

Recurrent UTI in Adult Women: Contemporary Management & Future Prospects

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Disclosures

- Speaker
 - Astellas
 - Pfizer
 - Ferring
 - Allergan
 - Medtronic
 - BBraun
- Advisory Boards / Consultancy
 - Pierre Fabre
 - AMS
 - Astellas
 - Teleflex

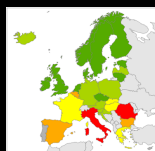
Urinary Tract Infection

- Defined as the inflammatory response of the urothelium to microbial pathogens
- Affect an estimated 150 million people each year worldwide Stamm & Norrby 2001 J. Infect. Dis. 183, 51–54
- UTIs account for 17.2% of all nosocomial infections in England Loveday et al. J. Hosp. Infect. 86, S1–S70 (2014).
- Recurrence accounted for 10.5 million outpatient consultations and 2–3 million emergency department visits in the USA alone Nicolle Crit. Care Clin. 29, 699–715 (2013).

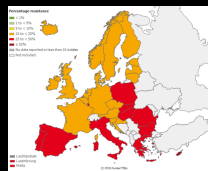
Definition of recurrent UTI?

- No universally accepted definition for rUTI
- Most commonly used is “2 in 6 months or 3 in a year”
 - Schoof and Hill 2005
 - Hooton and Stamm 2006
- Estimated 20-50% of young women with UTI will have another within a year
 - Mabeck et al Postgrad Med J 1972.
 - Brumbaugh and Mobley Expert Rev Vaccines. 2012.
- Finnish study showed older (>55yrs) more likely to have recurrence in first year (53% vs 36%)
 - Ikaheimo Clin Infect Dis 1996

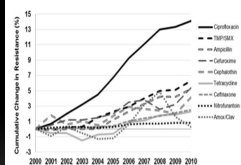
Antibiotic Avoidance and Stewardship



Fluoroquinolone Usage



Fluoroquinolone Resistance

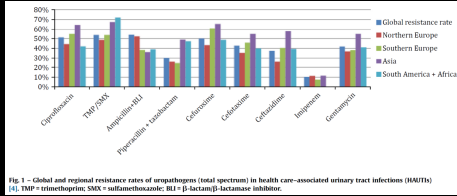


Antibiotic Resistance in Cystitis

ECO.SENS – 2003/11 N-Europe, Canada	NAUTICA – 2006 USA, Canada	ARESC – 2008 Europe, Brazil
SRGA standard	CLSI standard	CLSI standard
Ampicillin – 26/28%	Ampicillin – 38%	Ampicillin – 51%
TMP/SMX – 13/17%	TMP/SMX – 21%	TMP/SMX – 29%
Nalidixic acid – 4/10%	Nalidixic acid – n.d.	Nalidixic acid – 18%
Ciprofloxacin – 1/4%	Ciprofloxacin – 5%	Ciprofloxacin – 8%
Nitrofurantoin – 1/0.3%	Nitrofurantoin – 1%	Nitrofurantoin – 5%
Mecillinam – 2/1%	Mecillinam – n.d.	Mecillinam – 3%
Fosfomycin – 0.4/1%	Fosfomycin – n.d.	Fosfomycin – 1%

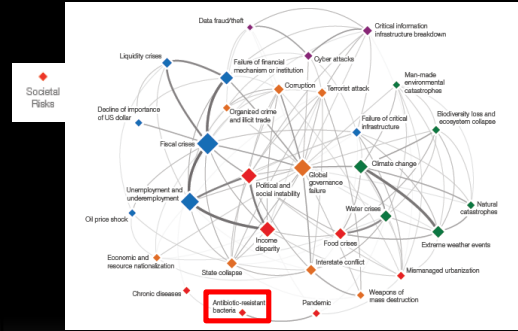
GG Zhanel et al. Int J Antimicrob Agents. 2005; 26(5):380-8.
KG Naber et al. Eur Urol. 2008; 54(5):1164-75.
G Kahlmeter et al. Int J Antimicrob Agents. 2012; 39(1):45-51.

Antimicrobial Resistance



Tandogdu Z, Cek M, Wagenlehner F, et al. World J Urol 2014;32:791-801.

Global Risks 2014 Ninth Edition

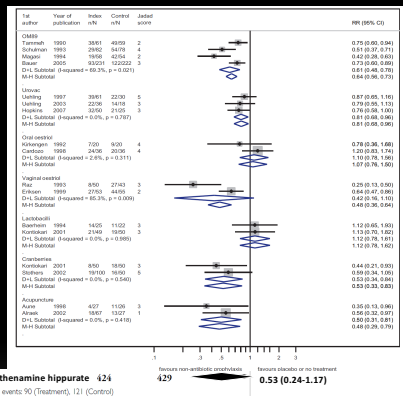


Contemporary Management

Contemporary Management

- Non-antibiotic (and non-invasive)
 - Cranberry Products
 - Topical Oestrogens
 - Methenamine Hippurate
 - Vaccines
- Antibiotics
 - Prophylactic Antibiotics
 - Self Start Therapy
- Intravesical agents

Non-antibiotic prophylaxis



Cranberry Products

- Postulated to acidify urine and reduce bacterial adhesion/prevent fimbrial expression
 - Some evidence that rUTIs reduced but optimum dose /duration unclear.
 - Original Cochrane review (2008) identified *some benefit* BUT
- Meta-analyses in updated review (2012) showed that compared with placebo, water or non-treatment, "cranberry products **did not significantly reduce the occurrence of symptomatic UTI overall**" (RR 0.86, 95% CI 0.71 to 1.04)
- Jepson et al. Cochrane Database 2012

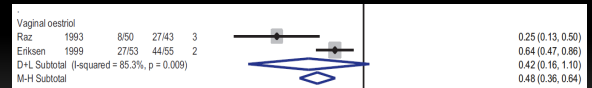
Cranberry Products



- Study funded by Ocean Spray Cranberries - 2 authors by the company - published Am J Clin Nutr; 2016 Jun; 103:1434-42
- 6/52 trial in 373 healthy women – randomised to a 240ml bottle of cranberry juice or identical-tasting placebo daily
- 39 investigator-diagnosed episodes of clinical UTI in the cranberry group compared with 67 episodes in the placebo group (antibiotic use-adjusted incidence rate ratio: 0.61; P = 0.016)
- For every woman who drank cranberry juice for 3.2 years, just one UTI would be prevented

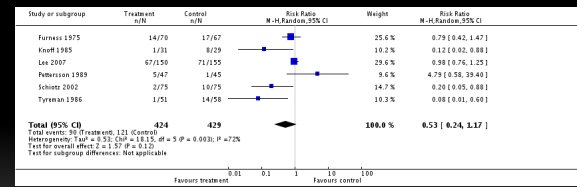
Topical Oestrogens

- Falling oestrogen levels lead to a change in vaginal flora and pH
- Local oestrogen can reverse this without SE of systemic oestrogen
Esposito *et al.* Gynaecological Endocrinology 1991
- Oestrogen may also enhance innate immune mechanisms against urinary tract infection
Lüthje *et al.* Science Translational Medicine 2013
- Systematic review found no reduction in UTIs with oral oestrogen but showed vaginal preparations superior to placebo (RR 0.25/0.64)
Perrotta *et al.* Cochrane Database 2008

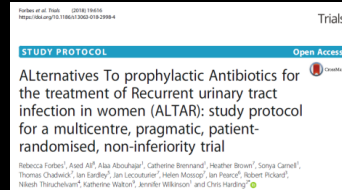


Methenamine Hippurate

- Methenamine has antibacterial properties - hydrolysed to formaldehyde in acid urine
- Systematic review highlighted heterogeneity of data *but some studies report reduction in symptomatic UTIs (RR 0.24)*
- ? Ineffective in pts with neuropathic bladder / abnormal renal tract.
- “There is a need for further large well-conducted RCTs to clarify...”



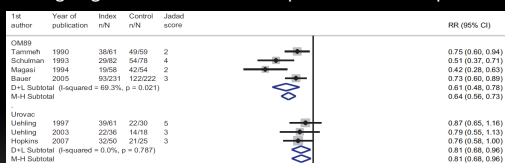
ALTAR trial



- Women with uncomplicated rUTI
- Randomised to prophylactic abx vs Methenamine for 12 months
- Primary Outcome – UTI incidence

Vaccines

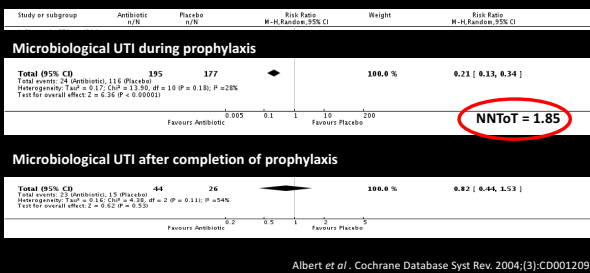
- Uro Vaxom® (OM-89) is only one recommended by EAU guidelines
EAU Guidelines Urinary Infections 2018
- Oral administration of immunologically active bacterial lysates of 18 *E coli* strains . Better than placebo in several RCTs.
- The vaginal vaccine Urovac® slightly reduced UTI recurrence and increased time to re-infection.
- New agent, UROMUNE® (under the tongue spray) currently undergoing multi-centre trials in Spain with UK trial planned.



Prophylactic Antibiotics

- Long term prophylaxis can range from 4 mths to 5 yrs!!
- 95% will remain UTI free but 50% relapse following cessation
Nicolle *et al.* Am J Med 2002
- Cochrane review of RCT's - RR 0.21 for single recurrence (NNT 1.85) but RR after prophylaxis 0.82
Albert *et al.* Cochrane Database 2004
- Single randomised study found prophylactic nitrofurantoin superior to oestrogen
Raz *et al.* Clin Infect Dis 2003

Antibiotic prophylaxis

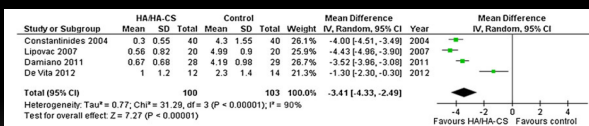


Self Start Antibiotics

- 85-95% of women with previous UTI can self diagnose successfully Gupta *et al.* Ann Intern Med 2001
- Clinical and Microbiological cure rates > 90%
- Best used in motivated women with previous culture confirmed cystitis Hooton NEJM 2012
- Advantages are less antimicrobial exposure and high patient satisfaction rates
- Post coital antibiotics reserved for group where it has been identified as the dominant risk factor.

Intravesical Treatments

- Glycosaminoglycan hyaluronic acid (HA) and chondroitin sulphate (CS) used to enhance protective function of urothelium. GAG layer damage / deficiency may be aetiological in rUTI.
- Agents available: Cystistat® (HA), Hyacyst® (HA), Gepan® (CS), iAluril® (HA & CS)
- Systematic review demonstrates ↓cystitis recurrence, UTI recurrence, and Pelvic Pain & Urgency/Frequency (PUF) total score. De Vita *et al.* Int Urogynecol J. 2013.
- Study limitations include the small no. of pts and possible bias. **"Further studies needed to validate this promising treatment..."**



Non-antibiotic options for recurrent urinary tract infections in women

Jonathan Barclay *speciality trainee in urology*, Rajan Veeratterapillay *consultant urological surgeon*, Chris Harding *consultant urological surgeon*

Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK



BMJ 2017;355:j5193 doi: 10.1136/bmj.j5193 (Published 23 November 2017)

- Review of high level evidence on treatment of recurrent UTIs
- Includes research recommendations

REVIEWS

Nonantibiotic prevention and management of recurrent urinary tract infection

Neha Sihra¹, Anna Goodman¹, Rhana Zakri¹, Arun Sahai¹ and Sachin Malde^{1*}

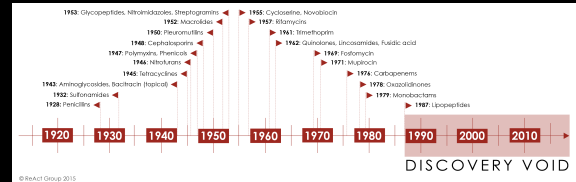
- Systematic review of all grades of evidence – Nature Reviews. Urology 2018, 15 (12): 750-776
- Thorough, detailed analysis of existing literature

Future Prospects

Future Prospects

- New antibiotics
- Vaccination
 - Mucosal multivalent bacterial vaccine
 - Virulence factor vaccines
- Bacterial Adhesion Inhibitors
- Immune Modulation
 - Boosting bacterial expulsion
 - Exogenous enhancement of innate immunity
- Natural flora modulation
 - Probiotics
 - Gastrointestinal decolonisation
- Acupuncture

New Antibiotics?



Thought unlikely....but....

New Antibiotics

BUJ-642; No. of Pages 3
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available at www.sciencedirect.com
 journal homepage: www.europeanurology.com/eufocus

EAU

Clinical Trial Update

Novel Antibiotics in the Treatment of Urinary Tract Infections

Kurt G. Naber^{a,*}, Florian M.E. Wagenlehner^b

^aDepartment of Urology, Technical University of Munich, Munich, Germany; ^bClinic for Urology, Pediatric Urology and Andrology, Justus Liebig University, Giessen, Germany

New Antibiotics

- Ceftolozane/tazobactam
 - novel cephalosporin combined with an established BLI
 - phase 3 study a total of 1083 hospitalized patients with complicated UTI or acute pyelonephritis
 - randomized 1:1 to ceftolozane/tazobactam (1.5 g IV tds) or levofloxacin (750 mg IV od) for 7 d.
 - Overall, ceftolozane/tazobactam showed better responses than levofloxacin

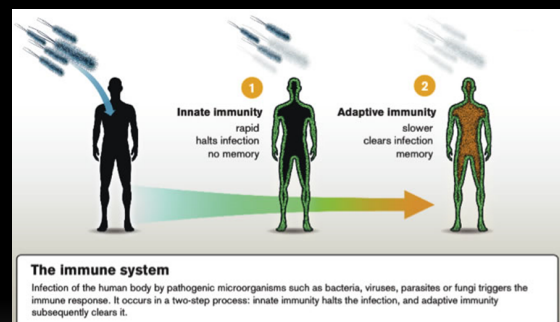
Wagenlehner et al
 Lancet 2015;385:1949–56.

New Antibiotics

- Ceftazidime/avibactam
 - Avibactam, a BLI, restores the activity of ceftazidime against several bacteria (eg, ESBL)
 - 2 phase 3 trials - 1033 patients with cUTI/APN randomized to ceftazidime/avibactam (2000/500 mg IV tds) or doripenem (500 mg IV tds)
 - Noninferiority was demonstrated for symptomatic resolution
 - Microbiological eradication was superior for ceftazidime/avibactam

Wagenlehner FM at *alClin Infect Dis* 2016;63:754–62.

Importance of Innate Immunity



<http://www.usbio.net/misc/nobel-prize-in-physiology-or-medicine-2011>

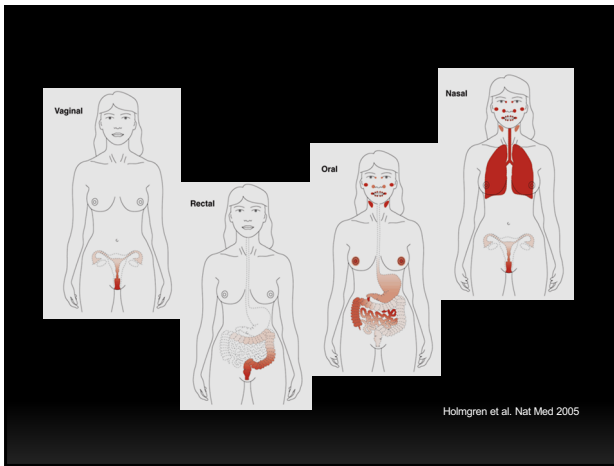
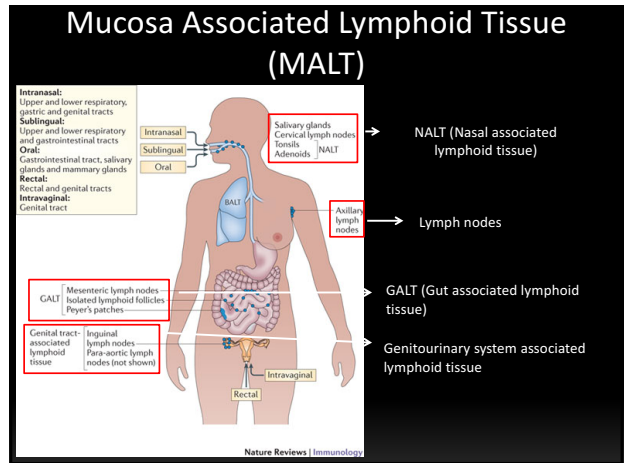
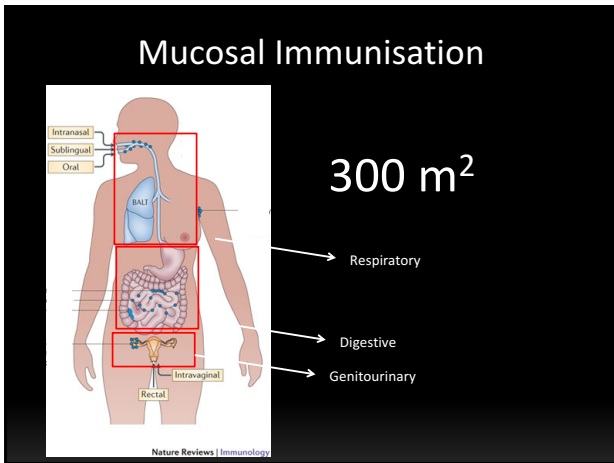


Table 1. Comparative anatomic dissemination of the mucosal SIgA antibody response after different routes of immunization

	Sublingual	Nasal	Oral
Upper respiratory	+++	+++	-
Lower respiratory	+++	+ to +++	-
Stomach	+ / +++	-	+ / +++
Small intestine	+++	-	+++
Colon	?	-	±
Rectum	?	-	±
Genital tract	+++	++	-
Blood	++	+++	+

Çuburu et al. Vaccine, 2007
Czerkinsky et al. Human Vaccines, 2011

Uromune® Multivalent Bacterial vaccine

A suspension of selected strains of 10⁹ inactivated bacteria/mL, for mucosal oral/sublingual administration (spray).

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus vulgaris*
- *Enterococcus faecalis*

Int Urogynecol J (2013) 24:127–134
DOI 10.1007/s00192-012-1853-5

ORIGINAL ARTICLE

Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections versus prophylactic treatment with antibiotics

M. F. Lorenzo-Gómez · B. Padilla-Fernández · F. J. García-Criado · J. A. Mirón-Canelo · A. Gil-Vicente · A. Nieto-Huertos · J. M. Silva-Abuín

Received: 11 April 2012 / Accepted: 3 June 2012 / Published online: 18 July 2012
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Uromune® - 15month Trial

- Observational retrospective study
- 319 patients with prophylactic treatment:
- Uromune: 159 patients treated during 3 months (group A)
- SMX/TMP: 160 patients treated during 6 months (group B)
- Evaluation variables:
 - Number of UTIs before the treatment.
 - Number of episodes of UTI after the initiation of treatment.
 - Number of positives urocultures (UC+).
- Data collection:
 - Before the treatment's beginning.
 - After 3, 9 and 15 months of treatment's initiation.

Uromune® - Patients' Epidemiological Data (before treatment)

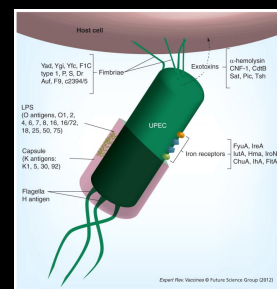
	A (Uromune)	B (SMX/TMP)	P
Age (years)	47.7	48.1	0.8536
Range of age	16-85	16-87	
Months of evolution	56.7	59.2	0.7641
Average of UTI in 6M	3.2	3.1	0.2789
Average of UC+ in 6M	2.4	2.2	0.6392
Average of UTI/month	0.53	0.51	0.6408
Average of UC+/month	0.41	0.36	0.2788

Uromune® - Trial Results

- Average number of episodes of UTI/month.

	Uromune	SMX/TMP	P
Pre	0.53	0.51	0.6408
0 to 3M	0.12	0.53	<0.0001
0 to 9M	0.08	0.41	<0.0001
0 to 15M	0.09	0.38	<0.0001
3 to 9M	0.06	0.35	<0.0001
3 to 15M	0.08	0.35	<0.0001
9 to 15M	0.10	0.34	<0.0001

Vaccination Against Virulence Factors

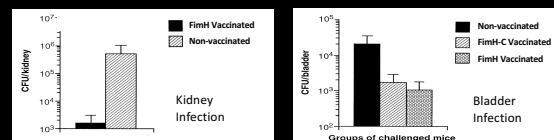


Fimbriae

- **Fimbriae or Pili** are Filamentous organelles expressed on the surface of gram-negative bacteria and mediate attachment to host tissues.
- First described by Duguid et al. in 1955
- Found on a variety of gram-negative bacteria including saprophytes, commensals and pathogens.
- Adhesin (FimH) binds to mannose oligosaccharides attached to uroplakin on surface of urinary bladder epithelium



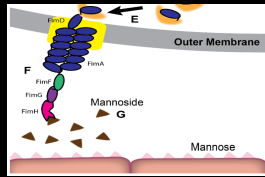
FimH Vaccine



Solomon Langermann et al. Science 276:607-611

- Fimbrial adhesin FimH has been used as an effective vaccine antigen in mouse models.
- Less immunogenicity and lack of safe & effective adjuvant has prevented use in humans.
- Several new safe and efficacious adjuvants for human use, which will facilitate use of FimH vaccines in clinical trials.

Bacterial Adhesion Inhibitors



Spaulding and Hultgren
Pathogens 2016; 5(1), 30.

- FimH-mediated cellular adhesion to mannosylated proteins is critical for uropathogenic *E. coli* (UPEC) to invade bladder epithelium.
- Small-molecule FimH bacterial adhesion antagonists, mannosides, have been developed and awaiting trials.

Bacterial Adhesion Inhibitors

- D-mannose postulated to prevent UPEC binding to urothelium via competitive antagonism
- Single RCT involving 308 women randomised to
 - NFT
 - D mannose
 - No Prophylaxis
- RR 0.24 $p < 0.0001$

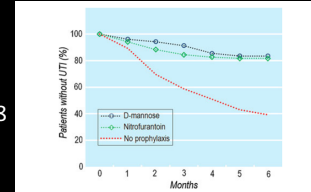
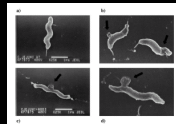


Fig 2 Kaplan-Meier plot showing the percentage of patients remaining cystitis-free during the 6-month clinical trial period

Immune Modulation:

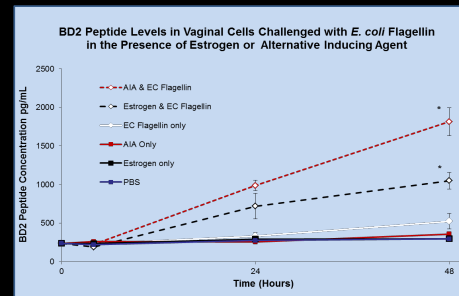
Exogenous Enhancement of Innate Immunity

- Innate immunity provides the immediate defences against infection and is the most important part of the body's response to UTI.
- Over the past 5-years, greater realisation that Estrogen enhances innate immunity. In particular, Estrogen enhances secretion of antimicrobial peptides (AMPs) in bladder and vaginal cells
- Antimicrobial peptides are:
 - Gene encoded 'natural antibiotics' secreted at epithelial surfaces.
 - Small, +ve charged (cationic) molecules
 - Broad spectrum (kill gram +ve & -ve bacteria, fungi & some viruses)
 - Target & disrupt microbial membranes



Membrane disruption in bacteria incubated with antimicrobial peptide

Exogenous Enhancement of Innate Immunity



In Newcastle University, Hyaluronic acid has been used to induce innate immune defences.

Probiotics

- Probiotic therapy and faecal transplant used successfully in treating severe *C. difficile* and pseudomembranous colitis.
- UTIs often preceded by presence of pathogenic microbiota in the vagina and urethra.
- Possible prevention strategy could be to normalise vaginal and urethral microflora by direct administration of probiotics
- Possibilities:
 - Inoculate asymptomatic bacteruria (ABU) strains of *E. coli* into bladder
 - Use commensal Lactobacilli in vagina to 'out-colonise' *E. coli*
 - Oral probiotics to displace pathogenic *E. coli* in gut



Probiotics

- Randomised study vs placebo of 100 women with a history of recurrent UTI
- UTI occurred in 7/48 15% of women receiving Lactin-V vs 13/48 27% of women receiving placebo (relative risk [RR], 0.5)
- High-level vaginal colonisation with Lactobacillus was associated with significant reduction in rUTI
- Authors concluded that "Lactin-V after treatment for cystitis is associated with a reduction in recurrent UTI."
- EAU guidelines suggest that Lactobacillus may be used in rUTI where suitable preparations available

Gastrointestinal Decolonisation

- Transplant pyelonephritis caused by ESBL *E. coli* intestinal colonization is a problem in renal transplant patients.
 - Decline in renal function with rUTI can result in ESRF necessitating further transplantation
 - But can't transplant while still colonised.
- Recently, first case report published of a patient with recurrent episodes of transplant pyelonephritis decolonized for ESBL-producing *E. coli* with a faecal microbiota transplantation.
 - Two weeks after faecal transplantation the rectal culture became ESBL negative.
 - During the follow up the patient did not develop symptoms of a UTI.

Singh R et al. Clin. Microbiol. Infect. 2014, 20, 977–978

Conclusions

- rUTI is prevalent in adult women.
- Non-antibiotic treatments preferable for recurrent UTI *where possible...*
- Several treatment options exist for rUTI with varying levels of supporting evidence.
- Further RCTs are needed to evaluate these treatments.
- New non-antibiotics treatments on the horizon

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