

Research Article

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## Frequency of Massive Proteinuria in Childhood Pyelonephritis and the Response to Antibiotic Therapy

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**Introduction:** Urinary tract infection (UTI) is one of the most common bacterial infections in childhood which can contribute to high blood pressure and renal failure later in life. There are different methods for evaluation of a child with UTI for differentiation of cystitis from acute pyelonephritis. One of which is measuring protein in urine. The aim of this study is to investigate the role of UTI in provoking proteinuria.

**Material and Methods:** This is Quasi- experimental study, before and after, in patients with acute pyelonephritis in Mofid Children's Hospital during 2004-2006. All pyelonephritic patients were treated by intravenous ceftriaxone for at least for 10 days. Random urine samples were taken from all patients at the onset of admission before starting the antibiotic and at the ninth day of treatment for the evaluation of urine protein and creatinine.

**Results:** 152 children between 1 to 2 years of age entered the study. The prevalence of proteinuria in the acute phase of pyelonephritis was 94.8%. According to our study the prevalence of proteinuria during pyelonephritis is higher in children less than 2 years old (97.3%) and 20% of patients showed nephrotic range of proteinuria. In all cases random urine samples were normal after completion of treatment ( $p < 0.005$ ).

**Conclusions:** the results of this study illustrate that proteinuria has a high frequency during UTI and acute pyelonephritis. Proteinuria during pyelonephritis may be massive and in the nephrotic range but should not be the cause of concern because in the majority of cases it disappears following treatment.

**Keywords:** Pyelonephritis; Proteinuria; Antibiotics; Child.

**Running Title:** Frequency of Massive Proteinuria in Pyelonephritis

### Introduction

Acute pyelonephritis is one of the most common infectious diseases in childhood with the prevalence of 3-7% in girls and 1-1.6% in boys. The proper diagnosis and treatment of this condition can prevent many complications [1]. One of the most prominent Laboratory parameters of UTI and consequent interstitial nephritis is proteinuria. The presence of proteinuria during an acute pyelonephritis has been shown in numerous studies but none of them has determined its range exactly.

Severe proteinuria has been reported with reflux nephropathy and chronic pyelonephritis, while in acute pyelonephritis proteinuria has been reported to be of a lower grade [2-6]. According to some studies the prevalence of proteinuria in UTI has been reported to be 63-83% [7]. With regard to the fact that proteinuria is an important sign to differentiate acute pyelonephritis from other urinary tract infections like cystitis, and that presence of proteinuria always worries both patients and doctors about renal problems, we have decided to study the prevalence and severity

of proteinuria in patients with UTI and illustrate its progression under antibiotic therapy.

### Materials and Methods

This is a quasi-experimental study which was done on patients with acute pyelonephritis in Mofid Children's Hospital from 2004 to 2006. The diagnosis of pyelonephritis has been made by urine analysis; urine culture and DMSA scan findings. All the patients have undergone treatment with ceftriaxone at a dose of 75 mg/kg for at least 7 days. A random urine sample from each patient was sent to the laboratory for evaluation of protein and creatinine concentration both before and after treatment. Urine creatinine was measured by Jaffe method and urine protein was determined by turbidimetric procedure with a spectrophotometry. All laboratory tests in this study were done in the same laboratory. All cases underwent ultrasonography of the urinary tract and voiding cystourethrogram (VCUG) in order to detect anatomical abnormalities. Patients with a known history of other renal disease (other than UTI or renal insufficiency) were excluded from the study. The urine protein/creatinine ratio of more than 0.5 in infants and 0.2 in children older than one year has been assumed as proteinuria. In cases that the urine protein to creatinine ratio were more than 2, proteinuria was assumed in nephrotic range (Nephrotic range proteinuria) [1]. Data were analyzed using SPSS 18.0 by t-test, ANOVA test and regression. The significance level for all tests was  $P < 0.05$ .

### Results

We studied 152 patients between 1-12 years old, (123 girls and 29 boys). In 60% of patients urine cultures were positive and in the remainder were negative. In all cases acute pyelonephritis was confirmed by DMSA scan and in 4.5% of cases renal scar was revealed. In 49% of patients, kidneys were normal by ultrasonography and in 51% urinary stasis and hydronephrosis were encountered. VCUG results showed that 86% of patients were normal and the remaining cases had different grades of vesicoureteral reflux with monotonous dispersal.

The frequency of proteinuria in acute phase of pyelonephritis was 94.8% (CI 95%). So we can say the prevalence of proteinuria in acute phase of pyelonephritis in normal population is between 90.9% - 98.7%. It is notable that this value is higher in children under 2 years (97.3%). Only 8 children (5.2%) showed a normal urinary

protein/creatinine ratio at the onset of treatment. However, 20% of patients showed nephritic range of proteinuria in acute phase of pyelonephritis. In all cases the second random urine sample showed no protein which demonstrate a statistically significant difference in proteinuria with  $P < 0.005$ . (Table 1)

Furthermore, in our study a statistically significant correlation between the level of proteinuria (urine protein) and the severity of leukocytosis and the level of serum CRP was seen (respectively  $P < 0.04$ ,  $R = 0.6$  and  $P < 0.02$ ,  $R = 0.36$ ). There was not a statistically significant correlation between the severity of changes in DMSA scan and kidney ultrasound and the level of urine protein.

### Discussion

When pyelonephritis is recurrent or is due to an anatomical defect like obstruction or vesicoureteral reflux, interstitial nephritis and renal dysfunction may ensue, which predominantly appears with distal tubular involvement [1]. Proximal tubular involvement causes excretion of tubular proteins, bicarbonate, amino acids, phosphorus and uric acid and presents as Fanconi syndrome. Distal tubular involvement causes impaired urine acidification, and increased calcium excretion which is called distal renal tubular acidosis, while collecting tubular involvement manifests itself as aldosterone resistance or impaired urinary concentration. Accordingly, during a pyelonephritis proteinuria, normal anion gap metabolic acidosis, hyperkalemia, hypokalemia, hyponatremia, hypernatremia, hypercalciuria, hypophosphatemia, and impaired urinary concentration are predictable. These derangements are consequences of acute inflammation of the kidney so they will disappear following treatment [2]. The severity and duration of these derangements will be influenced by the presence of predisposing factor for UTI, like anatomical defects. In the presence of these factors, these derangements may continue for a longer duration. On the other hand, these impairments might be as a result of antibiotic treatment, since many antibiotics used in UTI treatment can cause acute interstitial nephritis. The most important implicated antibiotics are cephalosporins like especially cephalexin, Cephalothin and cefotaxime, and also penicillins like amoxicillin, cloxacillin, methicillin and nafcillin can be named. In addition, acute interstitial nephritis can be seen with a variety of

other drugs such as ciprofloxacin, gentamicin, TMP – SMX, Nitrofurantoin and vancomycin. Other causes of impairments are high grade fever, repeated vomiting and severe stress which are more often seen with a delay in start of treatment [1, 3, 4, 5]. Vaden in 2004 in United States studied the protein excretion level during pyuria in dogs and reported that proteinuria doesn't increase during pyuria but it does increase during pyuria with hematuria [5]. Although results of animal research have less mistakes and greater validity, studies on the effect of childhood UTI on inducing proteinuria conditions like high fever, dehydration and other problems of acute pyelonephritis were not considered in these studies, therefore we cannot extrapolate the animals data directly to human beings. According to a study by Hernandez (2004) in Spain urine protein level increases during symptomatic urinary tract infections and none- symptomatic UTIs don't cause this change [6]. In a systematic review in adults and children in 2006, Joanne reported that the prevalence of proteinuria during bacteriuria is 5-9% [8]. While in a study by Simerville this prevalence was reported to be 63-83 % [7]. These studies reported only about the prevalence of proteinuria. In a study by Muhammad, a very severe proteinuria caused by UTI in a patient has been reported in which the level of proteinuria was reported 5 gr/day, however this is unexpected [9]. Byung reported urine Albumin/creatinine ratio to be 0.34-0.38 in his study [10]. In order to avoid false positive results and confusion in interpretation of findings the type of the test must be mentioned. Obviously in different methods of evaluation of urine protein, different amounts of protein in urine have been reported [11-14]. In the present study, proteinuria has been encountered in about 95% of patients in the acute phase of UTI which in all cases protein creatinine ratio normalized after completion of antibiotic treatment. This illustrates that proteinuria is induced by an acute process and is transient. According to our study the amount of proteinuria was not associated with changes in ultrasonography and DMSA scan. Thus proteinuria may not be caused by underlying renal problems or kidney damages.

### Conclusions

The results of this study indicate that the presence of proteinuria during a UTI is not only because of infection but also other factors such as acute phase reactions may play an important role.

Therefore, UTIs may cause elevation in urine protein level even sometimes transient but in a nephritic range. Results of this study confirm the assumption that during an acute pyelonephritis, proteinuria is frequent and sometimes in nephrotic range. Early recognition and awareness of this dysfunction can help reduce frequent laboratory tests and expenses, prevent both physician and parent anxiety and agitation about protein excretion and finally can lessen the duration of treatment and hospitalization.

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### Conflict of Interest

None declared

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