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Original Article

Clinical differentiation of acute pyelonephritis from lower urinary tract infection in children

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Background and Purpose: To evaluate clinical variables for diagnosing childhood acute pyelonephritis (APN) when technetium-99m dimercaptosuccinic acid (DMSA) scintigraphy is not available.
Methods: We retrospectively reviewed the records of 590 children with febrile UTI seen from January 1999 to February 2004. On the basis of DMSA scintigraphy performed within 7 days after admission, they were divided into APN (n = 237) or non-APN (n = 353) groups. Gender, age, clinical presentation, absolute neutrophil count, C-reactive protein (CRP), urinalysis, culture, and sonographic findings were recorded from charts.
Results: A CRP level of ≥66.4 mg/L, in patients with >2 days prior to admission had a sensitivity of 71.6% and a specificity of 72.5% for APN. Similarly, a CRP of >27.3 mg/L in patients with ≤2 days prior to admission and a white cell count of >14,990/mm^3 had sensitivities of 68.6% and 62.0% and specificities of 66.1% and 63.0%, respectively. Combining two or more variables did not result in better discrimination.
Conclusions: If a DMSA scan is not available, it is reasonable to treat a febrile UTI as APN if the CRP is >66.4 mg/L in a patient with >2 days of fever or if the CRP is >27.3 mg/L in a patient febrile for ≤2 days.

Key words: C-reactive protein; Diagnosis, differential; Pyelonephritis; Technetium Tc 99m dimercaptosuccinic acid; Urinary tract infections

Introduction

Urinary tract infection (UTI) is one of the most common bacterial infections in children, accounting for 4.6-5.9% of febrile episodes [1]. A significant proportion of children with febrile UTI have acute pyelonephritis (APN). APN may cause acute morbidity as well as irreversible renal scarring, possibly leading to hypertension and chronic renal failure [2,3]. To minimize or prevent parenchymal scarring, early and appropriate treatment of APN is crucial. Parenteral (7-10 days) or some oral antibiotics (14 days) are currently recommended for treating APN [4], while lower UTI only needs a 3- to 5-day course of therapy.

The differentiation of APN and lower UTI is challenging, however. Technetium-99m dimercaptosuccinic acid (DMSA) scintigraphy is now considered the standard method for diagnosis of APN [5,6], but is not available in all institutions. It also involves some degree of radiation exposure and is relatively expensive. Certain clinical and biochemical findings, e.g., flank pain; fever and chills; and increased white cell count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are traditionally thought to indicate upper UTI, but their diagnostic utility is unclear. The purpose of this study was to investigate the value of these signs for diagnosing APN in children in whom DMSA scintigraphy was used as the standard for diagnosis.

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Methods

This was a retrospective review of the records of all pediatric patients admitted to the Department of Pediatrics, Mackay Memorial Hospital between January 1999 and February 2004 with a febrile UTI who had

undergone DMSA renal scan. Our search yielded records for a total of 590 children (237 girls and 353 boys) aged 10 days to 207 months (mean, 16 months). Over that period, our department used the same basic protocol for evaluation and treatment of febrile UTI, and thus data from all patients were comparable throughout the study period.

Urine samples of patients under 2 years of age were collected by either suprapubic aspirate or transurethral bladder catheterization, while samples of older children were collected using a midstream catch. The diagnosis of UTI was based on a positive urine culture with $\geq 10^3$ colony-forming units/mL of a single microorganism from a suprapubic specimen, $\geq 10^4$ colony-forming units/mL from a catheterized specimen, or $\geq 10^5$ colony-forming units/mL from a midstream urine sample. All children in the study had temperatures of >38.5°C at presentation, and all had been treated with intravenous antibiotics (ampicillin 100 mg/kg per day plus gentamicin 50 to 75 mg/kg per day) empirically until the results of culture were available.

Renal sonograms were performed within the first 3 days after admission before DMSA scans by two pediatric nephrologists, using an Aloca SSD-1700 (Aloca Co., Tokyo, Japan) scanner with a 3.5-MHz transducer. The urinary tract was examined in both supine and prone positions. The sonograms were interpreted without knowledge of the results of DMSA scans. Ultrasonographic findings were considered abnormal when there were one or more areas of increased or decreased cortical echogenicity and/or loss of corticomedullary differentiation, with or without focal or diffuse renal enlargement.

Renal DMSA scintigraphy was performed within the first 7 days after admission. The scintigraphy results were considered positive for APN if renal DMSA uptake was focally, multifocally, or diffusely decreased or absent in the presence of a preserved renal contour. If the patient had had a previous UTI, the earlier DMSA scan results were compared, in order to differentiate old scars and new lesions. A renal scar was defined as a focal or generalized area of diminished isotope uptake associated with loss or contraction of functioning renal cortex. This appeared as wedge-shaped defectsor cortical thinning or flattening [7]. Voiding cystourethrography was performed 10 to 14 days after the infection resolved, to screen for vesicoureteral reflux.

The temperature and the duration of fever before diagnosis and after initiation of treatment were recorded. Initial symptoms and signs were also documented in detail. Laboratory investigations included white blood cell count, absolute neutrophil count (granulocyte count), CRP level (in 517 patients), blood culture, urinalysis, and urine culture. All blood and urine samples were obtained on the day the patients presented to hospital with fever.

The children were divided into APN and non-APN groups, according to results of DMSA scans. Descriptive data are provided for both groups and expressed as the mean plus or minus the standard deviation. Data from the groups were compared by use of the chi-squared test for categorical variables and *t* test for continuous variables. Statistical significance was assigned as a p value <0.05. A receiver operating characteristic (ROC) curve was used to define a cut-off value for the CRP and granulocyte count. The utility of the test was interpreted as fair when the area under the curve (AUC) was 0.50 to 0.75, good for an AUC of 0.75 to 0.92, very good for an AUC of 0.92 to 0.97, and excellent for an AUC of 0.97 to 1.00. Likelihood ratios (LRs) for CRP and granulocyte count were calculated based on the cut-off levels determined from the ROC curves.

Results

Patient characteristics

Of the 590 children with UTI, 237 (40.2%) had APN based on the DMSA scan and 353 (59.8%) did not. 331 children were less than 6 months old, of whom 118 (35.6%) had APN; 111 were between 6 months and 1 year, of whom 55 (49.5%) had APN; and 148 were older than 1 year, of whom 64 (43.2%) had APN. Among those younger than 6 months old, there were three times as many boys as girls. This ratio gradually reversed as the age increased, so that in patients older than 12 months, the female-to-male ratio was 2:1. A similar shift in gender predominance with age was seen in the subgroup of children with APN.

Clinical presentation and laboratory data

Children with APN were febrile for significantly longer before diagnosis and took longer to defervesce after treatment was begun than those without APN (Table 1). None of the other clinical variables differed significantly between the two groups. The CRP and granulocyte count were also significantly higher in patients with APN, and vesicoureteral reflux and/or abnormal ultrasonographic findings were more common in patients with APN. When the patients were stratified by duration of fever before diagnosis (≤2 or >2 days), the CRP

Table 1. Comparison of clinical variables in children with and without acute pyelonephritis (APN)

Variable	APN group (n = 237) No. (%)	Non-APN group (n = 353) No. (%)	*p*
Age (months; mean ± SD)	15.67 ± 24.77	16.29 ± 30.20	0.793
Gender, male	129 (54.4)	224 (63.4)	0.028
Fever alone	132 (55.7)	197 (55.8)	0.979
Gastrointestinal symptoms	47 (19.8)	70 (19.8)	1.000
Chilliness	16 (6.8)	17 (4.8)	0.316
Flank pain	13 (5.5)	13 (3.9)	0.296
Frequency/dysuria	13 (5.5)	28 (7.9)	0.252
Prolonged jaundice	2 (0.8)	7 (2.0)	0.268
Bacteremia	10 (4.21)	5 (1.4)	0.034
Febrile days prior to admission (mean ± SD)	2.57 ± 1.98	1.80 ± 1.60	<0.001
Days until defervescence (mean ± SD)	2.46 ± 1.84	1.40 ± 1.51	0.001
CRP level (mg/L) [n = 517; mean ± SD]	95.2 ± 83.3	32.8 ± 46.3	<0.001
With fever ≤2 days (mean ± SD)	67.5 ± 63.0	29.6 ± 36.4	<0.001
With fever >2 days (mean ± SD)	133.7 ± 91.6	55.3 ± 69.7	<0.001
Age ≤6 months (n = 304; mean ± SD)	88.7 ± 75.4	30.6 ± 36.8	<0.001
Age 6-12 months (n = 92; mean ± SD)	93.4 ± 82.3	27.7 ± 29.7	<0.001
Age >12 months (n = 121; mean ± SD)	112.4 ± 96.3	56.3 ± 74.0	0.001
Granulocyte count/mm^3 (mean ± SD)	18736 ± 7906	13598 ± 6593	<0.001
Presence of VUR	88/214 (41.1)	75/278 (27.0)	<0.001
Abnormal ultrasonographic findings	177/227 (78.0)	54/349 (15.5)	<0.001

Abbreviations: SD = standard deviation; CRP = C-reactive protein; VUR = vesicoureteral reflux

was significantly higher in both subgroups in patients with APN compared to those without. Among all patients with APN, the mean CRP was twice as high in those who had >2 days of fever compared with those with ≤2 days of fever, a statistically significant difference. In the 3 groups stratified by age (<6 months, 6 to 12 months, and >1 year), the CRP value was significantly higher in children with APN versus those without in each subgroup (Table 1). Therefore, we did not calculate operating characteristics for this test by age group.

Using ROC data, a cut-off of 66.4 mg/L for CRP in patients with >2 days of fever produced sensitivity and specificity values of 71.6% and 72.5% for diagnosis of APN. This was better than the performance of a CRP of >27.3 mg/L in patients with ≤2 days of fever or a granulocyte count of >14,990/mm^3 (Table 2). The AUC of the ROC curve for CRP in patients with >2 days of fever was 79.9%, a value that is considered good. For patients with ≤2 days of fever, the AUC for CRP was 73.8% and for the granulocyte count 70.0%, values that are fair. The positive LR (LR^+) for a CRP of >66.4 mg/L in patients with >2 days of fever was 2.60. In our series, the pretest odds of APN were 1 to 1.5; this LR^+ would increase the odds to 1.73 to 1. Alternatively, the pretest probability of 40.2% would be increased to 63.4% post-test. In patients with ≤2 days of fever, a CRP of >27.3 mg/L yielded an LR^+ of 2.02 and for a granulocyte count >14,990, the LR^+ was 1.68.

For the total sample of 590 patients, regardless of the duration of fever, a CRP of >42 mg/L plus a granulocyte count of >14,990/mm^3 had a sensitivity of only 50.0%, a specificity of 47.6%, and an LR^+ of 0.95 for APN. However, for either a CRP of >42 mg/L or a granulocyte count of >14,990/mm^3, the sensitivity was 85.9%, the specificity was 47.6%, and the LR^+ was 1.64. Calculations using various cut-off points are shown in Table 2.

Pathogens isolated from the 590 urine cultures included 447 isolates of *Escherichia coli*, 32 of *Proteus* spp., 38 of *Klebsiella pneumoniae*, 50 of enterococci, and 23 of various other bacteria. No correlation was found between the pathogens and the presence or absence of APN.

Ultrasonography

Ultrasonography was performed in 227 patients in the APN group and 349 patients in the non-APN group. In the APN group, one or more of those findings was documented in 177 of 227 patients (78.0%) in whom it was performed. In the 349 patients in the non-APN group, increased renal cortical echogenecity was documented in 14 patients (4.0%) and nephromegaly in 40 (11.7%). The sensitivity and specificity of abnormal

Table 2. Statistical calculations for diagnostic accuracy of C-reactive protein (CRP) and granulocyte count for the diagnosis of acute pyelonephritis

Variable	Sensitivity (%)	Specificity (%)	LR^+ (95% CI)	LR^- (95% CI)
CRP (>42 mg/L) [n = 236/517)	71.8	71.7	2.54 (2.08-3.09)	0.39 (0.31-0.49)
CRP (>20 mg/L) [n = 373/517]	84.5	55.6	1.90 (1.66-2.18)	0.27 (0.20-0.38)
CRP (>50 mg/L) [n = 195/517]	60.2	77.2	2.64 (2.09-3.32)	0.51 (0.43-0.61)
CRP (>66.4 mg/L) with fever >2 days (n = 86/157)	71.6	72.5	2.60 (1.73-3.89)	0.39 (0.27-0.56)
CRP (>27.3 mg/L) with fever ≤2 days (n = 163/360)	68.6	66.1	2.02 (1.63-2.50)	0.47 (0.35-0.62)
Granulocyte count (>14,990/mm^3) [n = 279/590]	62.0	63.0	1.68 (1.44-2.05)	0.60 (0.46-0.70)
CRP >42 mg/L plus granulocyte count >14,990/mm^3 (n = 266/517)	50.0	47.6	0.95 (0.80-1.13)	1.05 (0.87-1.25)
CRP >42 mg/L or granulocyte count >14,990/mm^3 (n = 340/517)	85.9	47.6	1.64 (1.45-1.84)	0.29 (0.20-0.42)

Abbreviations: LR^+ = positive likelihood ratio; CI = confidence interval; LR^- = negative likelihood ratio

[a]The cut-off values were chosen to achieve acceptable and relatively equal sensitivity and specificity.

ultrasonographic findings for diagnosing APN was thus 78.0% and 84.5%, respectively.

Discussion

The classical features of flank pain, fever and chills, increased white cell count, ESR and CRP, while often used to diagnose APN, have deficiencies in discriminating the condition [4,8], although some individual studies have suggested that resolution of fever during treatment and increased ESR or CRP level are useful in predicting APN [9-12]. In our study, we found that both the duration of fever prior to admission and the number of days after treatment began until the child defervesced were both significantly longer in the APN than in the non-APN group. A CRP of >66.4 mg/L (fever >2 days), of >27.3 mg/L (fever ≤2 days), and a granulocyte count of >14,990 cells/ mm^3 all produced a reasonable AUC. In a study of 111 children, Benador et al [13] found that a CRP of >20 mg/L was 89% sensitive and 25% specific in accurately identifying APN. Biggi et al [8] studied 101 children and concluded that a CRP above 40 mg/L was 90% sensitive but only 36% specific. Pecile et al [11] studied 100 children with UTI. Using a cut-off of 20 mg/L, CRP was 94.4% sensitive but only 31.9% specific. When they raised the cut-off to 50 mg/L, the sensitivity and specificity became 74.0% and 76.6%, respectively, which were similar to our results with a cut-off of 42 mg/L (71.8% and 71.7%). We also used those cut-off values from the literature to calculate the operating characteristics of the test based on data from our series. In our study, a CRP of >20 mg/L was 84.5% sensitive and 55.6% specific, while a CRP of >50 mg/L was 60.2% sensitive and 77.2% specific (Table 2). The discrepancies in the operating characteristics of CRP at various cut-off values in the different studies may be due to variations in the timing of CRP measurement in the series. We measured CRP when the patients first presented but then calculated the best cut-off for subgroups with fever for more or less than 2 days. We believe this is a practical approach because it is based on the history at presentation.

Information on the utility of the granulocyte count in the literature appears to be scarce. In our study, it was not quite as useful as the CRP, having a sensitivity of 62.0% and specificity of 63.0% at a cut-off of 14,990/mm^3. Trying to combine CRP and granulocyte count did not improve the accuracy of diagnosis but in fact increased the number of false positives. Biggi et al [8] also had the same result when trying to combine five different parameters to predict APN. Although in patients with fever >2days, a CRP of >66.4 mg/L gave an LR^+ of 2.60, it is still not an ideal diagnostic test for APN. We do not believe that CRP is an adequate substitute for a DMSA scan if the scan is available. If a scan is not available, though, one should consider treating a UTI with parenteral antibiotics for 7 to 14 days if CRP is higher than 66.4 mg/L in a patient with >2 days of fever or >27.3 mg/L in a patient with ≤2 days of fever. In either of those cases, the probability of APN is greater than 50%. However, CRPs of less than those values are not adequate to safely rule out APN.

Renal ultrasonography is usually the first imaging study to be performed in children with suspected APN,

but is poorly effective in detecting renal parenchymal involvement [8,14,15]. However, in our series, it had a relatively high sensitivity (78%) and specificity (84%). This may be because pediatric renal ultrasonography in our hospital was performed by two highly experienced pediatric nephrologists, not by technicians. Recently, it has been suggested that power Doppler ultrasound may be both sensitive and specific for APN [16], and more investigations of this imaging technique are awaited.

The latest research in the field of pediatric APN has focused on procalcitonin, a new marker of infection [11, 17,18]. Measured with either an immunoluminometric quantitative test or a rapid semiquantitative test, procalcitonin has a reported sensitivity of 70.3-94.1% and a specificity of 82.65-89.7% for the diagnosis of APN. Pecile et al [11] reported that a procalcitonin cut-off value of 0.8 ng/mL had a sensitivity of 83.3% and a specificity of 93.6%. As yet, however, this test is not widely available.

In conclusion, our results indicate that longer duration of fever prior to admission, longer duration of fever after treatment is begun, higher CRP level, and higher granulocyte count were all correlated with APN, with CRP level having the best sensitivity and specificity, although the cut-off chosen should be based on the duration of the fever at presentation. In the absence of DMSA scanning, however, the ideal diagnostic test to discriminate between APN and non-APN UTI still eludes us.

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