UTI: *Pain… and Progress!*

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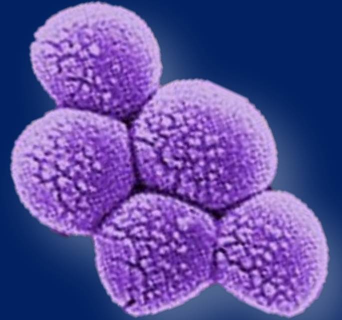
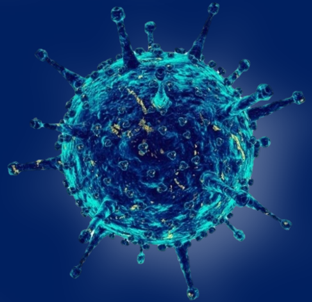
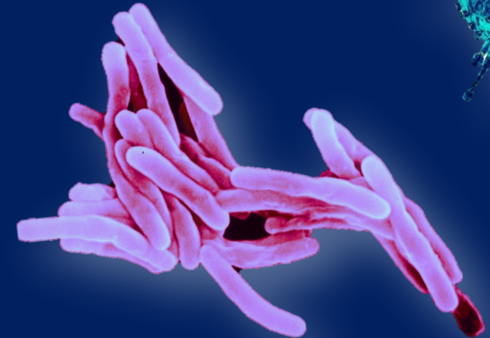


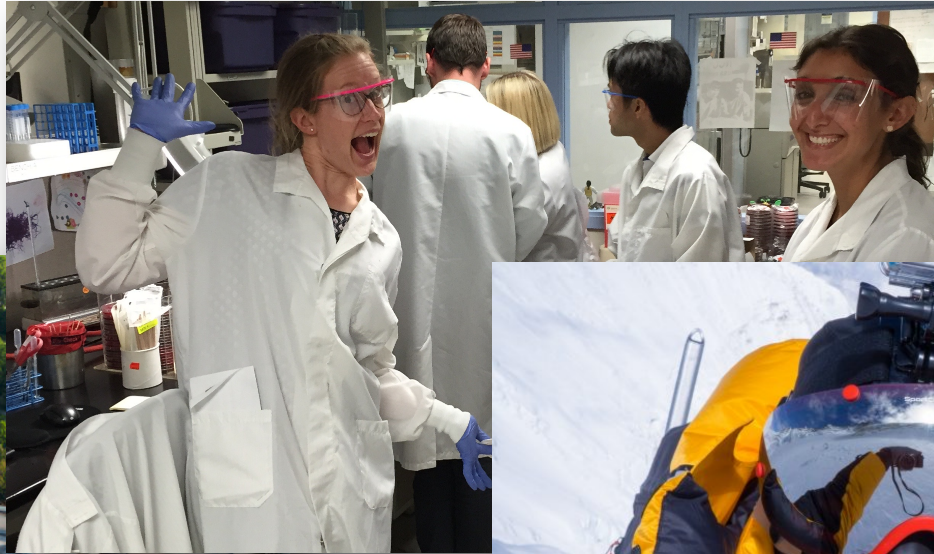


What's New in Medicine
Kennewick, WA
September 9, 2022



Antibiotic Update: *Disclosures*

Many conflicting interests…



No financial conflicts of interest

UTI: *WNIM Honorarium*

Hello. I'm **PAL-ergy**

Your pal in the fight against bogus antibiotic allergies.

Penicillin Allergy Assessment Tool

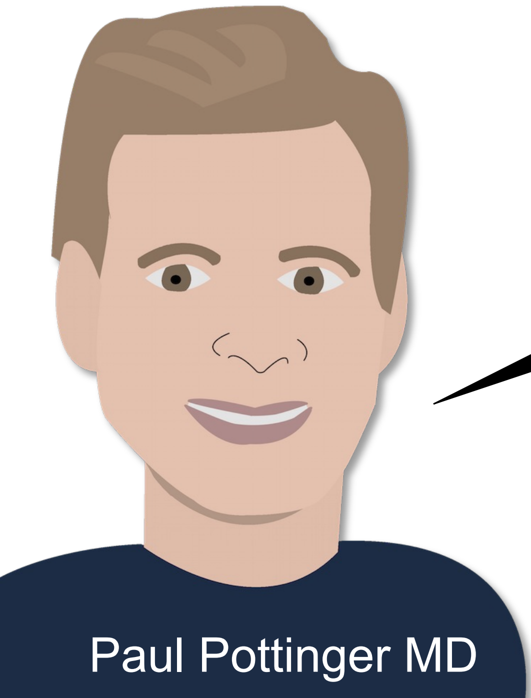
This is a place to add text. You can write anything you like here. Or here. Or even here. There is literally no limit to what you can write. So Fun!

Coming soon as an app!

UTI: *Disclaimer*

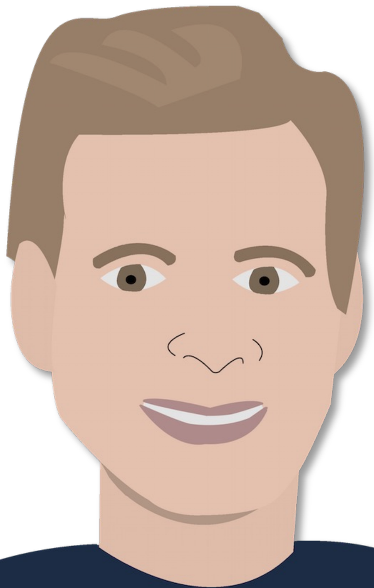
Off-Label Antibiotic Use

- Yep, we will discuss this.
- I will call it out.



UTI: *Objectives*

- Etiology & treatment for recurrent UTI
- Associate etiology & treatment of hospital-acquired UTI
- Describe the treatment of UTI in patients with indwelling catheter



Paul Pottinger MD

RUDY

rUTI: *Real UTI… or ASB?*

- Recurrent UTI (rUTI) common in older women.
- 27% of women with first UTI will have a recurrence within 6 months.
- Risk greatest in weeks following primary infection.
- rUTI pt average: 2.6 episodes / yr.

Brubaker *Female Pelvic Med* 2018

rUTI: *Risk Factors*

Same as First UTI!

- ✓ Sexual activity
- ✓ Condom use
- ✓ Diaphragm Use
- ✓ Spermicide Use
- ✓ Female sex (shorter anal-urethral distance)
- ✓ Atrophic vaginitis
- ✓ Urinary anatomic abnormalities
- ✓ Renal Stones
- ✓ Dehydration

rUTI: *Real UTI… or ASB?*

Important to get this right!

- Changed urine color or odor ≠ UTI
- Vaginal discharge ≠ UTI
- PPV for urgency falls with age… bladders may become "twitchy" in seniors… *not all that's "urgent" is UTI!*
- Delirium rarely caused by UTI... *Look for other sources!*
- Surveillance cultures rarely recommended (except before GU surgery or in pregnancy)
- *Only test when you suspect true UTI!*

Nicolle *CID* 2019

2006-09

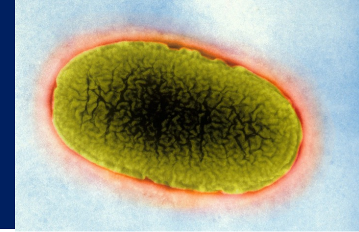
Diagnostic Value of Urine Dipstick Analysis

Dipstick	Sensitivity	Specificity	+ Likelihood Ratio	- Likelihood Ratio
Positive Leukocyte-esterase (LE)*	0.62	0.70	2.01	0.54
Positive Nitrite**	0.50	0.82	2.78	0.61
Positive LE *OR* Nitrate**	0.75	0.70	2.50	0.36
Both LE *AND* Nitrate Positive**	0.45	0.99	45	0.56

The accuracy of dipstick for diagnosis of UTI. Table adapted from data: Devillé et al.. *BMC Urol*. 2004;4:4. Likelihood ratios calculated from published data. *Non-urologic population. **General population.

Shepherd AK *Med Clin N Am* 2013

rUTI: *Diagnosis*

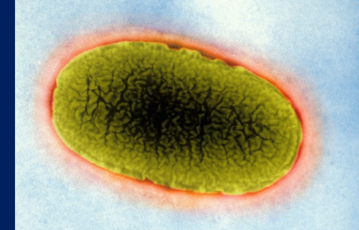


Does Urine Cx Help?

- 226 women with acute uncomplicated cystitis submitted midstream UCx and cath UCx.
- Void: *E.coli* strongly correlated with cath, but ***not*** *enterococcus* or *group B strep*.
  - ✓ If gram-positives grew in void, 61% had *E.coli* in cath, or were sterile.

Hooton *NEJM* 2013

rUTI: *Diagnosis*



Does Urine Cx Help?

- 226 wome[...] [...]ystitis
  submitt[...]
- Void[...] [...]ut ***not***
  ent[...]
  - ✓ If[...] [...]d *E.coli*
    in[...]

More evidence supporting empiric *E.coli* therapy up front in uncomplicated UTI… Culture if <u>recurrence</u>… but beware “unusual” pathogens.

Hooton *NEJM* 2013

rUTI: *When Doc & Pt Disagree*

Talking Points:

- Avoidance of harm (diarrhea, VVC,
  - ✓ Diarrhea
  - ✓ VVC
  - ✓ Allergy
  - ✓ Cognition…?
- Maintenance of effect ("I know you will need treatment at some point, we want oral options for then.")
- Cost may be less persuasive

Long-Term Antibiotic Use in Midlife Tied to Later Decline in Cognitive Function in Women

By Linda Carroll
March 24, 2022

NEW YORK (Reuters Health) - Women who report significant antibiotic use in midlife may be more likely to experience cognitive decline in later life, a new study finds.

An analysis of data from nearly 15,000 nurses revealed that women who reported at least two months of antibiotic exposure in midlife had lower mean cognitive scores seven years later, after adjustment for risk factors for cognitive decline.

The researchers behind the study, published in PLoS ONE, suggest the effect might be explained by changes in the microbiome due to the antibiotic use.

"A growing body of evidence supports that the gut microbiome may be linked to cognitive decline or the development of dementia," said Dr. Andrew T. Chan of Harvard Medical School and Massachusetts General Hospital, in Boston. "There is also evidence that long-term antibiotic use may alter the gut microbiome. Thus, our results showing that chronic antibiotic use in midlife was associated with cognitive function in later life supports a role for the gut microbiome on cognition."

Mehta *PLOS One* 2022

rUTI: *Delayed Rx?*

Waiting Might Be Fine!

RCT:

- Pts seen for suspected uncomplicated UTI.
- UA inconclusive or unimpressive.
- Std care vs. No abx prescribed until UCx positive 48 hours later.
  - ✓ Total abx consumption reduced.
  - ✓ No increase in pyelo… but pts in delayed arm had 37% longer sx duration.

Little *Brit Med J* 2010

Fluoroquinolone Alternatives: *Cystitis*

- Nitrofurantoin (*Macrobid*) 100mg PO BID x 5 days (caution in pyelo, GFR<30, age> 65)

OR

- TMP/SMX (*Bactrim*) resistance <20%: 1 DS PO BID x 3 days

OR

- Fosfomycin (*Monurol*) 3gm PO x 1 dose (not for pyelo!)
- TMP/SMX resistance >20%:
  - ✓ Cipro 500mg PO QD x 3 days *OR*
  - ✓ Cefpodoxime 100mg PO BID x 7 days

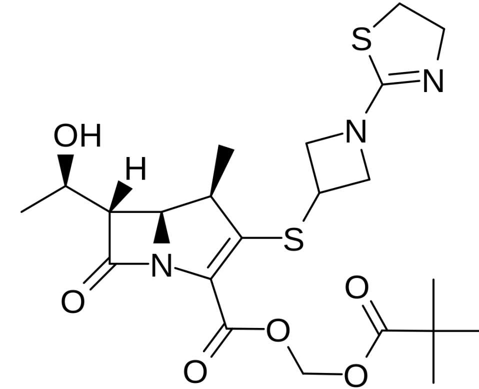
Do you know local E.coli resistance?

Modified IDSA recommendations soon

2012 IDSA Guidelines

ESBL E.coli: *Possible PO Carbapenem*

Tebipenem

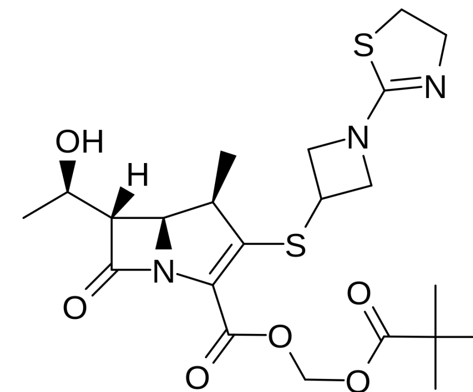


- cUTI: Non-inferior to IV ertapenem
- “Oral ertapenem”
- Dosing:
  - ✓ 600mg PO Q 8 H x 7-10 Days
  - ✓ Renal adjustment for reduced eGFR
  - ✓ be required.

Eckburg *IDWeek* 2020

ESBL E.coli: *Possible PO Carbapenem*

Tebipenem

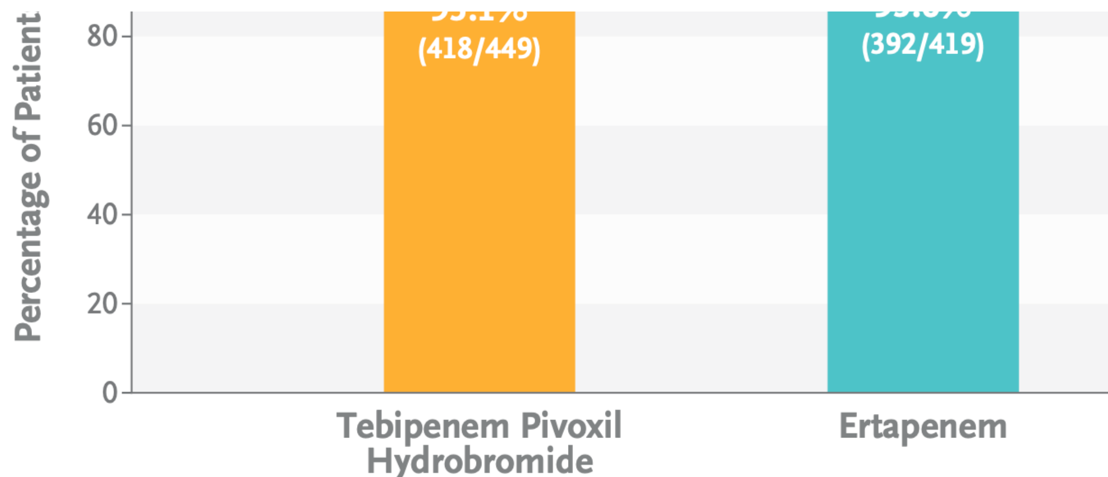


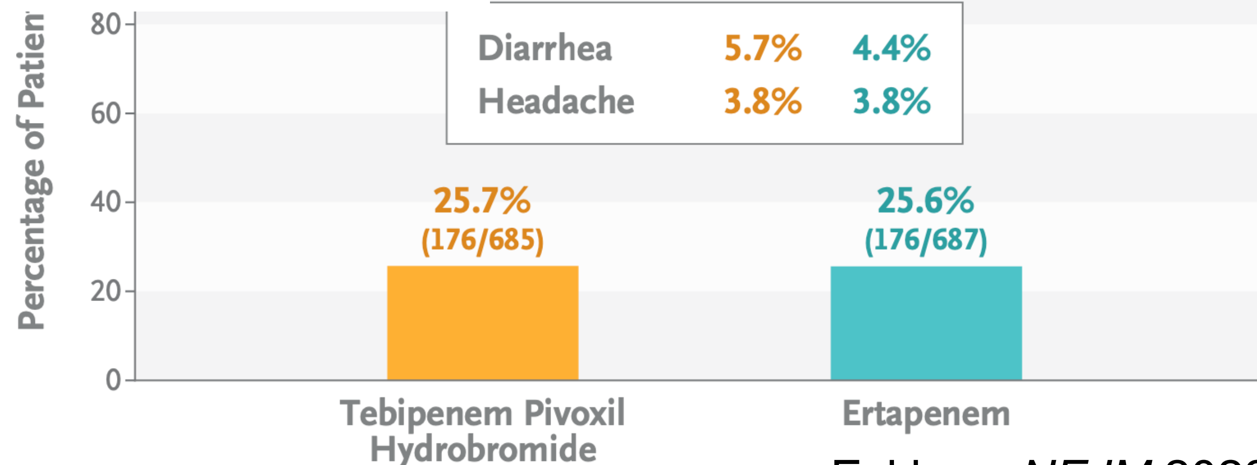
CONCLUSIONS

Among patients with complicated urinary tract infection or acute pyelonephritis, oral tebipenem pivoxil hydrobromide was noninferior to intravenous ertapenem in terms of overall response and had a similar safety profile.

Any Adverse Event

Most common

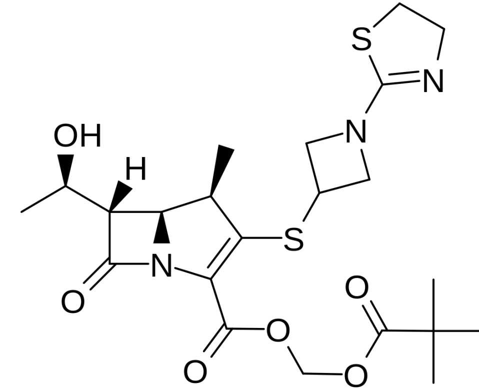




Eckburg *NEJM* 2022

ESBL E.coli: *Possible PO Carbapenem*

Tebipenem



6/27/22: “FDA ultimately concluded that Spero’s Phase 3 cUTI study of tebipenem HBr (ADAPT-PO) was insufficient to support approval and that additional clinical study would be required.”

rUTI: *Rising Resistance*

Antibiotic Susceptibility Not Looking Better Over Time

- 150,000 nationwide presenting to EDs with cUTI
- *E.coli* the single most predominant organism
    - ✓ FQ resistance > 15%
    - ✓ Nitrofurantoin resistance > 15%
    - ✓ TMP/SMX resistance > 25%
    - ✓ Ceftriaxone resistance 6%

Remember: NNT for <u>un</u>complicated cystitis is probably 4 or 5… meaning, TMP/SMX and nitro still good empiric firstline options

…FID 2022

Evaluation and Management of Acute, Uncomplicated UTI

Eligible woman telephones or presents to clinic with predominant symptoms of dysuria or urgency

Patient is triaged to a primary care consulting nurse

Patient offered the choice of ei healthcare provider or telephor patient request an

Any risk factor for complicated UTI?
- Resistance Factors (see Table 3)
- Age <18 or > 55?
- History of uro/gyn surgery or procedure within 6 months?
- Urinary catheter?
- Fever, chills, back pain?
- Nausea, vomiting?

NO

Allergies or intolerance prevent

NO

Review local resistance. Avoid antibic 20%. Prescribe one of the following:
1. Trimethoprim-sulfamethoxazole 1DS tab PO BID x 3 days OR
2. Nitrofurantoin 100mg QID x 3 days OR
3. Fosfomycin 3gm PO Once

Risk Factors for Antimicrobial Resistance

- Age > 60
- Prior History of UTI
- Chronic Medical Conditions
- Recent Hospitalization
- Any Recent Antibiotic Treatment
- Recent Travel Abroad

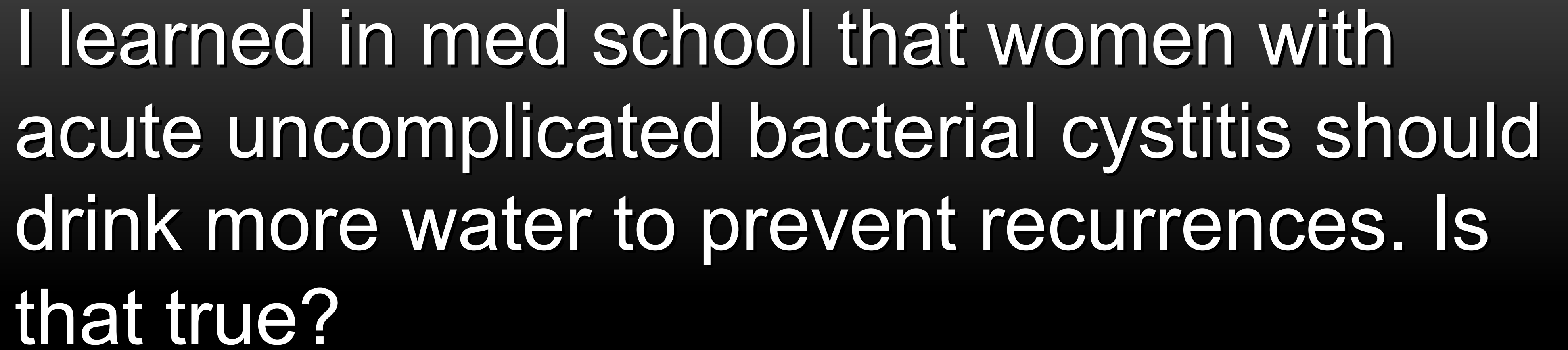
Figure 1. Adapted and modified from Sanjay S., et. al. The effectiveness of a clinical practice guideline for the management of presumed uncomplicated urinary tract infection in women, Am. J. Med., Volume 106, Issue 6, June 1999, Pages 636-641.

rUTI: *Telephone Triage*

- Fewer office visits.
- Fewer UA's and UCx's.
- More appropriate antibiotic selection.
- No increased incidence of harm or progression to pyelo.
- Likely improved pt satisfaction.
- *Please beware the caveats!*

Saint *Am J Med* 1999

rUTI: *Dehydration*



Paul Pottinger MD

rUTI: *Dehydration*

Drink To Your Health!

- ✓ 140 Bulgarian women with 1.5 L fluid / day
- ✓ Randomized to additional 1.5 L or no change
- ✓ Followed x 12 months
- ✓ Consider oral hydration!
- ✓ "Ensure the bowl is clear after you void."

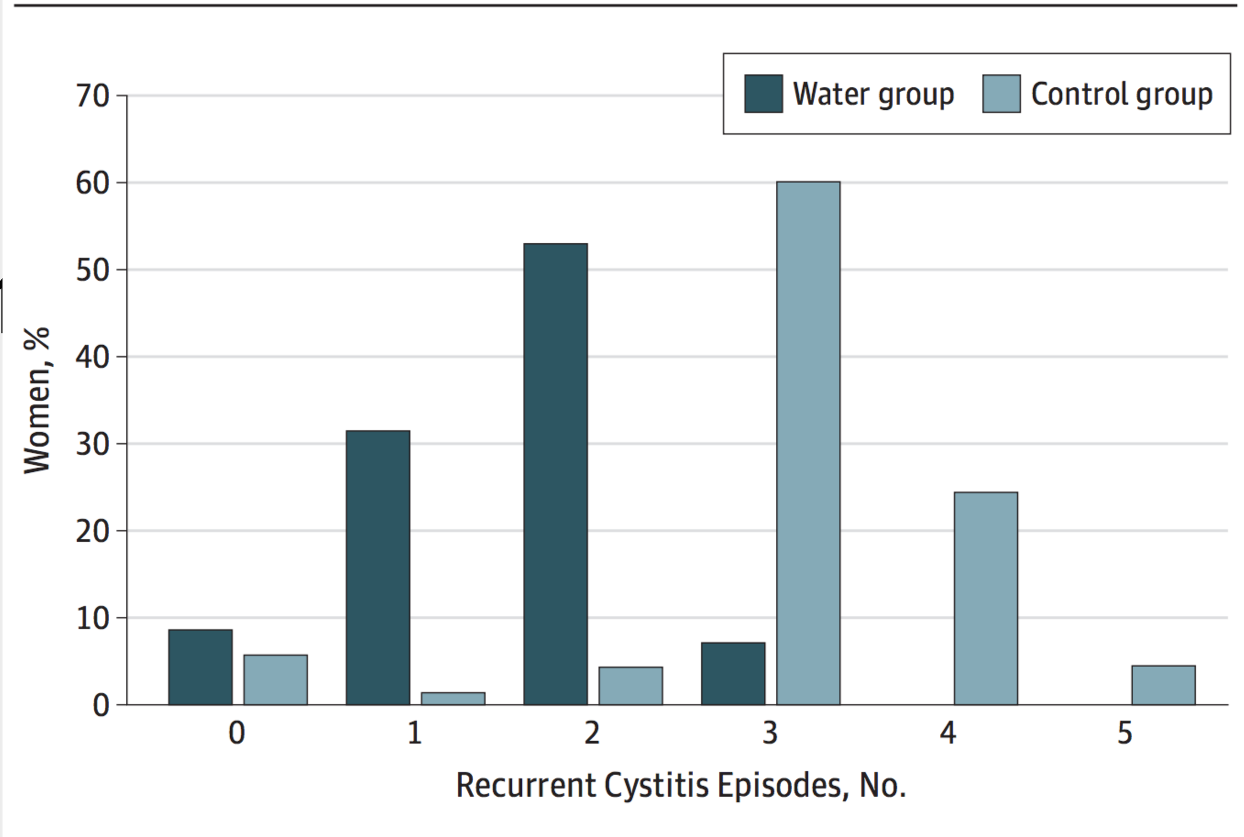


Figure 2. Recurrent Cystitis Episodes by Study Group

Number of recurrent cystitis episodes during the 12-month follow-up, percent of women by study group. All 140 women who underwent randomization were included in the analysis.

Hooton et al 2018

rUTI: *Pre-Menopause*

Sex-Associated rUTI

- Common trigger of symptomatic UTI
- Cause unclear… urethral trauma, microbe translocation seems likely. Spermicide a clear risk factor
- Post-coital abx can help… TMP/SMX (40 mg/200 mg) vs. placebo (0.3 vs 3.6 episodes per patient-year).
- Benefit similar to hydration.
- Post-coital voiding is safe, free, may help!
- Can spermicide with other contraception

Stapleton *JAMA* 1990

rUTI: *Pre-Menopause*

Antibiotic dosing for continuous or postcoital prophylaxis of recurrent cystitis in women

Antibiotic	Dosing for continuous prophylaxis	Dosing for postcoital prophylaxis
Nitrofurantoin	50 mg once daily **OR** 100 mg once daily	50 mg once **OR** 100 mg once
Trimethoprim-sulfamethoxazole	40 mg/200 mg (half a single-strength tablet) once daily **OR** 40 mg/200 mg (half a single-strength tablet) three times weekly	40 mg/200 mg (half a single-strength tablet) once **OR** 80 mg/400 mg (single-strength tablet) once
Trimethoprim	100 mg once daily	100 mg once
Cephalexin	125 mg once daily **OR** 250 mg once daily	250 mg once
Cefaclor	250 mg once daily	
Fosfomycin	3 g every 7 to 10 days*	

The choice of antibiotic should be based upon the susceptibility patterns of the strains causing the patient's previous cystitis, history of drug allergies, and potential for interactions with other medications. We mainly choose between nitrofurantoin and trimethoprim-sulfamethoxazole, if appropriate.

- All provide similar benefits
- Consider time-limiting to 3-month blocks

Hooton *UTD* 2022

rUTI: *Post-Menopause*

Post-Menopausal rUTI

- Atrophic vaginitis / vulvitis may cause rUTI.
- Cause unclear… Higher vaginal pH? Thin squames ➔ easier bacterial access?
- May still be associated with sex!
- Topical estrogen or "estring" generally safe, well tolerated, normalizes microbes, reduces UTI (RR 0.25-0.64)

Consider <u>local</u> HRT in rUTI with vulvar atrophy… but be patient! Benefits may take months to appear.

Beerepoot *J Urology* 2013

rUTI: *Post-Menopause*

Continuous Antibiotic Prophylaxis?

- Data mixed, but at least in short term can help
- Meta-analysis 430 women with rUTI 6-12 mo abx vs placebo
- Microbiologic recurrence 0 - 0.9 episodes per patient-year with abx vs 0.8 - 3.6 in placebo (RR 0.21, 95% CI 0.13-0.33).
- Clinical recurrence lower (RR 0.15, 95% CI 0.08-0.28).
- Benefit vanished after abx stopped (RR 0.82, 95% CI 0.44-1.53).
- Abx harms difficult to capture (resistance, CDI, etc).

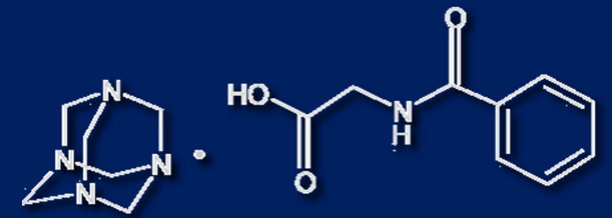
Albert *Cochrane* 2004

rUTI: *Post-Menopause*

Continuous Antibiotic Prophylaxis?

- Tempting, but should be last resort!
- Low-dose nitro or TMP/SMX most popular
- Consider limiting to 3 months then reassessing

rUTI: *Hippuric Acid?*



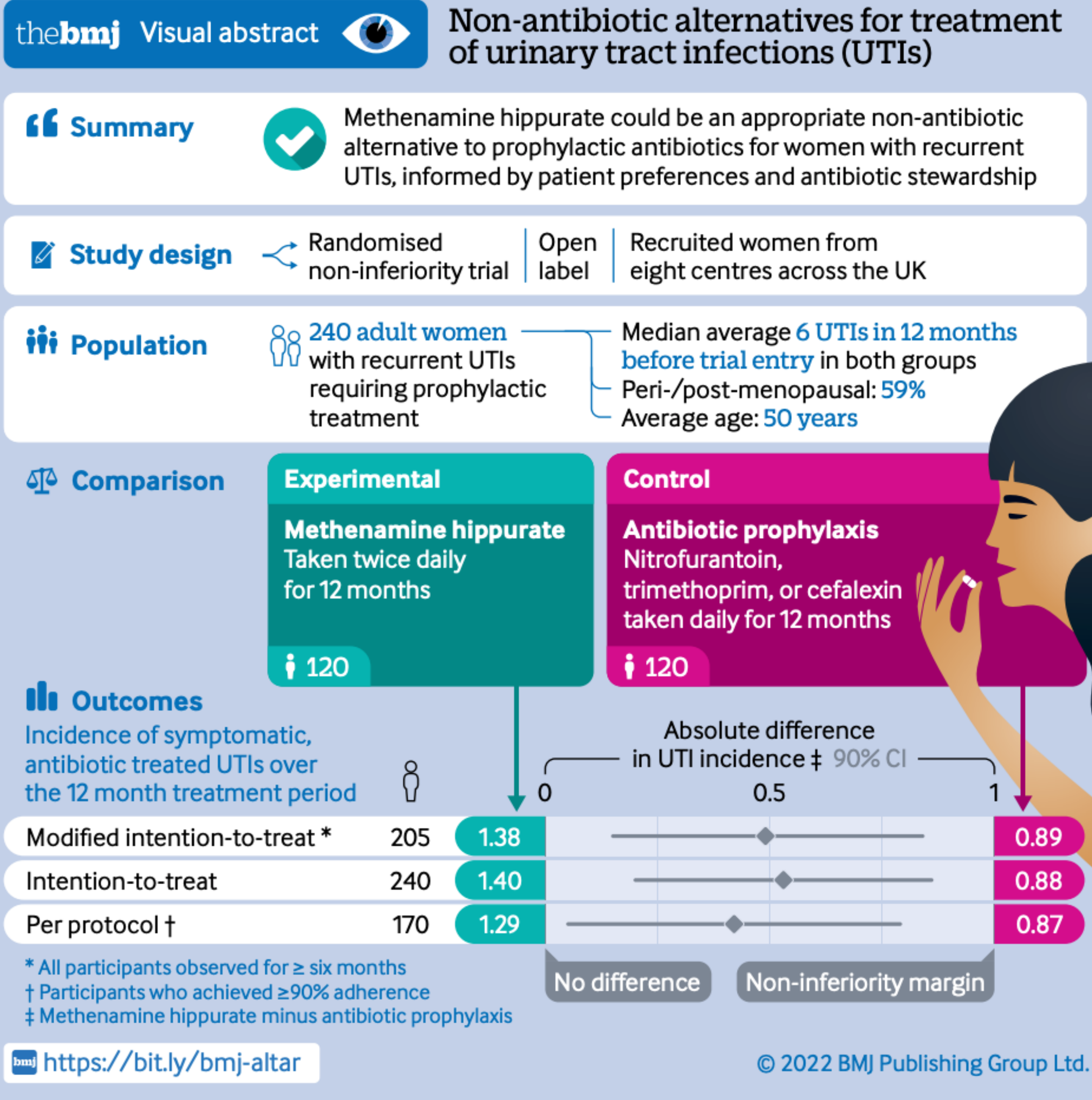
- Methenamine + Hippurate dissociates into organic acid and formaldehyde in bladder.
- Urine more hostile to *E.coli?*
- Meta-Analysis:
  - ✓ 13 studies, 2,032 pts
  - ✓ RR 0.24 if given for one week; benefits long term less impressive
  - ✓ Most common AE: Urethral burning (!)

Lee *Cochrane Rev* 2012

rUTI: *Hippuric Acid?*

ALTAR Trial

- Methenamine statistically non-inferior to abx prophylaxis
- AE comparable (24% in abx vs 28% in methenamine... generally mild)
- Open label design… larger trials welcome



Harding *Brit Med J* 2022

rUTI: *Cranberry Juice?*

- Molecular interference with *E.coli* pili adherence to uroepithelium?
- *No significant clinical be* including two recent ran to better prevention in o
- Easy, well-tolerated… p *L.crispatus* probiotics co

ellura®

PAC Potency

anti-adhesion activity

100%

<50%

inferior

inactive (0%)

PACs from concentrated juice extract

soluble

whole berry products

insoluble PACs from a blend of pomace* & juice

other cranberry products

insoluble PACs from pomace*

36 mg PAC

<36 mg PAC

average of <36 mg PAC

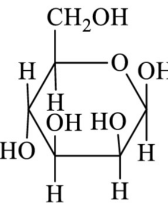
*pomace: is the pulp, seeds, stems, and skins of the berry.

rUTI: *Cranberry Juice?*

"Cranberry, in a formulation that is available and tolerable to the patient, may be offered as prophylaxis, including oral juice and tablet formulations, as there is not sufficient evidence to support one formulation over another when considering this food-based supplement. In addition, there is little risk to cranberry supplements, further increasing their appeal to patients. However, it must be noted that fruit juices can be high in sugar content, which is a consideration that may limit use in diabetic patients."

Anger *J Urology* 2019

rUTI: *D-Mannose?*

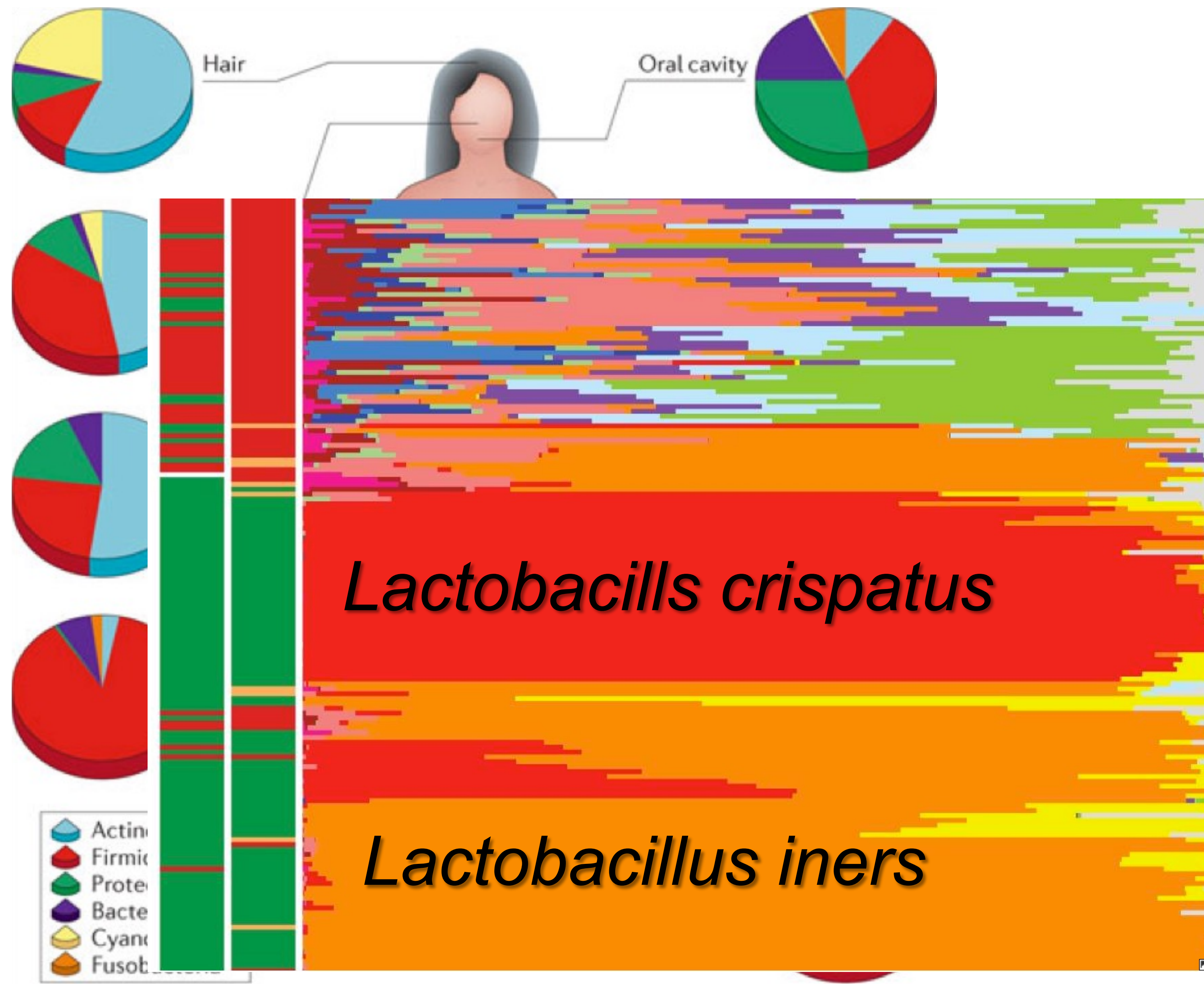


Same idea as PAC: Molecular interference with *E.coli* pili adherence to uroepithelium?

- ✓ 308 Croatian women with rUTI
- ✓ Randomized to D-mannose 2gm daily vs Nitrofuratoin 50mg Daily vs observation. rUTI at 6 months:
  - Observation 62 (60.8%)
  - D-mannose 15 (14.65) RR 0.239, P<0.0001
  - Nitrofurantoin 21 (20.4%) RR0.335, P<0.0001

Consider 2gm PO daily or BID… but do not over-promise results.

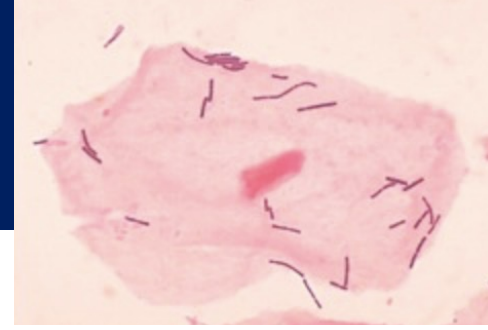
Kranjčec *World J Urology* 2014



Nature Reviews | Genetics

Fredricks *Plos One* 2012

rUTI: *Probiotics?*



- *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)

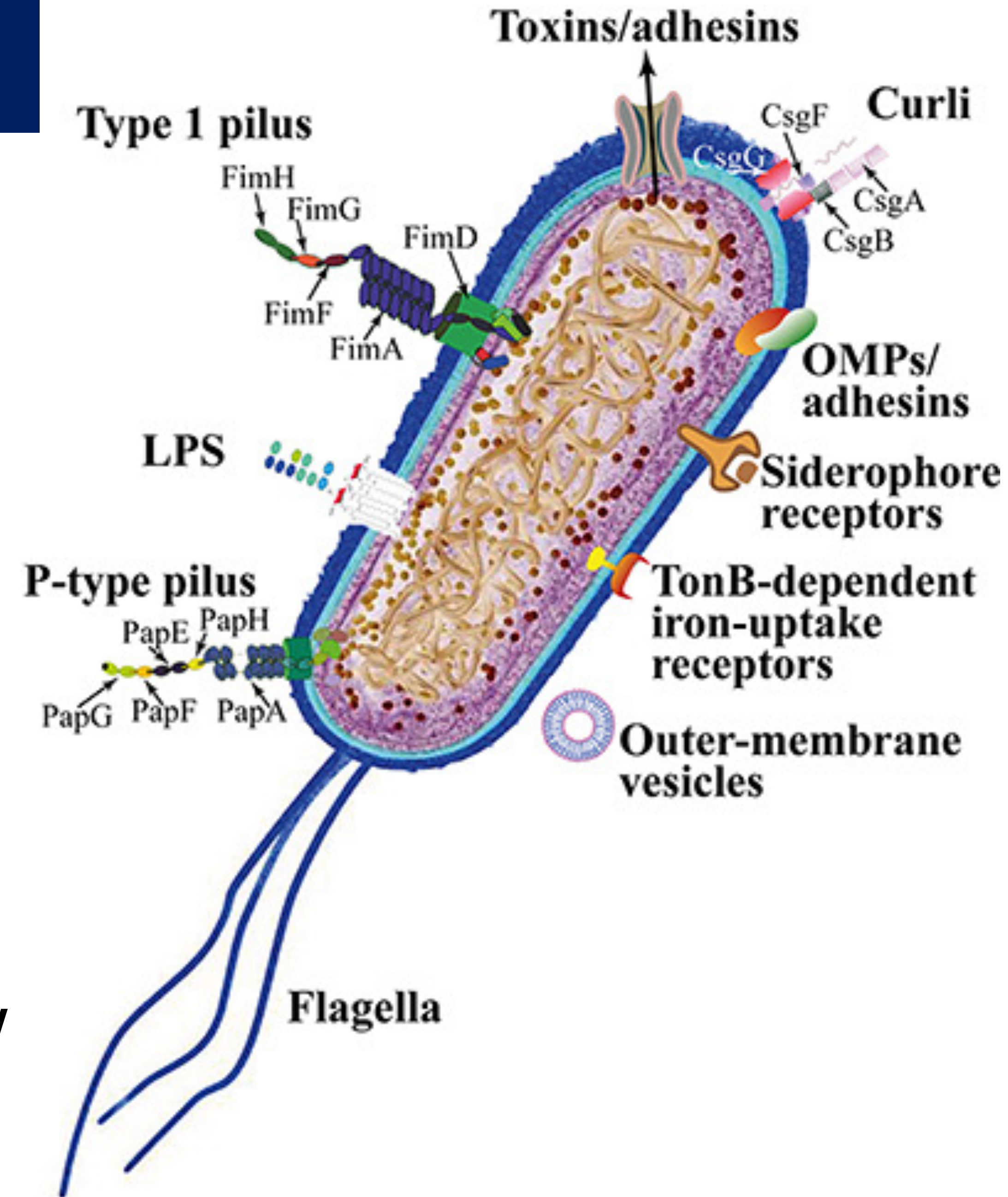
Outcome	*L.crispatus* (n=48)	Placebo(n=48)	Analysis
UTI Recurrence	7/48 (15%)	13/48 (27%)	RR 0.5 CI 0.2-2.1
High Level Vaginal *E.coli* colonization	RR 0.07	RR 1.1	P<0.01

Stapleton *CID* 2011

rUTI: *Post-Menopause*

Immunize against UTI?

- Some E.coli much more likely to infect than others… Uropathogenic E.coli (UPEC).
- Vaccines containing pathogen fragments trialed since late 1990s… often with modest benefit that wanes after weeks.
- New generation of vaccines now in development.



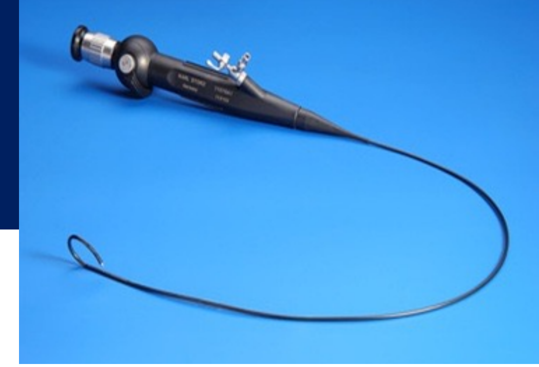
rUTI: *Post-Menopause*

Immunize against UTI?

- StroVac deployed in Germany:
- 124 vaccinees vs 49 Nitro, followed x 24 months.
- Success = 0-1 episodes / year
- Success in first 12 months: 86.8% in StroVac group vs 91.8% in Nitro group ($p = 0.22$).
- Side effects: 2.3% in the StroVac group chose no booster vs 18.4% in Nitro group stopped medication prematurely, mostly due to mild diarrhea.

Nestler *Int Urology Nephrology* 2021

rUTI: *Post-Menopause*



Need Help?

- Always consider intercourse association.
- Uterine or Rectal Prolapse may elevate risk.
- Check PVR.
- Consider renal U/S 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

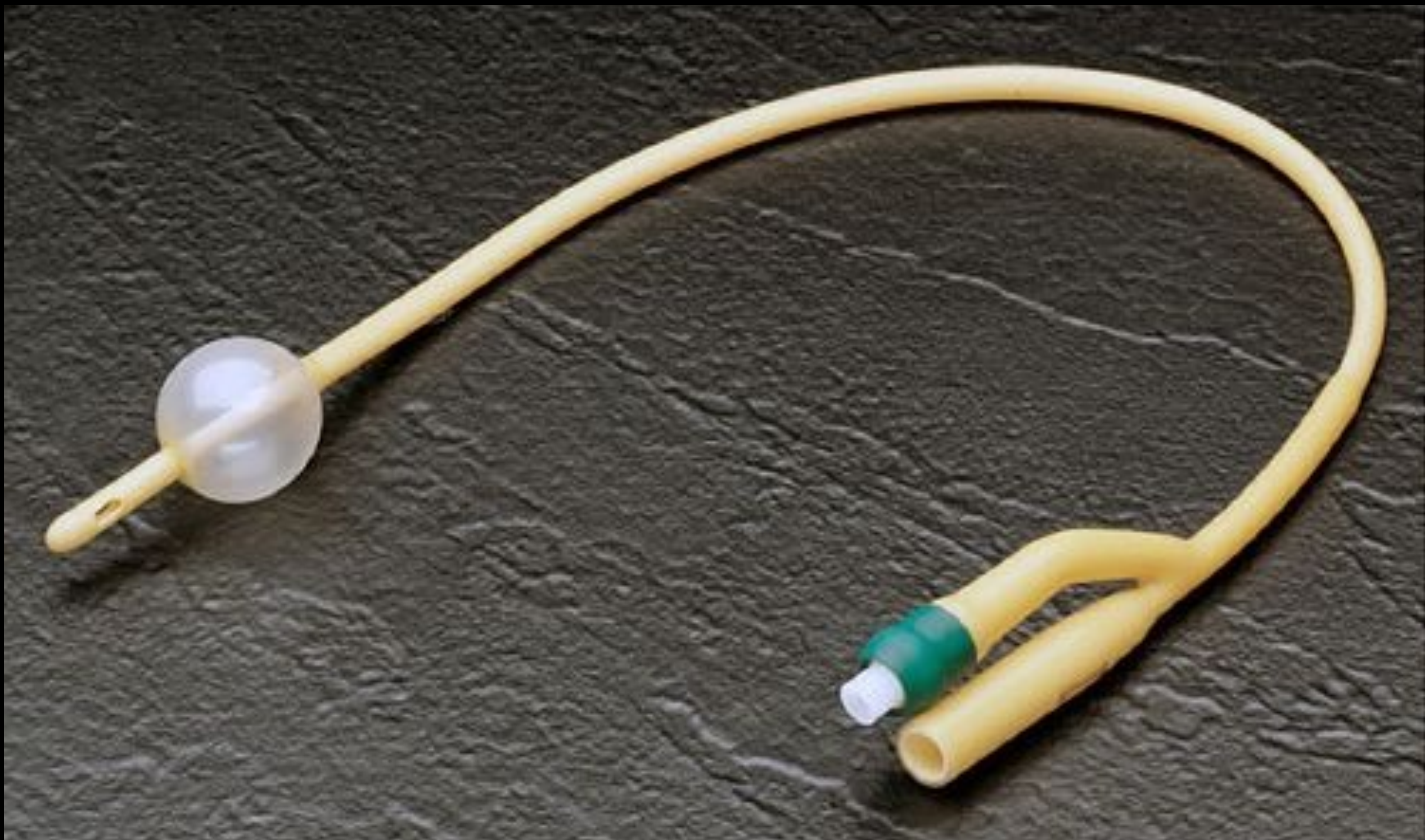
HISTORY AND PHYSICAL EXAM

– Confirm prior UTI diagnoses
– Obtain urinalysis, urine culture/sensitivity
– Perform pelvic exam

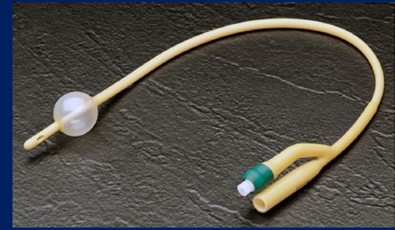
The Index Patient is an otherwise healthy adult female with a recurrent uncomplicated UTI. Patients with complicating factors such as the following are outside the scope of this document:

– Anatomic or functional abnormality of the urinary tract
– Immunocompromised host
– Multi-drug resistant bacteria

Anger *J Urology* 2019



CAUTI: *Prevention is Everything*

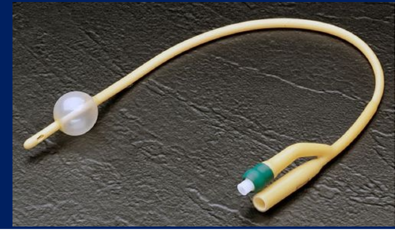


- Use foley only when necessary!
- Aseptic insertion technique
- Maintain securely, proper bag placement
- Know who has a Foley and why (!)
- Condom caths or PureWick when feasible
- Remove them ASAP

TIME + TUBE = TROUBLE

Disinvade your pt ASAP

CAUTI… or ASB?



Really important to get this right!

Foley Catheters!

- “One-Point Restraint”
- “WTF?”
- Beware the Auto-TURP… Securement is key!
- Colonization approaches 100% after a week…

CAUTI vs ASB: *Delirium & Bacteriuria*

I'm skeptical that my patient's delirium is due to bacteriuria… but their UCx is positive. What should I do?

Agree! Delirium alone very rarely due to bacteria in the urine

CAUTI vs ASB: *Delirium & Bacteriuria*

IDSA Guidelines

"In older patients with functional and/or cognitive impairment with bacteriuria and delirium (acute mental status change, confusion) and without local genitourinary symptoms or other systemic signs of infection (eg fever or hemodynamic instability), we recommend assessment for other causes and careful observation rather than antimicrobial treatment (strong recommendation, very low-quality evidence)."

Nicolle 2019

CAUTI vs ASB: *Delirium & Bacteriuria*

IDSA Guidelines

“Delirium in the frail and older nursing-home resident is a condition strongly associated with underlying dementia that may be precipitated by a number of infectious and noninfectious conditions, including medications and metabolic disorders. Data supporting an association between delirium and an underlying infection in nursing-home residents are limited, and existing studies exhibit a number of methodological flaws.”

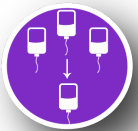
Rowe 2020

4 Moments of Stewardship: *CAUTI*

Boil our approach into 4 moments...

1. Does my pt have an infection that needs abx?

2. If so... have I ordered cultures before abx? And what empiric abx should I choose?



3. It's a new day... Can I stop abx, or deescalate spectrum, or convert IV to PO?

4. If abx still needed... how long should I treat?

Tamma *JAMA* 2019

Moment #1: *Does my pt need abx?*

UTI... or ASB?

- Colonization (asymptomatic bacteriuria): Endogenous flora ascends urethra (common in elderly). Abx NOT indicated.
- Infection (UTI): Inflammatory response to invasive bugs (rare). Abx for this subset only.

Diagnostic Value of Urine Dipstick Analysis

Dipstick	Se			
Positive Leukocyte esterase (LE)				
Positive Nitr				
Positive LE *OR* Nitrate**	0.7			
Both LE *AND* Nitrate Positive**	0.45	0.99	45	0.56

Positive predictive value of UA usually much, much lower in elderly or catheterized women than young women. *Your pre-test suspicion is key.*

The accuracy of dipstick for diagnosis of UTI. Table adapted from data: Devillé et al.. *BMC Urol*. 2004;4:4. Likelihood ratios calculated from published data. *Non-urologic population. **General population.

Shepherd AK *Med Clin N Am*

Moment #1: *UTI Testing....*

Microscopic analysis

Pyuria: majority of symptomatic UTIs have pyuria…
but *lower PPV among catheterized pts*

Gram stain for bacteria: >1 organism per hpf on
uncentrifuged urine is $>10^5$ on culture

Culture

Method: collect from mid-stream or sterilized tube port, not bag
Inoculate 1 to 10 μl onto agar plate

Criteria for *Enterobacteriaceae* UTI

- Symptomatic women
  10^2: sensitivity 95%, specificity 85% for cys
- Asymptomatic women
  10^5: used in high risk clinical settings & resea

These data from ambulatory voided urine, NOT catheterized pts!

Moment #2: *UTI Cultures....*

<u>U/A with Reflexive Culture</u>

1) Test shrewdly (look for other causes of fever or confusion)
2) U/A First
3) If U/A normal, no urine culture!
4) If U/A Abnormal, proceed to culture

<u>Benefits</u>

1) Without a positive culture, less temptation to treat.

<u>Caveats</u>

1) Neutropenic
2) Screening in pregnant women, pre-urologic surgery
3) What is “abnormal” U/A…?

BROAD SPECTRUM abx will select resistant mutants

rUTI: *Resource*

Management of Urinary Tract Infections in the Era of Increasing Antimicrobial Resistance

Amanda Kay Shepherd, MD[a,*], Paul S. Pottinger, MD[b]

Med Clin N Am July 2013 (PMID: 23809723)

Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline

Jennifer Anger, Una Lee, A. Lenore Ackerman, Roger Chou, Bilal Chughtai, J. Quentin Clemens, Duane Hickling, Anil Kapoor, Kimberly S. Kenton, Melissa R. Kaufman, Mary Ann Rondanina, Ann Stapleton, Lynn Stothers and Toby C. Chai

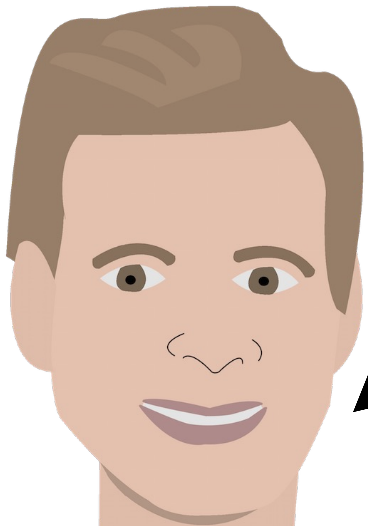
From the American Urological Association Education and Research, Inc., Linthicum, Maryland

https://doi.org/10.1097/JU.0000000000000296
Vol. 202, 282-289, August 2019

UTI: *Conclusions*

- rUTI
  - ✓ Confirm diagnosis
  - ✓ Treat per guidelines
  - ✓ Look for prevention strategies
- CAUTI
  - ✓ ASB vs UTI
  - ✓ Treat only if necessary
  - ✓ Shrewd use… meticulous device care

Truly... Thank You



Paul Pottinger MD

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