W15: Bladders Under Siege: Could Bacteriuria be the key to understanding refractory urge incontinence?

Workshop Chair: Kate H Moore, Australia
12 September 2017 11:00 - 12:30

Start	End	Topic	Speakers
11:00	11:10	Introduction to the Workshop	Kate H Moore
11:10	11:25	Intracellular Bacteria in Urge incontinence	Kylie Mansfield
11:25	11:40	Intracellular Enterobacter in *in vitro* models of UTI	Harry Horsley
11:40	11:50	Questions	All
11:50	12:00	Culture independent study of recurrent Bacteriuria in refractory DO	Kate H Moore
12:00	12:15	Urinary Microbiome in urge incontinence and relation to treatment response	Elizabeth Mueller
12:15	12:20	Summary and Clinical significance	Kate H Moore
12:20	12:30	Questions	All

Speaker Powerpoint Slides

Please note that where authorised by the speaker all PowerPoint slides presented at the workshop will be made available after the meeting via the ICS website www.ics.org/2017/programme Please do not film or photograph the slides during the workshop as this is distracting for the speakers.

Aims of Workshop

The overactive bladder (OAB) syndrome is the main cause of urge incontinence and urgency (generally associated with detrusor overactivity). Approximately 35% of patients with detrusor overactivity are unresponsive to current Antimuscarinic drugs. These "refractory" patients are a hard-core group of sufferers constantly expending health care resources in their search for relief. Recent studies find bacterial cystitis in approximately 30-50% of DO patients refractory to treatment. This workshop will bring together clinicians and scientists to discuss the recent findings on recurrent bacterial cystitis and reasons for antibiotic resistance in relation to the refractory state.

Learning Objectives

After this course the participants will be able to:

1. Critique the evidence linking bacteriuria with the aetiology of urge incontinence
2. Describe the interactions that occur between uropathogens and the urothelium
3. Predict the effect of antibiotics on the symptoms of urge incontinence

Target Audience

This workshop will be of interest to urogynaecologists, urologists, nurse continence advisors and basic scientists with an interest in the aetiology of urge incontinence and refractory detrusor overactivity, and the role of bacterial infection in these pr

Advanced/Basic

Advanced

Conditions for Learning

Interactive workshop, ideally restrict to 50 people (max 60)

Suggested Reading

1. Walsh CA, Moore KH. (2011) Overactive bladder in women: does low-count bacteriuria matter? A review. Neurourol Urodyn. 30(1):32-7
2. Walsh CA, Cheng Y, Mansfield KJ, Parkin K, Mukerjee C, Moore KH (2012) Decreased intravesical ATP in patients with refractory detrusor overactivity and bacteriuria. Journal of Urology, doi:pii: S0022-5347(12)05182-8
3. Vijaya G, Cartwright R, Derpapas A, Gallo P, Fernando R, Khullar V. (2013) Changes in nerve growth factor level and symptom severity following antibiotic treatment for refractory overactive bladder. Int Urogynecol J. 24(9):1523-8.
4. Horsley H, Malone-Lee J, Holland D, Tuz M, Hibbert A, Kelsey M, Kupelian A, Rohn JL. (2013) Enterococcus faecalis subverts and invades the host urothelium in patients with chronic urinary tract infection. PLoS One. 8(12):e83637.
5. Khasriya R, Sathiananthamoorthy S, Ismail S, Kelsey M, Wilson M, Rohn JL, Malone-Lee J. (2013) Spectrum of bacterial colonization associated with urothelial cells from patients with chronic lower urinary tract symptoms. J Clin Microbiol. 51(7):2054-62.
6. Moore KH, Malykhina AP. (2014) What is the role of covert infection in detrusor overactivity, and other LUTD? ICI-RS 2013. Neurourol Urodyn. 33(5):606-10.

7. Gill K, Horsley H, Kupelian AS, Baio G, De Iorio M, Sathiananamoorthy S, Khasriya R, Rohn JL, Wildman SS, Malone-Lee J. (2015) Urinary ATP as an indicator of infection and inflammation of the urinary tract in patients with lower urinary tract symptoms. BMC Urol. 15:7. doi: 10.1186/s12894-015-0001-1.
8. Sorrentino F, Cartwright R, Digesu GA, Tolton L, Franklin L, Singh A, Greco P, Khullar V. (2015) Associations between individual lower urinary tract symptoms and bacteriuria in random urine samples in women. Neurourol Urodyn. 34(5):429-33.
9. Thomas-White KJ, Hilt EE, Fok C, Pearce MM, Mueller ER, et al. (2015) Incontinence medication response relates to the female urinary microbiota. Int Urogynecol J 2015.
10. Cheng Y, Chen Z, Gawthorne JA, Mukerjee C, Varettas K, Mansfield KJ, Schembri MA, Moore KH. (2016) Detection of intracellular bacteria in exfoliated urothelial cells from women with urge incontinence. Pathog Dis. 74(7). pii: ftw067. doi: 10.1093/femspd/ftw067.

Other Supporting Documents, Teaching Tools, Patient Education etc

Evidence for intracellular bacteria in urge incontinence.

Kylie J Mansfield, Ying Cheng, Samantha Ognenovska, Zhuoran Chen, Kate H Moore,
School of Medicine, University of Wollongong, Australia

The role of subclinical infection in patients with urge incontinence has been largely ignored although recent evidence suggests that urinary tract infections (UTI) maybe involved in the aetiology of refractory Detrusor Overactivity (RDO) and several studies have reported that uropathogens such as *E. coli* may invade the urothelial cell layer using murine models and cell lines. Our aims were to 1) test for the presence of intracellular bacteria in the urine of patients with detrusor overactivity or mixed incontinence +/- a history of UTI, and compare this to a control group of patients with stress incontinence and no history of infection and 2) to examine cellular invasion as a pathogenic factor for three uropathogenic bacterial strains.

Mid-stream urine (MSU) specimens were collected from women: half was used for traditional microbiological diagnosis of UTIs, with the other half used for microscopic examination of exfoliated urothelial cells. Based on routine microbiology, bacterial cystitis was seen to be more common in patients with refractory DO.

Microscopy and Wright staining of concentrated urothelial cells demonstrated the presence of bacteria in the majority of samples. Filamentous bacterial cells, indicative of intracellular growth, were observed in 51% of patients and were significantly more common in patients with DO. On Wright staining, bacteria appeared intracellular at low-density in patient samples positive for each of the uropathogens examined, that is *E. coli, E. faecalis* and Group B *Streptococcus*, although this was seen more frequently in *E. coli* positive samples. Confocal microscopy revealed that both *E. coli* and *E. faecalis* were able to invade the urothelial cell. Due to technical difficulties relating to cross-reactivity of the antibodies used, the results for intracellular localisation Group B *Streptococcus* were inconclusive.

This study supports the possibility that a subset of patients with urge incontinence may have unrecognised chronic bacterial colonisation, maintained via an intracellular reservoir. In patients with negative routine microbiology, application of the techniques used in this study revealed evidence of infection, providing further insights into the aetiology of urge incontinence.

A urine-tolerant three-dimensional epithelial organoid from adult human bladder stem cells reveals novel aspects of host/pathogen interactions

Harry Horsley, Dhanuson Dharmasena, James Malone-Lee and Jennifer L. Rohn
Chronic UTI Group, Centre for Nephrology, University College London, United Kingdom

Urinary tract infection (UTI) constitutes an immense healthcare burden, not least because of its tendency to recur despite treatment, or to persist in a chronic form. Many questions still remain about the host/pathogen interactions during bladder infection, but current model systems have disadvantages. Traditional human bladder cell line monolayers bear no resemblance to the three-dimensional urothelium, and there is evidence that the mouse model of infection may not be entirely representative. Recent efforts using human organ- and stem-cell-derived organoid culture have yielded promising models, but none can withstand the presence of urine at the apical interface for more than a few hours. This is important because urine is the natural environment of UTI pathogens and may affect their behaviour, as well as the biological response of the epithelium to those pathogens. We therefore set out to create a human cell-based organoid culture with urine-tolerant properties.

Commercially available human bladder epithelial progenitor cell derivatives were grown and differentiated in 3D culture inserts for a maximum of 24 days, with specialized medium at the basal layer and sterile human urine at the apical liquid-liquid interface. A combination of confocal and electron microscopy showed this human urothelial organoid to be phenotypically similar to native human bladder tissue. Infection of the model with patient-isolated *Enterococcus faecalis*, a species common in chronic UTI cases, caused rapid apical live-cell shedding, which is one of the hallmarks of urine infection in human patients. Moreover, this common Gram-positive uropathogen invaded the intermediate and basal urothelial cells of the organoid, forming clear and numerous intracellular colonies. In contrast, a strain of uropathogen *E. coli* (UPEC) shown to be invasive in murine

models (UTI89) formed extensive biofilms on the organoid surface but did not exhibit an invasive phenotype. This result agrees with our previous published work with shed patient cells, which revealed superficial biofilms but again, no evidence for intracellular *E. coli* colonisation.

Considering the differences between the human and rodent bladder, we propose that further studies on patient material are needed before the question of UPEC's invasion behaviour can be settled. In conclusion, current advances in 3D tissue culture enabled us to grow physiologically relevant organotypic human models of the bladder. Human bladder biomimetics could be used as a reproducible test bed for chronic infective disease formation, treatment and resolution in humans.

Culture independent study of recurrent Bacteriuria in refractory DO

Kate H Moore, Zhuoran Chen, Lucy Bates, Mark Schembri
Pelvic Floor Unit, St George Hospital, Sydney, Australia

Urinary tract infection (UTI) has become an increasing problem in women with refractory detrusor overactivity (DO), affecting at least 40% of such women. At the same time the high rate of infections caused by antibiotic resistant bacteria impacts our ability to successfully treat UTIs. This is especially true for uropathogenic E. coli, which is responsible for over 80% of all UTIs and is increasingly becoming multi-resistant. Our aim was to investigate women with refractory DO and co-existent recurrent UTI over an extended time period. We carried out periodic analysis of urine using a combination of routine microbial culture as well as using culture-independent methods (rRNA analysis) to determine the composition of bacteria present in the urine during the same time period.

Multiple MSU specimens were collected (with careful labial toilet) from 39 women over a two year period (Median age 75, range 57-81 years). Half of the urine sample was sent to the Microbiology Unit, cultured routinely at a threshold of $>10^6$CFU/mL, to identify the major causative organism and antibiotic resistance. The results of routine culture, resistance patterns and isolates obtained from the agar plate were recorded. The remaining samples were stored in frozen aliquots (-20°C), from which total DNA was extracted. Genus-level characterization of the bacteria present in the urine samples was determined by employing 16S rRNA gene amplification and amplicon pyrosequencing (Willner et al 2014, mBio 5(2):1-10).

Symptoms were recorded at the time of urine collection and often the only UTI symptom was worsening urgency, frequency and urge leak. On average the women in the study experienced 8 UTI during the 6-24 months. Nine women with proven recurrent UTI and refractory DO provided multiple urine specimens (median 5 samples per patient; range 2-10, 42 specimens in total). Traditional microbiology culture results showed only 4 samples had no growth. 18 samples had a single dominant organism reported; 17 samples were reported as mixed perineal +/- Bowel flora. Three patients had documented changes in the bacterial flora on routine microbiology culture results over time. Of the18 samples with confirmed bacteria on routine microbiology, only 4 were not resistant to multiple antibiotics.

Culture-independent 16S rRNA sequencing has revealed that a diverse array of organisms are present in the urine samples from individual patients. Each patient yielded an average of 26.7 different genera (SD 11.2, Median 25, IQR 21, 36). Further assessment of these populations will determine how the bacterial populations vary in each patient over time. This finding is important as most Microbiology laboratories do not routinely report all organisms grown, preferring to report only the dominant organism, especially when there is mixed growth. However, if multiple bacteria are actually colonising the bladder, then treatment with antibiotics (specific for the predominant organism), may encourage unreported organisms to proliferate and become resistant.

This study demonstrated that the organisms isolated from women with recurrent UTI and refractory DO alter over time, as does antibiotic resistance. In these patients, reporting all identified bacteria may help guide treatment. Culture independent 16S rRNA sequencing data will enable us to profile all of the organisms present in the urine over an extended time period, and enable us to link changes in the bacterial population to episodes of symptomatic UTI.

Urinary Microbiome in Urge Incontinence and relation to treatment response

Elizabeth R. Mueller
Female Pelvic Medicine and Reconstructive Surgery, Loyola University Stritch School of Medicine, USA

The newly discovered female urinary microbiota has the potential to deepen our understanding of urinary tract health and disease, including common lower urinary tract conditions such as urinary incontinence and urinary tract infection. Studies using culture-independent techniques confirm prior reports of bacteria that reside in the female urinary bladder. These resident communities, the female urinary microbiota, possess characteristics that differ between women affected by urgency urinary incontinence and matched, unaffected controls. Enhanced urine culture techniques permit cultivation of organisms, including uropathogens, missed by standard urine culture, but detected by culture-independent sequencing techniques.

Based on the available data, it appears that the female urinary microbiota are similar to other human microbial niches in there is no one “normal” state, but rather variable between individuals. However, there are distinct trends. Most urine samples studied to date are not rich and contain one or two microbes that are substantially more abundant than others. These samples can be categorized on the identity of that or predominant microbe. Each category has been termed a “urotype” similar to the “enterotype” used by many gut microbiome researchers. At the genus level, the most common urotype is Lactobacillus. The next most common urotypes are Gardnerella, Corynebacterium, Streptococcus and Staphylococcus; other less common urotypes exist. Notably, these are all Gram-positive bacteria, quite unrelated to the Gram-negative bacteria, such as E. coli, responsible for the vast majority of acute uncomplicated urinary tract infection (UTI). Some samples are not predominated by a single organism or even two; they are placed in a urotype called “diverse.” The biological significance of predominance by any specific organism or the lack of a predominant microbe is not yet known. However, female urinary microbiota diversity appears to have associations with the host’s hormonal status, body mass index and certain clinical conditions.

Despite hopes of a finding a single “causative” organism (similar to H. pylori for stomach ulcers), community characteristics may be more important that the presence or absence of a particular microbe. This would be expected if the FUM play a protective role. For example, female urinary microbiota diversity appears to relate to the presence of urgency urinary incontinence (UUI). A recent report suggests that treatment response may be related to the number of unique organisms (richness) present prior to solifenacin treatment for UUI [1]. Following replication of this work, it may be possible to refine clinical estimates of treatment efficacy, based on a pre-treatment assessment of that individual patient’s urinary microbial community characteristics. Another report identified an association between UUI symptoms and several bacterial species, including a number of emerging Gram-positive pathogens; this report also found that Lactobacillus crispatus associates with the lack of symptoms, suggesting the possibility that L. crispatus may be beneficial to maintaining bladder health.

1. Thomas-White KJ, Hilt EE, Fok C, Pearce MM, Mueller ER, Kliethermes S, Jacobs K, Zilliox MJ, Brincat C, Price TK, et al.: Incontinence medication response relates to the female urinary microbiota. Int Urogynecol J 2015.

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Workshop 15:

Bladders Under Siege: Could Bacteriuria be the key to understanding refractory urge incontinence?

Workshop Chair: Prof Kate H Moore, Australia

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Workshop program

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- Kate Moore Professor, Urogynaecology, UNSW, Sydney
- Kylie Mansfield, Assoc. Professor, Physiology, Graduate School of Medicine, University of Wollongong
- Harry Horsley, Cell Biologist, Chronic UTI Group, Centre for Nephrology, UCH, London
- Elizabeth Mueller, Female Pelvic Medicine and Reconstructive Surgery, Loyola University Stritch School of Medicine, Chicago USA

Workshop program

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Introduction to the Workshop	Kate H Moore
Intracellular Bacteria in Urge incontinence	Kylie Mansfield
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Overactive bladder syndrome

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Patients suffer from urgency, frequency, nocturia, +/- urge incontinence;

Affects 17% of age 40 years;

Urodynamics:

reveals Detrusor Overactivity (DO)

i.e. bladder spasms

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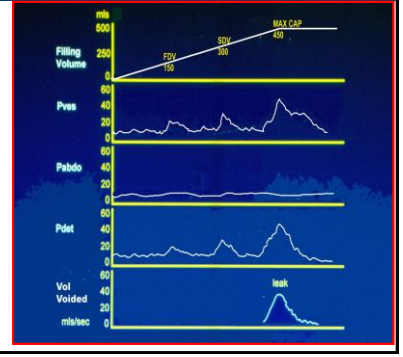
Typical bladder spasms seen on cystometry



Treatment of OAB

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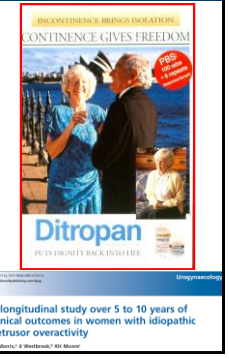
Standard treatment:
Antimuscarinic drugs with bladder training
Helpful in 50- 60%
Long-term cure in about 20%

Table 3. Outcome by category at time of last visit to the pelvic floor unit and following questionnaire administration

Final outcome groups	Last review appointment (n = 132)		After questionnaire administration (n = 71)	
Responded				
Cured	28 (21%)	49%	5 (7%)	35%
Much improved	37 (28%)		20 (28%)	
Not responded				
Little improved	32 (24%)	51%	30 (42%)	65%
No improvement	35 (27%)		16 (23%)	

Definition of Refractory =
Failed response after 2 different drugs etc, for more than 1 year of Rx
About 30% of patients



Controversy

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- Anecdotally, many women with DO/OAB report history of recurrent UTI, not always "proven UTI"
- However, patients often state that they had one or more classical symptoms, and antibiotics resolved these symptoms

PROBLEM:

- Kass' traditional threshold for "significant" bacteriuria (**≥10^8 CFU/L**) seemed unduly stringent
- UK + Australia: UTI = 10^8 CFU/L
- USA + Europe: UTI = 10^5 CFU/L

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Experimental work examining the relationship between bacteriuria and detrusor overactivity

Colin Walsh
MB BCh BAO MRCPI MRCOG PhD
Fellow, Pelvic Floor Unit, 2010 - 2012

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Common Microbiological Methods

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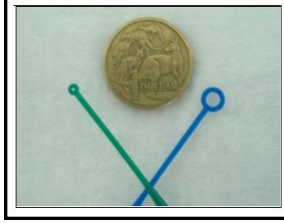
- Collaboration with Department of Microbiology
- Specimens cultured on Horse Blood Agar (at 35°C in 7% CO_2) and MacConkey agar (at 35°C in air)
- Agar inoculated using larger 10µL quantitative loop – yields positive result at 10^5 CFU/L



Significant pyuria defined as ≥10 white blood cells per mL on microscopy

1. Pilot Study

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2-year study of MSU specimens

- "Refractory" idiopathic DO
  - (*failed ≥2 anti-cholinergics etc for ≥ 1 yr with persistent disabling symptoms*)
- invited to attend whenever urge symptoms became exacerbated and they provided MSU, careful clean catch with labial saline rinse
-
- **Excluded:** Dysuria, fever, malodorous urine
- **Control MSUs**: women without OAB

IUGA

1. Pilot Study Findings!

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50 women with "refractory" IDO At time of worse symptoms	**50 controls** Age matched
168 MSU specimens	50 MSU specimens
Bacteriuria ≥10^6/L = 39%	**Bacteriuria ≥10^6 CFU/L = 6%**
P<0.0001	
Bacteriuria 10^6-10^8 CFU/L = 17%	**Bacteriuria 10^6-10^8 CFU/L = 2%**
P=0.0091	

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Urogynaecologia 2011; volume 25:e4

***Low-count* bacteriuria in refractory idiopathic detrusor overactivity versus controls**

Colin A. Walsh,[1] Wendy Allen,[1] Katrina Parkin,[1] Chinmoy Mukerjee[2] Kate H. Moore[1]

[1]Department of Urogynaecology St George Hospital, University of New South Wales, Sydney, [2]Department of Microbiology, St George Hospital, University of New South Wales, Sydney, Australia

39% of RDO urine specimens,

56% of RDO patients

had bacteriuria

Difficulty with publication:

MSU CRITICISED

2. Prospective Cross-Sectional Study of CSU

Purpose:
To address criticism regarding use of Mid stream urine Cultures in the Pilot Study

Hypothesis

1) ***Bacteriuria is more prevalent on CSU in incontinence versus continent controls***

2) ***Bacteriuria on CSU is more common in DO compared to other diagnoses***

IUGA international urogynecological association

Results: Incontinent v Continent

Urine culture result (CSU)	Incontinent (n=161)	Continent (n=75)	OR (95% CI)	P
"Low-count" bacteriuria 10^3-10^5 CFU/ml	12 (7.4%)	1 (1.3%)	5.9 (0.76 to 46.7)	**0.044**
"High-count" bacteriuria $>10^5$ CFU/ml	8 (5%)	1 (1.3%)	3.9 (0.47 to 31.5)	0.161
Any bacteriuria $\geq 10^3$ CFU/ml	20 (12.4%)	2 (2.7%)	5.2 (1.2 to 22.8)	**0.011**

60% of the positive urine cultures were "low-count" bacteriuria

82% of positive specimens grew E.coli

Results by Urodynamic diagnosis

Diagnosis (n=161)	n	Bacteriuria ($\geq 10^3$ CFU/ml)			Odds ratio (95% CI)	P
		Low count	*High count*	*Any (%)*		
Pure Detrusor Overactivity	40	3	3	6 (15)	6.4 (1.24 to 33.6)	**0.021**
Pure Urodynamic Stress Incontinence	53	3	1	4 (8)	2.98 (0.53 to 16.9)	0.231

3. Cohort Study - Methods

Prospective CSU cohort study in women with "refractory" DO

Eligible women who were mailed a personal invitation to attend PFU when urgency symptoms acutely worsened

Patient catheterised, CSU taken

RESULTS:

Overall, 27% of 56 CSU results showed significant bacteriuria,

28% (9/32) with refractory DO had bacteriuria on CSU

Conclusions

1) "Low-count" bacteriuria now known to be important in refractory DO

2) Women with refractory IDO have bacteriuria rates of
   39% of MSUs, 56% of patients
   27% of CSUs, 28% of patients
   without acute dysuria – at time of acute exacerbation of urge

3) Newly diagnosed DO have OR 5.9 low count bacteriuria compared to those with a stable bladder

Workshop program

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Summary and Clinical significance

Prof Kate H Moore, Australia

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So what is the clinical significance?

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Could prolonged bladder-specific antibiotics correct the problem?

There have been two open studies conducted by colleagues in London

Vik Khullar (St Marys Hospital London)

James Malone-Lee (UCL)

Positive results, but no controls

1. Trial of antibiotics in OAB patients

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Int Urogynecol J
DOI 10.1007/s00192-012-2038-y

ORIGINAL ARTICLE

Changes in nerve growth factor level and symptom severity following antibiotic treatment for refractory overactive bladder

G. Vijaya · R. Cartwright · A. Derpapas · P. Gallo · R. Fernando · V. Khullar

Patients = refractory OAB
Antibiotics = a 6 week course of rotating antibiotics
Three consecutive antibiotics were given for 2 weeks each

- Ciprofloxacin
- Doxycycline
- Cephalexin or co-amoxiclav

1. Trial of antibiotics in OAB patients

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Table 3 Overactive bladder (OAB) symptoms at baseline and after 6 weeks of antibiotic therapy

	Pre-treatment	After a 6-week course of antibiotics	*p*
Daytime frequency	12.8 (±3.5)[a]	8.7 (±2.7)[a]	<0.005
Nocturia	2.0 (1.0 to3.0)[b]	1.0 (0 to 3.0)[b]	<0.050
PPBC scores	5.0 (4.0 to 6.0)[b]	2.0 (1.0 to 4.0)[b]	<0.005
PPIUS scores	3.0 (1.0 to 5.0)[b]	2.0 (1.0 to 3.0)[b]	<0.005

PPBC Patients' Perception of Bladder Condition; *PPIUS* Patients' Perception of Intensity of Urgency Scale

[a] Values are expressed as: mean (standard deviation)

[b] Values are expressed as median (25th to 75th interquartile ranges)

Significant improvement in symptom scores but not placebo controlled

2. Antibiotic treatment of OAB

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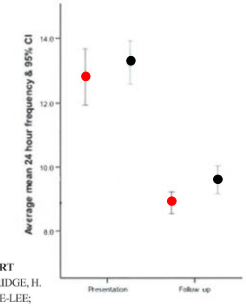
Patients in two groups:

1. n= 147, antibiotics given (nitrofurantoin or Ceplalexin)
2. n= 212, no antibiotics

Significant improvement in symptoms in both groups

But the antibiotic treated group improved over a shorter time course



THE ANTIBIOTIC TREATMENT OF OAB COHORT
K. GILL, R. KHASRIYA, A. KUPELIAN, L. BRACKENRIDGE, H. HORSLEY, S. SATHIANANTHAMOORTHY, J. MALONE-LEE;

Int Urogynecol J (2011) 22 (Suppl 1):S1–S195

RCT of antibiotics in refractory DO

Phase IIB RCT of antibiotic therapy vs placebo at St George Hospital + Wollongong

Women with urodynamically proven refractory DO

n = 120, 2:1 ratio of antibiotics versus placebo (with darifenacin in both groups)

6 weeks of rotating antibiotics (2 weeks each)

- Augmentin Duo (or trimethoprim)
- Norfloxacin
- Nitrofurantoin

All patients will be followed for 6 months

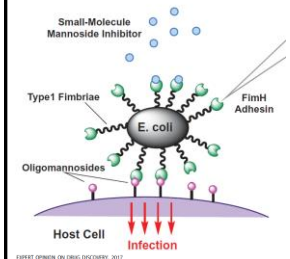
Bupa Health Foundation

RCT protocol

Washout -2.5 weeks	Primary complaint of urge incontinence MSU with appropriate antibiotic treatment of classical cystitis			
Randomization 0 weeks	Randomisation based on: severity of incontinence as indicated by the 24 hour pad test, previous history of UTI All outcome measures will be collected at 0 weeks including: 24 hour pad test, 3 day bladder diary, PPIUS, ICIQ, OABq and MSU			
	Active	**All**	**Control**	**Outcome measures**
0 to 2 weeks 2 to 4 weeks 4 to 6 weeks	Augmentin Duo Norfloxacin Nitrofurantoin	Darifenacin	Placebo	MSU
6 weeks				24 hours pad test 3 day bladder diary PPIUS, ICIQ OABq, MSU
10 weeks				MSU
14 weeks				MSU
18 weeks				MSU
6 months				24 hours pad test 3 day bladder diary PPIUS, ICIQ OABq, MSU

Recruitment is ongoing…

Other treatments for UTI



There are other treatments being discussed for UTI

- Mannosides
- Vaccinations
- Anti-inflammatory agents

- These could also apply for OAB/ DO

EXPERT OPINION ON DRUG DISCOVERY, 2017
VOL. 12, NO. 7, 711–721
https://doi.org/10.1080/17460441.2017.1331216
Taylor & Francis
REVIEW

Rational design strategies for FimH antagonists: new drugs on the horizon for urinary tract infection and Crohn's disease

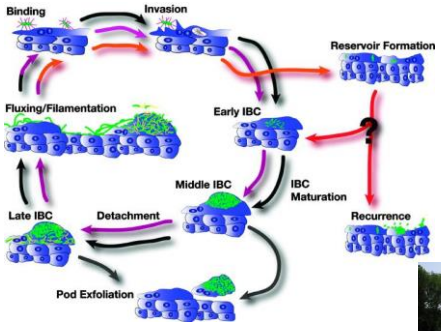
Laurel K. Mydock-McGrane[a], Thomas J. Hannan[a] and James W. Janetka[b]

Questions & discussion

Evidence for intracellular bacteria in urge incontinence.

Kylie J Mansfield, Ying Cheng,
Samantha Ognenovska, Zhouran Chen, Kate H Moore

E. Coli can colonise the urothelium



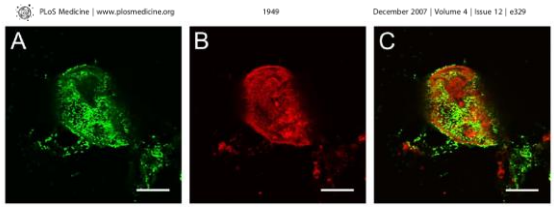
Justice et al., 2004 PNAS

OPEN ACCESS Freely available online PLOS MEDICINE

Detection of Intracellular Bacterial Communities in Human Urinary Tract Infection

David A. Rosen[1], Thomas M. Hooton[2], Walter E. Stamm[3], Peter A. Humphrey[4], Scott J. Hultgren[1*]

PLoS Medicine | www.plosmedicine.org 1949 December 2007 | Volume 4 | Issue 12 | e329



Urothelial cells from women with acute cystitis were stained with antibodies against E. coli (green) and uroplakin III (red).
Confocal microscopy revealed that these bacteria were intracellular.

AIM 1

- UTI is more common in patients with DO

To test for the presence of intracellular bacteria in the urine of patients with detrusor overactivity or mixed incontinence +/- a history of UTI, and compare this to a control group of patients with stress incontinence and no history of infection.

Pathogens and Disease, 74, 2016, ftw067
doi: 10.1093/femspd/ftw067
Advance Access Publication Date: 7 July 2016
Research Article

RESEARCH ARTICLE

Detection of intracellular bacteria in exfoliated urothelial cells from women with urge incontinence

Ying Cheng[1], Zhouran Chen[1], Jayde A. Gawthorne[2], Chinmoy Mukerjee[3], Kerry Varettas[3], Kylie J. Mansfield[4,*], Mark A. Schembri[2,†] and Kate H. Moore[1]

Methods

- Urine sample were collected from women undergoing management for incontinence.
- Urine sample:
  1. Routine microbiology culture (10^6-10^8 PFU/L)

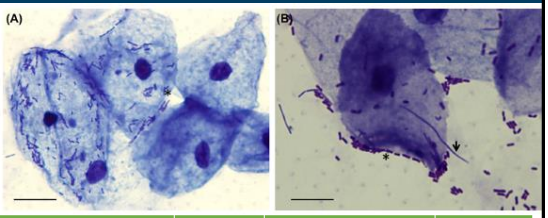
2. Fixation (1% formalin) -> concentration -> cytospin =>
   - Wright stain -> detect bacteria and filaments.
   - Immunocytochemistry (*E. coli* antibody)
   - Confocal Microscopy

- χ^2 analysis: compare presence/absence of bacterial filaments in DO and controls.

Results – clinical history (UTI)

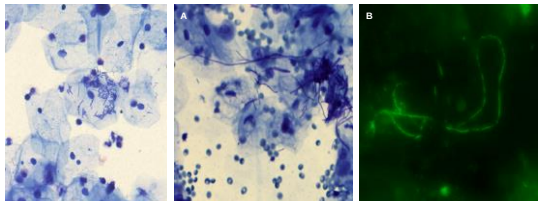
	Pure DO (n=47)	Mixed incontinence +/- UTI (n=21)	Control (n=20)
Recurrent UTI	10	7	0
Previous proven UTI	7	7	0
No prior proven UTI	30	7	20

Wright staining of urothelial cells



	Pure DO	Mixed incontinence +/- UTI	Control
Growth on routine micro	11%	27%	5%
Bacteria seen on Wright staining	75%	81%	55%

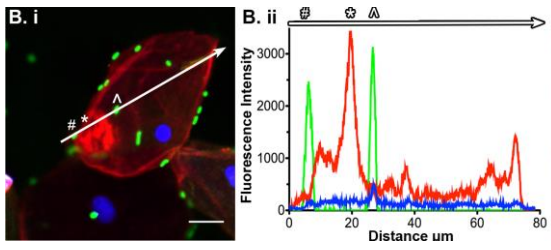
Filamentous bacteria: evidence of IBC's



Patient group	% patients with filament
Pure DO	82%
Mixed incontinence	23.5%
Control	27.3%

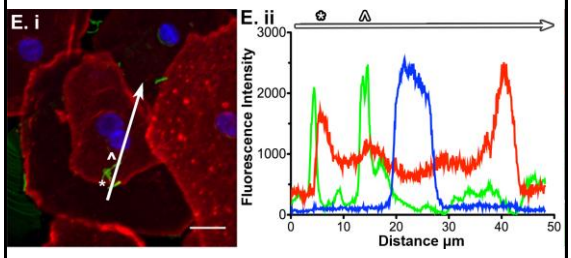
P < 0.0001

Confocal microscopy – bacteria outside the cell



Specific antibodies - *E. coli*
Urothelial cell membrane - Wheat-germ agglutinin (WGA)
Urothelial cell nucleus - DAPI

Confocal microscopy – bacteria inside the cell



Specific antibodies - *E. coli*
Urothelial cell membrane - Wheat-germ agglutinin (WGA)
Urothelial cell nucleus - DAPI

AIM 1: conclusions

Bacteria were commonly associated with urothelial cells

Intracellular bacteria were seen more commonly in patients with Detrusor Overactivity

Not all UTI is caused by *E. coli*

Bacterial strain identified by Micro	E. Coli	Enterococcus faecalis	Streptococcus
% specimens	38% (13/34)	17% (6/34)	26% (9/34)

We weren't just interested in what bacterial species were causing the infection but in how the bacteria were associated with the urothelial cells

AIM 2

To examine cellular invasion as a pathogenic factor for three uropathogenic bacterial strains.

Methods

121 MSU specimens were collected from 94 women
- routine microbiology to identify uropathogens
- evaluating bacterial colonisation

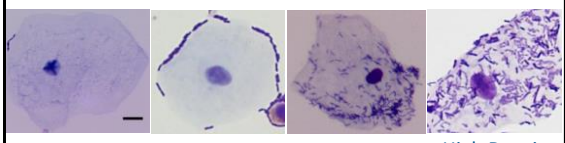
Exfoliated urothelial cells were concentrated onto a microscope slide.

A. Wright staining and light microscopy to categorize according to the presence, location and density of bacteria.

B. Confocal microscopy was used to demonstrate intracellular localisation of bacteria.
Cells were stained using specific antibodies to *E. coli* and *E. Faecalis*. The urothelial cell membrane was stained with Wheat-germ agglutinin (WGA) and the nucleus visualised with DAPI.

CLASSIFICATION SYSTEM USED

Approximately 100 randomly selected urothelial cells were examined at 40x magnification and categorized according to the presence of bacteria, the location of the bacteria and the bacterial density



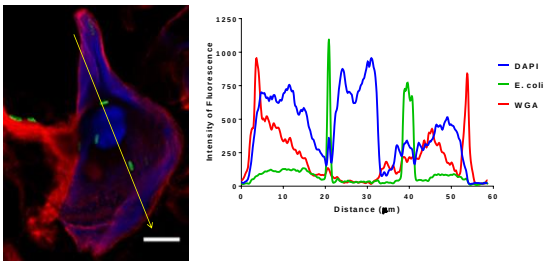
Low Density | High Density | Low Density | High Density

Appears Adjacent | Appears Intracellular

RESULTS – Wright staining

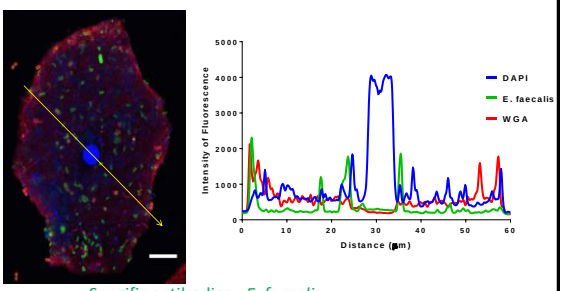
Bacterial strain identified by Micro	E. Coli	Enterococcus faecalis	Streptococcus
% urothelial cells clear of bacteria	13%	52%	58%
% of urothelial cells classified as "Appears Intracellular – low density"	72%	36%	30%

Confocal Results – *Escherichia coli*



Specific antibodies - *E. coli*
Urothelial cell membrane - Wheat-germ agglutinin (WGA)
Urothelial cell nucleus - DAPI

Confocal Results – *Enterococcus faecalis*



Specific antibodies - *E. faecalis*
Urothelial cell membrane - Wheat-germ agglutinin (WGA)
Urothelial cell nucleus - DAPI

AIM 2: Conclusions

The results of the current study demonstrate that all three uropathogens examined, *E. coli, E. Faecalis* and GBS are capable of intracellular growth

E. Faecalis and GBS demonstrated intracellular growth to a lesser extent that *E. coli*.

This suggests that intracellular growth might be a common characteristic of uropathogens

Intracellular growth may increase the likelihood of UTI and lead to the development of bladder dysfunctions such as DO possibly through a change in afferent nerve activity as a result of the altered inflammatory response.

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Subversion of host defenses by invasive uropathogens: modeling intracellular infection with a novel 3D primary culture

Harry Horsley

Harry Horsley

ICS 2017 FLORENCE

Affiliations to disclose†:

Nothing to disclose

† All financial ties (over the last year) that you may have with any business organisation with respect to the subjects mentioned during your presentation

Funding for speaker to attend:

- [ ] Self-funded
- [X] Institution (non-industry) funded
- [ ] Sponsored by:

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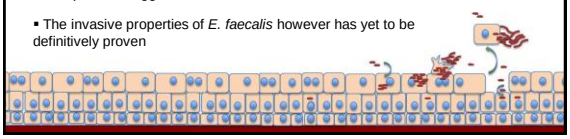
Background

- *E. coli* invades mouse and human urothelial cells in acute UTI
- The innate immune response to infection is cell shedding, leaving a gap, allowing bacteria to form quiescent reservoirs responsible for recurrent infection
- *E. coli* is the foremost invasive pathogen in acute UTI
- However, *Enterococcus faecalis* is commonly isolated in chronic UTI
- We previously showed close association of *E. faecalis* with the urothelium of LUTS patients suggestive of intracellular colonisation
- The invasive properties of *E. faecalis* however has yet to be definitively proven



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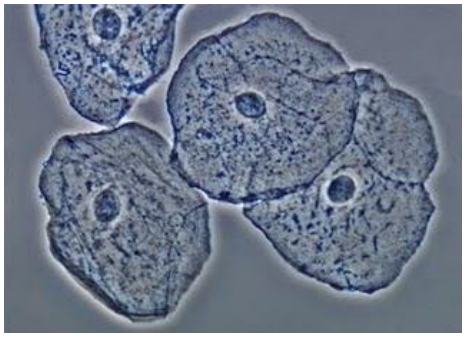
Urine microscopy



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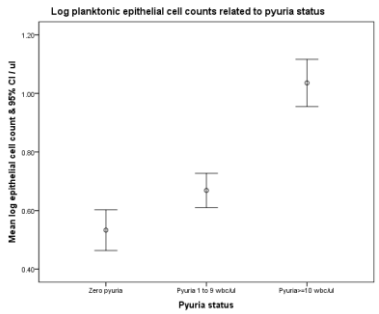
Cell shedding in 705 LUTS patients



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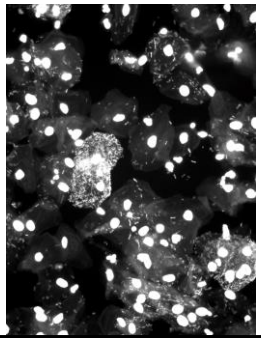
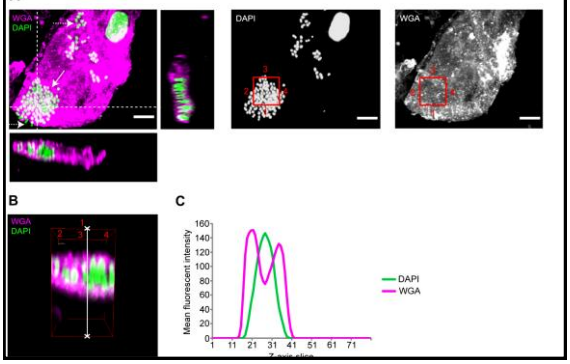
Urothelial Cell Shedding

Control cells

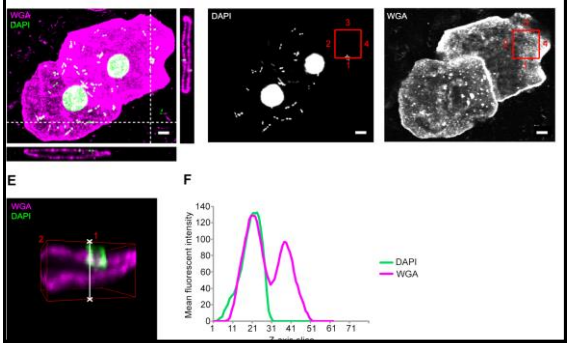
Patient cells



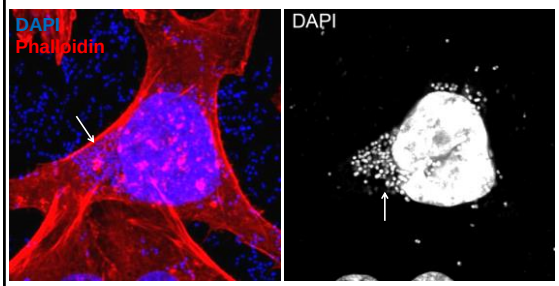
Patient urothelial cell – intracellular *E. faecalis*



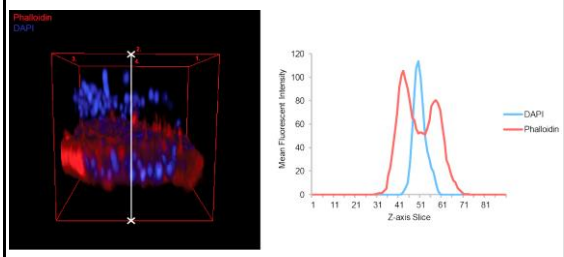
Patient urothelial cell – adherent *E. coli*



Infected T24 Cell Line



Results – Z-axis profile plot

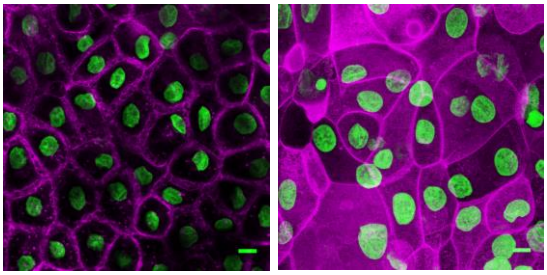


E. Faecalis invaded the cell line but E. Coli produced extracellular biofilms

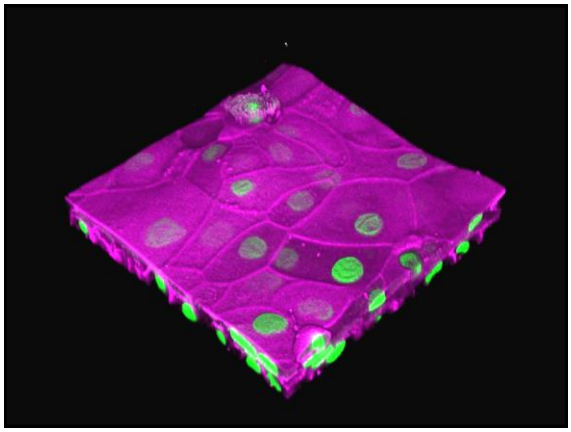
Engineered human urothelium

- Some LUTS may be generated by low-grade intracellular infection with *E. faecalis*
- All studies to date have relied on murine models and cancer cell lines to study the pathophysiology of UTI. Not physiologically relevant
- Produce a urine-tolerant organotypic culture using human bladder epithelial progenitor cells (HBEP) which mimics human urothelium.
- How do these cultures compare to native human bladder tissue?
- How does it respond to experimental infection?

Confocal Analysis – Cell morphology



Basal Cells | Umbrella Cells



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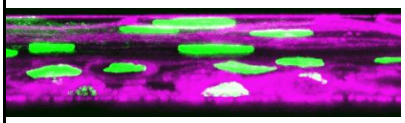
Cell layers



Reslice X/Y Maximum Projection. 3 Distinct layers

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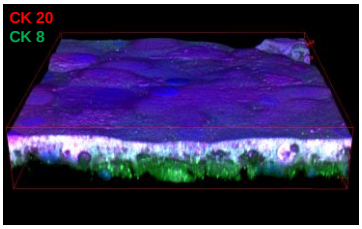
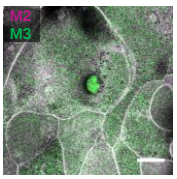
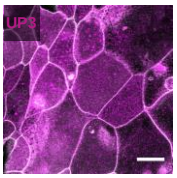
Characterisation







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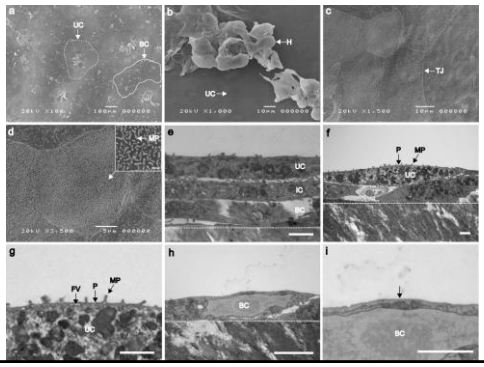
SEM / TEM



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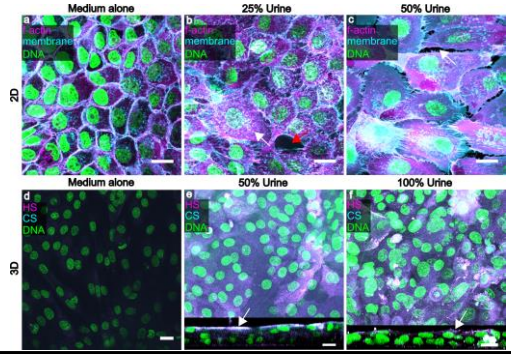
Urine dependence & GAG formation



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infection?

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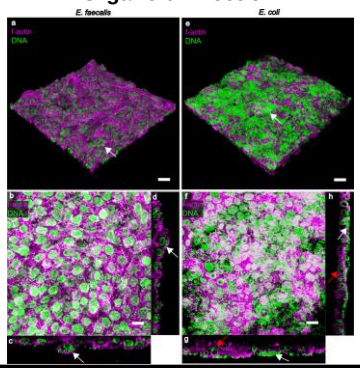
Organoid infection



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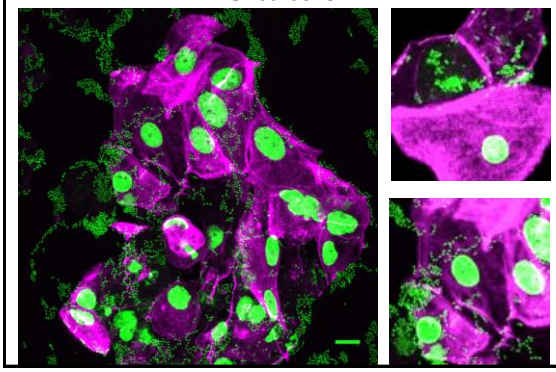
Shed cells



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Conclusion

- Our recent work, along with other studies, shows differences between the largely *E. coli*-based acute UTI mouse model and the situation in human patients suffering from LUTS, suggesting the mouse model may not be physiologically relevant in all cases
- Given that the mouse urothelium is developmentally and functionally different to native human tissue, we have engineered and extensively characterised organotypic human urothelium *in vitro*
- We will use this model as a reproducible and standardised test bed for chronic infective disease formation and treatment using our novel drug delivery system
- Engineered human bladder models may prove to be an invaluable research tool in understanding the pathogenesis and resolution of infectious urinary tract disease

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Thank you for listening

Thank you to the MS Society for funding this work

Big thank you to Jennifer Rohn, Prof. James Malone-Lee and the chronic UTI group (CUTI) at UCL

MS
Multiple Sclerosis Society

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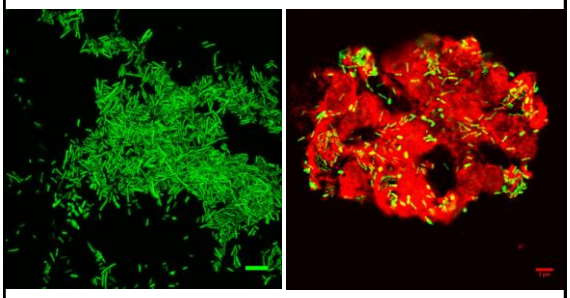
PNA-FISH: Culture-free visual identification



Under development (cell damage)

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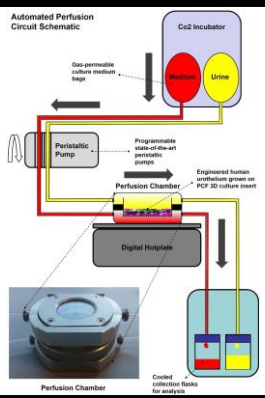

Workshop 15

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Culture independent study of recurrent Bacteriuria in refractory DO

Z Chen[1], L Bates[1], M-D Phan[2], M Schembri[2], KH Moore[1]

1. Department of Urogynaecology, St George Hospital, Kogarah, Australia

2. School of Chemistry & Molecular Biosciences, University of Queensland

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Background

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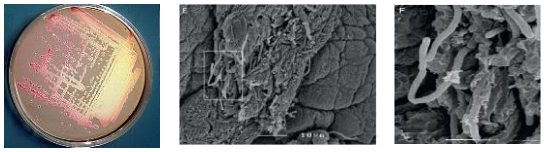
Clinical observation in Refractory DO patients

- Up to 40% of patients have recurrent UTI
- Antibiotic resistance and difficulty in managing DO symptoms

Limitations of routine microbiology

- Reports limited to single organism



Duell, Ulett et al. J Immunology 2012

UTI Pattern

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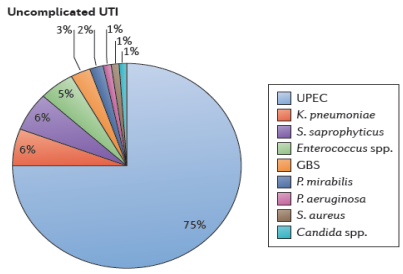

Risk factors

- Female gender
- Older age
- Younger age

Flores-Mireles et al NRM 2015

Aim/ Methods

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To investigate whether patients with Refractory DO have a persistent reservoir of bacteria in the bladder wall **(via Culture independent methods)**

Inclusion criteria

- Refractory DO
- History of recurrent UTI (≥ 2 infections/6months OR ≥ 3 infections/yr)

Methods

- MSU Routine Culture >10^8 CFU/L (for comparison)
- Culture independent method

Culture independent method

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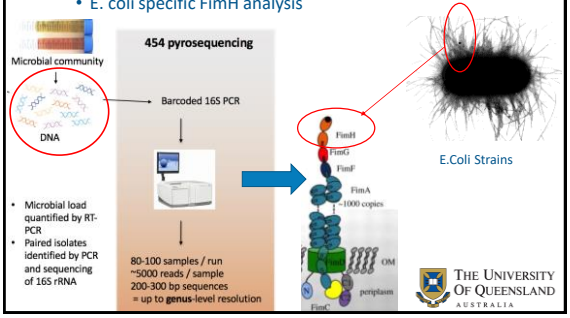
16s rRNA gene amplification + sequencing via **PCR**

- E. coli specific FimH analysis



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Results

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9 rDO women with proven recurrent UTI (42 MSU) in 24months

Median age 75y (57-81)

Previous 6-24 months 3-20 confirmed UTI

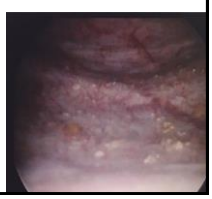
Average 8 UTI/women

No significant voiding dysfunction

All had topical vaginal oestrogen

All had cystoscopy

- No urethral stenosis or mesh erosion
- Typically displayed cystitis cystica



Routine culture results

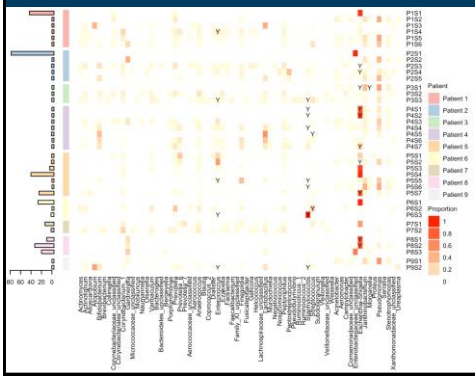
42 MSU (From 9 women)
5 samples "no growth"

20 samples had a reported single dominant organism
- **13** E. Coli (65%)
- 2 E. faecalis
- 2 Klebsiella
- 2 Streptoccocus
- 1 Citrobacter

17 reported as mixed growth

7/9 (78%) women had documented antibiotic resistance

Results of 16s rRNA Culture independent analysis

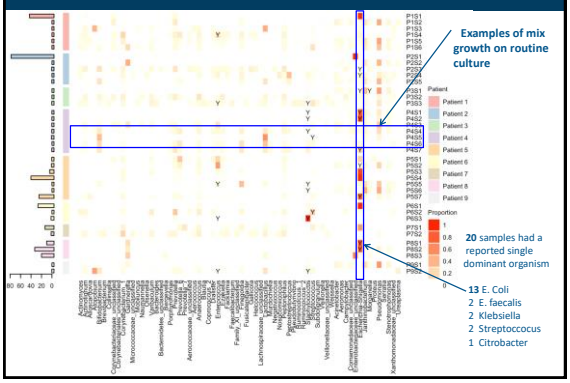


Diverse array of organism

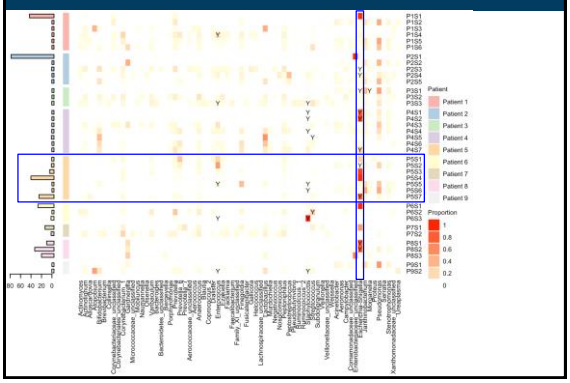
25 median species per patient (IQR 21-36)

Changing proportion of organism in each urine sample

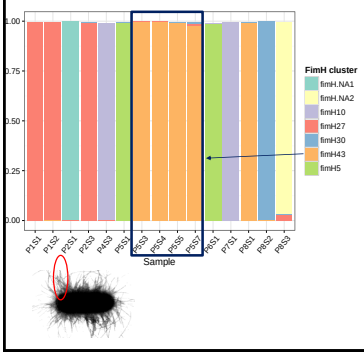
Results of 16s rRNA Culture independent analysis



Patient 5 – E.coli



E.Coli FimH amplicon PCR sequencing

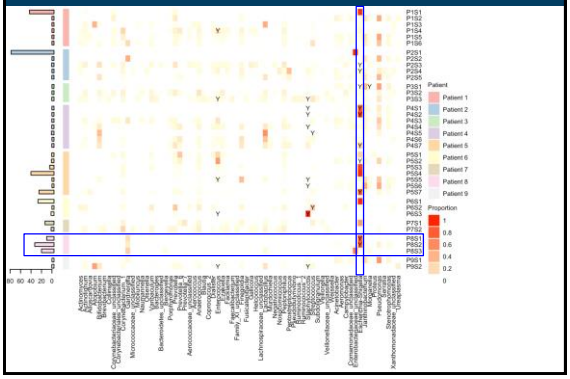


- Single persistent strain
- FimH43 predominant
- Clinically correlated because:

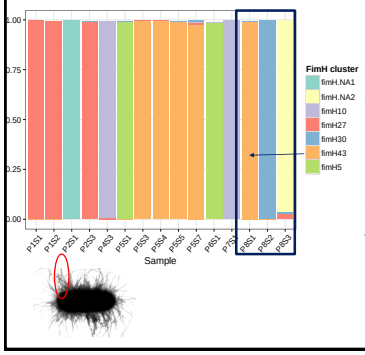
(1) E.coli seen on culture

(2) Antibiotic resistance to Amoxicillin + Trimethoprim

Patient 8 – E.coli



E.Coli FimH amplicon PCR sequencing



- E.Coli predominant, but constantly changing strain/resistance pattern
- FimH 43 same antibiotic resistance as Patient 5 (Amoxicillin + Trimethoprim)
- FimH 30 – ESBL

Conclusion

- First study of the microbiome of refractory DO patients with recurrent UTI
- Large number of bacteria detected in urine: median 25 species per patient (IQR 21-36)
- Organisms isolated on PCR change over time
- Further studies in this area may help link bacteria changes to exacerbation of DO symptoms

GIRLS JUST WANT TO HAVE FUM

"Female Urinary Microbiome"

E.R. Mueller, MD MSME
Professor, Departments of Urology & Ob/Gynecology
FPMRS Division & Fellowship Director
Loyola University Chicago Stritch School of Medicine

LOYOLA UNIVERSITY CHICAGO 1870 MAGIS • DEI • GLORIAM

Elizabeth R Mueller, MD

Affiliations to disclose†:

Astellas Pharma – Research Support

† All financial ties (over the last year) that you may have with any business organisation with respect to the subjects mentioned during your presentation

Funding for speaker to attend:

- [x] Self-funded
- [ ] Institution (non-industry) funded
- [ ] Sponsored by:

PERSPECTIVES

RECOGNIZING THE PROBLEM

How we changed our paradigm

Dogma-based clinical care

Urgency Urinary Incontinence (UUI)

The bladder is sterile
based on negative standard urine culture

UUI does not have a bacterial contribution
caused by neuro-muscular imbalance

Is This Our Best?

Should we accept the dogma/assumptions that:
UUI is a chronic condition
Life-long treatment: pill, implant, etc.

UTI is caused by a single uropathogen
invading a "sterile" field

That the bladder (lower urinary tract)
is actually sterile?

Consider a team of basic and clinical investigators using the Urinary Microbiota project as a framework

The Loyola Urinary Education and Research Collaboration (LUEREC)

This work was supported by NIH grants R01 (insert #), R21 DK097435, R56DK104718 and P20DK108268

Humans Are Superorganisms

2 integrated genomes

1. Genetically inherited human genome
   - (23,000 genes)
2. Environmentally acquired human microbiome
   - (over 1 million genes).

The two genomes must work harmoniously to maintain health

PERSPECTIVES

HISTORY OF URINARY CULTURES

How we got here

Historical Perspectives

- Urine deemed sterile in mid-1800's
  - vial of urine in a sealed container did not turn cloudy, while a vial of urine exposed to air or tap water did

"…fresh and healthy urine is perfectly free from bacteria or other minute organisms"

1. Duclaux E. (1920),
2. Bloom DA J of U 1994;151(2)
3. Roberts W. Br Med J 1881;2(1085)

Historical Perspectives

- In the 1950's, a colony count of 10^5 was the dividing line between contamination and pyelonephritis
  - Since then, this standard culture (SC) techniques has been adopted to LUT infections, despite several studies that suggest otherwise
- Jack Lapides suggested intermittent catheterization did not have to be sterile

1. Kass EH. Transactions of the Association of American Physicians. 1956;69:56-64
2. Lapides J. Journal of Urology 1972

Human Microbiome Project

- There are 10 bacteria for every single cell in the human body
- National Institutes Health Initiative to map the human microbiome of 5 body sites:
  - GI tract, mouth, vagina, skin, nasal cavity using culture-independent methods.
  - Bladder not included due to belief it was sterile and complexities of sample collection.

What if our understanding of the female lower urinary tract has rested on an invalid assumption?

Dogma – Null Hypothesis: 'Culture-negative' urine is sterile

Alternative hypothesis: 'Culture-negative' urine is NOT sterile

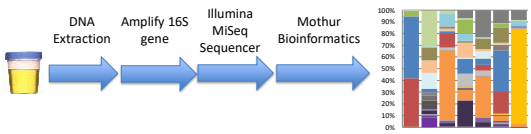
LESSON #1

GETTING AN ACCURATE SPECIMEN

The story begins

16S Ribosomal RNA (rRNA) Gene Sequencing

- The 16S gene is a molecular chronometer
  - Permits classification to the family or genus level

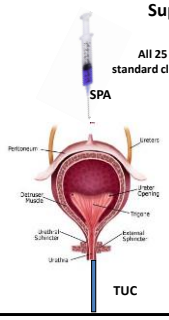


Quick Classification Update

Domain	Bacteria
Kingdom	Eubacteria
Phylum	Proteobacteria
Class	Gammaproteobacteria
Order	Enterobacteriales
Family	Enterobacteriaceae ←
Genus	*Escherichia* ←
Species	*Escherichia coli*

Obtain a urine sample that represents the bladder ONLY
From women with and without Lower Urinary Tract Symptoms (LUTS)

Transurethral catheter (TUC)
Suprapubic aspirate (SPA)



All 25 urine samples were negative by the standard clinical microbiology urine culture protocol

To assess possible contamination of SPA by skin microorganisms, we also collected
- **swabs of the suprapubic sample site**
- **needles that punctured the skin but did not enter bladder**

Therefore, 4 samples
1. **TUC**
2. **SPA**
3. **Skin**
4. **Needle**

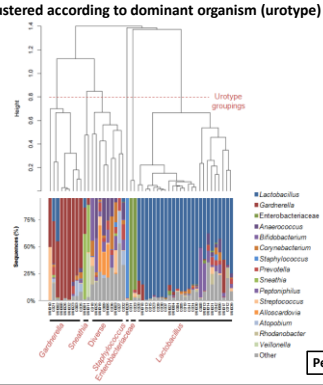
DNA evidence of bacteria in the bladder

- **TUC & SPA resemble each other**
- **TUC & SPA do not resemble controls (voided)**
- **SPA bypasses vulvo-vaginal contamination**
- ***Which bacteria?***

Wolfe et al. 2012. JCM. PMID: 22278835

Samples are often dominated by one organism

Clustered according to dominant organism (urotype)



Pearce et al. 2014

Summary

Bacteria are present in women with and without lower urinary tract symptoms

***Lactobacillus* and *Gardnerella* are common members of the FUM**

LESSON #2

ARE THE BACTERIA REALLY ALIVE?

The DNA evidence could be dead bacteria which would not be symptomatic

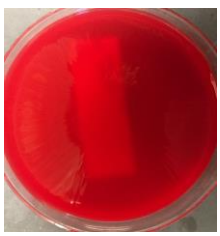
Are "culture negative" urines truly negative?

Protocol	Volume	Media	Atmospheric Conditions	Time
Standard Urine Culture (SUC)	1 uL urine	Blood Agar MacConkey Agar	Aerobic	24 hrs 35°
Enhanced Quantitative Urine Culture (EQUC)	100 uL urine	Blood Agar Chocolate Agar CNA Agar Anaerobic Blood Agar	Aerobic CO_2 Anaerobic	48 hrs 35°

Hilt et al. 2014. JCM. PMID: 24371246

This urine is not sterile

SUC **EQUC**

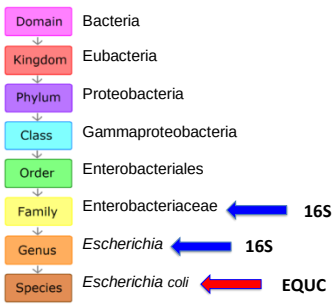


Blood agar, 1 ul, 24 hours

Blood agar, 100 ul, 48 hours, CO_2

Hilt et al. 2014. JCM. PMID: 24371246

Quick Classification Update



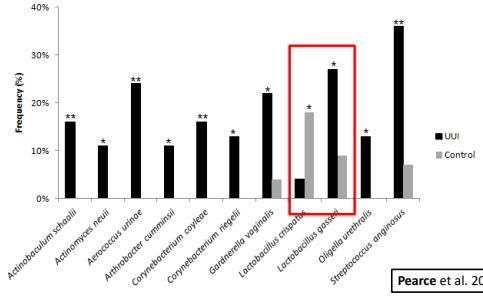
LESSON #3

URGENCY INCONTINENCE

The symptoms of UUI and UTI have so much overlap

Baseline FUMs of UUI and non-UUI cohorts differ

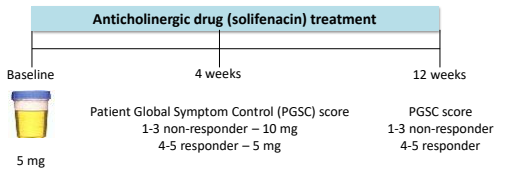
Some species are more common in UUI cohort
One is more common in non-UUI controls



Pearce et al. 2014

Response to UUI Treatment Study Design

Adult women with UUI (Questionnaire eligibility)	Controls without UUI symptoms (Questionnaire eligibility)



Clinicaltrials.gov Registry
NCT01642277

Cohort Comparison

- By design, *UUI symptoms were significantly worse in UUI cohort than in non-UUI controls*
- Similar with respect to race/ethnicity, diabetes, smoking
- The UUI population was:

Category	UUI	Non-UI	p-value
Older	61.5 (SD: 11.5)	49 (SD:14.7)	$p<0.001$
Heavier	32.7 (SD:8.4)	28 (SD:5.5)	$p<0.001$
Estrogen Negative	88%	43%	$p<0.001$
Hypertensive	35%	18%	$p=0.02$
Coronary artery disease	12%	2%	$p=0.02$

* post-menopausal and not on hormone replacement therapy

Use EQUC to compare women with and without UUI

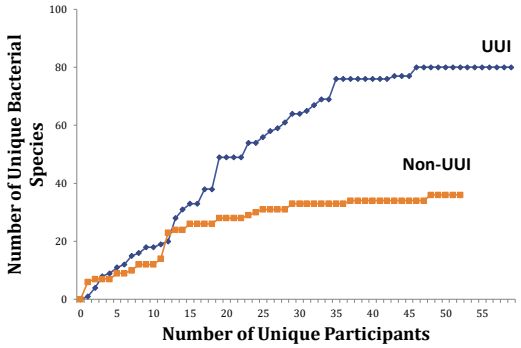
UUI + non-UUI	EQUC positive	EQUC negative
SUC positive	7	0
SUC negative	64	19

Standard urine culture had **false-negative rates** of
90.1% for total
90.3% for UUI
90.0% for controls

Pearce et al. 2014

Species Accumulation Curve

Baseline FUMs of UUI and non-UUI cohorts differ



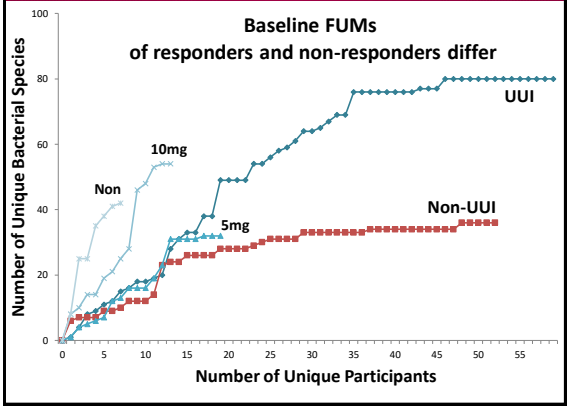
Response to UUI Treatment Study Design

Adult women with UUI (Questionnaire eligibility)	Controls without UUI symptoms (Questionnaire eligibility)

3 responder groups
5 mg responder
10 mg responder
Non-responder

Baseline
5 mg
12 weeks
PGSC score
1-3 non-responder
4-5 responder
4-5 responder – 5 mg

Clinicaltrials.gov Registry
NCT01642277



The baseline FUM of women with and without UUI differ

Some bacteria are associated with UUI
***Lactobacillus crisptatus* is associated with controls**

The baseline FUM is associated with response to oral UUI treatment

SUMMARY

And other lessons that we have learned

WHAT WE LEARNED THUS FAR

- The Female Urinary Microbiota (FUM) exist and they are alive
  - Wolfe et al., 2012
    - Hilt et al., 2014
- Some FUM members associate with lower urinary tract symptoms (UUI)
  - Others associate with the lack of UUI symptoms
  - The FUM can be associated with response to medication
    - Pearce et al., 2014
    - Pearce et al., 2015
    - Thomas-White et al. 2015
- The FUM is associated with post-instrumentation UTI
  - Brubaker et al. 2015
- The FUM is associated with post-surgery UTI
  - Fok et al., 2013
- The FUM influences the innate immune system of the urothelium
  - Nienhouse et al., 2014
  - Le et al., 2014
- The microbiota of calcium oxalate kidney stones
  - Barr-Baer et al., 2015

WE ALSO LEARNED THAT

Standard Urine Culture protocol is limited even in the context of conventional UTI diagnosis

Hilt et al., 2014
PMID: 24371246

Pearce et al., 2014
PMID: 25006228

Price et al., 2015
PMID: 26962083

MORE QUESTIONS THAN ANSWERS

- In adult women, especially those with urinary symptoms,
  what is the gold standard for UTI?
- How should we detect/treat of FUM dysbiosis?
- What causes UTI symptoms in patients with no known uropathogen?
- We must change our assumptions/language
  - If 'normal' is asymptomatic bacteriuria, what does the term mean?

TAKE HOME MESSAGE:

THERE IS A URINARY MICROBIOTA IN WOMEN

TAKE HOME MESSAGES:

As awareness of
the Female Urinary Microbiota
grows,
we must avoid antibiotic overuse.

Must change the paradigm
from "kill everything"
to "modulate to optimize health"

QUESTIONS?

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1870
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Preparing people to lead extraordinary lives

Summary and Clinical significance

Prof Kate H Moore, Australia

UNSW THE UNIVERSITY OF NEW SOUTH WALES

So what is the clinical significance?

Could prolonged bladder-specific antibiotics correct the problem?

There have been two open studies conducted by colleagues in London

Vik Khullar (St Marys Hospital London)

James Malone-Lee (UCL)

Positive results, but no controls

1. Trial of antibiotics in OAB patients

Int Urogynecol J
DOI 10.1007/s00192-012-2038-y

ORIGINAL ARTICLE

Changes in nerve growth factor level and symptom severity following antibiotic treatment for refractory overactive bladder

G. Vijaya · R. Cartwright · A. Derpapas · P. Gallo · R. Fernando · V. Khullar

Patients = refractory OAB
Antibiotics = a 6 week course of rotating antibiotics
Three consecutive antibiotics were given for 2 weeks each
- Ciprofloxacin
- Doxycycline
- Cephalexin or co-amoxiclav

1. Trial of antibiotics in OAB patients

Table 3 Overactive bladder (OAB) symptoms at baseline and after 6 weeks of antibiotic therapy

	Pre-treatment	After a 6-week course of antibiotics	*p*
Daytime frequency	12.8 (±3.5)[a]	8.7 (±2.7)[a]	<0.005
Nocturia	2.0 (1.0 to3.0)[b]	1.0 (0 to 3.0)[b]	<0.050
PPBC scores	5.0 (4.0 to 6.0)[b]	2.0 (1.0 to 4.0)[b]	<0.005
PPIUS scores	3.0 (1.0 to 5.0)[b]	2.0 (1.0 to 3.0)[b]	<0.005

PPBC Patients' Perception of Bladder Condition; *PPIUS* Patients' Perception of Intensity of Urgency Scale

[a] Values are expressed as: mean (standard deviation)

[b] Values are expressed as median (25th to 75th interquartile ranges)

Significant improvement in symptom scores but not placebo controlled

2. Antibiotic treatment of OAB

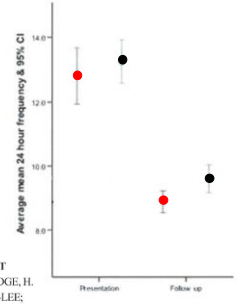
Patients in two groups:

1. n= 147, antibiotics given (nitrofurantoin or Ceplalexin)

2. n= 212, no antibiotics

Significant improvement in symptoms in both groups

But the antibiotic treated group improved over a shorter time course



THE ANTIBIOTIC TREATMENT OF OAB COHORT
K. GILL, R. KHASRIYA, A. KUPELIAN, L. BRACKENRIDGE, H. HORSLEY, S. SATHIANANTHAMOORTHY, J. MALONE-LEE;
Int Urogynecol J (2011) 22 (Suppl 1):S1–S195

RCT of antibiotics in refractory DO

Phase IIB RCT of antibiotic therapy vs placebo at St George Hospital + Wollongong

Women with urodynamically proven refractory DO

n = 120, 2:1 ratio of antibiotics versus placebo (with darifenacin in both groups)

6 weeks of rotating antibiotics (2 weeks each)
- Augmentin Duo (or trimethoprim)
- Norfloxacin
- Nitrofurantoin

All patients will be followed for 6 months

Bupa Health Foundation

RCT protocol

ICS 2017 FLORENCE

Washout -2.5 weeks	Primary complaint of urge incontinence MSU with appropriate antibiotic treatment of classical cystitis			
Randomization 0 weeks	Randomisation based on: severity of incontinence as indicated by the 24 hour pad test, previous history of UTI All outcome measures will be collected at 0 weeks including: 24 hour pad test, 3 day bladder diary, PPIUS, ICIQ, OABq and MSU			
	Active	**All**	**Control**	**Outcome measures**
0 to 2 weeks 2 to 4 weeks 4 to 6 weeks	Augmentin Duo Norfloxacin Nitrofurantoin	Diclofenacin	Placebo	MSU
6 weeks				24 hours pad test 3 day bladder diary PPIUS, ICIQ OABq, MSU
10 weeks				MSU
14 weeks				MSU
18 weeks				MSU
6 months				24 hours pad test 3 day bladder diary PPIUS, ICIQ OABq, MSU

Recruitment is ongoing…

Other treatments for UTI

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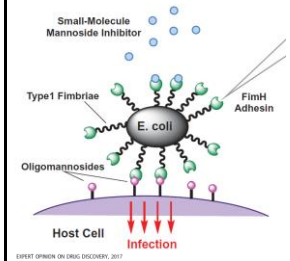

There are other treatments being discussed for UTI

- Mannosides
- Vaccinations
- Anti-inflammatory agents

- These could also apply for OAB/ DO

EXPERT OPINION ON DRUG DISCOVERY, 2017
VOL. 12, NO. 7, 711–731
https://doi.org/10.1080/17460441.2017.1331216
Taylor & Francis
REVIEW

Rational design strategies for FimH antagonists: new drugs on the horizon for urinary tract infection and Crohn's disease

Laurel K. Mydock-McGrane[a], Thomas J. Hannan[a] and James W. Janetka[b]

ICS 2017 FLORENCE

Questions & discussion