# 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  $\mu$ l) 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<sup>2</sup> 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<sup>5</sup> 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

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.<sup>1,2</sup> In women the prevalence was 58.7% in those older

### 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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than 60 years and 44.9% in those 40 to 59 years old.<sup>1</sup>

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/ $\mu$ l (pyuria) is made in a fresh, unspun specimen of urine.<sup>3–5</sup> 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.<sup>6</sup> He concluded that 10<sup>5</sup> 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.<sup>7</sup> Nevertheless, 10<sup>5</sup> 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/ $\mu$ l has proven to be the best surrogate marker of UTI since 1968.<sup>3–5</sup> Many centers use urine dipsticks as alternatives despite serious doubts about reliability.<sup>8,9</sup>

Meta-analyses of the use of urinary dipsticks in adults<sup>8,9</sup> and 1 in children<sup>10</sup> have been reported. Hurlbut and Littenberg concluded that dipsticks cannot exclude infection reliably in most clinical settings.<sup>9</sup> 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.<sup>8</sup> These values were all assessed at a urine culture threshold of 10<sup>5</sup> 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.<sup>11</sup> 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 latexfree 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/ $\mu$ l 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  $\mu$ mol/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  $(1 \ \mu l)$  was transferred by loop to chromogenic media, CPS ID2 (BioMerieux, Marcy l'Etoile, France), and spread. The plate was incu-

bated aerobically for 24 hours at 37C. Bacterial colonies were identified by color change and size.<sup>12</sup> The result was taken as positive if greater than  $10^5$  cfu/ml were generated after 24-hour culture.

Enhanced culture method (enhanced reference standard). The sample obtained by CSU was processed immediately. One ChromID CPS (BioMerieux) culture plate and 2 blood agar culture plates were inoculated with 200  $\mu$ l fresh unspun urine at the bedside and incubated. The chrome plates were incubated aerobically for 24 hours at 35 to 37C and the blood plates were incubated aerobically and anaerobically at 35 to 37C for 5 days. The lower threshold of 10<sup>2</sup> cfu/ml was used to identify a positive culture. An aliquot of each CSU also underwent the routine gold standard culture.

#### **Microscopic White Cell Count**

A fresh, unspun aliquot of urine was examined by microscopy. Urine (1  $\mu$ l) was loaded into a clean Neubauer hemocytometer counting chamber.<sup>13</sup> This preparation was examined using a ×20 objective with a ×10 eyepiece (magnification ×200). The leukocyte count (wbc/ $\mu$ l) was enumerated by counting cells in 5 large squares out of 9 and multiplying the result by 2 because the volume of the whole chamber was 0.9  $\mu$ l. If a cell overlapped a dividing line it was counted if the line ran along the top or right side and ignored if the line ran along the bottom or left side. These data were collected by specially trained doctors.

#### Statistics

The study followed the STARD.<sup>14</sup> The experiments were powered to detect a 75% sensitivity and 45% specificity so that 100 patients in each group culture positive/culture negative gave 85% power, alpha = 0.05. The challenge was to obtain the 100 patients with positive cultures. The data were analyzed using  $2 \times 2$  contingency tables to calculate the sensitivity and specificity<sup>15</sup> which were described with the 95% CI.<sup>16</sup> Statistical significance was checked using Pearson chi-square (SPSS®). Empty data points were excluded from analysis. Patients with missing data were compared with those analyzed using the variables of age, average 24-hour frequency, average 24-hour incontinence and urgency score by ANOVA. Differences in gender distribution were compared by Pearson chi-square.

## RESULTS

#### **Experiment 1**

This experiment analyzed data from 508 patients (432 women and 76 men). These patients were newly presenting with LUTS without acute frequency/dysuria between August 2, 2004 and January 6, 2009. Mean age was 51 years (SD 19). No patients were taking antibiotics. The study was conducted at the Whittington Hospital NHS Trust, London, United Kingdom.

Mean (SD) daily frequency was 11.73 (5.4), daily incontinence episodes 1.2 (1.7) and mean urgency score was 3.79 (3), reflecting the widespread overactive bladder symptoms. In fact 378 (74%) patients had OAB. Of these patients 132 (35%) had pyuria on microscopy, 90 (24%) with sterile pyuria and 79 (21%) had positive MSU cultures. Only 209 (55%) patients with OAB symptoms had normal urine.

The data for experiment 1 are shown in table 1. The key findings were that the sensitivity for the gold standard was 56% for leukocyte esterase (95% CI 46–66), 10% for nitrite (95% CI 6–18) and 56% for microscopic pyuria (95% CI 46–66) with specificities of 66% (95% CI 61–70), 99% (95% CI 98–100) and 72% (95% CI 67–76), respectively. The sensitivity of leukocyte esterase for microscopic pyuria was 81% (95% CI 75–87) and specificity was 83% (95% CI 78–87).

#### **Experiment 2**

In this experiment 470 women with LUTS without acute frequency/dysuria agreed to provide a CSU between October 1, 2007 and January 27, 2009.

Table 1.	Sensitivities and	d specificities of	f surrogate markers	against gold	standard and	enhanced	standard
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	Leukocyte Esterase		Nit	trite	Microscopic Pyuria		
	No. Culture Pos (%)	No. Culture Neg (%)	No. Culture Pos (%)	No. Culture Neg (%)	No. Culture Pos (%)	No. Culture Neg (%)	
		MSU samples: compa	rison of surrogate marker	s to gold standard 10 <sup>5</sup> cfu	/ml		
Pos	59 (12)	138 (27)	11 (2)	2 (0.4)	59 (125)	113 (22)	
Neg	47 (9)	264 (52)	95 (19)	400 (79)	49 (9)	290 (57)	
Chi-square	1	17	4	40		30	
·		CSU samples: compa	rison of surrogate markers	s to gold standard 10 <sup>5</sup> cfu,	/ml		
Pos	42 (9)	64 (14)	14 (3)	10 (2)	47 (10)	106 (23)	
Neg	29 (6)	335 (71)	57 (12)	389 (83)	24 (5)	293 (62)	
Chi-square	1	17	4	10		42	
·		CSU samples: comparis	on of surrogate markers to	o enhanced standard 10 <sup>2</sup> d	cfu/ml		
Pos	61 (13)	45 (10)	18 (4)	6 (1)	73 (16)	80 (17)	
Neg	76 (16)	288 (61)	119 (25)	327 (70)	64 (14)	253 (54)	
Chi-square	Ę	53	3	80		41	

Sensitivity is the proportion of patients with the disease correctly identified by the test. Specificity is the proportion of patients who are disease-free correctly identified by the test.

All values p < 0.001, df = 1.

Table 2.	Sensitivities	and	specificities	of	leukocyte	esterase	for
detecting	g pyuria						
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	MSU S	amples	CSU Samples		
	No. Pyuria	No. Pyuria	No. Pyuria	No. Pyuria	
	Pos (%)	Neg (%)	Pos (%)	Neg (%)	
Leukocyte esterase pos	140 (28)	57 (11)	98 (21)	8 (2)	
Leukocyte esterase pos	32 (6)	279 (55)	55 (12)	309 (66)	
Chi-square	19	98	16	67	

All values p < 0.001, df = 1.

Mean (SD) patient age was 57 years (18). Mean (SD) daily frequency was 10 (6), mean number of daily incontinence episodes was 1.4 (3) and mean urgency score was 5 (3). The data for this experiment are also shown in table 1. The key finding was that on using CSU the gold standard culture method ( $10^5$  cfu/ml) proved positive in 71 (15%) samples vs 106 (21%) positive for MSU.

In CSU samples the sensitivity for the gold standard was 59% for leukocyte esterase (95% CI 47–70), 20% for nitrite (95% CI 12-31) and 66% for microscopic pyuria (95% CI 54-77) with specificities of 84% (95% CI 80-87), 97% (95% CI 95-99) and 73% (95% CI 69-78), respectively. The sensitivity of leukocyte esterase for microscopic pyuria was 64% (95% CI 56-71) and specificity was 97% (95% CI 95-99). The enhanced method of CSU culture  $(10^2 \text{ cfu/ml})$ proved positive in 137 subjects (29%), inevitably more than the gold standard did in 71 (15%). Commensurately the surrogate markers were less sensitive for  $10^2$  cfu/ml (table 1). In CSU samples the sensitivity for the enhanced standard was 45% for leukocyte esterase (95% CI 36-53), 13% for nitrite (95% CI 8-20) and 53% for microscopic pyuria (95%CI 45–62) with specificities of 86% (95% CI 82–90), 98% (95% CI 96-99) and 76% (95% CI 71-80), respectively. Table 2 contains the data comparing the leukocyte esterase test results with the microscopic pyuria data.

## **Control Subjects**

The 42 volunteers with no LUTS (16 men and 26 women, mean age 34 years, SD 11) provided meticulously collected MSU specimens. Only 2 subjects (4.8%), both women, were leukocyte esterase positive and only 1 of these proved positive on urine culture, routine and enhanced. This woman provided the only nitrite positive specimen. Three controls (7%) showed pyuria on microscopy, 1 of these being leukocyte esterase positive.

# **Patients With Positive**

# **Cultures at Different Thresholds**

There were no symptom differences in average daily frequency, incontinence or urge score between patients showing a positive culture only at the threshold of  $10^5$  cfu/ml, MSU or CSU, and those with a positive CSU at the  $10^2$  cfu/ml threshold. The more sensitive culture did not identify a different symptomatic group (table 3).

# **STARD Participant Recruitment Analysis**

**Experiment 1.** A total of 615 patients (526 female, 89 male) with LUTS without acute dysuria were identified and 20 (3%) could not provide a sample. Thus, MSU from 595 patients was provided. Of these patients 87 (15%) had missing data for 1 or all of leukocyte esterase (84, 14%), nitrite (80, 13%) and microscopy (52, 9%). Thus, the total analyzed was 508 samples. Missing data resulted from equipment failure, equipment availability and omission of database entry during a busy clinic period. The patients with missing data did not differ from those analyzed with respect to age, gender, urinary frequency, urgency and incontinence (table 3).

**Experiment 2.** A total of 607 women with LUTS without acute frequency/dysuria provided a CSU, and 137 (23%) of these women had incomplete data for 1 or all of leukocyte esterase (103, 17%), nitrite (101, 17%) and microscopy (83, 14%), as did the culture results (48, 8%). These incomplete data arose from equipment failure and, more commonly, oversight in data entry and culture plate transport failure. The patients with missing data did not differ from those analyzed with respect to age, gender, urinary frequency, urgency and incontinence (table 3).

# DISCUSSION

The International Consultation on Incontinence guidelines on LUTS recommend dipstick testing as a

Table 3. Symptom profiles according to key patient groups

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Pt Group	Mean Age (SD)	Mean/SD 24-Hr Total Frequency Episodes (95% CI)	Mean/SD Urge Score (95% CI)	Mean/SD 24-Hr Total Incontinence (95% CI)
MSU Pos 10 <sup>5</sup> cfu/ml	50.84 (18.8)	11.73/5.4 (11.22–12.23)	3.79/3 (3.51–4.07)	1.20/1.7 (1.04–1.35)
CSU Pos 10 <sup>5</sup> cfu/ml	56.38 (18.5)	9.44/6 (7.88–11.01)	5.02/3.2 (4.19-5.84)	1.64/4.1 (0.57-2.71)
CSU Pos 10 <sup>2</sup> cfu/ml Missing data	56.38 (18.5) 50.81 (18.7)	9.59/5 (7.88–11.01) 11.84/5.2 (10.91–12.77)	4.76/3.5 (3.77–5.75) 3.76/3 (3.23–4.30)	2.18/3.9 (1.09–3.28) 1.01/1.4 (0.76–1.25)

These comparative data demonstrate similar symptom profiles from patients with  $10^5$  cfu/ml and  $10^2$  cfu/ml. The  $10^2$  cfu/ml did not select a subset. Similarly the symptom profiles of patients with missing data imply that there was no selection bias.

screening method.<sup>17</sup> However, data from this study imply that this recommendation is mistaken. If the guideline is followed many patients with UTI will go undiagnosed and untreated, which is no small matter given the prevalence of LUTS.

The data highlight several matters of considerable concern. The contrast between the MSU and the CSU data implies unacceptable contamination from the MSU, resulting in misleading results from the surrogate tests and culture. The suitability of a MSU for screening out UTI in women must be questioned. The CSU data confirm the position of microscopy of a fresh unspun specimen of urine in a hemocytometer for white cells as the best surrogate marker of infection available. The nitrite test performs particularly badly and leukocyte esterase achieved a sensitivity of only 59%.

Stamm et al first raised doubts about the validity of the  $10^5$  cfu/ml gold standard threshold for diagnosing UTI in reports on data applicable to acute frequency/dysuria in women.<sup>7</sup> This study, by comparing the gold standard with an enhanced method with a threshold of  $10^2$  cfu/ml, now raises concerns over a similar problem affecting patients with nondysuric LUTS. This must now be tested using Koch's postulates but there is justification for skepticism about the accuracy of routine urine culture at  $10^5$ cfu/ml.

The inclusion of controls, albeit younger, permits comparisons indicating that the study prevalence of pyuria (34% with MSU and 33% with CSU) and bacteriuria (21% with MSU at  $10^5$  cfu/ml and 29% with CSU at  $10^2$  cfu/ml) must be related to the disease process. This merits further scrutiny. The symptom analysis shows that 75% of patients had OAB symptoms with only 55% manifesting normal urine. This has not been reported previously and indicates the need for closer scrutiny of the etiology of OAB. The youth of the controls arises from the insistence on absent symptoms, particularly nocturia.

The use of an enhanced CSU culture with a threshold of 10<sup>2</sup> cfu/ml did result in a higher yield and reduced surrogate sensitivities. The routine methods assume dominant pathogenicity from the Enterobacteriaceae.<sup>18</sup> Applicability to acute infection does not justify use in nondysuric LUTS. We must establish valid, evidence-based criteria for diagnosing UTI in patients with LUTS.

## CONCLUSIONS

This study was conducted in a normal clinical practice, giving it wide applicability through urological services where the limitations of these tests must be acknowledged. These tests should no longer be recommended for screening. Our understanding of the etiology of important conditions such as OAB may be seriously at fault.

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