

## IS THERE MORE TO IT THAN JUST D.O?

### Hypothesis / aims of study

There is growing interest in chronic cystitis in the aetiology of overactive bladder (OAB). The tests used routinely to exclude urinary tract infection (UTI) have been discredited, catalysing a critical analysis of our assumptions. The methods used to test for infection are flawed and a negative result on culture and dipstick do not exclude infection or inflammation (1, 2). The detection of microscopic pyuria remains the best surrogate marker of infection. There are other measures of immune activation in the urinary tract that are suitable as independent arbiters of the true pathology (3). Urothelial cells when infected with microbes signal their distress by expressing ATP and can be seen microscopically to be associated with microbes.

The aim of this study was to use a consilience approach to assess if patients with OAB show signs of infection and inflammation when compared with controls.

### Study design, materials and methods

A prospective observational study was conducted from April 2011 to October 2014. Patients presenting with OAB were recruited from incontinence clinics and clean-catch midstream urine samples obtained and compared to age and menopausal matched controls. Symptoms were measured using the ICIQ FLUTs questionnaire, Whittington Urgency and Pain score. Light microscopy was performed on fresh clean catch urine samples for leucocytes and urothelial cell counts by blinded investigators and cultured using the enhanced sediment culture. Urothelial cells were stained and assessed using fluorescent microscopy. Aliquots of spun urine were frozen at -80°C which were analysed for Lactoferrin and IL6 by high sensitivity ELISA and ATP using a luciferin-luciferase assay.

### Results

There were 282 patient (mean age 63 sd=11) and 253 control visits (mean age 59 yrs sd=9). Linear mixed-effects models procedure was used to analyse the data with the group classification (Patient/Control) as an independent factor. Within the model the fixed effect was the group number and the dependant variables were selected in turn as LUTS score, urgency score, pain score, total bacterial growth on sediment culture, log pyuria and log epithelial cell shedding. Visit number was selected as the repeated effect. The analyses showed that group status (Patient/Control) was a significant predictor of total symptoms (Estimate of coefficient = -16.11, p<.0001); Pyuria (log pyuria) (Estimate of coefficient = -0.57, p<.0001); epithelial cell shedding (log epithelial cell count) (Estimate of coefficient = -0.30, p<.0001) and Log colony counts (Estimate of coefficient = -1.07, p<.0001).

In contrast to controls, patients demonstrated significantly greater bacterial growth characterised by culture of the centrifuged urinary sediment ( $Z=-5.981$ , p<.0001). The median log total colony counts in the patient group were 2.30 (interquartile range 1.54) and 1.50 (interquartile range 2.01) in the control group. The patient group also showed significantly higher levels of urinary leucocyte excretion and increased clue cell shedding ( $\beta=1.48$ , df=1, p<.0001). In the control group the mean clue cell proportion was 0.01, median 0.00 (sd=0.057, interquartile range=0.00) and in the patient group mean clue cell proportion was 0.19, median 0.17 (sd=0.16, interquartile range=0.17). 9.72% of the patients had a positive routine culture compared with 0.40% in the control group. 93.4% of patients had a positive spun sediment culture, significantly higher when compared to 70% of controls. The microbial diversity was distinctly different between patients and controls with recognised uropathogens predominating in the patient group. Urinary IL6 and Lactoferrin was also significantly higher in the patient group as compared with controls.

### Interpretation of results

There is strong evidence to suggest that patient with OAB have signs of infection and inflammation which distinctly differs from matched controls. This provides an alternative hypothesis to the pathophysiology of overactive bladder.

### Concluding message

This study supports that in patients with symptoms of OAB, infection and inflammation provides an alternative hypothesis.

### References

1. JUrol. 2010;183(5):1843-7.
2. PLoS medicine. 2007 Dec;4(12):e329. PubMed PMID: 18092884
3. J Clin Micro 2013: PubMed PMID: 23596238

### Disclosures

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