

Alterations of Peripheral Leukocyte Count, Erythrocyte Sedimentation Rate, and C-Reactive Protein in Febrile Urinary Tract Infection

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Introduction. The aim of this study was to assess the usefulness of peripheral leukocyte count, differential leukocyte count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level in febrile urinary tract infection (UTI) for defining the UTI level.

Materials and Methods. A total of 61 children aged between 1 and 10 years with documented febrile UTI (axillary temperature $\geq 38^{\circ}\text{C}$) were studied. They had a urine culture positive for infection. Laboratory investigations including peripheral total and differential leukocyte counts, ESR, and CRP were assessed in relation to the inflammatory responses. Leukocyte count results were available in all of the patients, ESR in 41, and CRP in 36.

Results. Leukocyte count was normal in 6 patients (9.8%). Lymphocytic leukocytosis was seen in 1 patients (1.6%), neutrophilic leukocytosis in 25 (41.0%), and relative neutrophilia in 29 (47.5%). Thirty patients (73.2%) had a high ESR and 23 (63.9%) had a positive CRP. In children with a high ESR, 12 (29.3%) had neutrophilic leukocytosis and 14 (34.1%) had relative neutrophilia. Relative neutrophilia and neutrophilic leukocytosis with positive CRP both were found in 11 patients (30.6%). Negative CRP with absence of neutrophilic leukocytosis was found in a significantly higher proportion of patients. There were no direct correlations between the severity of systemic inflammatory responses and urinary tract inflammatory response.

Conclusions. Findings of this study showed that ESR and differential leukocyte count are two valuable tests in febrile UTI and may be useful for localization of UTI level, but the total leukocyte count and CRP level as in qualitative methods are not useful, and many patients with febrile UTI do not have leukocytosis.

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INTRODUCTION

Not all episodes of urinary tract infection (UTI) in children can be classified as either pyelonephritis or cystitis by history and simple laboratory investigations; these are called "unspecified" UTIs. In primary care, a method for determining the site of infection should be rapid and inexpensive. On urinalysis, leukocyte casts in urinary sediment are

a classic finding indicating upper UTI, but these casts are easily overlooked if pyuria is massive, and they are easily dissolved, especially in alkaline urine.

Identifying the level of infection is important primarily in patients older than 1 to 2 years in order to determine low-risk patients who can be excluded from investigations and follow-up. A

number of tests for defining the level of UTI have been described including urethral catheterization, bladder washout, alterations in the concentrating ability of the kidney, determination of antibodies against the infecting bacteria, and detection of antibody-coated bacteria in urine.¹⁻⁶ Some of these tests are complicated and require special facilities, while others are simple, but usually nonspecific. Renal imaging studies such as urography and ultrasonography may reveal an inflammatory process in the kidney. Another technique that shows an inflammatory process in the kidney is renal scintigraphy. Meta-analyses of animal studies have shown high diagnostic values for modalities such as dimercaptosuccinic acid renal scintigraphy.^{7,8} In clinical practice, however, a problem with the scintigraphic techniques is the difficulty of differentiating acute inflammatory changes and already established renal scars.⁹

Serum C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) have been found to be of value in identifying those children with UTI who have marked host reactions.¹⁰ For ESR, moderate elevations are common in active inflammatory diseases and infections, but normal ESR cannot be used to exclude infections.¹¹ A characteristic pattern of response to infection includes progressive neutrophilic leukocytosis. Neutrophilic response in children is more intense than adults.¹² Serial measurement of CRP level has been advocated for monitoring of disease processes in childhood infections and for diagnosis of pyelonephritis.^{10,13-16} However, studies on the usefulness of CRP for the diagnosis of UTI have so far been confined to the study of school girls and patients with ileal conduits.^{10,14-17} This study was undertaken to determine the value of peripheral leukocyte count, ESR, and CRP as diagnostic guides in febrile UTI.

MATERIALS AND METHODS

The author retrospectively studied all children aged between 1 and 10 years with documented febrile UTI (axillary temperature $\geq 38^{\circ}\text{C}$) who admitted to emergency department of Dr Sheikh Children's Hospital during a period of 5 years (2002 to 2006). They did not have any other known site of infection or inflammation. Fever was used as the clinical sign that differentiated pyelonephritis from cystitis.

Data from the analyses of urine samples obtained by midstream method in toilet-trained children and by urine bags in infants and small children were used. Sampling by urinary catheter or suprapubic aspiration had not been done because parents usually deny it in our country. Urine cultures of midstream samples with only 1 grown microorganism and a colony count of 10^5 or more colony-forming units per milliliter were considered positive for infection. Urine cultures of samples obtained by urine bags considered positive if there was concurrent pyuria and growth of 1 organism with a colony count of 10^5 or more colony-forming units per milliliter. Pyuria was defined as 5 or more leukocytes in a high-power field in the urine sediment.¹⁸ Mild pyuria and severe pyuria were considered as 5 to 40 leukocytes per high-power field (HPF) and more than 40 leukocytes per HPF on urine sediment, respectively.

Peripheral leukocyte count (total and differential), serum level of CRP, and ESR had been evaluated in all of the patients. Leukocyte count had been done by automated leukocyte analyzer method, differential leukocyte count by Giemsa staining, CRP by qualitative method of latex-CRP (ENiSon, ENiSon Lab, Tehran, Iran), and ESR by Westergren method. Results of latex-CRP tests were reported according to the presence or absence of agglutination and size of agglutinated droplets on microscopic examination: no agglutination was considered negative; small-sized agglutinated droplets, 1+; medium-sized agglutinated droplets, 2+; and large-sized agglutinated droplets, 3+.

Results of peripheral leukocyte and differential leukocyte counts were compared with reference ranges for age.^{19,20} Table 1 presents criteria for normal and abnormal values of these two parameter. Accordingly, the patients were divided into 4 groups with: (1) normal leukocyte count, (2) neutrophilic leukocytosis or leukocytosis with an absolute increase in neutrophil count, (3) relative neutrophilia (an increase in the percentage of neutrophils without increased absolute leukocyte count), and (4) lymphocytic leukocytosis (an absolute increase in lymphocytes count). In addition, the patients were divided into two groups according to CRP and ESR results: CRP positives (1+ to 3+) or CRP negatives and those with low and high ESR (< 30 mm/h and $\text{ESR} \geq 30$ mm/h).

Nonparametric chi-square test was used to

Table 1. Normal Values of Total and Differential Leukocyte Counts According to Age of Children*

Age	Total Leukocyte Count, $\times 10^9/L$	Differential Leukocyte Count, %	
		Neutrophils	Lymphocytes
1 month	5.0 to 19.5	35	56
6 months	6.0 to 17.5	32	61
1 year	6.0 to 17.5	31	61
2 years	6.0 to 17.0	33	59
4 years	5.5 to 15.5	42	50
6 years	5.0 to 14.5	51	42
8 years	4.5 to 13.5	53	39
10 years	4.5 to 13.5	54	38

*Ranges of leukocyte number are estimates of 95% confidence limits. Neutrophils include band cells at all ages.

compare results and a P value less than .05 was considered significant.

RESULTS

Totally, 61 patients were included in this study, 41 of which (67.2%) were girls and 20 (32.8%) were boys. The age of patients ranged from 1 month to 10 years (mean, 17.9 ± 22.7 months). All patients had axillary temperatures of 38°C or higher (mean, $38.73^\circ\text{C} \pm 0.65^\circ\text{C}$).

Data on leukocyte count and differential leukocyte count were available for all, but ESR and CRP had been checked in 41 (67.2%) and 36 (59.0%) patients, respectively. Results of leukocyte count were as follows: normal in 6 patients (9.8%), lymphocytic leukocytosis in 1 (1.6%), neutrophilic leukocytosis in 25 (41.0%), and relative neutrophilia in 29 (47.5%). In patients who had abnormal differential leukocyte count, lymphocytic leukocytosis was found in a significantly lower proportion of patients ($P = .001$), and neutrophilia including absolute and relative neutrophilia in a significantly higher proportion of patients ($P = .002$).

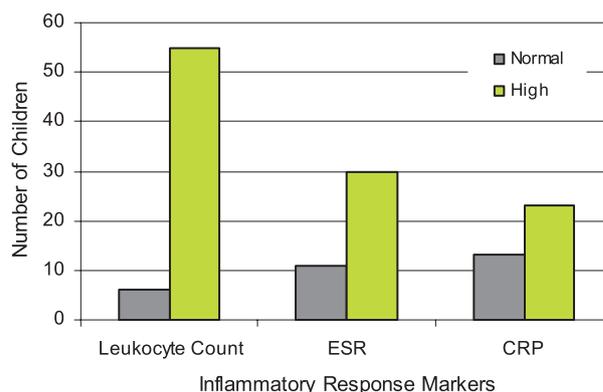
Among the children whose ESR results were available, 30 (73.2%) had a high ESR, which was the dominant finding ($P = .003$). Of these patients, 25 (61.0%) had a value between 30 mm/h and 99 mm/h and 5 (12.2%) had a value of 100 mm/h or higher. C-reactive protein was positive in 23 of 36 patients (63.9%; 1+ in 4, 2+ in 9, and 3+ in 10 patients). Patients with a positive CRP were not significantly more frequent than those with a negative CRP ($P = .96$). The Figure presents the results of the above tests in the patients.

In children with a high ESR, 12 (29.3%) had neutrophilic leukocytosis and 14 (34.1%) had relative neutrophilia. In those with an ESR lower than 30 mm/h, a significant proportion did not

have neutrophilic leukocytosis ($P = .008$). Relative neutrophilia and neutrophilic leukocytosis with positive CRP both were found in 11 patients (30.6%). Negative CRP with absence of neutrophilic leukocytosis was found in a significantly higher proportion of patients ($P = .02$).

In 33 children, results of both ESR and CRP were present. There were 17 patients (51.5%) with a high ESR and a positive CRP and there was no significant difference in ESR result between CRP positives and CRP negatives ($P = .86$). In 10 patients (30.3%), relative neutrophilia, positive CRP, and high ESR were found together, in 6 (18.2%), neutrophilic leukocytosis was present along with positive CRP and high ESR.

The patients' data were analyzed for finding any correlation between systemic inflammatory responses with urinary tract inflammatory response (severity of pyuria). There were no direct correlations between the severity of systemic inflammatory responses and urinary tract



Frequency of abnormal results of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and leukocyte count in children with febrile urinary tract infection. A CRP of 1+ to 3+ and an ESR of 30 mm/h or higher were considered high. A high leukocyte count was determined based on Table 1.

Table 2. Results of Inflammatory Responses in Relation to Pyuria Severity*

Inflammatory Markers	Urinary Leukocyte Count, /HPF		
	< 5 (No Pyuria)	5 to 40 (Mild Pyuria)	> 40 (Severe Pyuria)
Leukocyte count			
Normal	2 (18.2)	2 (9.5)	2 (6.9)
Lymphocytic leukocytosis	1 (9.1)	0	0
Neutrophilic leukocytosis	3 (27.3)	7 (33.3)	15 (51.7)
Relative neutrophilia	5 (45.5)	12 (57.1)	12 (41.4)
Total	11 (100)	21 (100)	29 (100)
ESR, mm/h			
≥30	3 (42.9)	13 (86.7)	14 (73.7)
<30	4 (57.1)	2 (13.3)	5 (26.3)
Total	7 (100)	15 (100)	19 (100)
CRP			
Negative	3 (37.5)	6 (46.2)	4 (26.7)
Positive	5 (62.5)	7 (53.8)	11 (73.3)
Total	8 (100)	13 (100)	15 (100)

*Values in parentheses are percents. Percentages do not total 100 due to rounding. HPF indicates high-power field; ESR, erythrocyte sedimentation rate; and CRP, C-reactive protein.

Table 3. Results of Leukocyte Count in Relation to Fever Severity*

Leukocyte Count	Fever, °C		
	38.0 to 38.5	38.6 to 39.5	> 39.5
Normal	4 (11.1)	2 (10.0)	0
Lymphocytic leukocytosis	1 (2.8)	0	0
Neutrophilic leukocytosis	12 (33.3)	10 (50.0)	3 (60.0)
Relative neutrophilia	19 (52.8)	8 (40.0)	2 (40.0)
Total	36 (100)	20 (100)	5 (100)

*Values in parentheses are percents.

inflammatory response ($P = .25$, $P = .55$, and $P = .10$ for leukocyte count, CRP, and ESR, respectively). There was no direct correlation between systemic inflammatory responses and severity of fever either ($P = .80$). Tables 2 and 3 depict the relations between systemic inflammatory responses and severity of fever and pyuria.

DISCUSSION

Peripheral leukocyte count, ESR, and CRP are simple noninvasive tests that are used for diagnosis of invasive bacterial infections and determining the UTI level. Peltola and Rasanen studied 52 children younger than 16 years old with a confirmed bacterial infection. In these patients, CRP was almost always highest at the time of admission. In contrast, ESR measurements reached a maximum only after several days of admission. This study showed that increased CRP values reflected bacteremic disease reliably.¹³ Different studies have been

repeatedly shown that high leukocyte counts are significantly more common (two- or three-folds) in children with bacterial infections than in those with viral infections.²¹⁻²⁸ Kramer and colleagues' study showed that a vast majority of young children with fever and a high leukocyte count do not have any underlying bacterial infection as a cause of their fever.²⁸ Lin and associates reported relatively low sensitivities for ESR and CRP as predictors of UTI in febrile infants.⁸ In their study, the most sensitive indicator for UTI was pyuria, and its combination with CRP and ESR improved the specificity to 98% and 97%, respectively. However, none of these markers were a sensitive indicator of UTI. Their investigation showed that febrile infants with a CRP higher than 20 mg/L and an ESR higher than 30 mm/h were at risk of UTI. In various studies, these two markers along with a leukocyte count higher than $15 \times 10^9/L$ have been suggested as the key findings in febrile infants.^{23,29-32} The present study also confirmed that most patients with febrile UTI did not show a concomitant alteration of leukocyte count, ESR, and CRP.

Jodal and colleagues studied school girls with symptomatic bacteriuria and correlated the clinical diagnosis of pyelonephritis or cystitis with the bladder washout test, serum antibody values, ESR, CRP, and concentrating ability of the kidney. The highest reliability was obtained by CRP.¹⁰ Increased CRP values (range, 25 mg/L to 300 mg/L) were found in all patients

classified as having pyelonephritis. In contrast, Hellerstein and coworkers found that serum CRP concentrations were not accurate in localizing the site of UTI in girls who did not have clinical signs of acute pyelonephritis.¹⁶ They found that the predictive value of positive CRP in patients with pyelonephritis was 57% and for negative test was 83%. Kiker and colleagues studied the usefulness of serum CRP as a means of localizing the site of UTI in patients with conduits, and positive urine culture. They concluded that CRP was of no value in distinguishing bacteriuria from conduit colonization.¹⁷

In 1999, Rasamoelisoa and colleagues retrospectively studied 361 febrile children. In this study, there was a direct correlation between CRP values and leukocytes level in presumed bacterial infections.³³ Krzemien and colleagues assessed relation between the clinical course of UTI, interleukin levels, inflammatory markers, and findings on renal scintigraphy. They found positive correlation between urinary interleukin-6 and interleukin-8 levels and ESR, CRP, and leukocyte count, but no relation was found between urinary cytokine levels and the presence of inflammatory changes detected by renal scintigraphy.³⁴ Results of this study in children with febrile UTI indicated that most of them did not have leukocytosis. Leukocytosis was found only in 42%, and 55% of the patients had a peripheral leukocyte count higher than $15 \times 10^9/L$. In addition, lymphocytic leukocytosis was very rare in the present study, while neutrophilia (absolute or relative) was found in 88% of the patients. This study confirmed that an ESR greater than 30 mm/h is a valuable test in diagnosis of febrile UTI, but CRP measurement by qualitative methods like CRP-latex is not useful for diagnosis of pyelonephritis in children. However, the retrospective nature of this study and lack of data on ESR and CRP of a proportion of the children warrant further investigation to confirm these findings.

CONCLUSION

According to the findings of this study, ESR and differential leukocyte count can be suggested as useful and valuable tests in febrile pyelonephritis. These tests can help us to localize UTI in the urinary tract. In contrast, the author concludes that peripheral leukocyte count and CRP measurement

by qualitative methods are not valuable tests for ruling out pyelonephritis and defining the UTI level. It seems that in febrile UTI pyelonephritis, the main leukocytes response is increase in the percentage of neutrophils rather than increase in absolute leukocyte count. It can also be concluded that most patients with pyelonephritis do not show alterations in CRP with ESR and leukocyte count concurrently, and also there is no direct correlation between systemic inflammatory responses (leukocyte count, ESR, CRP, and severity of fever) and urinary tract inflammatory response (pyuria).

CONFLICT OF INTEREST

None declared.

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