Original Article

Procalcitonin is a strong predictor of urine culture results in patients with obstructing ureteral stones: A prospective, pilot study

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Abstract

Purpose: The appropriate management of infected obstructing ureteral calculi is prompt genitourinary decompression. Urine cultures are the gold standard for confirming infection but often take 24–48 h to result. Although white blood cell (WBC) count is an important diagnostic laboratory test, it is a nonspecific inflammatory marker. Similarly, urinalysis (UA) can be misleading in the setting of a contaminated sample, bladder colonization, or in cases of a completely obstructed the upper urinary tract. Procalcitonin (PCT) has shown promise in predicting the presence and degree of bacterial infections. In this proof-of-concept study, we explore whether PCT is effective at predicting concomitant infections in the setting of obstructing ureteral stones.

Materials and Methods: This is a prospective, single-institution observational pilot study examining adult patients who presented to the emergency room with acute obstructing ureterolithiasis. In total, 22 patients were enrolled. At the time of presentation, data obtained were vital signs, WBC count, PCT, UA, urine, and blood cultures. Fisher-exact two-tailed *t*-tests and receiver operating characteristic statistics with area under the curve (AUC) calculations were used to determine the correlation between urine culture results and PCT, WBC count, nitrite-positive UA, heart rate, and fever.

Results: In total, 5/22 patients had bacteria-positive urine cultures. PCT ($P = 0.020$) and nitrite-positive UA (0.024) were the only statistically significant predictors of urine culture results. In comparing the AUC, PCT (0.812) was strongly correlated with eventual urine culture results.

Conclusions: This proof-of-concept pilot study gives encouraging results, in that PCT was a good predictor of positive cultures ($P = 0.02$, AUC 0.812). Given, the small sample size, one cannot directly compare PCT to other markers of infection. However, PCT shows promise in this arena and warrants future investigation.

Key Words: Obstructive ureterolithiasis, procalcitonin, urinary tract infections

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INTRODUCTION

Urinary sepsis, which carries a mortality rate of 16–26%, has various causes but mostly occurs in the setting of urinary tract obstruction.[1,2] Of these obstructive cases, 80% are due to ureteral calculi.[3] Early targeted therapy is essential to improving outcomes,[4,5] including urgent ureteral decompression, either with retrograde stent, or percutaneous nephrostomy tube placement. However, the majority of patients with ureteral stones present early in the disease process, oftentimes before signs of sepsis are evident. Determining which patients have an associated urinary tract infection (UTI), and are at-risk for sepsis, would help guide early intervention and potentially help mitigate the progression of the infectious process.

While urine and blood cultures are the gold standard for diagnosing concomitant infections, a decision regarding intervention, observation, or discharge from the hospital must often be made before culture results are available. Traditionally, clinical judgment, symptom scoring scales, white blood cell (WBC) count, and urinalysis (UA) are used to guide treatment.[6,7] However, symptoms may not correlate with the severity of disease, and traditional biomarkers have not proven to be particularly reliable. Although WBC count remains a cornerstone in the infectious workup, it is a nonspecific marker and cannot reliably differentiate bacterial from viral infections or other inflammatory states. Similarly, a contaminated sample, a completely obstructed upper tract, or a nitrite-negative organism may hinder the interpretation of a UA. Procalcitonin (PCT) appears to be effective in identifying bacterial etiologies and the degree of infection.[8,9]

PCT is a peptide precursor of calcitonin, a hormone involved in calcium hemostasis. It is detectable in the blood within 2 h of endotoxin injection, and its half-life is 22–26 h significantly less than other acute phase reactants.[10,11] PCT remains elevated until the infection has resolved. Prior studies have shown PCT levels to correlate with severity of disease.[8] More specifically, PCT has been broadly studied in the Intensive Care Unit setting and can serve as a guide to determine when to initiate antimicrobial therapy, its effectiveness, and when to de-escalate, or switch antibiotic agents.[12,13] PCT has been studied in several urology-specific disease states. Compared to other biomarkers, it has been shown superiority in predicting the severity of acute pyelonephritis in the emergency department (ED) setting.[14] It has also shown promise in predicting vesicoureteral reflux and renal damage in children presenting with their first febrile UTI.[15] The aim of this prospective pilot study is to establish if PCT is a relevant, surrogate biomarker for predicting UTIs in patients with obstructing ureteral calculi.

MATERIALS AND METHODS

An Institutional Review Board approved prospective observation study was performed at Rush University Medical Center from February 2014 to August 2014. Consecutive patients who presented to the ED with confirmed ureterolithiasis requiring urologic consultation were considered for enrollment in this study. Inclusion criteria included age >18 years old with a diagnosis of obstructive ureterolithiasis based on history, physical examination, and abdominal computed tomography scan results. Exclusion criteria included pregnant or breastfeeding patients, those on hemodialysis or peritoneal dialysis, a history of renal transplantation, the presence of cancer, immunodeficiency, HIV, or other immunosuppressed states. In patients who fulfilled the inclusion criteria, the following data were obtained at the time of diagnosis: Vital signs, PCT, WBC count, UA, urine culture, and blood culture. Furthermore, patient demographics, coexisting diseases, radiographic findings, and any urologic interventions were recorded. Systemic inflammatory response syndrome and sepsis were defined using the 2012 guidelines from the Society of Critical Care Medicine.

An upper limit of normal value was established for each variable, which was used to create a binomial distribution. Elevated WBC count, PCT, heart rate, and temperature were defined as follows: >10K/μl, >0.1 ng/mL, >99 beats/min, and 99.9° Fahrenheit (F), respectively. SPSS statistical software was then used to analyze this data. Two-by-two contingency tables were created using positive urine cultures as the gold standard test. Fisher-exact two-tailed tests were calculated, with significance defined as $P < 0.05$. In addition, receiver operating characteristic curves were created, and an area under the curve (AUC) was calculated for each variable. Finally, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for PCT using a 2 × 2 contingency table.

RESULTS

During the study period, 22 patients met the criteria for enrollment. Of the 22 patients, 10 (45.5%) were women, and 12 (54.5%) were men with a mean age of 47.9 years (range 27–77). A total of 9/22 (40.9%) patients had a history of nephrolithiasis before presentation [Table 1]. Ultimately, 10/22 patients underwent a urologic procedure during this admission, either for stent placement or ureteroscopy with holmium laser lithotripsy. In Table 2, patients and infectious variables are categorized according to urologic intervention. Of note, PCT was not used in the decision-making process for this study.

Table 1: Patient demographics

Variables	# (%)
Average age (years)	47.9 (27-77 mean)
Male	12 (54.5)
White	9 (40.9)
African-American	7 (31.8)
Hispanic or Latino	5 (22.7)
Asian	1 (4.5)
History of nephrolithiasis	10 (45.5)
History of prior surgery for stones	4 (18.2)
Diabetes mellitus	5 (22.7)
Hypertension	5 (22.7)
History of cancer	3 (13.6)
Coronary artery disease	1 (4.6)
Peripheral arterial disease	1 (4.6)
Obstructive sleep apnea	2 (9.1)
Chronic obstructive pulmonary dx	1 (4.6)
Congestive heart failure	0 (0)
Chronic kidney disease	0 (0)

Table 2: Stratification of patients and biomarker results according to intervention

	Medical expulsive therapy	Ureteroscopy, holmium laser lithotripsy	Stent
PCT + (>0.1)	2	0	5
WBC + (>10K)	3	2	6
Nitrite+urinalysis	1	0	3
HR + (>99 bpm)	1	1	3
Temperature (>99.9F)	0	0	1
SIRS+	0	2	3
Sepsis+	0	0	3
Total number of patients (%)	11 (50.0)	4 (18.2)	7 (31.8)

PCT: Procalcitonin, WBC: White blood cell, HR: Heart rate, SIRS: Systemic inflammatory response syndrome

In total, 5/22 patients had positive urine cultures (>10K bacteria). The values for PCT, WBC count, nitrite-positive UA, tachycardia, and temperature were compared for both positive and negative cultures. According to the Fisher-exact two-tailed test, only PCT ($P = 0.021$) and nitrite-positive UA ($P = 0.024$) were statistically significant predictors of eventual positive urine cultures [Table 3]. Furthermore, an AUC was calculated for each marker [Figure 1]. PCT was a strong predictor of concomitant infection in this cohort (AUC 0.812). The sensitivity, specificity, PPV, and NPV for PCT were also calculated using a 2 × 2 contingency table [Table 4].

DISCUSSION

In the presence of suspected sepsis, guidelines put forth by the Surviving Sepsis Campaign should be initiated, regardless of etiology. These initial steps include early diagnosis, resuscitation within 6 h of recognition, broad-spectrum antimicrobial therapy, and prompt imaging studies to help confirm the potential source.[16,17] In addition, for patients with upper urinary tract obstruction, it is recommended that genitourinary tract decompression, via JJ-stent or percutaneous nephrostomy tube be carried out within the first 6 h.

Table 3: Comparing diagnostic markers and eventual urine culture results

	Positive urine culture (*n*=5)		Negative urine culture (*n*=17)		*P*
	Positive	Negative	Positive	Negative	
PCT >0.1 ng/mL	4	1	3	14	0.021
WBC >10K	4	1	7	10	0.31
Nitrite + urinalysis	3	2	1	16	0.024
HR >99 bpm	3	2	2	15	0.055
Temperature >99.9F	1	4	0	17	0.23

PCT: Procalcitonin, WBC: White blood cell, HR: Heart rate

Table 4: Sensitivity, specificity, positive predictive value, and negative predictive value for procalcitonin as a predictor of positive urine cultures

PCT >0.1 ng/mL	Urine cultures #		
	Positive	Negative	
Positive	4	3	PPV=57.1
Negative	1	14	NPV=93.3
	Sensitivity=80.0	Specificity=82.3	

PCT: Procalcitonin, PPV: Positive predictive value, NPV: Negative predictive value

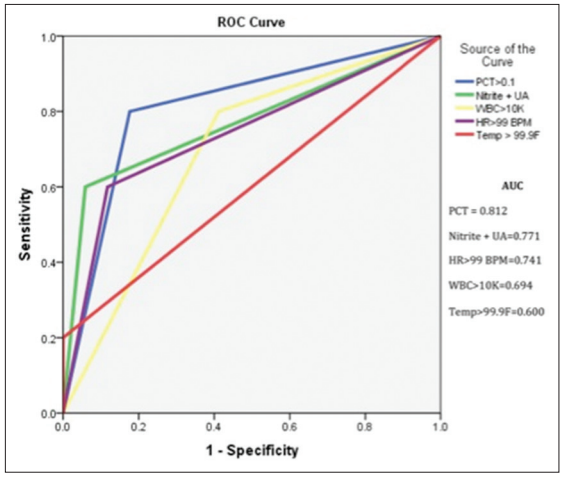

Figure 1: Receiver operating characteristic curves and associated area under the curve predicting positive urine cultures

Urologists often play a critical role in determining the timing of genitourinary decompression in the setting of ureteral obstruction. Although the threshold for early intervention should remain low, the presence and severity of an associated infection can be difficult to predict. As such, there is continued need for a more reliable diagnosis. Cultures, although the gold standard for confirming infection, typically take at least 24–48 h to result, and a clinical decision must often be made sooner.[2] This pilot study was initiated to determine if PCT shows promise in predicting positive urine cultures in those patients with obstructing ureteral stones. The results were encouraging, as PCT was a statistically significant marker of eventual urine culture growth ($P = 0.02$). Nitrite-positive UA was also a strong predictor ($P = 0.024$) and both outperformed tachycardia, leukocytosis, and temperature >99.9F. The

strength of PCT was similarly illustrated by an AUC of 0.812. Being a small, pilot study, the greatest weakness of this paper is its sample size. As such, a direct comparison between infectious markers is limited. However, we feel that the main goal of this study, as a proof-of-concept, was accomplished.

We feel that the results of this prospective, observational pilot study are compelling enough to warrant future investigation. We are hopeful that this can be the first step toward adding PCT and perhaps other biomarkers to our diagnostic armamentarium in those patients with obstructing ureteral stones. A larger prospective study could further investigate PCT's ability to predict infection against WBC count and other serum biomarkers, such as C-reactive protein and erythrocyte sedimentation rate. In addition, there is no consensus on the threshold value for a positive procalcitonin test. We opted to use the reference range of our institution, with a cutoff of 0.1 ng/mL. With a larger study, a threshold analysis could be completed to determine the most appropriate cutoff point for this biomarker.

CONCLUSIONS

This pilot study showed that PCT and nitrite-positive UA outperformed WBC count, tachycardia, and fever in predicting UTI in patients with obstructing ureteral stones. As such, we feel that a larger investigational study should be undertaken.

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Conflicts of interest
There are no conflicts of interest.

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