The Role of Procalcitonin for Acute Pyelonephritis and Subsequent Renal Scarring in Infants and Young Children

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Abbreviations and Acronyms

APN = acute pyelonephritis
CRP = C-reactive protein
DMSA = ^{99m}Tc-dimercaptosuccinic acid
NPV = negative predictive value
PCT = procalcitonin
PPV = positive predictive value
RS = renal scarring
UTI = urinary tract infection
VCUG = voiding cystourethrography
VUR = vesicoureteral reflux
WBC = white blood cell count

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Purpose: We assessed the usefulness of procalcitonin as a biological marker in diagnosing acute pyelonephritis and for predicting subsequent renal scarring in young children with a first febrile urinary tract infection.

Materials and Methods: Children 2 years old or younger with a first febrile urinary tract infection were prospectively studied. Renal parenchymal involvement was assessed by ^{99m}Tc-dimercaptosuccinic acid scan within 5 days of admission and after 6 months. Serum samples from all patients were tested for procalcitonin, C-reactive protein and white blood cell count measurements.

Results: The 112 enrolled patients (age range 24 days to 24 months old) were divided into acute pyelonephritis (76) and lower urinary tract infection (36) groups according to the results of ^{99m}Tc-dimercaptosuccinic acid scans. Median values of procalcitonin, C-reactive protein and white blood cell count at hospitalization were significantly higher in patients with acute pyelonephritis than in those with lower urinary tract infection. The area under receiver operating characteristic curves showed that procalcitonin was superior to C-reactive protein and white blood cell count as a marker for diagnosing acute pyelonephritis. Initial and post-antibiotic treatment procalcitonin values were significantly higher in children with renal scarring than in those without scarring ($p < 0.001$). Procalcitonin values at hospitalization and after treatment were independent predictors of later renal scarring on logistic regression analysis.

Conclusions: Our results indicate the superior diagnostic accuracy of procalcitonin for predicting acute pyelonephritis in children 2 years old or younger. Higher initial and posttreatment procalcitonin values are independent risk factors for later renal scarring.

Key Words: pyelonephritis, procalcitonin, infant, vesico-ureteral reflux

URINARY tract infection is a common bacterial infection in pediatric patients, especially in children younger than 2 years old, with a prevalence of 6.5% and 3.3% in girls and boys younger than 1 year old, respectively.[1] The nonspecific symptoms in febrile young children make the clinical differentiation between acute pyelonephritis and lower UTI difficult. Approximately 30% to 60% of cases in small children result in renal scarring after acute febrile UTI.[2–4] A delay in the diagnosis and treatment of APN in young children can increase the risk of kidney damage,[1,5] which may cause hypertension, proteinuria and end stage renal disease later in life.[2,6]

^{99m}Tc-dimercaptosuccinic acid is widely accepted as the gold standard

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for detecting APN, and assessing the extent and progression of renal damage.[7,8] However, factors like availability, as well as the costs and risks of exposing patients to radiation and sedation limit the widespread use of the DMSA scan. Furthermore, commonly used clinical and laboratory parameters do not accurately localize the UTI site.[8,9] Therefore, finding an accurate and readily available diagnostic test to predict APN is of great value in young children with a febrile UTI.

Procalcitonin is a 116 amino acid peptide and a precursor of calcitonin.[10] Its release during infection is induced directly by microbial toxins and/or indirectly by humoral factors or the cell mediated host response.[11,12] Most recent studies propose serum PCT as a better marker than C-reactive protein and white blood cell count in the early detection of APN in children.[13–21] In contrast, 2 studies show that the PCT test is not a sensitive marker for the early diagnosis of APN.[22,23] However, few studies have demonstrated a relationship between PCT and febrile UTI in children 2 years old or younger.[14,19] Furthermore, the association between PCT and vesicoureteral reflux remains controversial.[14,15,18,19,21,24] Therefore, we evaluated the role of serum PCT as a reliable marker for detecting APN in children 2 years old or younger with a first febrile UTI, and assessed its ability to predict the risk of subsequent RS. We also examined the association of PCT with VUR.

PATIENTS AND METHODS

Study Population and Inclusion Criteria

We prospectively studied children 2 years old or younger who were hospitalized with a febrile UTI in a 3-year period. The diagnosis of a first febrile UTI was based on fever (axillary temperature 38C or greater), leukocyturia (defined as 5 or more WBC per high power field), positive urine culture (defined as growth of a single microorganism 10^5 colony-forming units per ml or more collected from the midstream clean void urine specimen for toilet trained young children, or 10^4 colony-forming units per ml or more collected from a transurethral catheterized specimen), no history of UTI and kidney or bladder disease and no other coincidental infections.

All patients were treated empirically with combined intravenous cefazolin (100 mg/kg daily) and gentamicin (7.5 mg/kg daily) for at least 3 days, which was later adjusted according to the results of bacterial susceptibility tests for a treatment duration of 7 to 14 days. The institutional review board of Medical University Hospital approved the study protocol and all parents of the participants provided informed consent.

Imaging Studies

All patients underwent renal ultrasound for the detection of urinary tract anomalies within the first 3 days of hospital admission. DMSA scans were performed within the first 5 days of hospitalization to verify the presence of renal parenchymal lesions. APN was defined as the presence of focal or diffuse areas of decreased uptake without evidence of cortical loss.[7,8] To assess the severity of acute renal involvement on PCT values, a scoring system was used based on DMSA grading and modified by Benador et al.[21] Lesions were graded in 4 groups of 0—no lesion (lower UTI), 1—mild lesions (defect covering less than 10% of surface area), 2—moderate lesions (defect covering 10% to 30%) and 3—severe lesions (defect covering more than 30%). If the initial DMSA result was abnormal, a followup examination was performed at least 6 months later to evaluate the presence of RS. The diagnosis of APN was confirmed only in children with totally or partially reversible lesions on the followup scans. The presence of renal lesions was determined by 2 nuclear medicine physicians who were blinded to the study. VCUG was performed 1 to 2 weeks after completing treatment for the infection. VUR was graded 0 to V according to the International Reflux Study.[25]

Laboratory Measurements

Serum and urine indexes for laboratory investigations, including peripheral WBC and differential, CRP values, urinalysis, urine and blood cultures were measured in all patients at hospitalization and before the initiation of antibiotic treatment. Serum samples were also taken for PCT measurements at hospitalization and repeated 3 days later. A rapid and quantitative measurement of PCT was performed using enzyme-linked fluorescent assay in an automated VIDAS® instrument (VIDAS BRAHMS PCT, BRAHMS Diagnostica, Berlin, Germany). The detection limit was 0.05 ng/ml and PCT 0.5 ng/ml or greater was considered abnormal.

Statistical Analyses

All statistical analyses were performed using SPSS® for Windows (version 15.0). Nonparametric data were assessed by the Mann-Whitney U test or Kruskal-Wallis 1-way ANOVA, and expressed as medians and interquartile ranges (Q_1-Q_3). Logistic regression analysis was used to evaluate the impact of potential risk on the development of RS in patients. The receiver operating characteristic curve analysis was performed to assess quantitative variables at hospitalization for diagnosing APN and later RS. The diagnostic values of each cutoff point, including sensitivity, specificity, PPV, NPV and the likelihood ratio for a positive result, were all calculated with $p < 0.05$ considered statistically significant.

RESULTS

Patient and Clinical Characteristics

There were 66 boys and 46 girls 24 days to 24 months old (median age 5.0 months), with a diagnosis of a first febrile UTI (table 1). Escherichia coli was isolated as a single pathogen in the urine culture of 100 (89.3%) patients. The number of urine collections by catheterized vs clean void specimens was 103 vs 9.

Renal ultrasound revealed findings of normal (89), mild to moderate hydronephrosis (renal pelvic