Neurourology and Urodynamics

# Associations Between Individual Lower Urinary Tract Symptoms and Bacteriuria in Random Urine Samples in Women

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**Aims:** Previous studies have noted an association between a diagnosis of overactive bladder and bacteriuria, but little is understood about the relationship of bacteriuria to specific LUTS. We hypothesized that bacteriuria in women would be associated with increased self-reported symptom scores for a wide range of LUTS. **Methods:** Women were recruited from general gynecology and urogynecology outpatient clinics in a secondary care setting. Women completed the 12-item International Consultation on Incontinence Questionnaire for Female Lower Urinary Tract Symptoms and provided a clean-catch mid-stream specimen of urine for microscopy and culture. Women with acute urinary tract infection were excluded. Three statistical approaches (Mann–Whitney U-test, multivariable logistic regression, and receiver operating characteristic curves) were used to assess differences in symptom scores between women with and without bacteriuria. **Results:** Two hundred forty-seven women were recruited, aged 22–82. Sixteen of 247 urine samples (6.5%) demonstrated significant bacteriuria, growing a different range of organisms. Women with significant bacteriuria were more likely to have nocturia (OR 3.56, 95% CI 1.19–10.6, $P = 0.02$), urgency (OR 6.66, 95% CI 1.47–30.06, $P = 0.01$), bladder pain (OR 2.82, 95% CI 1–7.92, $P = 0.049$), urgency incontinence (OR 2.92, 95% CI 1.02–8.36, $P = 0.046$), nocturnal enuresis (OR 4.21, 95% CI 1.32–13.41, $P = 0.01$). After adjustment for age, parity, symptomatic prolapse, menopausal status and history of mid-urethral sling urinary urgency, bladder pain, nocturia, and nocturnal enuresis remained significantly associated. **Conclusions:** Bacteriuria is associated with a range of LUTS including nocturia, urgency, and bladder pain supporting a role for bacterial colonization in the pathogenesis of OAB symptoms. *Neurourol. Urodynam.* © 2014 Wiley Periodicals, Inc.

**Key words:** bacteriuria; incontinence; LUTS; OAB; urinary tract infection

## INTRODUCTION

Lower urinary tract symptoms have been commonly grouped as storage, voiding, and incontinence symptoms.[1] Reported prevalence rates vary widely, but around one quarter to one-half of all adult women report at least one clinically meaningful symptom.[2] These symptoms have strong positive associations with both age and obesity,[3,4] and thus public health importance of these conditions is likely to increase in line with current demographic trends.

LUTS research in women is mainly focused on "overactive bladder" (OAB), a term used to describe a subset of storage LUTS, currently defined as urgency, with or without urgency UI, usually with frequency and nocturia.[1] This standard definition clarifies that the diagnosis should only be made in the absence of urinary tract infection (UTI). Acute UTI may also cause severe but transient LUTS, including dysuria, urgency, frequency, and urgency urinary incontinence.[5] Thus the two conditions have substantially overlapping symptoms, and may be subject to diagnostic confusion.

Theories of the pathophysiology of LUTS in women have been anatomically centered on the parasympathetic motor supply to the bladder (the neurogenic hypothesis)[6] or in the detrusor muscle itself (the myogenic hypothesis).[7] More recent attention has focused on the urotheliogenic hypothesis. In both rodent and porcine models, the mucosal layer of the bladder is seen to augment detrusor function,[8] either through release of a variety of neurotransmitters, or through its own spontaneous electrical activity. The urothelium is not just a passive barrier, but is a responsive structure, able to detect thermal, mechanical, and chemical stimuli.[9] With the recognition of the urothelium as a mediator of bladder function, much recent attention has been concentrated on the role of urothelial inflammation and infection in the etiology of LUTS.[10]

Early cross-sectional studies of incontinence have noted a relationship between UTI and all cause incontinence.[11,12] This association could be caused by misclassification bias, but recent longitudinal studies in older post-menopausal women have also reported that a history of one or more lifetime UTIs is

Christopher Chapple led the peer-review process as the Associate Editor responsible for the paper.
Conflict of interest: Vik Khullar is a speaker, consultant, and paid investigator for Astellas Pharma, Allergan, and Pfizer. G. Alessandro Digesu is a speaker, consultant, and paid investigator for Astellas Pharma, AMS, Uroplasty, Medtronic, Pfizer.
Grant sponsor: UK Medical Research Council; Grant sponsor: National Institute for Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London
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Received 10 January 2014; Accepted 13 March 2014
Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/nau.22607

associated with new onset of urinary incontinence,[13] while a new onset of UTI is also more common among women with a history of incontinence.[14] Associations with specific subtypes of incontinence, or specific LUTS have not, however, been explored. Acute UTI is usually diagnosed when $\geq 10^5$ bacterial colony forming units (CFU)/ml are present. However, recent work has also explored a role for low-count bacteriuria ($10^3$–$10^5$ CFU/ml) in LUTS.[15] Studies have reported high bacterial carriage rates of 39% in women with urinary incontinence,[16] 29% in women with storage LUTS,[17] and 28% in women with specifically OAB symptoms.[18] There is emerging evidence that fastidious, anaerobic, and difficult-to-cultivate organisms may also be associated with LUTS.[19,20] Overall, women with various LUTS seem to have an increased likelihood of having an asymptomatic bacterial infection. However, in current clinical practice, many cases may be missed because they do not meet the $10^5$ CFU threshold for diagnosis, or because of routine use of laboratory cultures focused on isolating *Escherichia coli* using selective media.[21] Using these conventional culture techniques, among healthy individuals, bacteriuria is typically observed in approximately 5%, even with stringent criteria,[5] but recent work using bacterial ribosomal sequencing for identification, suggests that almost all individuals have some bladder colonization.[20,22]

Such asymptomatic bacteriuria is not usually considered clinically relevant, and screening or treatment of asymptomatic bacteriuria, is typically only recommended in certain circumstances, such as for pregnant women, or for patients prior to selected invasive genitourinary procedures. However, given the emerging evidence for so-called "asymptomatic" bacteriuria in the development of LUTS,[16,18,22] we aimed to test the hypothesis that bacteriuria might be associated with specific LUTS among the general population. The primary objective of this study was to evaluate the prevalence of bacteriuria among random urine samples collected from women attending general gynecology and urogynecology hospital outpatient clinics without overt symptoms of acute UTIs. Our secondary objective was to test for associations between individual lower urinary tract symptoms and subclinical bacterial infection using the ICIQ-Female Lower Urinary Tract Symptoms questionnaire (ICIQ-FLUTS), for evaluation of lower urinary tract symptoms and associated bother.

## MATERIALS AND METHODS

After ethical approval (NRES Committee London-Chelsea 12/LO/0394), between April 2012 and July 2013 adult women presenting to general gynecology and urogynecology outpatient clinics of a tertiary referral teaching hospital were recruited. Women with neurological dysfunction, urinary calculi, urinary tract malignancy, recurrent UTIs ($\geq$3 within 12 months), current pregnancy, or breast-feeding were excluded. A written consent form was obtained from all participants. Women completed the 12-item ICIQ-FLUTS. This is a self-administered 12-item questionnaire, including questions on incontinence, storage, and voiding symptoms. It provides very wide assessment of individual LUTS with extensive validation (grade A according to International Consultation on Incontinence grades of recommendation). The reference period for symptom assessment was the 4 weeks preceding the day that the questionnaire was administered. Most items from this questionnaire are scored on a 5-point scale, for example, following the response categorization of the stress incontinence item "Does urine leak when you are physically active, exert yourself, cough or sneeze?," the five responses available are: "never," "occasionally," "sometimes," "most of the time," and "all of the time." Participants provided a clean-catch, midstream voided urine sample into a sterile container and one aliquot was sent for routine microscopy, including counts of white cells and culture, including antibiotic sensitivity. All specimens were cultured onto chromogenic agar and incubated at 37°C in full air, following standard protocols for our hospital microbiology service. Bacterial counts were reported blinded to symptom status, with growth of $\geq 10^4$ CFU/ml of a specific organism considered a positive specimen. Cultures with mixed bacterial growth, which usually reflects vulvo-vaginal contamination, were excluded from analysis.

### Statistical Methods

We used three statistical approaches to assess differences in symptom scores between women with and without bacteriuria, with each analysis conducted using SPSS version 21.0 (IBM Corp., Armonk, NY). We first used the Mann–Whitney U-test to compare the scores as continuous variables. We then dichotomized the scores and used multivariable logistic regression, to control for the potential confounding effect of age, parity, symptomatic prolapse, menopausal status, and history of mid-urethral sling. For this analysis, we categorized cases as women reporting two or more voids at night, or more than eight voids by day, and for other symptoms report of ">=sometimes." Finally, we plotted receiver operating characteristic curves, with 95% confidence intervals. With wide previous estimates of rates of bacteriuria,[23] we were not able to prospectively power the study, but recruited a pragmatic sample.

## RESULTS

Two hundred forty-seven women, mean age 47 years (range 22–82), mean parity 1.38 (range 0–5) and mean BMI 26 kg/m$^2$ were recruited (Table I) either from gynecology clinics (n = 98) or urogynecology clinics (n = 149). Twenty-nine urine samples (11.7%) showed mixed bacterial growth, 16 (6.5%) demonstrated significant bacteriuria (6 from Gynecology vs. 10 from Urogynecology), growing a range of organisms including Proteus, Coliforms, *E. coli* and Enterococci (see Fig. 1). Women with bacteriuria were on average 3 years older (50 vs. 47; $P = 0.40$) with similar parity (1.7 vs. 1.4; $P = 0.34$). Bacteriuria was associated with elevated scores for all symptoms except hesitancy (see Table II), reaching statistical significance ($P < 0.05$) for nocturia, urinary urgency, and urgency incontinence. The strongest association was with nocturia (2.5 vs. 1.5 episodes/night; $P = 0.01$). In univariable logistic regression, patients with bacteriuria were more likely to have nocturia (OR 3.56, 95% CI 1.19–10.6, $P = 0.02$), urgency (OR 6.66, 95% CI 1.47–30.06, $P = 0.01$), bladder pain (OR 2.82, 95% CI 1–7.92, $P = 0.049$), urgency incontinence (OR 2.92, 95% CI 1.02–8.36, $P = 0.046$), nocturnal enuresis (OR 4.21, 95% CI 1.32–13.41, $P = 0.01$). After

**TABLE I. Demographic Characteristics of Women Enrolled**

| | |
|---|---|
| Age (years) | 47.28 (±14.67) |
| Parity | 1.38 (±1.30) |
| BMI (kg/m$^2$) | 26 (±5.85) |
| Ethnic background | |
| European | 190 (77%) |
| Afro-Caribbean | 45 (18.2%) |
| Arabic | 7 (2.8%) |
| Asian | 5 (2%) |

Values are given as number (percentage) or mean (±SD).

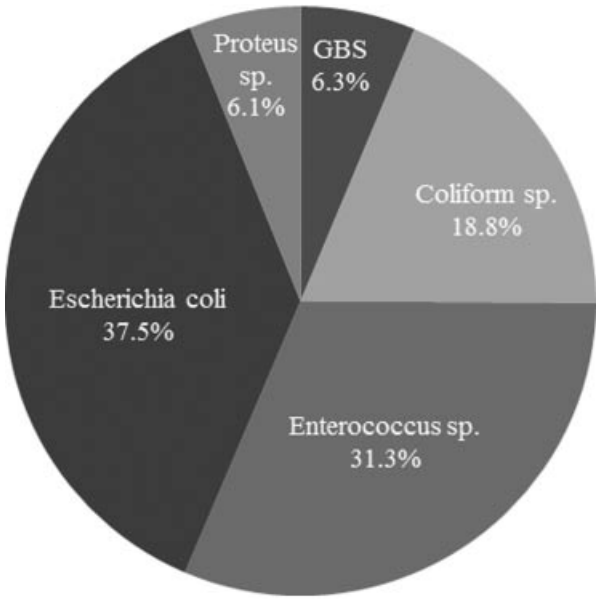


**Fig. 1.** Spectrum of organisms detected in urine samples.

adjustment for a wide range of potential confounders (including age, parity, symptomatic prolapse, menopausal status, and history of mid-urethral sling), nocturia, urinary urgency, bladder pain, and nocturnal enuresis remained significantly associated. Receiver operating characteristic curves demonstrated very modest test performance of bacteriuria as a predictor of LUTS. Results were nominally statistically significant only for nocturia (AUC 0.66, $P = 0.029$) and urgency (AUC 0.688, $P = 0.013$). Full results are shown in Table III and Figure S1.

## DISCUSSION

Our results indicate that among a heterogeneous population of care seeking women, bacteriuria may be present in association with a wide range of LUTS. In unadjusted analyses, we observed significant or near significant associations with both storage and incontinence LUTS. After adjustment for age, parity, and other potential confounding factors we observed associations only with storage symptoms, including urgency, nocturia, nocturnal enuresis, and also bladder pain. These findings support earlier reports of bacteriuria, including low count bacteriuria, as a common finding in women presenting for treatment of OAB.[16] These data also suggest the possibility of residual confounding in previous studies reporting excess bacteriuria among women with urinary incontinence[18] that have not adjusted for demographic factors.

Previous work suggests that quiescent bacterial communities may form a chronic reservoir for reinfection, leading to fluctuating bacteriuria among women with chronic LUTS.[10,24] The cross-sectional nature of our data preclude conclusions about a causal association between LUTS and bacteriuria, or indeed the direction of causation. Although we adjusted for a wide range of potential confounders, there remains a risk of other unmeasured potential mediators (such as use of continence pads, and use of systemic or topical estrogen), and unmeasured potential confounders (including presence of anatomic prolapse, or comorbidities), which would have provided further insight. These findings may represent the stable effects of chronic urothelial inflammation on LUTS, but for some women might instead represent transient prodromal LUTS among women with incipient acute UTI. Previous work, recruiting exclusively women seeking care for LUTS,[16] or using young "healthy" women[21] as controls, may be subject to significant selection or spectrum biases. The strengths of the study include the use of a validated symptom questionnaire, which allowed us to identify associations with specific LUTS, which have not been previously reported. Recruitment of women from a range of gynecology and urogynecology clinics should enhance generalizability. Importantly also our analyses were blinded to symptom status, limiting the possibility of observer biases. The sample size, while larger than previous studies of bacteriuria and incontinence provides adequate power for relatively small effects, but clinically relevant associations may still have been missed.

### Clinical Relevance

These results demonstrate that bacteriuria is common for women with a range of LUTS. Current recommendations

**TABLE II. Symptom Scores Among Women With and Without a Finding of Bacteriuria**

| | Mann–Whitney U-test | | | Univariable logistic regression | | | Multivariable logistic regression[a] | | |
|---|---|---|---|---|---|---|---|---|---|
| ICIQ-FLUTS symptom item | Bacteriuria, mean (SE) | No bacteriuria, mean (SE) | *P* | OR | 95% CI | *P* | OR | 95% CI | *P* |
| Nocturia | 2.50 (0.38) | 1.46 (0.09) | *0.01* | 3.56 | 1.19–10.60 | *0.02* | 3.21 | 1.02–10.14 | *0.046* |
| Urinary urgency | 2.44 (0.32) | 1.67 (0.09) | *0.03* | 6.66 | 1.47–30.06 | *0.01* | 7.02 | 1.49–33.05 | *0.01* |
| Bladder pain | 1.69 (0.38) | 0.95 (0.08) | 0.05 | 2.82 | 1.00–7.92 | *0.049* | 3.28 | 1.13–9.54 | *0.03* |
| Daytime frequency | 1.50 (0.38) | 0.96 (0.09) | 0.15 | 1.82 | 0.65–5.11 | 0.26 | 1.85 | 0.65–5.31 | 0.25 |
| Hesitancy | 0.56 (0.29) | 0.78 (0.08) | 0.25 | 0.74 | 0.20–2.70 | 0.65 | 0.93 | 0.25–3.51 | 0.92 |
| Straining | 0.56 (0.27) | 0.53 (0.07) | 0.87 | 1.05 | 0.28–3.90 | 0.94 | 1.17 | 0.31–4.50 | 0.81 |
| Intermittency | 0.94 (0.25) | 0.94 (0.08) | 0.86 | 0.99 | 0.33–2.97 | 0.98 | 1.08 | 0.34–3.41 | 0.89 |
| Urgency incontinence | 1.94 (0.36) | 1.12 (0.09) | *0.02* | 2.92 | 1.02–8.36 | *0.046* | 2.29 | 0.72–7.36 | 0.16 |
| Incontinence episode frequency | 2.44 (0.42) | 1.48 (0.11) | *0.02* | 2.32 | 0.81–6.63 | 0.12 | 1.61 | 0.48–5.48 | 0.44 |
| Stress incontinence | 2.13 (0.45) | 1.31 (0.11) | 0.06 | 2.03 | 0.73–5.68 | 0.18 | 1.73 | 0.56–5.37 | 0.34 |
| Insensible incontinence | 0.88 (0.30) | 0.54 (0.07) | 0.22 | 2.14 | 0.70–6.55 | 0.18 | 1.69 | 0.52–5.49 | 0.38 |
| Nocturnal enuresis | 0.94 (0.38) | 0.29 (0.05) | 0.06 | 4.21 | 1.32–13.41 | *0.01* | 5.04 | 1.42–17.89 | *0.01* |

OR, odds ratio; CI, confidence interval.

Italics indicate $P < 0.05$.

[a]Includes age, parity, symptomatic prolapse, menopausal status, and mid-urethral sling as covariates.

**TABLE III. Receiver Operator Characteristics**

| Symptoms | Area under the curve | SE[a] | *P*[b] | 95% Confidence interval | |
|---|---|---|---|---|---|
| | | | | Lower bound | Upper bound |
| Nocturia | 0.664 | 0.070 | *0.029* | 0.527 | 0.802 |
| Urinary urgency | 0.688 | 0.060 | *0.013* | 0.571 | 0.804 |
| Bladder pain | 0.626 | 0.075 | 0.094 | 0.479 | 0.773 |
| Daytime frequency | 0.569 | 0.077 | 0.358 | 0.418 | 0.720 |
| Hesitancy | 0.471 | 0.073 | 0.705 | 0.328 | 0.615 |
| Straining | 0.504 | 0.076 | 0.957 | 0.356 | 0.653 |
| Intermittency | 0.507 | 0.076 | 0.928 | 0.358 | 0.655 |
| Urgency incontinence | 0.641 | 0.073 | 0.061 | 0.498 | 0.784 |
| Incontinence episode frequency | 0.614 | 0.073 | 0.130 | 0.471 | 0.757 |
| Stress incontinence | 0.602 | 0.075 | 0.177 | 0.455 | 0.749 |
| Insensible incontinence | 0.575 | 0.079 | 0.322 | 0.419 | 0.730 |
| Nocturnal enuresis | 0.613 | 0.082 | 0.135 | 0.452 | 0.773 |

Italics indicate $P < 0.05$.

[a]Under the non-parametric assumption.

[b]Null hypothesis: true area = 0.5.

suggest screening women with LUTS using urinalysis to exclude pyuria, hematuria, proteinuria, and glycosuria.[25] Although the causal link and optimal treatment remains unclear, our findings suggest that we should additionally routinely screen for low count bacteriuria using formal microscopy and culture among women presenting with LUTS. Screening for asymptomatic bacteriuria is highly controversial among otherwise healthy women, but may define a subgroup of women with infective etiology for LUTS. Persistent bacteriuria in particular may have an important role in the progression of LUTS and asymptomatic bacterial infection may be missed because of a higher threshold of $10^5$ for diagnosis, lack of more specific culture techniques or routine laboratory cultures focused on isolating *E. coli* using selective media.[21] In current clinical practice, screening for bacteriuria is typically restricted to pregnant women or women undergoing invasive genitourinary procedures.[23] Treatment for asymptomatic bacteriuria in other patient populations has not generally been found to improve outcomes. These observational data do not support routine treatment of bacteriuria among women with LUTS, pending further research.

### Future Research

Healthy bacterial flora are increasingly recognized as an important defense to infection. Recent data suggest that almost all healthy individuals have urinary colonization with benign bacteria. The urinary microbiome of healthy individuals may influence disease processes.[20–22] Antibiotic therapy may be associated with significant adverse effects, including nausea, diarrhea, and skin rashes. Perhaps more importantly, indiscriminate use of antibiotics to clear asymptomatic bacteriuria may lead to development of symptomatic infections, including reinfection with organisms of increased antimicrobial resistance.[23] Identification of specific organisms or serotypes associated with LUTS, may allow us to selectively target patients for antibiotic therapy. Current work using bacterial 16s ribosomal sequencing to characterize the urinary microbiome in health and disease, should allow us to design appropriate trials of selective antibiotic use. One promising alternative to antibiotics is the use of live microorganisms (probiotics) to prevent and treat urinary infection.[26] A further important research question that arises from our study is whether probiotic treatment for asymptomatic bacteriuria may improve LUTS. Bacterial infection can trigger neutrophil infiltration into the bladder mucosa, producing cytokine IL-6 and other mediators of inflammation. These inflammatory mediators can alter the activity of sensory nerves in the bladder mucosa and could lead to the symptoms of urgency, nocturia, bladder pain, urgency incontinence, and nocturnal enuresis highlighted in this paper. Recent studies have demonstrated a plausible role of inflammatory biomarkers in the development of lower urinary tract symptoms. Future work should also investigate this population of women with asymptomatic bacteriuria, to assess associations between putative urinary biomarkers (such as NGF, BDNF, and MCP1) and low count bacteriuria or urothelial inflammation.[27]

## CONCLUSIONS

This study highlights the strong association of bacteriuria with specific storage LUTS in women. Chronic bacterial colonization of the urothelium may play an important role in the etiology of these symptoms for some women, and further investigation of the range of urothelial colonizers in relation to LUTS may lead to more effective targeted therapies.

## ACKNOWLEDGMENTS

The study was supported by a grant from the UK Medical Research Council but the funding body had no involvement in analysis or preparation of the manuscript. The work of Franklin, Khullar and Digesu is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London.

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## Supporting Information

Additional supporting information may be found in the online version of this article.