

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

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### Purpose

Over the past few decades, our ability to diagnose, treat, and manage recurrent urinary tract infection (rUTI) long-term has evolved due to additional insights into the pathophysiology of rUTI, a new appreciation for the adverse effects of repetitive antimicrobial therapy ("collateral damage"),<sup>1</sup> rising rates of bacterial antimicrobial resistance, and better reporting of the natural history and clinical outcomes of acute cystitis and rUTI. For the purposes of this guideline, the Panel considers only recurrent episodes of uncomplicated cystitis in women. This guideline does not apply to pregnant women, patients who are immunocompromised, those with anatomic or functional abnormalities of the urinary tract, women with rUTIs due to self-catheterization or indwelling catheters, or those exhibiting signs or symptoms of systemic bacteremia, such as fever and flank pain. This guideline also excludes those seeking prevention of urinary tract infections (UTIs) in the operative or procedural setting. In this document, the term UTI will refer to acute bacterial cystitis unless otherwise specified. This document seeks to establish guidance for the evaluation and management of patients with rUTIs to prevent inappropriate use of antibiotics, decrease the risk of antibiotic resistance, reduce adverse effects of antibiotic use, provide guidance on antibiotic and non-antibiotic strategies for prevention, and improve clinical outcomes and quality of life for women with rUTIs by reducing recurrence of UTI events.

### Methodology

The systematic review utilized to inform this guideline was conducted by a methodology team at the Pacific Northwest Evidence-based Practice Center. Determination of guideline scope and review of the final evidence report to inform guideline statements was conducted in conjunction with the rUTI Panel. A research librarian conducted searches in Ovid MEDLINE (1946 to January Week 1 2018), Cochrane Central Register of Controlled Trials (through December 2017) and Embase (through January 16, 2018). Searches of electronic databases were supplemented by reviewing reference lists of relevant articles. An update literature search was conducted on September 20, 2018.

### Guideline Statements

#### Evaluation

1. Clinicians should obtain a complete patient history and perform a pelvic examination in women presenting with rUTIs. (Clinical Principle)
2. To make a diagnosis of rUTI, clinicians must document positive urine cultures associated with prior symptomatic episodes. (Clinical Principle)
3. Clinicians should obtain repeat urine studies when an initial urine specimen is suspect for contamination, with consideration for obtaining a catheterized specimen. (Clinical Principle)

4. Cystoscopy and upper tract imaging should not be routinely obtained in the index patient presenting with rUTI. (Expert Opinion)
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)
6. Clinicians may offer patient-initiated treatment (self-start treatment) to select rUTI patients with acute episodes while awaiting urine cultures. (Moderate Recommendation; Evidence Level: Grade C)

#### **Asymptomatic Bacteriuria**

7. Clinicians should omit surveillance urine testing, including urine culture, in asymptomatic patients with rUTIs. (Moderate Recommendation; Evidence Level: Grade C)
8. Clinicians should not treat ASB in patients. (Strong Recommendation; Evidence Level: Grade B)

#### **Antibiotic Treatment**

9. Clinicians should use first-line therapy (i.e., nitrofurantoin, TMP-SMX, fosfomycin) dependent on the local antibiogram for the treatment of symptomatic UTIs in women. (Strong Recommendation; Evidence Level: Grade B)
10. Clinicians should treat rUTI patients experiencing acute cystitis episodes with as short a duration of antibiotics as reasonable, generally no longer than seven days. (Moderate Recommendation; Evidence Level: Grade B)
11. In patients with rUTIs experiencing acute cystitis episodes associated with 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 seven days. (Expert Opinion)

#### **Antibiotic Prophylaxis**

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)

#### **Non-Antibiotic Prophylaxis**

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

#### **Follow-up Evaluation**

14. Clinicians should not perform a post-treatment test of cure urinalysis or urine culture in asymptomatic patients. (Expert Opinion)
15. Clinicians should repeat urine cultures to guide further management when UTI symptoms persist following antimicrobial therapy. (Expert Opinion)

#### **Estrogen**

16. In peri- and post-menopausal women with rUTIs, clinicians should recommend vaginal estrogen therapy to reduce the risk of future UTIs if there is no contraindication to estrogen therapy. (Moderate Recommendation; Evidence Level: Grade B)

## INTRODUCTION

rUTI is a highly prevalent, costly, and burdensome condition affecting women of all ages, races, and ethnicities without regard for socioeconomic status or educational level.<sup>2</sup> The incidence and prevalence of rUTI depend on the definition used. Approximately 60% of women will experience symptomatic acute bacterial cystitis in their lifetime.<sup>3</sup> An estimated 20-40% of women who have had one previous cystitis episode are likely to experience an additional episode, 25-50% of whom will experience multiple recurrent episodes.<sup>4,5</sup> The exact numbers are unclear, as most epidemiologic studies utilize diagnosis codes that may overestimate true numbers due to overuse of UTI and rUTI codes in patients who have not yet undergone culture or evaluation.<sup>3</sup> Regardless of the definition, the evaluation and treatment of UTI costs several billion dollars globally per year, reaching approximately \$2 billion per year in the United States.<sup>6</sup>

## Terminology and Definitions

For the purposes of this guideline, the Panel considers only recurrent episodes of uncomplicated cystitis in women. "Uncomplicated" means that the patient has no known factors that would make her more susceptible to develop a UTI, while "complicated" indicates that other complicating factors may put one at higher risk for UTI and decreased treatment efficacy. Such complicating factors may include an anatomic or functional abnormality of the urinary tract (e.g., stone disease, diverticulum, neurogenic bladder), an immunocompromised host, or infection with multi-drug resistant (MDR) bacteria. In this guideline, the term UTI

will refer to culture-proven acute bacterial cystitis and associated symptoms unless otherwise specified. While most providers have confidence in making a diagnosis of acute cystitis, diagnostic criteria are imprecise and vary considerably. Strong evidence suggest that the diagnosis of acute cystitis should include the combination of laboratory confirmation of significant bacteriuria with endorsement of acute-onset symptoms referable to the urinary tract.<sup>7,8</sup> Without symptoms, bacteriuria of any magnitude is considered asymptomatic bacteriuria (ASB).

While there are multiple definitions for rUTI,<sup>9</sup> this Guideline endorses the two most commonly used definitions of two episodes of acute bacterial cystitis within six months or three episodes within one year. These definitions typically consider these episodes to be separate infections with resolution of symptoms between episodes, and do not include those who require more than one treatment or multiple antibiotic courses for symptomatic resolution, as can occur with inappropriate initial or empiric treatment. Any patient experiencing episodes of symptomatic acute cystitis after previous resolution of similar symptoms meets the criteria for rUTI. However, it should be noted that those patients initially treated for uncomplicated bacterial cystitis who recur rapidly (i.e. within two weeks of initial treatment) after symptom resolution or display bacterial persistence without symptom resolution may be reclassified as complicated and require imaging, cystoscopy, or other further investigation for bacterial reservoirs. The definitions used in this guideline can be found in Table 1.

**TABLE 1: Guideline Definitions**

Term	Definition
Acute bacterial cystitis	A culture-proven infection of the urinary tract with a bacterial pathogen associated with acute-onset symptoms such as dysuria in conjunction with variable degrees of increased urinary urgency and frequency, hematuria, and new or worsening incontinence
Uncomplicated urinary tract infection	An infection of the urinary tract in a healthy patient with an anatomically and functionally normal urinary tract and no known factors that would make her susceptible to develop a UTI
Complicated urinary tract infection	An infection in a patient in which one or more complicating factors may put her at higher risk for development of a UTI and potentially decrease efficacy of therapy. Such factors include the following: <ul style="list-style-type: none"> <li>Anatomic or functional abnormality of the urinary tract (e.g., stone disease, diverticulum, neurogenic bladder)</li> <li>Immunocompromised host</li> <li>Multi-drug resistant bacteria</li> </ul>
Recurrent urinary tract infection	Two separate culture-proven episodes of acute bacterial cystitis and associated symptoms within six months or three episodes within one year
Asymptomatic bacteriuria	Presence of bacteria in the urine that causes no illness or symptoms
<b>The index patient for this guideline is an otherwise healthy adult female with an uncomplicated recurrent urinary tract infection</b>	

## Index Patient

The index patient for this guideline is an otherwise healthy adult female with an uncomplicated rUTI. The infection is culture-proven and associated with acute-onset symptoms as discussed below. This guideline does not apply to pregnant women, patients who are immunocompromised, those with anatomic or functional abnormalities of the urinary tract, women with rUTIs due to self-catheterization or indwelling catheters or those exhibiting signs or symptoms of systemic bacteremia, such as fever and flank pain.<sup>4</sup> This guideline also excludes those with neurological disease or illness relevant to the lower urinary tract, including peripheral neuropathy, diabetes, and spinal cord injury. Further, this guideline does not discuss prevention of UTI in operative or procedural settings.

## Symptoms

In UTI, acute-onset symptoms attributable to the urinary tract typically include dysuria in conjunction with variable degrees of increased urinary urgency and frequency, hematuria, and new or worsening incontinence. *Dysuria is central in the diagnosis of UTI*; other symptoms of frequency, urgency, suprapubic pain, and hematuria are variably present. Acute-onset dysuria is a highly specific symptom, with more than 90% accuracy for UTI in young women in the absence of concomitant vaginal irritation or increased vaginal discharge.<sup>10,11</sup>

In older adults, the symptoms of UTI may be less clear. Given the subjective nature of these symptoms, careful evaluation of their chronicity becomes an important consideration when the diagnosis of UTI is in doubt. Acute-onset dysuria, particularly when associated with new or worsening storage symptoms, remains a reliable diagnostic criterion in older women living both in the community and in long-term care facilities.<sup>12-14</sup> Older women frequently have nonspecific symptoms that may be perceived as a UTI, such as dysuria, cloudy urine, vaginal dryness, vaginal/perineal burning, bladder or pelvic discomfort, urinary frequency and urgency, or urinary incontinence, but these tend to be more chronic in nature. The lack of a correlation between symptoms and the presence of a uropathogen on urine culture was discussed in a systematic review of studies evaluating UTI in community-dwelling adults older than 65 years. Symptoms such as chronic nocturia, incontinence, and general sense of lack of well-being (e.g., fatigue, malaise, weakness), were common and not specific for UTI.<sup>15</sup> While these guidelines do not include women with chronic symptoms common in urology, such as overactive bladder (OAB), guidelines from the American

Geriatrics Society (AGS) and the Infectious Diseases Society of America (IDSA) agree that evaluation and treatment for suspected UTI should be reserved for acute-onset (<1 week) dysuria or fever in association with other specific UTI-associated symptoms and signs, which primarily include gross hematuria, new or significantly worsening urinary urgency, frequency and/or incontinence, and suprapubic pain.<sup>16-19</sup>

## Diagnosis

Typically, for a diagnosis of cystitis, acute-onset symptoms should occur in conjunction with the laboratory detection of a uropathogen from the urine, typically *E. coli* (75-95%), but occasionally *other pathogens such as other Enterobacteriaceae, P. mirabilis, K. pneumoniae, and S. saprophyticus*. Other species are rarely isolated in uncomplicated UTI.<sup>20,21</sup>

Urine culture remains the mainstay of diagnosis of an episode of acute cystitis; urinalysis provides little increase in diagnostic accuracy.<sup>22</sup> There are significant limitations that constrain the ability of this guideline to recommend strict cut-off definitions correlating with clinically meaningful results. Standard agar-based clinical culture has been used since the 19th century with few technical refinements; more recent studies demonstrate that a large proportion of urinary bacteria are not cultivatable using these standard conditions. The definition for clinically significant bacteriuria of  $10^5$  colony forming units (CFU)/mL was published more than 60 years ago and likely represents an arbitrary cut-off.<sup>23-27</sup> The origin of this cut-off derives from evidence that the use of this threshold in asymptomatic individuals is relevant to reducing the over detection of contaminating organisms. More than 95% of subjects with  $>10^5$  CFU/mL bacteria in a clean-catch specimen had definite bacteriuria on a catheterized specimen, while only a minority of patients with lower bacterial counts exhibited bacterial growth from a catheterized urine sample.<sup>23</sup> These data were obtained from asymptomatic women, however, and do not reflect the population in whom there is a suspicion of UTI.

In symptomatic women, however, several studies have identified subsets of women with pyuria and symptoms consistent with a UTI but colony counts  $<10^5$  CFU/mL in voided urine.<sup>28-35</sup> One study of more than 200 premenopausal, non-pregnant women who presented with at least two symptoms of acute cystitis compared colony counts in a midstream, clean-catch urine sample to specimens obtained by urethral catheterization. Approximately 40% of the women who had *E. coli* grow from a catheterized specimen had colony counts  $<10^5$  CFU/mL in the voided sample.<sup>35</sup> In multiple

studies, a threshold of  $\geq 10^2$  CFU/mL *E. coli* from voided specimens had 88-93% positive predictive value for bladder bacteriuria in patients with a high suspicion of UTI.<sup>31,35</sup> Lower midstream urine colony counts ( $>10^2$  CFU/mL) have been associated with bladder bacteriuria on catheterization in symptomatic women with pyuria, suggesting that  $\geq 10^2$  CFU/mL of a single uropathogen may be a more appropriate cut-off in appropriately selected patients in whom there is strong suspicion of infection.<sup>36,37</sup>

Many laboratories, however, will not report colony counts  $<10^3$  CFU/mL. In addition, it is likely that the strict use of a low threshold will lead to overdiagnosis. As such, clinical judgment determining when a culture result represents clinically significant bacteriuria must factor in the clinical presentation of a patient, the urine collection method used, and the presence of other suggestive factors such as pyuria. Although a  $10^5$  CFU/mL threshold for bacterial growth on midstream voided urine may help distinguish bladder bacteriuria from contamination in asymptomatic, pre-menopausal women, a lower  $10^2$  CFU/mL threshold may be appropriate in symptomatic individuals. Further, no specific threshold for urinary colony count has been demonstrated to identify those symptomatic patients at risk for progression to pyelonephritis or those who would benefit from more aggressive antimicrobial management.

### Molecular Diagnostics

Sensitive culture-dependent and -independent techniques have revealed that the lower urinary tract, even in asymptomatic, healthy individuals, hosts a complex microbial community that is likely important in the maintenance of normal bladder function.<sup>22,38,39</sup> Thus, in the strictest definition, all individuals are likely "bacteriuric." In fact, it has been suggested that ASB may protect patients with rUTI from additional symptomatic episodes.<sup>40</sup> Thus, more sensitive culture-based or molecular bacterial detection methods (e.g., high-throughput sequencing, polymerase chain reaction-based detection methods) are not necessarily beneficial in the diagnostic evaluation of patients with suspected bacterial cystitis. Sensitive detection of microorganisms will likely be associated with increased diagnostic confusion and dilemmas, including overdiagnosis and associated overtreatment. While there is some early evidence that molecular diagnostic methods to rapidly identify uropathogen antibiotic susceptibility may help to avoid delayed or inappropriate antimicrobial treatment,<sup>41</sup> the impact of such tests on the accuracy of diagnosis is not

documented and cannot yet be recommended for incorporation into clinical practice. While the current definitions of UTI rely on the unlikely principle that only those organisms detectable with agar-based culture are clinically concerning, the converse that all detectable organisms are pathogenic is also inaccurate. Thus, despite a growing desire for the accurate diagnosis of UTI in patients with suggestive symptoms, particularly those who lack positive urine cultures or who have vague lower urinary tract symptoms (LUTS), extreme caution must be taken to avoid reliance on this technology when its utility remains unproven and the potential for increased harm remains significant.

### Antimicrobial Stewardship and the Consideration of Collateral Damage

In the past 20 years, antimicrobial resistance among uropathogens has increased dramatically. For example, increases in extended-spectrum  $\beta$ -lactamase (ESBL)-producing isolates has been described among patients with acute simple cystitis worldwide.<sup>1,42,43</sup> Uncomplicated UTI is one of the most common indications for antimicrobial exposure in otherwise healthy women. Fluoroquinolones have been linked to infection with methicillin-resistant *S. aureus* and increasing fluoroquinolone resistance in gram-negative bacilli, such as *P. aeruginosa*, while broad spectrum cephalosporins have been linked to subsequent infections with vancomycin-resistant Enterococci, ESBL-producing *K. pneumoniae*,  $\beta$ -lactam-resistant Acinetobacter species, and *C. difficile*.<sup>1</sup>

Adhering to a program of antimicrobial stewardship with attempts to reduce inappropriate treatment, decrease broad-spectrum antibiotic use, and appropriately tailor necessary treatment to the shortest effective duration, may significantly mitigate increasing fluoroquinolone and cephalosporin resistance.<sup>44</sup> Non-adherence to guidelines for the treatment of acute cystitis, however, is more common in patients who have rUTIs than patients with an isolated episode of acute cystitis.<sup>45</sup> When patients present with acute cystitis and a history of rUTIs, many providers will employ strategies of lengthening antimicrobial course, broadening antibiotic treatment, or increasing antibiotic doses for each episode, despite the absence of evidence to support such practices. Sometimes patients pressure providers to give non-guideline-based treatments with the hope that the number of recurrent episodes will be reduced or the time between acute cystitis episodes will be lengthened. These strategies have not been demonstrated to be efficacious and have the potential for harm to the individual and community, directly

contradicting the principles of antibiotic stewardship.<sup>46,47</sup> As antimicrobial resistance patterns vary regionally, the specific treatment recommendations for acute cystitis episodes and rUTI prophylaxis may not be appropriate in every community. Providers should combine knowledge of the local antibiogram with the selection of antimicrobial agents with the least impact on normal vaginal and fecal flora. An antibiogram provides a profile of the local results of antimicrobial sensitivity testing for specific microorganisms. Aggregate data from single hospital or healthcare systems are cumulatively summarized, usually annually, providing the percentage of a given organism sensitive to a particular antimicrobial. This information is often available from a facility's primary laboratory that provides culture results.

In a study of more than 25 million emergency department visits during which a UTI was diagnosed, urinary symptoms were only identified in 32%. In the subset of older individuals (aged 65 to 84 years), this prevalence of symptoms fell to 24%.<sup>48</sup> The prevalence of antibiotic-resistant bacteria, risk of continued rUTIs as well as progression to later pyelonephritis is enhanced by unnecessary antibiotic treatment of ASB without any demonstrable benefit. These data demonstrate the important role of rUTI overtreatment in promoting antimicrobial resistance. While the Panel recognizes that there are financial and time costs associated with obtaining urinary cultures, such studies remain an important aspect of care, as culture-directed, not empiric, therapies are associated with fewer UTI-related hospitalizations and lower rates of intravenous antibiotic use.<sup>49</sup> The diligence of obtaining cultures for each symptomatic episode is thought to be beneficial through minimizing collateral damage and the potential need for further treatment in the event of inappropriate empiric therapy.

Collateral damage describes ecological adverse effects of antimicrobial therapy, such as alterations of the normal gut microbiome that can help select drug-resistant organisms and promote colonization or infection MDR organisms.<sup>1</sup> The effects of specific antibiotics on normal fecal flora promote drug resistance and increased pathogenicity. *E. coli* isolates continue to demonstrate high *in vitro* susceptibility to nitrofurantoin, fosfomycin, and mecillinam.<sup>32,50</sup> These antimicrobials have minimal effects on the normal fecal microbiota.<sup>51-53</sup> In contrast, antimicrobials that alter the fecal flora more significantly, such as trimethoprim-sulfamethoxazole (TMP-SMX) and fluoroquinolones, promote increased rates of antimicrobial resistance.<sup>53, 54</sup>

Continued intermittent courses of antibiotics in rUTI patients are associated with significant adverse events, which may include allergic reactions, organ toxicities, future infection with resistant organisms, and *C. difficile* infections, particularly in older adults. Thus, substantial effort should be made to avoid unnecessary treatment unless there is a high suspicion of an acute cystitis episode.<sup>55</sup> Even with short courses of more targeted antibiotics, multiple treatments over time may in aggregate impact both the individual and community. Indeed, asymptomatic women with a history of rUTIs randomized to treatment for ASB in a placebo-controlled trial were more likely to have additional symptomatic cystitis episodes in a year of follow-up than those randomized to placebo.<sup>40</sup> In a longer study of over two years of follow up, women with rUTIs treated with the goal of eradicating residual bacteriuria demonstrated a higher prevalence of antibiotic resistance, a higher incidence of pyelonephritis, and a poorer quality of life in comparison to those in the non-treatment group.<sup>56</sup>

### Education and Informed Decision Making

The prevalence of antibiotic-resistant bacteria is enhanced by the unnecessary antibiotic treatment of ASB.<sup>56</sup> Given the subjectivity of patient-reported symptoms and the lack of clear diagnostic criteria on laboratory testing, the diagnosis of UTI is highly imprecise. While no evidence exists to support the concept of withholding antimicrobials from patients with rUTIs, providers must bear in mind that continued intermittent courses of antibiotics are associated with significant adverse events, particularly in older patients. Substantial effort should be made to avoid unnecessary treatment unless there is a high suspicion of UTI.

For uncomplicated patients with episodes of acute cystitis, there is minimal risk of progression to tissue invasion or pyelonephritis. Additionally, urinary tract symptoms do not reliably indicate risk or presence of "bacteremic bacteriuria" ("urosepsis") or pyelonephritis. In a representative study of older patients with bacteremia who had the same bacterial species cultured from the urine, ascertainment of the patients' symptoms at the time of infection revealed that only one of 37 participants aged 75 and older had symptoms consistent with UTI, such as dysuria.<sup>57</sup> Multiple randomized placebo-controlled trials have demonstrated that antibiotic treatment for acute cystitis offers little but mildly faster symptomatic improvement compared to placebo in patients with acute dysuria and significant bacteriuria.<sup>58-61</sup> However, the incidence of pyelonephritis in these patients is low and is not

substantially different in individuals receiving antibiotics versus those treated with supportive care of analgesics and hydration.<sup>62</sup> As deferring treatment is associated with a small risk of progression to pyelonephritis,<sup>59</sup> antibiotic treatment of suspected UTI remains common practice, but expectant management with analgesics while awaiting culture results is likely underutilized.

In a large clinical trial, a substantial proportion of women agreed to placebo randomization<sup>63</sup> without other treatments to ameliorate symptoms. This suggests that many women may be willing to attempt temporizing measures with symptomatic and non-antimicrobial management when the benefits and potential harms of intermittent antimicrobial treatment are adequately discussed. It is reasonable to consider an approach to the diagnosis and treatment of rUTI as one of shared decision-making, in which patients are educated about the inaccuracy of diagnostic testing, the benefits and potential risks of antimicrobial use, and the alternatives to standard antibiotic treatment. It is likely that far fewer patients will opt for more aggressive treatments when counseled appropriately. Many patients and providers do not know that uncomplicated cystitis typically is self-limited and rarely progresses to more severe disease.<sup>15,63,64</sup> If this were explained, the goals of care could be more clearly defined as the amelioration of symptoms, the prevention of long-term complications, and the more appropriate use of antibiotics.<sup>10</sup>

The Panel also supports discussion with patients regarding certain modifiable behaviors, including changing mode of contraception and increasing water intake, that have been shown to reduce the risk of rUTI. Sexually active women may consider alternatives to barrier contraceptives and spermicidal products.<sup>65</sup> The increased risk of UTI associated with spermicidal use is likely due to the deleterious effect on lactobacillus colonization and/or the vaginal microbiome.<sup>66</sup> Increased water intake should be recommended to those consuming less than 1.5 L per day as a recent study showed that increased water intake was also associated with a lower likelihood of having at least 3 UTI episodes over 12 months (<10% versus 88%) and a greater interval between UTI episodes (143 versus 84.4 days,  $p < 0.001$ ).<sup>67</sup> Unfortunately, there are many commonly held myths surrounding rUTI lifestyle modification. Case-control studies clearly demonstrate that changes in hygiene practices (e.g., front to back wiping), pre- and post-coital voiding, avoidance of hot tubs, tampon use, and douching do not play a role in rUTI prevention.<sup>65,68</sup> This reframing of the discussion surrounding UTI is likely to

benefit both individual patients and the health care system as a whole.

## METHODOLOGY

The systematic review utilized to inform this guideline was conducted by a methodology team at the Pacific Northwest Evidence-based Practice Center. Determination of the guideline scope and review of the final systematic review to inform guideline statements was conducted in conjunction with the rUTI Panel.

## Panel Formation

The rUTI Panel was created in 2017 by the American Urological Association Education and Research, Inc. (AUAER). This guideline was developed in collaboration with the Canadian Urological Association (CUA) and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chairs who in turn appointed the additional panel members with specific expertise in this area in conjunction with CUA and SUFU. Additionally, the Panel included patient representation. Funding of the Panel was provided by the AUA with contributions from CUA and SUFU; panel members received no remuneration for their work.

## Searches and Article Selection

A research librarian conducted searches in Ovid MEDLINE (1946 to January Week 1 2018), Cochrane Central Register of Controlled Trials (through December 2017) and Embase (through January 16, 2018). Searches of electronic databases were supplemented by reviewing reference lists of relevant articles. An update search was conducted for additional publications on September 20, 2018.

The methodology team developed criteria for inclusion and exclusion of studies based on the Key Questions and the populations, interventions, comparators, outcomes, timing, types of studies and settings (PICOTS) of interest. For populations, inclusion focused on women with rUTIs (defined as  $\geq 3$  UTIs in a 12-month period or  $\geq 2$  UTIs in a 6-month period; studies were also included in which rUTI was not defined, but the mean or median number of UTIs in a 12 months period was  $\geq 3$ ). Exclusions included pregnant women, women with rUTIs due to self-catheterization or indwelling catheters, and prevention of UTI in operative or procedural settings. Subgroups of interest were based on age, history of pelvic surgery, and the presence of diabetes mellitus. For interventions, evaluations included diagnostic tests for rUTI (urine

dipstick, urinalysis with microscopy, urine culture, urine or serum biomarkers), antibiotics for treatment of acute UTI and prevention, cranberry, lactobacillus, estrogen, and other preventive treatments. For studies on treatment and prevention of UTI, outcomes were UTI recurrence, UTI related symptoms, recurrence rate, hospitalization, antimicrobial resistance, and adverse effects associated with interventions. The Panel included randomized and non-randomized clinical trials of treatments for acute UTI and preventive interventions in women with rUTIs, studies on the diagnostic accuracy of tests for rUTI, and prospective studies on the association between risk factors and progression to symptomatic UTI in women with ASB. For questions related to treatment of acute UTI, methodologists included systematic reviews, supplemented by primary studies published after the reviews.

Using the pre-specified criteria, two investigators independently reviewed titles and abstracts of all citations. The methodology team used a two-phase method for screening full-text articles identified during review of titles and abstracts. In the first phase, investigators reviewed full-text articles to identify systematic reviews for inclusion. In the second phase they reviewed full-text articles to address key questions not sufficiently answered by previously published systematic reviews, or recent publications to update previously published systematic reviews. Database searches resulted in 6,153 potentially relevant articles. After dual review of abstracts and titles, 214 systematic reviews and individual studies were selected for full-text dual review, and 65 studies in 67 publications were determined to meet inclusion criteria and were included in this review. An additional 10 publications were identified in the updated literature search and added to the review.

### Data Abstraction

For each study that met inclusion criteria, a single investigator abstracted information on study design, year, setting (inpatient or outpatient), country, sample size, eligibility criteria, dose and duration of the intervention, population characteristics (age, race, UTI history, diabetes, prior genitourinary surgery, and other treatments), results, and source of funding. For included systematic reviews, a single investigator abstracted study characteristics (number and design of included studies, definition of rUTI, study settings, study dates, treatment and follow up duration), population characteristics (age, diabetes history, surgical history, prior treatments), interventions,

methods and ratings for the risk of bias, synthesis methods, and results. The methodology team calculated relative risks and 95% confidence intervals if necessary for included outcomes, from data reported in the studies. All data abstractions were reviewed by a second investigator for accuracy. Discrepancies were resolved through discussion and consensus.

### Risk of Bias Assessment

Two investigators independently assessed risk of bias using predefined criteria. Disagreements were resolved by consensus. For clinical trials, we adapted criteria for assessing risk of bias from the U.S. Preventive Services Task Force.<sup>69</sup> Criteria included use of appropriate randomization and allocation concealment methods, clear specification of inclusion criteria, baseline comparability of groups, blinding, attrition, and use of intention-to-treat analysis. Methodologists assessed systematic reviews using AMSTAR 2 (Assessing the Methodological Quality of Systematic Reviews) criteria.<sup>70</sup> Studies were rated as “low risk of bias,” “medium risk of bias,” or “high risk of bias” based on the presence and seriousness of methodological shortcomings.

Studies rated “low risk of bias” are generally considered valid. “Low risk of bias” studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; blinding of patients, care providers, and outcome assessors; and appropriate analysis of outcomes.

Studies rated “medium risk of bias” are susceptible to some bias, though not necessarily enough to invalidate the results. These studies do not meet all the criteria for a rating of low risk of bias, but any flaw present is unlikely to cause major bias. Studies may be missing information, making it difficult to assess limitations and potential problems. The “medium risk of bias” category is broad, and studies with this rating vary in their strengths and weaknesses. Therefore, the results of some medium risk of bias studies are likely to be valid, while others may be only possibly valid.

Studies rated “high risk of bias” have significant flaws that may invalidate the results. They have a serious or “fatal” flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of high risk of bias studies could be as likely to reflect flaws in study design and conduct as true difference between compared



interventions. Methodologists did not exclude studies rated high risk of bias *a priori*, but high risk of bias studies were considered to be less reliable than low or medium risk of bias studies, and methodologists performed sensitivity analyses without high risk of bias studies to determine how their inclusion impacted findings.

### Data Synthesis and Rating the Body of Evidence

The methodology team constructed evidence tables with study characteristics, results, and risk of bias ratings for all included studies, and summary tables to highlight the main findings.

For interventions to prevent rUTIs, investigators performed meta-analysis using the random effects DerSimonian and Laird model in RevMan 5.3.5 (Copenhagen, Denmark) when there were at least three studies that could be pooled. Investigators stratified analyses of antibiotics by the specific antibiotic and stratified analyses of estrogen according to whether they were administered systemically or topically. Sensitivity analysis was performed by excluding high risk of bias trials. For antibiotic treatment of acute UTI, investigators reported pooled estimates from systematic reviews. Heterogeneity is reported via  $I^2$  calculations. Investigators did not update meta-analyses from prior reviews with the results of new trials, but examined whether the findings of new trials were consistent with the reviews. For other Key Questions, there were too few studies to perform meta-analysis.

### Determination of Evidence Strength

The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes not only individual study quality but consideration of study design, consistency of findings across studies, adequacy of sample sizes, and generalizability of samples, settings, and treatments for the purposes of the guideline. Investigators graded the strength of evidence for key comparisons and outcomes for each Key Question, using the approach described in the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) *Methods Guide for Comparative Effectiveness and Effectiveness Reviews*.<sup>71</sup> Strength of evidence assessments were based on the following domains:

- Study limitations, based on the overall risk of bias across studies (low, medium, or high)
- Consistency of results across studies (consistent,

inconsistent, or unable to determine when only one study was available)

- Directness of the evidence linking the intervention and health outcomes (direct or indirect)
- Precision of the estimate of effect, based on the number and size of studies and confidence intervals for the estimates (precise or imprecise)
- Reporting bias, based on whether the studies defined and reported primary outcomes and whether we identified relevant unpublished studies (suspected or undetected)

The AUA categorizes body of evidence strength as Grade A (well-conducted and highly-generalizable randomized controlled trials [RCTs] or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.<sup>72</sup>

### AUA Nomenclature: Linking Statement Type to Evidence Strength

The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (Table 2). **Strong Recommendations** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. **Moderate Recommendations** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. **Conditional Recommendations** are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates that the statement

**TABLE 2: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength**

	<b>Evidence Strength A (High Certainty)</b>	<b>Evidence Strength B (Moderate Certainty)</b>	<b>Evidence Strength C (Low Certainty)</b>
<b>Strong Recommendation</b>  (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa)  Net benefit (or net harm) is substantial  Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa)  Net benefit (or net harm) is substantial  Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa)  Net benefit (or net harm) appears substantial  Applies to most patients in most circumstances but better evidence is likely to change confidence  (rarely used to support a Strong Recommendation)
<b>Moderate Recommendation</b>  (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa)  Net benefit (or net harm) is moderate  Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa)  Net benefit (or net harm) is moderate  Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa)  Net benefit (or net harm) appears moderate  Applies to most patients in most circumstances but better evidence is likely to change confidence
<b>Conditional Recommendation</b>  (No apparent net benefit or harm)	Benefits = Risks/Burdens  Best action depends on individual patient circumstances  Future research unlikely to change confidence	Benefits = Risks/Burdens  Best action appears to depend on individual patient circumstances  Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear  Alternative strategies may be equally reasonable  Better evidence likely to change confidence
<b>Clinical Principle</b>	A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
<b>Expert Opinion</b>	A statement, achieved by consensus of the Panel, that is based on members clinical training, experience, knowledge, and judgment for which there is no evidence		

can be applied to most patients in most circumstances and that future research is unlikely to change confidence. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence could change confidence. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence is likely to change confidence. Body of evidence strength Grade C is only rarely used in support of a Strong Recommendation. Conditional Recommendations also can be supported by any evidence strength. When body of evidence strength is Grade A, the statement indicates that benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is unlikely to change confidence. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances and better evidence could change confidence. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens, alternative strategies may be equally reasonable, and better evidence is likely to change confidence.

Where gaps in the evidence existed, the Panel provides guidance in the form of **Clinical Principles** or **Expert Opinions** with consensus achieved using a modified Delphi technique if differences of opinion emerged.<sup>73</sup> A Clinical Principle is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. Expert Opinion refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence.

### Peer Review and Document Approval

An integral part of the guideline development process at the AUA is external peer review. The AUA conducted a thorough peer review process to ensure that the document was reviewed by experts in the diagnosis and treatment of UTIs in women. In addition to reviewers from the AUA PGC, Science and Quality Council (SQC), and Board of Directors (BOD), the document was reviewed by representatives from CUA and SUFU as well as external content experts. Additionally, a call for reviewers was placed on the AUA website from November 19-30, 2018 to allow any additional

interested parties to request a copy of the document for review. The guideline was also sent to the Urology Care Foundation to open the document further to the patient perspective. The draft guideline document was distributed to 114 peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 50 reviewers provided comments, including 38 external reviewers. At the end of the peer review process, a total of 622 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC, SQC, and BOD as well as the governing bodies of CUA and SUFU for final approval.

## GUIDELINE STATEMENTS

### Evaluation

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

Patients with rUTIs should have a complete history obtained, including LUTS such as dysuria, frequency, urgency, nocturia, incontinence, hematuria, pneumaturia, and fecaluria. Further information to obtain includes any history of bowel symptoms such as diarrhea, accidental bowel leakage, or constipation; recent use of antibiotics for any medical condition; prior antibiotic-related problems (e.g., *C. difficile* infection); antibiotic allergies and sensitivities; back or flank pain; catheter usage; vaginal discharge or irritation; menopausal status; post-coital UTIs; contraceptive method; and use of spermicides or estrogen- or progesterone-containing products. Details of prior urinary tract or pelvic surgery should be obtained, and patients should be queried as to travel history. Baseline genitourinary symptoms between infections may also be illuminative, including the number of voids per day, sensation of urge to void, straining to void, a sensation of incomplete emptying, pelvic pressure or heaviness, vaginal bulge, dysuria, dyspareunia, as well as the location, character, and severity of any baseline genitourinary or pelvic pain or discomfort. UTI history includes frequency of UTI, antimicrobial usage, and documentation of positive cultures and the type of cultured microorganisms. Risk factors for complicated UTI, as previously discussed, should also be elucidated.

Patient history should document the symptoms the patient considers indicative of a UTI, the relationship of acute episode to infectious triggers (e.g. sexual intercourse), antimicrobials used for each episode,

responses to treatment for each episode, as well as the results of any prior diagnostic investigations. It is also important to note the relationship of infections to hormonal influences (e.g., menstruation, menopause, exogenous hormone use) as well as concomitant medication usage or behaviors that may alter infection susceptibility, including prior antimicrobial treatment, immunosuppressive medications, and topicals such as spermicides.

A physical examination including an abdominal and detailed pelvic examination should be performed to look for any structural or functional abnormalities. Pelvic support for the bladder, urethra, vagina, and rectum should be documented, noting the compartment and stage of any clinically significant prolapse. The bladder and urethra should be palpated directly for evidence of urethral tenderness, urethral diverticulum, Skene's gland cyst, or other enlarged or infected vulvar or vaginal cysts. A focused examination to document any other infectious and inflammatory conditions, such as vaginitis, vulvar dermatitis, and vaginal atrophy (genitourinary syndrome of menopause) should also be performed. The pelvic floor musculature should be examined for tone, tenderness, and trigger points.<sup>74</sup> A focused neurological exam to rule out occult neurologic defects may also be considered. Evaluation for incomplete bladder emptying to rule out occult retention can be considered for all patients, but should be performed in any patient with suspicion of incomplete emptying, such as those with significant anterior vaginal wall prolapse, underlying neurologic disease, diabetes, or a subjective sensation of incomplete emptying.

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

While there are multiple definitions for rUTI, this guideline stresses microbial confirmation of the underlying pathology, defining rUTI as at least two **culture-proven** symptomatic uncomplicated acute cystitis episodes in six months or three within one year in which symptom resolution occurred between culture-proven events. Microbial confirmation at the time of acute-onset urinary tract-associated symptoms and signs, which primarily include dysuria, urinary frequency and urgency, and new or worsening incontinence with or without gross hematuria, is a critical component to establish a diagnosis of rUTI. Continued documentation of cultures during symptomatic periods prior to instituting antimicrobial

therapy helps to provide a baseline against which interventions can be evaluated, to determine the appropriate pathway within the treatment algorithm, and to allow for the tailoring of therapy based on bacterial antimicrobial sensitivities. One propensity-matched cohort study (n=48,283) found that, among women with rUTI, obtaining a urine culture >50% of the time was associated with decreased risk of hospitalization (OR 0.79, 95% CI 0.67 to 0.93) and intravenous antibiotics (OR 0.91, 95% CI 0.86 to 0.97). However, cultures were also associated with increased office visits (OR 1.06, 95% CI 1.03 to 1.10) and diagnosis of pyelonephritis (OR 1.14, 95% CI 1.02 to 1.27).<sup>49</sup> As previously discussed, determining when a culture represents clinically significant bacteriuria must factor in the clinical presentation of a patient, the urine collection method used, and the presence of other suggestive factors such as pyuria. As mentioned previously, a 10<sup>5</sup> CFU/mL threshold for bacterial growth on midstream voided urine may help distinguish bladder bacteriuria from vaginal contamination in asymptomatic, pre-menopausal women, but a lower 10<sup>2</sup> CFU/mL threshold may be appropriate in symptomatic individuals.

Disorders such as interstitial cystitis/bladder pain syndrome, OAB, genitourinary syndrome of menopause, urinary calculi, infectious bacterial or fungal vaginitis, vulvar dermatitis, non-infectious vulvovestibulitis, vulvodynia, hypertonic pelvic floor muscle dysfunction, and less commonly carcinoma *in situ* of the bladder have significant symptom overlap with acute bacterial cystitis. Moreover, these conditions may coexist with episodes of cystitis, isolated or recurrent. A lack of correlation between microbiological data and symptomatic episodes should prompt a diligent consideration of alternative or comorbid diagnoses, as may be the case in women with gross hematuria. Many such women lacking microbial confirmation may be incorrectly treated for UTI when they should be evaluated for bladder cancer.

In addition, patients with a long history of culture-proven symptomatic episodes of cystitis that occur at a lower frequency than that which is specified in the definition used in this document (two episodes within six months or three episodes within one year) may also be appropriate to include under the umbrella of rUTI. Patients consistently presenting with one to two symptomatic infections per year for multiple years will likely benefit from a more proactive management strategy similar to that suggested herein for patients with rUTI.

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

It is important to establish the association of acute-onset urinary symptoms with documented microbiological evidence of infection. Contamination of urine specimens with skin and vaginal bacteria can result in high rates of suboptimal or unnecessary treatment, resulting in poor patient outcomes and higher health care costs.<sup>75</sup> The potential for contamination with midstream urine collection necessitates careful evaluation of specimen quality and the cultured species reported. While variably defined, contamination should be suspected when the specimen exhibits growth of normal vaginal flora (e.g. lactobacillus), mixed cultures containing more than one organism, or even low quantities ( $<10^3$  CFU/mL) of a pathogenic organism in an asymptomatic patient.<sup>76-80</sup> Further, concomitant urinalysis can provide additional guidance; the presence of epithelial cells or mucus on microscopic urinalysis may also suggest contaminant.<sup>77</sup> Growth of organisms thought to be contaminants (e.g., Lactobacilli, Group B Streptococci, Corynebacteria, and non-saprophyticus coagulase-negative Staphylococci) generally do not require treatment. When there is high suspicion for contamination, clinicians can consider obtaining a catheterized specimen for further evaluation prior to treatment.<sup>35,81</sup>

While a suprapubic aspirate provides the most accurate urinary sampling, it is not practical in most settings, and a mid-stream urine specimen is typically adequate to provide a sufficient quality specimen for analysis;<sup>82-84</sup> however, care must be taken to avoid contamination. Contamination of urinary samples varies considerably due to multiple factors associated with urine collection and storage. Under optimal conditions, a mid-stream voided specimen may provide contamination rates of less than 1%, with specificity and sensitivity for UTI greater than 98% and 95%,<sup>85-87</sup> respectively. Poor collection, storage, and processing techniques, however, can produce contamination rates of 30-40%.<sup>81,88</sup>

The largest contribution to this variability results from post-collection processing, particularly with regards to specimen storage.<sup>88,89</sup> As urine can be easily seeded with commensal flora, low numbers of contaminant bacteria can continue to proliferate when stored at room temperature, leading to increased numbers of false-positive cultures or uninterpretable results. IDSA

and the American Society for Microbiology (ASM) agree that urine should not sit at room temperature for more than 30 minutes to facilitate accurate laboratory diagnosis of UTI.<sup>90-92</sup> Several observational studies describe significant increases in colony counts after storage at room temperature for more than a few hours,<sup>93-95</sup> while delayed cultures on urine specimens kept refrigerated or preserved in urine transport solutions, such as boric acid or other preservative solutions, demonstrate high agreement with the results of immediate culture.<sup>95-98</sup> Thus, samples should either be transported to the lab in urine transport media in vacuum-filled tubes or refrigerated (2°C to 10°C) immediately to reduce artifactual bacterial proliferation. Further, the clinician should discourage patients from bringing samples from home due to the high potential for inadequate storage and erroneous results.

While there is no definitive evidence that urethral cleansing improves specimen quality or reduces contamination,<sup>76-79</sup> clinical laboratories and expert opinion still supports preparation of the urethral meatus and surrounding vaginal epithelium with a cleaning or antiseptic solution prior to providing a voided specimen.<sup>92</sup> Care should also be taken to avoid contact of the collection cup with the skin or vaginal epithelium. Labial spreading is highly effective at reducing contamination, halving the contamination rates seen without attention to this detail.<sup>99</sup> The initial urinary stream should be discarded, and the subsequent midstream sample sent to the laboratory for analysis.<sup>100</sup> Oral instruction provided to patients may not be sufficient; written instructions for sample collection may be more effective at reducing contamination rates for voided specimens.<sup>88</sup> Such instructions can even be placed on the wall of the clinic bathroom.

The vaginal and skin microbiota in asymptomatic women can contain many bacterial species thought of as pathogens, including *S. aureus*, *S. viridans*, Enterococci, Group B Streptococci, low-temperature-tolerant Neisseriae, and members of the family Enterobacteriaceae, including *E. coli*.<sup>81</sup> It is important to note that several conditions can present with dysuria unrelated to acute cystitis, such as atrophic vaginitis, and are also associated with increases in vaginal bacteria and/or other disturbances in the vaginal microbiota that increase the likelihood of an abnormal urine culture misdiagnosed as a UTI. In these circumstances and in patients who may have a difficult time performing a high-quality clean-catch specimen (e.g. morbidly obese or wheelchair-bound patients), it is reasonable to consider straight or "in-and-out" catheterization after sterile preparation of the urethra

to reduce specimen contamination.<sup>92</sup>

The lack of clear-cut rules for the distinction of contamination from clinically-significant positive urine cultures stresses the importance of provider judgment in the interpretation of urine culture results. The diagnosis of a cystitis episode in patients with or without a history of rUTI should be based on the combination of thorough clinical assessment with urine testing, with careful consideration of the specimen quality, bacterial identity and quantity, and possible comorbid microbial disturbances.

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

Cystoscopy and upper tract imaging are not routinely necessary in patients with uncomplicated rUTI due to low yield of anatomical abnormalities. However, if a patient does not respond appropriately to treatment of uncomplicated UTI (i.e. poor symptomatic or microbiological response to initial treatment or rapid recurrence of infection, particularly if with the same organism repeatedly), the patient should be considered to have a complicated UTI, thereby necessitating further evaluation of the urinary tract via cystoscopy and upper tract imaging. Cystoscopy may be useful in the evaluation of complicated UTI to assess for anatomical or structural abnormalities (e.g., bladder diverticuli, ectopic ureteral orifices, ureteral duplication, presence of foreign bodies). In patients with previous pelvic surgery, cystoscopy can be helpful to assess for anatomic abnormalities from the previous surgery, including urethral stricture or obstruction, foreign body such as mesh, bladder stones, fistula, or urethral/bladder diverticulum.

In a single-institutional cohort study of 163 women who had abdominopelvic imaging available, cystoscopy identified only 9 cases of significant clinical findings. Of those, only five cases were uniquely identified on cystoscopy and missed on imaging modalities.<sup>101</sup> Further, a meta-analysis reviewing the utility of cystoscopy, imaging, and urodynamics found that cystoscopy was not warranted, and imaging was unlikely to be of value in the absence of symptoms of upper tract disease or other gynecological problems in women presenting with rUTI.<sup>102</sup> In patients with gross hematuria in the presence of a positive urine culture and no risk factors for urothelial malignancy (e.g., age under 40, non-smoker, no environmental risk), cystoscopy is not necessary. If any risk factors are present, cystoscopy should be performed. Additionally, further evaluation for bladder cancer should be

performed in the presence of gross hematuria without documented infection.

Upper tract imaging is not routinely necessary in the evaluation of uncomplicated rUTI due to low yield. In a prospective observational study of the diagnostic yield of intravenous urography (IVU) with respect to referral source and presenting features, 91.7% of patients presenting with rUTI had normal IVU.<sup>103</sup> Further, Fair et al. reported that only 5.5% of IVUs were considered to have positive findings in a population of 164 female patients with a history of rUTI; however, none of the findings affected management approach.<sup>104</sup> Higher yield may be found in "high-risk" patients, such as those presenting with gross hematuria, persistent microscopic hematuria between infections, pyelonephritis, or other instances of atypical presentation.<sup>105</sup> For any patient with suspicion for pyelonephritis, or history of hematuria without infection or renal calculi, upper tract imaging is recommended.

#### **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)**

In women with a history of rUTIs with acute symptoms consistent with urinary infection, the Panel reviewed the literature related to obtaining urine culture or urinalysis versus not performing such urine tests to dictate treatment decisions. Although no studies were identified specifically designed to document direct effects of procuring urinalysis and urine culture with antibiotic sensitivities prior to initiating treatment, the Panel determined each episode should be clinically evaluated as a unique event. As described previously, urinalysis can determine the presence of epithelial cells suggesting contamination.<sup>77</sup> Such information from a urinalysis may indicate that obtaining a catheterized specimen is reasonable to accurately evaluate the patient's culture results;<sup>92</sup> however, urinalysis provides little increase in diagnostic accuracy.<sup>22</sup>

A propensity-matched cohort study was identified that included 48,283 women with uncomplicated UTIs. Of these women, 61% had at least one urine culture, 6.9% had imaging, and 2.8% had cystoscopy. The study found that having a urine culture >50% of the time was associated with fewer UTI-related hospitalizations and lower rates of intravenous antibiotic use compared with not having cultures >50% of the time, but higher rates of UTI-related office visits and slightly increased risk of pyelonephritis diagnosis.<sup>49</sup> Another study indicated that obtaining a culture was

associated with no difference in the likelihood of follow-up visits within two weeks for continued UTI symptoms (adjusted OR 1.11, 95% CI 0.65 to 1.90).<sup>106</sup> However, these findings do not account for the rapidly evolving environment of both antibiotic resistance patterns and stewardship expectations. The Panel does recognize that, in select patients with rUTIs with symptoms of recurrence, presumptive treatment with antibiotics can be initiated prior to finalization of the culture results based on prior speciation, susceptibilities, and local antibiogram. For reliable patients, the Panel recommends a process of shared decision-making with regards to deferring therapy prior to obtaining results from the urine culture. Since progression of acute cystitis to pyelonephritis is uncommon, initiation of conservative non-antibiotic treatments, such as urinary analgesics, while awaiting urine culture results may be reasonable in select circumstances when the clinician deems that patient safety will not be compromised. The Panel does not advocate use of either point of care dipstick or home dipstick analysis to diagnose rUTI or guide treatment decisions due to the poor sensitivity and specificity of these modalities.

In patients who present for rUTI management without any microbiological information regarding prior presumed episodes of acute cystitis, it is reasonable to proceed with the assumption of rUTI if their clinical history is consistent with that diagnosis (e.g., acute-onset dysuria, urinary frequency and urgency with resolution upon antimicrobial treatment) and institute appropriate treatment. However, every effort should be made to obtain microbiological data to confirm the diagnosis, follow clinical responses to management, and allow modification of treatment plans as needed.

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

In select circumstances, employing a shared decision-making process with informed patients, initiation of a short treatment course of antibiotic therapy at the discretion of the patient (self-start) therapy may be offered for acute symptomatic episodes in patients with diagnosis of rUTI. (Table 3) Two trials emerged in the literature analysis that compared intermittent versus daily dosing for self-start treatment.<sup>107,108</sup> These two medium risk of bias trials found no difference between intermittent dosing versus daily dosing in risk of  $\geq 1$  UTI over 12 months (2 studies, RR 1.15, 95% CI 0.88 to 1.50,  $I^2=0\%$ ). One of the trials that examined self-start

therapy in the context of prophylaxis after exposures to different possible UTI-predisposing conditions (e.g., sexual intercourse, traveling, working or walking for a long time, diarrhea or constipation) found that a single dose of antibiotics was no different than a short course of daily antibiotics (RR 1.15, 95% CI 0.87 to 1.51).<sup>108</sup> Initial and subsequent antibiotics varied (nitrofurantoin, TMP-SMX, norfloxacin, ciprofloxacin, amoxicillin, cefaclor, cefuroxime); selection of antibiotics was based on susceptibility testing and prior use. One medium risk of bias crossover trial (n=38) found that intermittent self-administered TMP-SMX for treatment of acute symptoms was associated with increased risk of  $\geq 1$  UTI versus daily prophylactic TMP-SMX (68% versus 6.1%, RR 11.16, 95% CI 2.86 to 43.63).<sup>109</sup> Intermittent dosing was also associated with increased UTI frequency (2.2 versus 0.2 microbiologically confirmed episodes per patient-year,  $p < 0.001$ ). Most UTI episodes in women on intermittent dosing resolved with single dose TMP-SMX treatment, and the rest responded to 10 to 20 day courses of antibiotics. There was no difference in risk of any adverse event (8.8% versus 15.2%, RR 0.58, 95% CI 0.15 to 2.24).

Although the original concept behind self-start therapy allowed for women to treat their UTI without obtaining a culture, given more recent goals to reduce overuse of antibiotics and the development of antibacterial resistance, the Panel recommends obtaining culture data for symptomatic recurrences when feasible. However, the Panel appreciates that, in certain situations, procurement of a urine culture will not be possible and empiric therapy may be allowed in select circumstances when the clinician deems such patients reliable with communication and self-assessment of symptoms. Patients must also understand the need to limit frequent or extended courses of antimicrobial therapy. Self-start therapies should utilize the choices of antibiotics that would be prescribed for acute symptoms (Table 3), accounting for the patient's prior culture and sensitivities as well as local antibiograms. Antibiograms provide the clinician critical data regarding choice of agents, particularly when selecting empiric antibiotics pending urine culture and sensitivity results. Such information can typically be obtained from a hospital's primary laboratory. Documentation by the clinician of the frequency of such self-initiated treatment episodes and course of symptom resolution will assist in defining an individualized strategy for therapy and determining necessity for alterations in strategy.

**Asymptomatic Bacteriuria**

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

Without symptoms, bacteriuria of any magnitude is considered “ASB.” While pregnant women and patients scheduled to undergo invasive urinary tract procedures do benefit from treatment, substantial evidence supports that other populations, including women with diabetes mellitus and long-term care facility residents, do not require or benefit from additional evaluation or antimicrobial treatment.

In women with rUTIs, there is no evidence that identification of ASB between UTI episodes provides useful prognostic information. Prospective observational studies have found no differences in rates of hypertension, chronic kidney disease, renal dysfunction, abnormal renal imaging, or mortality in women with or without bacteriuria.<sup>90</sup> Additionally, evidence exists to suggest a lack of effectiveness of treatment for ASB, which serves as indirect evidence that identification of ASB by surveillance testing would not result in improved clinical outcomes, unless an alternative effective treatment exists.<sup>40</sup>

**8. Clinicians should not treat ASB in patients. (Strong Recommendation; Evidence Level: Grade B)**

Evaluation and treatment of rUTIs should be performed only when acute cystitis symptoms are present. In women with rUTIs, there is no evidence that treatment of ASB results in improved clinical outcomes, and there is clear evidence that these practices can cause harm (e.g., antibiotic side effects, development of opportunistic infections [e.g., *C. difficile*], antibiotic resistance). One randomized trial of women (n=673, median 40 years of age) with a history of rUTIs and ASB found that antibiotic treatment (versus no antibiotics) was associated with an increased risk of symptomatic recurrence (47% versus 13%, RR 3.17, 95% 2.55 to 3.90) and development of antibiotic-resistant organisms.<sup>40</sup> These findings suggest that ASB may actually prevent the development of symptomatic UTIs. In addition, a recent systematic review concluded that antimicrobial treatment of ASB does not appear to improve microbiologic outcomes, morbidity, or mortality.<sup>110</sup> Current evidence also indicates that screening/treatment of ASB does not reduce UTI rates, morbidity, or mortality in “high-risk” patients (elderly, immunosuppressed, renal transplant patients, diabetics).<sup>90,111</sup> The only clearly recognized indications for screening/treatment of ASB are 1) pregnant

women, and 2) patients undergoing elective urologic surgery.<sup>90,112</sup>

*ASB and Struvite Stones*

Certain bacteria (most commonly *P. mirabilis*) produce urease and are associated with the development of infection (struvite) stones in the urinary tract. When infection stones are present, complete removal of the stones is required in order to eradicate the associated UTI. However, there is no clear evidence that identification and treatment of ASB caused by urease-producing organisms prevents struvite stone formation. Furthermore, this practice exposes patients to the inherent risks associated with recurrent antibiotic therapy. For these reasons, the Panel does not recommend the routine treatment of urease-producing bacteriuria (including *P. mirabilis*) in the absence of UTI symptoms or documented urinary tract stones. However, in certain patients with recurrent struvite stones, screening for and treating urease-producing bacteriuria may be indicated if other measures have not been able to prevent stone formation. This is an area where more research is required.

**Antibiotic Treatment**

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

There is limited but older data from a Cochrane review of studies published from 1977 to 2003 that compares antibiotics for uncomplicated UTIs. This systematic review included 21 RCTs (N=6,016) of one antibiotic versus another for treatment of uncomplicated UTI.<sup>113</sup> The systematic review found no differences between fluoroquinolones,  $\beta$ -lactams (e.g., penicillins and its derivatives, cephalosporins), or nitrofurantoin versus TMP-SMX in the likelihood of short-term (within two weeks of treatment) or long-term (up to 8 weeks) symptomatic or bacteriological cure; relative risk estimates were close to 1.0 for all comparisons and outcomes. Results were similar when trials of fluoroquinolones or  $\beta$ -lactams were stratified according to whether the duration of treatment was 3 days or 7 to 10 days, or when trials of fluoroquinolones were stratified according to the specific medication (ciprofloxacin, ofloxacin, or norfloxacin). Fluoroquinolones (2 trials, pooled RR 0.08, 95% CI 0.01 to 0.43;  $I^2=0\%$ ) and nitrofurantoin (3 trials, pooled RR 0.17, 95% CI 0.04 to 0.76;  $I^2=0\%$ ) were



each associated with lower likelihood of rash than TMP-SMX. There was no difference in risk of discontinuation due to adverse events, though estimates were imprecise and favored fluoroquinolones (3 trials, RR 0.37, 95% CI 0.12 to 1.14;  $I^2=39\%$ ) and nitrofurantoin (3 trials, pooled RR 0.69, 95% CI 0.34 to 1.41;  $I^2=0\%$ ). There was no difference between fluoroquinolones or nitrofurantoin with respect to risk of resistance or other adverse events (e.g., pyelonephritis, diarrhea), though some estimates were imprecise and not all harms were reported for all comparisons. There was no difference between  $\beta$ -lactams and TMP-SMX in rates of rash or other harms.

The systematic review also found no differences between nitrofurantoin or fluoroquinolones versus  $\beta$ -lactams in short or long-term symptomatic or bacteriological cure.<sup>113</sup> Fluoroquinolones were associated with decreased risk of rash compared with  $\beta$ -lactams (2 trials, RR 0.10, 95% CI 0.02 to 0.56;  $I^2=0\%$ ); there were no other statistically significant differences between fluoroquinolones or nitrofurantoin versus  $\beta$ -lactams in likelihood of short- or long-term symptomatic or bacteriological cure, though some estimates were imprecise. Data on risk of resistance was very sparse and imprecise.

A systematic review that evaluated the comparative effectiveness of different antibiotics for uncomplicated UTIs<sup>114</sup> included 12 RCTs (N=5,514), 11 of which were published from 2002 to 2009. Antibiotics assessed in the studies reviewed were amoxicillin-clavulanate, gatifloxacin, ciprofloxacin, norfloxacin, TMP-SMX, nitrofurantoin, fosfomycin, and pivmecillinam. A network meta-analysis was performed with results reported using ciprofloxacin as the reference treatment. The network meta-analysis found amoxicillin-clavulanate to be inferior to ciprofloxacin for likelihood of short-term (5 days to 2 weeks) clinical cure (OR 0.07, 95% CI 0.02 to 0.24), long-term (29 to 49 days) clinical cure (OR 0.31, 95% CI 0.19 to 0.53), and short-term bacteriological cure (OR 0.17, 95% CI 0.08 to 0.35). However, there was only a single trial of amoxicillin-clavulanate. There were no statistically significant differences between other antibiotics versus placebo in the likelihood of short- or long-term clinical or bacteriological cure. In a randomized trial of women with uncomplicated UTI, five-day nitrofurantoin compared with single-dose fosfomycin resulted in a significantly greater likelihood of clinical and microbiological resolution at four weeks after therapy.<sup>115</sup>

Gatifloxacin, a fluoroquinolone that is not currently

available in the United States or Canada at the time of this publication, generally performed similarly to ciprofloxacin, with other antibiotics trending towards inferior results. Therefore, the review concluded that ciprofloxacin and gatifloxacin appear to be the most effective treatments for UTI, and amoxicillin-clavulanate the least effective. However, all analyses were based on small numbers of trials; no antibiotic other than ciprofloxacin was evaluated in more than three trials. There were no statistically significant differences between other antibiotics versus ciprofloxacin in risk of adverse events, though estimates were imprecise. In addition to the small number of trials available for each comparison within the network, other shortcomings of this analysis include failure to report direct and indirect estimates separately, the consistency between direct and indirect estimates, and uncertainty in treatment rankings.<sup>116</sup>

This systematic review highlights a key concept discussed in the IDSA 2011 guidelines for treatment of acute uncomplicated UTI. Specifically, if antimicrobial therapies for UTI are compared based upon efficacy in achieving clinical and/or bacteriological cure, there is relatively little to distinguish one agent from another. However, the IDSA guidelines introduced the concepts of *in vitro* resistance prevalence and ecological adverse effects of antimicrobial therapy or collateral damage as key considerations in choosing UTI treatments.<sup>91</sup> The three first-line agents available in the United States (i.e., nitrofurantoin, TMP-SMX, fosfomycin) are effective in treating UTI but are less likely to produce collateral damage than are second-line agents.<sup>91</sup> TMP-SMX is not recommended for empiric use in areas in which local resistance rates exceed 20%.<sup>91</sup> Table 3 shows first-line agents recommended by the IDSA guidelines. Second-line or alternate therapies include  $\beta$ -lactam agents or fluoroquinolones and are generally chosen because of resistance patterns and/or allergy considerations. With the exception of fosfomycin, single-dose antibiotics should not be used in the treatment of patients with rUTI.<sup>91</sup> As noted, fluoroquinolone agents have potentially adverse side effect profiles, including QTc prolongation, tendon rupture, and increased risk of aortic rupture, leading to FDA black box warnings in recent years.<sup>117</sup>

**10. Clinicians should treat rUTI patients experiencing acute cystitis episodes with as short a duration of antibiotics as reasonable, generally no longer than seven days. (Moderate Recommendation; Evidence Level: Grade B)**

**TABLE 3: First-line therapy for the treatment of uncomplicated symptomatic UTI**

Treatment effects	Nitrofurantoin	TMP-SMX	Fosfomycin
Cure rate	88-93%	90-100%	83-91%
Antimicrobial spectrum	narrow: <i>E. coli</i> , <i>S. saprophyticus</i>	typical uropathogens	Covers VRE, ESBL GNRs
Collateral damage	No	Minimal	No
Resistance	Low, stable X 50y	Increasing	Currently low
Dose & duration	100 mg BID X 5d	One DS BID X 3d	3 g single dose

There is limited high quality up to date evidence of comparative trials on the length of antibiotic therapies for complete resolution of UTI symptoms. Generally, all antibiotics have risks; as such, stewardship should be exercised to balance symptom resolution with reduction in risk of recurrence.

There are two systematic reviews that compared shorter versus longer courses of antibiotics for UTI.<sup>118-120</sup> Single-dose antibiotics were associated with increased risk of short-term (<2 weeks after treatment) bacteriological persistence versus short-course (3 to 6 days; 5 studies, RR 2.01, 95% CI 1.05 to 3.84,  $I^2=36\%$ ) or long-course (7 to 14 days; 6 studies, RR 1.93, 95% CI 1.01 to 3.70,  $I^2=31\%$ ) antibiotic therapy. There were no differences in risk of longer-term (>2 weeks) bacteriological persistence, short-term symptomatic persistence, risk of reinfection, any adverse event, or discontinuation due to adverse events.

Three-day courses of antibiotics, irrespective of class, were associated with increased risk of long-term (4 to 10 weeks from end of treatment) bacteriological failure (18 studies, RR 1.31, 95% CI 1.08 to 1.60,  $I^2=30\%$ ) versus more prolonged (5 to 10 day) therapy, but there were no differences in risk of short-term (2 to 15 days from end of treatment) bacteriological failure (31 studies, RR 1.19, 95% CI 0.98 to 1.44,  $I^2=0\%$ ) or short- or long-term symptomatic failure (24 studies, RR 1.06, 95% CI 0.88 to 1.28,  $I^2=15\%$  and 10 studies, RR 1.09, 95% CI 0.94 to 1.27, respectively). When the analysis was restricted to trials in which the same antibiotic was utilized in each treatment arm, short-course therapy (3 day) was associated with increased risk of short- and long-term bacteriological failure (18

studies, RR 1.37, 95% CI 1.07 to 1.74,  $I^2=0\%$  and RR 1.43, 95% CI 1.19 to 1.73,  $I^2=0\%$ , respectively), but effects on short- or long-term bacteriological failure was not statistically significant. A three-day course of antibiotics was associated with decreased risk of adverse effects (29 studies, RR 0.83, 95% CI 0.74 to 0.93,  $I^2=14\%$ ), discontinuation due to adverse events (24 studies, RR 0.28 to 0.91,  $I^2=42\%$ ), and gastrointestinal adverse events (24 studies, RR 0.81, 95% CI 0.67 to 0.97,  $I^2=11\%$ ) compared with longer duration therapy. As such, clinicians should treat rUTI patients with as short a duration of antibiotics as reasonable, generally no longer than seven days.

**11. In patients with rUTIs experiencing acute cystitis episodes associated with 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 seven days. (Expert Opinion)**

Many such infections will be caused by organisms producing ESBLs. Generally, such organisms are susceptible only to carbapenems. However, before considering that these infections require intravenous antimicrobials, clinicians should order fosfomycin susceptibility testing, as many MDR uropathogens, including ESBL-producing bacteria, retain susceptibility to fosfomycin and/or nitrofurantoin. Consultation with an Infectious Diseases specialist may be appropriate for assistance in the management of such infections.

#### Antibiotic Prophylaxis

**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)**

For evidence-based treatment of rUTIs, a large body of evidence exists in support of antibiotic prophylaxis. The systematic review for this guideline identified twenty-eight trials evaluating antibiotics for prevention of rUTI.<sup>107,108,121-147</sup> Most were rated as medium to high risk of bias, predominately for non-reporting of factors used in the assessment of bias (e.g., unclear randomization, allocation concealment, or blinding methods; high or unclear attrition; failure to report intention-to-treat analysis). Sample sizes ranged from 26 to 308 (total N=2,758). Ten trials demonstrated that antibiotics perform better than placebo,<sup>121,131,134,135,138,142-144,146,147</sup> and the results were consistent across antibiotics. Ten trials evaluated nitrofurantoin,<sup>121,125,126,128,129,133,137,139,141,146</sup> five trials TMP-SMX,<sup>122,123,140,146,147</sup> four trials TMP,<sup>126,127,136,145</sup> one trial cephalexin,<sup>131</sup> one trial fosfomycin,<sup>130,137</sup> and one trial tested various antibiotics in intermittent versus daily regimens.<sup>108</sup> In addition, some older studies used antibiotics that are no longer used routinely in practice (e.g., norfloxacin,<sup>128,138,139,142</sup> perfloracin,<sup>132</sup> prulifloxacin,<sup>130</sup> cinoxacin,<sup>134,135,143-145</sup> and cefaclor<sup>126</sup>). The duration of preventive treatment ranged from 6 to 12 months. In eight trials, the mean age of enrollees was  $\geq 50$  years;<sup>108,123,130,133,136,137,141,146</sup> in the other trials the mean age was in the 30's or low 40's, so both peri- and post-menopausal women and younger pre-menopausal women have been studied in these trials. The number of UTIs in the 12 months prior to initiating prophylaxis ranged from 2 to 7 in trials that reported this information.

While the studies reviewed are relevant to the issue of UTI prevention, it must be noted that most of the relevant RCT studies on antibiotic prophylaxis were published prior to 1995. While the quality of these studies is acceptable, results from them may be less applicable (i.e. prophylaxis may be less effective) given the changing antibiotic resistance patterns that have occurred over time. As such, results should be interpreted in light of current resistance patterns.

*Prophylactic Antibiotics Associated with Decreased Likelihood of UTI Recurrence Compared with Placebo*

When comparing prophylactic antibiotic use to placebo or no antibiotic, antibiotics were associated with a decreased likelihood of experiencing  $\geq 1$  UTI recurrence versus placebo or no antibiotics (11 studies, RR 0.26, 95% CI 0.18 to 0.37,  $I^2=14\%$ ; ARD -46%, 95% CI -

56% to -37%).<sup>121,131,133-135,138,142-144,146,147</sup> All of the trials evaluated daily dosing of antibiotics except for one,<sup>147</sup> which evaluated intermittent dosing of TMP-SMX with sexual intercourse. This trial also found antibiotics to be more effective than placebo for preventing rUTI (RR 0.11, 95% CI 0.02 to 0.75). All of the trials compared antibiotics versus placebo except for one study of nitrofurantoin versus no antibiotics that reported similar effects on risk of rUTI (RR 0.34, 95% CI 0.22 to 0.51).<sup>133</sup>

With antibiotic use, there is an increased risk of adverse events, including pulmonary and hepatic side effects. Antibiotics were associated with increased risk of any adverse event (6 studies, RR 1.73, 95% CI 1.08 to 2.79,  $I^2=0\%$ ; ARD 12%, 95% CI 1% to 22%)<sup>131,134,135,138,144,147</sup> and vaginitis (3 studies, RR 3.01, 95% CI 1.27 to 7.15,  $I^2=0\%$ ; ARD 18%, 95% CI 0.05 to 0.32).<sup>134,138,147</sup> There was no interaction between the antibiotic used and risk of adverse events. There were no differences in risk of withdrawal due to adverse events (4 studies, RR 2.76, 95% CI 0.64 to 11.84,  $I^2=0\%$ )<sup>131,134,138,143</sup> or gastrointestinal adverse events specifically (2 studies, RR 2.52, 95% CI 0.28 to 22.87,  $I^2=0\%$ ),<sup>138,147</sup> but data were sparse and estimates imprecise.

Overall, antibiotic prophylaxis reduced the number of clinical recurrences when compared to placebo in pre- and post-menopausal women with rUTIs. The results of the trials on prophylactic antibiotics consistently demonstrate the positive effect of this preventive treatment, while acknowledging the increase in mild, moderate, and severe adverse events associated with antibiotic use. The effect of the antibiotic prophylaxis lasted during the active intake time period. Once the antibiotics were stopped, UTIs recurred and equaled the placebo arm outcomes.

*Comparison of Prophylactic Antibiotics*

Among eight trials of one antibiotic versus another for prevention of rUTI,<sup>126,128-130,137,139,145,146</sup> six evaluated comparisons involving nitrofurantoin.<sup>126,128,129,137,139,146</sup> Nitrofurantoin was compared against fosfomycin (one trial),<sup>137</sup> TMP (one trial),<sup>129</sup> TMP-SMX (one trial),<sup>146</sup> norfloxacin (two trials),<sup>128,139</sup> and cefaclor (one trial).<sup>126</sup>

There was no difference between nitrofurantoin versus other antibiotics in risk of experiencing  $\geq 1$  UTI (6 studies, RR 0.81, 95% CI 0.63 to 1.03,  $I^2=0\%$ ). When stratified according to the specific antibiotic to which nitrofurantoin was compared, findings were also generally consistent in showing no differences in risk of UTI recurrence, with no differences versus fosfomycin,

TMP-SMX, norfloxacin, and cefaclor (p for interaction 0.79). However, nitrofurantoin was associated with a decreased risk of rUTI compared to TMP in one trial (RR 0.58, 95% CI 0.36 to 0.94; ARD -28%, 95% CI -50% to -5%).<sup>129</sup> One trial of nitrofurantoin versus fosfomycin was published in 2007 (RR for  $\geq 1$  UTI 0.87, 95% CI 0.44 to 1.71);<sup>137</sup> all of the other trials were published in or before 1995.

While quinolones have been studied as prophylaxis, the use of fluoroquinolones, such as ciprofloxacin, for prophylactic antibiotic use is not recommended in current clinical practice. In 2008 the U.S. FDA issued a black box warning on the increased risk of tendinitis and tendon rupture associated with ciprofloxacin.<sup>148</sup> These serious side effects associated with fluoroquinolone use, which also include QT interval prolongation, seizures, and *C. difficile* infection, generally outweigh the benefits of its use for uncomplicated UTI.

There is little evidence on the benefits of rotating antibiotics used for prophylaxis. In a different population of inpatient hospital treatment of infection, informed switching strategies,<sup>149,150</sup> have been used that take the frequency of antibiotic resistance mutations into account. They used local antibiogram-guided therapy, which can potentially serve as a valuable strategy to curb resistance. However, there is not enough evidence in the existing published literature to reach reliable conclusions regarding the efficacy of cycling antibiotics as a means of controlling antibiotic resistance rates.

#### *Adverse Events Associated with Prophylactic Antibiotics*

There was no difference in risk of any adverse event (4 studies, RR 1.59, 95% CI 0.58 to 4.42,  $I^2=89\%$ ), but estimates were inconsistent,<sup>128,129,139,146</sup> and nitrofurantoin was associated with increased risk of study withdrawal compared to other antibiotics (norfloxacin, TMP, and TMP-SMX) (4 studies, RR 2.42, 95% CI 1.14 to 5.13,  $I^2=5\%$ ; ARD 7%, 95% CI 1% to 13%).<sup>126,128,129,139</sup> All trials except for one<sup>139</sup> found nitrofurantoin associated with increased risk of any adverse event (RR estimates ranged from 2.00 to 2.40). There were no differences between nitrofurantoin and other antibiotics in risk of gastrointestinal adverse events (3 studies, RR 1.78, 95% CI 0.57 to 5.50,  $I^2=0\%$ ),<sup>128,137,146</sup> or vaginitis (2 studies, RR 0.45, 95% CI 0.13 to 1.54,  $I^2=0\%$ ),<sup>128,146</sup> but estimates were imprecise. Other side effects included vaginal and oral candidiasis, skin rash, and nausea.

While nitrofurantoin remains a first-line choice for treatment of acute UTI as recommended by IDSA,<sup>91</sup> and has been shown to be effective as a prophylactic antibiotic for UTI prevention, all antibiotics including nitrofurantoin have potential risks. These risks should be discussed with patients prior to prescribing for short-, medium-, or long-term prophylaxis. Nitrofurantoin is commonly prescribed in women of all ages and has rare but potentially serious risks of pulmonary and hepatic toxicity.<sup>151-154</sup> The rate of possible serious pulmonary or hepatic adverse events has been reported to be 0.001% and 0.0003%, respectively.<sup>155</sup> One 2015 systematic review<sup>156</sup> observed no pulmonary or hepatotoxic events related to nitrofurantoin among 4,807 patients from 27 controlled trials. A 2018 retrospective chart audit<sup>157</sup> of an urban academic medical center found 0.7% of patients experienced possible serious pulmonary or hepatic adverse effects, and 0.15% (5 of 3,400 patients) were highly suspicious for having a serious lung or liver reaction. These patients were more likely to have long-term exposure to nitrofurantoin, highlighting the need for caution when prescribing long-term and avoiding nitrofurantoin in patients with chronic lung disease.

Nitrofurantoin use in older adults has been controversial. Nitrofurantoin is listed as a potentially inappropriate medication for older adults by the AGS Beers Criteria,<sup>158</sup> with the strength of recommendation as strong and a listed quality of evidence of low. The 2015 Beers update has been modified to recommend avoidance of nitrofurantoin when creatinine clearance is below 30mL/min. The rationale for avoiding nitrofurantoin included pulmonary toxicity, hepatotoxicity, and peripheral neuropathy, with concern about long-term use if other alternatives are available for use. Nitrofurantoin-induced lung injury<sup>159-164</sup> can occur in the acute, subacute or chronic setting, most commonly presenting with a dry cough and dyspnea.<sup>165</sup> The mechanism underlying pulmonary toxicity is related to the direct effects of nitrofurantoin metabolites on lung tissue.<sup>166</sup> Acute pulmonary reactions appear after a mean of nine days from starting nitrofurantoin therapy, while symptoms of subacute and chronic pulmonary reactions develop between one and six months of treatment, respectively.<sup>162</sup> In a 1980 analysis of 921 reported cases by Holmberg et al.,<sup>151</sup> 47% of cases of chronic respiratory disease occurred after more than 12 months of nitrofurantoin therapy. Risk assessment, shared decision-making, and clinical monitoring is important to avoid the potential adverse events associated with nitrofurantoin.

Potential adverse effects of gastrointestinal

disturbances and skin rash are commonly associated with antibiotics, including TMP, TMP-SMX, cephalexin, and fosfomycin.<sup>167,168</sup> Gastrointestinal disturbances and skin eruptions are the most common adverse reactions associated with TMP and TMP-SMX.<sup>169</sup> TMP-SMX has been uncommonly associated with other adverse effects.<sup>170</sup> These adverse effects include neurologic effects (e.g., aseptic meningitis, tremor, delirium, gait disturbances), decreased oxygen carrying capacity (e.g., methemoglobinemia, blood dyscrasia), toxic epidermal necrolysis (e.g., drug hypersensitivity, fixed drug eruption), reproductive toxicity (e.g., structural malformations including neural tube, small for gestational age, hyperbilirubinemia), interactions with other drugs (e.g., inhibition of the P450 system), hypoglycemia, hyperkalemia and nephrotoxicity. Long-term administration of TMP-SMX appears to be safe, though hematologic and laboratory monitoring may be indicated.

#### *Consideration of Antibiotic Resistance*

In general, there is sparse reporting of antibiotic resistances, with little data specifically on the impact of long-term antibiotic therapy on antibiotic resistance. There are data on the effects of antibiotic prescribing on antimicrobial resistance in individual patients.<sup>171</sup> A 2010 systematic review and meta-analysis demonstrated that individuals prescribed an antibiotic for UTI develop bacterial resistance to that antibiotic. In five studies of urinary tract bacteria (14,348 participants), the pooled odds ratio for resistance was 2.5 (95% CI 2.1 to 2.9) within 2 months of antibiotic treatment and 1.33 (95% CI 1.2 to 1.5) within 12 months. The effect is greatest in the month immediately after treatment but may persist for up to 12 months.<sup>171</sup> Antibiotic resistance is related to an individual's bacterial gene pool since resistance is carried on plasmids and integrons and can be transferred between commensal organisms and potential pathogens. As such, even transient use of antibiotics can affect the carriage of resistant organisms and impact the endemic level of resistance in the population. The potential harms related to acquiring an antibiotic resistant infection should be factored into the decision to give antibiotic prophylaxis for UTI prevention.

#### *Dosing and Duration of Prophylactic Antibiotics*

The most tested schedule of antibiotic prophylaxis (TMP, TMP-SMX, nitrofurantoin, cephalexin) was daily dosing. However, fosfomycin used prophylactically is dosed every 10 days. Four trials compared different antibiotic dosing strategies.<sup>107-109,132</sup> Three trials<sup>107-109</sup>

compared intermittent versus daily dosing, and one trial<sup>132</sup> compared once weekly versus once monthly dosing.

As previously reviewed under the discussion of self-start therapy, two medium risk of bias trials found no difference between intermittent dosing versus daily dosing in risk of  $\geq 1$  UTI (2 studies, RR 1.15, 95% CI 0.88 to 1.50,  $I^2=0\%$ ).<sup>107,108</sup> One of the trials compared a single dose of antibiotics for exposures to different UTI-predisposing conditions (e.g., sexual intercourse, traveling, working or walking for a long time, diarrhea or constipation) versus daily antibiotics (RR 1.15, 95% CI 0.87 to 1.51).<sup>108</sup> The other intermittent dosing trial compared a single dose of ciprofloxacin after sexual intercourse with daily dosing (RR 1.24, 95% CI 0.29 to 5.32).<sup>107</sup>

The duration of antibiotic prophylaxis in the literature ranged from 6 to 12 months, and after stopping, the frequency of UTI has been shown to resume to the prior state of rUTI frequency. In clinical practice, the duration of prophylaxis can be variable, from three to six months to one year, with periodic assessment and monitoring. Some women continue continuous or post-coital prophylaxis for years to maintain the benefit without adverse events, but it should be noted that continuing prophylaxis for years is not evidence-based.

Continuous antimicrobial prophylaxis regimens for women with rUTIs have been recommended by several trials.<sup>126,128,129,145-147</sup> The dosing options for continuous prophylaxis include the following:

- TMP 100mg once daily
- TMP-SMX 40mg/200mg once daily
- TMP-SMX 40mg/200mg thrice weekly
- Nitrofurantoin monohydrate/macrocrystals 50mg daily
- Nitrofurantoin monohydrate/macrocrystals 100mg daily
- Cephalexin 125mg once daily
- Cephalexin 250mg once daily
- Fosfomycin 3g every 10 days

#### *Antibiotic Prophylaxis in Women Who Experience Post-Coital UTIs*

In women who experience UTIs temporally related to sexual activity, antibiotic prophylaxis taken before or after sexual intercourse has been shown to be effective

and safe. This use of antibiotics is associated with a significant reduction in recurrence rates. Additionally, intermittent dosing is associated with decreased risk of adverse events including gastrointestinal symptoms and vaginitis.

In a 1990 randomized double-blind placebo-controlled trial of 27 sexually active women with a median age of 23, post-coital antibiotics were shown to be more effective than placebo in reducing UTI recurrences.<sup>147</sup> Other older studies of post-coital antibiotic prophylaxis published between 1975 and 1989<sup>172-175</sup> were non-randomized but had similar results supporting post-coital dosing. In one study of 135 women, post-coital dosing was as effective as daily dosing.<sup>107</sup> Antibiotic prophylaxis should be offered to women with rUTIs temporally related to sexual intercourse, to be taken either before or after sexual activity. This prophylaxis approach targets the antibiotic to the time frame when these women are most vulnerable to UTIs, thus minimizing use of antibiotics, decreasing risk of adverse events, and potentially reducing direct and indirect costs of rUTIs.

Recommended instructions for antibiotic prophylaxis related to sexual intercourse include taking a single dose of an antibiotic immediately before or after sexual intercourse. Dosing options for prophylaxis include the following:

- TMP-SMX 40mg/200mg
- TMP-SMX 80mg/400mg
- Nitrofurantoin 50-100mg
- Cephalexin 250mg

#### Non-Antibiotic Prophylaxis

#### **13. Clinicians may offer cranberry prophylaxis for women with rUTIs. (Conditional Recommendation; Evidence Level: Grade C)**

There has been a growing concern regarding antibiotic resistance in the setting of recurrent UTI. In 2015 the World Health Organization increased awareness of the issue of the growing world-wide phenomenon of antimicrobial resistance through its publication Global Action Plan on Antimicrobial Resistance (AMR).<sup>176</sup> AMR is one factor that has led to an increasing interest in the scientific community to study non-antibiotic modalities in the prevention of rUTI, including the use of probiotics and the consumption of cranberry products.

Cranberries have been studied as a preventative

measure for UTI for decades, but recently cranberry has been the subject of an increasing number of randomized clinical trials. These studies have used cranberry in a variety of formulations including juice, cocktail, and tablets. The proposed mechanisms of action is thought to be related to proanthocyanidins (PACs) present in cranberries and their ability to prevent the adhesion of bacteria to the urothelium. It must be noted that PACs are found in varying concentrations depending on formulation used, and many of the cranberry products used in the studies noted below were explicitly formulated for research purposes. The availability of such products to the public is a severe limitation to the use of cranberries for rUTI prophylaxis outside the research setting and must be discussed with patients. Juice studies have used a variety of juices and cocktails in varying volumes of daily consumption and have included cranberry of varying concentrations within the overall volume of product ingested. Likewise, cranberry tablets include variability in dosing and are not subject to the same regulatory environment as antimicrobial drugs. Many studies do not include validation of PAC dosage. Further, clinical studies have also not routinely reported side effects.

The systematic review identified eight randomized trials including cranberry versus placebo/no cranberry (6 RCTs, one with a lactobacillus arm)<sup>177-182</sup> and cranberry versus antibiotics (2 RCTs).<sup>122,136</sup> Four RCTs studied cranberry in a beverage form, and five studied cranberry tablets/capsules. Risk of bias was variable across the studies. Cranberry was associated with decreased risk of experiencing at least 1 UTI recurrence than placebo or no cranberry (5 trials, RR 0.67, 95% CI 0.54 to 0.83 ARD -11%, 95%CI -16% to 5%).<sup>177-181</sup> Kontiokari et al. found a 20% reduction in UTIs (versus control) with 50 mL of daily cranberry-lingonberry juice concentrate over six months.<sup>177</sup> Maki et al. used one 240mL serving of cranberry beverage daily versus placebo and found the antibiotic use-adjusted incidence rate ratio to be 0.61, 95% CI 0.41 to 0.91, P=0.016.<sup>178</sup> Stothers found that both cranberry juice and cranberry tablets significantly decreased the number of patients experiencing at least 1 symptomatic UTI per year (to 20% and 18%, respectively) compared with placebo (to 32%, p<0.05).<sup>179</sup> Takahashi et al. randomized women to 125 mL of daily cranberry juice (UR65) or placebo over 24 weeks. In a subgroup analysis of women aged 50 years or more, relapse of UTI was observed in 16 of 55 patients (29.1%) in the cranberry group versus 31 of 63 (49.2%) in the placebo group.<sup>180</sup> Cranberry fruit powder was also found to reduce UTIs significantly

(10.8% versus 25.8%,  $p = 0.04$ ) in women who received 500 mg daily for 6 months.<sup>181</sup> This study noted that the cranberry fruit powder, which includes the pulp, seeds, and peel, had a PAC content of 0.56%.

There was no statistically significant difference between daily cranberry versus antibiotics in risk of experiencing  $\geq 1$  UTI after 6 or 12 months, but the pooled estimate was based on only two trials, favored antibiotics (not statistically significant), and was imprecise (RR 1.30, 95% CI 0.79 to 2.14,  $I^2=68\%$ )<sup>122,136</sup> The Beerepoot trial<sup>122</sup> compared cranberry versus TMP-SMX (RR 1.09, 95% CI 0.92 to 1.28). The study found cranberry was associated with a decreased number of clinical UTI recurrences (mean 4.0 versus 1.9,  $p=0.02$ ) and shorter time to first recurrence (median 4 versus 8 months,  $p=0.03$ ); however, effects were no longer present in the 3 months following discontinuation of treatment. Researchers noted cranberry was associated with a lower risk of resistance in *E. coli* isolates than TMP-SMX in patients with symptomatic recurrence (resistance to TMP or TMP-SMX  $\sim 15\%$  versus  $\sim 90\%$  and resistance to amoxicillin  $\sim 25\%$  versus  $\sim 80\%$ ). The McMurdo trial<sup>136</sup> compared cranberry to TMP (RR 1.76, 95% CI 1.00 to 3.09) and found no difference in time to recurrence (median 84 versus 91 days,  $p=0.48$ ). Additionally, it was found that 31.6% of microbial isolates in symptomatic UTI recurrences were TMP-susceptible in the TMP and cranberry groups combined.

Not all studies have included a methodology to examine a hypothesized mechanism of action in humans, which have included both inhibition of adherence mechanisms and urinary content changes that make the urine generally less habitable to uropathogens. Clinical studies have also not routinely reported side effects. 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.

#### *Lactobacillus*

While *Lactobacillus* probiotics have been studied with greater interest in recent years given growing concerns for antibiotic resistance, the Panel is unable to recommend the use of *Lactobacillus* as a prophylactic agent for rUTI given the current lack of data indicating benefit in comparison to other available agents. The

systematic review identified five trials evaluating *Lactobacillus* for prevention of recurrent UTI.<sup>124,183-186</sup> Sample sizes ranged from 30 to 238 (total  $N=464$ ) and the duration of treatment ranged from 5 days to 12 months. Three trials compared *Lactobacillus* versus placebo,<sup>183,184,186</sup> one trial compared *Lactobacillus* versus an antibiotic,<sup>124</sup> and one trial compared *Lactobacillus* versus skim milk-based *Lactobacillus* growth factor.<sup>185</sup> All of the trials evaluated *Lactobacillus* via vaginal suppository, except for one trial<sup>124</sup> of oral *Lactobacillus* versus an antibiotic. *Lactobacillus* species were *rhannosus*, *reuteri*, and *crispatus*.

There was no difference between *Lactobacillus* vaginal suppositories versus placebo in risk of experiencing  $\geq 1$  UTI in 3 trials of younger (mean age in 20's or 30's) women (RR 1.01, 95% CI 0.45 to 2.26,  $I^2=55\%$ ).<sup>183,184,186</sup> The *Lactobacillus* species and dosing schedules varied across trials (twice weekly, daily for 5 days, or daily for 5 days then weekly for 10 weeks).

One trial ( $n=138$ , mean age 64 years) found no differences between daily oral *Lactobacillus* (*rhannosus* GR-1 and *reuteri* RC-14) versus TMP-SMX at 12 months in mean number of clinical UTI recurrences (3.3 versus 2.9, mean difference 0.4, 95% CI -0.4 to 1.4) or likelihood of experiencing  $\geq 1$  UTI (79% versus 69%, RR 1.15, 95% CI 0.98 to 1.34), though *Lactobacillus* was associated with shorter time to first recurrence (median 3 versus 6 months,  $p=0.02$ ).<sup>124</sup>

#### *Increased Water Intake*

One medium risk of bias trial of women with recurrent UTIs who reported  $<1.5$  L/day of fluid intake at baseline ( $n=140$ , mean age 36 years) found increased water intake associated with fewer UTI recurrences compared with no additional fluids (mean 1.7 versus 3.2 UTI episodes over 12 months,  $p<0.001$ ).<sup>67</sup> Increased water intake was also associated with lower likelihood of having at least 3 UTI episodes over 12 months ( $<10\%$  versus  $88\%$ ) and greater interval between UTI episodes (143 versus 84.4 days,  $p<0.001$ ). The increased fluid intake intervention was based on provision of three 500 mL bottles of water to be consumed daily. Daily fluid intake increased from 0.9 L/day to 2.2 L/day in the increased water intake group compared with no change in the no additional fluids group. While these data are promising, no conclusions can be drawn as to whether or not increased water intake is beneficial to women who regularly drink higher quantities of fluids than those reported in this study or those who may be at a lower risk for UTI recurrence.

### Other Preventive Methods

Ten trials were identified evaluating various other prophylactic agents, including D-mannose, methenamine, herbs/supplements, intravesical hyaluronic acid/chondroitin, biofeedback, and immunoactive therapy, for prevention of recurrent UTI.<sup>125,127,133,140,187-192</sup> However, the Panel cannot recommend these agents as it was not possible to draw reliable conclusions regarding their effectiveness due to the small number of trials for each treatment, imprecise estimates, and methodological shortcomings in the trials.

**D-mannose.** Two high risk of bias trials compared a prophylactic antibiotic (TMP-SMX or nitrofurantoin) versus D-mannose.<sup>133,140</sup> Antibiotics were associated with increased risk of  $\geq 1$  UTI versus D-mannose, though the difference was not statistically significant, and heterogeneity was present (2 studies, RR 2.56, 95% CI 0.80 to 8.19,  $I^2=88\%$ ).<sup>133,140</sup> The risk estimate was greater in a trial of TMP-SMX (91.7% versus 20.0%, RR 4.58, 95% CI 2.75 to 7.65)<sup>140</sup> than in a trial of nitrofurantoin (20.4% versus 14.6%, RR 1.41, 95% CI 0.77 to 2.58).<sup>133</sup> A difference in the trials is that the TMP-SMX trial used a crossover design, and the nitrofurantoin trial used a parallel group design; the age of women enrolled in the trials was similar. In both studies, antibiotics were associated with shorter time to UTI recurrence (24 versus 43 and 52.7 versus 200 days).

**Methenamine.** Two high risk of bias trials compared a prophylactic antibiotic (nitrofurantoin or TMP) versus methenamine (1g every 12 hours for up to 1 year).<sup>125,127</sup> Antibiotics were associated with decreased risk of  $\geq 1$  recurrent UTI (2 studies, RR 0.64, 95% CI 0.48 to 0.87,  $I^2=0\%$ ). Results were similar in both trials. One of the trials also compared antibiotics versus topical povidone iodine and found no difference between trimethoprim versus topical iodine in risk of UTI recurrence.<sup>127</sup>

**Herbal Therapies.** Two trials evaluated herbal therapies for prevention of rUTI.<sup>187,188</sup> One medium risk of bias trial (n=174, mean age 54 years) found no difference between herbal therapy (Nasturtium and horseradish) versus placebo in the mean number of UTIs after 3 months of treatment (mean UTIs 0.43 versus 0.37,  $p=0.28$ ) or 3 months following the end of treatment (mean UTIs 0.74 versus 0.63,  $p=0.26$ ).<sup>187</sup> A high risk of bias (open-label) trial found no differences between treatment with three different herbal therapies (berberine/arbutin/birch, berberine/arbutin/birch/ forskolin, or PAC) for 12 weeks in risk of  $\geq 1$  UTI at 24

weeks.<sup>188</sup>

**Intravesical Hyaluronic Acid/Chondroitin.** Two small, medium risk of bias trials evaluated intravesical hyaluronic acid plus chondroitin for prevention of rUTI.<sup>189,190</sup> One trial (n=54, mean age 35 years) found intravesical hyaluronic acid plus chondroitin (weekly for 4 weeks, then monthly for 5 months) associated with decreased risk of experiencing  $\geq 1$  UTI at 12 months (52% versus 100%, RR 0.52, 95% CI 0.36 to 0.75), mean number of UTIs (0.67 versus 4.19,  $p<0.001$ ), and longer time to UTI recurrence (185.2 versus 52.7 days,  $p<0.001$ ) than intravesical saline.<sup>189</sup> Intravesical hyaluronic acid was also associated with better scores on the SF-36 (78.6 versus 53.1,  $p<0.001$ ). Harms were not reported. Another trial (n=26, mean age 60 years) found intravesical hyaluronic acid plus chondroitin (weekly for 4 weeks, then biweekly for 4 weeks) associated with fewer UTI episodes (1 versus 2.3,  $p<0.01$ ), lower VAS pain score (1.6 versus 7.8,  $p<0.001$ ), less pelvic pain and urgency/frequency symptoms (PUF scale, 11.2 versus 19.6,  $p<0.001$ ), better sexual function (sexual function questionnaire 2.4 versus 6.3,  $p=0.001$ ), and better quality of life (King's Health Questionnaire 18.4 versus 47.3,  $p<0.001$ ) versus once weekly oral SMX 200 mg and TMP 40 mg 12 months after the end of treatment, though there were no differences on any of these outcomes 2 month after the end of treatment.<sup>190</sup> No harms were recorded. While these studies show promise, further study is needed to assess generalizability, long-term outcomes, and overall feasibility.

**Biofeedback and Immunoactive Therapy.** A medium risk of bias trial (n=451, mean age 44 years) found no differences between an immunoactive therapy (oral OM-89S, a lyophilized lysate of 18 *E. coli* strains) versus placebo or nitrofurantoin in mean number of UTIs, UTI incidence, likelihood of experiencing at least 1 UTI, or time to next UTI.<sup>191</sup> A high risk of bias trial (n=86, mean age 23 years) found 12 months of uroflowmetry biofeedback (25%), biofeedback training of the pelvic floor muscles (24%), or both (20%) were associated with a decreased likelihood of experiencing  $\geq 1$  UTI than no treatment (90%).<sup>192</sup> The trial was rated high risk of bias due to open-label design, high attrition, and failure to conduct intention-to-treat analysis.

### Follow-up Evaluation

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



There are no studies that address whether or not screening urinalysis or urine culture following clinical cure of a documented UTI is beneficial in those with a history of rUTI. Extrapolating from the ASB literature, the Panel does not endorse microbiological reassessment (i.e. repeat urine culture) after successful UTI treatment as this may lead to overtreatment. The Panel does recognize, however, that certain clinical scenarios, such as planned surgical intervention in which mucosal bleeding is anticipated, may prompt screening. It should again be emphasized that symptom clearance is sufficient. In patients with rapid recurrence (particularly with the same organism), clinicians may consider evaluation on and off therapy to help identify those patients who warrant further urologic evaluation. Additionally, repeated infection with bacteria associated with struvite stone formation (e.g., *P. mirabilis*) may prompt consideration of imaging to rule out calculus.

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

After initiating antimicrobial therapy for UTI, clinical cure (i.e. UTI symptom resolution) is expected within three to seven days. Although there is no evidence, the Panel felt it reasonable to repeat a urine culture if UTI symptoms persist beyond 7 days. Although a second antibiotic can be given empirically, this should only be done after a urine sample is obtained for culture. This will minimize unnecessary treatment of patients with persistent UTI/pain symptoms who are culture-negative.

**Estrogen**

**16. In peri- and post-menopausal women with rUTIs, clinicians should recommend vaginal**

**estrogen therapy to reduce the risk of future UTIs if there is no contraindication to estrogen therapy. (Moderate Recommendation; Evidence Level: Grade B)**

Clinicians should recommend vaginal estrogen therapy to all peri- and post-menopausal women with rUTI to reduce the risk of rUTI. This is in contrast to oral or other formulations of systemic estrogen therapy, which have not been shown to reduce UTI and are associated with different risks and benefits. Patients who present with rUTI and are already on systemic estrogen therapy can and should still be placed on vaginal estrogen therapy. There is no substantially increased risk of adverse events. However, systemic estrogen therapy should not be recommended for treatment of rUTI. Multiple randomized trials using a variety of formulations of vaginally applied estrogen therapy demonstrated a decreased incidence and time to recurrence of UTI in hypoestrogenic women. Table 4 shows the formulations and dosing of several commonly used types of vaginal estrogen therapy. A systematic review of vaginal estrogen therapy for genitourinary syndrome of menopause concluded there was insufficient evidence to favor one formulation of vaginal estrogen over another.<sup>193</sup> However, a Cochrane Review suggested that vaginal cream may be more effective than the estrogen ring in preventing UTI.<sup>194</sup> Given the lack of clear superiority of one type of vaginal estrogen, clinicians should recommend the formulation of vaginal estrogen that is preferred by the patient.

The systematic review identified four trials (mean age  $\geq 65$ , N=313) comparing estrogen versus placebo or no estrogen and found estrogen to be associated with a reduced risk of experiencing  $\geq 1$  UTI versus placebo or no estrogen that was nearly statistically significant (4 trials, RR 0.59, 95% CI 0.35 to 1.01,  $I^2=76\%$ ).<sup>195-198</sup> There were no statistically significant differences in risk

**TABLE 4 Commonly used vaginal estrogen therapy**

Formulation	Composition	Strength and Dosage
Vaginal tablet	Estradiol hemihydrate*	10 mcg per day for 2 weeks, then 10 mcg 2-3 times weekly
Vaginal ring	17b-estradiol	2 mg ring released 7.5 mcg per day for 3 months (changed by patient or provider)
Vaginal cream	17b-estradiol	2 g daily for 2 weeks, then 1 g 2-3 times per week
	Conjugate equine estrogen	0.5 g daily for 2-weeks, then 0.5 g twice weekly
* Estradiol hemihydrate comes in a 4mcg tablet; however, this has not been studied for prevention of rUTI.		

of recurrent UTI when trials were stratified according to use of oral (2 trials, RR 0.95, 95% CI 0.63 to 1.44,  $I^2=2\%$ )<sup>195,196</sup> or topical estrogen (2 trials RR 0.42, 95% CI 0.16 to 1.06,  $I^2=85\%$ ).<sup>197,198</sup>

One trial evaluating estriol vaginal cream (0.5 mg nightly for 2 weeks, then twice weekly)<sup>198</sup> found topical estrogen associated with a decreased risk of experiencing  $\geq 1$  UTI (RR 0.25, 95% CI 0.13 to 0.50), decreased annualized UTI incidence (median 0.5 versus 5.9 episodes,  $p<0.001$ ), and fewer days of antibiotic use after 8 months (6.9 versus 32.0,  $p<0.001$ ) than placebo.

As part of shared decision-making, the clinician should weigh the risks associated with vaginal estrogen therapy with its benefits in reducing UTIs. Given low systemic absorption, systemic risks association with vaginal estrogen therapy are minimal. Vaginal estrogen therapy has not been shown to increase risk of cancer recurrence in women undergoing treatment for or with a personal history of breast cancer.<sup>199-201</sup> Therefore, vaginal estrogen therapy should be considered in prevention of UTI women with a personal history of breast cancer in coordination with the patient's oncologist.

## FUTURE DIRECTIONS

A better understanding of rUTI pathophysiology will greatly aid in our ability to design more effective, mechanistically-based treatments. Critical expansion of our understanding of both host and pathogen factors that result in rUTI is mandated. Additionally, refinement of how UTI is defined must be considered. Indeed, delineating differences between ASB with concomitant non-specific LUTS secondary to storage dysfunction or diverse conditions such as IC/BPS and OAB versus true rUTI may eventually rely on development of innovative urine or serum biomarkers that can differentiate between these entities.<sup>202</sup> Relying on results from the urinary dipstick test, including leukocyte esterase and nitrate, lacks the necessary level of sensitivity and specificity for diagnostic accuracy. In this context, defining initiatives for partnering with our primary care colleagues and patients to provide education regarding rUTI definitions, evaluation, and treatment will provide an impactful narrative for the future.

Urine culture results, even those from extended quantitative urine culture techniques, do not reflect any aspect of the host response. Investigations of more defined host biomarkers, such as cytokines or serum inflammatory markers, may allow more precise analysis of the host response which reflects a true UTI. Further

refinements of bacterial molecular genetic technologies may help point-of-care testing with faster identification of potential uropathogens. By extension, the types and content of bacteria which inhabit the urinary tract as part of the native microbiome will change our understanding of how host-bacterial interactions contribute to development of rUTI.

Emerging data regarding the microbiome of the human bladder, bowel, and vagina, including the contribution of both traditional and viable but non-culturable bacteria, viruses, bacteriophages, fungi, and helminths, will define a more accurate portrait of the healthy balance, as well as pathogenic dysbiosis that may contribute to rUTIs. Depletion or alteration of the normal host microbiome and host innate barriers and innate immune system may lead to development of rUTI. A better understanding of the relationship between the urinary microbiome and bladder health may fundamentally transform our earlier belief that urine is "sterile." Indeed, the reconstitution of our native immune system, potentially by changing the microbiome of the gut with the use of probiotics and even fecal transplants, may be a pathway to resolution of rUTI for select patients. Modulation of the host response to bacterial infection is a key dynamic for which limited information currently exists.

A worldwide crisis has emerged due to rapid expansion of MDR bacteria, foreshadowing the devastating implications of the eventual inefficacy of many of our broad-spectrum antimicrobial agents.<sup>176</sup> Current concepts of antibiotic stewardship have provoked a further initiative to develop agents outside the traditional pipeline of antibiotics. On a more immediate time frame is the need for comprehensive randomized controlled trials for non-antibiotic prevention therapies, including probiotics and cranberry formulations. The influence of our environments including the foods we eat, how they are prepared, and their source may become increasingly important as the area of food science expands. Future efforts may uncover other food sources with preventative mechanisms.

Implementation of novel technologies, such as vaccines for urinary pathogens, may represent a future direction for prevention strategies. Use of mannosides as therapeutic entities to prevent bacterial adhesion to the urothelium may represent a narrow-spectrum treatment strategy associated with few systemic manifestations.<sup>203</sup> Modulation of host responses, such as the use of non-steroidal anti-inflammatory agents, have been suggested as a useful adjunct in both preclinical and clinical studies.<sup>204,205</sup>

We must also expand our perspective of rUTI to include prevention. There currently exists an NIH-funded research consortium addressing this mission- the Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium.<sup>206</sup> The PLUS consortium is dedicated to promoting prevention of LUTS (including UTIs) across the woman's life spectrum, including UTIs, utilizing a socioecologic construct.<sup>207</sup> Critical to these investigative efforts is the discovery of methods to suppress symptoms without use of antibiotics and direct studies that support a broader view of rUTI from the host-pathogen perspective. The PLUS consortium also seeks to identify modifiable risk factors for acute cystitis which can be tested in a prospective prevention trial. Through multiple efforts, which include identifying modifiable socioecological risk factors, understanding host responses involved in UTI and understanding pathogen virulence factors, we will discover new methods in diagnosis and treatment of rUTI.

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#### ABBREVIATIONS

AHRQ	Agency for Healthcare Research and Quality
AMR	Antimicrobial resistance
ASB	Asymptomatic bacteriuria
ASM	American Society for Microbiology
AUA	American Urological Association
CUA	Canadian Urological Association
EPC	Evidence-based Practice Center
ESBL	Extended-spectrum $\beta$ -lactamase
IDSA	Infectious Diseases Society of America
IVU	Intravenous urography
LUTS	Lower urinary tract symptoms
MDR	Multi-drug resistant
OAB	Overactive bladder
PAC	Proanthocyanidins
PGC	Practice Guidelines Committee
RCT	Randomized controlled trial
rUTI	Recurrent urinary tract infection
SQC	Science & Quality Council
SUFU	Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction
TMP-SMX	Trimethoprim-sulfamethoxazole
UTI	Urinary tract infection

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## CONFLICT OF INTEREST DISCLOSURES

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This document was written by the Recurrent Urinary Tract Infection Guideline Panel of the American Urological Association Education and Research, Inc., which was created in 2017. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair in coordination with the Canadian Urological Association (CUA) and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU). Membership of the panel included specialists with specific expertise on this disorder. The mission of the panel was to develop recommendations that are analysis-based or consensus-based, depending on panel processes and available data, for optimal clinical practices in the diagnosis and treatment of recurrent urinary tract infection.

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While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ('off label') that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not in-tended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

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