

Recurrent & Chronic UTI in Adult Women: Diagnosis & Management

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Medical Director, Convatec Group

First a bit about me

- Consultant Urologist at Mid Yorkshire Hospitals NHS Trust
- Medical Director for Global Continence Care & Ostomy Care, Convatec Group
- Training:
 - Qualified in Manchester
 - Urology training in Yorkshire and Northeast (Newcastle)
 - Subspecialty training at Duke University, NC, USA and University of British Columbia, Vancouver, Canada.
 - PhD in Immunology – Female Recurrent UTI
 - Fellowship in Female Urology and Reconstructive Surgery
- Interests in recurrent UTI, incontinence & bladder problems
- Member of Medical Panel for Bladder Health UK
- Specialist advice to NICE regarding UTI

What is the definition of recurrent UTI (rUTI)?

- No universally accepted definition
- 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

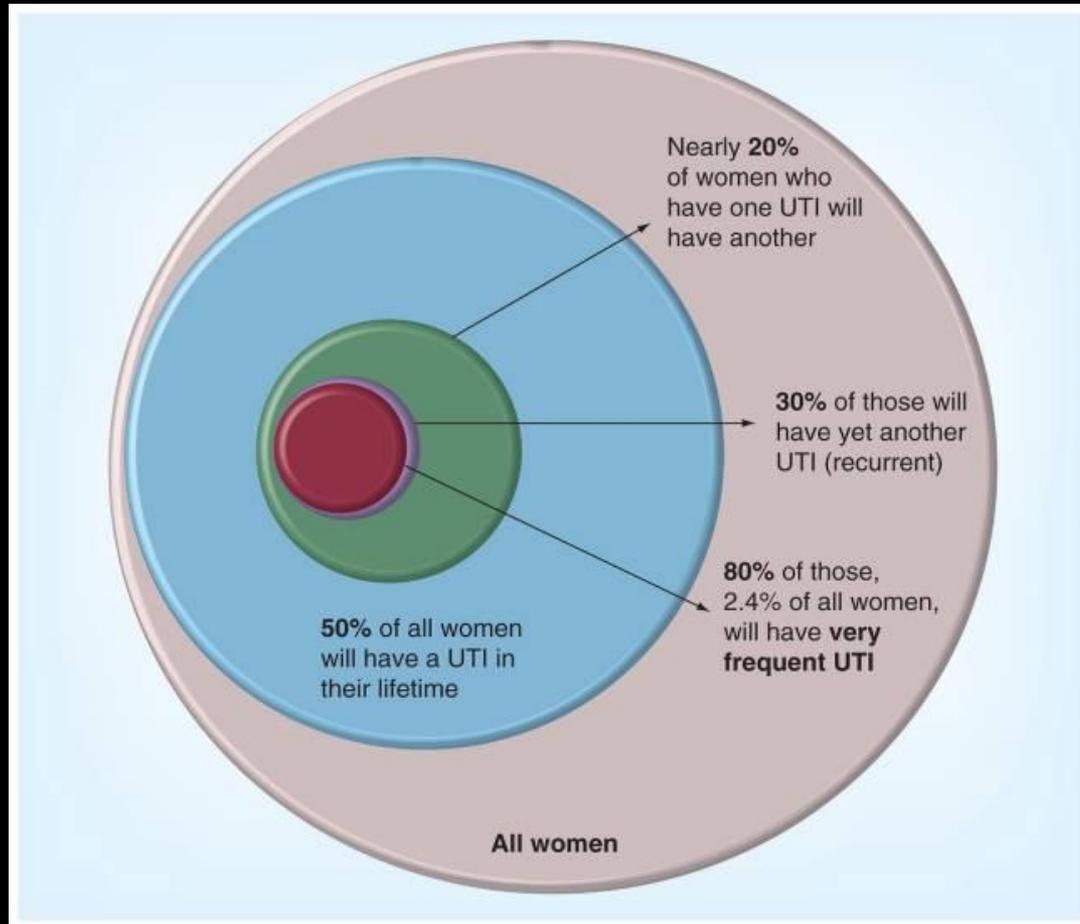
Mabeck *et al* Postgrad Med J 1972.

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

Common Problem



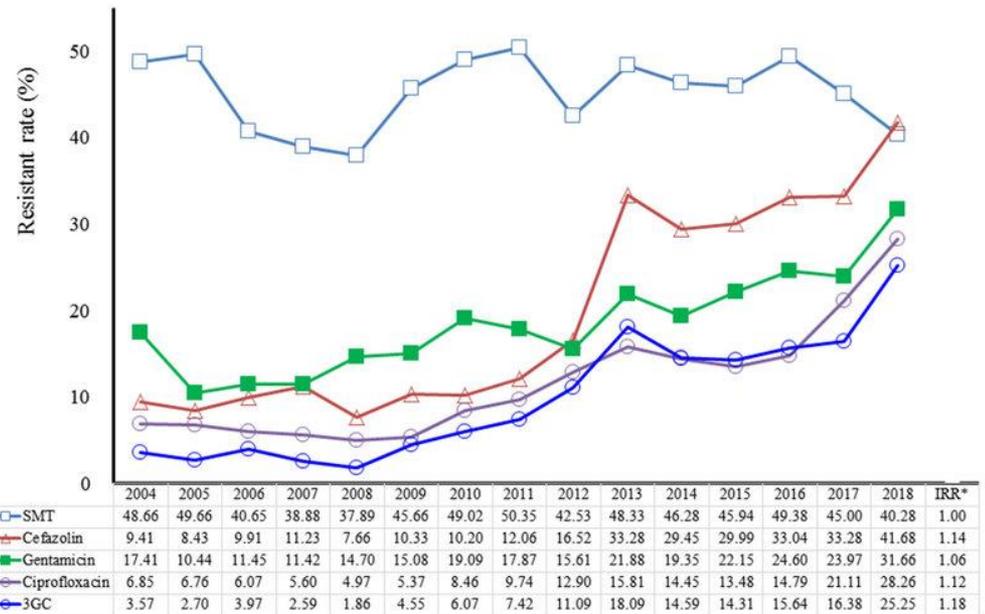
Antibiotic Resistance in UTI

Nitrofurantoin <1.5% – 13.3%
Fosfomycin <1.5%

Amoxicillin-clavulanic acid
 Developed countries 3.1% – 40%
 Developing countries 48% – 83%

Ciprofloxacin
 Developed countries 5.1% – 39.8%
 Developing countries 55.5% – 85.5%

Trimethoprim-sulfamethoxazole
 Developed countries 14.6% – 37.1%
 Developing countries 54% – 82%



Kot, B. *PJM* 68 (2019): 403 - 415.

Chen, H. *et al* (2020). *Antibiotics*. 9. 501.

Global Risks 2014 Ninth Edition

 Societal
Risks



NAME OF THE TEST : CULTURE SENSITIVITY

ON CULTURE: *Escherichia coli* >10⁵ cfu/ml
 ANTIBIOTIC SUSCEPTIBILITY TESTING

FIRST LINE DRUGS	SENSITIVITY	SECOND LINE DRUGS	SENSITIVITY
AMPICILLIN	R	AMIKACIN	R
CEFUROXIME	R	NETILMICIN	R
CEFTAZIDIME	R	GENTAMICIN	R
CEFTRIAZONE	R	IMIPENEM	R
CEFEPIME	R	MEROPENEM	R
CEFIXIME	R	LEVOFLOXACIN	R
CEFOPERAZONE+ SULBACTAM	R	OFLOXACIN	R
AMOXICILLIN+CLAVULUNATE	R	NORFLOXACIN	R
PIPERACILLIN+TAZOBACTAM	R	NITROFURANTOIN	R
CIPROFLOXACIN	R	TIGECYCLINE	I
FOSFOMYCIN	R	POLYMICIN B	I
COLISTIN	I		

NOTE: R- RESISTANT, I- INTERMEDIATE SENSITIVE, S- SENSITIVE
 *COUNTS >10⁵ CFU/ML ARE CONSIDERED SIGNIFICANT.
 SIGNIFICANCE TO BE CORRELATED CLINICALLY.



Dr Avreen Singh Shah MC...
 @dr_avreen

Where are we heading to?.
 Options for such a patient

- @niteshkuro
- @GoumasUrologia
- @ArunkumarDr
- @DrParimalGharia
- @Mohamedendourol
- @AnilElhence @drnmreddy
- @optionurol @UroZedman
- @docdilipmishra @so_uro

#MedTwitter

5:43 am · 30 Oct 2022 · Twitter for Android

4 Retweets 2 Quote Tweets 25 Likes



Dr Anish K ... @op... · 30 Oct

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25



This Talk

- 3 Sections
 - How bacteria cause infection
 - Diagnostics
 - Management

- Happy to take questions at the end

How Bacteria Cause Infection

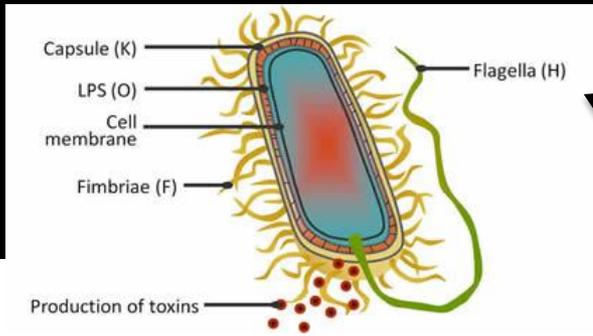
2. How bacteria cause infection

- a) Colonisation of adjacent surface
 - Vagina
 - Peri-urethra
 - Penile urethra/glans
- b) Transfer to bladder
 - Planktonic movement (flagella)
 - Proliferation within biofilm
- c) Attachment to bladder epithelium
 - Expression of adhesins (FimH)
- d) Proliferation
 - Acquisition/expression of virulent genotype/phenotype
- e) Invasion
 - Excitement of inflammatory response

a) Colonisation of adjacent epithelial surface

- Spread from ano-rectum
- Overwhelm vaginal defensins and establish 'niche' within biofilm
- 'Receptive' or 'permissive' vaginal cells favour *E. coli* attachment and proliferation
 - Genetic susceptibility (polymorphisms)
- Adjuncts
 - High pH
 - Low oestrogenisation

b) Transfer to bladder



Flagella

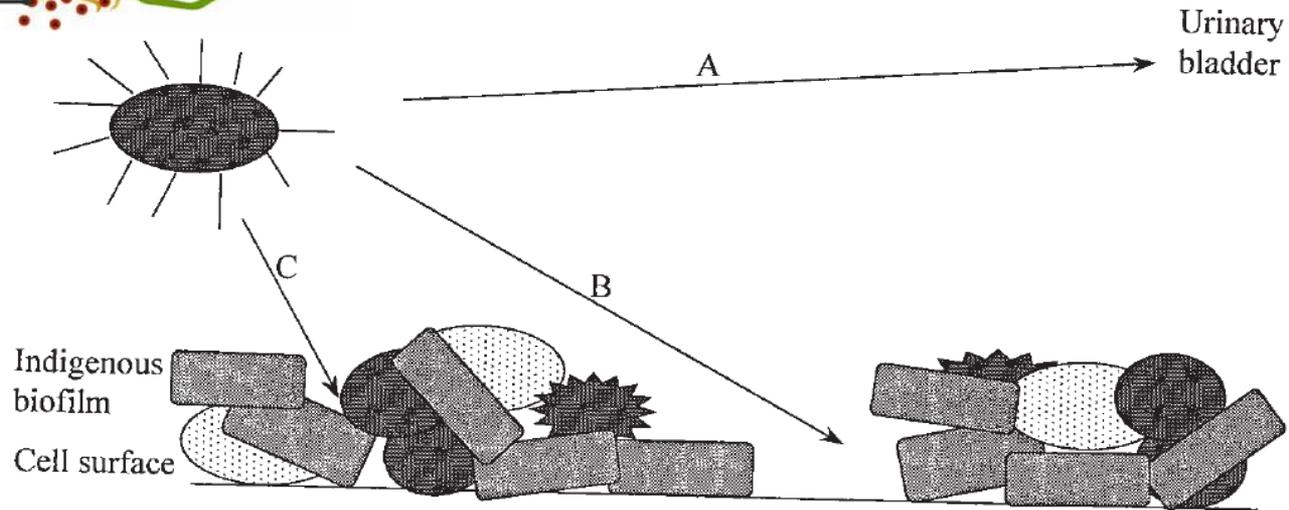


FIGURE 1. When fimbriated, uropathogenic *Escherichia coli* enters the urogenital mucosa from the intestine, it may do so by spreading along the mucosa or by coming directly from the fluid phase into the bladder (A). It may also attach itself to the bare surface of a vaginal epithelial cell (B) or become part of the cell's bacterial biofilm (C), in which it either remains or becomes the dominant organism. When a patient has a bladder infection, the urogenital flora is invariably dominated by the infecting pathogen. The biofilm shown represents that from healthy premenopausal women. Lactobacilli (rods) dominate and coexist with gram-positive cocci (dark open and spiked circles representing capsule) and coliforms (clear, oval shape).

c) Attachment to Bladder Mucosa

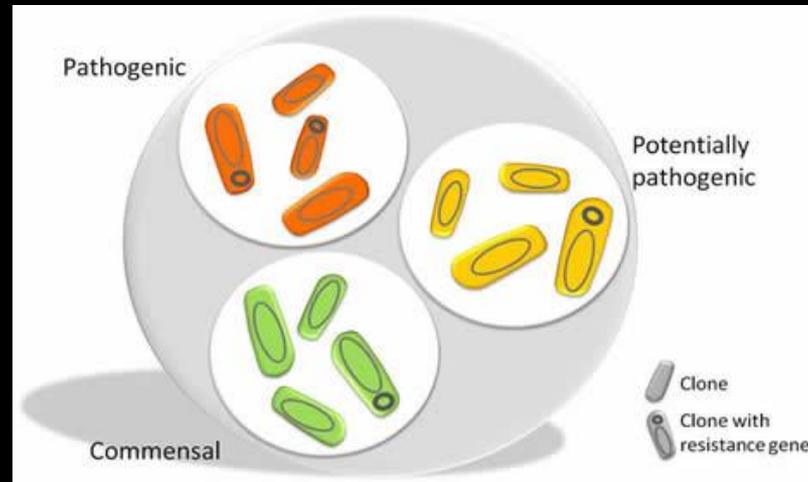
Bacterium



Uroplakin on surface of bladder epithelial cell

Fimbriae
Type 1
'p'

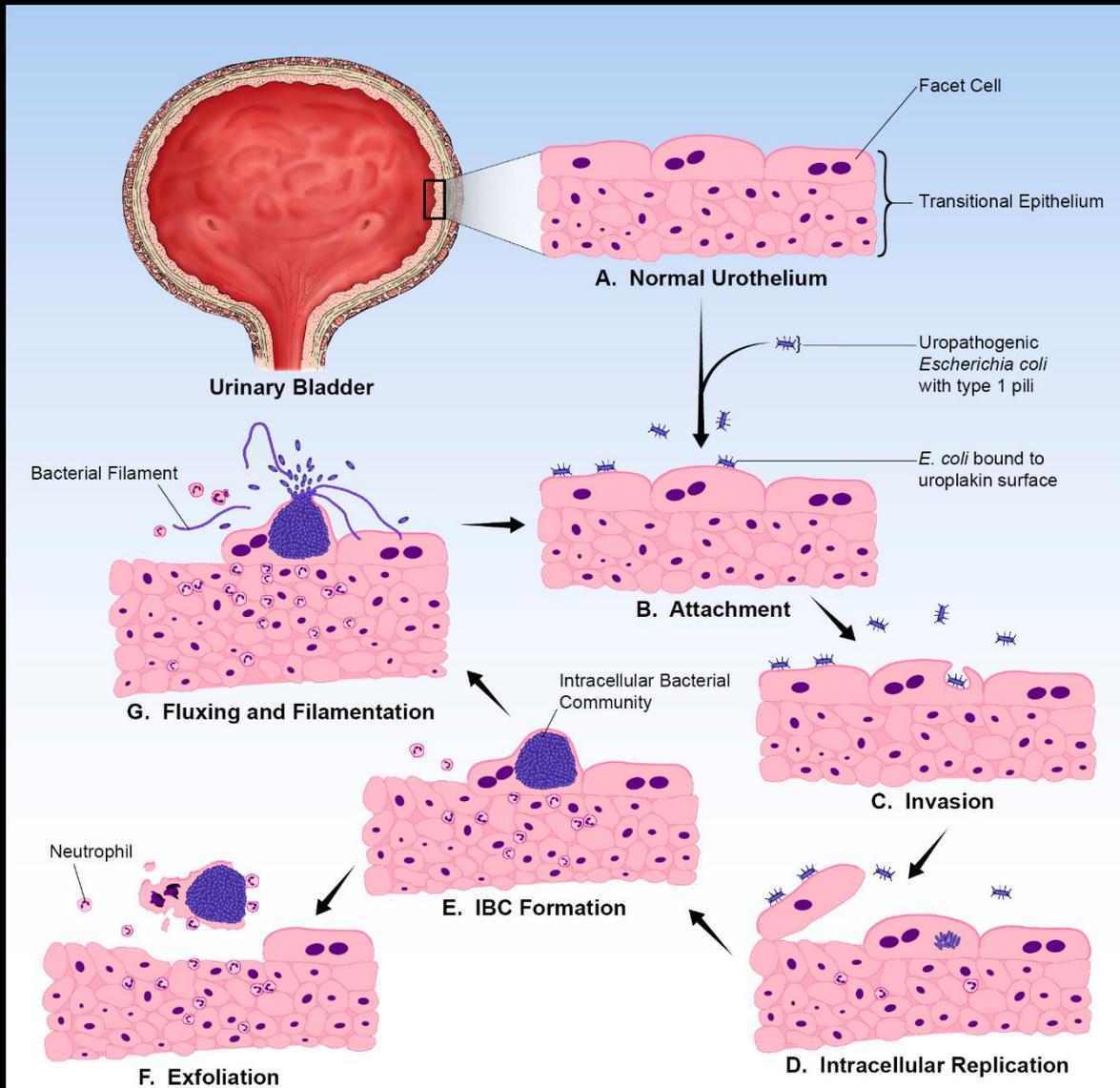
d) Acquisition of invasive and proliferative phenotype in *E. coli*



- Expression from existing genome
 - Previously ‘hidden’ until bladder entered
- Acquisition of new genetic material
 - ‘Horizontal’ gene transfer - genes from other bacteria
 - ‘Vertical’ mutation - persistence and proliferation of bacteria with survival advantage (‘survival of the fittest’)

e) Invasion – setting off the host inflammatory response

- Activation of Toll-like receptors (TLR) on the bladder epithelial surface
- Release of haemolysins to drill into bladder cell
- Release of endotoxins – causes temperature
- Possible establishment of dormant intra-epithelial forms (L-forms)



Diagnostics

Diagnostics in Simple Cystitis

Symptoms

- Symptoms are highly predictive - Frequency / pain / Dysuria / Haematuria in the absence of vaginal discharge is 80% accurate Bent JAMA 2002
- Combined figures from nine studies reviewed by Scottish Intercollegiate Guidelines Network (SIGN) showed that 70% of non-pregnant women under 50 with symptoms of UTI had bacteriuria www.sign.ac.uk
- Empirical treatment with an antibiotic for otherwise healthy women presenting with severe or ≥ 3 symptoms of UTI.

When to culture?

SIGN guidelines recommend:

“Take urine for culture to guide change of antibiotic for patients who do not respond to trimethoprim or nitrofurantoin.”

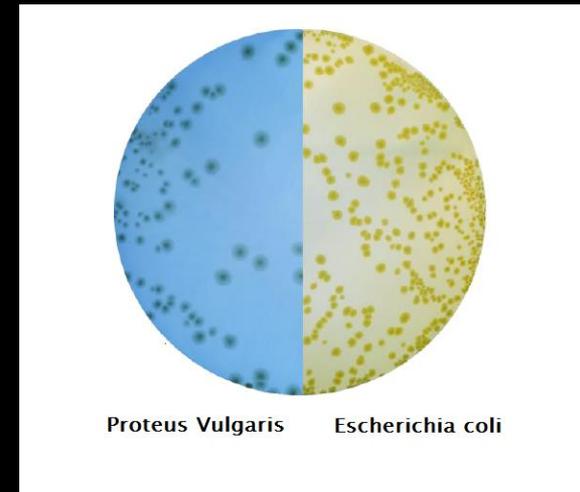


NICE are a bit less clear:

- When treating take account of: “previous urine culture and susceptibility results”
- If a urine sample has been sent for culture and susceptibility testing and an antibiotic prescription has been given, review the choice of antibiotic when microbiological results are available

History of Urine Culture

- Studies from the 1950s remain the basis of quantification - $\geq 10^4$ cfu/ml
(Kass EH – Bacteriuria and the diagnosis of infection of the urinary tract. Arch Int. Med 1957)
- *E.coli* targeted organism, uncomplicated, non-pregnant, pre-menopausal women
- Manual microscopy – VERY labour intensive, prone to errors.
- Assumptions – practically, growth of $<10^5$ cfu/ml in a non pregnant female taken as representing contamination



Bacteria growing on Cystine Lactose Electrolyte Deficient (CLED) Agar

Current Methods in Urine Culture

- Automated microscopy – Particle recognition, flow cytometry
- Automated inoculation of samples – Kiestra
- Still use selective agar.
- Incubate for 24hrs, either direct sensitivities are performed (if >30 white cells) or selected sensitivities if culture reveals $\geq 10^4$ cfu/ml PURE growth
- Still use historical quantification methods $\geq 10^4$ cfu/ml PURE growth.
- No strict protocol for collection.



Problems with Standard Cultures

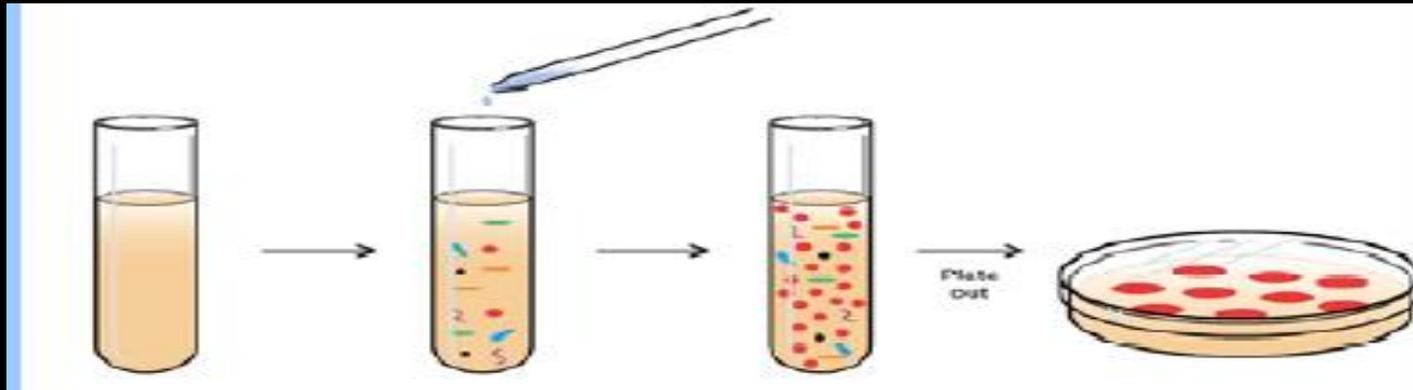
- Original Kass diagnostic criteria based on a small number of pregnant women suffering from pyelonephritis. Threshold recognised as too high in studies as far back as 1980s.

Stamm *et al.* N Engl J Med. 1982; 307(8):463-8.

- Standard urine culture is **optimised for growing *E.coli*, other UTI causing bacteria can easily be missed.**
- Compared to Enhanced quantitative urine culture (EQUC), which cultures in 3-different types of medium:
 - Standard cultures missed 67% of uropathogens overall
 - Standard cultures missed 50% in participants with severe urinary symptoms

Liquid Broth & Enrichment Medium Culture

- Liquid medium may better replicate liquid environment in the bladder
- The term enrichment is used to describe fluid medium that increase the number of a pathogen by containing enrichments and substances that improve bacterial growth



Medium contains select nutrients to help promote growth of UTI organisms

Sample is added to the medium

UTI causing organisms can multiply more easily

Enriched sample is plated onto appropriate agar medium.

Molecular Techniques Support Validity of Treatment Based on Symptoms

- Belgian primary care study did qPCR and culture for *E. coli*.
- Urine from 220 women with UTI symptoms and 86 without.
- Symptomatic group:
 - 80.9% urine cultures were positive.
 - 95.9% were *E. coli* qPCR-positive.
- Control group:
 - 10.5% urine cultures were positive.
 - 11.6% were *E. coli* qPCR-positive.
- Authors concluded that almost all women with typical urinary symptoms & negative culture still had a *E. coli* infection

Heytens et al. Clinical Microbiology and Infection. 2017

Chronic Urinary Tract Infection Campaign (CUTIC)

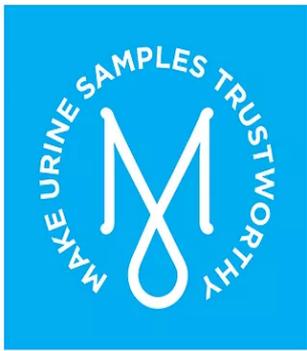
CUTIC was established in 2016 to campaign for recognition of the diagnosis of chronic urinary tract infection:

- To define NICE Guidelines for cUTI where none are currently available and a consistent quality standard for the treatment of recurrent UTI.
- For improvement in testing and treatment, not just for those with chronic urinary tract infections but all those diagnosed with UTI
- To support and promote the work of specialist treatment centres in the UK and internationally
- To support and promote the emerging scientific research into chronic urinary tract infections and the urinary microbiome disproving the oft stated “urine is sterile”

CHRONIC
URINARY TRACT INFECTION
CAMPAIGN



contactcutic@gmail.com
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www.cutic.co.uk

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The main charities behind the MUST Campaign are:



The Urology Foundation believes that better research, training and education leads to better diagnosis, treatment and care for all the millions of people suffering from a urological condition or cancer. These include cancers and diseases of the bladder, kidney, prostate and testes, male infertility, erectile dysfunction and incontinence.



MAMA Academy aims to end all preventable stillbirths in the UK through raising awareness of Babyloss and stillbirth prevention methods to professionals and empowering parents with safer pregnancy information, supporting those bereaved throughout mortality investigations and funding and assisting medical research into the prevention of baby loss. We also aim to provide every expectant mother with a MAMA Wellbeing Wallet by 2020 to save more babies lives



Bladder Health UK

Bladder Health UK is a national, patient based support organisation that provides resources to help sufferers live positively with chronic bladder illnesses. Working in partnership with key stakeholders we aim to ensure people with bladder health issues can expect a consistent level of healthcare support and treatment; encourage research into new treatments and personal management strategies; and educate and inform industry, academia and the Health Service through real life experiences.

The MUST Campaign is also supported by:

[Bladder and Bowel UK](#)

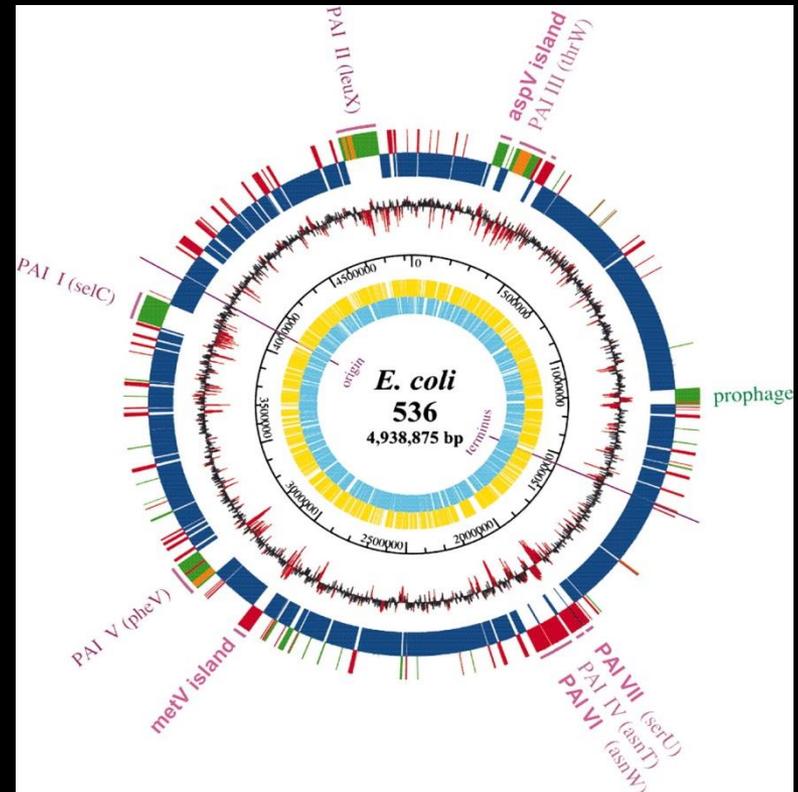
[CUTIC - Chronic Urinary Tract Infection Campaign](#)

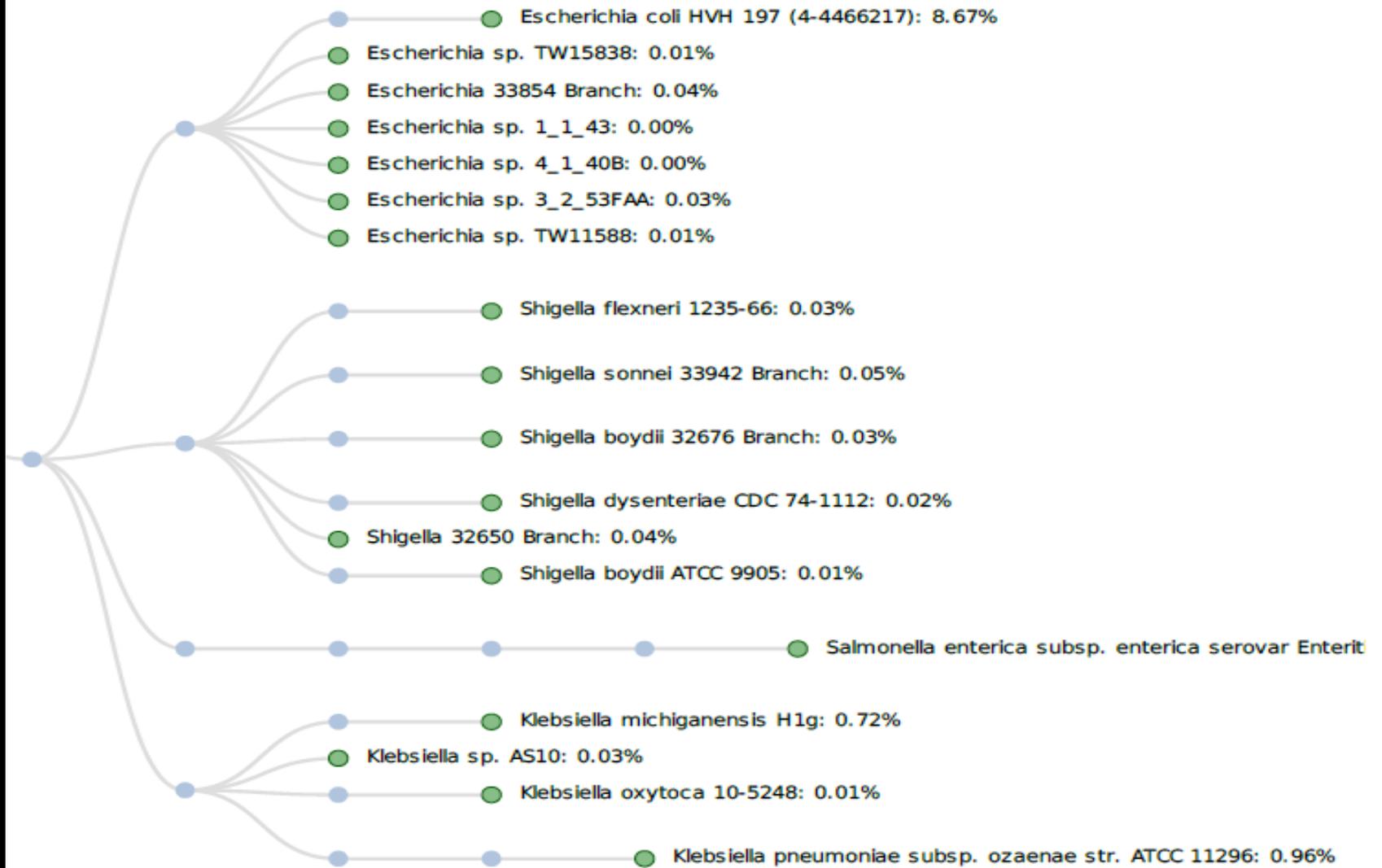
[The Patients Association](#)

[ERIC \(Children's Bowel and Bladder\)](#)

Enhanced Genotyping of Pathogens

- Large numbers of *E. coli* strains have had their genome sequenced. Identifying specific 'pathogenicity islands' i.e. genes present in UTI strains but not commensal ones.
- Pathogenicity information can be collected and allow the use of highly specific treatments that attack pathogens but not commensals





Other Investigations

- Many clinicians choose USS and cystoscopy in order to rule out a complicated UTI
- Persisting inflammatory cystitis often exhibits non-visible haematuria despite resolution of UTI
- Patients are often keen to know “nothing is wrong”
- Clinicians tend to remember specific cases

What does published literature say?

- rUTIs are common among healthy women and most have normal anatomical / physiological LUT

Hooton Int J Antimicrob Agents 2001

- Very little evidence exists regarding the role of imaging and cystoscopy – mostly case series or expert opinion

- No consensus or consistency among clinicians

Franco Best Pract Res Clin Obstet Gynaecol 2005

Van Horst J Urol 2001



What does published literature say?

- **Engel et al. J Urol 1980** – there is a role for cystoscopy but not IVU – 153 patients – 89% of IVUs = NAD
- **Nickel et al. Can J Surg 1991** – a role for investigation with imaging and cystoscopy – 186 women - >20% abnormalities, >10% surgical intervention
- **Van Haarst et al. Urology 2001** – no role for investigation – 100 women <40yrs – 1% abnormal imaging 22% abnormal cystoscopy -“never relevant”
- **Dason et al. CUAJ 2011** – “seems unnecessary to perform cystoscopy on all women presenting with recurrent uncomplicated UTI given this low pre-test probability”
- **Pat et al. Int Urogynecol J 2022** – The routine use of cystoscopy and ultrasound in female patients with rUTIs should not be recommended as they yield few abnormalities and lead to additional costs.

What about the guidelines?

- “An extensive routine workup including cystoscopy, imaging, etc., is not routinely recommended as the diagnostic yield is low. “
- “However, it should be performed without delay in atypical cases, for example, if renal calculi, outflow obstruction, interstitial cystitis or urothelial cancer is suspected.”

EAU Guidelines - Urological Infections 2022

- “No evidence regarding criteria for referral or which investigations to undertake”
- “Adults with a recurrent upper urinary tract infection (UTI) or recurrent lower UTI where the cause is unknown are referred for further investigation.”

SIGN guideline 88 – 2012 (No mention in SIGN 160 – 2020)

NICE Draft UTI in Adults Quality Standard 2022

- “Consider non-urgent referral for bladder cancer in people aged 60 years and over with recurrent or persistent unexplained urinary tract infection.”

NICE Guidance for referral for suspected urological cancer 2021

Summary

- No consensus regarding the investigation of rUTI
- Literature amounts to case series only – majority suggest investigation is unnecessary for the majority
- Guidelines not uniform
- Majority of positive findings not clinically significant

When to refer (a pragmatic approach)?

Urgent referral :

- **Recurrent urinary tract infections (rUTI) associated with haematuria (visible or non-visible) for investigations to exclude urological cancer**

Routine referral:

- Women who have a risk factor for an abnormality of the urinary tract:
 - a past history of urinary tract surgery or trauma
 - a past history of bladder or renal calculi
 - obstructive symptoms such as straining, hesitancy, poor stream
 - urea splitting bacteria on culture of the urine such as Proteus or Yersinia
 - **persistent bacteriuria despite appropriate antibiotic treatment**
 - a past history of abdominal or pelvic malignancy
 - symptoms of a fistula such as pneumaturia
- Women who are immunocompromised or who have diabetes
- Women who have a known abnormality of their renal tract who might benefit from surgical correction (E.g. cystocele, vesicoureteric reflux, bladder outlet obstruction , etc.)
- Women who have not responded to preventive treatments

Management

Management

- Non-antibiotic (and non-invasive)
 - Cranberry Products
 - D-Mannose
 - Topical Oestrogens
 - Methanamine Hippurate
 - Vaccines
- Antibiotics
 - Prophylactic Antibiotics
 - Self Start Therapy
 - Extended Courses
- Intravesical agents
 - GAG Replacement
 - Gentamicin
- Natural flora modulation
 - Probiotics
 - Gastrointestinal decolonisation

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)

Tastes Good.

Good For You.



D-Mannose

- Mannose inhibit bacterial adhesion but urine conc. not high enough with oral preparations
- 1 randomised trial of 308 pts with rUTI:
 - D-Mannose 2g in 200mls water o.d. for 6-mths
 - D-Mannose vs Nitrofurantoin prophylaxis vs Placebo
 - Recurrent UTI in:
 - D-Mannose – 14.6%
 - Nitrofurantoin – 20.4%
 - Placebo – 60.8%
 - Authors conclude “D-mannose may be useful for UTI prevention”



Topical Oestrogens

- Falling oestrogen levels lead to a change in vaginal flora and pH
- Local oestrogen can reverse this without adverse effects of systemic oestrogen

Esposito Gynaecological Endocrinology 1991

- Systematic review found no reduction in UTIs with oral oestrogen but showed vaginal preparations superior to placebo (RR 0.25/0.64)

Perrotta Cochrane Database 2008

Methanamine Hippurate

- Methanamine has antibacterial properties - hydrolysed to formaldehyde in acid urine
- Some studies report reduction in symptomatic UTIs (RR 0.24)
- Does not appear effective in patients with neuropathic bladder or renal tract abnormalities

ALternatives To prophylactic Antibiotics for the treatment of Recurrent urinary tract infection in women (ALTAR)



- A multicentre, pragmatic patient-randomised non-inferiority trial comparing Methenamine Hippurate with low dose antibiotic prophylaxis for the prevention of rUTI in women both during a 12-month period of use and in the subsequent 6-months following completion of the prophylactic medication.
- Follow-up assessments took place at 3-month intervals for 18 months . At each visit, pts were asked about the occurrence of any UTIs, treatment compliance and adverse events.
- In all other respects participant care followed standard pathways in participating secondary care NHS sites
- Between June 2016 and June 2018, 240 participants were randomised. The modified intention to treat (mITT) analysis comprised of 205 (85%) participants:
 - 102 – antibiotic prophylaxis
 - 103 – methenamine hippurate

Incidence of Antibiotic Treated UTI

	Number included in analysis	Incidence rate (95% CI)	Absolute difference (90% CI)	Incidence rate ratio‡ (95% CI)
Modified intention-to-treat				
Antibiotic prophylaxis	102	0.89 (0.65-1.12)	0.49 (0.15-0.84)†	1.52 (1.16-1.98)
Methenamine hippurate	103	1.38 (1.05-1.72)	<1	
Intention-to-treat				
Antibiotic prophylaxis	120	0.88 (0.65-1.11)	0.53 (0.20-0.86)	1.58 (1.24-2.03)
Methenamine hippurate	120	1.40 (1.08-1.73)	<1	
Per-protocol				
Antibiotic prophylaxis	84	0.87 (0.61-1.13)	0.42 (0.05-0.79)	1.44 (1.02-2.02)
Methenamine hippurate	86	1.29 (0.93-1.66)	<1	
Strict per-protocol				
Antibiotic prophylaxis	82	0.83 (0.58-1.08)	0.30 (-0.08-0.67)	1.35 (1.06-1.71)
Methenamine hippurate	71	1.13 (0.76-1.50)	<1	

†Primary outcome. ‡ Adjusted for menopausal status (pre and peri/post), prior UTI frequency (<4 and ≥4) and site (random effect).

**Methenamine hippurate was non-inferior to antibiotic prophylaxis.
This result was confirmed in all sensitivity analysis populations**

Vaccines

- Uro Vaxom[®] (OM-89) is only one recommended by EAU guidelines EAU Guidelines Urological Infections 2015
- 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.

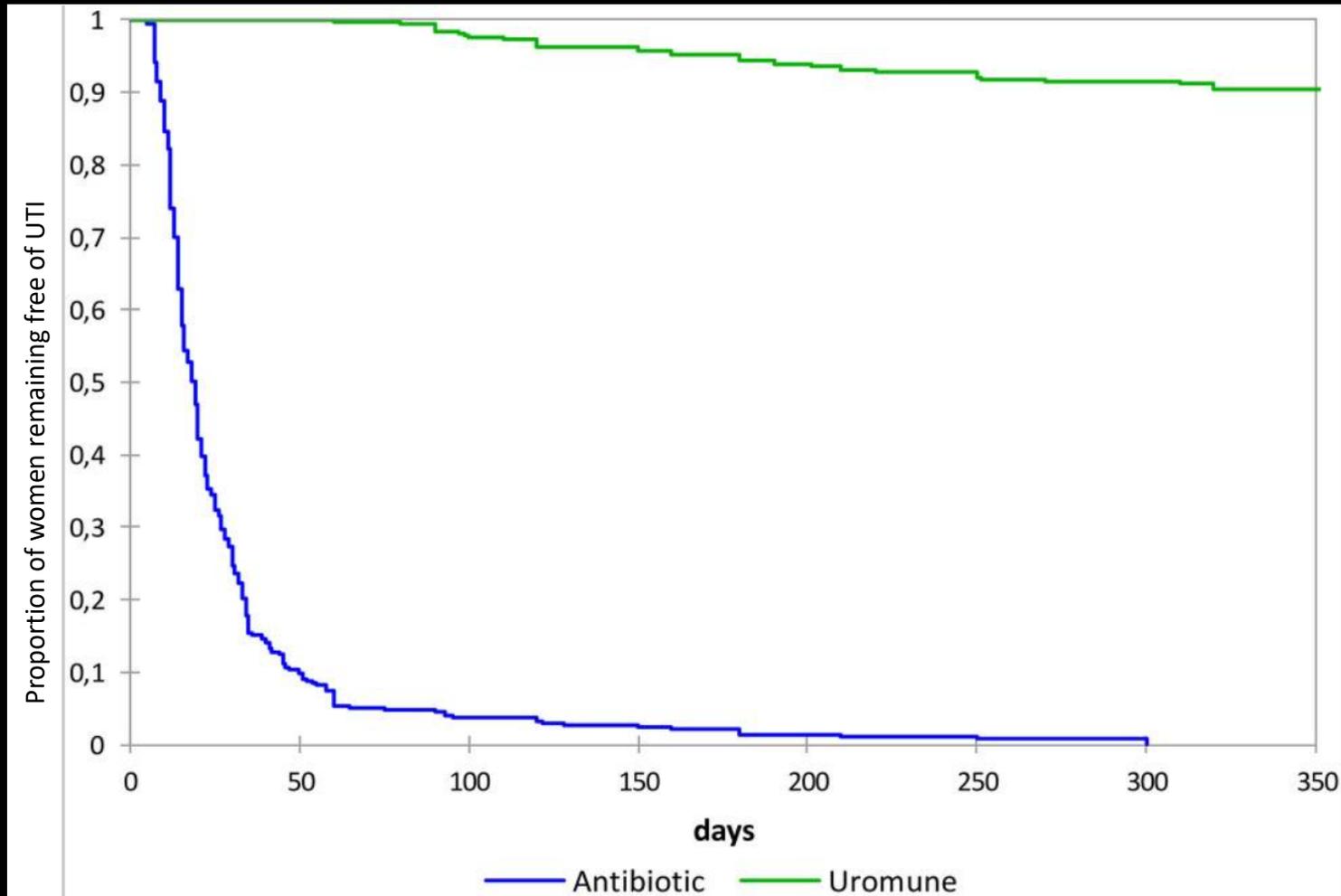
1st author	Year of publication	Index n/N	Control n/N	Jadad score		RR (95% CI)
OM89						
Tammeh	1990	38/61	49/59	2		0.75 (0.60, 0.94)
Schulman	1993	29/82	54/78	4		0.51 (0.37, 0.71)
Magasi	1994	19/58	42/54	2		0.42 (0.28, 0.63)
Bauer	2005	93/231	122/222	3		0.73 (0.60, 0.89)
D+L Subtotal (I-squared = 69.3%, p = 0.021)						0.61 (0.48, 0.78)
M-H Subtotal					0.64 (0.56, 0.73)	
Urovac						
Uehling	1997	39/61	22/30	5		0.87 (0.65, 1.16)
Uehling	2003	22/36	14/18	3		0.79 (0.55, 1.13)
Hopkins	2007	32/50	21/25	3		0.76 (0.58, 1.00)
D+L Subtotal (I-squared = 0.0%, p = 0.787)						0.81 (0.68, 0.96)
M-H Subtotal					0.81 (0.68, 0.96)	

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
- Observational retrospective study
- 669 patients with prophylactic treatment:
- Uromune: 360 patients treated for 3 months (group A)
- SMX/TMP: 339 patients treated for 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+).



Uromune[®] - Study Results



	Free of new UTI after the prophylactic treatment	
	Yes	No
Patients treated 3 months with Uromune	325	35
Patients treated 6 months with antibiotics*	0	339

*SMX/TMP or Nitrofurantoin.

The E.mbrace Study



- RCT to evaluate an investigational single dose vaccine called ExPEC9V for prevention of invasive E.coli Disease (IED)
- Participants must be
 - Adults 60 years of age or older
 - Have had a urinary tract infection in the past 2 years.
- All participants will be randomly assigned into either:
 - Active vaccine group (receive ExPEC9V) *or*
 - Placebo vaccine group
- Study will be conducted in N. America, Europe & Asia-Pacific with 3-year follow-up.
- The Investigational Vaccine Group will be enrolled in 2 parts
 - Part 1 will enroll 9,278 participants
 - There will be an interim analysis after 500 participants recruited
 - Part 2 will then enroll an additional 9,278 participants if the interim analysis does not indicate futility.

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
 - 79% risk reduction for recurrence while on prophylaxis
 - 18% risk reduction for recurrence after completing prophylaxis

Albert *et al.* Cochrane Database 2004

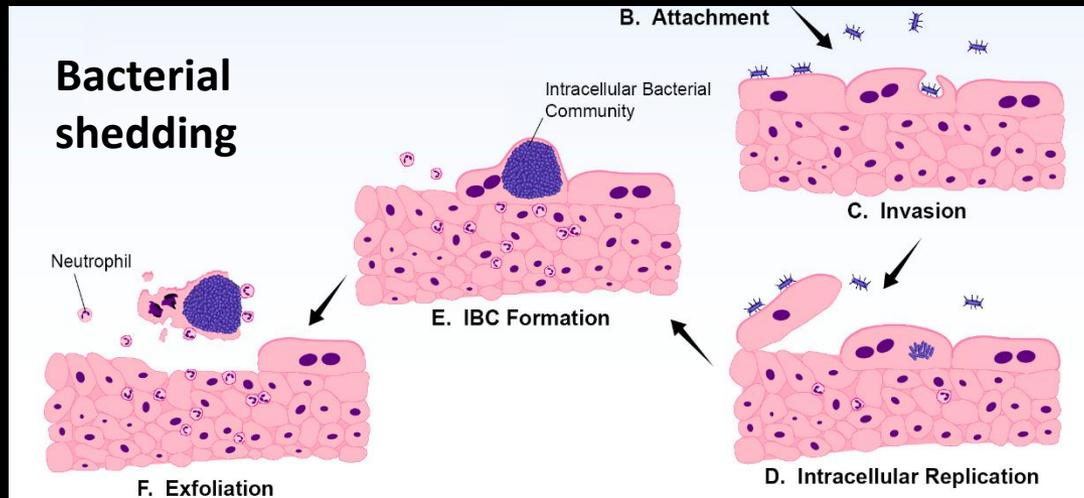
- Single randomised study found prophylactic nitrofurantoin superior to oestrogen

Raz *et al.* Clin Infect Dis 2003

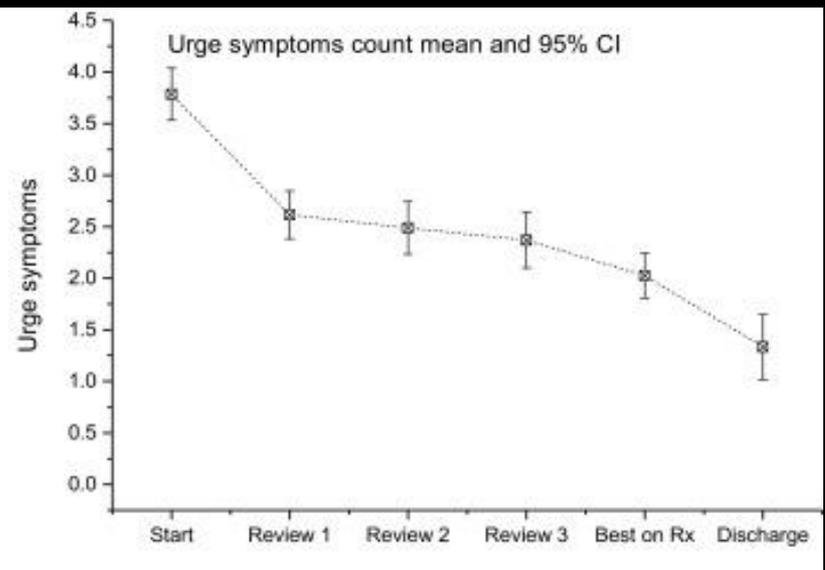
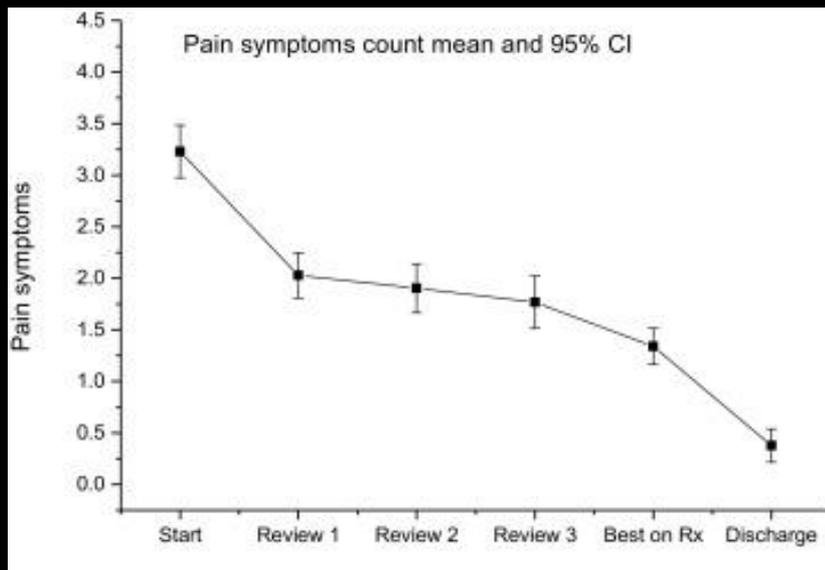
Self Start Antibiotics

- 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.

Extended Course Antibiotics

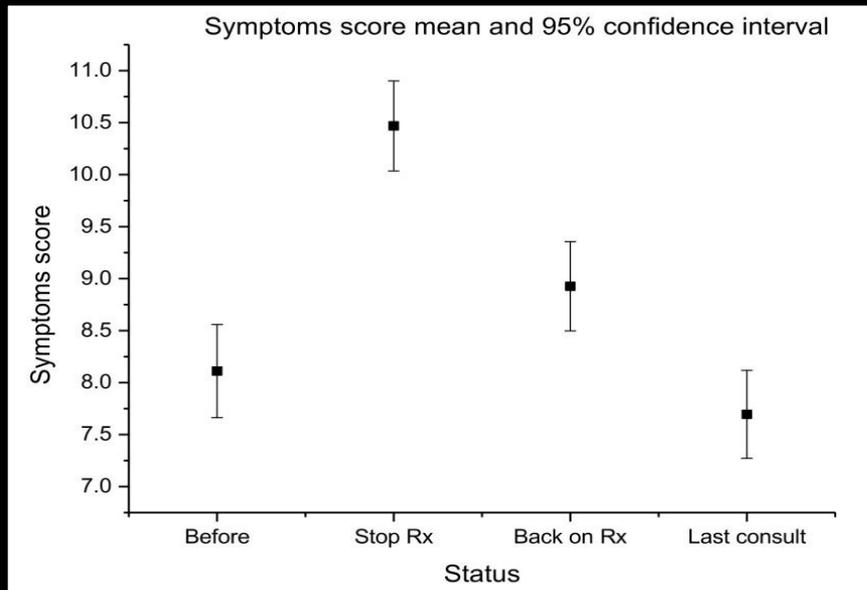


- Bladder cells have slow turnover (3-months)
- Bacteria can hide within bladder cells and are exfoliated ('shed') giving 'flare ups'
- Longer courses of antibiotics prevent bacteria from replicating and re-entering bladder
- Allows time for complete removal of bacteria



Swamy *et al* Int Urogynecol J. 2018; 29(7): 1035-43

- 624 Females, average of 6.5 yrs symptoms
- Full-dose abx: cefalexin, nitrofurantoin, or trimethoprim plus methenamine hippurate.
- Treatment length ranged from 9 -15 months (but some kept going....)
- Treatment was associated with a reduction in:
 - lower urinary tract symptoms (F = 98; p = 0.0001),
 - frequency (F = 75; p = 0.0001),
 - urgency (F = 90; p = 0.0001),
 - pain (F = 108; p = 0.0001),
 - voiding symptoms (F = 10; p = 0.002),



Swamy *et al* Int Urogynecol J.
2019; 30(3):409-414

- 221 Patients (210 F: 11 M), average of 6.5 yrs symptoms
- Crossover study showed significant improvement in lower urinary tract symptoms.
- After unplanned treatment cessation, 199 patients (90%; female = 188; male = 9) reported deterioration.

Intravesical Treatments

- GAG layer damage may play a role in rUTI.
- Hyaluronic acid (HA) and chondroitin sulphate (CS) used to enhance protective function of urothelium.
- 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

Goddard JC, Janssen DAW. Int Urogynecol J. 2018

- **“Further studies needed to validate this promising treatment...”**

UTI Prevention: Gentamicin Instillation

- 22 patients before and after intravesical gentamicin
 - Fewer symptomatic UTI's (median 4 vs. 1 episodes; $p < 0.004$)
 - Fewer courses of oral antibiotics after initiating gentamicin (median 3.5 vs. 1; $p < 0.01$).
 - Days of oral antibiotic therapy decreased from 15 before to 5 after gentamicin.
 - Fewer telephone encounters for UTI concerns per patient (median 3 vs. 0; $p = 0.03$).



Cox L, He C, Bevins J, et al. Can Urol Assoc J 2017;11:E350-4.

- 27 patients treated with intravesical gentamicin over a 2-year period.
 - Patients taught to instill gentamicin into bladder on a nightly basis.
 - 22 pts had significantly less UTI
 - No side effects

P Abrams *et al.* Neurourol Urodyn. 2017; 36(8):2109-2116

Probiotics



Probiotics

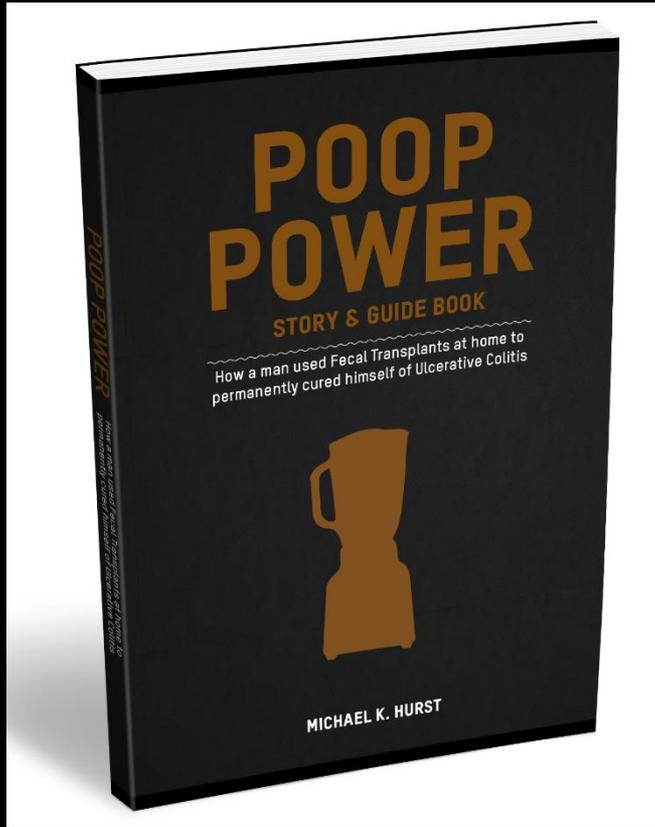
- Probiotic therapy used successfully in treating severe *C.dificile* and pseudomembranous colitis.
- UTIs often preceded by presence of pathogenic microbiota in the vagina and urethra.
- Possible prevention strategy could be to normalise vaginal and urethral microflora by direct administration of probiotics
- 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

- Cochrane review 2015, 9 RCTs and 735 patients
- No statistically significant benefit
- “Benefit cannot be ruled out as number of patients was small and trials had poor methodological reporting - high reporting and attrition bias”
- Low incidence of side effects - vaginal discharge, genital irritation and diarrhoea only affected 23/735 women
- Best results with Lactobacillus – **EAU guidelines** suggest that Lactobacillus may be used in rUTI where suitable preparations available

Gastrointestinal Decolonisation



Gastrointestinal Decolonisation

- Case report published of 60 year old patient with ESRD and 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.
- Another case report published of 73 year old patient with IBS and rUTI showed no UTI recurrence within 8-months f/u and IBS symptoms also improved.
- It is now offered at some NHS sites.

Conclusions

- Chronic UTI is prevalent in adult women.
- Several treatment options exist for rUTI with varying levels of supporting evidence.
- Further trials are needed to evaluate newer treatments.
- New non-antibiotics treatments likely to become more important in the future.

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