Approach to the Patient with Recurrent Urinary Tract Infections

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Disclosures

- I have no financial disclosures and will not discuss off-label use

Learning Objectives

- Improve diagnostic skills in evaluating causes for recurrent UTIs
- Decrease antimicrobial use by choosing non-antibiotic prophylaxis strategies for recurrent UTIs
- Streamline care for patients by knowing when to refer for specialty care for recurrent UTIs
- Identify patients eligible for vaginal estrogens to decrease risk of UTIs
- Reduce need for intravenous antibiotics by utilizing oral therapy for ESBL producing organisms in cystitis

Structure

- Definitions
- Initial workup
- Management
- Prevention
- Treatment

Definitions

- Recurrent UTI
  - 2 infections in a 6-month period OR
  - 3 infections in a 12-month period
- Asymptomatic bacteriuria
  - Presence of bacteria in urinary tract (or in urinary specimen) without symptoms of infection
  - Often associated with asymptomatic pyuria
- UTI Triggers
  - Clear temporal association with onset of infection
  - Sexual intercourse, catheterization or catheter change, pelvic exam

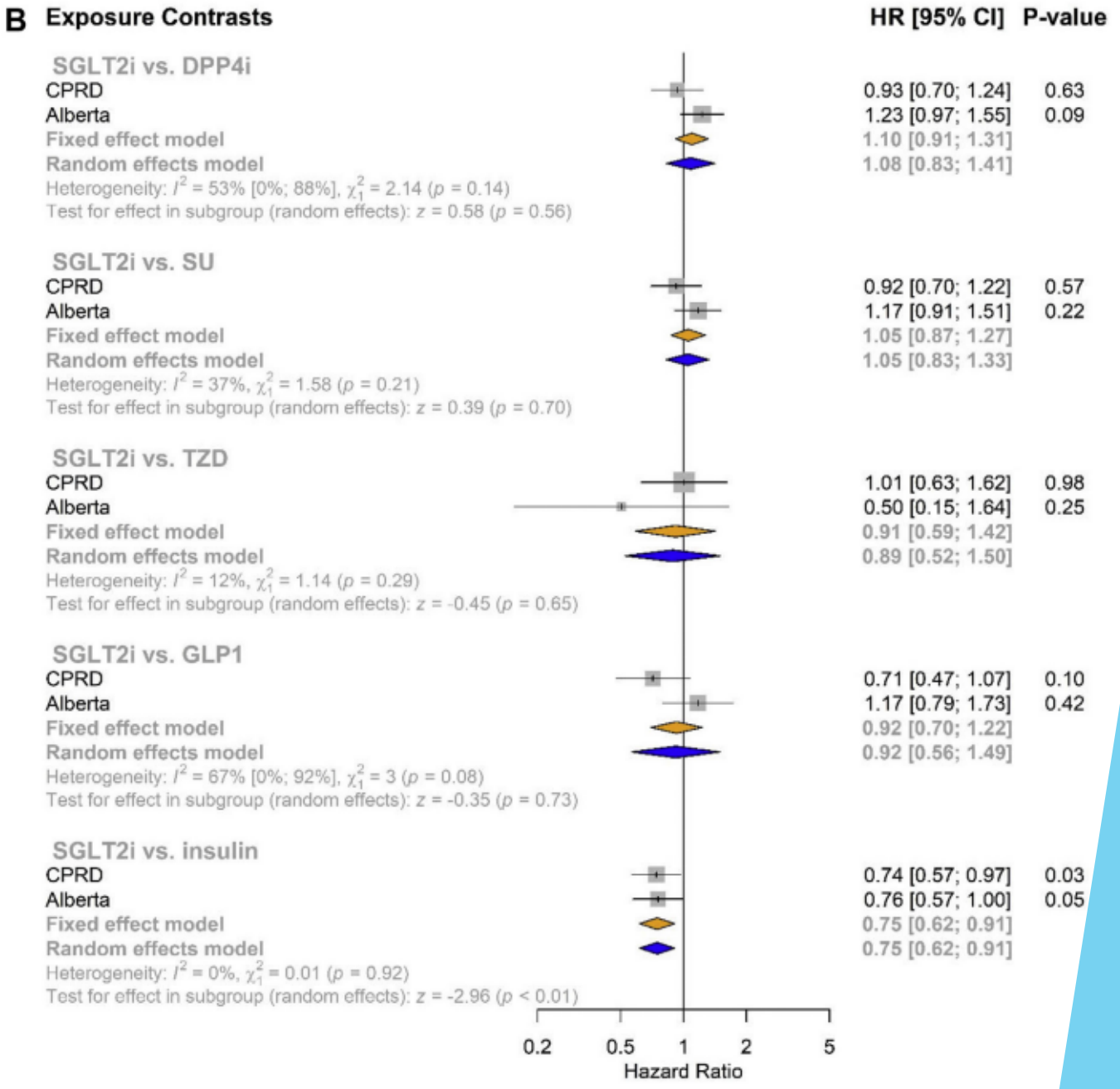
Initial Workup

- History
  - UTI lifetime history
    - Timing, pattern, severity
    - Association with incontinence or retention
  - Antimicrobial history (for UTI or otherwise)
  - Urological history
  - Neurological history
  - Sexual history
  - OB/GYN history, including onset of menopause
- Medications
  - New or changed medications near onset of recurrent UTI
  - Risk factors for urinary retention (anticholinergic drugs)
  - Immunosuppressive medications

SGLT-2 Inhibitors

- Increasing use/indications for this medications
- Known risk of perineal necrotizing infections
- Do they increase UTI risk?
  - Increase in infections related to genital candidiasis, vulval abscess and Fournier gangrene
- Data for recurrent UTI lacking

Alkabbani W et al Canadian Journal of Diabetes, 2022



Initial Workup (2)

- Physical Examination
  - Careful abdominal exam
  - Palpation for CVA tenderness
  - GU exam for anatomical anomalies, chronic catheters, other etiologies of symptoms (*Candida* etc.)
  - Bedside bladder scan for post void residual
- Urinalysis
  - Adequacy of micro- not interpretable if high levels of epithelial cells
  - Pyuria ≠ infection, however lack of pyuria makes UTI unlikely
  - Hematuria ≠ infection, warrants further investigation
  - Glucosuria

Initial Workup (3)

- Chemistry
  - Elevated BUN/Creatinine prompts more rapid imaging
  - Glucose/A1c
- Microbiology
  - Monomicrobial vs polymicrobial?
  - Consistent organism or varied?
  - Usual urine pathogens or “odd-balls” or relatively avirulent (*E. faecium*, *Candida*)?
  - Antimicrobial resistance patterns

Which patients need additional workup

- US
  - Guidelines are mixed, unclear if beneficial, low risk
- CT
  - Hematuria
  - History of stones or other upper track disease
  - Recurrent pyelonephritis (>1/year)
  - Persistent organism (excluding E. coli)
- Referral for cystoscopy
  - Hematuria
  - Recurrent pyelonephritis (>1/year)
  - Persistent organism (excluding E. coli)
  - Anatomical concerns (e.g. fistula)

Alternative diagnoses

- Nephrolithiasis
- Interstitial cystitis
- Urge incontinence
- Atrophic vaginitis
- Vulvovaginal candidiasis

Addressing Risk Factors

- Diabetes with Hyperglycemia
  - Poor control increases risk of UTI
  - Improve glucose control
- Symptoms of overflow incontinence or neurogenic bladder
  - Timed voiding
  - Refer to urology for treatment
- Pattern of Post-coital onset
  - Consider post-coital prophylaxis

Hine JL et al al Diabetic Medicine 2017

Table 3 Adjusted odds ratios of infection in people with Type 2 diabetes with moderate [HbA_{1c} 53–69 mmol/mol (7–8.5%)] and poor [HbA_{1c} > 69 mmol/mol (> 8.5%)] glycaemic control, compared with people with good glycaemic control [HbA_{1c} < 53 mmol/mol (< 7%)]

	Moderate glycaemic control			Poor glycaemic control		
	Adjusted odds ratio of infection	95% CI	*P*	Adjusted odds ratio of infection	95% CI	*P*
All infections	1.11	1.05–1.18	< 0.001	1.35	1.25–1.45	< 0.001
Upper respiratory tract infections	1.05	0.96–1.16	0.30	1.06	0.93–1.19	0.39
Bronchitis	1.22	1.12–1.33	< 0.001	1.38	1.23–1.55	< 0.001
Influenza-like illness	0.86	0.6–1.22	0.40	0.87	0.57–1.35	0.54
Pneumonia	0.88	0.58–1.33	0.56	1.73	1.07–2.79	0.03
All respiratory tract infections	1.12	1.05–1.20	< 0.01	1.25	1.14–1.37	< 0.001
Intestinal infectious diseases	1.07	0.81–1.41	0.62	0.88	0.60–1.29	0.51
Herpes simplex	1.58	0.94–2.65	0.08	1.39	0.73–2.66	0.32
Skin and soft tissue infections	1.05	0.96–1.16	0.28	1.35	1.20–1.52	< 0.001
Urinary tract infections	1.12	1.00–1.26	0.06	1.18	1.01–1.38	0.04
Genital and perineal infections	1.53	1.24–1.90	< 0.001	3.02	2.41–3.77	< 0.001

Covariates adjusted for: age, gender, deprivation quintile, smoking status, comorbidities, general practice and diabetes duration.

Nephrolithiasis

- Problem
  - Kidney stones are common
  - Recurrent UTIs are common
- Consider stone treatment if recurrence with:
  - Same organism each time
  - Improvement then relapse each time
  - Non-obstructing stones on imaging
  - Failure of other management options
- Rationale- retrospective study from Mayo:
  - 46 patients with recurrent UTIs and non-struvite stones
  - 89% had recurrent UTI resolution after stone treatment
  - Median: 3.1 UTI/year pre-treatment, 0.5 UTI/year post-treatment
  - Residual stones associated with persistent of recurrent UTI

Agarwal D et al World Journal of Urology 2020

Medical Management Options

- Stepwise approach
- Therapies not mutually exclusive
- Focus on lowest risk/lowest cost first
- Shared decision making with patients/families

Vaginal Estrogens

- First line in all eligible post-menopausal patients
  - Oral estrogens are ineffective
- Efficacy: known for many years
- Mechanisms:
  - Change in vaginal flora
  - Change in vaginal pH
  - Estrogen sensitive vaginal and urethral epithelial cells

Variable	Estriol Group (N = 50)	Placebo Group (N = 43)
Episodes of bacteriuria	12	111*
Symptomatic	10	103*
Asymptomatic	2	8
Total person-mo of observation	310	225
Urinary tract infections per patient-yr	0.5	5.9†

*P<0.005.

†P<0.001.

Raz and Stamm, NEJM 1993

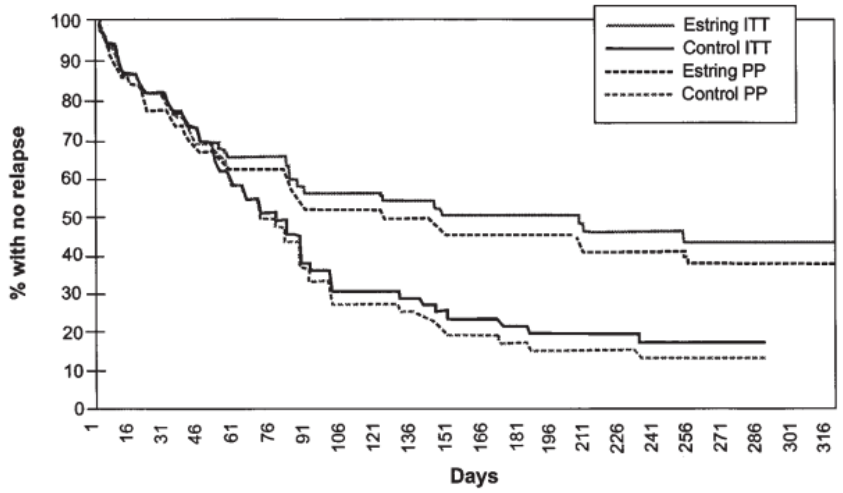


Fig 1. Time to first recurrence curves for control and Estring-treated subjects by intent-to-treat *(ITT)* and per-protocol *(PP)* groupings. Kaplan-Meier analysis shows that cumulative proportion of subjects remaining free of urinary tract infection was significantly higher in vaginal ring group than in control group ($P = .008$ by log-rank test).

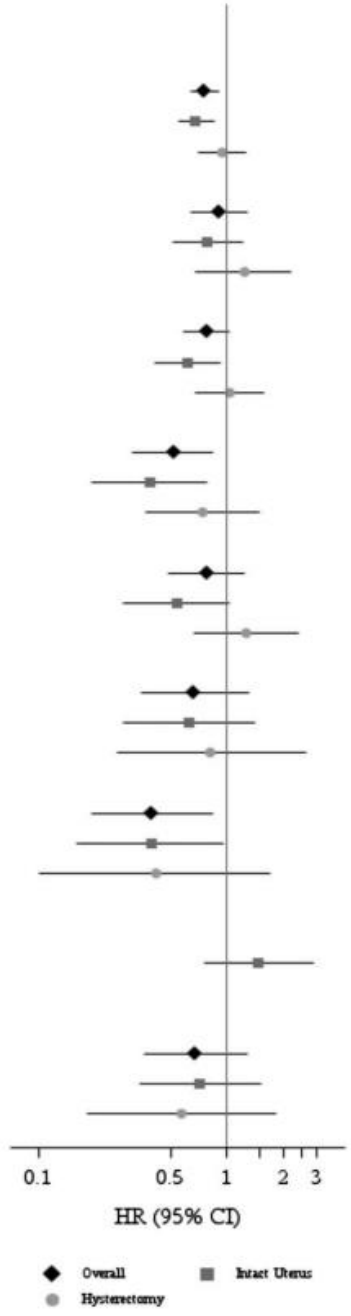
Eriksen, AJOC 1999

Vaginal Estrogen Safety

- Barriers to usage- adherence and safety concerns
- The Women's Health Initiative Observational Study evaluated safety for patients post menopausal not on systemic therapy
- No signal of increased adverse events
- Marked difference from results of systemic estrogen

Crandall et al Menopause 2018

End points	VE use N Events (rate)	No VE use N Events (rate)	HR (95% CI) Model 1	HR (95% CI) Model 2
GIE				
Overall	153 (14.0)	5906 (21.0)	0.69 (0.59, 0.81)	0.76 (0.64, 0.91)
Intact Uterus	96 (12.0)	4110 (19.9)	0.63 (0.51, 0.77)	0.68 (0.55, 0.86)
Hysterectomy	57 (19.7)	1796 (24.1)	0.83 (0.63, 1.08)	0.94 (0.70, 1.26)
Breast cancer				
Overall	40 (3.6)	1185 (4.1)	0.86 (0.62, 1.18)	0.91 (0.64, 1.29)
Intact Uterus	26 (3.2)	858 (4.0)	0.78 (0.53, 1.15)	0.79 (0.51, 1.22)
Hysterectomy	14 (4.7)	327 (4.2)	1.06 (0.61, 1.85)	1.23 (0.68, 2.21)
Death				
Overall	59 (5.3)	2592 (8.7)	0.67 (0.52, 0.87)	0.78 (0.58, 1.04)
Intact Uterus	32 (3.9)	1683 (7.7)	0.58 (0.41, 0.82)	0.62 (0.41, 0.93)
Hysterectomy	27 (9.0)	909 (11.3)	0.85 (0.58, 1.25)	1.04 (0.68, 1.58)
CHD				
Overall	20 (1.8)	1311 (4.5)	0.44 (0.29, 0.69)	0.52 (0.31, 0.85)
Intact Uterus	10 (1.2)	865 (4.0)	0.35 (0.19, 0.65)	0.39 (0.19, 0.78)
Hysterectomy	10 (3.4)	446 (5.6)	0.61 (0.33, 1.15)	0.74 (0.37, 1.50)
Stroke				
Overall	20 (1.8)	902 (3.1)	0.63 (0.40, 0.98)	0.78 (0.49, 1.24)
Intact Uterus	9 (1.1)	619 (2.9)	0.41 (0.21, 0.80)	0.54 (0.28, 1.04)
Hysterectomy	11 (3.7)	283 (3.6)	1.08 (0.59, 1.99)	1.27 (0.67, 2.40)
Colorectal cancer				
Overall	13 (1.2)	486 (1.6)	0.72 (0.41, 1.25)	0.67 (0.35, 1.31)
Intact Uterus	9 (1.1)	342 (1.6)	0.70 (0.36, 1.36)	0.63 (0.28, 1.41)
Hysterectomy	4 (1.3)	144 (1.8)	0.76 (0.28, 2.07)	0.82 (0.26, 2.62)
Hip Fracture				
Overall	10 (0.9)	582 (2.0)	0.49 (0.26, 0.92)	0.40 (0.19, 0.85)
Intact Uterus	6 (0.7)	409 (1.9)	0.42 (0.19, 0.94)	0.40 (0.16, 0.96)
Hysterectomy	4 (1.3)	173 (2.2)	0.67 (0.25, 1.81)	0.42 (0.10, 1.69)
Endometrial cancer				
Overall	NA			
Intact Uterus	11 (1.3)	222 (1.0)	1.27 (0.69, 2.33)	1.47 (0.75, 2.90)
Hysterectomy	NA			
PE/DVT				
Overall	12 (1.1)	600 (2.0)	0.59 (0.33, 1.05)	0.68 (0.36, 1.28)
Intact Uterus	9 (1.1)	385 (1.8)	0.68 (0.35, 1.31)	0.72 (0.34, 1.53)
Hysterectomy	3 (1.0)	215 (2.7)	0.43 (0.14, 1.33)	0.57 (0.18, 1.81)



Vaginal Estrogens: Pearls

- Effects take time, have patience
  - Induction:
    - 7-14 days of nightly application
  - Maintenance:
    - 2-3 nights per week
  - Restart at induction of lapse in therapy
- Can be used in combination with other approaches
- No contribution to resistance
- If ER/PR breast CA or Gyn Malignancy- touch base with Oncology

D-Mannose

- Over the counter dietary supplement
- Supplementation leads to elevated urine levels as it is not fully metabolized by humans (compared with other sugars)
- Mechanism of action: saturation of E. coli fimbriae, blocking adhesion to urothelial cells
- Main adverse effect: bloating and diarrhea at higher doses

Evidence of Benefit

- RCT: 6 months- Placebo vs NF vs D-mannose
  - Women with Recurrent UTI
  - D-mannose efficacy similar to NF, superior to placebo
  - Caveats- 75% of isolates: E coli
- Additional study- prophylaxis for urodynamic studies
  - D-mannose + probiotic + N-acetyl cysteine vs antibiotics x 7 days

Table 2 Causative microorganism of the initial UTI and events during prophylaxis

	D-mannose group ($n = 103$)	Nitrofurantoin group ($n = 103$)	No prophylaxis group ($n = 102$)	P
Isolated bacteria in acute cystitis n (%)				0.98
E. coli	81 (78.6)	78 (75.7)	77 (75.5)	
Other	13 (12.6)	18 (17.5)	17 (16.7)	
Two microorganisms	9 (8.8)	7 (6.8)	8 (7.8)	
Recurrent acute cystitis during prophylaxis, n (%)	15 (14.6)	21 (20.4)	62 (60.8)	0.001
Median time from prophylactic therapy start to cystitis symptoms onset (days) median (IQ range)	43 (15–50)	24 (15–36)	28 (20–42)	0.12
Complications during prophylaxis, n (%)	8 (7.8)	29 (27.2)		0.001
Diarrhea	8 (100)	10 (34.4)		
Nausea		6 (20.7)		
Headache		3 (10.3)		
Skin rash		1 (3.6)		
Vaginal burning		9 (31.0)		

Kranjcec B et al World Journal of Urology 2014

	Patients analyzed	Group A Prulifloxacine			Group B D-mannose and N-acetylcysteine		
Sex		**Men**	**Women**	**Tot**	**Men**	**Women**	**Tot**
N° patients	75	21	17	38	18	19	37
% UTIs		9.5%	5,8%	7.89%	5.5%	5.2%	5.4%
Germ isolated		*Escherichia coli* 100%			*Escherichia coli* 100%		

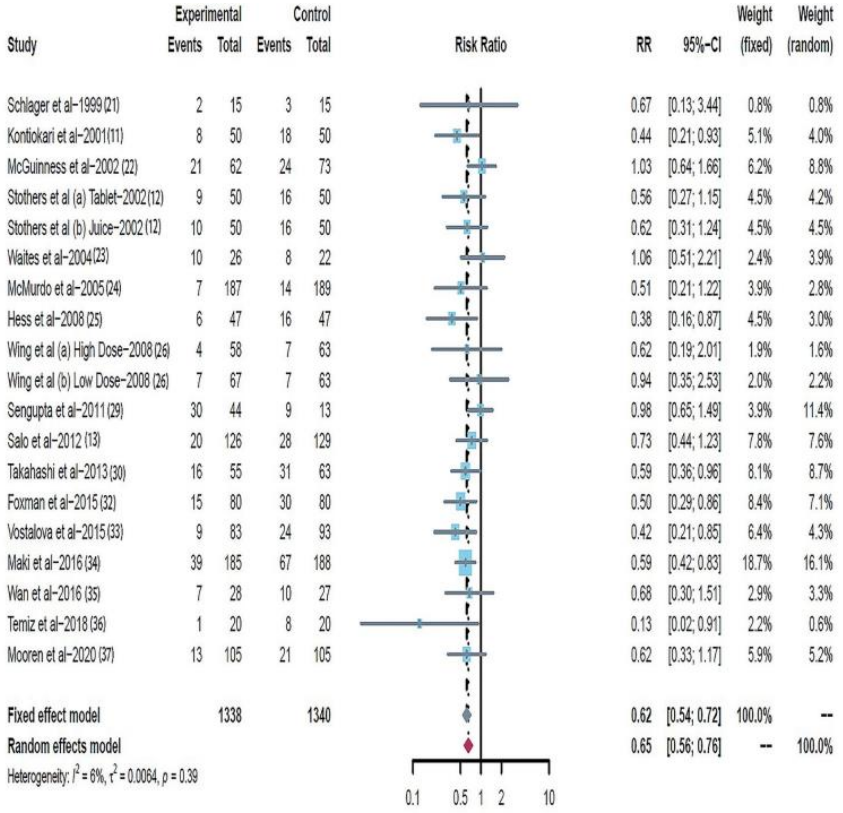
Palleschi G et al Archives of Italian Urology and Androgyny 2017

D-Mannose Pearls

- Overall limited evidence
  - Not a pharmaceutical so fewer studies required
  - May not be as effective in non-E. coli pathogens
- Most studies dose 2-3 grams per day
- Can be combined with other methods
- Safety seen across studies, minimal adverse effects
- No contribution to resistance
- Some products are including with other supplements (probiotics, cranberry etc.), may be a marketing technique

What About Cranberry?

- Two recent meta-analyses, suggest 25-30% RRR
- Studies fraught with heterogeneity: population, dose, type, UTI definition
- Benefit may be driven by studies in children/young adults
- Safe, if ineffective



Xia JY et al PLOS One 2021

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of partici-pants (RCTs)	Certainty of the evidence (GRADE)
	Risk with place-bo/control	Risk with any cranberry product			
Symptomatic, culture-verified UTI Women with recurrent UTI	243 per 1,000	180 per 1,000 (134 to 241)	RR 0.74 (0.55 to 0.99)	1555 (8)	⊕⊕⊕⊖ MODERATE [1]
Symptomatic, culture-verified UTI Elderly men and women in institutions	113 per 1,000	105 per 1,000 (76 to 147)	RR 0.93 (0.67 to 1.30)	1489 (3)	⊕⊕⊕⊖ MODERATE [2]
Symptomatic, culture-verified UTI Children	289 per 1,000	153 per 1,000 (104 to 225)	RR 0.53 (0.36 to 0.78)	428 (4)	⊕⊕⊕⊖ MODERATE [3]
Symptomatic, culture-verified UTI Adults with bladder emptying issues or multiple sclerosis	440 per 1,000	427 per 1,000 (343 to 524)	RR 0.97 (0.78 to 1.19)	464 (3)	⊕⊕⊖⊖ LOW [2 3]
Symptomatic, culture-verified UTI People with a susceptibility to a UTI due to an in-tervention	231 per 1000	109 per 1000 85 to 141	RR 0.47 (o.37 to 0.61)	1434 (6)	⊕⊕⊖⊖ LOW [2 3]

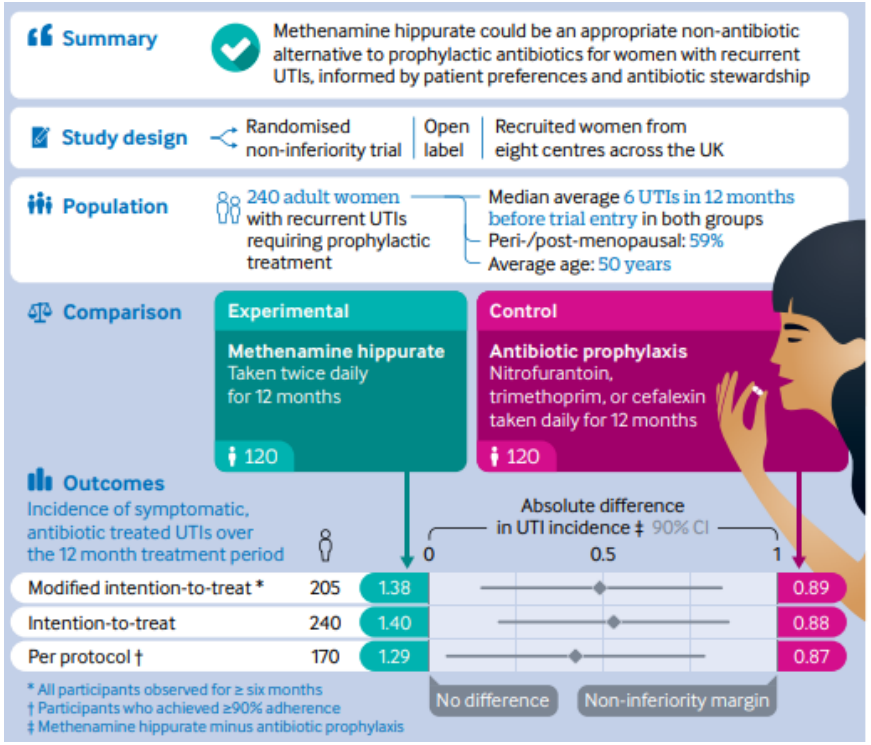
Williams G, Cochrane Database of Systematic Reviews 2023

Methenamine

- Cyclic hydrocarbon, developed in late 19th century
- Initially used with madelate, but now hippurate (Hiprex)
- Absorbed with oral administration and excreted in urine
  - No significant effects at physiologic pH
  - In acidic urine (pH 6 or lower), is converted to formaldehyde and NH3
- Has been used to try to prevent UTI for decades
- 2014 Cochrane review did not show benefit in preventing symptomatic UTI
  - Significant heterogeneity in these studies (duration of therapy, risk factors)

Methenamine Contemporary Data

- BMJ trial showed methenamine to be non-inferior (NI margin 10%) to daily prophylaxis
  - Difference of 0.49 UTIs per year compared with antibitoics
- A second trial (n=92) found similar reduction in UTI with trimethoprim and methenamine
  - Breakthrough UTI had higher resistance rates in trimethoprim group



Harding C et al BMJ 2022

	Number of UTI recurrences prior to prophylaxis	Number of UTI recurrences within 1 year after prophylaxis	*p* value
Full cohort	3.9 ± 1.8	1.6 ± 1.8	<0.01
Trimethoprim (ITT)	4.0 ± 2.1	1.5 ± 1.7	
Methenamine hippurate (ITT)	3.7 ± 1.5	1.6 ± 1.9	
Trimethoprim (PP)	4.3 ± 2.2	1.8 ± 2.1	
Methenamine hippurate (PP)	3.5 ± 1.3	1.4 ± 1.5	

Botros C et al International Urogynecology Journal 2022

Methenamine Considerations

- Dosing- 1g BID for Hippurate salt
- Urinary Acidification
  - Controversial, in vitro data support, clinical data mixed
  - Classically 2 grams of Vit C per day, goal urine pH 6 or less
  - Recent trials did not use this in their protocol
- Unclear efficacy if urease producing organisms (e.g. Proteus)
  - May be more of a reason to try with Vit C
- Drug-Drug interaction with Sulfonamides (must stop during treatment)
- Requires hydration, caution in gout patients

Probiotics

- Studies of probiotics are difficult to interpret
  - Different strains, delivery methods, quality assurance
- Cochrane review in 2015 did not show any consistent effect
- Role of supplementation vs diet controvesial

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Probiotics				
Symptomatic bacterial UTI in adults and children in patients with and without recurrent UTI **Probiotics versus placebo** (follow-up)	**395 per 1000**	**296 per 1000** (197 to 446)	**RR** 0.75 (0.50, 1.13)	352 (6)	⨁⨁⨀⨀ **low**	Risk of bias was assessed at unclear or high in most domains and suggest that results are imprecise or overestimate probiotic effects versus placebo
Symptomatic bacterial UTI in adults and children with recurrent UTI **Probiotics versus placebo** (follow-up)	**421 per 1000**	**315 per 1000** (227 to 425)	**RR** 0.74 (0.54, 1.01)	275 (4)	⨁⨁⨀⨀ **low**	Risk of bias was assessed at unclear or high in most domains and suggest that results are imprecise or overestimate probiotic effects versus placebo
Symptomatic bacterial UTI in women with recent UTI **Probiotics versus antibiotics** (follow-up)	**666 per 1000**	**745 per 1000** (632 to 885)	**RR** 1.12 (0.95, 1.33)	223 (1)	⨁⨁⨀⨀ **low**	Risk of bias was assessed at unclear or high in most domains and suggest that results are imprecise or overestimate probiotic effects versus antibiotics. Imprecision also due to small sample from only one RCT
Symptomatic bacterial UTI in children with VUR **Probiotics versus placebo** (follow-up)	**270 per 1000**	**145 per 1000** (64 to 332)	**RR** 0.54 (0.24, 1.23)	96 (1)	⨁⨁⨀⨀ **low**	Risk of bias was assessed at unclear or high in most domains of and suggest that results are imprecise or overestimate probiotic effects versus placebo. Imprecision also due to small sample from only one RCT

Suppressive Antibiotics

- Last resort
- Effective in short term-medium term
- Risk of resistance in long term
- Loss of oral agents for treatment
- Common agents:
  - NF 50 or 100mg po QHS
  - TMP 100mg daily
  - Cephalexin 250 mg daily
  - Fosfomycin 3g q 10 days

Alternative: Bundle Approach

- Combing non-antibiotic therapies may help avoid suppressive antibiotics
- "Real-world" or "Pragmatic" Approach
  - Analogous to infection prevention bundles
- Italian single center pre-post quazi-expiermental study
  - Females >18 with frequent UTI symptoms at least 1 culture + in 6 months
  - Bundle:
    - Oral hydration + bowel regimen (osmotic laxatives, if needed) + physical activity
    - Cranberry juice/proanthocyanins + D-mannose
    - Oral probiotic cocktail + vaginal probiotic suppository (2x/week)
- Results: 80.5% of patient reported improved overall quality of life

Table 3 Incidence of UTIs and treatments in the six months before and after treatment

UTIs characteristics ($n = 41$)	Baseline	Post-bundle	p
Number of episodes, mean ± SD (range)	4.3 ± 2.6 (1–11)	1.1 ± 1 (0–4)	**< 0.001**
Antibiotic courses, mean ± SD (range)	3.5 ± 2.1 (1–9)	0.5 ± 0.4	**< 0.001**
Duration of each ATB cycle, mean ± SD (range)	5 ± 2.6 (2–12)	2.5 ± 0.9 (2–5)	0.04
Overall days of antibiotic therapy	679	53	**< 0.001**

Venturini S et al Probiotics and Antimicrobial Proteins 2023

Difficult Treatment: ESBL-producing organisms

- Extended Spectrum Beta-lactamases are a group of enzymes
  - Resistance to cephalosporins is a defining feature, often require IV carbapenem therapy
  - Most E. coli ESBLs are due to CTX-M
  - Often ESBLs are on the same plasmid as other resistance mechanisms that confer resistance to quinolones and TMP/sulfa
    - Clavulanic acid is a relatively good inhibitor of some ESBLs
    - Given renal clearance of amoxicillin and clavulanic acid, concentration of these antibiotics in the bladder can be many times that of systemic concentration
    - Some micro labs may suppress the MIC to amoxicillin/clavulanic acid, but it can be effective in cystitis (even if MIC in the I/R range)
  - Other oral options:
    - Nitrofurantoin – pulmonary toxicity rare in acute course, caution if CrCl< 40
    - Fosfomycin – testing not routine, resistance rare in *E. coli*, increasing in Klebsiella

Difficult Treatment: *Enterococcus sp.*

- Enterococcus is a common urinary pathogen and a common colonizer
- Intrinsically resistant to cephalosporins, it will often colonize the bladder after treatment with these agents
  - In addition, prior use of vancomycin can be associated with *E. faecium* (usually VRE)
  - *E. faecium* is less virulent than *E. faecalis*
- Due to high urinary concentration of aminopenicillins, ampicillin and amoxicillin are associated with high rate of success regardless of ampicillin and vancomycin resistance
- For penicillin allergy:
  - Fosfomycin and nitrofurantoin
  - Can ask micro lab to un-suppress quinolone
  - Penicillin skin testing

Table 2
Fourteen- and 30-day clinical success by antibiotic in patients with lower urinary tract infections due to *Enterococcus* spp.

	14-day composite	*P*-Value	30-day composite	*P*-value
Aminopenicillin				
Amoxicillin (PO)	34/36 (94.4)	0.019	30/36 (83.3)	0.071
Ampicillin (IV)	27/36 (75.0)	0.091	25/36 (69.4)	0.529
Amoxicillin/clavulanate (PO)	10/11 (90.9)	0.463	7/11 (63.3)	0.463
Ampicillin/sulbactam (IV)	5/8 (62.5)	0.102	5/8 (62.5)	0.482
Non-aminopenicillin				
Linezolid[a] (PO/IV)	35/41 (85.4)	0.448	32/41 (78)	0.164
Fosfomycin (PO)	24/30 (80.0)	0.723	19/30 (63.3)	0.270
Nitrofurantoin (PO)	10/13 (76.9)	0.604	9/13 (69.2)	0.894
Doxycycline[b] (PO/IV)	3/3 (100)	0.680	2/3 (66.7)	1.000
Daptomycin (IV)	1/2 (50.0)	0.329	1/2 (50.0)	0.501

NB: ~80% Vancomycin resistance; aminopenicillin noninferior for non-*E. faecium* species

Montes de Oca JE et al. International Journal of Antimicrobial Agents 2023

Take Home Points

- Close evaluation of symptoms and pattern of UTI can decrease treatment of non-infectious syndromes
- Microbiological pattern over time can give clues to causes of recurrent UTI
- Patients with recurrent symptoms and hematuria or history of nephrolithiasis may require additional workup, and possibly stone treatment to help with recurrent UTI
- Vaginal estrogens are safe and effective in most patients and do not carry the same risks as systemic estrogens
- Combining multiple non-antibiotic strategies such as D-mannose and methenamine can help to avoid the need for long term suppressive antibiotics
- Risk of resistance increases with long term suppressive antibiotics
- Some mechanisms of resistance can be overcome by utilizing increased urinary concentration of beta-lactams compared with serum

References

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