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Review Article

A Review of Nonantibiotic Agents to Prevent Urinary Tract Infections in Older Women

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A B S T R A C T

Objective: This article provides a comprehensive literature review on nonantibiotic agents used for the prevention of urinary tract infections (UTIs) in women ≥45 years of age.
Design: A structured review was performed by conducting a literature search to identify relevant studies pertaining to the use of nonantibiotic agents to prevent UTIs in women who were perimenopausal through postmenopausal. Recommendations were made for or against the use of each nonantibiotic agent, unless data were unavailable. Levels of evidence were assigned to each recommendation made.
Setting and participants: Studies on the prevention of UTIs with women subjects ≥45 years of age in the community, inpatient, and long-term care settings were considered for inclusion.
Measure: The efficacy and safety of using ascorbic acid, cranberry products, D-mannose, estrogens, lactobacilli, and methenamine hippurate for prevention of UTIs was assessed.
Results: There is evidence to support use of estrogens (A-I) in postmenopausal women, and cranberry capsules (C-I) in women ≥45 years of age for the prevention of UTIs. There was a lack of evidence to make recommendations for or against the use of ascorbic acid, cranberry juice, cranberry capsules with high proanthocyanidin (PAC) content, D-mannose, lactobacillus, and methenamine hippurate in this population.
Conclusions/Implications: Current studies support that estrogens and cranberry capsules may have a role in preventing UTIs in women ≥45 years of age. Further research is needed to elucidate the role of these nonantibiotic agents and how they may be used to decrease antibiotic use.
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Urinary tract infections (UTIs) are the most common infections in older women, and recurrent UTIs (defined as 2 infections in 6 months or 3 or more infections in 1 year) are prevalent in this population as well.[1–4] This is due to risk factors such as decreasing estrogen levels during menopausal changes leading to increased vaginal pH and *Enterobacteriaceae* colonization in the vagina, incontinence, postvoid residual urine, and urinary catheterization.[5] Adult patients are at a high risk of receipt of antibiotics for UTIs when potentially inappropriate, with an estimate of ~40% not meeting clinical evidence for diagnosis.[6,7] Increased exposure to antibiotics is problematic because of the risks of subsequent infections or colonization with antimicrobial resistant bacteria, *Clostridioides difficile* infections, and other antibiotic-related adverse events.[7,8] Continuous low-dose antibiotic prophylaxis is effective at preventing recurrent UTIs, although the optimal duration and doses are not clearly defined.[9] Moreover, these regimens are only exacerbating the issue of increased antibiotic exposures. Lower doses may be of greater concern because subtherapeutic antibiotic concentrations have been found to increase mutagenesis and horizontal gene transfer, which can further promote antibiotic resistance.[10] Common nonantibiotic agents used for preventing UTIs include ascorbic acid, cranberry products, D-mannose, estrogens, lactobacilli, and methenamine hippurate.[11] The data for

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their use specifically in women ≥45 years of age are limited, and no clear consensus on their safety or efficacy exists. However, these agents offer the advantage of potentially decreasing antibiotic use by working to prevent recurrent UTIs, and as an alternative to continuous low-dose prophylactic antibiotics. This structured review describes the available literature of using ascorbic acid, cranberry products, D-mannose, estrogens, lactobacilli, and methenamine hippurate for prevention of UTIs in women ≥45 years of age. A literature search of PubMed, Embase, and Google Scholar was conducted from inception until August 1, 2018 using the following terms: *ascorbic acid*, *cranberry*, *cranberry extract*, *cranberry juice*, *cranberry products*, *D-mannose*, *estrogens*, *estriol*, *estradiol*, *lactobacilli*, *methenamine hippurate*, *older women*, *postmenopausal women*, *urinary tract infection prevention*, and *vitamin C*. Studies were included if they met the following criteria: interventional or observational in nature, written in English, investigated the UTI-preventive effect of any 1 of the nonantibiotic agents of interest, and involved women ≥45 years of age. Recommendations were made for or against the use of each agent based on the quality of the data, the generalizability to women ≥45 years of age, and if the outcome was related to clinical outcomes of UTI prevention, unless evidence was unavailable. Levels of evidence were assigned to each recommendation based on the criteria used in the Infectious Disease Society of America (IDSA) guideline methods (Table 1).[12] Recommendations were completed independently by 2 authors (C.M.G., M.A.H.) and adjudicated if discrepancies were present (K.L.L.).

Ascorbic Acid (Vitamin C)

Recommendation

No recommendation for or against the use of ascorbic acid can be made. There is a lack of evidence on its use in preventing UTIs in women ≥45 years of age.

Clinical efficacy

Ascorbic acid, or vitamin C, has been studied as an agent to prevent UTIs based on the hypothesis that acidifying the urine can be an adjuvant therapy for UTIs.[13] However, several subsequent studies have disproven that vitamin C can achieve enough of a decrease in urine pH to be effective in preventing UTIs.[13–17] Although found to be used for prevention of UTIs in older women, there have been no appreciable clinical studies generalizable to this population.[18]

Safety

Ascorbic acid therapy carries a risk for hyperoxaluria, and calcium oxalate stones.[19–21] Patients who consume more than 1 g of ascorbic acid daily are observed to be at a higher risk for kidney stone formation. Other potential side effects include diarrhea, abdominal cramping, and other gastrointestinal side effects.[22]

Cranberry Products

Recommendation for Cranberry Capsules

Cranberry capsules at a dose of 500 mg twice daily may be used for preventing UTIs in women ≥45 years of age.

Level of Evidence

Poor evidence to support a recommendation for use of cranberry capsules, evidence from ≥1 properly randomized controlled trial (C-I).

Recommendation for Cranberry Capsules With High Proanthocyanidin (PAC) Content

No recommendation for or against the use of cranberry capsules with high PAC content can be made. Only 1 study was identified that found no reduction in bacteriuria with pyuria, but it did not investigate UTIs as an outcome.

Recommendation for Cranberry Juice

No recommendation for or against the use of cranberry juice can be made. Two studies were identified, one of which found a reduction in pyuria and bacteriuria but not UTIs, and another that found no difference in UTI prevention when compared to placebo, but it was not generalizable to women ≥45 years of age.

Clinical efficacy

The components of cranberries, including polyphenols (found in urine) and PACs (not found in urine), have been shown to exhibit inflammatory modulations and inhibit *Escherichia coli* adhesion to uroepithelial surfaces.[23–28] However, type A PACs, which are exclusive to cranberry and blueberries, are not found in the urine of patients who drink cranberry juice.[26] Clinical trials have evaluated the role of various cranberry products, including (1) cranberry capsules, (2) cranberry capsules with high PAC content, and (3) cranberry juice.[29–37] Cranberry juice and cranberry capsules are similar in that they contain all of the various components of cranberry. However, cranberry juice is formulated as a fluid, which may have the additional benefit of "flushing out" bacteria.[38] Cranberry capsules with high PAC content are different in that they rely on PACs as the main active ingredient.

Cranberry capsules

A 2009 study evaluated the use of Cran-Max 500-mg cranberry concentrate capsules (mg of PACs not mentioned) vs trimethoprim 100 mg prophylaxis, both taken once daily, for prevention of UTIs in community-dwelling older women ≥45 years of age.[32] The treatment

Table 1
Levels of Evidence

Category, Grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from 11 centers); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

The above levels of evidence are the Infectious Diseases Society of America–US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines.

Table 2
Summary of Studies on Nonantibiotic Drugs Used for Prevention of UTIs in Older Women

Title, First author, Journal and Year of Publication	Study Population	Study Design	Treatment Intervention	Endpoints	Findings
Ascorbic acid (vitamin C)					
No studies available in older women population (≥45 y) for prevention of UTIs					
Cranberry capsules					
Reduction of Bacteriuria and Pyuria After Ingestion of Cranberry Juice Avorn J *JAMA* 1994	Older women residing in a long-term care facility (n = 153) Mean age = 78.5 y	Randomized, double-blind, placebo- controlled trial	300 mL of cranberry juice daily for 6 mo	Bacteriuria ($\geq 10^5$ CFUs/mL) + pyuria (WBCs on microscopy)	Bacteriuria + pyuria was found in 28.1% of urine samples collected from the placebo group vs 15.0% in the cranberry group, adjusted OR = 0.42 (95% CI 0.23-0.76; $P = .004$)
Reduction of Bacteriuria and Pyuria Using Cranberry Juice Haverkorn MJ *JAMA* 1994	Older persons of a hospital nursing department (n = 38; men = 9, women = 29) Mean age = 81 y	Randomized, controlled, crossover study	15 mL of cranberry juice mixed with water twice daily or placebo for 4 wk, and then regimens were switched	Bacteriuria ($\geq 10^5$ Enterobacteriaceae CFUs/mL)	Fewer occurrences of bacteriuria during the period when cranberry juice was being taken ($P = .004$)
Does Ingestion of Cranberry Juice Reduce Symptomatic Urinary Tract Infections in Older People in Hospital? A Double-Blind, Placebo-Controlled Trial McMurdo ME *Age Ageing* 2005	Older adult inpatients without history of recurrent UTIs (n = 376; men = 121, women = 255) Mean age = 81 y	Randomized, double-blind placebo-controlled trial	300 mL of cranberry juice daily for 35 d following randomization, until hospital discharge, or at occurrence of first symptomatic UTI	Time to onset of first symptomatic UTI (culture positive for single organism and more than 10^4 CFUs/mL)	Nonstatistical difference of 7.4% in the placebo group vs 3.7% in the cranberry group developing a UTI was found (RR 0.51, 95% CI 0.21-1.22, $P = .112$)
Cranberry capsules with high proanthocyanidin (PAC) content					
Effect of Cranberry Capsules on Bacteriuria Plus Pyuria Among Older Women in Nursing Homes: A Randomized Clinical Trial Juthani-Mehta M *JAMA* 2016	Older women in nursing homes (n = 185) Mean age = 87 y	Randomized, double-blind, placebo-controlled trial	Cranberry capsules containing 72 mg proanthocyanidins (for 360 d)	Presence of bacteriuria ($\geq 10^5$ CFUs/mL of 1 or 2 bacteria) and pyuria (WBCs on microscopy)	Adjusted analysis found a rate of 29.1% in the cranberry group vs 29.0% in the control group of the primary outcome (OR 1.01, 95% CI 0.61-1.66, $P = .98$)
Cranberry juice					
Cranberry or Trimethoprim for the Prevention of Recurrent Urinary Tract Infections? A Randomized Controlled Trial in Older Women McMurdo MET *J Antimicrob Chemother* 2009	Community-dwelling women with recurrent UTIs (n = 137) Mean age = 63 y	Randomized, double-blind, controlled trial	500-mg cranberry extract daily or 100-mg trimethoprim daily for 6 mo	Proportion of patients with a recurrence of antibiotic-treated UTI	In the cranberry group, 36.2% vs 20.5% in the trimethoprim had an antibiotic-treated UTI (RR 1.616, 95% CI 0.93-2.79, $P = .084$)

Effectiveness of Cranberry Capsules to Prevent Urinary Tract Infections in Vulnerable Older Persons: A Double-Blind Randomized Placebo-Controlled Trial in Long-term Care Facilities Caljouw MAA, *J Am Geriatr Soc* 2014	Long-term care facility residents (n = 928; men = 225, women = 225) Median age = 84 y Stratified into 2 cohorts: high risk (n = 516) and low risk (n = 412) of UTI	Randomized, double-blind, placebo-controlled trial	1 cranberry capsule (9-mg PAC) twice daily or placebo for 12 mo	Incidence of UTI Clinical definition: Symptom or positive testing (nitrite test, leukocyte esterase test, dipslide or culture) Strict definition: Symptoms plus positive urine dipslide or culture Positive culture defined as $\geq 10^5$ CFUs/mL bacteria with no more than 2 organisms	High-risk cohort: Using the clinical definition, there were 98 UTI events/253 (38.7%) residents in cranberry group and 125 UTI events/263 (47.5%) residents in placebo group meeting the clinical definition (HR 0.74, 95% CI 0.57-0.97, $P = .03$) Using the strict definition, there were 45 UTI events/253 (17.8%) residents in cranberry group and 46 UTI events/263 (17.5%) residents in placebo group (HR 1.02, 95% CI 0.68-1.55, $P = .91$) Low-risk cohort: Using the clinical definition, there were 59 UTI events/205 (28.8%) residents in cranberry group and 51 UTI events/207 (24.6%) residents in placebo group (HR 1.22, 95% CI 0.84-1.77, $P = .3$). Using the strict definition, there were 17 UTI events/205 (8.3%) residents in cranberry group and 16 UTI events/207 (7.7%) residents in placebo group (HR 1.11, 95% CI 0.56-2.2, $P = .76$). Hazard ratios representative of incidence of UTI per 100 person-years at risk
D-Mannose No studies available in older women population (≥45 y) for prevention of UTIs					
Estrogens					
A Controlled Trial of Intravaginal Estriol in Postmenopausal Women With Recurrent Urinary Tract Infections Raz R *N Engl J Med* 1993	Postmenopausal women with a history of recurrent UTI (n = 93) Mean age = 65 y	Randomized, double-blind, placebo-controlled trial	Topically applied estriol cream (0.5 mg) applied twice weekly for 8 mo	Annualized median incidence of UTI defined by symptoms plus laboratory evidence of UTI (Pyuria—at least 8 WBCs per mm^3, and bacteriuria of $\geq 10^5$ CFUs/mL)	Annualized median incidence of UTI was lower in the estrogen group: 0.5 vs 5.9 per patient-year, $P < .001$
A Randomized, Open, Parallel-Group Study on the Preventive Effect of an Estradiol-Releasing Vaginal Ring (Estring) on Recurrent Urinary Tract Infections in Postmenopausal Women Erickson B *Am J Obstet Gynecol* 1999	Postmenopausal women with history of recurrent UTI (n = 108) Mean age = 68 y	Randomized, open, placebo-controlled trial	36 wk of an intravaginal 2-mg estrogen ring	Time to first bacteriologically confirmed UTI with symptoms A dipstick for nitrites, microscopic evaluation of the urine sample, or a urine culture result ($>10^5$ CFUs/mL)	Kaplan-Meier event-free survival (time without UTI) was significantly higher in the Estring group compared to placebo (45% vs 20%, $P = .008$, log-rank test)

(*continued on next page*)

Table 2 (*continued*)

Title, First author, Journal and Year of Publication	Study Population	Study Design	Treatment Intervention	Endpoints	Findings
Effectiveness of Estriol-Containing Vaginal Pessaries and Nitrofurantoin Macrocrystal Therapy in the Prevention of Recurrent Urinary Tract Infection in Postmenopausal Women Raz R *Clin Infect Dis* 2003	Postmenopausal women outpatients with a history of recurrent UTIs (n = 150)	Randomized, double-blind, controlled trial	0.5 mg estriol–containing vaginal pessary daily for 2 wk and then once every 2 wk for 9 mo plus oral placebo compared to nitrofurantoin monohydrate 100-mg capsule orally once every night plus placebo vaginal pessary daily for 2 wk then once every 2 wk for the remainder of the study period	Absence of symptomatic or asymptomatic bacteriuria ($>10^5$ CFUs/mL)	Patients in the estriol group had a higher incidence of UTIs (both symptomatic and symptomatic) compared to nitrofurantoin monohydrate, 58/86 (67.4%) vs 37/85 (43.5%), $P = .0003$. Absence of symptomatic or asymptomatic bacteriuria: 28/86 (32.6%) vs 48/85 (56.4%), $P \leq .0003$.
Lactobacillus					
Lactobacilli vs Antibiotics to Prevent Urinary Tract Infections: A Randomized, Double-Blind, Noninferiority Trial in Postmenopausal Women Beerepoot MA, *Arch Intern Med* 2012	Postmenopausal women with recurrent UTIs (n = 252) Mean age = 64 y	Randomized, double-blind, placebo-controlled noninferiority trial	Trimethoprim/sulfamethoxazole, 480 mg, once daily or oral capsules containing 109 CFUs of *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 twice daily	Mean number of symptomatic UTIs At least 1 UTI during the 12 mo	There was a mean of 2.9 UTIs in the trimethoprim/sulfamethoxazole group and 3.3 in the lactobacilli group, between-treatment difference of 0.4 UTIs per year (95% CI −0.4 to 1.5) was outside the noninferiority margin. At least 1 UTI occurred in 69.3% in the trimethoprim-sulfamethoxazole group and 79.1% in the lactobacilli group.
Methenamine hippurate					
No studies available in older women population (≥45 y) for prevention of UTIs					

CFUs, colony-forming units; CI, confidence interval; HR, hazard ratio; OR, odds ratio; WBCs, white blood cells.

period lasted 6 months and found no difference between groups in incidence of UTIs. The authors concluded that this low-dose antibiotic had little advantage over cranberry concentrate and had more adverse effects, notably development of itch or rash. However, there was a lack of a placebo group to evaluate the effectiveness of the cranberry capsules. A larger study from 2014 evaluated cranberry 500-mg capsules (9-mg PACs) taken twice daily compared to placebo. The study included patients aged ≥65 years residing in a long-term care facility (LTCF; n = 928; 703/928 women) who were not on warfarin or had a life expectancy of ≤1 month. This cohort was split into 2 groups: (1) high risk for UTI and (2) low risk for UTI.[33] A broad UTI definition was based on the presence of at least 1 of the following: micturition-related symptoms and signs; positive nitrite test, leukocyte esterase test, dipslide, or culture; antibiotic treatment for UTI; or UTI reported in the medical record. The strict UTI definition included the presence of micturition-related symptoms and signs confirmed with a positive dipslide or culture. After 12 months, the high-risk group had fewer UTIs, 98/253 (0.42 UTIs/resident) in the cranberry group vs 125/263 (0.53 UTIs/resident) in the placebo group with a hazard ratio of 0.74 (95% confidence interval 0.57-0.97, $P = .03$). When applying a stricter UTI definition, no differences in UTI events were found in this high-risk group, and no differences were found in the low-risk group with either definition. Although the findings are limited to higher-risk patients and the less strict definition, it may still be reasonable to consider as an implication to a "real-word" clinical setting.[39]

Cranberry capsules with High PAC content

Targeting cranberry dosage standardized to higher PAC content has also been investigated, as a laboratory study concluded that cranberry powder standardized to 72-mg PACs per day had the greatest reduction in *E coli* virulence.[23] However, a randomized controlled trial using cranberry product capsules with a standardized 72-mg PAC daily dose for patients in an LTCF failed to show a reduction in bacteriuria with pyuria, alluding that UTI-preventive effects of cranberry products may also come from polyphenols or other cranberry substances.[34]

Cranberry juice

Randomized controlled trials from the 1990s that included postmenopausal women residing in LTCFs and a hospital nursing department found that 300 mL of cranberry juice ingested daily reduced the odds of having bacteriuria with pyuria, but they did not measure symptomatic UTIs.[29,30] Another study from 2005 investigated if 150 mL of cranberry juice administered twice daily could prevent symptomatic UTIs.[31] In this study, older hospitalized patients, including both men and women, were found to have a non–statistically significant lower rate of symptomatic UTIs if drinking the cranberry juice compared to drinking a matching placebo beverage, 7/187 (3.7%) vs 14/189 (7.4%), respectively (relative risk 0.51, 95% confidence interval 0.21-1.22, $P = .112$). The authors commented on a lower than expected UTI rate, which made the study underpowered. Thus, only 1 study on older women living in LTCFs who were considered at high risk for a UTI found a reduction in UTIs when taking 500-mg cranberry capsules (standardized to 9-mg PACs) twice daily, when using a broad aforementioned UTI definition.[33] However, another study found that 500-mg cranberry extract (mg of PACs not mentioned) capsules once daily may be as effective as trimethoprim 100 mg once daily.[32] Studies that investigated cranberry juice only showed a reduction in bacteriuria with pyuria and non–statistically significant reductions in UTIs.[29,30] Table 2 outlines the outcome definitions in more detail and provides a summary of these studies, along with the other studies that are discussed throughout this review.

Safety

Adverse effects were seldom reported in trials evaluating cranberry use for preventing UTIs, but were primarily gastrointestinal and generally mild.[29–36,40] Several of the aforementioned studies excluded patients with a history of kidney stones.[32,34] However, the association of cranberry and kidney stones is not well described, but rather is derived from increases in calcium oxalate production observed after cranberry extract ingestion.[41] Safety concerns with cranberry therapy also exist in the form of drug interactions with warfarin therapy, but the evidence is somewhat conflicting.[42,43] Although pharmacokinetic studies have not convincingly reproduced the same results, case reports have described increases in the International Normalized Ratio and risk of bleeding.[43,44]

D-Mannose

Recommendation

No recommendation for or against the use of D-mannose to prevent UTIs in women ≥45 years of age can be made. One randomized controlled trial found variable results for preventing UTIs in women, but it included a much younger cohort.

Clinical efficacy

D-Mannose is a simple sugar that acts as a competitive inhibitor of virulence factor FimH adhesion, which is positioned at the tip of type 1 fimbriae of enteric bacteria to hinder adhesion to epithelial cells of the urinary tract.[45] A single randomized, placebo-controlled trial was identified that investigated its use in prevention of UTIs in women with recurrent UTIs and found favorable results when compared to low-dose nitrofurantoin and no treatment.[46] However, this study included women ≥18 years of age and therefore may be more representative of a younger, premenopausal women population.

Safety

In the study mentioned, D-mannose had significantly fewer side effects than nitrofurantoin. D-Mannose is a sugar and therefore has theoretical dysglycemia concerns, but animal models failed to identify metabolic effects using concentrations up to 20% D-mannose during long-term use.[47]

Estrogens

Recommendation

Vaginally applied estriol cream or estrogen-containing silicone rings may be used to prevent UTIs in women ≥45 years of age who are postmenopausal.

Level of Evidence

Good evidence to support a recommendation for use, evidence based on ≥1 properly randomized controlled trial (A-I).

Clinical efficacy

Because of the important role of estrogen and the vaginal microbiome, vaginally applied estrogens have been studied for prevention of UTIs in postmenopausal women. Decreases in estrogen levels in postmenopausal women can affect vaginal pH and normal flora, causing decreases of *Lactobacillus* sp colonization and overgrowth of Enterobacteriaceae.[48]

A randomized controlled trial of postmenopausal women who had a history of recurrent UTIs in the prior year explored the utility of estriol

cream for UTI prevention. Notable exclusion criteria were use of indwelling catheters and receipt of prophylactic antibiotics in the past. Women treated with 0.5 mg of estriol cream nightly for 2 weeks and then twice weekly thereafter for a total of 8 weeks had a lower incidence of symptomatic, culture-confirmed UTIs compared to those given a placebo cream, 0.5 vs 5.9 UTIs per patient year ($P < .001$).[49] Another randomized, open, parallel-group design study looked into using a silicone ring that delivers 2 mg of estradiol intravaginally for prevention of recurrent UTIs compared to no treatment for 36 weeks. Postmenopausal women who had a history of ≥3 UTIs treated during the previous 12 months were included. Exclusion criteria included ongoing treatment with lactobacillus products, and ongoing treatment with antibiotics. The estradiol intravaginal treatment in this study had a larger proportion of participants remaining UTI free during the study period, 45% compared to 20%, $P = .008$.[50] Estriol pessaries were studied compared to low-dose nitrofurantoin.[51] In a study of postmenopausal women with a history of ≥3 symptomatic episodes of UTI in the last year or ≥2 in the last 6 months, estriol pessaries were compared to low-dose nitrofurantoin. Similar to the other studies, women with previous use of prophylactic antibiotics were excluded, as well as those with previous indwelling catheter use. Estriol pessaries studied contained 0.5 mg of estriol and were placed twice weekly whereas the nitrofurantoin group received 100 mg by mouth daily for a total duration of 9 months of treatment. UTI episodes were significantly higher in the estrogen-receiving treatment arm compared to the nitrofurantoin arm, 124/86 women vs 48/85 women ($P = .003$). Therefore, this formulation was not shown to have the same beneficial results as the cream or the ring. Of note, the estriol pessary dosage form did not change the extent of *Lactobacillus* spp colonization or the vaginal pH that was seen in the previous study of estriol cream.[49,51]

Safety

Common adverse effects in the above studies of vaginal estrogens in postmenopausal women were mild and involved local irritation at the application site.[49–51] Although prothrombotic substances are not found to be as elevated as with oral hormonal therapy, patients with a history of venous thromboembolism were excluded from all 3 studies mentioned.[52] A year-long observation of women using an estriol-releasing vaginal ring did not find an increase in the risk of venous thromboembolism during the follow-up, which is reassuring.[53] However, this is just 1 study, and patients with multiple risk factors including history of venous thromboembolism must be considered with initiation of hormone therapy.

Another safety consideration is suspected or confirmed hormone-related malignancy, as this was also excluded from studies.[49–51] The American College of Obstetrics and Gynecology (ACOG) released a position statement considering the evidence that lacks an associated risk of breast cancer recurrence with vaginal estrogen therapy.[54] However, clinicians are apprehensive about the use of estrogen therapy in breast cancer survivors.[54] Locally applied vaginal estrogens have lower serum estrogen concentrations compared to systemic therapy, but there is some degree of systemic absorption.[53,55] Patients treated with aromatase inhibitors may be at a higher risk of estrogen-based cancer recurrence with exogenous estrogen therapy. A risk-benefit assessment for the use of vaginal estrogen therapy must be based on patient-specific factors and consider the endocrine therapy used to prevent breast cancer recurrence as well as including the patient's oncologist in the decision-making process.

Lactobacilli

Recommendation

No recommendation for or against the use of lactobacilli to prevent UTIs in women ≥45 years of age can be made. Only 1 study that involved lactobacilli administered orally was identified, but it was not placebo-controlled.

Clinical efficacy

As noted above, the interaction between estrogen, vaginal pH, and lactobacilli colonization of the vaginal flora plays a role in urogenital infections in women.[48,56] Lactobacilli have been studied in both oral and intravaginal administration methods as a way to directly increase vaginal colonization.[56–60]

A single study was identified that involved an oral preparation containing lactobacilli strains *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 taken twice daily compared to antibiotic prophylaxis in postmenopausal females.[60] This oral lactobacilli preparation was compared to administration of sulfamethoxazole-trimethoprim (480-mg trimethoprim) once daily in a double-blind, noninferiority trial. The study population included postmenopausal women with recurrent UTIs, and after 1 year it was concluded that lactobacilli probiotics did not meet noninferiority. Utilizing the guidance set out by Consort 2010 for reporting noninferiority trials, the results of the analysis lead to inconclusive results in the ability of the authors to prove noninferiority.[61] The patients treated with sulfamethoxazole-trimethoprim prophylaxis had uropathogens with resistance to more antimicrobials as compared to the lactobacilli-treated patients.[60] Although this is helpful in showing decreased emerging resistance compared to a low-dose antibiotic regimen, a major limitation is that this was not a placebo-controlled trial.

Safety

Adverse effects reported with lactobacilli in the clinical data were generally localized to the genitourinary system, including vaginal irritation and abnormal vaginal discharge.[58–60] With the use of lactobacilli, there is a risk of development of infections in certain patient populations.[62] Patients with diabetes and immunocompromising conditions were excluded from the clinical trials evaluated.[58–60] Reports do exist of lactobacilli bacteremia in patients receiving lactobacilli probiotics; however, many are immunocompromised patients.[62–66] Although generally thought of as safe, lactobacilli supplementation carries some risk of infection that must be considered, especially in patients with immunocompromising conditions.

Methenamine Hippurate

Recommendation

No recommendation for or against the use of methenamine hippurate to prevent UTIs in women ≥45 years of age can be made. Only 1 small study was identified and found a significant reduction in catheter changes, but it did not study UTIs.

Clinical efficacy

Methenamine hippurate acidifies urine and converts to formaldehyde in the urine, which prevents bacterial invasion of the urinary tract and is approved by the United States Food and Drug Administration (FDA) for prophylactic treatment of UTIs.[67]

There have been several smaller studies looking into the clinical efficacy of this drug that are exclusively from the 1980s or earlier. Overall, methenamine hippurate significantly reduced UTIs in girls and younger women with recurrent UTIs better than placebo, although less effective than low-dose antibiotic therapy.[67,68] One study analyzed the effects of methenamine hippurate in 8 geriatric patients with heavy urine infections estimated by odor, cloudiness, encrustation, and frequency of catheter blocks.[69] The study found that methenamine hippurate at a dose of 2 g, 3 times daily given for 34 days, was able to significantly reduce the number of times a catheter needed to be changed, as the days between catheter changes

were 6 in the pretreatment period and 12 in the treatment period ($P = .008$). However, this study is limited because of its small size and its endpoint being catheter changes rather than UTIs prevented.

Safety

Methenamine hippurate has been well tolerated in clinical trials, and common side effects reported include the following: rash, nausea, upset stomach, abdominal cramps, mild transaminitis, and dysuria.[70]

Discussion

Overall, cranberry capsules and estrogens were found to have some favorable data and were therefore recommended as therapeutic options to prevent UTIs in women ≥45 years of age. Of note, estrogens were studied and are recommended only for women who are postmenopausal. This population is distinct from younger women populations because of their changing menopausal statuses and estrogen levels, which put them at risk for UTIs. Nonantibiotic agents offer an alternative to daily low-dose antibiotics, and their use has been found to be relatively safe compared to placebo. There was a lack of data on using the other nonantibiotic agents of interest. The current literature focused on UTI prevention in the women ≥45 years of age is extremely limited, and this review summarizes the currently available efficacy and safety data. Future studies are warranted to further elucidate the place in therapy of nonantibiotic agents for prevention of UTIs in older women.

This review does not address other nonpharmacologic strategies that should be used adjunctively to prevent UTIs. These would include proper Foley catheter care, post-coital voiding, general hygiene, and hydration.[71,72] All of these are also of utmost importance in this patient population. Clinical trials have shown that providing proper urinary catheter care can decrease catheter-associated UTIs, which was not a focus in this review but a related topic. Interestingly, a recent pilot study showed that increased water intake also decreased UTIs in healthy younger women with recurrent UTIs.[38]

The current climate of antibiotic resistance necessitates targeted strategies to combat unnecessary antibiotic therapy. Preventing UTIs and overuse of antibiotics in women ≥45 years of age is a target for antibiotic stewardship efforts. Using this review could help to carefully evaluate patients who may be eligible to receive nonantibiotic agents to prevent UTIs, and determine which agents may be most appropriate.

Conclusion and Implications

There have been several nonantibiotic agents studied in the setting of UTI for prevention of UTIs in women ≥45 years of age. Cranberry capsules and vaginally applied estrogens (if postmenopausal) have been shown to be effective in preventing UTIs in this population and therefore may have the advantage of potentially deterring overuse of antibiotics. Current data is lacking to make recommendations for or against the use of ascorbic acid, cranberry juice, cranberry capsules with high PAC content, D-mannose, lactobacilli, and methenamine hippurate in this specific patient population.

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