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ORIGINAL PAPER

A multicenter case–control study of diagnostic tests for urinary tract infection in the presence of urolithiasis

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Abstract Urinary stone disease (USD) alone can cause much morbidity, but when present in conjunction with urinary tract infection, complications and morbidity increase even more. This study investigated the clinical and laboratory findings in patients who had USD with and without infection and evaluated the most suitable diagnostic value for urinary tract infection parameters before urine culture results were available. In a prospective fashion, patients who presented to the emergency department with a complaint of colicky flank pain (with or without hematuria) and who were diagnosed as having urolithiasis with ultrasound were evaluated for 1 year. The gold standard for the diagnosis of urinary tract infection was urine culture. The most suitable diagnostic value for urinary tract infection parameters was determined by receiver operating characteristic (ROC) curves. Logistic regression was used to identify independent variables that predicted a positive urine culture. Of the 192 eligible patients, 177 agreed to participate in the study. Of the clinical and laboratory characteristics analyzed, urine WBC, blood WBC, and fever were significantly different between culture positive and negative patients ($p < 0.001$, $p = 0.04$ $p = 0.012$, respectively). Using ROC curve analysis, pyuria (over 10 WBCs per HPF), fever over 37.9°C, and leucocytosis over 11,300 were the best predictors of a positive culture result. The logistic regression model for leukocytosis >11,300 (OR 2.1), pyuria (OR 2.8), and temperature >37.9°C (OR 3.1) showed a significantly increased risk of having a positive urine culture (correct class 87.9%). While a single physical examination or laboratory finding cannot predict urinary tract infection in USD patients with complete reliability, the presence of pyruria, fever, and leukocytosis significantly increases the odds of a positive urine culture.

Keywords Emergency · Stone disease · Infection · Diagnosis · Predictive signs

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Introduction

Background

Urologic stone disease (USD) is a common condition, with an incidence in some populations as high as 12% [1]. Generally, patients with urinary stone disease are initially evaluated and diagnosed in the emergency department (ED), since the cardinal symptom of USD is the acute onset of severe abdominal, flank, and/or back pain [2]. Although acute pain in most patients will resolve without complications, a substantial subset will experience more serious manifestations such as unremitting pain, systemic infection, or post-renal acute renal failure.

The presence of pyuria, fever, leukocytosis, and/or bacteriuria suggests the diagnosis of urinary tract infection (UTI) with a possible infected obstructed kidney or pyonephrosis [3]. Because such conditions are potentially life-threatening, in the presence of these findings, hospitalization (and possibly emergency drainage or surgery) and IV antibiotics are recommended [3].

Until the results of urine culture are ready, accurate criteria to determine the presence of UTI in USD patients will prevent the unnecessary use of antibiotics, admission to the hospital, and wasting of economic resources. This study aimed to determine the most suitable diagnostic parameter for identifying USD patients who had UTI before their urine culture results were available.

Materials and methods

Study design and setting

This prospective study was conducted in the EDs of three tertiary care teaching hospitals and one community hospital. The study protocol was approved by our University Medical Faculty Hospital Ethical Review Board and by the institutional ethics board of each participating center in the trial.

Selection of participants and data collection

Patients (age 18–65 years) presenting to the emergency department with a complaint of colicky flank pain (with or without hematuria) and diagnosed with urolithiasis by ultrasound were approached for inclusion in the study between January 1, 2008 and December 30, 2008. Those giving written informed consent were evaluated in the ED with a routine urinalysis, urine culture, blood tests (WBC and creatinine), and ultrasound performed in the radiology department. Data were collected by senior emergency medicine residents on study forms. Exclusion criteria included failure to grant consent, unstable patients, antibiotic usage within the previous 3 days, urinary tract instrumentation, and cardiac, renal, or hepatic failure.

Data collection and analyses

Fever was defined as an axillary temperature of $\geq$38°C [4]. Leukocytosis was defined as white blood cell count of $\geq 12{,}000 \times 10^3$ cells/mm^3 [5]. Urine analyses were performed on an auto-analyzer; pyuria was defined as a leukocyte count of $\geq$5 per HPF and hematuria as a RBC count of >5 per HPF on a centrifuged specimen [6]. Samples for urine culture were obtained from midstream urine. Urine cultures were performed by the single-colony method, with the blood EMB agar set to be 10 μl/environment. The cultures were interpreted 24 h later; infection was diagnosed if the colony count was $\geq$1,000 colony-forming units (CFU) per milliliter of urine. Cultures were considered contaminated if more than one organism was isolated or if nonpathogens were isolated, e.g. *Acinetobacter* species, candida, *Gardnerella vaginalis*, *Micrococcus* species, *Streptococcus viridans*, staphylococcus (non-aureus), or *Corynebacterium* species. Cases with contaminated cultures were excluded from data analysis.

Ultrasound was performed in the radiology department by a staff radiologist. Hydronephrosis was classified as present or absent; visualization of the stone or unilateral hydronephrosis was considered evidence of urolithiasis [7, 8].

Primary data analysis

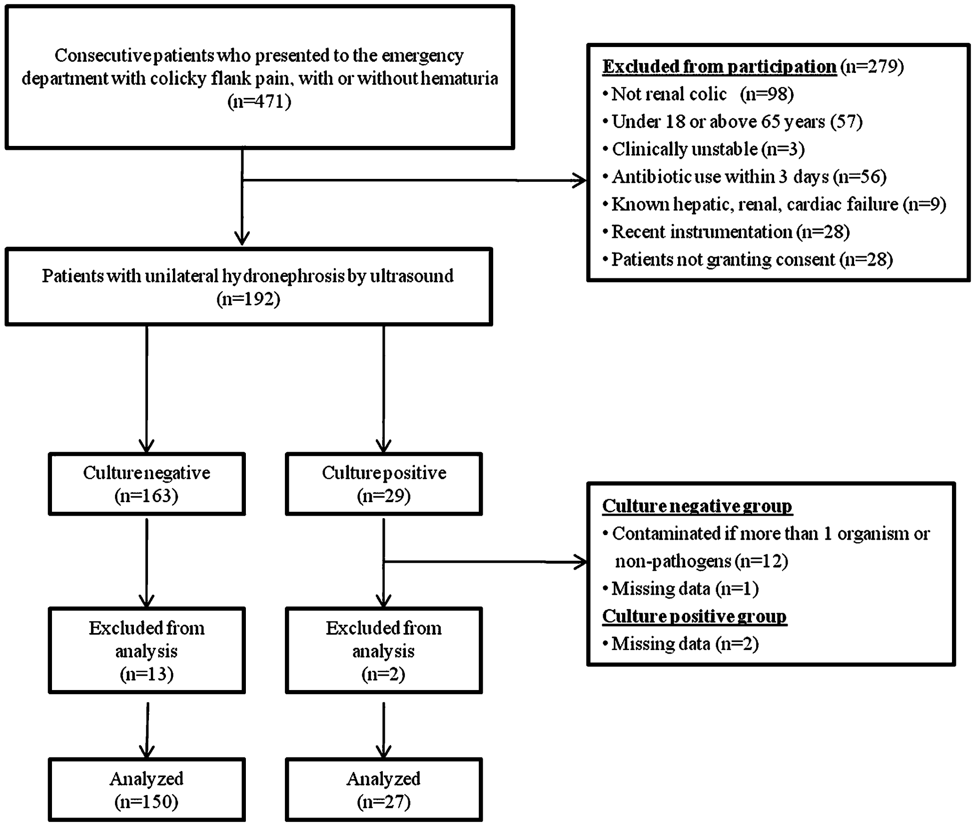
Baseline characteristics, physical examination, and laboratory findings of the culture positive (CP) and culture negative (CN) groups were compared using SPSS version 16.0 for Windows (SPSS Inc., Chicago, USA). Demographic and clinical features of the patients are reported with mean ± standard deviation, median, interquartile range (IQR), 95% confidence intervals, and percent (%). Distribution of the data was determined to be normal with the Kolmogorov–Smirnov test. To compare nominal data, Student's t test was used. To compare percentages, chi-square testing was used. Receiver operating characteristic (ROC) curves were used to calculate sensitivity and specificity of continuous variables at all observed threshold values. The area under the curve (AUC) was calculated with its 95% confidence interval (CI). A CI with a lower limit of more than 0.5 was considered significant. Positive and negative likelihood ratios were calculated. The cut-off values obtained by ROC analysis were evaluated in a logistic regression model as independent variables, with a positive culture result as the outcome variable.

Results

Characteristics of study subjects

Four-hundred seventy-one consecutive patients were assessed for eligibility and 279 patients were excluded for a variety of reasons (Fig. 1). Ultimately, 177 patients satisfied the inclusion criteria and were included in the study. Mean age was 42 years. Twenty-seven patients (15.3%) had a positive urine culture (CP group) whereas the remaining 150 patients (84.7%) had a negative urine

Fig. 1 Patient flow



culture (CN group). The mean ages and proportions of males and females were similar in both groups.

Main results

Chief complaints, physical examination, laboratory and radiologic findings of the CP and CN patients are shown in Table 1. No significant differences were found between CP and CN patients in the percentage of those with dysuria ($p = 0.403$), flank pain ($p = 1.000$), polyuria ($p = 0.803$), hematuria ($p = 0.655$), or hydronephrosis ($p = 0.931$). However, axillary temperature $\geq$38°C and leukocytosis were more common in CP (10,500 $\pm$ 3,750, $p = 0.012$) than in CN (8,300 $\pm$ 2,150, $p = 0.05$) patients. Urine leukocyte counts were significantly greater in CP [35 (IQR 77)] than in CN [6 (IQR 13)] patients ($p < 0.001$). The incidence of hydronephrosis was similar in both groups, 65.3% in CP, and 66.6% in CN patients ($p = 0.93$).

ROC curve analysis results are shown in Table 2: values with the highest sensitivity and specificity ("cut-off values"), AUC with 95% CI, as well as positive and negative likelihood ratios. Using ROC analysis, pyuria (positive LR 2.78, negative LR 0.3, sensitivity 0.78 and specificity 0.72), fever (positive LR 4.27, negative LR 0.7, sensitivity 0.56 and specificity 0.80), and leukocytosis over 11,300/mm^3 (positive LR 3.09, negative LR 0.87, sensitivity 0.63 and specificity 0.83) were determined to be the best predictors of a positive urine culture.

The logistic regression model for leukocytosis (over 11,300/mm^3; OR: 2.1; 95% CI: 1.2–9.9, $p = 0.035$), pyuria (OR 2.8; 95% CI 1.5–61.9, $p = 0.014$), and fever (OR 3.1; 95% CI 1.8–13.6, $p = 0.006$) showed a significantly increased odds of having a positive urine culture (χ^2 21.562, $df = 2$, $p < 0.001$, correct class 87.9%). This regression model predicted 146 of 150 negative urine cultures and 24 of 27 positive urine cultures. With this model, only four patients would have had a false positive result.

Discussion

This study reports the diagnostic value of clinical and laboratory findings for assessing risk of a positive urine culture in patients with urinary stone disease. ROC analysis revealed leukocytosis (>11,300 WBC/mm^3), pyuria (>10 WBC/HPF on spun sediment), and fever (>37.9°C) as being the only factors predictive of a positive culture.

Urinary stones may increase the risk of UTI whether they themselves are infected or not. Previous studies found that 80–85% of USD patients are discharged from the ED, 20% are hospitalized, and over 24% are treated with oral or parenteral antibiotics due to accompanying infection [9]. If

Table 1 Clinical, laboratory, and imaging characteristics in urine culture positive (CP, $n = 27$) and urine culture negative (CN, $n = 150$) patients with urolitiasis presenting to our emergency department

Chacteristic	CP	CN	*p*
Age	41	42	0.829
Gender (M%)	59%	68%	0.261
Flank pain	27 (100%)	146 (97%)	1.000
Hematuria	10 (37%)	47 (31%)	0.655
Dysuria	15 (55%)	68 (45%)	0.403
Pollakiuria	5 (19%)	33 (22%)	0.803
Fever (≥38°C)	7 (26%)	12 (8%)	0.012*
Flank tenderness	27 (100%)	135 (76%)	0.227
Urine analysis			
Urine density	1015 (IQR 9)	1020 (IQR 12)	0.323
Urine PH	6 (IQR 1.50)	5.5 (IQR 1.00)	0.464
Urine RBC/HPF	21 (IQR 65)	19 (IQR 45)	0.562
Urine WBC/HPF	35 (IQR 77)	6 (IQR 13)	<0.001*
Urine protein	5 (18%)	18 (12%)	0.220
Urine nitrite	2 (0.54%)	1 (0.06%)	0.134
Other			
Leucocytosis $\geq 12{,}000 \times 10^3$ cells/mm^3	10,400	8,370	0.044*
Hydronephrosis	18/27	98/150	0.931

Table 2 Performance of fever, pyuria, and leucocytosis as variables to predict a positive urine culture in 177 patients with urolithiasis presenting to our emergency department

Criterion	Sensitivity	Specificity	+LR	95% CI	−LR	95% CI
Fever > 37.9°C	56	80	4.27	2.6–7.0	0.69	0.4–1.2
Urine WBC > 10/HPF	78	72	2.78	2.2–3.5	0.31	0.1–0.7
Leukocytosis > 11,300/mm^3	63	83	3.09	1.4–6.8	0.87	0.4–1.7

clinicians could reliably determine which patients have UTI, they would be able to make more informed decisions about which patients might require empiric antibiotic therapy or admission.

Dysuria by itself is a common reason for antibiotic use. Although dysuria commonly accompanies UTI, in our study, dysuria was not a discriminating factor to indicate infection, occurring in 45% of those with, and 54% of those without positive urine cultures. Stones may cause dysuria, with or without superimposed infection, by obstructing the ureter at the ureterovesical junction, resulting in irritative voiding symptoms or inflammation of the distended ureteral mucosa [10].

Urinalysis is the test most commonly used in the assessment of patients who may have USD, and urine leukocyte counts have been used as indicators of infection [6, 9]. In our study, leukocyte counts in the CP group were statistically higher than those in the CN group. However, the white blood cell count of the CN group [6 (IQR 13)] was almost at the limit of pyuria in the CN group. Although the presence of pyuria is the most commonly used parameter to diagnose UTI, local trauma caused by urinary stones may produce pyuria without infection [11]. Making the diagnosis of infection in USD patients based on urine white blood cell counts should be re-evaluated.

Hydronephrosis is an important predisposing factor for infection in urolithiasis (3). The presence of hydronephrosis and fever suggests the possibility of a UTI, which warrants at least hospitalization and IV antibiotics; some patients may need to be treated as surgical emergencies [12]. Some authors suggest that antibiotic prophylaxis is unlikely to benefit patients with severe hydronephrosis secondary to upper tract obstruction [13, 14]. The presence of hydronephrosis in our patients was not predictive of a positive urine culture.

No single physical finding or laboratory result was adequate to predict a positive urine culture in patients with USD. The regression model using the risk factors of WBC > 11,300/mm^3, urine WBC > 10/HPF on a spun sediment, and temperature >37.9°C was highly accurate for predicting positive and negative cultures.

Limitation

The study had some limitations such as the heterogeneity of clinical parameters and a small sample size. Direct estimation, based on data, is impracticable because of larger sample size requirements.

We realize that a multicenter study has some restrictions. To overcome these problems, we developed protocols to include management of the ED approach and a record of laboratory test results without interpretation. However, further discussions on standardization of ultrasonography examinations and the interpretation of urine culture are needed.

Conclusion

UTI in patients with urolithiasis needs to be diagnosed accurately so that antibiotics can be started before culture results are available. No single physical examination finding or laboratory test can accurately predict which patient with urolithiasis will have a positive urine culture. In this derivation study, urolithiasis patients with leukocytosis, pyuria, and fever had a higher incidence of positive urine culture than those without these findings. These findings need to be confirmed in a validation study to be performed in the future.

Article summary

1. Why is this topic important?

Without a urine culture result, no single physical examination or laboratory finding is adequate to predict urinary tract infection. If accurate markers could be found which predicted a positive urine culture, physicians could more easily decide which patients required empiric antibiotics and/or hospital admission.

2. What does this study attempt to show?

The study aimed to evaluate the most suitable diagnostic value of various historical, clinical, laboratory, and imaging findings for predicting a positive urine culture in patients with urolithiasis presenting to one of several emergency departments.

3. What are the key findings?

Urine cultures were positive more often if WBC was greater than 11,300/mm3, urine WBCs were >10/HPF on a spun specimen, and the patient's temperature was over 37.9°C.

4. How is patient care impacted?

In this derivation set, absence of the three findings mentioned above predicted a negative urine culture in patients with urolithiasis. In these patients, antibiotics might be witheld until the results of urine culture are available. Our findings need to be validated in a larger prospective study.

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