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Etiology, Clinical Profile, and Related Factors of Serious Bacterial Infection in Children Hospitalized with Fever without A Source

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ABSTRACT

BACKGROUND AND OBJECTIVE: Fever in children is one of the most common reasons that cause parents to go to the pediatric clinic for medical care. Differentiating between benign self-limiting viral disease and a serious bacterial infection is a major challenge for pediatricians. The present study was conducted to determine the etiology, clinical profile, and related factors of serious bacterial infection in children hospitalized with fever without a source.

METHODS: This descriptive-analytical and cross-sectional study was performed on 241 children with fever greater than or equal to 38 ºC without other symptoms hospitalized in pediatric emergency ward of Ali-Ebne-abitaleb hospital in 2020. Demographic information and laboratory findings of patients as well as other information was obtained through history taking and recorded in information form. Then, children were examined for viral or bacterial fever in two groups.

FINDINGS: Out of 241 examined children, 90 patients (37.3%) had severe bacterial infection (SBI) and 151 patients (62.7%) had viral infection. There was a significant difference between variables such as age, number of siblings, history of respiratory infections in parents and birth weight between the two bacterial and viral groups (p=0.001). The white blood cell count, neutrophil percentage, platelets and duration of fever were significantly different between the two groups (p=0.001).

CONCLUSION: Results showed that some laboratory and clinical factors are different between the two bacterial and viral groups and can help us differentiate them.

KEY WORDS: *Fever without A Source, Children, Bacterial Infection, Viral Infection.*

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Introduction

Fever in children is one of the most common causes that draw parents to pediatric clinics for medical care and is one of the most common causes that results in hospitalization in pediatric group and is a challenge for clinicians due to wide spectrum clinical presentations and differential diagnosis (1-3). In some references, the prevalence of referrals to pediatric clinics due to fever is estimated at 19 to 30% and in others about 50% (2, 3). On the other hand, the age of 3-36 month is more challenging for pediatricians due to the lack of cooperation of child for physical examination and appropriate antibiotic choosing (4).

Fever occurs in the body during the reaction to the release of internal febrile agents during infections, inflammatory processes, rheumatism and malignancy, as well as external febrile agents such as microbes and toxins (1). Globally, 5.4 million children under the age of 5 die, accounting for approximately 50% of all deaths from infectious diseases, many of which are manifested by fever (5). Occasionally children develop fever without a source (FWS), especially at less than 36 months of age, and history and physical examination cannot determine the source of the infection. The cause of fever may be mild viral infections that are usually self-limiting to serious bacterial infections (SBIs) such as urinary tract infections, bacteremia, and bacterial meningitis (6, 7).

Differentiating between benign self-limiting viral disease and a serious bacterial infection is an important challenge for pediatricians (5, 6). This diagnosis remains challenging because a wide range of infections can cause fever in a child. Overlapping manifestations of serious bacterial infections (SBI) with other viral, fungal, parasitic, and systemic inflammatory diseases and neoplasms complicate the diagnosis (8).

Sudden fever greater than or equal to 38 degrees Celsius without other symptoms is a diagnostic conundrum in children under 36 months of age. These patients are difficult to assess because of difficulty of differentiating self-limiting viral disease from a serious bacterial infection. Incomplete immune system in the first months of life increases the importance of fever in the baby. Generally, a baby with a fever is more likely to develop a serious bacterial infection. Many experts believe that infants less than 28 days old should be hospitalized and treated. Children older than 2 months who have a fever are more likely to have viral causes, but there is also the possibility of a serious bacterial infection. However, in this age group, it is easier to make a diagnosis based on symptoms and clinical examination. Serious bacterial infections include occult bacteremia, meningitis, pneumonia, osteomyelitis, septic arthritis, and urinary tract infections. Serious bacterial infection occurs in 7-13% of cases, the most common cause of which is urinary tract infection with a prevalence of 5-13%. Bacteremia occurs in 1-2% of cases and meningitis in 0.2-0.5 cases. Infants with normal appearance are more likely to have viral causes, the most common of which are rhinovirus, adenovirus, enterovirus, influenza, and parainfluenza (9).

With the development of the Haemophilus influenzae and pneumococcal vaccines, the rate of infection with these pathogens has greatly decreased. Generally, a child with a fever without a source at the age of less than 28 days or more than 28 days with toxic appearance and abnormal clinical signs such as tachycardia and tachypnea should be hospitalized and treated. However, Philadelphia Rochester and Boston criteria can be used in children older than 28 days and with a non-toxic appearance (9).

Phasuk et al. in 2020 showed that evaluation of fever in children requires more attention in the field of urinary tract diseases (4) or in Toll's study, it was suggested that examination of patients with fever without a source in areas that do not receive vaccination against Hinf and PCV depends on blood culture and initiation of imperial antibiotics (10). Trippella et al. showed that the use of inflammatory markers such as procalcitonin is also very helpful in diagnosing patients with fever without a source (11).

Due to the necessity of diagnosis and treatment of fever without a source and differentiation of a self-limiting viral disease from a serious bacterial infection, the present study was conducted to determine the etiology, clinical profile and related factors of serious bacterial infection in children hospitalized with fever without a source.

Methods

The present study was performed after obtaining the permission from Ethics Committee of Zahedan University of Medical Sciences with the code IR.ZAUMS.REC.1399.004 and obtaining permission from the hospital director. This descriptive-analytical cross-sectional study was conducted in 2020. The study population consisted of all children with fever greater than or equal to 38 °C without other symptoms and for less than a week in the pediatric emergency

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department of Ali Ibn Abitaleb Hospital in Zahedan in 2020. After the necessary arrangements, the researcher was present in the pediatric emergency department and began to collect information by explaining the purpose of the study to the parents of hospitalized children.

The sample size included 241 patients with fever without a source who were admitted to the emergency department in a period of 11 months and after evaluation were included in the study according to the inclusion criteria. All children from birth to 3 years with fever without a source that had a rectal temperature greater than or equal to 38° C, no chronic disease (liver failure, renal failure, heart disease malignancy), no underlying immunodeficiency, and children who have not been treated with immunosuppressive drugs were included in the study.

Data collection tools included demographic information form containing age, sex, number of siblings, information about the course of the disease such as duration of fever, previous illness, accompanying symptoms, birth weight, child exposed to cigarette smoke, history of recent respiratory infection in the family, obtained through history and recorded in the information form. Laboratory results registration form included complete blood cell count, urine and fecal examination, blood culture, urine culture and cerebrospinal fluid culture and the form of registration of symptoms and course of patient hospitalization.

In this study, no additional tests were performed on the patient and the results of routine tests performed on patients were used. Boston diagnostic criteria were used in the examination of patients less than 3 months of age, and for older ages, Nelson Pediatric Symptom-Based Diagnosis was used (9). Patients also underwent a full physical examination at the beginning of hospitalization and important and positive points of the examination were recorded in the information form.

Chest radiographs were also requested in some patients with respiratory symptoms. During hospitalization, patients were evaluated for general condition and fever. In cases where more than 5 white blood cells were reported in a urine test and confirmed by positive urine culture, urinary tract infection was diagnosed and in cases where blood culture with a single positive pathogen was reported, it was considered bacteremia. Cases with positive cerebrospinal fluid culture were considered as meningitis. In some cases, BACTEC blood culture was used. Children were examined for viral or bacterial infections in two groups. Data were analyzed using independent t-test and chi-square in SPSS 20 and $p<0.05$ was considered significant.

Results

A total of 407 patients aged 0-36 months with fever without a source were admitted to the pediatric emergency department. 166 patients were not included due to lack of inclusion criteria. Of these 166 patients, 5 patients had underlying immunodeficiency, and 161 children had chronic diseases (liver failure, renal failure, malignancy, heart disease). Finally, 241 eligible patients were included in the study.

The mean age of children was 16.98±9.03. 50.6% were girls and 49.4% were boys. Of the 241 children studied, 90 patients (37.3%) had a serious bacterial infection (SBI) and 151 patients (62.7%) had a viral infection. In patients with severe bacterial infection, 28 had bacteremia, 15 had pneumonia, 44 had urinary tract infection and 3 children had meningitis. There was a total of 71 positive cultures, including 28 positive blood cultures, 44 positive urine cultures and 3 positive cerebrospinal fluid cultures (Table 1).

Comparison of mean clinical and laboratory variables in bacterial and viral groups showed that the mean number of white blood cells, platelets, neutrophils and duration of fever in the bacterial infection group was higher than the viral infection group and this difference was statistically significant ($p<0.05$) (Table 2).

Among the variables, age, number of siblings, history of respiratory infections in parents and birth weight were significantly different between bacterial and viral groups. The mean age of children in the bacterial infection group was lower than the viral infection group ($p=0.001$). Also, in terms of child weight, in the bacterial group, the number of children weighing less than 2500 g was more than the viral infection group and the mean weight between the two groups was statistically significant (Table 3).

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Table 1. Demographic, clinical and laboratory characteristics of patients

Variable	Mean±SD or number(%)	Minimum and maximum
Age (months)	16.98±9.03	0.36-16
White blood cell count	12.39±5.12	2-4.23
Hemoglobin	11.49±1.27	6.5-8.17
Platelets	384.21±155.27	125-890
Neutrophils	44.51±27.88	12-95
Duration of fever	2.99±1	1-6
Hospital stay	4.7	2-14
Gender		
Girl	122(50.6)	
Boy	119(49.4)	
Siblings		
Does not have	24(10)	
One	131(54.4)	
Two and more	86(35.7)	
Weight		
less than 2500	18(7.5)	
2000-4000	213(88.4)	
More than 4000	10(4.1)	
Recent family history of respiratory infection		
Yes	69(28.6)	
No	172(71.4)	
Cigarettes		
Yes	98(40.7)	
No	143(59.3)	
CSF Culture		
Positive	3(1.2)	
Negative	238(98.8)	
Blood culture		
Positive	28(11.6)	
Negative	213(88.4)	
Urine culture		
Positive	40(16.6)	
Negative	201(83.4)	

Table 2. Comparison of mean clinical and laboratory variables in bacterial and viral groups

Group Variable	Bacterial Mean±SD	Viral Mean±SD	p-value
WBC	17.98±1.77	9.06±3.19	0.0001
HB	11.58±1.6	11.44±1.02	0.453
PLT	462.97±148.82	337.27±139.62	0.0001
NT	77.22±10.02	25.02±12.64	0.0001
Duration of fever	3.36±0.96	2.77±0.96	0.0001

Table 3. Comparison of demographic and clinical variables between bacterial and viral groups

Group Variable	Bacterial n=90 Mean±SD number(%)	Viral n=151 Mean±SD number(%)	p-value
Age	11.9±8.56	20.1±7.9	0.0001
Gender			
Girl	43(47.8)	79(52.3)	0.495
Boy	47(52.2)	72(47.7)	
Siblings			
Does not have	4(4.4)	20(13.2)	0.0001
One	25(27.8)	106(70.2)	
Two and more	61(67.8)	25(16.6)	
Recent family history of respiratory infection			
Yes	41(45.6)	28(18.5)	0.0001
No	49(54.4)	123(81.5)	
Cigarettes			
Yes	41(45.6)	57(37.7)	0.233
No	49(54.4)	94(62.3)	
Weight			
Less than 2500	13(14.4)	5(3.3)	0.004
2000-4000	72(80)	141(93.4)	
More than 4000	5(5.6)	5(3.3)	
CSF Culture			
Positive	3(3.3)	0(0)	0.024
Negative	87(96.7)	151(100)	
Blood Culture			
Positive	28(31.1)	0(0)	0.0001
Negative	62(68.9)	151(100)	
Urine Culture			
Positive	40(44.4)	0(0)	0.0001
Negative	50(55.6)	151(100)	

Discussion

In the present study, 241 children were studied. Of these, 37.3% had a serious bacterial infection (SBI) and 62.7% had a viral infection. In the United States, the prevalence of serious bacterial infections in children younger than 3 months is reported to be 37.5% (12, 13). In several other studies, the prevalence of serious bacterial infections has been reported to be 10-11% (13-15). Perhaps the higher percentage of bacterial infections in our study than these studies is due to the fact that in the present study, only patients admitted to the emergency department were included in the study.

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The findings of the present study showed that the majority of children had a fever due to a viral infection. The most common cause of fever without a source is viral infections, and the main challenge in this regard is the difficulty of distinguishing serious bacterial infections from viral infections (16-18). It is not always easy for physicians to differentiate a serious bacterial infection that requires prompt and appropriate antibiotic treatment from other self-limiting viral diseases. To date, according to conservative guidelines, most physicians admit all infants less than three months old to the hospital and begin experimental antibiotic treatment. But this approach has created problems such as rising medical costs and antibiotic resistance (14). Many studies attempt to establish a classification system that can guide physicians in diagnosing SBI from its limiting viral disease (14, 19-21).

The findings of the present study showed that the most common serious bacterial infection as a cause of fever was urinary tract infection. In order to confirm this finding, it can be said that urinary tract infection is the most common serious bacterial infection in children with fever without a source (8, 14, 22). In the study by Ishimine et al., the most common diagnosis among bacterial infections was urinary tract infections (51%) (18). Furthermore, about 11% of patients had bacteremia in the present study. In most previous studies, the overall percentage of bacteremia has been reported to be 3-8% (23), which is higher in the present study. The results of the study also showed that the percentage of cases of bacteremia was 31% and meningitis was 7.7%, while in previous studies, the prevalence of bacteremia and meningitis were reported to be 1% and 0.6%, respectively (21).

Regarding the comparison of demographic variables between the two groups of bacterial and viral infections, in the present study, the mean age of children in the bacterial infection group was lower than the viral group and there was a significant difference. In fact, children with a younger average age had a bacterial infection. Consistent with these results, In the study of Cho et al., 167 infants less than 3 months old with a fever of more than 38 degrees were identified and in fact, the age of patients with bacterial infection has been reported to be low (24). In fact, age is the first factor in considering a patient with a diagnosis of fever. Children less than three months old, and especially less than one month old, are more likely to have a serious bacterial infection, which confirms the results of the present study. Also, the risk of non-specific fever is lower in children between 3 and 36 months, and at older ages, fever with bacterial infection and without specific symptoms is almost uncommon (25). Comparison of clinical and laboratory findings between the two groups of bacterial and viral showed that among the variables, the number of white blood cells, neutrophil percentage, platelets and duration of fever were significantly different between the two groups. In a study by Olaciregui et al., white blood cell count was suggested as a predictor of bacterial infection. However, the difference between this study and the present study was in the age of the studied children; in their study, only children under 3 months were evaluated (26).

In a study conducted by Cho et al. to determine the predictors of severe bacterial infections in infants younger than 3 months, the mean white blood cell count was significantly different between the two groups of serious bacterial infection and non-bacterial infection. In this study, it was suggested that patients with high white blood cell counts could be considered as a high-risk group for severe bacterial infection (24), which is consistent with the results of the present study.

In another study conducted by Gomez et al. on children with a fever without a source, the number of white blood cells was suggested as a predictor of bacterial infection (15), which is consistent with the results of the present study. In the present study, the mean count of white blood cells was higher in the bacterial infection group and this mean was significantly different between the two groups. In one study, children with a fever above 40 °C and those with a white blood cell count above 15,000 were three times more likely to have bacteremia than those with a white blood cell count below 15,000 (27).

One of the limitations of the present study was that only children with outpatient fever were studied in the hospital and children who were followed up on an outpatient basis were not included in the study. The results of the study showed more cases of viral infections as a cause of fever without a source. Paying attention to factors that differed between the bacterial and viral groups can help differentiate between the two.

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