W27: Bladders under Siege: Update re Role of Inflammation in Refractory Urge Incontinence

Workshop Chair: Kate Moore, Australia

Start	End	Topic	Speakers
		Introduction to the Workshop: Rationale and brief history	Kate Moore
		Recent RCT of rotating antibiotics: Results, and findings of cytokine analyses in 196 samples from trial participants	Zhuoran Chen
		What does the cytokine response in Refractory DO tell us about pathogenesis	Kylie Mansfield
		Inflammation in relation to afferent nerve activity	LUKE GRUNDY
		Discussion	Kate Moore Kylie Mansfield LUKE GRUNDY Zhuoran Chen

Aims of Workshop

Approximately 35% of patients with detrusor overactivity are unresponsive to current antimuscarinic; these Refractory patients are a hard core group of sufferers. Recent studies from London, Sydney and Chicago have indicated that refractory patients are more likely to have bacteriuria, and changes in their microbiome, which are associated with a poor response to treatment.

In the last 3 years, basic scientists and clinicians have made significant advances in our knowledge about the relationship between inflammation, molecular signalling of "urgency" , with pathophysiological changes in the immune response such as cytokine production, associated with urge incontinence. This workshop will bring together scientists and clinicians to discuss these recent findings.

Learning Objectives

Critique the evidence linking inflammation with aetiology of urge incontinence

Target Audience

Urogynaecology and Female & Functional Urology

Advanced/Basic

Intermediate

Suggested Learning before Workshop Attendance

Brierley, S. M, Goh, K. G. K., Sullivan, M. J., Moore, K. H., Ulett, G. C. & Grundy, L (2020) Innate immune response to bacterial urinary tract infection sensitises high-threshold bladder afferents and recruits silent nociceptors. Pain. 161 (1): 202-210

Chen Z; Moore KH; Mansfield KJ; Ognenovska S; Allen W; Parkin K; Mukerjee C; Aryal NR; Gebski V (2020) Effect of antibiotics on urine leakage in women with refractory detrusor overactivity: A phase IIb randomized trial', Neurourology and Urodynamics, http://dx.doi.org/10.1002/nau.24525

Hsu-Dong Sun, Shiu-Dong Chung (2009) Could Overactive Bladder be a Chronic Inflammatory Disorder? Incontinence and Pelvic Floor Dysfunction 3 (Suppl 1):17-19

Chamoun MN, Blumenthal A, Sullivan MJ, Schembri MA, Ulett GC (2018) Bacterial pathogenesis and interleukin-17: interconnecting mechanisms of immune regulation, host genetics, and microbial virulence that influence severity of infection. Critical Reviews in Microbiology1-22

Overview of Workshop

Professor Kate Moore, Urogynaecologist from UNSW in Sydney will give the Introduction.

At the ICS meeting in Milan, Italy, our group held the first workshop which was also entitled **Bladders under Siege: the Role of Inflammation in Refractory Urge Incontinence,** which outlined our recent understanding regarding increasing evidence for the role of low grade bacterial cystitis in women with Refractory Detrusor Overactivity, and explained the preliminary evidence suggesting that a Randomised Controlled Trial was needed in this field. The present introduction will re-visit this underlying data.

Dr Zhuoran Chen, Senior Lecturer in Urogynaecology at UNSW, will present the results of the recently published Phase 2B RCT of six weeks of rotating antibiotics (Augmentin, Nitrofurantoin, Norfloxacin two weeks for each agent, coupled with Darifenacin), followed by six months of outcome follow up. The main findings were that antibiotic therapy achieved a substantial reduction in leakage on 24 hour pad test and leaks per day on bladder diary ($p = 0.008$) which did not occur in patients on placebo (tablets that were identical to the antibiotics). For ethical reasons, antibiotics were given to patients with a clinically bothersome UTI,

which occurred in 4% of the antibiotic group , but occurred in 33% of patients on placebo during the first six weeks. Over the six months of follow up, clinical over-ride antibitotics had to be given to 14% of the antibiotic group, but 50% of the placebo group. Trial recruitment was curtailed, partly because of this ethical concern, but also because of difficult recruitment after introduction of publically funded Botox injections.
Dr Chen also presents results from the analysis of urinary cytokines results taken during the six month study. The main findings were that pro-inflammatory cytokines, such IL-1a, IL-6, IL-8 were all reduced in the antibiotic group compared to the placebo group.

Associate Professor Kylie Mansfield, Physiologist from University of Wollongong, gives a more in depth overview of the physiological function of pro-inflammatory and anti-inflammatory cytokines in the bladder. She will present the results of a large cross section of urinary cytokines in refractory DO versus controls, using a Multiplex Array sampling of 27 different cytokines. She will explore how pro-inflammatory, chemokines and regulatory cytokines are changed in refractory DO patients with and without UTI. She will also examine how the cytokines changes seen in patients with refractory DO relate to a possible role of innate lymphocytes in the pathogenesis of the condition and how these findings relate to increased urgency in patients with refractory DO.

Dr Luke Grundy, head of the Pain Physiology Laboratory at University of Adelaide, will present the results of an in-vivo model of bacterial-cystitis induced bladder inflammation. Using an elegant ex-vivo bladder-nerve recording preparation he will show how the inflammatory infiltrate from the infected mouse contains an array of cytokines that provoke increased afferent nerve discharge from the bladder in the absence of changes in the contractile properties of the mouse detrusor muscle. Inflammatory supernatants decreased the activation threshold of sensory nerves and increased peak firing frequency to bladder filling, causing increased signalling to the spinal cord at lower bladder volumes. Hence for the first time we have physiological data to explain why inflammation would provoke increased urgency.

Discussion: The Panel will then discuss the interplay between the clinical results of the RCT, the cytokine results from the refractory DO patients , and the laboratory results from the in-vivo mouse cystometry model, to develop our understanding of the relationship between inflammation and refractory urgency.