HHS Public Access

Author manuscript

Climacteric. Author manuscript; available in PMC 2020 June 01.

Published in final edited form as:

Climacteric. 2019 June ; 22(3): 242–249. doi:10.1080/13697137.2018.1551871.

The Etiology and Management of Recurrent Urinary Tract Infections in Postmenopausal Women

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Abstract

Urinary tract infections (UTI) are one of the most common infections and affect up to 50% of women in their lifetime, with almost half of these women experiencing a recurrence in 6–12 months. Menopause predisposes women to rUTI, as normally lower levels of estrogen lead to changes in the urogenital epithelium and subsequently urogenital microbiome. The recently discovered urobiome is now known to have different compositions in both healthy and unhealthy bladders, including a role in the pathophysiology of rUTI, and may be a therapeutic target for prevention and treatment options for rUTI. In postmenopausal women with frequent UTI, the diagnosis of acute UTI should be made using a combination of the symptom assessment and urine diagnostic studies. The choice of UTI antibiotic should include consideration of efficacy, collateral effects, and side effects. Some women may be candidates for self-start therapy, in which the patient accurately recognizes her UTI symptoms and then starts previously prescribed antibiotics. A large component of the management of women with rUTI is prevention. Urobiome research for bladder health and disease is a young field of investigation with significant potential to improve care for postmenopausal women affected by rUTI through novel, evidence-based prevention and treatment strategies.

Keywords

Urinary microbiome; urinary tract infection; urobiome; bladder; bladder health

Introduction

Recurrent urinary tract infection (rUTI) affects people of all ages and genders; postmenopausal women are disproportionately affected.[1] Urogynecologists play a key role in providing care for affected women, often through collaboration with specialists in infectious disease, urology, and primary care. Confirmation of the diagnoses guides prevention and treatment options. Emerging knowledge of the urinary microbiome (urobiome) is a potential tool in both evaluation and management of women with rUTI.

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Investigation of the human microbiome began with the Human Microbiome Project,[2] a large population-based study in healthy adults that cataloged the microbes inhabiting up to 18 different human body niches, excluding the bladder based on the prevailing dogma that the lower urinary tract was a sterile environment. A culture-independent technique, sequencing of the 16s rRNA gene,[3] was used to document the presence of the urobiome under carefully controlled conditions.[4,5] The urobiome is now known to have different compositions in both healthy and unhealthy bladders, and could play a role the pathophysiology of bladder disease, including rUTI pathophysiology.[6–8] Given this central role, the urobiome may be a therapeutic target for prevention and treatment options for rUTI. In this article, we will explore how the urobiome affects our clinical approach to rUTI and highlight key aspects of the diagnosis, evaluation, and management of postmenopausal women with rUTI.

Epidemiology and Pathophysiology

Urinary tract infections (UTI) are one of the most common infections and affect up to 50% of women in their lifetime, with almost half of these women experiencing a recurrence in 6–12 months.[9] A subset of women experience rUTI, with estimates ranging from 2–10%.[1] While there are variable definitions of rUTI, a commonly accepted clinical definition is ≥3 UTIs in a 12 months[10–12] or ≥2 UTIs in 6 months. [11,12] A commonly accepted major professional society guideline defines rUTI as ≥3 symptomatic and medically diagnosed UTIs in the previous 12 months, with demonstration of resolution before diagnosis of the subsequent infection.[13] The demonstration of resolution is important, as UTI treatment is not universally effective; patients may experience symptom improvement without microbial resolution. This concept is especially important in the context of rUTI diagnosis and management. Relapse is defined as a recurring UTI after therapy resulting from persistence of the pretherapy isolate, generally occurring ≤2 weeks after initial treatment.[14,15] Reinfection is defined as a recurring UTI caused by a different pathogen from that causing the original infection, generally occurring >2 weeks after initial treatment.[15]

Known risk factors for rUTI include diabetes, functional disability, recent sexual intercourse, prior history of urogynecological surgery, incomplete bladder emptying (elevated post-void residual), accidental bowel leakage, and urinary incontinence.[16] While coitally-associated UTIs occur,[15] these are less common in postmenopausal women. Additional specific risk factors for postmenopausal women include: history of premenopausal UTI, cystocele, and blood group Ag secretory status.[17]

It is clear that menopause is a predominant risk factor for rUTI and that the urogenital microbiome undergoes changes as women age, often reducing a woman's natural defense mechanisms against UTI. The pathophysiology of a single acute UTI in premenopausal women is very different than that of rUTI in postmenopausal women. The healthy premenopausal vagina is known to be largely colonized by *Lactobacillus* species,[18] which depend on glycogen produced by vaginal epithelial cells. Lactobacilli ferment glycogen and create lactic acid, which is inhibitory to other bacteria,[19,20] therefore maintaining a protective vaginal microbiome and preventing dysbiosis and infection. Lactobacilli also maintain vaginal health by preventing adherence of uropathogens to the vaginal epithelium. [21,22] Genitourinary syndrome of menopause (GSM),[23] which include changes in the

urogenital epithelium associated with postmenopausal levels of estrogen, leads to less epithelial glycogen production and subsequently less *Lactobacillus* and lactic acid production, and elevated pH,[24] making the environment more vulnerable to uropathogens and infection.

Diagnosis and Evaluation

In postmenopausal women with frequent UTI, the diagnosis of acute UTI should be made using a combination of the symptom assessment and urine diagnostic studies.[13,25] Table 1 displays the clinical summary, diagnostic evaluation and treatment protocols for a variety of presentations of rUTI in postmenopausal women. In many affected women, there is symptom overlap (dysuria, urinary urgency and frequency) with other common conditions such as GSM, overactive bladder (OAB), and bacteriuria. Up to 50% of postmenopausal women have symptomatic GSM.[23,26,27] The prevalence of OAB increases with age and is associated with symptoms of urinary urgency, often associated with urinary incontinence and frequency.[28,29] Similarly, the prevalence of bacteriuria detected on standard urine culture in the absence of UTI symptoms increases with age. In a prospective observational study of 61 women with an average age of 78, up to one third of these women had asymptomatic bacteriuria on voided specimens as defined by $\geq 10^5$ CFU/ml.[30]

The classic symptoms of “cystitis” (a.k.a. lower tract UTI) include dysuria, frequency, urgency, and suprapubic pain. Older women may report other symptoms as well, including foul odor, incomplete emptying, constipation, hematuria, generally feeling “ill”, and altered mental status.[31] While altered mental status in elderly patients may be related to UTI, mentation changes in the setting of a positive urine culture are often inappropriately attributed to UTI, and this imprecision may lead to overtreatment and unnecessary antibiotic use.[32] Alarm symptoms that should prompt clinicians to consider further diagnostic workup include gross hematuria, passage of tissue or feculent material in the urine, history of urogenital mesh-based procedure, or history of urologic malignancy. Fever, tachycardia, or costovertebral tenderness should raise concern for an upper tract UTI, such as pyelonephritis.

Pelvic examination is not required for postmenopausal women prior to treatment for infrequent, sporadic UTI. However, in postmenopausal women with an uncertain diagnosis or consideration of frequent/recurrent UTI, the pelvic examination should assess estrogen adequacy in urogenital tissues and search for other findings that would alter planned therapy, such as suburethral masses, pelvic organ prolapse, foreign bodies, or fistulous tracts. Since decreased detrusor muscle function increases with age, a post void residual volume should be obtained to assess for incomplete emptying, which can be a cause for lower urinary tract symptoms as well as rUTI.

Clinicians are familiar with the common modalities used for UTI testing (Table 2). Despite common use, the standard culture has limitations that may be especially pertinent for clinicians providing care for women with rUTI. There is clear evidence that the standard culture does not detect all relevant uropathogens,[4,5,33] and new urine culture techniques are available to detect these microbes documented.[33] Unlike the standard urine culture,

expanded quantitative urinary culture (EQUC)[6,33] inoculates 100x more urine (100μl) on diverse types of media, anaerobic conditions, varying temperatures, and time periods up to 5 days, with a lower threshold of detection than standard urine culture at 10 CFU/ml. This method has been shown to correlate well with 16s rRNA gene sequencing data, providing evidence that the bacterial DNA identified in urine via culture-independent techniques are indeed associated with living, culturable microbes.[33] EQUC has also been recently compared to standard urine culture in a mostly postmenopausal cohort of women with rUTI and was found to identify up to twice as many uropathogens as standard urine culture and identified these uropathogens up to three times more frequently.[34] We consider the use of EQUC in rUTI patients with multiple negative standard urine cultures or symptoms that do not improve with standard urine culture-directed treatment.

In women with rUTI, there is no consensus regarding a test of cure following UTI treatment. Test of cure can be useful for differentiating relapse vs. failure of treatment, confirming uropathogen eradication and potentially preventing relapse, and documentation to support the diagnosis of rUTI rather than relapse or reinfection. Potential drawbacks of a test of cure include the clinical uncertainty for interpretation of a positive urine culture in the absence of patient symptoms. An alternative to the test of cure via urine culture is treat until pyuria has resolved, which is a marker for host response and inflammation and also has been shown to correlate well with lower urinary tract symptoms.[35]

During evaluation of postmenopausal women with frequent UTI, the clinician should review prior UTI testing results, requesting them from other providers as necessary. Once the diagnosis of rUTI has been established, the patient should initiate prevention measures with reassessment in 3–6 months. There is scant evidence regarding the yield of additional routine testing, however certain clinical scenarios warrant further evaluation. Women with persistent relapses or reinfections despite preventative measures, continued infection with urea-splitting organisms, elevated serum creatinine, neurogenic bladder dysfunction, hematuria, concern for urinary tract malignancy, or a history childhood UTIs, renal calculi, or genitourinary surgery may benefit from cystoscopy and/or upper tract imaging.[36]

A cystoscopy, simply performed in the office, provides view of the bladder and urethra. In a study of 118 women with rUTI undergoing cystoscopy, significant abnormalities were seen in 8%.[37] The upper urinary tract can be imaged by renal ultrasound or computed tomography.[38–40] There is limited evidence for upper tract imaging in rUTI patients, with one study of 116 mostly postmenopausal women with rUTI undergoing either renal ultrasound, CT scan, or IVP showing significant abnormalities in 0.9%.[41] CT scan is more sensitive and specific in most cases, however ultrasound has the benefit of no radiation and reduced cost.[42] A pelvic MRI is the imaging modality of choice when urethral diverticulum is suspected.[43,44] Due to the overall limited evidence for further diagnostic workup of women with rUTI with cystoscopy and upper tract imaging, the decision to pursue is often guided by individual clinical judgement and consultation with providers specializing in management of rUTI.

Caring for women with rUTI can benefit from a team approach. Women that have a history of a mesh-based surgery, urogenital tract abnormalities, a significant smoking history or

other alarm symptoms, or continued rUTI despite the abovementioned prevention strategies should be referred to a specialized provider. In complex patients, rUTI care necessitates a multi-disciplinary approach, with the involvement of Female Pelvic Medicine and Reconstructive Surgery, Infectious Disease and Urology.

Treatment

In postmenopausal women with a confirmed diagnosis of rUTI, the mainstay treatment of intervening acute UTI is oral antibiotics. Table 3 summarizes an evidence-based approach to treatment of UTI in adult women with rUTI. When available, urine culture results and sensitivities should guide treatment. The antibiotic should be chosen based on prior culture results and community resistance levels when treatment is started without culture results; the antibiotic choice can be modified, if necessary, when the culture results become available. The benefits of immediately starting empiric antibiotics include prompt symptom relief[45] and decreased bladder inflammation; these benefits must be considered against the possibility of unnecessary or inappropriate antibiotic use, potentially contributing to growing antibiotic resistance. A patient-centered treatment approach includes a communication with the patient and, when appropriate, her family about rUTI care. Patients should feel prepared to initiate evaluation (and treatment, as directed) when she has first symptoms of a UTI. Components of that preparation include techniques for symptom relief, UTI testing (providing urine sample), and treatment as directed. Patients should have orders (standing orders) for urine testing so that she may submit a urine specimen without having to contact a doctor.

The diagnosis of acute UTI is generally made using a combination of urine diagnostic studies and symptoms. Symptoms can be associated with bacterial colony count of $<10^5$ CFU/ml or lack of uropathogen detection by the standard urine culture. Conversely, some women have a positive urine culture, but no UTI symptoms, often referred to as “colonization” or “asymptomatic bacteriuria.” This is terminology that pre-dates discovery of the urobiome; there is little guidance for interpretation of such findings.[46,47]

Symptom relief is key. Adequate hydration, bladder-specific and general pain relievers are recommended, regardless of antibiotic choice. Phenazopyridine is highly effective as a local bladder analgesic.[48] Non-steroidal anti-inflammatory drugs have been studied as both an adjunct and as an alternative to UTI antibiotics. Ibuprofen can lead to a reduction in antibiotic use, although investigators reported a small increase in burden of symptoms during the initial treatment.[45]

The choice of UTI antibiotic should include consideration of efficacy, collateral effects and side effects. Underlying patient health conditions may affect selection and dosing. Nitrofurantoin and trimethoprim/sulfamethoxazole are appropriate first-line agents with known efficacy and minimal potential for collateral damage.[49] Trimethoprim/Sulfamethoxazole should only be used if community resistance is known to be <20% or if the uropathogen is known to be sensitive. Fosfomycin has the benefit of one-time dosing, with similar efficacy rates.[49,50] If early pyelonephritis is suspected, nitrofurantoin and fosfomycin should be avoided.

Some women may be candidates for self-start therapy, in which the patient accurately recognizes her UTI symptoms then starts previously prescribed antibiotics.[51] In carefully selected women with rUTI, accuracy of UTI self-detection ranges from 86–92%.[51,52] Typical candidates: 1) have had previous documented positive urine cultures, 2) have symptom relief with antibiotics, 3) will reliably provide a pre-treatment urine specimen, 4) comply with treatment, and 5) will follow-up. The choice of a self-start antibiotic depends on resistance patterns from prior cultures, local community antibiotic resistance, effectiveness in relieving symptoms and tolerance of the medications. Benefits of self-start therapy include patient empowerment with active treatment participation and decreased patient anxiety, phone calls, clinic visits, and laboratory testing. There is a small risk of inappropriate exposure to antibiotic, for example, when a uropathogen is resistant to her usual antibiotic.

Prevention

Prevention is a major component of rUTI care in postmenopausal women. While the goal of management is to significantly reduce UTI, it is not always realistic eliminate UTI completely or indefinitely. Table 4 summarizes the evidence-based approach to UTI prevention in this population. Despite no evidence to support efficacy, several prevention strategies are often recommended, such as loose-fitting clothing, white cotton underwear, voiding immediately after coitus, and wiping “front-to-back” after urination or defecation.

Postmenopausal estrogen levels are associated with lower levels of *Lactobacillus* and higher pH in the urogenital niche.[53,54] Restoring the urobiome to its protective state and avoiding dysbioses are key in preventing rUTI. Alterations to the protective state of the urobiome can also be caused by certain behaviors and hygienic practices. Smokers have decreased vaginal lactobacilli;[55] vaginal moisturizers, personal lubricants, douches, and spermicides suppress the growth of *Lactobacillus* in vitro.[56–58] Vaginal estrogen replacement reduces UTI risk, a beneficial effect not seen with oral estrogen.[59] Within the first 12 weeks of use, *Lactobacillus* is restored and there is an associated recovery of the host defenses.[24]

D-Mannose, an over-the-counter monosaccharide sugar, acts in decreasing bacterial adherence to the bladder mucosa; it is nearly as effective as daily nitrofurantoin 50 mg daily and superior to placebo in preventing UTI over 6 months in women with rUTI.[60]

Methenamine salts, prescribed as methenamine, enact their antibacterial properties via conversion to formaldehyde in acidified urine. A Cochrane review showed that methenamine prevent UTI in those with a normal urinary tract and a nonneuropathic bladder, with a low rate of adverse events.[61]

There is biologic plausibility for probiotics and UTI prevention. However, due to the small number of available studies, the Cochrane Review did not find benefit of oral probiotics.[62] In pre-menopausal women, a phase 2 clinical trial demonstrated efficacy for vaginal *Lactobacillus crispatus,* which is not yet commercially available, for rUTI reduction.[63]

Cranberry products, which contain proanthocyanodin, have long been associated with bladder health; however a Cochrane review found that cranberry products had no significant

effect on preventing UTI.[64] Since that review, two randomized placebo-controlled trials reporting conflicting results: one showed that cranberry reduced postoperative UTI in women undergoing elective gynecological surgery,[65] while the other showed no difference in rates of bacteriuria and pyuria in female nursing home residents.[66] Ascorbic acid (Vitamin C) has been shown to decrease UTI rate in pregnant women;[67] however, there is no evidence supporting its use in prevention of rUTI in postmenopausal women.

Antibiotics, provided daily or post-coitally, are effective preventative measures. Post-coital antibiotics reduce the rate of UTI in women with coitally-associated UTI.[68,69] When there is no post-coital association with rUTI, daily continuous antibiotic prophylaxis for 6–12 months reduces UTI risk compared with placebo.[70]

When rUTI episodes continue despite the previously described prevention strategies have failed, intravesical antibiotic instillations can be used.[71,72] This approach uses direct delivery of the antibiotic to the bladder (instillation time of at least one hour) with low systemic absorption, avoiding potential systemic side effects. Gentamicin is the most studied intravesical antibiotic.[73,74] Select patients complete their instillations at home, allowing prolonged antibiotic dwell times overnight.

The Urobiome, rUTI and Bladder Health

There is much to learn about care of postmenopausal women with rUTI; many of the studies guiding recommended treatment and prevention options have not focused on this population. The urobiome is a potential tool for treatment and prevention options in rUTI management. In some bladder conditions, such as overactive bladder, there are urobiome differences in patients and controls.[7] In a study of 60 patients with overactive bladder with urge urinary incontinence compared to 58 controls, there were decreased levels of *Lactobacillus* and increased levels of *Gardnerella* and nine other genera of bacteria.[6] At the species level, there were differences between groups for *Lactobacillus,* with *Lactobacillus gasseri* more common in patients and *Lactobacillus crispatus* more common in controls. The composition of the urobiome in overactive bladder patients can even affect treatment response, with one study showing that responders were more likely to have less bacteria and less diverse urobiomes.[75] Contrastingly, patients with interstitial cystitis were found to have greater abundance of *Lactobacillus* in their urobiome when compared to controls (species differences not reported).[8]

Urobiome research for bladder health and disease is a young field of investigation with significant potential to improve care for post-menopausal women affected by rUTI through novel, evidence-based prevention and treatment strategies.

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Table 1:

Clinical Heterogeneity of Women with Recurrent UTI: Adult women with recurrent UTI have varying clinical situations, requiring individualization of care.

Scenario	Patient HPI	Exam	Urine Studies	Imaging	Management	Follow-Up
1	78yo non-sexually active woman reports frequent UTIs, which respond to UTI antibiotics	-Vulovaginal atrophy -Normal post-void residual	3 positive urine cultures of $>10^5$ CFU/ml *E. Coli* in last 12 months	None	-Vaginal estrogen -Consider D-mannose	-Standing order for UA and reflex urine culture -Follow-up 3–6 months
2	55yo sexually active woman reports frequent UTIs, sometimes associated with intercourse, variable response to UTI antibiotics	-Vulvovaginal atrophy -Normal post-void residual	1 positive urine culture for 10,000–50,000 CFU/ml *E. coli*, 2 negative urine cultures	None	-Vaginal estrogen -Consider post-coital antibiotics	-Standing order for UA and reflex urine culture -Follow-up 3 months -Consider EQUC
3	53yo sexually active woman with frequent UTIs and dyspareunia	Suburethral mass Normal post-void residual	3 positive urine cultures for $>10^5$ CFU/ml *E. coli* x2 and *Pseudomonas*	Pelvic MRI shows urethral diverticulum	Diverticulum excision	-Follow-up after surgery to ensure that rUTI resolves
4	62yo woman with history of smoking and mesh midurethral sling reports frequent UTIs	Normal post-void residual	3 positive urine cultures $>10^5$ CFU/ml for *Proteus*, *Enterococcus*, and *E. coli*; microscopic hematuria	Cystoscopy documents urethral mesh erosion, CT urogram shows non-obstructive renal stone	-Urology consult for stone removal -Surgical removal of mesh exposure	-Follow-up after surgery to ensure that rUTI resolves
5	82yo woman with persistently positive urine cultures and symptoms despite appropriate antibiotic treatment	Vulvovaginal atrophy Normal post-void residual GFR 47	Multiple positive urine cultures $>10^5$ CFU/ml for *Klebsiella pneumoniae* x5, *E. Coli*, and *Enterobacter* in last 12 months. All treated with only 2 documented negative urine cultures.	Cystoscopy normal CT scan normal	-Vaginal estrogen -D-mannose -Methenamine	-Antibiotic for UTI suppression selected in conjunction with PCP -Follow-up 3–6 months

Table 2:

Common Clinical Tests for UTI

Test	Usage	Notes
Urine Dipstick	• Utility limited in the evaluation of postmenopausal women with rUTI, due to decreased sensitivity • In postmenopausal women, sensitivities for voided urines are similar, however urine dipstick is less sensitive for catheterized urines, which is the optimal route of evaluation in a postmenopausal woman with frequent UTI	• Screening test with sensitivity ranging from 66–88% in patients of all ages and genders[76–78] • Sensitivity of 50–55.6% in catheterized urines, and 73.7–84.2% in voided urines when using a cutoff of $\geq 10^5$ CFU/ml, they found positive dipstick (positive for either leukocyte esterase or nitrites) in a study of 75 postmenopausal women with irritative bladder symptoms. • Sensitivity of 44.2% in catheterized urines when using the cutoff of $\geq 10^3$ CFU/ml in a study of >2000 women with OAB (age not reported).[79]
Urinalysis	• Useful adjunct to determine whether urine culture testing is needed and/or to determine whether empiric UTI treatment should be initiated before urine culture results are available. • Leukocyte esterase: enzyme produced by leukocytes, and represents the presence of white blood cells (WBCs).[80] Nitrites: represent the presence of gram-negative bacteria which convert urinary nitrate to nitrite.[80] Blood in the urine is common during active UTI.	• Sensitivity of 95.6% when combination of leukocyte esterase and pyuria, representing the inflammatory host response,[81] in predicting a positive urine culture in the general population.[76] • If microscopic hematuria, defined as ≥3 red blood cells per HPF, is persistent after treatment of the acute infection, further should be considered. Testing may include assessments to detect urinary tract malignancy (cystoscopy and upper urinary tract imaging), nephropathy, or other benign renal disease.[82,83]
Urine Culture, Standard	• Identifies uropathogenic species present in the urine and is widely used today as a gold standard for UTI diagnosis. • Involves incubation of 1μl of urine on a combination of blood and MacConkey agar at 35°C for 24 hours, and is designed to detect uropathogenic *E. Coli*.	• Criteria of $\geq 10^5$ CFU/ml of a single organism originally developed in the 1950s as a predictor of those that would develop urosepsis after kidney surgery.[84,85] • A lower cut-off of $\geq 10^2$ CFU/ml in the setting of UTI symptoms has a high predictive value for UTI.[86,87] • UTI may be polymicrobial, with several different uropathogens causing the UTI.[88] Clinicians should be familiar with the reporting patterns of their microbiology laboratories. For example, a laboratory report of “growth of multiple organisms suggestive of contamination,” is often interpreted by providers as a negative result for UTI.

Table 3:

Treatment of UTI in Adult Women with Recurrent UTI[45,48–51,89]

Type	Name	Dosing	Notes
Symptom Relief	Pyridium Ibuprofen	100–200mg TID x2 days 400mg TID x3 days	-Orange discoloration of urine -Can mask symptoms of UTI, do not use >2 days -Caution in renal impairment -Can decrease need for antibiotics
1st line Antibiotics	Nitrofurantoin monohydrate/macrocrystals Trimethoprim/Sulfamethoxazole Fosfomycin	100mg BID x5 days 160/800mg BID x3 days 3g x1 dose	-Minimal resistance -Avoid if early pyelonephritis suspected -Avoid if resistance known to exceed 20% -Avoid if used for UTI in previous 3 months -Minimal resistance -Avoid if early pyelonephritis suspected -Slightly less efficacious
2nd line Antibiotics	Ciprofloxacin Beta-Lactams	250 BID x3 days OR 500mg ER daily x3 days 3–7 day course	-Resistance prevalence high in some areas -Higher risk for collateral damage (prolonged QT interval, tendon rupture) -Less efficacious -More adverse events -Avoid ampicillin or amoxicillin alone – poor efficacy and high resistance
Self-start Antibiotics	Nitrofurantoin monohydrate/macrocrystals Trimethoprim/Sulfamethoxazole Fosfomycin	Same as above Same as above Same as above	Same as above Same as above Same as above

Table 4:

Prevention of UTI in Adult Women with Recurrent UTI[15,24,56,59–74,90–94]

Type	Dosing	Notes
Vaginal estrogen -Tablets -Creams -Ring	Estradiol (Vagifem) 10mcg 2x/week Estradiol (Estrace) 0.5mg 2x/week Conjugated vaginal estrogens (Premarin) 0.5mg 2x/week Estradiol (Estring) 2mg every 3 months	-most consistent low dosing -affordable -instruct patients 0.5mg is a pea-sized amount -benefit of long-term dosing -patient or provider can replace -usually most expensive
D-Mannose	2g dissolved in 200ml water daily	-over-the-counter product -low rate of side effects
Methenamine	1g twice a day	-converts to formaldehyde in acidified urine -does not induce bacterial resistance -caution in renal and/or hepatic impairment
Antibiotics - continuous -Nitrofurantoin monohydrate/ macrocrystals -Trimethoprim/Sulfamethoxazole -Trimethoprim -Cephalexin -Fosfomycin	50–100mg daily 40/200mg daily to every 3 days 100mg daily 125–250mg daily 3g every 10 days	-caution rare pulmonary toxicity with chronic use -avoid if Cr Cl <30 ml/min
Antibiotics – post-coital -Nitrofurantoin monohydrate/ macrocrystals -Trimethoprim/Sulfamethoxazole -Cephalexin	50–100mg x1 40/200mg – 80/400mg x1 250mg x1	
Antibiotics – intravesical -Gentamicin	40–80mg in 50ml normal saline	-time periods of 1 hour to overnight
Widely Used Despite Limited Evidence for Efficacy		
Vaginal probiotic	Daily x5 days, then weekly x10 weeks	-may be best if used in conjunction with vaginal estrogen
Vitamin C	1–3g three to four times per day	-goal of urine acidification
Cranberry	2 capsules daily	-equivalent to 20oz servings of cranberry juice -equivalent to 72mg of active ingredient proanthocyandin