

INTRODUCTION

Bacterial cystitis is a potential aetiological factor in the development of refractory detrusor overactivity (DO). One proposed mechanism is the release of inflammatory cytokines from the bladder as a sensitising agent to the suburothelial afferent nerves, leading to enhanced signalling and urgency¹.

AIM

Using women currently enrolled in a randomised control trial (RCT) of antibiotics in refractory DO, we aimed to examine the **relationship between antibiotic treatment and the concentration of urinary cytokines** from women with refractory DO.



METHODS

Randomised double blinded, placebo controlled trial; of darifenacin plus either antibiotic or placebo (2:1 ratio). Interim futility analysis is currently underway.

Inclusion criteria: post-menopausal women >50yrs, urodynamically proven detrusor overactivity (DO), refractory to treatment (failed bladder training and ≥2 anti-cholinergics within 12months).

Exclusion criteria: voiding dysfunction, neurogenic DO, previous pelvic radiotherapy, eGFR<60ml/min.

Patients had a 2.5week washout to establish a baseline (0 weeks), then were randomised into either Darifenacin 15mg daily plus 6weeks of antibiotics (2weeks each of Norfloxacin, Augmentin Duo and Nitrofurantion) or placebo. Midstream urine (MSU) was collected at 0, then 2, 4 and 6 weeks (treatment period), then again one and five months post treatment. MSU was split for routine microscopy; categorised as either UTI (single bacterial culture of >10⁶CFU/L) or “any bacteriuria” (≥2 bacterial species cultured ± pyuria ± epithelial cells; mixed growths may be precursor to later UTI in refractory DO²).

Then remaining MSU was centrifuged to remove all particulates and frozen at -80°C. Cytokines crucial in the host response to bacterial cystitis (IL-1α, IL-4, IL-6, IL-8, IL-10, CXCL10 (IP-10), TNF-α, IL-1 receptor antagonist and MCP-1)³ were measured using ELISA (as directed by manufacturer). Cytokines were compared between antibiotic and placebo groups (Mann-Whitney test).

RESULTS

Table 1: Presence of bacteriuria (UTI or mixed growth) in antibiotic or placebo treated women.

		Antibiotic (n=12)	Placebo (n=7)
All collection points	UTI	14% (10/72)	21% (9/42)
	“Any bacteriuria”	49% (35/72)	62% (26/42)
Treatment period (weeks 2,4 and 6)	UTI	14% (5/36)	24% (5/21)
	“Any bacteriuria”	36% (13/36)	57% (12/21)

- The antibiotic treated women had consistently (although not significantly) lower rates of UTI and mixed growth cultures when compared to placebos.
- “Any bacteriuria” was the most common culture result (**Table 1**).
- IL-6, IL-8 and CXCL-10 persistently maintained (but not significantly) lower levels across the study period when compared to placebos (**Figure 1A-C**).
- When all time points were grouped together and the treatment groups compared for all bacterial cultures, IL-6, IL-8 and CXCL-10 were significantly lowered in the antibiotic group (**Figure 1D-F**). The same result was observed when only the classical UTI was compared (P=0.045, P=0.006 and P=0.004 for the respective cytokines).

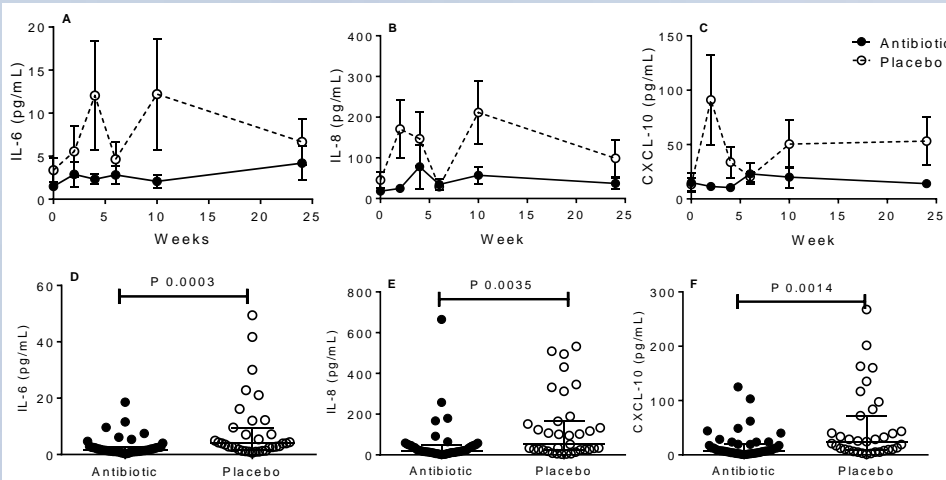


Figure 1: Concentration of IL-6 (A), IL-8 (B) and CXCL-10 (C) across the 6month collection period. Concentration of urinary IL-6 (D), IL-8 (E) and CXCL-10 (F) in patients with bacteriuria (UTI + “any bacteriuria”).

CONCLUSIONS

Our results suggest that antibiotics reduce the incidence of bacteriuria, and also the concentration of cytokines released as a response.

IL-6, IL-8 and CXCL-10 are all associated with the innate immune system. As such, their decrease may lead to reduced tissue damage in response to infection and ultimately less stimulation to afferent nerves, thus inhibiting the sensation of urgency.

This has important implications for our understanding of the aetiology of refractory DO in women who do not respond to pharmacotherapy.

REFERENCES

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