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The Epidemiology of Co-Infections in Febrile Children Younger than 5-Years-Old in Emergency Department; A Cross-Sectional Hospital-Based Study

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Abstract

Background
Fever is one of the most common causes of children's referral to pediatric emergency department (ED), and almost 20% of General ED referrals relate to febrile children. When it comes to febrile pediatrics patients, co-infection is a very important issue to discuss. This topic has been considered in current literature so, we considered to examine the epidemiology of these co-infections in febrile children younger than 5 years in emergency department.

Materials and Methods: This cross-sectional study was carried out retrospectively with the enrollment of children younger than 5-years-old (accessible sampling) in the emergency department of Mofid Hospital, Tehran, Iran, during November 2017 to December 2018. After designing and completing a check list.

Results: Totally, 388 patients with the mean age of 25.4 ± 12.4 months were studied (51.5% Girl). The source of infection was unclear after using all of the diagnostic tools in 27.5% of cases. Based on the findings fever-associated diarrhea (132 patients, 46.9%), and cellulitis (1 patient, 0.4%) were the most and least frequent source of infections, respectively. The co-incidence of different source of infections showed that the most frequent co-infections were sepsis and UTI; otitis and UTI; pneumonia and UTI; pneumonia and URI; and sepsis and otitis.

Conclusion
It seems that co-infections have been significantly increased in girls and in the age range of 6-36 months. The most and least prevalent infections were fever-associated diarrhea and cellulitis among the patients with at least one type of infection. The co-incidence of different source of infection showed that the most frequent co-infection were sepsis and UTI; otitis and UTI; pneumonia and UTI; pneumonia and URI; and sepsis and otitis.

Key Words: Children, Co-Infection, Febrile, Epidemiology.

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1- INTRODUCTION

Fever is one of the most common causes of children's referral to pediatric emergency department (ED) and almost 20% of general ED referrals is related to febrile children (1). This percentage even reached to more than 70% in children's specialized hospitals (2, 3). The incidence of serious bacterial infections although low, is still very important; so, protocols for management of febrile children have been formulated (4-7). The factors such as degree, convulsion, rapid onset, and response to medications do not show the severity of fever. Therefore, in febrile children with signs of danger, sepsis evaluation may be necessary by doing blood culture, urine culture, chest X-ray and lumbar puncture. Low-risk children, however, can be monitored or followed up on an outpatient basis according to their age (8). When it comes to febrile pediatrics patients, co-infection is a very important issue to discuss. This topic has been considered in current literature.

For example, Mahajan et al. reported that febrile infants ≤60 days of age with viral infections are at significantly lower, but non-negligible risk for sever bacterial infections, including bacteremia and bacterial meningitis (9). Positive urine and blood cultures simultaneously with infections such as otitis and cellulitis, considering the patient's urine difference and morbidity in people with multiple co-infection is very important. Since fever is one of the main complaints in the ED, having sufficient knowledge of the epidemiology and management of fever is necessary for physicians and medical staff. So, we considered to examine the epidemiology of these co-infection in febrile children younger than 5-years-old in ED.

2- MATERIALS AND METHODS

2-1. Study design and setting

This cross sectional study was carried on febrile children who referred to the ED of Mofid Hospital, Tehran, Iran, during November 2017 to December 2018. The protocol of the study was approved by Ethics Committee of Shahid Beheshti University of Medical Sciences (Ethics code: IR.SBMU.MSP.REC.1396.710). The study did not impose any additional costs on the patients and all diagnostic and therapeutic procedures were performed according to the in-charge physician's opinion and in accordance with the hospital protocols. Informed consent was received from patients' parents.

2-2. Participants

Using census sampling, all febrile children younger than 5-years-old who were referred to the mentioned ED during one-year study period were included retrospectively. The exclusion criteria were family history of hereditary disease, immunodeficiency, consumption of antipyretic agents before arrival to the ED, and those who needed cardiopulmonary resuscitation. The children were divided into four groups of age according to Philadelphia classification (10).

2-3. Data gathering

A predesign checklist consisted of demographic variables (age, gender), vital signs (blood pressure, pulse rate, respiratory rate, O2 saturation), physical examination findings, laboratory findings (ESR, CRP, blood culture, urine analysis, CBC, urine culture, stool culture and analysis, CSF analysis), imaging (Chest x ray), and final diagnosis regarding the source of infection was used for data gathering. A trained medical student was responsible for data collection under the direct supervision of an emergency medicine specialist.

2-4. Definitions

In the neonate or infant <2 to 3 months of age, the threshold for concerning fever is 38 °C (100.4 °F); in infants and children 3 to 36 months old, the threshold is 39 °C (102.rF). In children >36 months old, the definition of significant fever is not fixed (10). Final diagnosis regarding the source of infection was made based on the results of cultures, laboratory and imaging findings, as well as physical examination.

2-5. Statistical analysis

Then, data were analyzed using SPSS software version 22.0. Mean ± standard deviation (SD) or frequency and percentage were used for reporting the descriptive variables. T-test, Chi-square and Fisher exact tests were used for analysis. P-value<0.05 was considered as the level of significance.

3- RESULT

Totally, 388 patients with the mean age of 25.4 ± 12.4 (range = newborn to 5 years) were studied (51.5% Girls). The baseline characteristic of studied participants is shown in **Table.1**. The most frequent number of cases were in 6 – 36 months (58.5%). Sources of infections are shown in **Table.2**. The source of infection was unclear after using all of the diagnostic tools in 27.5% of cases. Based on the findings fever-associated diarrhea (132 patients, 46.9%), and cellulitis (1 patient, 0.4%) were the most and least frequent source of infections, respectively.

Table-1: Baseline characteristics of studied children, n=281.

Variables	Values
Gender	
Girl	200 (51.5)
Boy	188 (48.5)
Age	
29 -56 days	8 (2.1)
57 days- 6 month	67 (17.3)
6 – 36 months	227 (58.5)
36 months – 5 years	86 (22.2)
Vital signs	
Systolic blood pressure (mmHg)	96.01 ± 7.47
Diastolic blood pressure (mmHg)	72.94 ± 8.66
Respiratory rate (/minute)	21.526 ± 3.8
Pulse rate (/minute)	103.897 ± 11.22
Laboratory findings	
Hemoglobin (g/dl)	10.791 ± 1.35
White blood cells (10^3/HPF)	13.234 ± 6.57
Platelet ($\times 10^9$/liter)	304.663 ± 160.17
ESR (mm/1hour)	33.012 ± 31.31
CRP (mg/L)	71.258 ± 13.09
Positive cultures	
Urine	73 (18.9)
Blood	26 (6.7)
Stool	52 (13.4)
Source of infection	
Unknown	107 (27.5)
Diagnosed	281 (72.5)
Number of co-incident infections*	
1	123 (43.8)
2	102 (36.3)
>3	56 (19.9)

Data are presented as mean ± standard deviation or frequency (%). ESR: Erythrocyte sedimentation rate; CRP: C reactive protein. *: in patients with diagnosed source of infection (n = 281).

Table-2: The source of infection based on results of cultures, laboratory and imaging findings, as well as physical examination, n=281.

Source*	Number (%)
Diarrhea	132 (46.9)
Urine tract infection	125 (44.4)
Meningitis	2 (0.7)
Viral respiratory infection	98 (34.8)
Otitis	26 (9.2)
Upper respiratory infection	67 (23.8)
Cellulitis	1 (0.4)
Pneumonia	27 (9.6)

*: in patients with diagnosed source of infection (n = 281). Some patients had more than one source of infection.

Of 388 patients, no source of infection was found in 107 patients, one infection in 123 patients, two co-infection in 102 patients, three infections in 27 patients, four infections in 22 patients, five infections in four patients, seven co-infection in 2 patients and one patient suffered from 8 co-infection. The co-incidence of different source of infection are shown in **Table.3**. The most frequent co-infection were sepsis and UTI; otitis and UTI; pneumonia and UTI; pneumonia and URI; and sepsis and otitis. Presence of co-infection was significantly associated with girl's gender (p=0.005), age range of 3-36 months (p=0.04), higher CRP level (p= 0.007), higher platelet (p = 0.022), higher respiratory rate (p < 0.0001), higher pulse rate (p < 0.001), lower systolic blood pressure (p < 0.0001), and lower diastolic blood pressure (p = 0.001) (**Table.4**). The mentioned association was non-significant regarding ESR (p = 0.745), WBC (p = 0.196), and Hb levels (p = 0.329).

Table-3: Co-incidence of infections in patients with diagnosed source of infection (n = 281).

Variables	Diarrhea	UTI	VRI	URI	Pneumonia	Otitis
Diarrhea						
UTI	20.0					
VRI	53.1	36.7				
URI	40.3	52.2	32.8			
Pneumonia	25.9	66.7	37	66.7		
Otitis	7.7	84.6	23.1	50.0	26.9	
Sepsis	3.8	100	7.7	53.8	33.3	61.5

Data are presented as percentage. VRI: Viral respiratory infection, URI: Upper respiratory infection, UTI: Upper tract infection.

Table-4: Correlation between presences of co-infection and baseline characteristics of studied patients.

Variables	Presence of co-infection		P-value
	No (n = 123)	Yes (n =158)	
Gender			
Boy	66 (53.2)	58 (46.8)	0.005
Girl	57 (36.3)	100 (63.7)	
Age			
29 -56 days	0 (0.0)	8 (100.0)	0.040
57 days- 6 months	17(36.2)	30(63.8)	
6 – 36 months	77(47.5)	85(52.5)	
36 months – 5 years	29(45.3)	35(54.7)	
Vital signs			
Systolic blood pressure (mmHg)	97.9 ± 6.6	93.8 ± 7.9	< 0.001

Diastolic blood pressure (mmHg)	74.6 ± 7.3	69.9 ± 10.9	0.002
Respiratory rate (/minute)	21.0 ± 3.5	22.6 ± 3.9	< 0.001
Pulse rate (/minute)	102.4 ± 10.0	107.6 ± 11.9	< 0.001
Laboratory findings			
Hemoglobin (g/dl)	10.6 ± 1.4	10.7 ± 1.1	0.329
White blood cells (10^3/HPF)	13110.1	6303.2	0.196
Platelet ($\times 10^9$/liter)	14086.8	6207.2	0.016
ESR (mm/1hour)	34.7 ± 32.2	33.6 ± 24.7	0.745
CRP (mg/L)	49.6 ± 38.9	103.1 ± 186.7	0.007

Data are presented as mean ± standard deviation or frequency (%). ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein.

4- DISCUSSION

It seemed that co-infection have been significantly increased in girls and age range of 6-36 months. The most and least prevalent infections were fever-associated diarrhea and cellulitis among the patients with at least one type of infection. The co-incidence of different source of infection showed that the most frequent co-infection were sepsis and UTI; otitis and UTI; pneumonia and UTI; pneumonia and URI; and sepsis and otitis. Presence of co-infection was significantly associated with higher CRP level, higher platelet, higher respiratory rate, higher pulse rate, lower systolic blood pressure, and lower diastolic blood pressure. Tibbles and colleagues studied emergency department management of pediatric patients with cyanotic heart disease and fever in 2012. They retrospectively analyzed pediatric ED patients age 18 years or younger with a previous diagnosis of CCHD who presented with a fever from January 2000 to December 2005. Of 809 total ED encounters, 248 (30.6%) were eligible for inclusion. Of those meeting inclusion criteria, 59 (23.8%) required supplemental oxygen and 67 (27%) received intravenous fluid. ED diagnoses were febrile illness in 120 (48.4%), pneumonia in 35 (14.1%), upper respiratory infection in 19 (7.7%), viral syndrome in 17 (6.9%), gastroenteritis in 17 (6.9%), otitis media in 10 (4.0%), bronchiolitis in 5 (2.0%), pharyngitis in 3 (1.2%), croup in 3 (1.2%), bronchitis in 3 (1.2%), urinary tract infection in 3 (1.2%), mononucleosis in 2 (0.8%), pericarditis in 2 (0.8%), influenza in 1 (0.4%), cellulitis in 1 (0.4%), bacteremia in 1 (0.4%), and potential endocarditis in 1 (0.4%). In terms of patient disposition, 53.2% were discharged, 44.4% were floor admissions, and 2.4% were intensive care unit admissions (18). The prevalence of infections appears to be different from our findings. We reported diarrhea as the most common cause of fever and urinary tract infections as the next prevalent cause, while Tibbles (18) reported idiopathic feverish disease and pneumonia as the most common causes. The prevalence of urinary tract infections in this study was much lower than our finding. Kumara and colleagues studied the incidence of urinary tract infections in infants and children ages 4 months to 6 years with febrile diarrhea. The patients were evaluated for state of hydration, and also urine samples were collected. Eighty patients were enrolled in the study. The number of specimens obtained by clean catch midstream was 20, and by bladder catheterization was 60. None of the urine specimens obtained by both methods of collection grew any organism. There was no increased incidence of infections in male children whether circumcised (10/60) or uncircumcised (50/60). The mean temperature was 102.8 °F (range = 101 °F to 105 °F). They concluded that there is no increased incidence of UTIs in infants and children (4 months to 6 years of age) with febrile diarrhea (15). We achieved different results, the co-incidence of UTI and diarrhea in children was about 20%.

Tasnee Chonmaitree and colleagues studied viral upper respiratory tract infection and otitis media complication in young children. Each child was observed for 1 year to assess the occurrence of URI, acute OM (AOM), and OM with effusion (OME) complicating URI due to specific viruses. More than 60% of episodes of symptomatic URI among young children were complicated by AOM and/or OME. Young age and specific virus types were predictors of URI complicated by AOM. For young children, the strategy to prevent OM should involve prevention of viral URI (19). This finding confirms our reports about the co-incidence of infections and the age of children. We also reported more incidence of co-infection in age range of 6-36 months. Among the vital signs, increased pulse rate and respiratory rate, along with decreased systolic and diastolic blood pressure had statistically significant relationship with co-infection but it was clinically insignificant. This result was similar to Elmuntasir Taha Salah's study. Elmuntasir Taha Salah and colleagues studied the use of vital signs as predictors for serious bacterial infections in children with acute febrile illness in a pediatric emergency setting in Sudan. The severity of infection was classified as serious or not serious bacterial infection. Vital signs and oxygen saturation were recorded and compared to the final outcome of these children. They showed that 10 percent of patients were classified as having serious bacterial infection. Tachycardia and tachypnea were the most sensitive and specific in predicting serious bacterial infections with (80%, 86.6 % sensitivity), and (97.4%, 83.7% specificity), respectively. High temperature, severe hypoxemia and hypotension were the least sensitive but highly specific signs of serious bacterial infections (20). This study can be used as a decision rule in future if studied with higher population with more complete data. Due to the existence of the mentioned co-infection, it is recommended that in dealing with febrile children after finding one source of fever, we should think about another concomitant source of infection in children, so that we can consider the right treatment with awareness of it.

4-1. Limitations of the study

The child's habit and socio- cultural context that can influence the pain experience of children and was not controllable in the present study.

5- CONCLUSION

It seems that co-infection have been significantly increased in girls and age range of 6-36 months. Of 388 patients, no source of infection was found in 107 patients, one infection in 123 patients, two co-infection in 102 patients, three infections in 27 patients, four infections in 22 patients, five infections in four patients, seven co-infection in 2 patients and one patient suffered from 8 co-infection. The most and least prevalent infections were fever-associated diarrhea and cellulitis among the patients with at least one type of infection. The co-incidence of different source of infection showed that the most frequent co-infection were sepsis and UTI; otitis and UTI; pneumonia and UTI; pneumonia and URI; and sepsis and otitis.

6- AUTHORS' CONTRIBUTION

All the authors have contributed to drafting/revising the manuscript, study concept. All of the authors declared their accountability for all parts of the article.

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8- CONFLICT OF INTEREST: None.

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