

# RECURRENT URINARY TRACT INFECTIONS



Keila Muñiz, MD

St. Joseph's Physicians Urogynecology

# LEARNING OBJECTIVES

- Definition
- Epidemiology
- Evaluation
- Treatment
- Prevention



# What are Recurrent UTIs?

- $\geq 2$  infections in six months or  $\geq 3$  infections in 12 months
- Acute simple cystitis
  - No s/sx of upper tract or systemic infection
- Usually reinfection rather than relapse
- Does not apply to pregnant women or renal transplant patients



# EPIDEMIOLOGY



# Incidence

- rUTI is common!
  - Young women: 27% experienced at least 1 infxn within 6 mo and 2.7% had 2<sup>nd</sup> recurrence in same period<sup>1</sup>
  - E. Coli more commonly the culprit<sup>2</sup>
  - Women 17-82yo: 44% had a recurrence within 1 yr<sup>3</sup>
  - 11.3 million women had at least 1 UTI treated with Abx in 1995<sup>4</sup>
    - Estimated annual cost \$1.6 billion
    - Over 20 yrs, \$25.5 billion



# Risk Factors

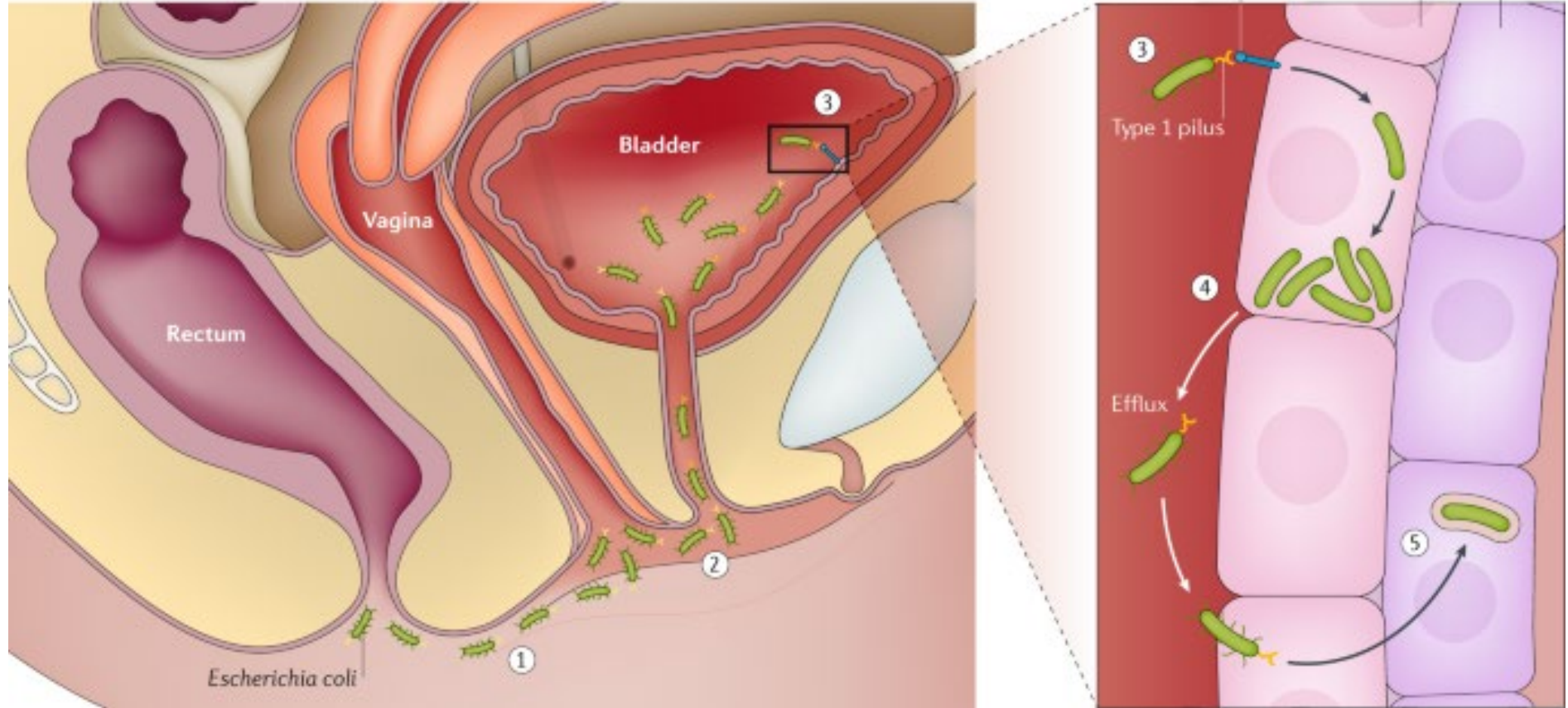
## Behavioral:

- Intercourse<sup>5</sup>
- Spermicide use<sup>6,7</sup>
- Case control study n=482<sup>8</sup>
  - Spermicide, new sex partner, UTI ≤15yo, mother with rUTI
- No association with voiding, freq of urination, delayed voids, wiping patterns, douching, hot tub use, tight clothes, BMI<sup>8</sup>

## Anatomic/Urologic: important for post-menopausal women

- Case control study n=202<sup>9</sup>
  - Urinary incontinence (41 vs 9 %)
  - Anterior vaginal wall prolapse (19 vs 0 %)
  - Large PVR (28 vs 2 %)
- Less important in pre-menopausal women<sup>10</sup>
  - No differences seen in urethral length, PVR or voiding<sup>10</sup>

# Pathogenesis

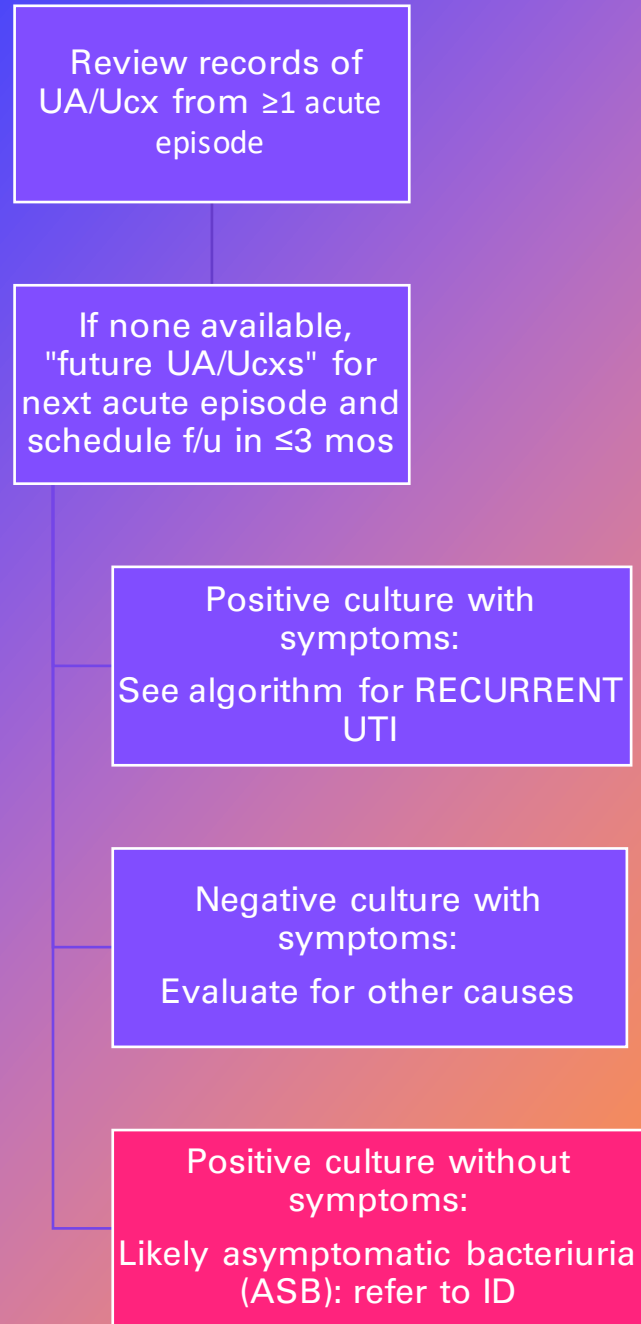


Gupta K, Stamm WE. Pathogenesis and management of recurrent urinary tract infections in women. *World J Urol* 1999; 17:415.  
Sihra, N., et al. Nonantibiotic prevention and management of recurrent urinary tract infection. *Nat Rev Urol* 15, 750–776 (2018).

# EVALUATION







# Phase 1: Evaluation of Symptoms and Culture Data

# Confirm the Diagnosis!



Dysuria is the key symptom

Frequency, urgency, gross hematuria and suprapubic pain may be reported but variable

In young women: 90% probability of UTI when reporting dysuria and frequency in absence of vaginal discharge or irritation

Dx less likely if pt reports vaginal discharge or irritation

Urinary odor and cloudiness not reliable UTI sx

**Urine culture is key!**

# Negative Culture...now what?

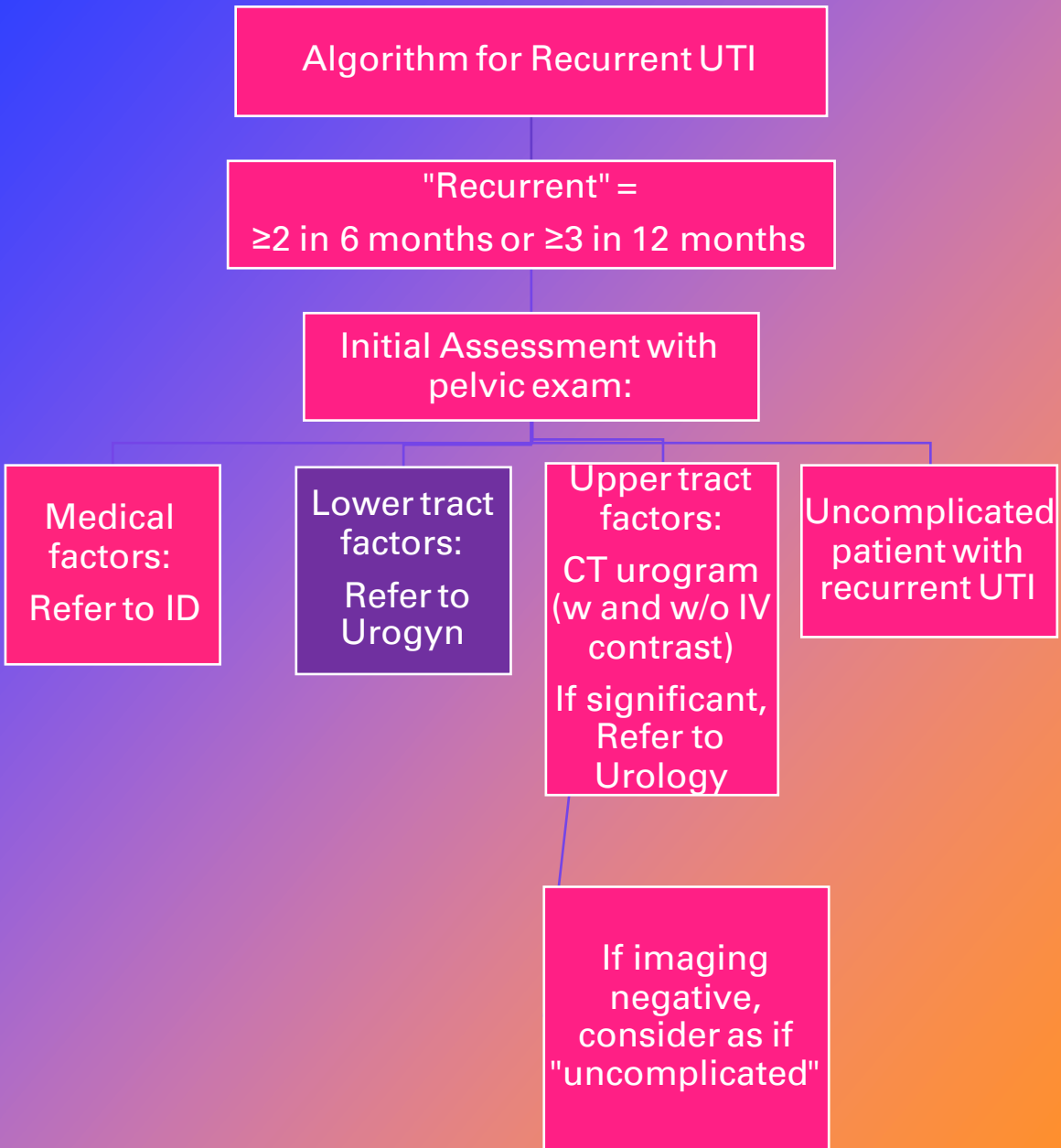
- Evaluate for other causes:
  - If hematuria present on UA ( $\geq 3$  RBC) refer to urology or urogynecology
  - Vaginitis
  - Genitourinary Syndrome of Menopause
  - Cervicitis
  - HSV
  - Urethritis
  - Interstitial Cystitis/Painful Bladder Syndrome
  - Vulvodynia



# Positive Culture but NO Symptoms

- Asymptomatic Bacteriuria (ASB) = positive culture (>100K CFU) without Sx
  - ID consult
- **ASB should not be treated with antibiotics!**
- Treatment
  - Unlikely to sterilize urine
  - Contributes to increased antibiotic resistance
  - Does not necessarily lead to decreased UTIs
- Only indications for treatment of ASB are pregnancy and planned invasive urinary tract procedures!





## Phase 2: Evaluation of Women with Documented rUTI



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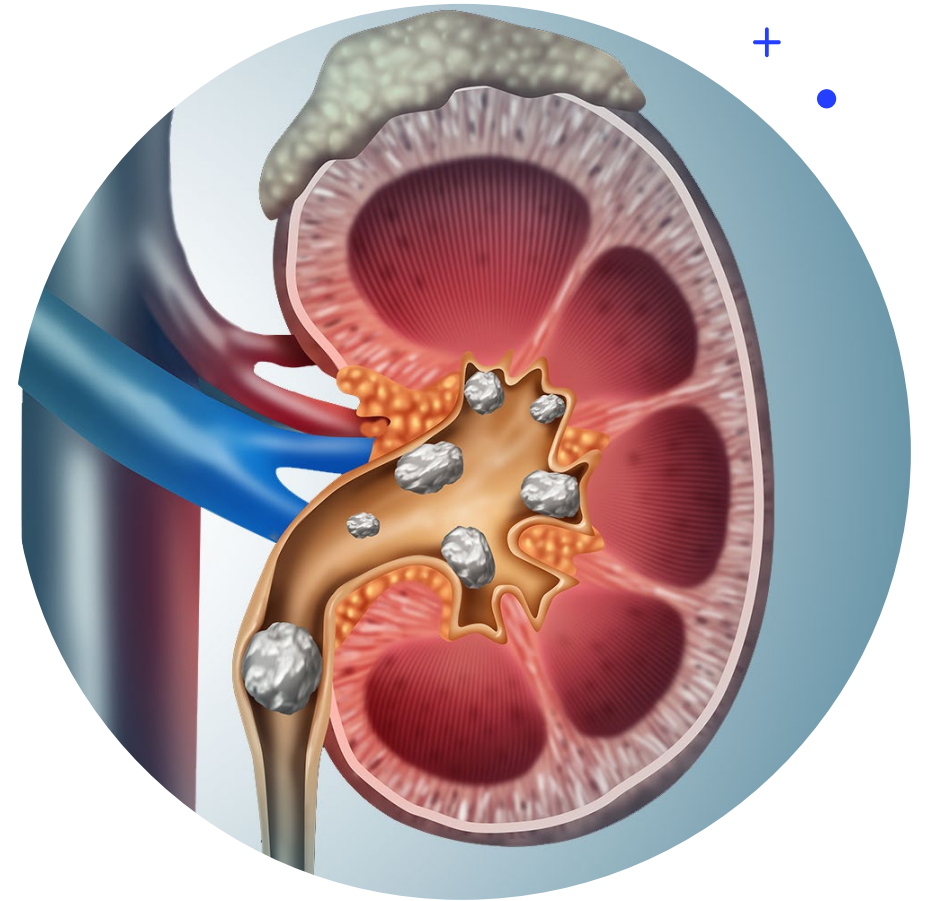
# Medical Factors

- Chronic renal failure or impaired functions
  - BMP
- Immunosuppression
- Chronic catheterization
- Multiple antibiotic allergies



# Upper Tract Factors

- Hx of surgery on kidneys or ureters
- Hx of treatment for kidney stones
- Gross hematuria outside of UTIs
- Pyelonephritis or urosepsis
- Proteus UTI





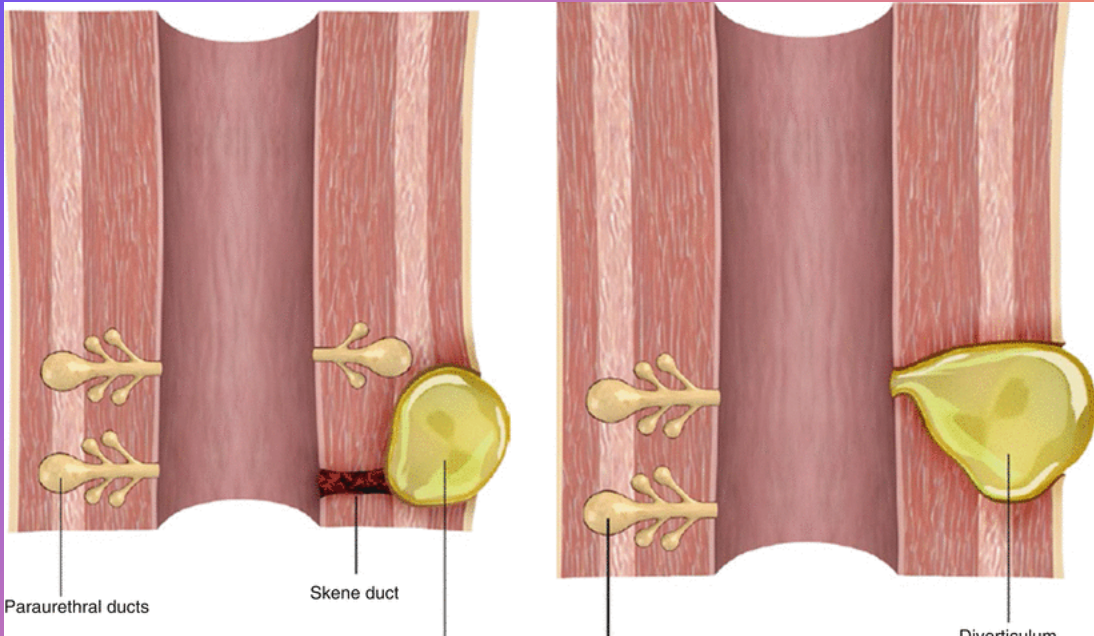
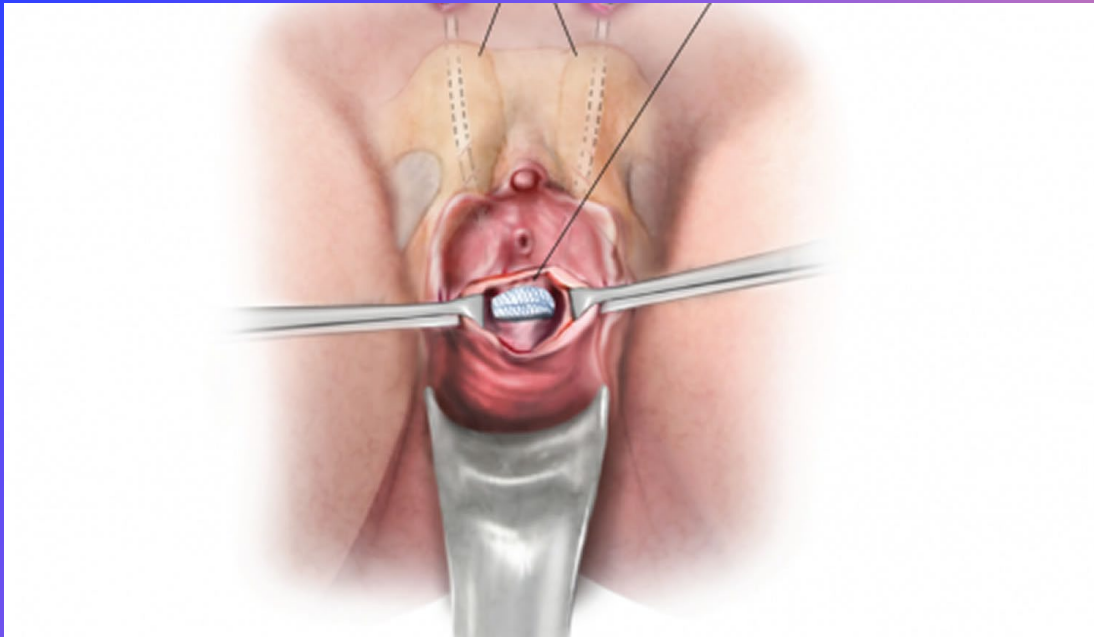
# Imaging in Certain Cases

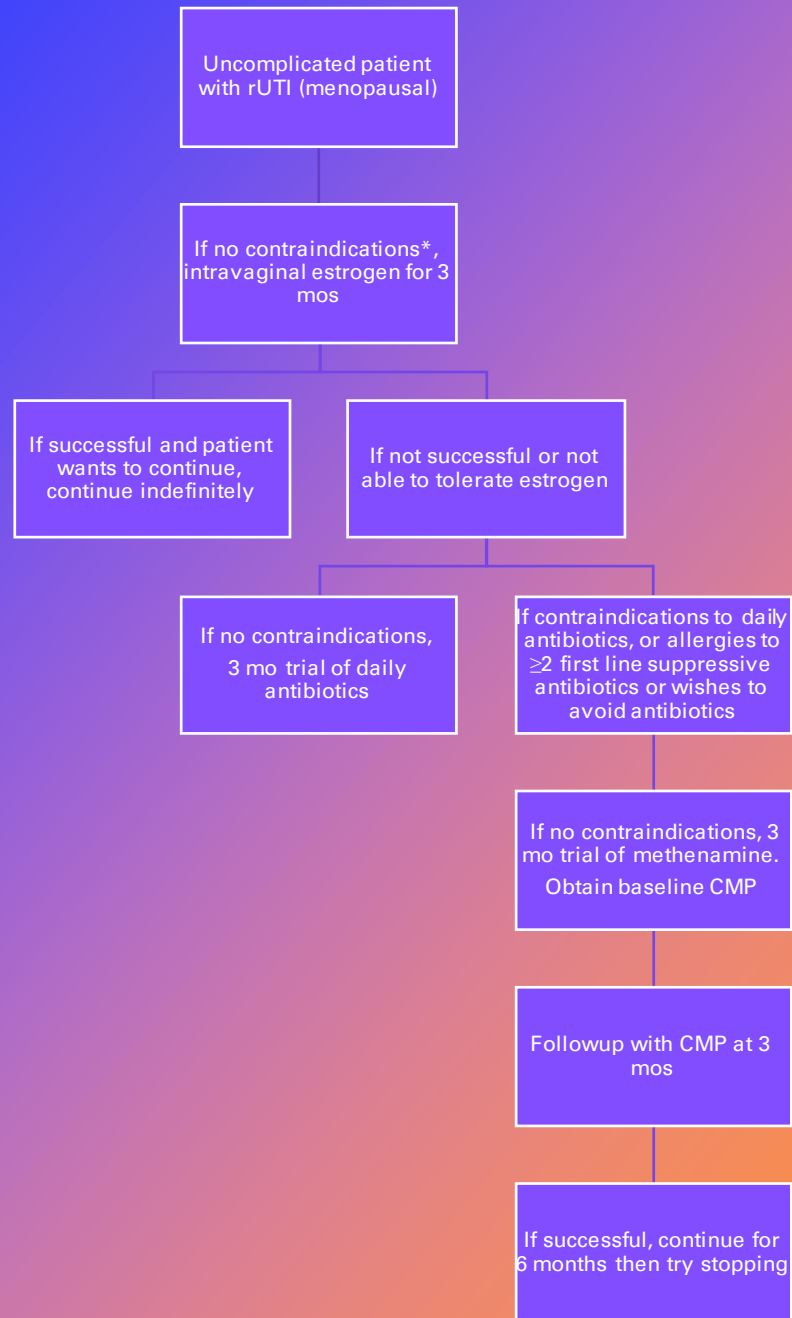
- CT urogram or Renal US
- Relapsing infection
- Repeated isolation of Proteus
  - Associated with stones
- Hx of passing stones
- Hematuria after resolution of infection



# Lower Tract Factors

- Hx of bladder, urethra or anti-incontinence surgery
- Hx of pelvic surgery with mesh
- Hx of UTI following pelvic surgery
- Urethral diverticulum, periurethral or vaginal wall cyst
- PVR >200cc
- Vaginal or uterine prolapse beyond hymen
- Hx of pelvic radiation





# Phase 3: Management of Women with uncomplicated rUTI: Menopausal

Uncomplicated patient  
with rUTI (premenopausal  
or postmenopausal after  
estrogen)

If no contraindications, 3  
mo daily trial of antibiotics  
(consider post-coital if  
associated with sex)

If successful, continue  
for total 6 mos, then  
try stopping

Infections continue-  
refer to ID

## Phase 3 : Management of Women with Uncomplicated rUTI: Pre- or Post- menopausal

Trial of Antibiotic Suppression

# Treating Acute Episodes

## First Line

- Nitrofurantoin (Macrobid, NOT Macrochantin) 100 mg BID for 5d
- TMP/SMX 160/800 mg BID for 3d
- Trimethoprim 100 mg BID for 3d
- Fosfomycin 3g single dose (\*\*for resistant orgs\*\*)

## Second Line

- $\beta$ -Lactams:
- Augmentin 500 mg BID for 5 d
- Cefpodoxime 100 mg BID for 5d
- Cefdinir 300mg BID for 5da
- Cefadroxil 500 mg BID for 5d
- Cephalexin 500mg QID for 5d

## Third Line

- Fluoroquinolones:
- Cipro 250 mg BID for 3d
- Cipro 500mg qd for 3d
- Levofloxacin 250 mg qd for 3d

# PREVENTION



# Behavioral Measures



- Hydration

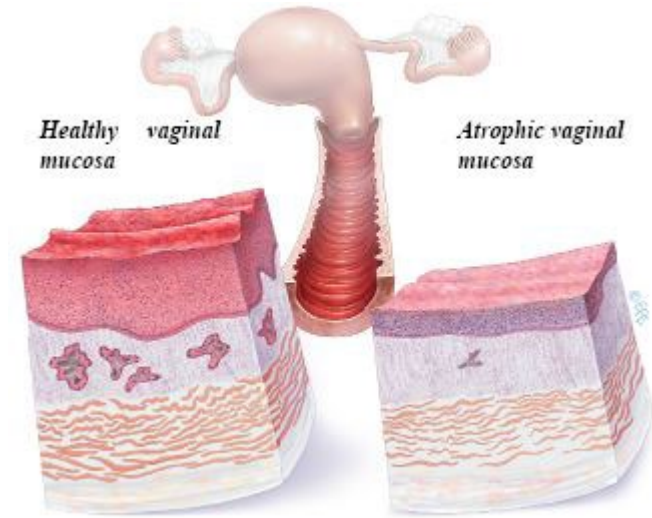
- RCT of 140 women with  $<1.5\text{L}$  daily at baseline<sup>14</sup>
  - Increased fluid intake, decreased incidence of cystitis by 50%
  - Additional 1.5 L compared to usual fluid intake, had fewer cystitis episodes (1.7 vs 3.2) and fewer Abx courses (1.9 vs 3.6 courses)
- Meta-analysis of 7 RCTs<sup>15</sup>
  - Increased fluid intake reduced risk of cystitis recurrence at 6 mos (OR 0.13, 95% CI 0.07-0.25)
  - Reduction not statistically significant at 12 mos (OR 0.39, 95% CI 0.15-1.03)

- Hygiene

- Wiping front to back

# Vaginal Estrogen

- Postmenopausal women with rUTI
- Normalization of vaginal flora: increase in lactobacilli, decrease in E.coli<sup>16</sup>
- Mild AE (pelvic cramping, increased discharge)
- Caution with estrogen-dependent tumors
- RCT of 93 postmenopausal women: vaginal estrogen reduced incidence of UTI vs placebo<sup>17</sup>
  - 0.5 vs 5.9 episodes per patient year; RR 0.25
- RCT of 108 postmenopausal women: vaginal estrogen ring less likely to have rUTI after 36 wks vs placebo (51% vs 80%)<sup>18</sup>
- Not as effective as Abx ppx
  - RCT of 171 postmenopausal women: incidence of rUTI higher with vaginal estrogen vs daily nitrofurantoin (2 vs 0.8 episodes per patient year)<sup>19</sup>
- Oral estrogen not been shown to be effective





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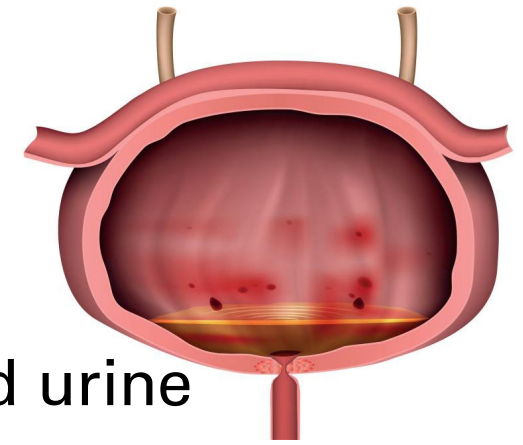
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# Estrogen Formulations

- Estrin: 7.5mcg released daily, replaced q3 mos
- Vagifem tablet insert: 10mcg nightly for 2 wks then twice/wk
- Vaginal cream: 0.5-1g nightly for 2 weeks then twice per week
  - Premarin 0.625mg per gram
  - Estrace 100mcg per gram



# Methenamine Hippurate



- Methenamine salts converted to formaldehyde in acidified urine  
→ bacteriostatic
- ALTAR trial<sup>20</sup>
  - Multicenter, noninferiority RCT: 240 women with rUTI
  - Abx ppx n = 120 vs Methenamine Hippurate n =120
  - Incidence of Abx-treated UTIs in 12 mo period: 0.89 episodes per person year in Abx group vs 1.38 in methenamine group
  - Absolute difference of 0.49 (90% CI 0.15 to 0.84) confirming non-inferiority
- Consider in patients with Abx intolerances or resistance
- 1g PO BID
- Further study needed regarding efficacy, risk on antimicrobial resistance, effect on urine pH, risk of serious complications and long-term safety data
- Baseline CMP and repeat at 3mos, avoid in renal or hepatic disease

# Antimicrobial PPx in Select Cases

- Attempt antibiotic-sparing preventive modalities prior
- Frequent UTI recurrences ( $\geq 2$  in 6 mos) and bothered by sx to choose Abx ppx despite potential AE
- **Always ensure Diagnosis!**
- Do NOT use Abx ppx with recurrent Sx not specific to UTI
  - Mental status changes w/o GU sx or fever
  - Even if associated with bacteriuria
  - Likely ASB
- Consider Abx susceptibilities of previously isolated uropathogens
- AE: toxicities, resistance, alteration of microbiome, secondary C. difficile
- No evidence that rUTI leads to HTN or renal disease in absence of anatomic or functional abnormalities of GU tract



# Antimicrobial PPx in Select Cases

## Post-coital

- Single postcoital dose
- Abx options similar to continuous ppx
- Nitrofurantoin, TMP/SMX, Trimethoprim,  $\beta$ -Lactams
- RCT: Placebo (n=11) vs Postcoital Abx (n=16)<sup>21</sup>
  - Infection rate lower with postcoital Abx (TMP/SMX 40/200mg) vs placebo
  - 0.3 vs 3.6 episodes per patient-year
- Other studies show comparable reduction for nitrofurantoin, cephalexin, fluoroquinolones including ciprofloxacin<sup>22-27</sup>
- TMP/SMX 80/400mg post coital
- Nitrofurantoin 100mg postcoital
- Trimethoprim 100 mg postcoital
- Cephalexin 250mg postcoital

## Continuous

- No temporal relation to sexual activity
- Avoid fluoroquinolones
- Doses lower than those for Tx
- TMP/SMX 40 mg/200 mg qHS
- Trimethoprim 100 mg qHS
- Cephalexin 125 or 250 mg qHS
- Nitrofurantoin 50 or 100 mg qHS (less preferred as potential complications with long-term use)
- Fosfomycin in setting of allergies and Abx suppression
- Fosfomycin 3g every 7-10 d<sup>28,29</sup>

# Continuous Antimicrobial PPx

- 2004 Cochrane Meta-analysis: 10 trials<sup>30</sup>
  - Abx reduced microbiologic and clinical recurrence vs placebo
  - Microbiologic recurrence: 0 to 0.9 episodes per patient-year in Abx group vs 0.8 to 3.6 in placebo group; RR 0.21, 95% CI 0.13-0.33
  - Clinical recurrence: RR 0.15, 95% CI 0.08-0.28
  - No difference in microbiologic recurrence rates following discontinuation of ppx
- Efficacy in patients with underlying urologic abnormalities<sup>31</sup>
  - RCT of 400 adults who performed CIC: Abx ppx vs no ppx
  - Abx ppx reduced rate of clinical cystitis (1.3 vs 2.6 episodes per patient-year, RR 0.52, 95% CI 0.44-0.61) and microbiologically confirmed cystitis (0.74 vs 1.5 episodes per patient-year, RR 0.49, 95% CI 0.39-0.6)
- Avoid in patients with indwelling catheters: risk of resistance
- No evidence that one regimen is superior to any others<sup>30,32</sup>
- Increasing resistance to Trimethoprim and TMP/SMX



# Duration

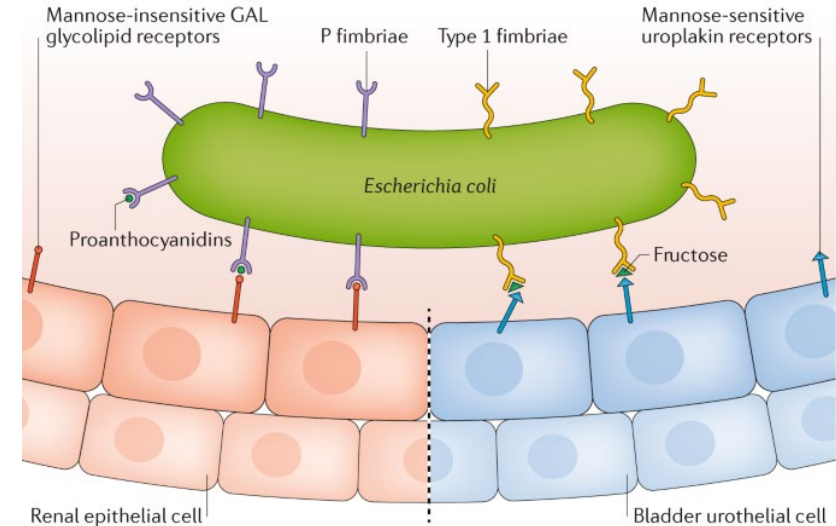


- Initial trial of 3 months
- If no recurrences, discuss continuing for 6 mos
- Most women revert back to previous pattern once ppx stopped<sup>30,32</sup>
  - Cochrane Meta-analysis: RR for at least one microbiologic recurrence 0.82, 95% CI 0.44 -1.53<sup>30</sup>
- Consider ID consult past 6 mos if infections continue
- TMP/SMX use up to 5 years reported as effective and well tolerated<sup>33,34</sup>
- Nitrofurantoin safe and well tolerated up to 12 mos<sup>35</sup>
  - Rarely associated with pulmonary reactions, chronic hepatitis, neuropathy
  - Avoid with Cr Clearance <30 mL/min

# Any Benefit?

- **Cranberry**

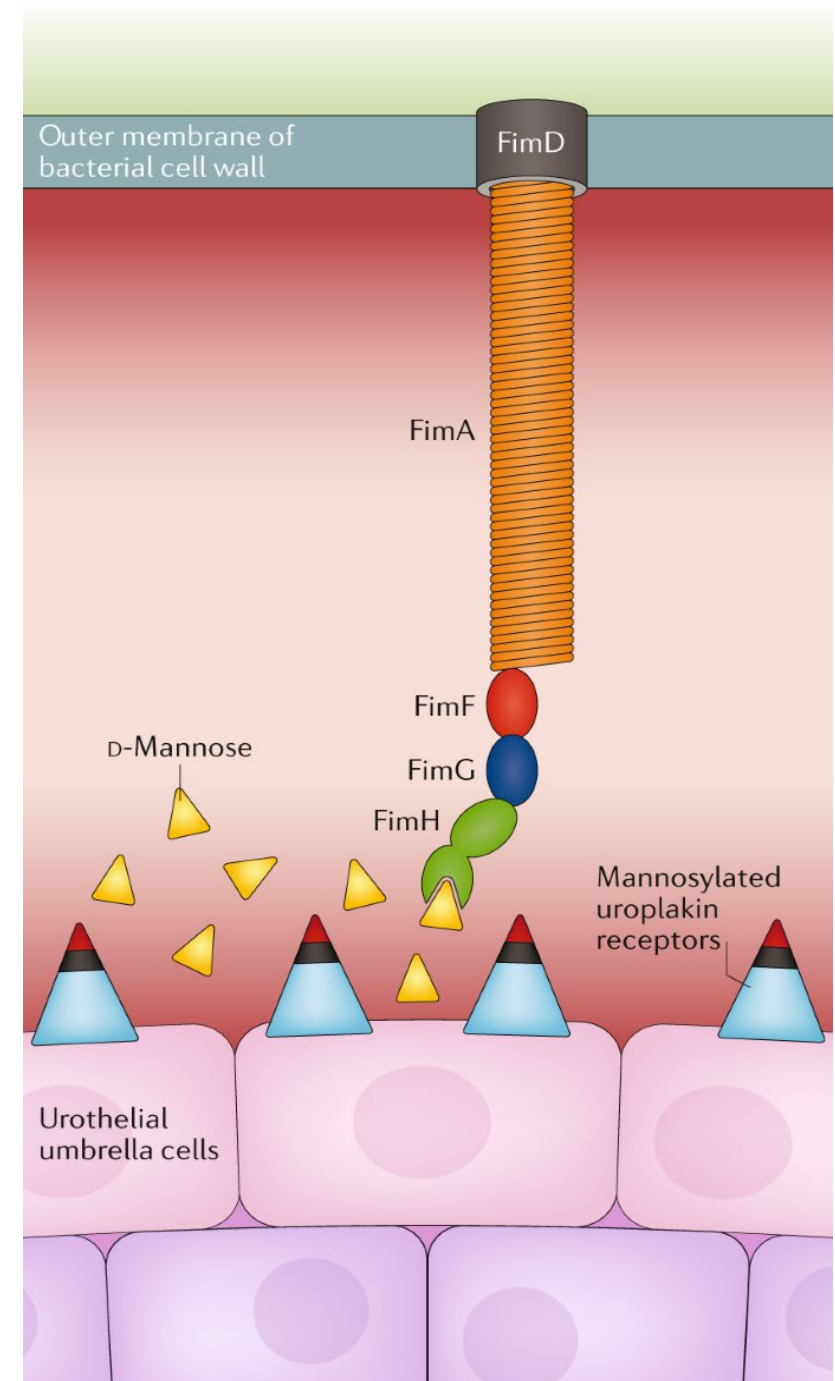
- Cochrane meta-analysis<sup>36</sup>
  - Did not significantly reduce symptomatic UTI (RR 0.74, 95% CI 0.42-1.31)
- Trial of 185 female nursing home residents<sup>37</sup>
  - Cranberry capsules (72 mg) vs placebo for 1 year
  - Cranberry capsules did not reduce rates of bacteriuria plus pyuria (29% for both groups) or symptomatic UTI (10 vs 12 episodes)
- Meta-analysis found cranberry products significantly reduced incidence of UTIs<sup>38</sup>
  - Not restricted to RCTs, lower quality evidence
- Cranberry juice inhibits adherence of uropathogens to uroepithelial cells<sup>12,39,40</sup>
- Reduction in urinary P-fimbriated *E. coli* strains in cranberry group in study of 176 women<sup>41</sup>
  - Isolates during intervention: 10 of 23 (43.5%) in cranberry juice group and 8 of 10 (80.0%) in placebo group (P=.07)
  - Not statistically significant but supports biological plausibility of cranberry activity



# Any Benefit?

- **D-Mannose**

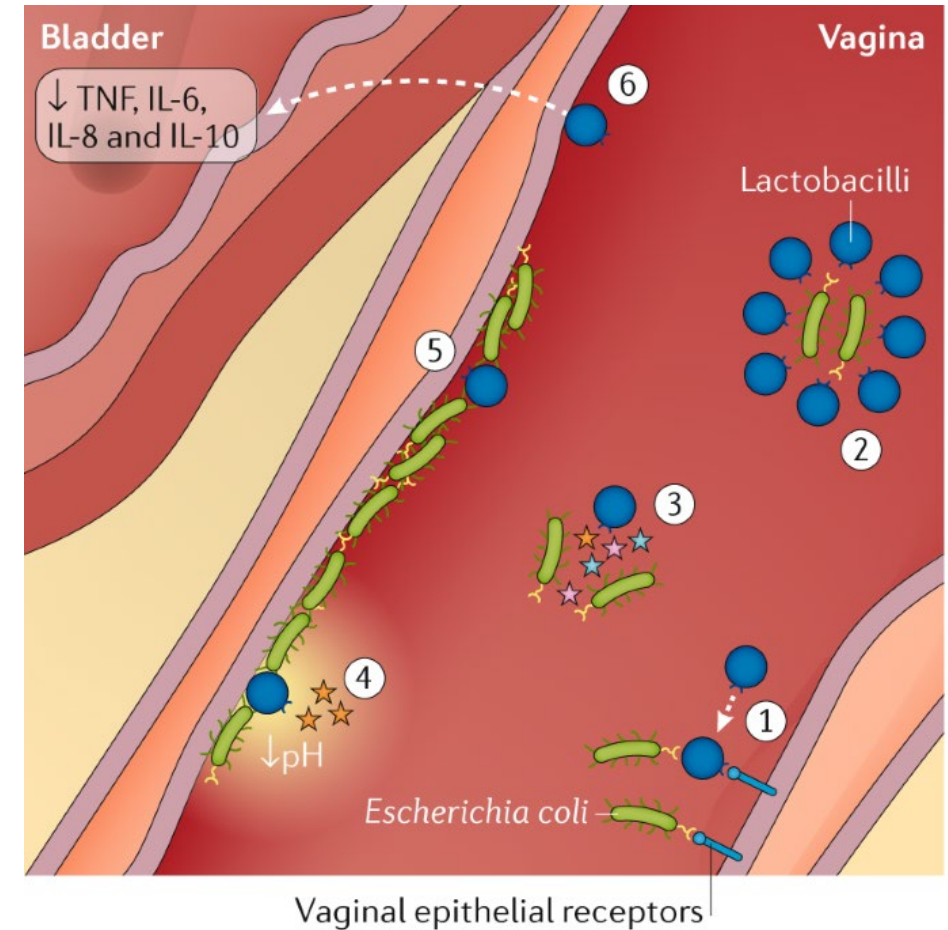
- Hypothesized to competitively bind to bacterial surface ligands → decrease number of bacteria attaching to bladder mucosa → alters host-bacterial interaction in favor of host<sup>42</sup>
- Clinical evidence on effectiveness for preventing cystitis is sparse and of low quality<sup>43,44</sup>
- RCT of 308 women: D-mannose vs nitrofurantoin vs no ppx<sup>45</sup>
  - D-mannose and Abx groups had lower risk of rUTI vs no ppx ( $p < 0.0001$ )
  - No significant difference between D-mannose and nitrofurantoin groups



# Any Benefit?

## • Probiotics

- Review of 4 RCTs, only one demonstrated reduction in rates of cystitis recurrence<sup>46</sup>
- RCT of postmenopausal women<sup>47</sup>
  - TMP/SMX (n=127) vs Lactobacillus tablets (n=125) for 12mos
  - Women in Lactobacillus group had more frequent clinical recurrences over 1 year (mean 3.3 vs 2.9 events) and shorter time to recurrence (3 versus 6 mos) than antibiotic group
- RCT of premenopausal women<sup>48</sup>
  - Vaginal Lactobacillus Tx (n=50) well tolerated, achieved high levels of vaginal colonization, decreased rates of rUTI (15 vs 27% compared to placebo)
- Mechanisms<sup>12,49</sup>:
  - Blocking attachment
  - Production of hydrogen peroxide
  - Maintenance of low pH
  - Anti-inflammatory cytokine response







# Take Home Points



- Confirm diagnosis
- Assess and refer for structural or functional abnormalities of GU tract
- Start with non-antimicrobial preventive strategies
- Vaginal Estrogen in Postmenopausal patients
- Consider Methenamine
- Abx ppx selectively: potential AE often outweigh benefit of reducing risk of infection

# References

1. Foxman B. Recurring urinary tract infection: incidence and risk factors. *Am J Public Health* 1990; 80:331.
2. Foxman B, Gillespie B, Koopman J, et al. Risk factors for second urinary tract infection among college women. *Am J Epidemiol* 2000; 151:1194.
3. Ikkäheimo R, Siitonen A, Heiskanen T, et al. Recurrence of urinary tract infection in a primary care setting: analysis of a 1-year follow-up of 179 women. *Clin Infect Dis* 1996; 22:91.
4. Foxman B, Barlow R, D'Arcy H, et al. Urinary tract infection: self-reported incidence and associated costs. *Ann Epidemiol* 2000; 10:509.
5. Hooton TM, Scholes D, Hughes JP, et al. A prospective study of risk factors for symptomatic urinary tract infection in young women. *N Engl J Med* 1996; 335:468.
6. Fihn SD, Boyko EJ, Normand EH, et al. Association between use of spermicide-coated condoms and Escherichia coli urinary tract infection in young women. *Am J Epidemiol* 1996; 144:512.
7. Fihn SD, Boyko EJ, Chen CL, et al. Use of spermicide-coated condoms and other risk factors for urinary tract infection caused by Staphylococcus saprophyticus. *Arch Intern Med* 1998; 158:281.
8. Scholes D, Hooton TM, Roberts PL, et al. Risk factors for recurrent urinary tract infection in young women. *J Infect Dis* 2000; 182:1177.
9. Raz R, Gennesin Y, Wasser J, et al. Recurrent urinary tract infections in postmenopausal women. *Clin Infect Dis* 2000; 30:152.
10. Hooton TM, Stapleton AE, Roberts PL, et al. Perineal anatomy and urine-voiding characteristics of young women with and without recurrent urinary tract infections. *Clin Infect Dis* 1999; 29:1600.
11. Gupta K, Stamm WE. Pathogenesis and management of recurrent urinary tract infections in women. *World J Urol* 1999; 17:415.
12. Sihra, N., Goodman, A., Zakri, R. et al. Nonantibiotic prevention and management of recurrent urinary tract infection. *Nat Rev Urol* 15, 750–776 (2018).
13. Gupta K. Acute simple cystitis in females. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on March 8, 2023)
14. Hooton TM, Vecchio M, Iroz A, et al. Effect of Increased Daily Water Intake in Premenopausal Women With Recurrent Urinary Tract Infections: A Randomized Clinical Trial. *JAMA Intern Med* 2018.
15. Scott AM, Clark J, Mar CD, Glasziou P. Increased fluid intake to prevent urinary tract infections: systematic review and meta-analysis. *Br J Gen Pract* 2020; 70:e200.
16. Beerepoot MA, Geerlings SE, van Haarst EP, et al. Nonantibiotic prophylaxis for recurrent urinary tract infections: a systematic review and meta-analysis of randomized controlled trials. *J Urol* 2013; 190:1981.
17. Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med* 1993; 329:753.
18. Eriksen B. A randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. *Am J Obstet Gynecol* 1999; 180:1072.
19. Raz R, Colodner R, Rohana Y, et al. Effectiveness of estriol-containing vaginal pessaries and nitrofurantoin macrocrystal therapy in the prevention of recurrent urinary tract infection in postmenopausal women. *Clin Infect Dis* 2003; 36:1362.
20. Harding C, Mossop H, Homer T, et al. Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women: multicentre, open label, randomised, non-inferiority trial. *BMJ* 2022; 376:e068229.
21. Stapleton A, Latham RH, Johnson C, Stamm WE. Postcoital antimicrobial prophylaxis for recurrent urinary tract infection. A randomized, double-blind, placebo-controlled trial. *JAMA* 1990; 264:703.
22. Chew LD, Fihn SD. Recurrent cystitis in nonpregnant women. *West J Med* 1999; 170:274.
23. Pfau A, Sacks T, Engelstein D. Recurrent urinary tract infections in premenopausal women: prophylaxis based on an understanding of the pathogenesis. *J Urol* 1983; 129:1153.
24. Pfau A, Sacks TG. Effective prophylaxis of recurrent urinary tract infections in premenopausal women by postcoital administration of cephalexin. *J Urol* 1989; 142:1276.
25. Pfau A, Sacks TG. Effective postcoital quinolone prophylaxis of recurrent urinary tract infections in women. *J Urol* 1994; 152:136.
26. Nicolle LE, Harding GK, Thompson M, et al. Prospective, randomized, placebo-controlled trial of norfloxacin for the prophylaxis of recurrent urinary tract infection in women. *Antimicrob Agents Chemother* 1989; 33:1032.
27. Melekos MD, Asbach HW, Gerharz E, et al. Post-intercourse versus daily ciprofloxacin prophylaxis for recurrent urinary tract infections in premenopausal women. *J Urol* 1997; 157:935.
28. Rudenko N, Dorofeyev A. Prevention of recurrent lower urinary tract infections by long-term administration of fosfomycin trometamol. Double blind, randomized, parallel group, placebo controlled study. *Arzneimittelforschung* 2005; 55:420.
29. Costantini E, Zucchi A, Salvini E, et al. Prulifloxacin vs fosfomycin for prophylaxis in female patients with recurrent UTIs: a non-inferiority trial. *Int Urogynecol J* 2014; 25:1173.
30. Albert X, Huertas I, Pereiró II, et al. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. *Cochrane Database Syst Rev* 2004; :CD001209.
31. Fisher H, Oluboyede Y, Chadwick T, et al. Continuous low-dose antibiotic prophylaxis for adults with repeated urinary tract infections (AnTIC): a randomised, open-label trial. *Lancet Infect Dis* 2018; 18:957.
32. Smith AL, Brown J, Wyman JF, et al. Treatment and Prevention of Recurrent Lower Urinary Tract Infections in Women: A Rapid Review with Practice Recommendations. *J Urol* 2018; 200:1174.
33. Stamm WE, McKeivitt M, Roberts PL, White NJ. Natural history of recurrent urinary tract infections in women. *Rev Infect Dis* 1991; 13:77.
34. Nicolle LE, Harding GK, Thomson M, et al. Efficacy of five years of continuous, low-dose trimethoprim-sulfamethoxazole prophylaxis for urinary tract infection. *J Infect Dis* 1988; 157:1239.
35. Brumfitt W, Hamilton-Miller JM. Efficacy and safety profile of long-term nitrofurantoin in urinary infections: 18 years' experience. *J Antimicrob Chemother* 1998; 42:363.
36. Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev* 2012; 10:CD001321.
37. Juthani-Mehta M, Van Ness PH, Bianco L, et al. Effect of Cranberry Capsules on Bacteriuria Plus Pyuria Among Older Women in Nursing Homes: A Randomized Clinical Trial. *JAMA* 2016; 316:1879.
38. Luís Á, Domingues F, Pereira L. Can Cranberries Contribute to Reduce the Incidence of Urinary Tract Infections? A Systematic Review with Meta-Analysis and Trial Sequential Analysis of Clinical Trials. *J Urol* 2017; 198:614.
39. Sobota AE. Inhibition of bacterial adherence by cranberry juice: potential use for the treatment of urinary tract infections. *J Urol* 1984; 131:1013.
40. Schmidt DR, Sobota AE. An examination of the anti-adherence activity of cranberry juice on urinary and nonurinary bacterial isolates. *Microbios* 1988; 55:173.
41. Stapleton AE, Dziura J, Hooton TM, et al. Recurrent urinary tract infection and urinary Escherichia coli in women ingesting cranberry juice daily: a randomized controlled trial. *Mayo Clin Proc* 2012; 87:143.
42. Zopf D, Roth S. Oligosaccharide anti-infective agents. *Lancet* 1996; 347:1017.
43. Kranjčec B, Papeš D, Altarac S. D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. *World J Urol* 2014; 32:79.
44. Cooper TE, Teng C, Howell M, et al. D-mannose for preventing and treating urinary tract infections. *Cochrane Database Syst Rev* 2022; 8:CD013608.
45. Kranjčec, B., Papes, D. & Altarac, S. D-Mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. *World J. Urol.* 32, 79–84 (2014).
46. Barrons R, Tassone D. Use of Lactobacillus probiotics for bacterial genitourinary infections in women: a review. *Clin Ther* 2008; 30:453.
47. Beerepoot MA, ter Riet G, Nys S, et al. Lactobacilli vs antibiotics to prevent urinary tract infections: a randomized, double-blind, noninferiority trial in postmenopausal women. *Arch Intern Med* 2012; 172:704.
48. Stapleton AE, Au-Yeung M, Hooton TM, et al. Randomized, placebo-controlled phase 2 trial of a Lactobacillus crispatus probiotic given intravaginally for prevention of recurrent urinary tract infection. *Clin Infect Dis* 2011; 52:1212.
49. Gupta K. Recurrent simple cystitis in women. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on March 8, 2023)
50. Murphy, F. J., Zelman, S. & Mau, W. Ascorbic acid as a urinary acidifying agent. 2. Its adjunctive role in chronic urinary infection. *J. Urol.* 94, 300–303(1965).
51. McDonald, D. F. & Murphy, G. P. Bacteriostatic and acidifying effects of methionine, hydrolyzed casein, and AA on the urine. *N. Engl. J. Med.* 261, 803–805 (1959).
52. Castello, T., Girona, L., Gomez, M. R., Mena Mur, A. & Garcia, L. The possible value of ascorbic acid as a prophylactic agent for urinary tract infection. *Spinal Cord* 34, 592–593 (1996).



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[keila.muniz@sjhsyr.org](mailto:keila.muniz@sjhsyr.org)