduce the incidences of early-onset GBS infection, although they do not influence the epidemiology of late-onset GBS infection. In addition, *E coli* was the most common pathogen responsible for SBI, especially UTI. Recent reports have shown the emergence of resistant organisms and changes in epidemiology of bacterial infections, especially increases in members of the *Enterobacteriaceae* family.[27,29] One study in Utah reported that more than half of SBI pathogens in febrile young infants were resistant to ampicillin.[30] In our study, plasmid-mediated extended-spectrum lactamases were detected in up to 9.1% (20/219) of patients with UTI due to *E coli* and in 10% (1/10) of patients with UTI due to *Klebsiella pneumoniae*. Considering that a certain percentage of UTI cases in young infants are associated with bacteremia (4.7% in our study), empirical ampicillin may provide inadequate coverage in these febrile young infants.

Table 4

Comparison of pathogens in febrile infants with SBI in the different age groups.

		SBI		
	Total	**Age 0–29 d**	**Age 30–59 d**	**Age 60–89 d**
n (SBI/total)	279/498	66/122	88/162	125/214
UTI	254	60	78	116
E coli	219	49	67	103
E coli with bacteremia	10	4	5	1
Enterococcus	18	3	6	9
KP	10	5	2	3
KP with bacteremia	1	1	0	0
GBS	3	2	0	1
GBS with bacteremia	1	1	0	0
Bacteremia	30	11	13	6
GBS	16	4	7	5
GBS with meningitis	6	1	3	2
E coli	12	6	5	1
KP	1	1	0	0
MRSA	1	0	1	0
MRSA with meningitis	1	0	1	0
Meningitis	9	1	4	4
GBS	6	1	3	2
E coli	2	0	0	2
MRSA	1	0	1	0

E coli = *Escherichia coli*, GBS = group B Streptococcus, KP = Klebsiella pneumoniae, MRSA = methicillin-resistant Staphylococcus aureus, SBI = severe bacterial infection, UTI = urinary tract infection.

There are limitations in our study. Since it is a retrospective study, the timing of laboratory analysis included serum markers, urine culture, and blood culture were uncertain. Associated symptoms, physical finding of the patients upon admission, and detail of core temperature measurement which relied on accurate record were not included.

5. Conclusion

Clinical presentations (such as body temperature at triage) and blood laboratory parameters (such as WBC count, total neutrophil count, and CRP level) may provide clues for the initial differentiation of infants with SBI in the pediatric ED. However, in the neonatal group, further analysis and hospitalization should be considered owing to the unpredictability of their clinical course. Moreover, *E coli* is the most common pathogen in young febrile infants and drug resistance may be observed in certain patients. In addition, even with routine antenatal GBS screening, the prevalence of GBS infection in young infants remained high during our study period.

Author contributions

H.P.W. conceived of the presented idea. E.P.L designed the study. Y.J C performed the computations and verified the analytical methods. B.Y.L. reviewed the medical records and acquired the data. Y.T.C drafted the manuscript. All authors discussed the results and contributed to the final manuscript.
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