The Inadequacy of Urinary Dipstick and Microscopy as Surrogate Markers of Urinary Tract Infection in Urological Outpatients With Lower Urinary Tract Symptoms Without Acute Frequency and Dysuria

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Purpose: Diagnosing urinary infection in patients with chronic lower urinary tract symptoms without dysuria is a critical step. In this study we scrutinize the sensitivity and specificity of dipstick urinalysis and microscopic pyuria (10 or more white blood cells per μl) to identify infection in such patients.

Materials and Methods: This was a prospective, blinded, observational cohort study of urological outpatients with painless lower urinary tract symptoms. Midstream and catheter urine samples were analyzed. A total of 508 midstream urine samples were used to compare leukocyte esterase, nitrite dipstick and urine microscopy with cultures seeking 10^5 cfu/ml. Similarly 470 catheter urine samples were used to compare the same surrogates with 10^5 cfu/ml and with an enhanced culture method seeking 10^2 cfu/ml. A comparison of leukocyte esterase against microscopic pyuria was made using the 508 midstream and 470 catheter specimens of urine. Midstream urine specimens were provided by 42 normal volunteers for comparison.

Results: For a midstream urine culture at 10^5 cfu/ml leukocyte esterase was 56% sensitive, nitrite was 10% sensitive and microscopic pyuria was 56% sensitive. Specificities were 66%, 99% and 72%, respectively. For a catheter specimen of urine culture at 10^5 cfu/ml leukocyte esterase was 59% sensitive, nitrite was 20% sensitive and microscopic pyuria was 66% sensitive. Specificities were 84%, 97% and 73%, respectively. The enhanced culture of catheter specimen of urine at 10^2 cfu/ml was positive in 29% of patients vs 15% at 10^5 cfu/ml.

Conclusions: Despite official guidelines and widespread use these tests cannot be considered appropriate for diagnosing urinary tract infection in patients with lower urinary tract symptoms, and should be abandoned in this context.

Key Words: urinary tract, pyuria, urinalysis

Abbreviations and Acronyms

CSU = catheter specimen of urine
LUTS = lower urinary tract symptoms
MSU = midstream urine
OAB = overactive bladder
STARD = Standards for Reporting Diagnostic Accuracy
UTI = urinary tract infection
wbc = white blood cells

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DIAGNOSING acute frequency and dysuria as cystitis, and diagnosing loin pain, tenderness and fever as pyelonephritis are not difficult. It is when less overt symptoms arise without pain or pyrexia that the methods of screening for urinary infection are problematic. In 2 recent multinational, population based studies the prevalence of LUTS was reported as 3% to 10% in men 40 to 49 years old, and increased to 24% to 29% in those 70 to 80 years old.[1,2] In women the prevalence was 58.7% in those older

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than 60 years and 44.9% in those 40 to 59 years old.[1]

There are 3 techniques used to exclude a diagnosis of UTI. A midstream urine sample is submitted to culture, urinalysis by dipstick is performed and less commonly the microscopic identification of 10 or more wbc/μl (pyuria) is made in a fresh, unspun specimen of urine.[3–5] The dipstick, an indirect measure, identifies pyuria by detecting leukocyte esterase and the bacterial conversion of nitrate to nitrite.

The diagnosis of UTI from a MSU culture has rested on the Kass criteria gleaned from studying MSU in asymptomatic women.[6] He concluded that 10^5 cfu/l of a known urinary pathogen, isolated by aerobic culture using Enterobacteriaceae selective media, discriminated between true bacilluria and contamination. Kass never claimed a threshold for use with cystitis, ie frequency/dysuria symptoms. However, 10^5 cfu/ml has been widely adopted. Stamm et al demonstrated that a threshold of 10^2 cfu/ml was more appropriate for acute frequency/dysuria.[7] Nevertheless, 10^5 cfu/ml remains the gold standard used to validate surrogate tests. To our knowledge no data exist on criteria specific to nondysuric LUTS. In the microscopic examination of fresh, unspun urine in a hemocytometer for pyuria, 10 or more wbc/μl has proven to be the best surrogate marker of UTI since 1968.[3–5] Many centers use urine dipsticks as alternatives despite serious doubts about reliability.[8,9]

Meta-analyses of the use of urinary dipsticks in adults[8,9] and 1 in children[10] have been reported. Hurlbut and Littenberg concluded that dipsticks cannot exclude infection reliably in most clinical settings.[9] Deville et al reported a leukocyte esterase sensitivity of 0.76 (95% CI 0.6–0.98) and a specificity of 0.46 (95% CI 0.32–0.68) for the diagnosis of urinary infection, and a nitrite sensitivity of 0.49 (95% CI 0.38–0.62) and specificity of 0.85 (95% CI 0.73–1.0) in the primary care setting.[8] These values were all assessed at a urine culture threshold of 10^5 cfu/ml. In these studies the sensitivity and specificity vary considerably, which may be a problem of variation in test performance.

In this study we measured the sensitivity and specificity of microscopic pyuria and of dipstick analysis for detecting UTI in a gold standard MSU culture of 10^5 cfu/ml. The patients had LUTS without acute frequency/dysuria or pyrexia. To scrutinize the gold standard CSU samples were also submitted to nonselective culture for a threshold of 10^2 cfu/ml, this being designated an enhanced reference standard.

Nitrite tests for the presence of a bacterial metabolite so the suitable gold standard for comparison would be the results of urine culture. Leukocyte esterase is used as surrogate evidence of pyuria, which is itself a surrogate for infection. Thus, there are 2 potential standards to compare against, that of urine culture and microscopic pyuria.

METHODS

The study was approved by the Moorfields and Whittington Hospitals Research Ethics Committee. Data were collected from patients with LUTS referred to a specialist incontinence clinic. Patients describing acute frequency/dysuria or who were suspected of having pyelonephritis were excluded from study as were those taking antibiotics. A bespoke software package was deployed to collect symptoms and test data prospectively. Patients and researchers were blind to microbiological outcomes. Patients recorded symptoms using a validated questionnaire, and urinary frequency and incontinence episodes were noted. From these data an urgency score (0 to 10) was calculated using a validated method.[11] Data were also collected from a sample of asymptomatic controls.

Experiment 1 was a study of MSU samples using the gold standard 10^5 cfu/ml. MSU samples were obtained, an aliquot was tested by dipstick for leukocyte esterase (positive indicates trace and above) and nitrite, an aliquot was sent for routine laboratory culture, and a fresh aliquot was examined immediately by microscopy. In experiment 2 we studied CSU samples using the gold standard of 10^5 cfu/ml and an enhanced reference standard 10^2 cfu/ml. A sample of corresponding female patients with LUTS was seen to obtain a CSU. The specimens were examined similarly but in addition aliquots were submitted to an enhanced culture.

MSU Collection

Samples were obtained by the midstream clean catch method and patients were instructed in the method. The patients began urinating into the toilet or urinal. After a few seconds of urine flow a sterile container was placed into the stream and approximately 60 ml were collected without interruption of flow. The container was then removed from the stream.

CSU Collection

The procedure was performed on female patients only and by a doctor or specialist nurse. The introitus was cleaned with sterile saline. A self-lubricating small plastic latex-free 12Fr catheter (LoFric®) was passed under aseptic conditions into the bladder to drain a specimen into a sterile container.

Leukocyte Esterase and Nitrite Tests

The urine was dipped using a Multistix® 8 SG. The leukocyte esterase pad sensitivity of the dipstick was stated to be 15 wbc/μl when trace positive and this level was considered positive for the study. The nitrite test pad sensitivity of the dipstick was stated to be 13 to 22 μmol/l (0.06 to 0.1 mg/dl) nitrite ions. These data were collected by clinic doctors and nurses.

Routine culture method (gold standard). The sampled urine was treated fresh or after overnight storage at 4C at the hospital laboratory. Unspun urine (1 μl) was transferred by loop to chromogenic media, CPS ID2 (BioMerieux, Marcy l'Etoile, France), and spread. The plate was incu-