The Value of C-reactive Protein, Procalcitonin, Interleukin-6 Levels to Predict Urinary Tract Infection in Children with Fever without A Focus

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Abstract

Objective: Urinary tract infections (UTIs) are one of the most common causes of acute fever without a focus in children between 1-36 months old, although obtaining urine for urine analysis is technically difficult in this age group. Therefore, there is a need for clinical and laboratory evidence to predict UTIs. The aim of this study is to determine the frequency of urinary tract infections in children between 1-36 months with acute fever of without a focus and the laboratory evidence, like C-reactive protein, procalcitonin, and interleukin-6 levels, that would help to predict urinary tract infections.

Material and Methods: Febrile children presenting to a pediatric emergency department, ages ranging between 1-36 months old and body temperature being ≥38.0°C, with a source of fever that was undetectable clinically, were enrolled in this prospective study. Patients were evaluated according to clinical and laboratory findings. The data were analyzed using SPSS software, version 15.0.

Results: A total of 90 patients were enrolled in this study. The median age was 7 months. The frequency of urinary tract infections was 25%. Escherichia coli was detected in all cases with positive urine cultures. There was no difference in clinical features between children with and without urinary tract infections. Laboratory findings, including white blood cell count, absolute neutrophil count, peripheral blood smear, and interleukin-6, were not statistically different between the two groups, whereas C-reactive protein and procalcitonin levels were significantly higher in the UTI group (p<0.05).

Conclusion: In conclusion, UTI is a frequent infection in 1-36-month-old children with fever without a focus, and the urine test with urine culture must certainly be assessed in these children. Laboratory findings, including C-reactive protein and procalcitonin, can be used as supporting evidence. There is a need for large trials evaluating the value of interleukin-6 levels to predict urinary tract infections in children. *(J Pediatr Inf 2014; 8: 165-70)*

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Introduction

Fever, an important and worrisome symptom for families, is one of the most frequent reasons of admittance to hospital in childhood period. Fever is responsible for the 15% of first admittance to emergency department in children under three years old (1, 2).

In the physical examination of 20% of febrile infants and children, no focus likely to cause fever cannot be found and this case group is defined as "fever with unknown origin". The disease of the majority of the children diagnosed with fever without a focus has a mild course and is caused by viral diseases (1, 3).

Urinary tract infection (UTI) is the most common bacterial infection in children between one-36 months old with acute fever without a focus (1, 4, 5). It was reported to have a prevalence of 2.1-7.0% in the British literature (6-8). In a Turkish study, on the other hand, UTI prevalence in the same age group was reported to be 16.0% (9).

Although the most common cause of "the fever without a focus" in one-36 months old infant and children group is UTI, obtaining urine

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for urine analysis is technically difficult in this age group. Therefore, there is a need for clinical and laboratory results in order to predict UTI. In a previous study, it was found that the prevalence of UTI in children under two years with the body temperature of ≥39.0 ºC was higher in comparison to children with the body temperature of 38.0-38.9°C (6).

C-reactive Protein (CRP) is recognized as a reliable method in differentiating bacterial and viral infections (1, 10-13). Prokalsitonin (PCT), is acute phase reactant and considered as a new index for bacterial infections. Previous studies reported that PCT could be used as a more reliable index in comparison to CRP and ESH in determining acute pyelonephritis and kidney damage (13-16). Interleukin-6 (IL-6) has come into use as a sepsis index especially in neonatal. It was found that IL-6 was high in infections caused by sepsis and especially gram (-) bacteria (17-21). There are some studies regarding its use in differentiating upper and lower UTIs. However, there exist no studies in the literature where IL-6 level was evaluated with regards to predicting UTI in children with acute fever without a focus aged between one-36 months.

The aim of this study is to determine the frequency of urinary tract infections, in children between one-36 months children with acute fever without a focus, and the laboratory like C-reactive protein, procalcitonin, interleukin-6 levels, that would help to predict the urinary tract infections.

Material and Methods

The study was prospectively designed between December 2001-November 2012. Febrile children that admitted to the pediatric emergency department, aged between one-36 months old, with the body temperature ≥38.0°C, (measured by tympanic method) and with no source of fever detected in the history and physical examination, and eventually diagnosed with "acute fever without a focus" ere included.

Children with acute fever with a focus in the history and/or physical examination (coughing, nasal flow, sneezing, dysuria, ear ache, otitis, etc.); children admitted with complaints of fever, but no fever detected on the admission or during the follow-up; children vaccinated in the last 2 to 72 hours; children who had antibiotic treatment in the last 7 days and diagnosed with fever for an unspecified source and those with a fever lasting for more than 7 days; children with immunodeficiency and chronic diseases; those with urine catheter and ventriculoperitoneal shunt; children with a recurrent UTI and urinary system anatomic dysfunction were excluded from the study.

Parents were informed about the aim and methods of the study; those whose informed consent was obtained were included in the study.

Age, gender, season of admission, body temperature values measured at home and on admission (°C), how quickly the temperature dropped during the monitoring in the hospital, how long the fever lasted, the other accompanying symptoms, physical examination results (respiration rate, respiratory systems symptoms, top pulse rate, blood pressure, hepatomegaly and splenomegaly), laboratory results [complete blood count and white blood cell count, absolute neutrophil count, erythrocyte sedimentation rate (ESR), peripheral blood smear, C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin (PCT), complete urine test, chest x-ray blood and urine cultures], the antibiotics used and their duration of use and the hospital-stay durations of the patients were all recoded down in detail. Detailed physical inspection of each case was performed.

Complete blood count was performed by electronic cell counter (Beckman Coulter LH 780, USA). Reference cell of the device for white blood cell was 4-10.5 x 1000 /µL, for hemoglobin 12-15 g/dL. For the evaluation of peripheral smear, after standardly coloring by Giemsa, 100 cells were counted; in white blood cell count, lymphocyte, neutrophil and immature neutropil count was evaluated based on the age group. The cases with over 5% immature neutropil were recorded as shift to the left (22).

Erythrocyte sedimentation rate was measured with the ALİFAX THL spa device. The reference range of the device was ESH: 0-20 mm/hour. *C-Reactive Protein* was measured bynephelometric method with the (BN™ II System simens, C-reactive protein reagentrlanda). The reference range of the device was CRP, 0.0-0.4 mg/dL. *Procalsitonin* was measured with 'cobas e 411 analyzer', ECL technology. The reference range of the device was 0.0-0.05 ng/mL. *Interleukin -6* was measured by MLX Luminometer Catalog Number ML1000 DYNEX TECHNOLOGIES, Inc. The reference range of the device was 0.0-12.7 pg/mL. Interleukin-6 was investigated in 74 cases (22 cases in UTI, 52 cases in the other group).

After the genital area of the patients was cleaned with suds, the plastic urine bag was attached to enclose the urethra as well. Standard urine test was evaluated by using the LabUMat & Urised - Complete Urine Analyzer System (77 ELEKTRONIKA). Urine sediment was performed by the removal of the upper part of the tubed urine rotating for 5 minutes at 2000 speed and by transferring the leftover at the bottom onto a lamina and

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examining it under the microscope. Dipstick with nitrite (+), leukocyte esterase (+) and the presence of more five erythrocyte and/orleukocyte was accepted as significant in favor of UTI (23).

Urine samples in children with difficulty of urinary bladder control were taken through catheter; and those who managed to control their urinary bladder, through mid-flow urine. By rubbing urine culture, the sample available, one EMB and one bloody medium, they were planted loosely. It was placed in a 37ºC incubator in a waxed jar. It was evaluated based on the hemolysis state of the bacteria that grew the following day. Blood culture was tested with BacT/ALERT® 3D Microbial Detection System. It was evaluated based on the hemolysis state of the bacteria that grew up to seven days; antibiogram was tested in those with growth.

Urinary tract infection diagnosis was confirmed in those with abnormal urine analysis tests and (>105 colony-forming units (CFU)/L of a single uropathogenic bacteria in a clean catch sample (23). Those with more than one microorganism grown in their urine culture were considered as contamination (n=12). Contaminated cases were excluded from the study. Those with growth in the urine culture were grouped as Group 1 (n=30); those without growth Group 2 (n=60).

Statistical analysis

Data analysis was performed using SPSS program (Statistical Package for the Social Sciences) for Windows 15.0. Whether the distribution of continuous and discrete numeric variables were close to being normal was tested by the Kolmogorov Smirnov test. Regarding descriptive statistics for continuous and discrete numeric variables, average was illustrated as ±, standard deviation or median (lowest - highest) and categorical variables as case number and '%'.

Significance of difference between the groups regarding values was analyzed by the Student's t test, and significance of difference regarding median values by the Mann Whitney U test. Categorical variables were evaluated by the Chi-square test; for $p<0.05$, the results were considered to be statistically significant.

This study was carried out by the authorization of Ministry of Health, Ankara Education and Researh Hospital, Local Education Planning and Coordination Committee.

Results

A total of 102 children aged between one-36months (median 7 months) children with acute fever without a focus admitted to Pediatric Emergency Department with fever complaints were included in the study. As the urine samples of twelve cases were contaminated, they were excluded from the study. Growth was found in the urine culture of 30 (33.3%) of the a total of 90 cases. *E. coli* grew in the urine culture of all the patients in whom growth was detected.

UTI was found in 20.0% (n=4) of the cases aged 1-3 months (n=20) and in 37.1% (n=26) of the cases aged 3-36 months (n=70). There is no statistically significant difference between Groups 1 and 2 (p>0.05).

All the children were administered age-appropriate vaccination.

Although urinary tract infections were least common in summer months (13.3%, n=4), no seasonal difference was found between Group 1 and 2 (p=0.147).

No statistically significant difference was found between Groups 1 and 2 regarding the temperature measured on admission and at home before admission, and between the length of period the fever dropped and number of day with fever during the hospital stay (p>0.05). Hospital follow-up period in those UTI was found was 2.5 days (1-8), in those UTI was not found, 5 days (1-20) (p=0.001).

It was found that CRP, ESH and PCT levels in Group 1 were statistically higher than those of Group 2 (p<0.05) (Table 1). No difference was found between the IL-6 levels (p=0.523).

Discussion

The most common cause of with "fever without a focus" inone-36 month-old group of infants and children is UTIs. However, obtaining urine for analysis is technically difficult in this age group.Therefore, there is a need for clinical and laboratory results to predict UTI. In this study, 33.3% UTI prevalence was found in one to 36 month-old group of infants and children diagnosed with "fever without a focus". No statistically significant difference was found regarding the temperature measured on admission and at home before admission, the length of period the fever dropped and number of day with fever during the hospital stay between the group diagnosed with urinary tract infection and the group whose temperature was measured on admission and at home before admission. While CRP, ESH and PCT levels in patients diagnosed with urinary tract infection was high, there was not any difference for IL-6 levels.

Fever in childhood is one of the most common reasons of doctor visits; it causes both families and physicians to be alarmed. Majority of the children taken to physicians due to fever are those under three years old

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Table 1. Laboratory and culture results of groups with and without growth in the urine culture (n=90).

Variables	Group 1 (n:30)	Group 2 (n:60)	p-value
Hemoglobin (gr/dL) (average±SD)	10.9±1.0	10.9±1.0	0.767[a]
White blood cell count (10³/mm³)	13.7 (3.7-32.5)	14.0 (3.6-34.8)	0.387[b]
Absoluteneutrophilcount (10³/mm³)	8.4 (1.7-22.5)	7.9 (0.9-29.3)	0.369[b]
Peripheral smear [n (%)]			0,730[c]
Segmented cells	15 (50.0)	28 (46.3)	
Lymphocytes	15 (50.0)	32 (53.7)	
Number of cases with high clubbing count [n (%)]	17 (47.2)	24 (44.4)	0.795[c]
Thrombosiscount (*10³/mm³)	354.2±117.0	355.6±111.5	0.952[a]
Erythrocyte sedimentation rate (mm/hour)	25.5 (2.0-106.0)	7.5 (2.0-111.0)	0.002[b]
C-reactive protein (mg/dL)	5.1 (0.3-17.1)	1.7 (0.3-27.0)	0.004[b]
Procalcitonin (ng/mL)	0.79 (0.1-30.2)	0.25 (0.1-7.1)	0.034[b]
Interleukin-6 (n:74) (pg/mL)	25.6 (0.4-125.2)	31.0 (2.6-235.3)	0.523[b]

[a]: Student's t test; b: Mann Whitney U test; c: Pearson's Chi-Square test
*: Column percentage
**: [median (min-max)]

and no clear source of infection was found in the history and physical examination in 20% of these cases (1, 2). Urinary tract infection is the most common bacterial infection in children diagnosed with fever without a focus (24). Prevalence of UTI in febrile children under two was reported to be 2.1-7.4% (6-8, 25). In a study done by Machado et al. (26), UTI prevalence was reported to be 7.4%. In a study done by Lin et al. (27), on the other hand, over 20% growth was found in the urine culture of febrile infants. Prevalence of UTI in low risk febrile children under two without a fever focus was found as 16% in studies done in Turkey (9). In this study, 33.3% UTI prevalence was found in children diagnosed with without a fever focus. The reason why this rate is more prevalent in comparison to other studies is that UTI prevalence in our country is higher and since the study was done in a tertiary hospital, we thought that there could be patient transfer from epicenter hospitals.

Fever is usually the only symptom of urinary tract infection in infants under two years old (24, 28, 29). In a previous study, it was found that UTI prevalence in children with ≥39.0 ºC body temperature was higher than children with 38.0-38.9ºC (6). In a multi-centered study done in pediatric emergency departments involving children under two years old, it was reported that UTI prevalence in children with ≥39.0 ºC body temperature was higher than children with 38.0-38.9ºC (6). No difference was found in our study regard the level of temperature and duration in children in regard to and without ITU.

Urinary tract infection is the most common bacterial infection especially in female children (24). It was reported in the literature that UTIs were more common in infants and females (1, 2, 4-6). In our study, on the other hand, there was no difference in regard to gender between those groups diagnosed and not diagnosed with UTI. It is possible to conclude that the probable reason for this could be that the study group was smaller than other groups.

Acute phase indexes like CRP, ESH and PCT levels, in children with urinary tract infection can be higher as it is the case in our study. It was reported in previous studies that PCT could be used as a more reliable index in comparison to CRP and ESH in determining acute pyelonephritis and kidney scar (13-16). In our study, it was found that CRP, ESH and PCT levels in cases with UTI were higher.

There have been studies regarding the use of interleukin-6 level in detecting lower and upper UTIs and determining the renal scar. While IL-6 level was useful in some of these studies, some other concluded that it was useless (17-21). There are no studies in the relevant literature regarding the place of IL-6 in predicting the UTIs in children with acute fever without a focus. It was found in our study that IL-6 was not a useful index in predicting UTIs in children with acute fever without a focus.

Conclusion

In conclusion, UTI is a common infection in children between one to 36 months old with acute fever without a

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focus, and children should definitely be examined by their urine and urine cultures. Laboratory results of CRP, ESH and PCT can be used as supportive findings. There is a need for additional studies where interleukin-6 levels are evaluated.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ministry of Health, Ankara Training and Education Hospital.

Informed Consent: Informed consent was obtained from patients and their parents who participated in this study.

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