# #306 β-Lactam group antibiotics protects against intracellular bacteria and reduces the incidence of urinary tract infection in women with refractory DO

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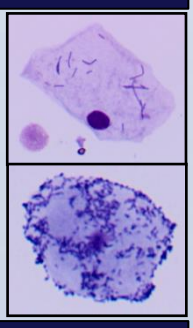
## INTRODUCTION

Intracellular localisation of bacteria is known to occur in up to 80% of women with urge incontinence, as determined by Wright staining and immunofluorescence[1].

These bacteria avoid antibiotic treatment and expulsion by micturition[1], resulting in increased shedding of urothelial cells by the bladder to rid itself of the invaded bacterium.

## AIM

Determine whether a prolonged rotating course of antibiotics could diminish the internalised bacterium, and reduce the degree to which they appear intracellular (on Wright stain) in the shed cells over time.



## METHODS

Randomised double blinded, placebo controlled trial; of darifenacin plus either antibiotic or placebo (2:1 ratio).

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

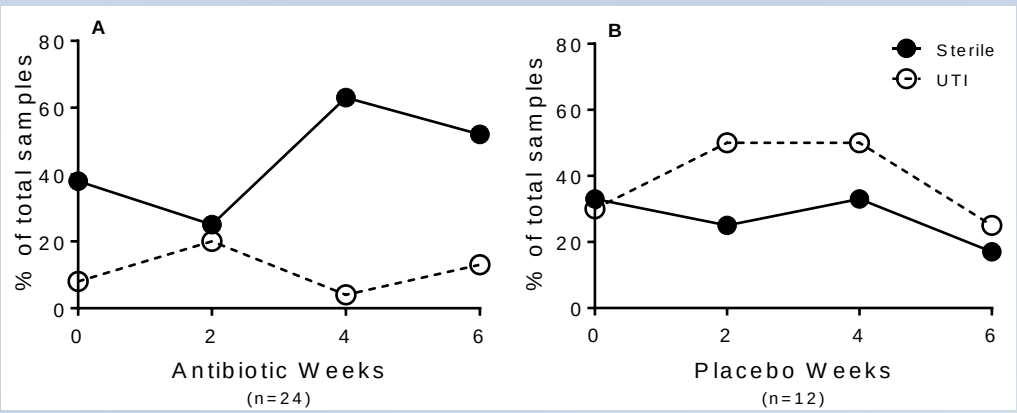
Exclusion criteria: Voiding dysfunction, neurogenic DO, previous pelvic radiotherapy, eGFR<60ml/min.

Patients commenced 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) were collected at 0, 2, 4 and 6 weeks, half were sent for routine culture (UTI defined as single bacterial culture of >$10^6$CFU/L) and the remaining was centrifuged to concentrate urothelial cells onto microscope slides and Wright stained.

Approximately 100 cells were counted by light microscopy and categorised according to the presence of bacteria, the location (attached to cell membrane or appears intracellular), and the bacterial density (low or high density (LD/HD)). The mean percentage (±SEM) of each category was calculated. Interim analysis is underway check for futility before continuing the study. T-tests were conducted between antibiotic and treatment groups.

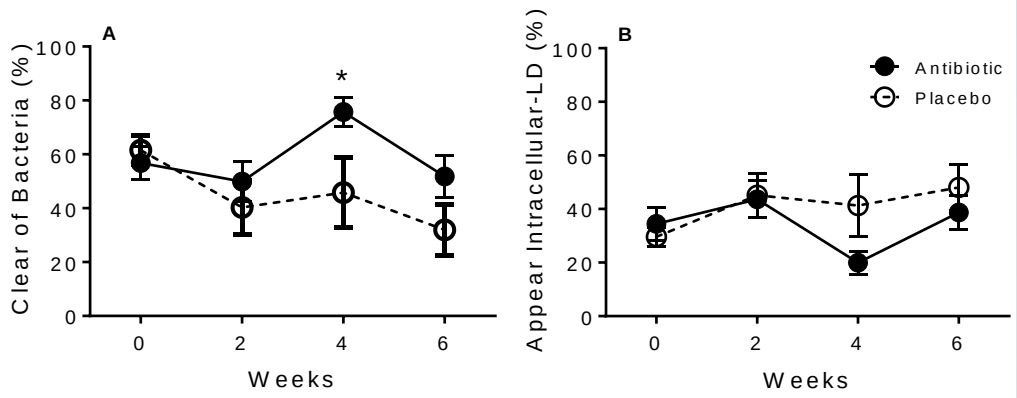
## RESULTS

**Figure 1:** Distribution of MSU culture result during the 6week treatment period.




- Augmentin Duo (week 4) was the most effective in reducing the incidence of classical UTI in refractory DO (**Figure 1A**).
- At the same time, we saw a significant increase in the percentage of cells clear of bacteria on Wright staining (**Figure 2A**).

**Figure 2:** Bacterial association of exfoliated urothelial cells during the 6week treatment period.




- Of the three antibiotics used in this study, β-Lactams (such as Augmentin) have been reported to have a greater intracellular action and increase in efficacy the longer the treatment period[2].
- This may be what we are observing.

## CONCLUSIONS

Treatment of women with refractory DO using antibiotics that possess the greatest intracellular action (such as β-Lactams), may significantly decrease the presence of intracellular bacteria.

This would subsequently decrease the likelihood of an intracellular reservoir for recurrent infections[3], and presumably decrease the incidence of clinically significant bacteruria.

## REFERENCES

1. Cheng et al., *Pathog Dis* (2016) 74(7): 10.1093/femspd/ftw1067
2. Carryn et al., *Infect Dis Clin N Am.* (2003) 3:615-634.
3. Justice et al., *Proc. Natl. Acad. Sci. U.S.A.* (2004) 101:1333-1338.