

## URINARY CYTOKINES IN REFRACTORY URGE INCONTINENCE: RELATIONSHIP WITH BACTERIURIA

### Hypothesis / aims of study

Despite considerable research, the aetiology of refractory detrusor overactivity (DO) remains unknown. One potential contributing factor is bacterial cystitis, as studies have shown that urinary tract infections (UTI), are present in 30-56% of patients with refractory DO versus only 6-11% of patients with newly diagnosed DO or 1-5% control patients [1]. As UTI is associated with an inflammatory cytokine response, and previous small studies have suggested increased cytokine levels in overactive bladder (n=17-20 pts) [2, 3]. Thus we investigated urinary levels of the pro-inflammatory cytokines monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6) and interleukin-1 $\alpha$  (IL-1 $\alpha$ ) in a large sample of women with urodynamically diagnosed refractory idiopathic DO, newly diagnosed DO, and controls with no urgency. We hypothesized that cytokine levels would be increased in refractory DO.

### Study design, materials and methods

Midstream urine samples were collected from patients recruited to this study from a regional urogynaecology clinic. Any current UTI and previous UTI was noted. Three patient groups were studied: refractory DO (who had failed response to at least 2 antimuscarinic medications for at least 12 months) (n=41), newly diagnosed DO (n=33) and control (n=44). Patients were excluded if they had mixed incontinence (urge and stress incontinence), as determined by cystometry, or a history of any neurological dysfunction.

Urinary levels of the cytokines MCP-1, IL-1 $\alpha$  and IL-6, were quantitated by enzyme-linked immunosorbent assays following the manufacturer's instructions. Cytokine concentrations were compared based on the 3 conditions, and based on subgroup analysis for a current diagnosis of UTI, or a history of UTI [given as median cytokine concentration (pg/mL) with interquartile range, IQR]. Comparison of all 3 groups was performed using ANOVA, comparison of the DO groups versus controls was performed using Mann Whitney U test.

### Results

Women with refractory DO exhibited a significantly higher prevalence of a current UTI and previous history of UTI compared to controls (Table 1, p = 0.01). The levels of MCP-1 and IL-6 did not vary significantly across the three patient groups on ANOVA (Table 1) although the median concentration of interleukin-1 $\alpha$  was significantly elevated in women with newly-diagnosed DO compared to controls (p = 0.048).

Table 1: UTI symptoms/ urinary cytokine concentrations (pg/mL) in 3 patient groups.

	Controls (n=44)	Newly diagnosed DO (n= 33)	Refractory DO (n = 41)
Current UTI	5%	6%	32%
History of UTI	23%	27%	46%
MCP-1	20.8 (3.9, 61.7)	37.4 (11.8, 71.75)	28.7 (8.5, 63.3)
IL-6	1.0 (0.2, 3.9)	1.4 (0.3, 6.0)	1.2 (0.4, 7.0)
IL-1 $\alpha$	64.2 (13.6, 138.1)	110.3 (43.8, 254.4)	73.2 (11.1, 159.8)

When cytokine concentrations were analysed by UTI history, the median levels of MCP-1 were significantly higher in women with both DO diagnoses combined, who had positive history of UTI, versus controls with a positive history of UTI [median 32.8 (10.1, 87.3) vs 10.1 (0.0, 17.0), p = 0.02] (Fig 1)

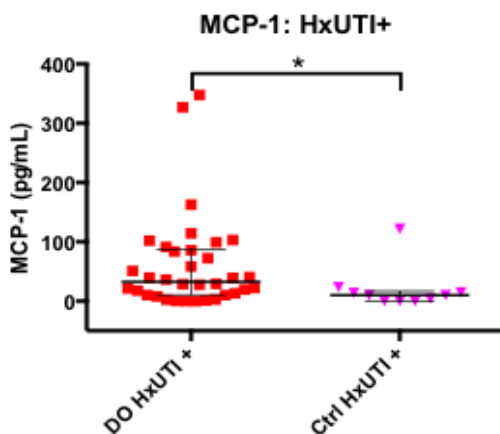


Fig 1. Urinary MCP-1 in relation to UTI History  
MCP-1 levels in DO patients with UTI history (DO HxUTI+, n=34) compared to controls with UTI history (Ctrl, HxUTI+, n=10). p<0.05\*, Mann-Whitney U test.  
Dark horizontal bar = median,  
Light horizontal bar = IQR

In the DO patients who had a current infection at the time of MSU collection, the IL-6 levels were significantly elevated (median 7.08 (1.64-12.76),  $p=0.008$ , Mann-Whitney U test) compared to those DO patients without an infection at collection (median 0.94 (0.25-2.7) (Fig 2).

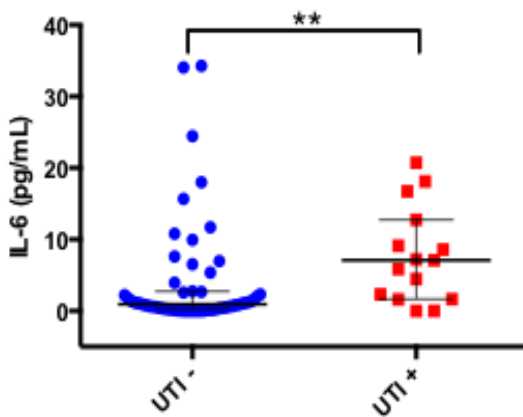


Fig 2. Urinary IL-6 in DO patients with a current UTI (n=15) and in DO patients without a UTI (n=56) ( $p<0.01^{**}$ ).

Dark horizontal bar = median,  
Light horizontal bar = IQR

#### Interpretation of results

Using a reasonably large sample of patients who had urodynamic diagnoses, the inflammatory cytokine (IL-1 $\alpha$ ) was clearly elevated in newly diagnosed (acute) DO patients compared to controls. However, IL-1 $\alpha$  was similar in refractory DO and controls, which was unexpected. Perhaps the pro-inflammatory cytokine (IL-1 $\alpha$ ) was “switched off” or “worn out” during the prolonged chronic DO condition. For the first time, MCP-1 levels were reported to be significantly higher in DO patients with history of UTI, compared to controls. Urinary IL-6 was elevated in DO patients with current UTI, compared to DO without UTI, as expected.

#### Concluding message

In this sample of 118 patients, UTI was again more common in refractory DO. Because UTI is known to induce the release of pro-inflammatory cytokines, we expected that these cytokines should play a role in the pathogenesis of refractory DO. The enhanced pro-inflammatory levels appeared more striking in the newly diagnosed DO than refractory DO cases, suggesting perhaps a greater “acute-phase” cytokine response. Anti-inflammatory cytokines are more important in Refractory cases. Future work may reveal that.

#### References

1. Moore KH, et al. (2014) Role of covert infection in DO? ICI-RS Neurol & Urod 33: 606
2. Ghoniem G, et al. (2011) Analysis of urinary cytokines in OAB. Int UroG J 22:953–961
3. Tyagi P, Barclay D, et al (2010) Urine cytokines suggest an inflammatory response in OAB: a pilot study. Int Urol Nephrol. 42:629-35.

#### Disclosures

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