

Management options for Recurrent UTI (rUTI)



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Disclosures

I have nothing pertinent to disclose

Objectives

- Offer effective preventive therapies for rUTI
 - Non-medical; Medical and antibiotics
- Reduce use of antibiotics (abx) in the treatment of rUTI
- Select optimal abx therapy for rUTI

Premise of this talk

It would be best to manage
rUTI without antibiotics or at
least as little as possible

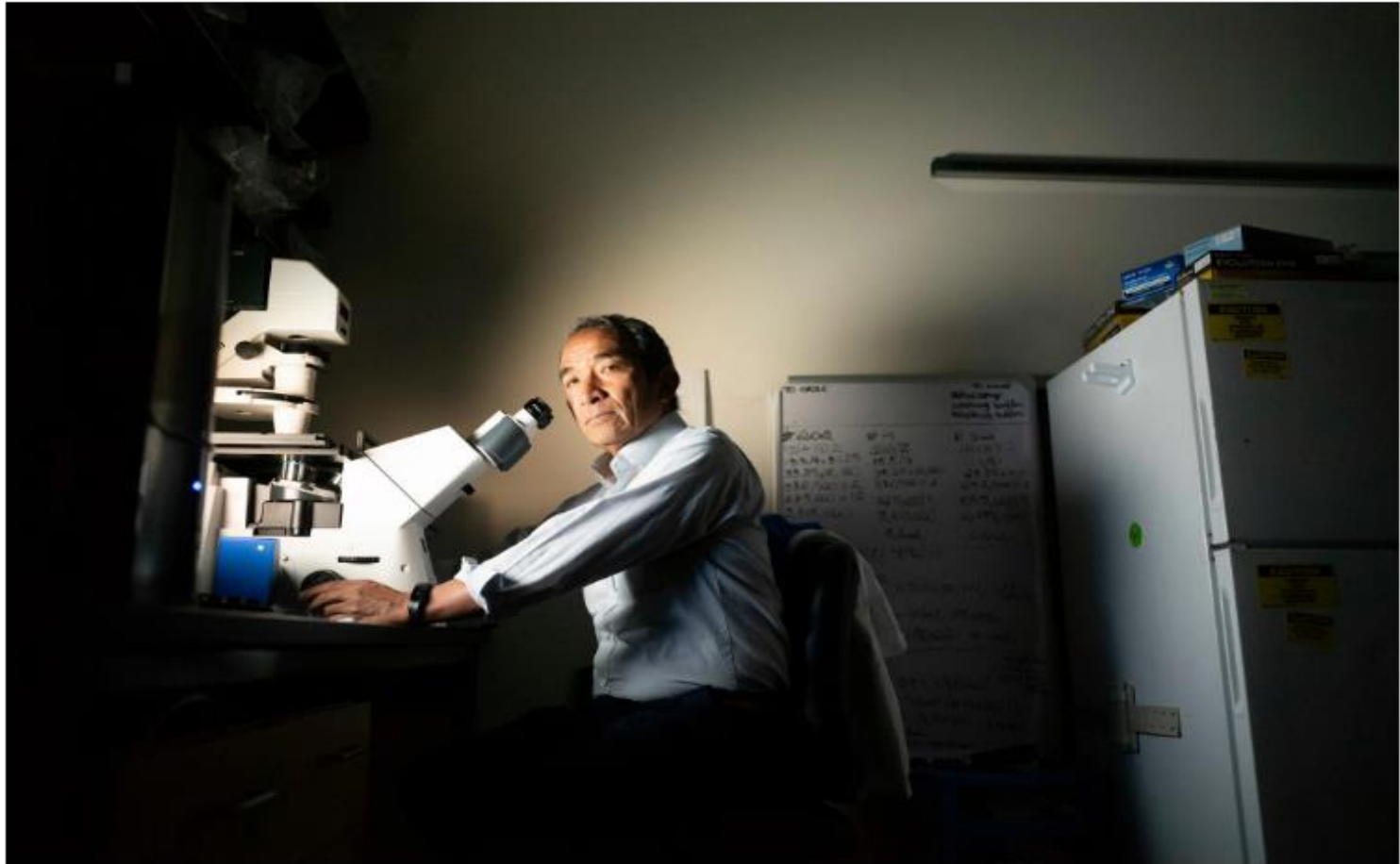
Outline

- Epidemiology
 - Doom and Gloom
- Work-up
- Recurrent UTI prevention
 - Behavioral prevention
 - Non-pharmaceutical (OTC) prevention
 - Non-antibiotic pharmaceutical prevention
 - Antibiotic prevention options
 - Hope for more options in the future
- Summary

DEADLY GERMS, LOST CURES

Urinary Tract Infections Affect Millions. The Cures Are Faltering.

As the infections become increasingly resistant to antibiotics, some standard treatments no longer work for an ailment that was once easily cured.



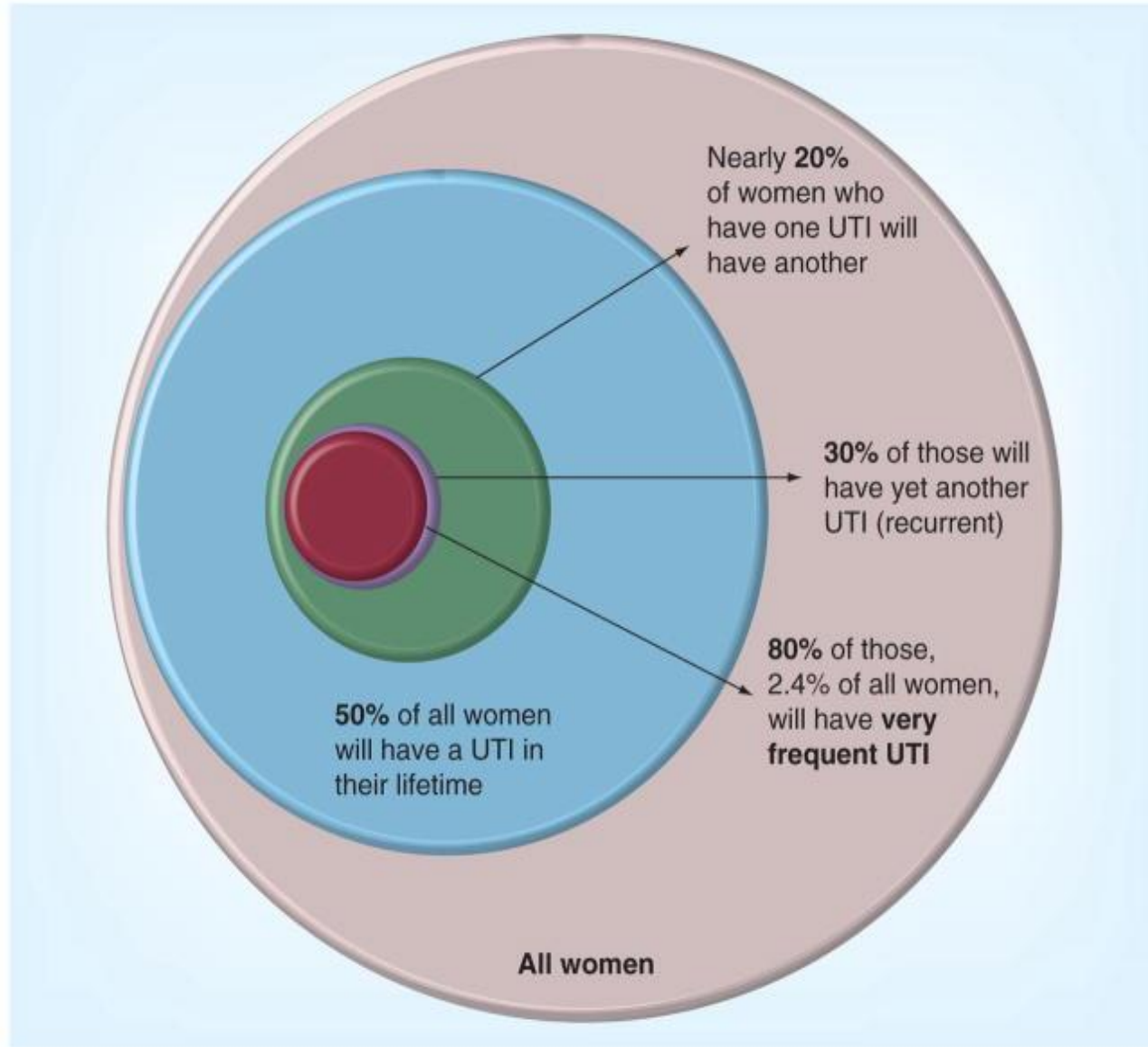
Dr. Lee Riley of the University of California, Berkeley, has been studying antibiotic-resistant strains of *E. coli*, which can cause urinary tract infections. "We've suspected maybe some of these U.T.I. cases may be food-borne," he said. Brian L. Frank for The New York Times

By [Matt Richtel](#)

July 13, 2019



Scope of the problem



Brutal Truth

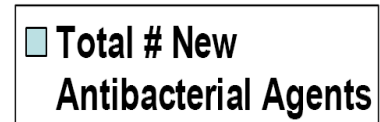
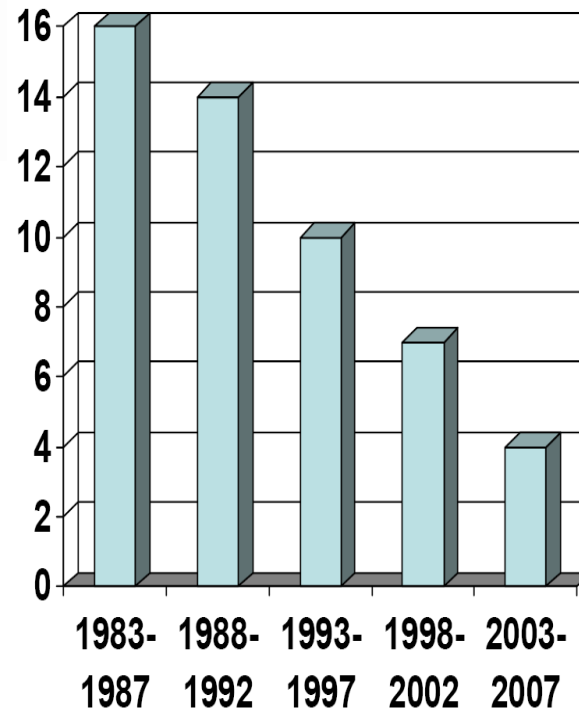
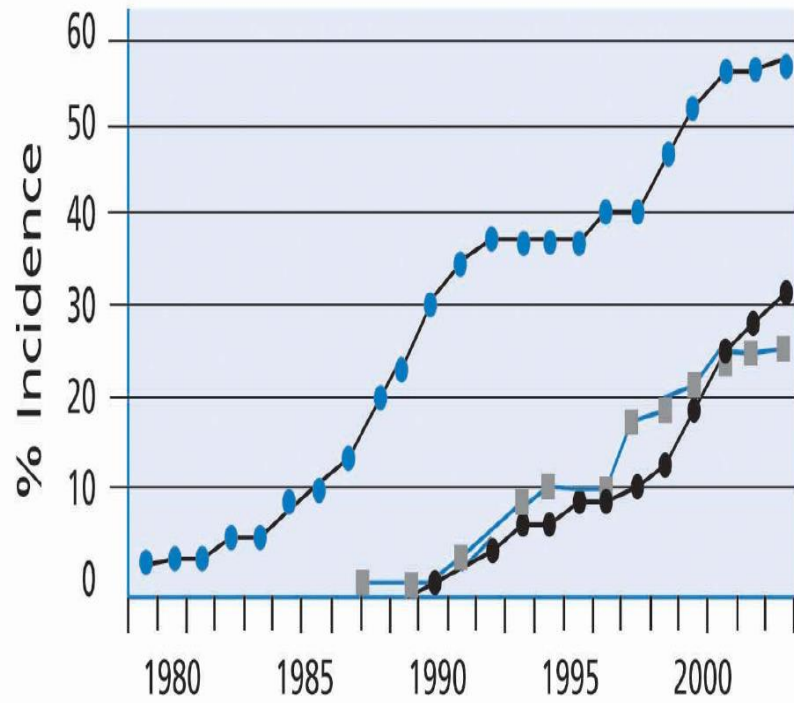
- Abx Resistance is on the rise (and it's our fault).
- Abx pipeline is all but dry.

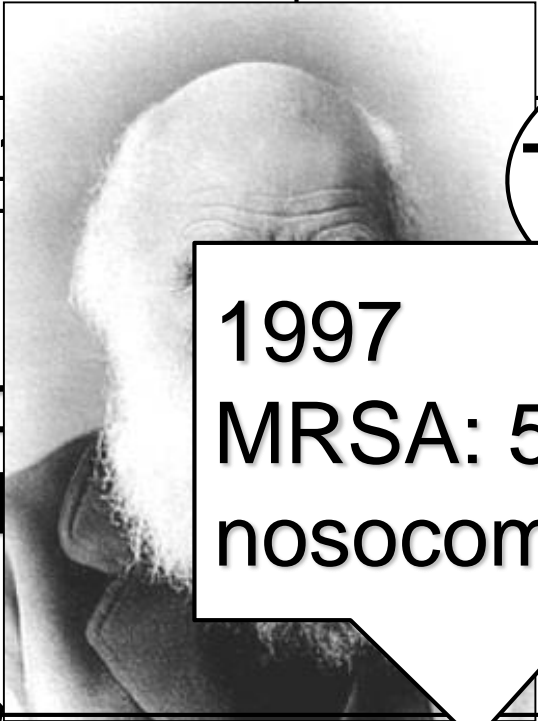
BAD BUGS, NO DRUGS

As Antibiotic Discovery Stagnates ...
A Public Health Crisis Brews



“BAD BUGS, NO DRUGS”





Told you so

1959
Methicillin
to kill MRSA

1997
MRSA: 50% US
nosocomial staph infxns

Charles Darwin
(1809-1882)

Healthy kids
A-MRSA



Recurrent UTI (rUTI)

- Defined as: Resolution of symptoms/bacteriuria of prior UTI with repeat within 6 months or 3 a year
- Subcategories:
 - Relapse is a second UTI with the same pathogen within 2 weeks
 - Reinfection is a repeat infection more than 2 weeks later – may or may not be same pathogen
- Pathogenesis same as with sporadic infection
 - ?some from reservoir of pathogens remaining in bladder epithelium
- No evidence that rUTI leads to health problems (hypertension/renal dz)
- 27% of women will have recurrence in 6 months after first UTI, 2.7% had second recurrence during same time

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Diagnostic Value of Common UTI Symptoms

Symptom	Sensitivity	Specificity	+ Likelihood Ratio	- Likelihood Ratio
Dysuria	0.78	0.36	1.22 (1.11-1.34)	0.61 (0.50-0.74)
Frequency	0.90	0.17	1.09 (1.02-1.16)	0.58 (0.32-0.79)
Urgency	0.75	0.36	1.17 (1.04-1.31)	0.70 (0.57-0.86)
Fever	0.10	0.89	0.90 (0.45-1.80)	1.01 (0.93-1.10)
Vaginal Discharge*			0.65 (0.51-0.83)	1.10 (1.01-1.20)
Hematuria**			1.68 (1.06-2.66)	0.89 (0.82-0.98)

Table 1. The accuracy of symptoms for diagnosis of UTI. Data adapted from: Giesen et al.

BMC Family Practice 2010, 11:78 *Based on $\geq 10^2$ CFU/mL **Based on $\geq 10^3$ CFU/mL

Symptoms

- Meta-analysis: 90% probability of cystitis when dysuria & frequency without vaginal discharge or irritation
- Elderly are different:
 - Changes in mental status
 - Vague symptoms of malaise
- High prevalence of bacteriuria

History and Physical to identify risk factors.

(Explain to your patient the pathogenesis of UTIs
she may identify a risk factor that you overlooked)

Recurrent UTI (History)

When it usually is...

- Dysuria/frequency/suprapubic or low back pain
- Cluster of infections
- High frequency of intercourse
- Spermicide use within past year
- New/Mult. sex partner within past year
- ≤ 15 yo at first UTI
- 1st degree relative with history of UTI
- Recent *E. coli* UTI
 - Typically within 30-60 days
- For women over 50:
 - 53% risk of repeat UTI in 6 months



Risk Factors-Behavioral

- ASSOCIATED

- Sexual intercourse
 - New sex partner
- Spermicide use in past yr.
 - Spermicide coated condoms
 - Diaphragms
- Recent antibiotic use

Hooton 1996, Fihn 1998,
Smith HS 1997

- NOT ASSOCIATED

- pericoital voiding patterns, urinary frequency, wiping patterns, douching, hot tub use, use of tights, BMI.

Scholes 2000

Risk Factors-Anatomy/Function

- Mean distance from the urethra to anus was significantly shorter in women with rUTI vs. controls.
(4.8 vs 5.0 cm, $p=0.03$)
- Presence of cystocele in post-menopausal women: 19% cases vs 0% controls
- Urinary incontinence (all types) post menopausal women: 41% cases vs 9% controls
- Elevated post void residual post-menopausal women: 28% cases vs 2% controls
- Constipation present in 33% girls with rUTI vs 0% controls
- >50+ yo
 - Incomplete emptying
 - Declining functional status

Risk Factors-Genetic

- Increased susceptibility to vaginal colonization with uropathogens even during asymptomatic periods
 - Having a mother with history of UTIs, first UTI before age 16
 - Scholes 2000
 - Nonsecretor of ABH blood group antigens uroepithelial cells show enhanced adherence of uropathogenic e. coli compared with secretor cells secondary to globoseries glycoplipd receptors that bind uropathogenic E. coli
 - Lomberg 1986, Stapleton 1992
 - Interleukin-8 receptor (CXCR 1): inflammatory cytokine promotes neutrophil migration across infected uroepithelium. CXCR1 expression significantly lower in pyelonephritis prone children and their relatives than controls
 - Godaly 1998, Lundstedt 2007

rUTI

Physical Exam and Lab

- **Culture to establish infection and r/o persistence/resistance**
 - Fewer prescriptions with culture based treatment
- Post-void residual
- STI screen if Sx c/w urethritis
- Wet mount for Trich and BV, if patient has vaginal discharge
- Rarely need bigger urologic workup
 - Abd X-ray, Cystoscopy, IVP, US all low yield
 - No risk factor predictive of abnormal work-up

Asymptomatic microscopic hematuria side note

- Hematuria is only diagnosed on **microscopy**.
 - Urine dipsticks are screening, not diagnostic
- Asymptomatic microscopic hematuria definition in low-risk women <50 without gross hematuria:
 - ACOG >24 RBCs/HPF
 - AUA >2 RBCs/HPF
- Ongoing discussion/debate

LAB

- Urine Collection:
 - Mid-stream urine with labia spread most reasonable
 - Cath?
- Dip? – Best to rule IN rather than rule OUT infection
 - Culture when LE and nitrite negative but Sx.
- Culture
 - Typically consider $>10^5$ cfu/ml as positive however in Sx women $>10^2$ coliforms 95% sensitivity
- Microscopy
 - Pyuria (>10 leuks/HPF); RBCs

Get urine cultures.

Why get cultures?

- Limit ineffective antibiotic exposure
- Relapse vs. Reinfection
- Prior patient microbiologic data improved rate of accuracy of empiric treatment against UTI pathogen 32-76%

rUTI Bacteria. . . Are they the same?

- Case-Control Study
 - 420 Women - rUTI v. Not
 - Microbiological findings & susceptibility profiles
- Bacteria
 - E. Coli most common in both groups
 - 2nd most common
 - rUTI: Enterococcus
 - NOT: Staph saprophyticus
- Susceptibility
 - Nitrofurantoin only agent that maintained susceptibility in BOTH groups

Urine culture - Delayed prescription

- Without treatment 25-42% of uncomplicated UTI will resolve spontaneously
 - In absence of effective treatment only 2-3% of uncomplicated cystitis will progress to pyelonephritis
- RCT: pts seen for suspected uncomplicated UTI
 - UA inconclusive or unimpressive
 - Std care vs.
 - No abx prescribed until Ucx positive 48 hr later
 - **Total abx consumption reduced**
 - No increase in pyelonephritis
 - Patients in delayed arm had 37% longer sx duration
- Retrospective review of 636 patients (916 cxs)
 - ~50% treated empirically
 - 26% of those treated required antibiotic change*

Briefly

Treatment for uncomplicated UTI

- Meta-analysis: 90% probability of cystitis when dysuria & frequency without vaginal discharge or irritation
- Elderly are different:
 - Changes in mental status
 - Vague symptoms of malaise
 - High prevalence of bacteriuria

Commonly Used Antimicrobial Agents and Regimens

Drug	Dosing	Side effects	Other Considerations	Pregnancy Class	Breastfeeding AAP ¹ /LactMed ²	Price
Nitrofurantoin	100mg PO BID X 5 days	Nausea, vomiting, diarrhea, hypersensitivity reactions including hepatitis	Rare cases of pulmonary fibrosis in long term use	B* [§]	Hemolysis with G-6PD deficient infant/Avoid <1month old or G-6PD deficient	100mg tabs, #20, \$70
TMP/SMX	1 DS tab PO BID x 3 days	Nausea, vomiting, rash including Steven-Johnson-Syndrome in rare cases.	Increased bleeding risk with warfarin. Risk of hyperkalemia with low GFR or when combined with ACE-I, ARBs, aldosterone antagonist. Multiple drug interactions	C [§]	None reported/Avoid in ill or premature infants	800mg-160mg tabs, #20, \$4
Fosfomycin	3g PO x 1	Nausea, diarrhea, vaginitis	After treatment one should expect improvement in symptoms over a few days	B	NA/Limited data, avoid <2mo old	3g tab, #1, \$80
Ciprofloxacin	250mg PO BID x 3 days	Nausea, vomiting, headache	Risk of <i>Clostridium difficile</i> colitis and tendon rupture in those using corticosteroids	C	None reported/Little risk	500mg tabs, #100, \$4 1000mg XL tabs, #50, \$465.00 ^{&}

Table 3.

1. Ressel G. *Am Fam Physician*. 2002;65(5):979–980.

2. LactMed: Drugs and Lactation Database. 2010. Available at: <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~v5mwMX:1>. Accessed December 5, 2012.

*Contraindicated at term

[§]ACOG recommends using during first trimester only if no other options³⁶

[&] Prices estimated at target.com, walmart.com, and drugstore.com



Empiric Abx Treatment

- Nitrofurantoin (Macrobid) 100mg PO BID x 5d
 - avoid in pyelo OR
- TMP/SMX (Bactrim) [®] <20%: 1 DS PO BID x 3d OR
- Fosfomycin (Monurol) 3gm PO x 1 dose
 - avoid in pyelo
- TMP/SMX resistance >20%:
 - Cipro 500mg PO QD x 3 days *OR*
 - Cefpodoxime 100mg PO BID x 7 days

Nitrofurantoin

- Tissue penetration poor due to rapid renal clearance, 25% unchanged drug excreted in urine – NOT for pyelo
- Interferes with cell wall synthesis
- Bacteriocidal in urine concentration levels
- Minimum GFR 45 ml/min (older ref 60ml/min)
- Rare but significant side effects:
 - idiopathic pulmonary fibrosis, peripheral neuropathy, autoimmune hepatitis
 - Pneumonitis 1.1%; thrombocytopenia 2.3%
- 2012 Beers criteria strongly recommends to avoid using in adults > 65 since rare side effects more common in elderly
- Breastfeeding: avoid < 1 month old or with G-6PD deficiency

Fosfomycin

- 3 grams (one “sachet”) mixed in 4-8 oz of water po **x1**
- Well-tolerated, few side effects but more than FQ (HA, diarrhea)
- Sx improve over a few days
- Bactericidal-inhibits cell wall growth
- Predominant excretion of active form in urine, poor tissue penetration – NOT for pyelo
- Broad activity against both GN and GP, including ESBL
- Breastfeeding: limited data, avoid <2 mos old
- Cost (Good RX) approx \$80.00/dose



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Change Behaviors

- Post-coital voiding
- Stop douching
- No hot tubs
- Weight loss (BMI 30+)
- Avoiding tight non-cotton underwear / pantyhose
- Altered sexual practices
- Stopping or starting douching
- Changing Wiping Patterns
- BMI
- Bubble baths
- Caffeine
- Chronic disease
- STIs

Eventhough data doesn't yet support any of these recommendations individual choice / Experimentation might still be reasonable

Effect of Increased Daily Water Intake in Pre-menopausal Women With Recurrent Urinary Tract Infections

A Randomized Clinical Trial

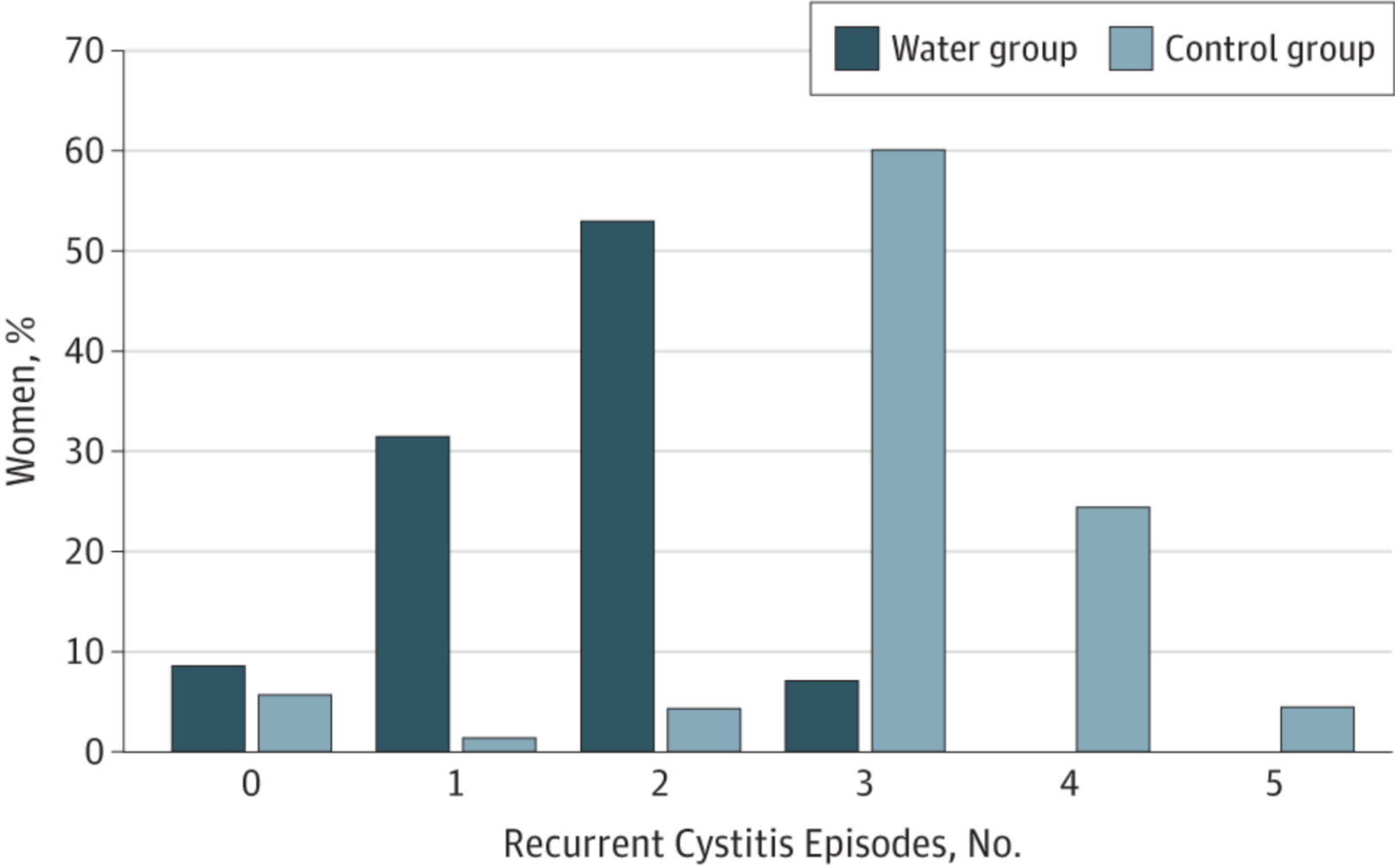
Thomas M. Hooton, MD¹; Mariacristina Vecchio, PharmD²; Alison Iroz, PhD²; [et al](#)

[» Author Affiliations](#) | [Article Information](#)

JAMA Intern Med. 2018;178(11):1509-1515. doi:10.1001/jamainternmed.2018.4204

- 140 women experiencing ≥ 3 /year rUTI and drinking < 1.5 L of water
- Randomized open-label
 - 1.5 L water or no additional
- Mean number of Abx regimens during 12 mo F-up: 1.9 (1.7-2.2) vs. 3.6 (3.3-4.0)

Effect of Increased Daily Water Intake in Premenopausal Women With Recurrent Urinary Tract Infections



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Symptomatic Treatment

- RCT: 494 women
 - Fosfomycin vs. Ibuprofen 3X400mg (3 days)
 - Additional abx as necessary
 - Significantly fewer courses of abx
 - ~60% reduction
 - Pyelonephritis
 - 5 cases in Ibuprofen group
 - 1 in Fosfomycin
 - Recurrences*
 - 11% vs. 6%

Cranberry products

Type A proanthocyanidins (PAC) inhibit the adherence of P fimbriae of E. coli to the uroepithelial cell receptors



“ We do not routinely suggest cranberry products to reduce the incidence of recurrent UTI. Although there are plausible biological mechanisms for such an effect, clinical studies to date have not definitively demonstrated efficacy in prevention of recurrent UTIs. However for women with rUTI who are interested in trying cranberry products and can tolerate it there is likely little harmful effect.”

Thomas Hooton, MD-2016

Cranberry vs. TMP-SMX



- RCT; 221 **premenopausal** women
 - Cranberry 500mg BID vs. TMP-SMX 480mg daily
- After 12 months mean number with at least one symptomatic UTI
 - Cranberry: 4.0
 - TMP-SMX: 1.8
- Fecal E.Coli isolates after one month
 - Cranberry: 23.7% TMP-SMX resistant
 - TMP-SMX: 86.3% resistant

Problems with Cranberries for Preventing UTIs?

2012 Cochrane Library



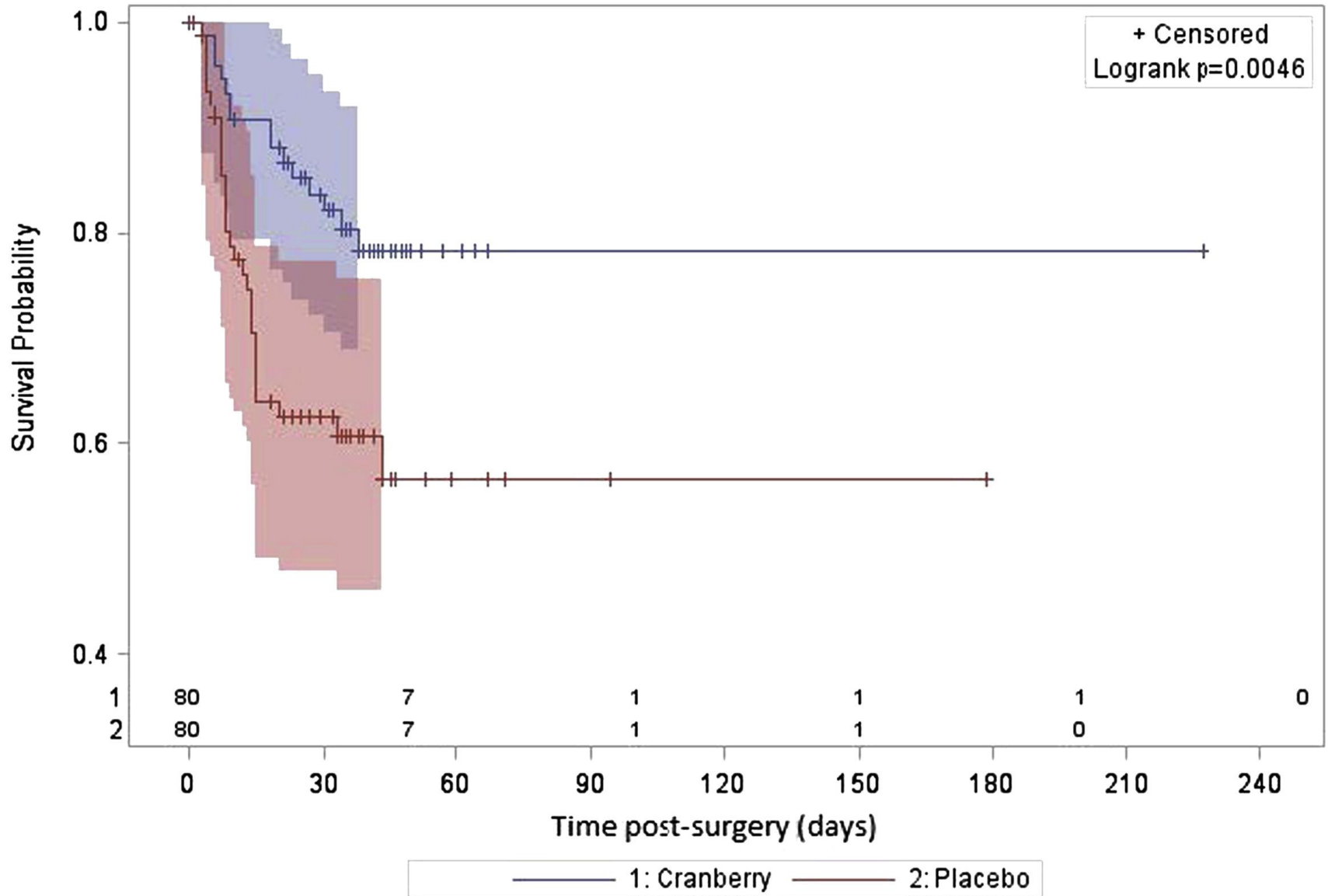
- 24 studies (n=4472, 6 cross-over, 11 parallel)
- Cranberry products DID NOT significantly ↓ incidence of UTIs at 12 months compared with placebo/water/not treatment
— RR 0.74 (95% CI 0.42–1.31)
- Most studies reported low compliance

Cranberry Summary



- Molecular interference with E.coli pili adherence to uroepithelium?
- Cheap, easy, well-tolerated... worth a try
- Not all cranberry is created equal
 - Ellura claims highest proportion of PAC
 - But its expensive - patients should know data

Maybe the story isn't over



D-Mannose

- Animal studies show inhibition of fimbria of uropathogenic bacteria
- RCT: 308 women with rUTI
 - 2g D-Mannose v. Nitrofurantoin v. nothing
 - rUTI rate 15% v. 20% v. 60% after 6 months
- More clinical trials needed
- Careful in Diabetics
- Easy & well-tolerated... perhaps worth a try

Oral Probiotics

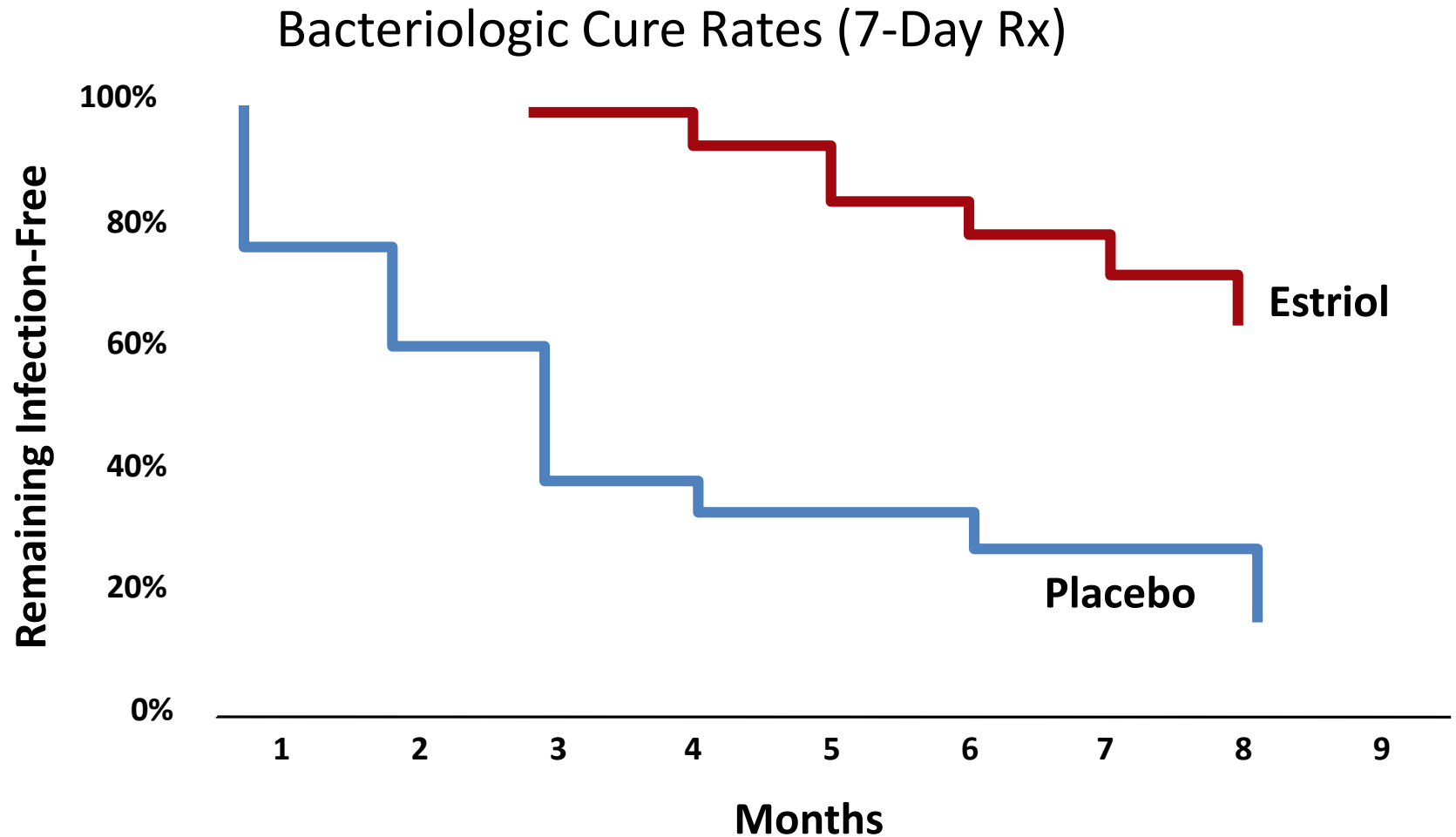
- Theory:
 - Replace ureteropathogenic E.Coli
 - Production of antimicrobial products, competition with uropathogens for Iron/nutrients and mucosal surface
- Cochrane: 9 studies of 735 (One RCT)
 - Small sample sizes
 - High risk of bias
 - Poor methodology
- No clear benefit
- Not quite harmless
 - Diarrhea, nausea, constipation
- Good choice in women with dual need

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Vaginal Estriol Cream Therapy

Elderly Women with Recurrent UTI



VAGINAL Estrogen and rUTI

- Lowers vaginal pH
 - E group: pH decrease from 5.5 to 3.8
 - Placebo: NO change
- Supports environment for lactobacillus (produces lactic acid, inhibits enteric pathogens)
 - PMP 20-30% have lactobacilli in vagina
 - With E percentage may incr. to 60-100%
- Modulates mucosal barrier to infection in lower urogenital tract

Estrogen Prophylaxis

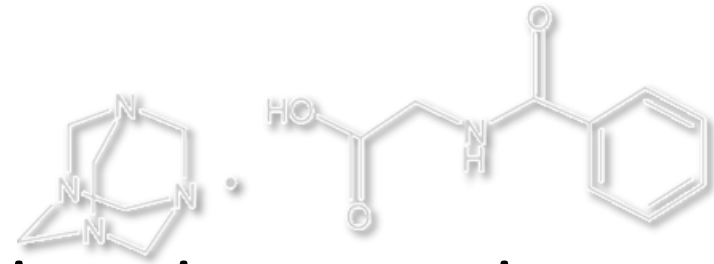
- 2016 Systematic Review
 - 5 Trials: 596 patients
- Vaginal estrogens: ALL preparations of vaginal estrogen reduced the number of UTIs compared to placebo or baseline.
- Oral estrogens :
 - 2 Studies, 72 patients
 - NO reduction in UTIs compared to placebo
 - One with reduction of urgency & dysuria



Estrogen Prophylaxis Dosing

- Vaginal estrogens: ALL preparations of vaginal estrogen reduced the number of UTIs compared to placebo or baseline.
 - CREAMS: Daily X 2 weeks then ½ gram twice weekly @ HS
 - Estrace (Mexican Yams); Premarin (Horse)
 - Tablets: Vagifem/Yuvafem – same as above
 - Estring: 1 ring Q 3 months (lowest dose)
- Some women can't use estrogen
 - Vaginal/Uterine cancer
- Some won't

Methenamine (Hiprex)



- Methenamine + Hippurate dissociates into organic acid and formaldehyde in bladder.
- Urine more hostile to E.coli?

Meta-Analysis:

- 13 studies, 2,032 pts
- RR 0.24 if given for one week
 - **Benefits long term less impressive**
- Most common AE: Urethral burning
- DOSING: 1 g PO twice daily



More effective in combination with vitamin C

- Urine acidification – Data thin
- Urinalysis confirmation

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Antibiotic Prophylaxis/RX for rUTI

- Regimen
 - PRN (self-treatment)
 - Post-coital
 - Continuous
- Best Drugs

Self-treatment with antibiotics

- Self-start, intermittent therapy
- Consider standing urine culture orders, though self-diagnosis accurate >85 to 95% of the time
- More infections but less antibiotics
 - 2.2 per year vs. 0.2 with continuous
 - Good candidates: clearly documented rUTIs, motivated, compliant
- Patient satisfaction high
 - Clinical and microbiologic resolution prompt
 - Few adverse outcomes
- Call if symptoms worsen or no better in 48 hours
- Personal Opinion:
 - Typically best for hx. c/w 3-4 infections per year

Peri-Coital Antibiotic Prophylaxis

- History has to make sense
- Small RCT
 - Placebo: 9/11 developed UTI (3.6 UTI per-patient yr)
 - TMP-SMX: 2/16 (0.3 UTI per-patient yr)
- Drug choice / timing unclear
 - TMP/SMX 1 DS PO x 1
 - Nitro 50mg
- TMP-SMX effective regardless of frequency
- In women with sexual intercourse-related rUTI, post-coital prophylaxis seems to be as effective as daily intake (Cochrane review)

Continuous Antibiotic Prophylaxis



- 2010 Cochrane Review
 - 19 RCTs with 1120 women
- Continuous Abx using cotrimoxazole, nitrofurantoin, cephalexin or a quinolone:
 - ↓ rates of RUTI compared with placebo
- Effect lasts during active Abx. intake only
- Side effects frequent
- No conclusions on optimal duration, schedule, or doses
 - Daily vs. QOD, or weekly. Monthly less effective

Continuous Prophylaxis cont.

- Typically, initiate for 6 months, stop, reassess
- Can be (safely) used for 2–5 yrs
- No apparent modification of natural history
- Emergence of resistance infrequent but sometimes problematic

Recommended Regimens

Continuous Prophylaxis

- Trimethoprim 100 mg
- Trimethoprim/sulfamethoxazole 40/200 mg
 - daily and 3X/WK effective
- Nitrofurantoin 50–100 mg
- TMP/SMZ 40/200
- Cephalexin, 125-250mg
- Fosfomicin 3 g sachet Q 10 days

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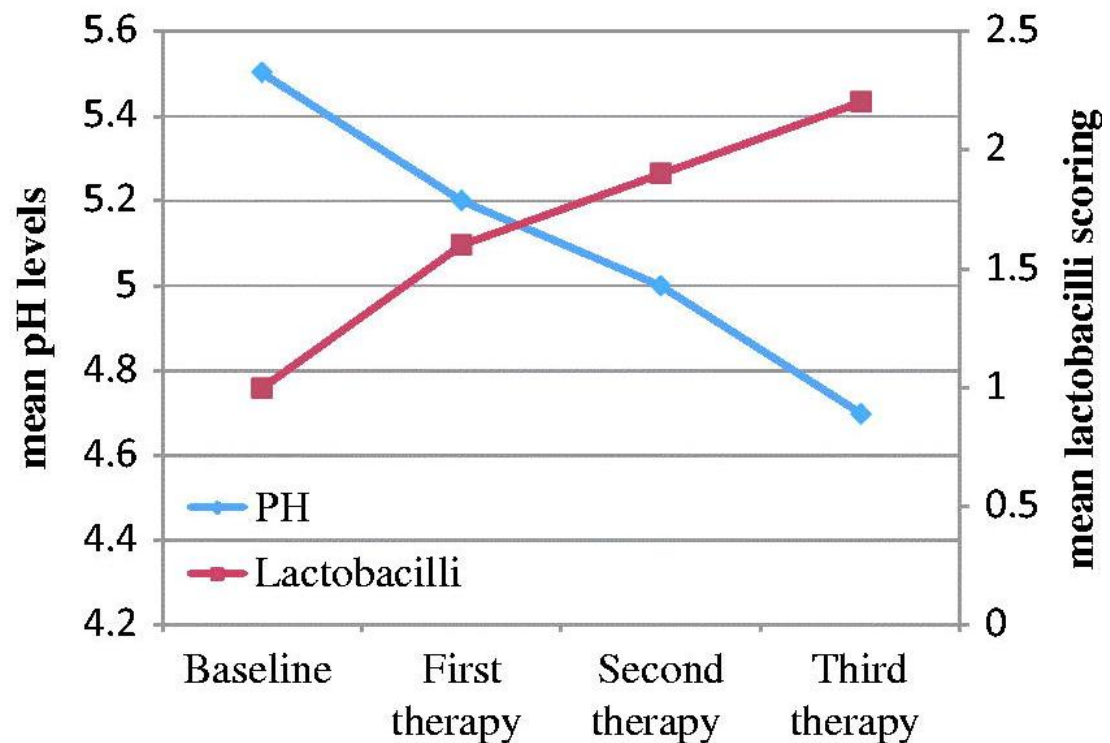
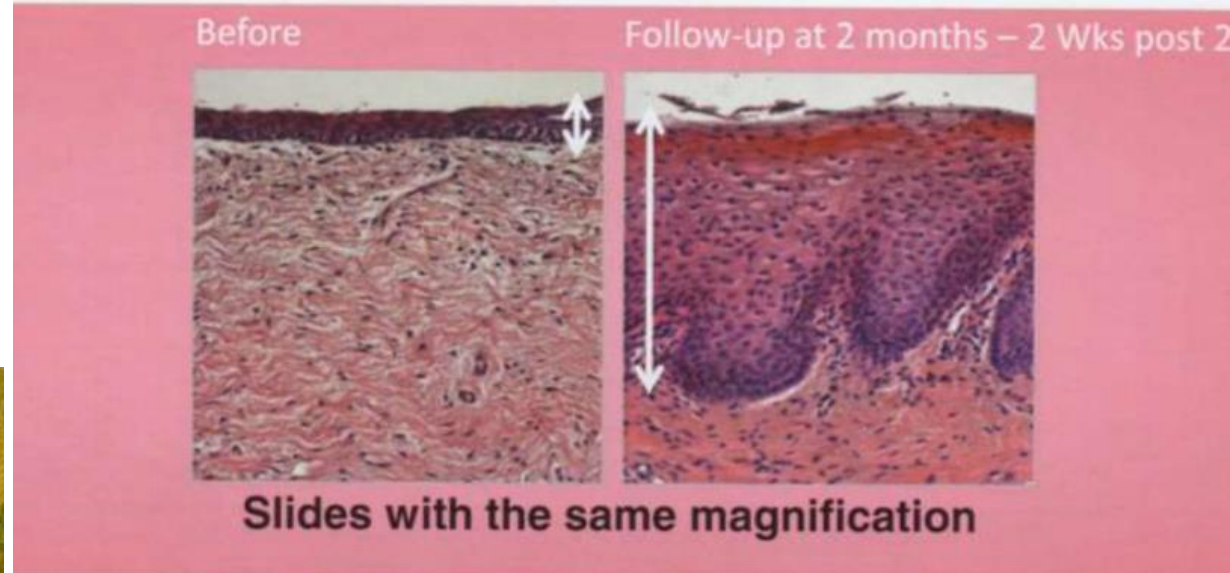
Vaginal Pro-Biotics



- Lactobacillus crispatus is normal vaginal flora, drives down pH, keeps E.coli at bay.
- Phase 2 trial of Lactin-V (Ocel) Suppositories (daily x 5, then weekly x 10)
- Phase 3 ongoing

Outcome	<i>L.crispatus</i> (n=48)	Placebo (n=48)	Analysis
UTI Recurrence	7/48 (15%)	13/48 (27%)	RR 0.5 CI 0.2-2.1
High Level Vaginal <i>E.coli</i> colonization	RR 0.07	RR 1.1	P<0.01

MonaLisa Touch™ - Cynosure



The 'end-all' probiotic???

- Fecal Microbia Transplantation for Recurrent C. Diff Infection Reduces rUTI Frequency

Pardi TR et al 2017

rUTI Summary

Treatment Options

- **Behavioral**
 - **1.5L of more water daily**
 - Change contraceptive method
 - Post-coital voiding if its not too much trouble
- **Non-Antibiotic**
 - Ibuprofen, Pyridium/Uribel, fluids and patience
 - **VAGINAL ESTROGEN** (if appropriate)
 - Hiprex and Vitamin C (**in particular short term**)
 - Maybe
 - Cranberry Pills
 - D-Mannose
 - Probiotic
 - Hopefully Lactobacillus vaginal suppository soon

rUTI Summary cont.

Treatment Options

- **Antibiotics**

- Self-start intermittent 3d
 - More UTIs but less Abx
- Post-coital single dose
 - More effective, if Hx suggestive
- Low-dose prophylaxis
 - 6 mo stop, reassess (*have data up to 5 yrs*)
 - Tmp 100mg; Nitro 50-100mg; Fosfomycin 3g Q 10 days



Consider renal imaging if urinary pH ≥ 8 (struvite calculi) or if failure to find other reversible cause (yield $< 10\%$).

Cystoscopy rarely reveals reversible cause (imaging alone has very high NPV)

Van Haarst *Urology* 2001 Lawrentschuk *I J Urol* 2006

Findings That Warrant Further Evaluation of Recurrent UTI

Asymptomatic microhematuria

Evidence of fistula (eg, fecaluria or pneumaturia)

Gross hematuria following treatment of infection

History of malignancy in the abdomen or pelvis

History of urolithiasis

History of urologic surgery or trauma

Immunocompromised state (eg, diabetes)

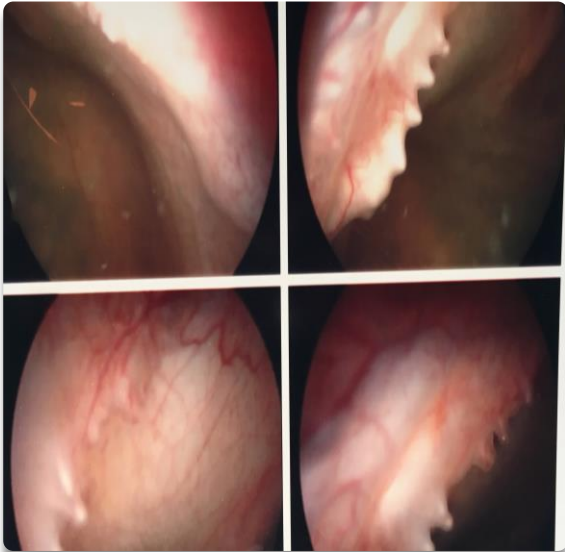
Outflow obstruction

Persistent bacteriuria following treatment with antibiotic to which it is sensitive

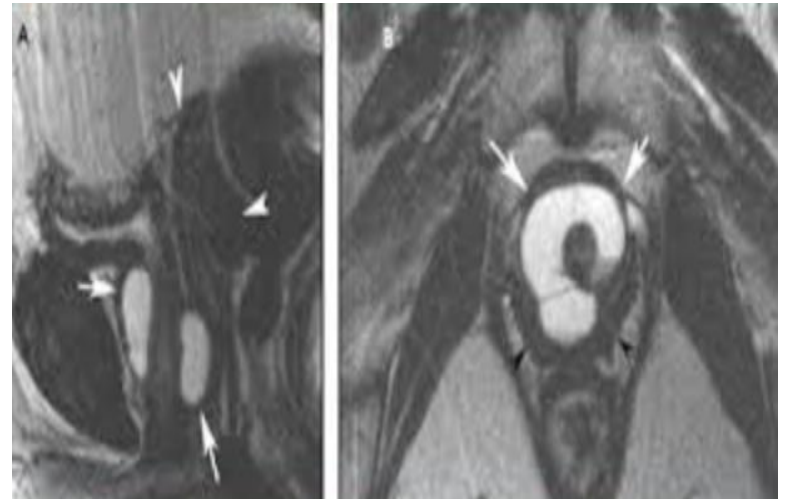
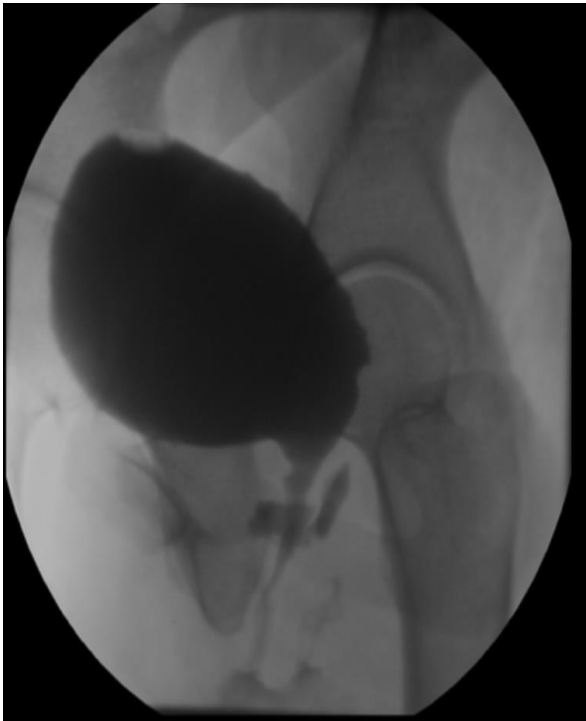
Recurrent pyelonephritis

Urea-positive bacteria associated with urolithiasis

On rare occasions we find



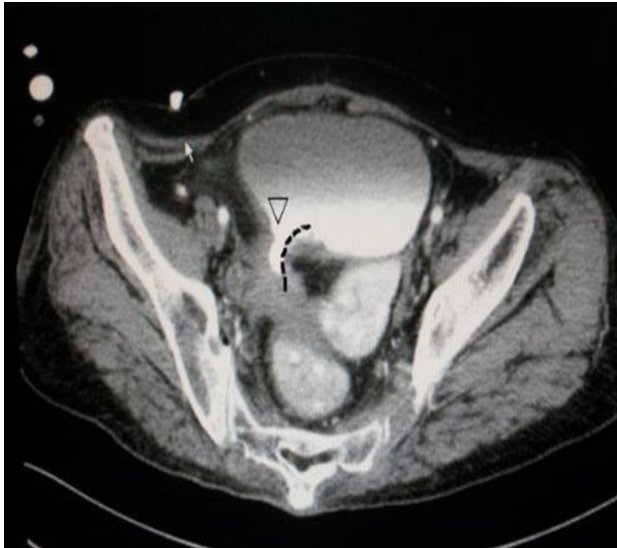
Urethral diverticulum



Vesicoureteral reflux



Colovesical fistula



Uh Oh!

Culture & Susceptibility

ENTEROBACTER CLOACAE COMPLEX

Antibiotic	Interpretation	Microtiter MIC mcg/mL
Ampicillin	Resistant	>16
	Method: <i>MICROTITER MIC (MCG/ML)-SELECT</i>	
Ampicillin/sulbactam	Resistant	>16
	Method: <i>MICROTITER MIC (MCG/ML)-SELECT</i>	
Aztreonam	Resistant	>8
	Method: <i>MICROTITER MIC (MCG/ML)-SELECT</i>	
Cefazolin	Resistant	>16
	Method: <i>MICROTITER MIC (MCG/ML)-SELECT</i>	
Cefepime	Susceptible-dose Dependent	8
	Method: <i>MICROTITER MIC (MCG/ML)-SELECT</i>	
Cefotetan	Resistant	>32
	Method: <i>MICROTITER MIC (MCG/ML)-SELECT</i>	
Ceftazidime	Resistant	>16
	Method: <i>MICROTITER MIC (MCG/ML)-SELECT</i>	
Ceftriaxone	Resistant	>2
	Method: <i>MICROTITER MIC (MCG/ML)-SELECT</i>	
Ciprofloxacin	Resistant	>2
	Method: <i>MICROTITER MIC (MCG/ML)-SELECT</i>	
Doxycycline	Resistant	>8
	Method: <i>MICROTITER MIC (MCG/ML)-SELECT</i>	
Ertapenem	Resistant	>1
	Method: <i>MICROTITER MIC (MCG/ML)-SELECT</i>	