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Lesson 17 Volume 40

Recurrent Uncomplicated UTIs in Women: A Case Based Approach*

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to:

- Define how microbiological assessment of suspected symptomatic UTIs with urinalysis and urine culture and susceptibilities influences diagnostic assessment, treatment decisions and monitoring of treatment efficacy in patients with recurrent UTI.
- Describe how the goals of management of recurrent UTI have shifted from urinary sterilization to improving patient quality of life, minimization of recurrences and prevention of serious adverse events and infection sequelae.
- Define how antibiotic stewardship impacts UTI treatment and prophylaxis, balancing alleviating symptoms and preventing recurrence with reducing adverse events, minimizing inappropriate antibiotic usage and minimizing collateral damage.

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INTRODUCTION

Symptomatic urinary tract infection, or acute bacterial cystitis, affects approximately 60% of women at some point.[1] Recurrent UTI, in which UTI recurs after a period of symptomatic resolution, affects 20% to 40% of women with prior cystitis episodes.[2,3] rUTI is costly and burdensome, affecting women of all ages, races and ethnicities without regard for socioeconomic status, educational level or sexual orientation.[4]

New insights into the pathophysiology and natural history of rUTI have evolved our approach to infections. "Collateral damage,"[5] the adverse effects of repetitive, antimicrobial therapy, negatively impacts society through worsening antimicrobial resistance and increased infection susceptibility and severity in individual patients. The goals of rUTI treatment have therefore shifted from urinary sterilization to improving outcomes and quality of life for women with rUTI while preventing antibiotic overuse, improving antimicrobial agent selection and reducing adverse effects of antibiotic use.

While most providers feel comfortable making a diagnosis of UTI, in practice, diagnostic criteria are variable and imprecise. Strong evidence suggests that UTI diagnosis should include both laboratory confirmation of "*significant bacteriuria*" with *acute-onset* "*symptoms referable to the urinary tract*."[6,7] **Recurrent UTI is defined as 2 separate culture-proven episodes of symptomatic acute cystitis within 6 months or 3 episodes within 1 year.[8]**

Acute-onset urinary symptoms include dysuria with varying urinary urgency and frequency, hematuria, suprapubic pain and new or worsening incontinence. In women of all ages, *acute-onset dysuria* without vaginal discharge is highly specific for UTI.[9-11] **No evidence exists that antimicrobial treatment of bacteriuria in patients with non urological symptoms, such as delirium, fatigue, weakness, confusion, falls or worsening cognitive impairment, improves outcomes**.[7] Expert consensus supports reserving UTI evaluation for women exhibiting acute-onset (<1 week) dysuria or fever with specific urinary symptoms, primarily gross hematuria, new or significantly worsening urinary urgency, frequency and/or incontinence, and suprapubic pain.[12,13]

Bacteriuria consistent with cystitis has classically been defined as $^{3}10^{5}$ CFU/ml. However, this definition represents an arbitrary cutoff.[14-16] No specific CFU threshold denotes risk of progression to pyelonephritis or sepsis. Monomicrobial specimens with $\geq 10^{2}$ CFU/ml may still represent infection in symptomatic patients.[17] Uncomplicated UTI is most commonly caused by *Escherichia coli* (75%-95%), but *Proteus mirabilis*, *Klebsiella pneumoniae* and *Staphylococcus saprophyticus* may be relevant. Organisms thought to be commensals generally do not require treatment.[18,19]

The following case-based approach explores the practical applications of the guideline statements from the American Urological Association[8] in the management of recurrent, *uncomplicated* cystitis episodes in women.

CASE 1

Case 1 is a 25-year-old G0P0 woman with multiple episodes of dysuria and hematuria that typically start 1 to 2 days after penetrative sexual intercourse. During a symptomatic infection, she will typically go to an urgent care center, where she is given antibiotic treatment. The urgent care center usually calls to tell her the cultures are positive for *E. coli*. She shows you one test demonstrating >100,000 CFU pan-sensitive *E. coli*. She states that her symptoms resolve with treatment, usually 5 to 7 days of nitrofurantoin. Between infections, she has no urinary or vaginal pain or bothersome symptoms. She is otherwise healthy and takes only an oral contraceptive.

Guideline Statement 1. Clinicians should obtain a complete patient history and perform a pelvic examination in women presenting with rUTIs. (Clinical Principle)

Patient history should document symptoms experienced during UTI episodes, frequency of episodes, specific triggers (eg intercourse), responses to treatment and prior diagnostic investigations. *Baseline* genitourinary symptoms, such as dysuria, frequency, urgency, nocturia, incontinence, hematuria, pelvic pressure, vaginal bulge, as well as the location, character and severity of any chronic genitourinary pain, can be informative. History of constipation, back or flank pain, vaginal discharge or irritation, hormonal influences (eg menstruation, menopause, exogenous hormone use) and medications that alter infection susceptibility (eg other antimicrobials, immunosuppression) may influence rUTI management.

Physical examination, including abdominal and pelvic exam, should evaluate for structural or functional abnormalities. Examination should note the compartment and stage of any prolapse, any infectious or inflammatory conditions, such as vaginitis, vulvar dermatitides, or vaginal atrophy, and any gross neurological deficits. The bladder, urethra and pelvic floor should be palpated for masses, cystic structures, tenderness or myofascial trigger points.[20] Post-void residual assessment should assess patients with suspicion of incomplete emptying, as in anterior prolapse, neurological disease, diabetes or a sensation of incomplete emptying.

The patient mentions that she remembers some kind of urological surgery as a child, recalling a test involving a catheter and an x-ray. She also thinks she may have been on a daily antibiotic, but eventually "grew out of it."

Guideline Statement 4. Cystoscopy and upper tract imaging should not be routinely obtained in the index patient presenting with a rUTI. (Expert Opinion)

In young women without prior urological interventions, cystoscopy and urinary tract imaging is unnecessary.[21] Such testing can be considered in patients with a history of previous pelvic surgery, including vaginal mesh placement, to assess for anatomical abnormalities, including urethral stricture, foreign bodies, bladder stones, fistula or diverticulum. In patients with no risk factors for bladder cancer describing gross hematuria with infections, cystoscopy is not necessary; if any risk factors are present, it can be considered. Upper tract imaging (ultrasound/

ABBREVIATIONS: CFU=colony-forming units, ESBL=extended-spectrum beta-lactamase, rUTI=recurrent urinary tract infection, SE=side effect, TMP-SMX=trimethoprim-sulfamethoxazole, UTI=urinary tract infection

computerized tomography) may be valuable for patients with a history of pyelonephritis, hematuria or renal calculi.

Given her history, however, cystoscopy and upper tract imaging may help ensure there is no anatomical contribution to her UTI risk. If she remains refractory to UTI prophylaxis, urodynamics can be considered to rule out voiding dysfunction.

After benign cystoscopy and renal ultrasound, she returns to discuss treatment (see figure). She details her attempts at management, which include front-to-back wiping, voiding after intercourse and having her partner shower before sex. Certain modifiable behaviors *can* reduce UTI risk. **Increased water intake for those consuming less than 1.5 L per day is one approach to reduce UTI recurrence by approximately 50%.**[22] Spermicidal products, particularly nonoxynol-9, can impair natural host defenses against UTI; sexually active women using spermicides should consider alternative contraceptive methods.[23] **However, case-control studies demonstrate that changes in hygiene practices (eg front-to-back wiping), pre- and post-coital voiding, avoidance of hot tubs, tampon use and douching do not significantly impact rUTI risk.**[23,24] Focusing on these approaches reinforces the shame and self-blame common in rUTI, which can have profound negative impacts on self-esteem, intimacy and relationship satisfaction.

Education and informed decision-making in rUTI management can better empower patients. **Many patients do not know that UTI is typically self-limited and rarely progresses to more severe disease.**[25] The incidence of pyelonephritis and sepsis is low and is not substantially different in individuals receiving antibiotics vs. supportive care.[26] Multiple randomized, placebo-controlled trials demonstrate little benefit to antibiotics for UTI beyond modestly faster symptomatic improvement.[27] Discussion of the natural history of rUTI, limitations of diagnostic testing, benefits and risks of antibiotics, and non-antibiotic treatment alternatives may help limit antibiotic use to situations in which it is likely to improve outcomes. This discussion can help align the goals of both patient and provider to the amelioration of symptoms rather than administration of antibiotics.

After this discussion, the patient expresses that she is tired of antibiotics. She has had numerous yeast infections and would like to try a "more natural" approach. She fears increased water intake may not be sufficient, asking if any over-the-counter UTI prevention products might provide benefit.

Guideline Statement 13. Clinicians may offer cranberry prophylaxis for rUTIs. (Conditional Recommendation; Evidence Level: Grade C)

Cranberries alter urinary pH and prevent bacterial adhesion through the action of proanthocyanidin.[28] Several placebo-controlled trials have suggested a similar efficacy of cranberry to daily, low-dose antibiotic treatments in UTI prevention.[29-31]

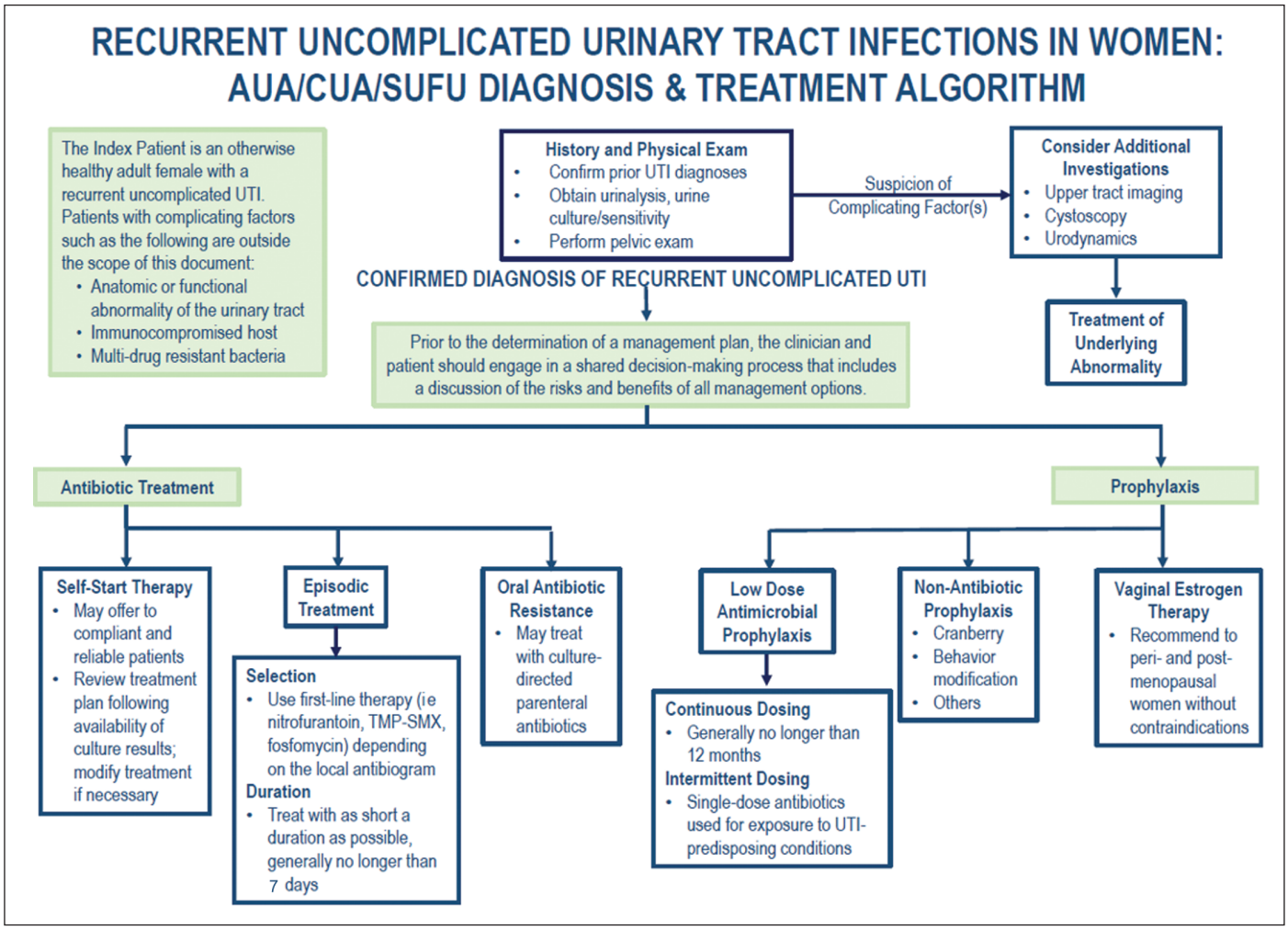

Figure. AUA recurrent UTI guidelines algorithm.

Table 1. First-line therapy for uncomplicated symptomatic UTI

Treatment Effects	Nitrofurantoin	TMP-SMX	Fosfomycin
Dose and duration	100 mg twice daily × 5 days	1 double strength twice daily × 3 days	3 gm single dose
Cure rate	88%–93%	90%–100%	83%–91%
Antimicrobial spectrum	Narrow: *E. coli*, *S. saprophyticus*	Typical uropathogens	Covers vancomycin-resistant enterococcus, ESBL gram-negative rods
Collateral damage	No	No	No
SEs	Few SEs with short duration	Occasional severe SEs reported	Few
Resistance	Low, stable × 50 yrs	Increasing	Low

Given the low incidence of side effects, cranberry is reasonable for rUTI patients with good access to care.

While there is not sufficient evidence to support any one formulation, tablets may be more convenient as the volume of cranberry juice needed to achieve adequate proanthocyanidin intake[28] can be burdensome. As many over-the-counter cranberry supplements appear to have little proanthocyanidin,[32,33] a tablet for which documented quality control ensures a specified proanthocyanidin quantity may be best. **At the moment, additional supplements, such as D-mannose, vitamin C and other vitamin cocktails, probiotics etc, lack sufficient data to allow their recommendation to patients.[8]**

The patient begins infection prophylaxis with cranberry and increased hydration. Initially she did well. However, after 5 months, she presents with acute-onset dysuria and hematuria after intercourse. She denies any fevers, chills or flank pain, but is very uncomfortable and desires treatment.

Guideline Statement 5. Clinicians should obtain urinalysis, urine culture and sensitivity with each symptomatic acute cystitis episode prior to initiating treatment in patients with rUTIs. (Moderate Recommendation; Evidence Level: Grade C)

Due to poor sensitivity and specificity, dipstick analyses provide little information. **Diagnostic testing, including urinalysis, urine culture and sensitivity, should be obtained for each symptomatic episode whenever possible.** Obtaining urine cultures >50% of the time is associated with fewer UTI-related hospitalizations and lower rates of intravenous antibiotic use; those without cultures have more UTI-related office visits and progression to pyelonephritis.[34] Analgesics can provide some relief while awaiting culture results, and antibiotics can be initiated prior to culture finalization based on prior speciation, susceptibilities, and local antibiogram if needed.

For this acute episode, urinalysis demonstrates 3+ leukocyte esterase, 3+ nitrites, and no squamous epithelial cells. The patient's culture grows >100,000 CFU pan-sensitive *E. coli*. While initially willing to attempt hydration and urinary analgesics (phenazopyridine), after 3 days, she remains symptomatic and requests definitive treatment.

Guideline Statement 9. Clinicians should use first-line therapy (ie nitrofurantoin, TMP-SMX, fosfomycin) for the treatment of symptomatic UTIs in women dependent on the local antibiogram. (Strong Recommendation; Evidence Level: Grade B)

Few available data differentiate the antimicrobials commonly used for UTI in achieving symptomatic and/or bacteriological cure.[35] **The first-line agents in the United States are effective in treating UTI, but less likely to produce collateral damage (table 1).[36]** Despite extensive use, community *E. coli* isolates continue to demonstrate susceptibility to nitrofurantoin and fosfomycin. Local resistance rates to TMP-SMX can be higher, so appropriate first-line treatment should consider the local antibiogram. Second-line therapies, including β-lactams and fluoroquinolones, are selected when resistance patterns and/or allergy considerations require. Fluoroquinolone agents should be prescribed with caution given potential adverse effects, including QTc prolongation and tendon rupture.[37]

Guideline Statement 10. Clinicians should treat rUTI patients with an acute cystitis episode with as short a duration of antibiotics as reasonable, generally no longer than 7 days. (Moderate Recommendation; Evidence Level: Grade B)

Good stewardship aims to provide sufficient treatment while minimizing antibiotic burden. In 2 systematic reviews, there were no differences between longer (7–14 days) and shorter (3–6 days) antibiotic courses regarding long-term (>2 weeks) bacteriological persistence, symptomatic persistence or risk of reinfection.[38,39] Shorter courses of antibiotics had fewer side effects, less discontinuation due to adverse events, and fewer gastrointestinal adverse events compared to longer therapy.

The patient's symptoms resolve after a 5-day course of nitrofurantoin, but she would now like more aggressive prevention measures.

Guideline Statement 12. Following discussion of the risks, benefits, and alternatives, clinicians may prescribe antibiotic prophylaxis to decrease the risk of future UTIs in women of all ages previously diagnosed with UTIs. (Moderate Recommendation; Evidence Level: Grade B)

Substantial evidence exists to support the use of antibiotic prophylaxis over placebo to reduce clinical recurrences in pre- and post-menopausal women with rUTIs.[8,40,41] There are few data detailing the impact of long-term, low-dose antibiotic therapy on individual or community antibiotic resistance. Common side effects include vaginitis, diarrhea, oral candidiasis, skin rashes and nausea, although more serious side effects can occur. The low collateral damage and efficacy of nitrofurantoin support its first-line use.[36,40] Nitrofurantoin use in older adults is controversial and must be weighed against the alternative risks of no treatment or other antibiotic side effects (table 2).

For patients in whom infections are reliably related to specific triggers (eg sexual intercourse, travelling, diarrhea

Table 2. Prophylactic options for recurrent UTI

Continuous prophylaxis:	
Nitrofurantoin	50–100 mg daily
Trimethoprim	100 mg daily
TMP-SMX	40 mg/200 mg daily or 3 times per wk
Cephalexin	125–250 mg daily
Fosfomycin	3 gm every 10 days
Intermittent prophylaxis:	
Nitrofurantoin	50–100 mg
TMP-SMX	40 mg/200 mg 80 mg/400 mg
Cephalexin	250 mg

or constipation), single-dose intermittent prophylaxis at risk exposure appears similar in efficacy to continuous prophylaxis and may be associated with decreased adverse events.[41,42]

Unfortunately, the effects of antibiotic prophylaxis do not endure past their active intake. While studies typically examined prophylaxis durations of 6 to 12 months, in clinical practice, some women continue prophylaxis for years without adverse events. This approach, however, is not evidence-based and should only be undertaken after communicating the need for continued monitoring and the unclear risks of long-term use.

Of note, there are low-quality data to support prophylactic use of methenamine hippurate,[43,44] a prescription bacteriostatic agent that acts by producing ammonia and formaldehyde in acidic urine. While it has little utility in UTI treatment, multiple retrospective studies have described efficacy in reducing symptomatic UTI episodes in rUTI patients with few adverse effects.[45] As yet, however, no high-quality prospective trials have compared this therapy to antibiotic prophylaxis.

As her infections always follow intercourse, this patient opts for post-coital prophylaxis with nitrofurantoin. She also mentions that she is traveling to Europe and is anxious about infections during the trip.

Guideline Statement 6. Clinicians may offer patient-initiated treatment (self-start treatment) to select rUTI patients with acute episodes. (Moderate Recommendation; Evidence Level: Grade C)

In select circumstances, it is reasonable to provide patients with a short antibiotic course, accounting for prior culture susceptibilities and local antibiograms, to begin at their discretion. While culture data for symptomatic recurrences should be acquired when feasible, it can be challenging in certain situations. In general, self-start treatment should be reserved for patients with accurate self-assessment of symptoms and reliable communication patterns. With nitrofurantoin prophylaxis, however, this patient never needed the self-start antibiotics and remained free from infections for 6 months, at which point she discontinued treatment.

CASE 2

Case 2 is a 38-year-old G0P0 woman with recurrent episodes of dysuria, urinary frequency and pelvic discomfort who presents with concerns for acute UTI. Episodes occur frequently, often more than once a month. She feels like episodes occur more frequently when traveling or during periods of increased stress. She denies any flank pain, hematuria, fevers or chills. When episodes occur, she will call her primary doctor's office for an antibiotic. Antibiotics help a little, but the dysuria can persist for weeks, so she typically gets 14 days of ciprofloxacin each time. Between episodes, she still complains of frequency and bladder pressure. She takes 10 mg escitalopram daily for anxiety but denies other medical comorbidities.

She has had several cultures, typically when her symptoms persist after antibiotic treatment, which demonstrate:

1. 100,000 CFU group B *Streptococcus*
2. 25,000 CFU *E. coli*, 10,000 CFU mixed flora
3. Mixed urogenital flora
4. 25,000 CFU *Enterococcus*

One microscopic urinalysis accompanying culture #2 demonstrates 1+ leukocyte esterase, negative nitrites, and 26 squamous epithelial cells.

Internal examination is uncomfortable with tenderness throughout the pelvic floor musculature, but minimal pain with bladder palpation. In addition, she has burning at the vaginal vestibule and a whitish vaginal discharge.

Guideline Statement 2. To make a diagnosis of rUTI, clinicians must document positive urine cultures associated with prior symptomatic episodes. (Clinical Principle)

The patient is symptomatic, but aspects of her presentation are inconsistent with rUTI. Her urine cultures do not provide definitive evidence of infection. Culture-based antibiotic treatment does not quickly resolve her symptoms. She has similar symptoms between "infections." Her cultures have some bacteria that are considered uropathogens (*E. coli*) but also exhibit vaginal commensals with contamination on the only urinalysis. Better diagnostic information is needed to rule out confounding diagnoses.

Multiple conditions can present similarly to UTI, such as interstitial cystitis/bladder pain syndrome, overactive bladder, genitourinary syndrome of menopause, urinary calculi, bacterial or fungal vaginitis, vulvar dermatitides, vulvovestibulodynia, high-tone pelvic floor muscle dysfunction and bladder carcinoma. Moreover, these conditions may coexist with episodes of cystitis. **In evaluating each symptomatic episode prospectively, the absence of a clear relationship between microbiological data and symptomatic episodes should prompt consideration of an alternative diagnosis.**

Recently, more and more patients, particularly those with *chronic* cystitis-like symptoms, have been undergoing sensitive molecular bacterial detection assessments to evaluate for "occult UTI" in the setting of negative/equivocal culture results. These sensitive techniques, however, detect bacteria even in asymptomatic individuals. Such tests cannot at present be recommended in clinical practice and may promote increased diagnostic confusion, overdiagnosis, and overtreatment.

Guideline Statement 3. Clinicians should obtain repeat urine studies when initial urine specimen is suspect for contamination, with consideration for obtaining a catheterized specimen. (Clinical Principle)

Credible microbiological evidence of infection should accompany acute-onset urinary symptoms to diagnose UTI; concomitant urinalysis should evaluate for contamination with

skin and vaginal bacteria (eg epithelial cells or mucus) that can lead to unnecessary treatment. Particularly in patients who cannot provide a high-quality clean catch specimen, such as obese or wheelchair-bound patients, straight catheterization may provide more accurate results.[46]

In this patient, the combination of vaginal discharge, contamination on urinalysis, and non-classic symptoms suggests a catheterized sample could improve diagnostic accuracy. Given her vaginal discharge, a vaginal swab is also acquired, revealing substantial yeast. She is started on fluconazole orally and topical miconazole. Her symptoms improve immediately, and she returns to her baseline by the time her urine culture comes back without bacterial growth.

Three months later, she presents again with dysuria, worsening urinary urgency, and suprapubic discomfort. A catheterized specimen shows 3+ leukocyte esterase, 2+ nitrites, without mucus or epithelial cells. She starts phenazopyridine while awaiting the culture, which demonstrates >100,000 CFU *E. coli*, sensitive to nitrofurantoin.

Each episode of acute-onset urinary symptoms should be treated as an individual occurrence. Even patients with urological comorbidities, such as interstitial cystitis/bladder pain syndrome or overactive bladder, can develop acute cystitis. She takes nitrofurantoin for 5 days and notes improvements in the dysuria but continues to have persistent frequency and urgency. One week after completing the course, she calls asking for additional antibiotics.

Guideline Statement 15. Clinicians should repeat urine culture to guide further management when UTI symptoms persist following antimicrobial therapy. (Expert Opinion)

If symptoms persist beyond antibiotic therapy, it is reasonable to repeat a urine culture. Although a second antibiotic can be given empirically, most patients are willing to defer treatment until the results of the second culture are available. Preemptively lengthening the antimicrobial course, broadening antibiotic treatment, or increasing antibiotic doses is not efficacious and has the potential for significant harm.[7]

Resolution of symptoms is expected within 3 to 7 days of starting antimicrobial therapy. **The presence of refractory symptoms after appropriate, culture-directed therapy should raise concern for a comorbid condition.** Her repeat culture is negative, and she continues to have significant pelvic floor pain and hypertonicity. She agrees to try pelvic floor physical therapy and returns to the office 6 months later with the resolution of her frequency and pressure.

CASE 3

Case 3 is an 84-year-old independently living G3P3 woman with recurrent episodes of dysuria, urinary frequency and urgency, and urgency incontinence without any obvious antecedent event. She has had ~2 episodes a year for the past few years. She has multiple cultures on record, demonstrating *Klebsiella* or *E. coli*. She is typically treated with a 3-day course of TMP-SMX, which resolves her symptoms completely.

She has a history of hypertension, controlled on medications, and osteoarthritis. She had a lumpectomy for breast cancer but has been cancer-free and off treatment for 12 years. Between infections, she has mild urinary frequency and nocturia, but these are not bothersome. She is uncomfortable from some vaginal dryness and burning that improves with topical petroleum jelly.

On pelvic examination, she has vulvovaginal changes consistent with atrophy, including thinning and flattening of the epithelium, labia minora regression, and erythema of the posterior vaginal vestibule.

Although she currently denies the symptoms she associates with infections, she requests urine culture as she continues to have vulvar burning and irritation.

Guideline Statement 7. Clinicians should omit surveillance urine testing, including urine culture, in asymptomatic patients with rUTIs. (Moderate Recommendation; Evidence Level: Grade C)

Many struggle with defining "asymptomatic" for patients with chronic genitourinary symptoms. **One helpful principle is that acute-onset urinary symptoms are an essential aspect of presumptive infections.[8]** At this presentation, even the patient has a low suspicion of UTI and complains only of chronic symptoms of vaginal dryness. Thus, despite current symptoms and a history of rUTI, her presentation is not consistent with acute cystitis, making urine testing inappropriate.

She would, however, appreciate strategies aimed at preventing UTI recurrences. Even though she does not meet the strict definition of rUTI, patients with 1 to 2 symptomatic infections per year for years are likely to benefit from proactive management strategies,[8] particularly if they are at risk for serious infectious sequelae.

Table 3. Commonly used vaginal estrogen therapy

Formulation (brand name)	Composition	Strength and Dosage
Vaginal tablet (Vagifem®)	Estradiol hemihydrate	10 µg per day for 2 wks, then 10 µg twice weekly
Vaginal inserts (Imvexxy®, Yuvafem®)	17β-estradiol	4 µg or 10 µg per day for 2 wks, then twice weekly
Vaginal ring (Estring®)	17β-estradiol	2 mg ring releasing 7.5 µg per day, changed every 3 mos
Vaginal creams:		
Estradiol 0.01% (Estrace®)	17β-estradiol	2 gm daily for 2 weeks, then 1 gm 2–3 times per week
Estrogens (Premarin®)	Conjugate equine estrogen	0.5 gm daily for 2 weeks, then 0.5 gm twice weekly

Guideline Statement 16. In peri- and post-menopausal women with rUTIs, clinicians should recommend vaginal estrogen therapy to reduce the risk of future UTIs. (Moderate Recommendation; Evidence Level: Grade B)

Vaginal estrogen can be offered to all peri- and post-menopausal women with rUTI, with multiple randomized trials demonstrating decreased incidence and improved time to recurrence of UTI in hypoestrogenic women.[47] For this patient, vaginal estrogen provides additional benefit, treating her vaginal burning and dryness.

As she is anxious about estrogen given her history of breast cancer, it is helpful to address common misconceptions about estrogen-based treatments. Vaginal estrogen differs from systemic estrogen replacement, which does not reduce UTI recurrence and has different risks. **Given low systemic absorption, vaginal estrogen therapy has few side effects and has not been shown to increase cancer recurrence in women undergoing treatment for or with a personal history of breast cancer.[48]**

As insufficient evidence exists to support one estrogen formulation (table 3) over another, the most effective approach is the one with which she will be most compliant. The patient agrees to a trial of vaginal estrogen cream but calls 6 months later requesting antibiotics. At her annual physical, her urine culture is positive for 50,000 CFU *Klebsiella*. She denies any acute changes in her symptoms, instead noting significant improvements in her vaginal dryness.

Guideline Statement 8. Clinicians should not treat asymptomatic bacteriuria in patients. (Strong Recommendation; Evidence Level: Grade B)

In women with rUTIs, *including* diabetics, long-term care facility residents and patients with spinal cord injuries, treatment of asymptomatic bacteriuria does not reduce UTI rates, morbidity or mortality.[49] **Repeated antibiotic courses are associated with significant adverse events, particularly in older adults**.[50] Substantial effort should be made to avoid unnecessary treatment unless there is a high suspicion of UTI.

Six months later, she makes an urgent appointment for new, acute-onset dysuria, urgency, and bladder discomfort. She denies any fevers/chills, flank pain or hematuria. After starting on TMP-SMX, the culture reveals >100,000 CFU *E. coli* resistant to TMP-SMX and positive for extended-spectrum beta-lactamase.

Guideline Statement 11. In patients with rUTIs and urine cultures resistant to oral antibiotics, clinicians may treat with culture-directed parenteral antibiotics for as short a course as reasonable, generally no longer than 7 days. (Expert Opinion)

The most common multi-drug resistant uropathogens are organisms producing ESBL, which are frequently susceptible only to carbapenems. Before committing to intravenous antimicrobials, however, clinicians can consider fosfomycin susceptibility testing. Some multi-drug resistant uropathogens, including ESBL-producing *E. coli*, may be susceptible to fosfomycin and/or nitrofurantoin. However, fosfomycin is not always readily available, can be expensive, or can require prior authorization, preventing timely treatment. Managing drug-resistant infections may require consultation with an infectious diseases specialist.

Susceptibility testing in this patient reveals that fosfomycin is an option for treatment, and her symptoms resolve after a single dose. She asks if she should return for urine testing, to be certain she has cleared the infection.

Guideline Statement 14. Clinicians should not perform a post-treatment test of cure urinalysis or urine culture in asymptomatic patients. (Expert Opinion)

Positive post-treatment culture would only signify asymptomatic bacteriuria, which does not warrant treatment. Thus, microbiological reassessment after symptomatic resolution provides no clinically relevant information and would only lead to overtreatment.

CONCLUSIONS

There are still fundamental knowledge gaps in our understanding of rUTI, such as the role of the urinary microbiome in bladder health, host factors that influence UTI risk and microbial factors determining pathogenic potential. Our current diagnostic methods also have significant deficiencies: standard urine culture has no objective definition of positivity and provides no measure of the host response. Combined with the growing crisis of multi-drug resistance, the role of providers in antibiotic stewardship cannot be overstated. These gaps serve to reinforce the concept that clinician judgment and responsibility are central in rUTI treatment and management.

DID YOU KNOW?

- Microbiological assessment (urinalysis, urine culture and susceptibilities) with any symptomatic episode is central in rUTI diagnosis, management, treatment and monitoring of treatment efficacy.
- Treatment of asymptomatic bacteriuria should be avoided: acute-onset urinary symptoms, particularly dysuria, should be present to consider evaluation or treatment for UTI.
- Management of rUTI should focus on alleviating symptoms, preventing recurrence and reducing adverse events, not on microbiological sterilization.
- Non-antibiotic approaches to symptomatic management and prophylaxis are a reasonable alternative to antibiotics in many patients.
- Treatment of UTI should use the shortest possible course of an effective antibiotic with the least collateral damage, and prophylactic approaches are preferred over repeated intermittent antibiotic treatment when UTIs recur.

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Study Questions Volume 40 Lesson 17

1. The initial evaluation of an *asymptomatic* patient with a suspicion of recurrent urinary tract infections should include
   a. history and physical exam including pelvic exam
   b. history and physical and microscopic urinalysis, urine culture and susceptibilities
   c. history and physical exam including pelvic exam and cystoscopy
   d. history and physical exam including pelvic exam and computerized tomographic urogram

2. In residents of long-term care facilities, the symptoms or signs that should prompt urgent evaluation for UTI with urinalysis, urine culture and susceptibility testing are
   a. increased confusion
   b. gross hematuria
   c. worsening fatigue
   d. acute fall

3. In a 24-year-old woman with no comorbidities, no medications and a normal exam who experiences recurrent UTI unrelated to sexual intercourse, the best approach to infection prophylaxis is
   a. daily low-dose antibiotics
   b. post-coital antibiotics
   c. vaginal estrogen supplementation
   d. phenazopyridine

4. In rUTI patients who would like to avoid antibiotics for the prevention of UTI recurrences, a viable option for prophylaxis is
   a. D-mannose
   b. vitamin C
   c. cranberry extract
   d. probiotics

5. A 74-year-old woman has completed antibiotics for treatment of an episode of acute cystitis. She is now completely asymptomatic. The next step is
   a. no testing
   b. urine dipstick with reflex culture
   c. urinalysis, urine culture and sensitivities
   d. cystoscopy