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

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Abbreviations and Acronyms

ARD = absolute risk difference
EPC = evidence-based practice center
NGS = next-generation sequencing
PAC = proanthocyanidin
PCR = polymerase chain reaction
RCT = randomized control trials
ROB = risk of bias
rUTI = recurrent urinary tract infection
SAE = serious adverse event
SOE = strength of evidence
ULR = update literature review
UTI = urinary tract infection
WAE = withdrawal due to adverse events

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Purpose: In 2019 the American Urological Association (AUA) released the evidence-based guideline "Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline." Information supporting the guideline came from a 2019 systematic evidence review prepared for the AUA by the Pacific Northwest Evidence-based Practice Center (EPC). The AUA used evidence found for 11 Key Questions (Appendix C) in the EPC's report to derive 16 Guideline Statements. In 2021 the EPC conducted an Update Literature Review (ULR) assessing abstracts from new studies published since the 2019 systematic review. The AUA asked the EPC to further assess a subset of studies included in the ULR report, to support potential changes to the 2019 guideline.

Materials/Methods: A systematic-review utilized research from the Oregon Health & Science University. Pacific Northwest EPC was used to update the 2019 AUA Guideline on rUTI in women with new evidence published through 2021.

Results: Updates were made to reflect changes in literature since 2019. Updates include recent publications on antibiotic prophylaxis, non-antibiotic prophylaxis, and estrogen therapy.

Conclusion: The presence of rUTI is crucial to the health of patients and its effects must be considered for the welfare of society. This document will undergo updating as the knowledge regarding current treatments and future treatment options continues to expand.

Keywords: recurrence; urinary bladder; urinary tract infections; women

BACKGROUND

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"), 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,

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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.

METHODS

The AUA ULR process occurs 24-36 months after release of a guideline to access for currency of the guideline statements. Using the same Key Questions and inclusion/exclusion criteria from the original scoping document, a literature search is run to identify studies from the end of the last literature search to present time. Based on the ULR report, the Panel determines whether the data supports, challenges, complements, or does not add to the current body of evidence for each guideline statement.

The ULR Panel discusses the findings to the guideline's currency as it relates to each individual guideline statement and key question under review. If any statement edits are proposed or new statements are developed based on findings from key questions, the ULR Panel may vote to recommend the guideline for amendment. Otherwise, the ULR Panel may vote that the guideline is current as is or requires only minor supporting text updates, or requires a full guideline revision based on the necessity of extensive updates. For the RUTI guideline, all statements were deemed current, but supporting text was updated based on the findings discussed below.

For the 2021 ULR the EPC reviewed abstracts for 19 studies in 21 publications. Based on initial abstract review, the AUA requested further assessment of 11 of these studies:

- Four randomized controlled trials (RCTs) on cranberry prophylaxis[1-4]
- One secondary report of an RCT on water intake for prophylaxis[5]
- One RCT and one systematic review of D-mannose prophylaxis[6,7]
- One RCT and one systematic review of methenamine prophylaxis[8,9]
- One RCT and one systematic review on estrogen therapy[10,11]

The EPC reviewed lists of primary studies in the three systematic reviews to identify any overlap both with those included in the EPC's previous systematic review, and with primary studies included in the ULR.

Risk of Bias Assessment

One investigator assessed risk of bias (RoB) using the same predefined criteria used in the 2019 report, while a second investigator reviewed these assessments. For clinical trials, the EPC uses criteria adapted from the U.S. Preventive Services Task Force,[12] including use of appropriate randomization and allocation concealment methods, baseline comparability of groups, blinding, attrition, and use of intention-to-treat analysis. The EPC used AMSTAR[13] to assess RoB for systematic reviews. Studies are rated as low, moderate, or high RoB, based on the presence and seriousness of methodologic shortcomings.

Synthesis and Strength of Evidence

The EPC extracted Summary of Evidence tables from the 2019 review for the relevant Key Questions, added assessments of new studies to them, and combined results of old and new studies where appropriate. The EPC updated or assessed the strength of evidence (SOE) for key comparisons and outcomes, using the approach described in the AHRQ EPC *Methods Guide for Comparative Effectiveness Reviews*.[14] SOE assessments were based on the following domains: studies' methodologic limitations, consistency of results across studies, directness of evidence linking intervention and outcome, and precision of the estimate of effect. Based on the assessment of these domains, the EPC graded the SOE for each comparison and outcome as high, moderate, low, or very low. One investigator assessed SOE, and the second reviewed these assessments.

RESULTS

The ULR report focused on reviewing estrogen therapy, D-mannose prophylaxis, and methenamine for the treatment of rUTI. The systematic review of estrogen therapy[10] contained eight studies: one that was included in the ULR, four included in the 2019 review, and three that did not meet inclusion criteria for that review. All of the eight studies included in the systematic review of D-mannose prophylaxis[7] were also assessed for the 2019 review, and three met inclusion criteria. Finally, the systematic review of methenamine prophylaxis[9] included six studies: one included in the ULR, two included and one excluded in 2019, and two not in English.

Of the eight RCTs further assessed by the EPC, two were published only as abstracts: the secondary publication[15] of a previously included trial of water intake, and a study of D-mannose prophylaxis.[6] A third study was not in English.[16] Further evaluation of these three trials was not conducted. One trial was evaluated by the EPC that was not requested by the AUA[1] because it included cranberry along with Lactobacillus prophylaxis and was comparable to an included study that assessed this combination with added D-mannose.[2] For the six remaining RCTs the EPC assessed RoB and SOE. RoB was high for one study,[11] and moderate for the remaining five (Appendix A).[1-4,8]

Antibiotic Versus Methenamine Prophylaxis

The 2019 review found low-strength evidence that rates of UTI recurrence were lower with antibiotic (nitrofurantoin or trimethoprim) than with methenamine prophylaxis, based on two trials with high RoB (Table B.1). One new study had moderate

Appendix A. *RoB Assessments*

RoB Table. Randomized Controlled Trials

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition reported?	Attrition: differential (>10%)/ high (>20%)?	Intention to treat analysis?	RoB
Babar, 2021	Yes	Unclear	No	Yes	Yes	Yes	Yes	Yes	No, No	Yes	Moderate
Botros, 2021	Yes	Yes	Yes	Yes	No	No	No	Yes	No, Yes (10.1%)	No (6.5% excluded)	Moderate
Bruyere, 2019	Yes	Yes	No (water intake)	Yes	Unclear	Unclear (double-blind)	Unclear (double-blind)	Yes	No, No	No (14% excluded)	Moderate
Ferrante, 2021	Unclear	Unclear	No	Yes	No	No	Yes	Yes	Yes (17% vs 35%), Yes (26%)	Yes	High
Koradia, 2019	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No, No	Yes	Moderate
Murina, 2021	Yes	Unclear	Yes	Yes	No	No	No	Yes	No, No	Yes	Moderate

RoB,[8] and its results were inconsistent with the earlier evidence, showing no difference in efficacy between trimethoprim and methenamine. None of the three studies showed differences in adverse events (AE) between treatments (very low SOE). Taken together, the three studies provided very low-strength evidence of no difference between methenamine and antibiotics. As such, the Panel continues to support the statement that "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. (Conditional Recommendation; Evidence Level: Grade B)." The study findings show promise of methenamine as an alternative to prophylactic antibiotics in UTI prevention, which is important in the era of antimicrobial resistance.

Non-Antibiotic Prophylaxis

The 2019 review included five studies of cranberry prophylaxis compared with placebo or no cranberry, and two of cranberry versus antibiotic (Table B.2). Three of the four new trials of cranberry prophylaxis combined cranberry with different non-antibiotic agents, and the fourth compared high-dose to low-dose cranberry; thus, the new studies could not be combined with those assessed in 2019 or with each other.

The study comparing doses of cranberry (proanthocyanidins [PAC]) did not show a difference in UTI recurrences or in AEs between doses,[3] nor did a study of cranberry, propolis (a natural resinous mixture produced by honey bees), and zinc show differences compared with placebo.[4] A combination of cranberry, D-mannose, and Lactobacillus also did not show differences in outcomes compared with no treatment in one trial.[2] SOE for findings in all three of these studies was

Appendix B. *Summary of Findings Tables*

Table B.1. *Summary of Findings: Key Question 6*

Number of Studies; Number of Subjects	Outcome	RoB	Consistency[a]	Directness	Precision	Strength of Evidence	Main Findings
			Antibiotic versus methenamine				
2 RCTs; N = 144	≥1 UTI recurrence	High	Consistent	Direct	Precise	Low	Pooled Relative Risk (RR) 0.64 (95% Confidence Interval (CI) **0.48 to 0.87**); Absolute risk difference (ARD) -27% (95% **CI -43% to -11%**)
1 RCT;[8]a N = 86	≥1 UTI recurrence	Moderate	—	Direct	Imprecise	—	65.1% (28/43) vs. 65.1% (28/43), p = 1.00
Overall SOE 3 RCTs, N = 230	≥1 UTI recurrence	High	Inconsistent	Direct	Imprecise	Very low	Pooled RR 0.77 (95% CI 0.54 to 1.09); I^2 = 59.5%
2 RCTs; N = 144	Any AE	High	Inconsistent	Direct	Imprecise	Very low	Pooled RR 1.24 (95% CI 0.02 to 67.8)
1 RCT;[8]a N = 86	Specific AEs	Moderate	—	Direct	Imprecise	—	Few events, no differences between groups
Overall SOE 3 RCTs, N = 230	AEs	High	Inconsistent	Direct	Imprecise	Very low	No statistically significant difference
			Antibiotics versus d-mannose				
2 RCTs; N = 326	≥1 UTI recurrence	High	Inconsistent	Direct	Imprecise	Very low	Pooled RR 2.56 (95% CI 0.80 to 8.19)
1 RCT; N = 206	Any AE	High	Cannot assess	Direct	Imprecise	Very low	RR 3.62 (95% CI **1.74 to 7.55**)

Relevant Guideline Statement: 12, antibiotic prophylaxis

New studies shaded blue; studies from 2019 review unshaded; statistically significant results in **bold**

[a] Botros 2021 presented with Key Question 7 (non-antibiotic prophylaxis) in Updated Literature Review, but since methenamine was included as an antibiotic comparator in Question 6 of the 2019 report, we moved the study here to combine with earlier studies. A second citation, Botros 2020, reported the same study as a conference abstract only.[21]

Table B.2. *Summary of Findings: Key Question 7*

Number of Studies; Number of Subjects	Outcome	RoB	Consistencya	Directness	Precision	Strength of Evidence	Main Findings
Cranberry versus placebo or no cranberry							
5 RCTs; N=1017	≥1 UTI recurrence	Moderate	Consistent	Direct	Precise	Moderate	RR 0.67 (95% CI **0.54 to 0.83**); ARD -11% (95% CI -16% to 5%)
5 RCTs; N=855	Harms	Moderate	Consistent	Direct	Imprecise	Low	Limited evidence on various harms did not suggest increased risk of harms with cranberry
Cranberry *(dose NR)* + ***propolis*** + ***zinc*** *(DUAB®)* ***versus placebo***							
1 RCT;[4] N=85	≥1 UTI recurrence	Moderate	Cannot assess	Direct	Imprecise	Very low	53% (20/38) vs. 64% (23/36), p=0.33 (per protocol results reported for efficacy) a
1 RCT;[4] N=85	Harms	Moderate	Cannot assess	Direct	Imprecise	Very low	Serious Adverse Event (SAEs): 7.1% (3/42) vs. 2.3% (1/43), p=0.32
Cranberry versus antibiotics							
2 RCTs; N=358	≥1 UTI recurrence	Moderate	Inconsistent	Direct	Imprecise	Very low	Pooled RR 1.30 (95% CI 0.79 to 2.14)
2 RCTs; N=358	Withdrawal due to adverse events (WAE)	Moderate	Consistent	Direct	Imprecise	Low	Pooled RR 0.81 (95% CI 0.38 to 1.70)
High-dose versus low-dose cranberry *(37 vs 2 mg/d PACs)*							
1 RCT;[3] N=145	≥1 UTI recurrence	Moderate	Cannot assess	Direct	Imprecise	Very low	Hazard ratio 0.73 (95% CI 0.45 to 1.16)
1 RCT;[3] N=145	Harms	Moderate	Cannot assess	Direct	Imprecise	Very low	SAE 0% vs 0%; WAE 1% vs 1%
Cranberry *(36 mg/d PACs)* + ***Lactobacillus*** + ***Vitamin A*** *(BK Pro-Cyan®)* ***versus placebo***							
1 RCT;[1] N=89	≥1 UTI recurrence	Moderate	Cannot assess	Direct	Precise	Low	9.1% vs. 33.3%, **p=0.0053**
1 RCT;[1] N=89	Harms	Moderate	Cannot assess	Direct	Imprecise	Very low	Any AE: 6.8% (3/44) vs 0% (0/45), p=0.19 WAEs: 0% vs 0%
Cranberry *(dose NR)* + ***D-mannose*** + ***Lactobacillus*** *(Lactoflorene Cist®)* ***daily versus 10 days/month versus no treatment***							
1 RCT;[2] N=55	≥1 UTI recurrence	Moderate	Cannot assess	Direct	Imprecise	Very low	Daily vs. none: 32% vs. 65%, p=0.06 10d/mo. vs. none: 37% vs. 65%, p=0.11 (EPC calculated) b
1 RCT;[2] N=55	Harms	Moderate	Cannot assess	Direct	Imprecise	Very low	No AEs reported
Increased water intake							
1 RCT; N=140	UTI frequency	Moderate	Cannot assess	Direct	Precise	Low	1.7 vs. 3.2 UTI episodes over 12 months (**p < 0.001**)
1 RCT; N=140	AEs	Moderate	Cannot assess	Direct	Precise	Low	No serious AEs; no difference in headaches or gastrointestinal symptoms

Relevant Guideline Statement: 13, non-antibiotic prophylaxis
New studies shaded blue; studies from 2019 review unshaded; statistically significant results in **bold**
[a] Bruyere 2019 reported statistically significant benefit from treatment for some outcomes (UTI frequency over 3 months, after adjusting for baseline differences between groups, and time to onset of first episode), but not in the number of patients with one or more UTIs.
[b] Discrepancies between numbers reported in Murina 2021, Table 2 and percents reported in Table 2, text, and abstract. Episodes of UTI vs. patients with UTI also unclear.

very low. The fourth study[1] compared high-dose cranberry with Lactobacillus and vitamin A to placebo, and provided low-strength evidence that fewer patients had UTI recurrences with treatment (9.1% versus 33.3%, p=0.0053). Rates of AEs were low and did not differ between groups in any new study (very low SOE). This study did not impact the current guideline statement because it combined cranberry with two other substances. As such, the Panel continues to support the statement that "Clinicians may offer cranberry prophylaxis for women with rUTIs. (Conditional Recommendation; Evidence Level: Grade C)."

Estrogen Therapy

One new study with high RoB compared estrogen therapy to placebo in 35 women (Table B.3).[11] This study showed that women treated with estrogen had fewer UTI recurrences, similar to the findings of four studies on estrogen treatment included in the 2019 review. The difference was statistically significant with the addition of the new study (RR 0.58, 95% CI 0.39 to 0.87), but the SOE remained low. The new study did not report AEs. As such, the Panel continues to support the statement that "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)."

Future Research

There is growing interest in the study of other mechanisms to allow for the more rapid and accurate identification and treatment of infection. Molecular testing technologies have the potential to provide such

Table B.3. *Summary of Findings: Key Question 11*

Number of Studies; Number of Subjects	Outcome	RoB	Consistencya	Directness	Precision	Strength of Evidence	Main Findings
Estrogen versus placebo or no estrogen							
4 RCTs; N=313	≥1 UTI recurrence	Moderate	Inconsistent	Direct	Precise	Low	Pooled RR 0.59 (95% CI 0.35 to 1.01); all studies enrolled women >65 years of age
1 RCT;[11] N=35	≥1 UTI recurrence	High	–	Direct	Precise	–	61% (11/18) a vs 94% (16/17), **p=0.041**
Updated SOE 5 RCTs, N=348	≥1 UTI recurrence	Moderate	Inconsistent	Direct	Precise	Low	Pooled RR 0.58 (95% CI **0.39 to 0.87**), I^2=67.8%
2 RCTs; N=180	Harmsb	Moderate	Consistent	Direct	Imprecise	Low	Limited evidence found SAEs and WAEs uncommon with either estrogen or placebo/no estrogen
Estrogen versus antibiotics							
1 RCT; N=150	≥1 bacteriuria episode	Moderate	Cannot assess	Direct	Precise	Low	RR 1.53 (95% CI **1.11 to 2.10**)
1 RCT; N=150	Any AE	Moderate	Cannot assess	Direct	Imprecise	Very low	RR 0.99 (95% CI 0.66 to 1.47)

Relevant Guideline Statement: 16, estrogen therapy
New studies shaded blue; studies from 2019 review unshaded; statistically significant results in **bold**
[a] Ferrante 2021 reports as 9/18 in text, 11/18 in abstract; latter more consistent with reported p-value. Literature search identified a second identical abstract from 2018, but the EPC was only able to find a 2021 publication.
[b] Adverse events not reported by treatment arm in Ferrante 2021.

information, and hold promise for the future by providing a more complete characterization of genitourinary microbes. Polymerase chain reaction (PCR) and next-generation sequencing (NGS) provide a direct assessment of urinary DNA to identify the bacteria present. PCR involves rapid DNA amplification and matching of that DNA to a small set of pre-selected known organisms.[17] PCR testing is very sensitive, provided that the causal organism of interest is present in the PCR test panel. NGS analyzes all microbial DNA within a urine sample and compares it to a database of species, further increasing sensitivity. In studies of patients with and without UTI, PCR has shown good concordance with culture. However, while symptomatic culture-negative patients were frequently found to have E. coli in their urine by quantitative PCR (qPCR), so were a significant number of controls.[18,19] Studies comparing NGS to urine culture showed that NGS detects more bacteria and a greater range of organisms within a given urine sample. However, these studies do not examine the positivity rates in culture-negative patients. In a recent study, 44 patients with suspected acute UTI were randomized to treatment based on either culture or NGS.[20] Although the NGS group had a greater improvement in their symptoms, 21 of 22 asymptomatic subjects recruited as controls were also positive for bacteria by NGS. To date, more evidence is needed before these technologies become incorporated into the guideline, as there is concern that adoption of this technology in the evaluation of lower urinary tract symptoms may lead to overtreatment with antibiotics.

Appendix C. *Key Questions*

The scope and clinical questions for this review were determined in conjunction with a panel convened by the AUA. The panel selected the following key questions for review:

1. In women with a history of recurrent UTI with symptoms of recurrence, what is the accuracy of tests for diagnosis of recurrent infection?
2. In women with a history of recurrent UTIs with symptoms of recurrence, what are the effects of obtaining urine culture or urinalysis versus not obtaining these tests to inform treatment decisions on clinical outcomes?
3. In women with ASB, what risk factors are associated with progression to symptomatic UTI?
4. In women with a history of recurrent UTIs, what are the benefits and harms of surveillance testing for ASB/UTI in between episodes of UTIs?
5. In women with acute UTIs (single episode or recurrent), what are the benefits and harms of commonly used antibiotic for acute cystitis episodes?
6. In women with recurrent UTIs, what are the benefits and harms of antibiotic prophylaxis?
7. In women with recurrent UTIs, what are the benefits and harms of non-antibiotic prophylaxis?
8. In women with recurrent UTIs and drug resistance, what the benefits and harms of therapies for treating recurrent UTI?
9. In women treated for recurrent UTIs, what is the association between different measures of cure (microbiological cure, absence of urinary biomarkers of infection, or symptom improvement) and likelihood of symptom recurrence or time to symptom recurrence?
10. In women treated for recurrent UTIs, what are the benefits and harms of documenting microbiological cure or obtaining biomarkers to assess for cure versus clinical assessment?
11. In women with recurrent UTIs, what are the benefits of hormonal treatments for preventing future UTIs?

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