Brief description of patient problem/setting (summarize the case very briefly)

L.R. is a 43 yo F 30212 w/ a pmhx of hypothyroidism and pshx of 2 c-sections presenting today w/ cc of dysuria and urinary frequency x3 days. Pt states she had 4 UTIs last year and this is a chronic issue for her. UA is positive for nitrites and leukocyte esterases, indicating another UTI.

Search Question: Clearly state the question (including outcomes or criteria to be tracked)

In woman w/ recurrent UTIs (≥2 in 6 months or 3≥ in 12 months), do nonantibiotic prophylactic strategies reduce the incidence of symptomatic, culture-verified UTIs compared to placebo?

Question Type: What kind of question is this? (boxes now checkable in Word)

√ Treatment

Study type: Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)? Please explain your choices.

Blinded RCTs are appropriate to compare non-antibiotic interventions to a placebo. RCTs will determine causality between nonantibiotic interventions and a reduction in UTIs. These studies minimize bias and best determine if nonantibiotic prophylaxis reduces recurrence of UTIs. If RCTs were unavailable, I would consider prospective cohort studies to evaluate recurrence over time.

PICO search terms:

Population	Intervention	Comparison	Outcome
Woman	Non-antibiotic prophylaxis	Placebo	Incidence of UTI
Recurrant UTI	Cranberry	Control	Symptomatic UTI
≥2 UTIs in 6 months	D-mannose	No treatment	UTI recurrence
≥3 UTIs in 12 months	Probiotics		Prevention

Search tools and strategy used:
Please indicate what databases/tools you used, provide a list of the terms you searched together in each tool, and how many articles were returned using those terms and filters. Explain how you narrowed your choices to the few selected articles. For example, if your search returned 25 articles among the several databases used, what was the process used to determine which four articles to use?

PubMed
Search Terms - ("Urinary Tract Infections"[Mesh] OR UTI OR cystitis) AND ("recurrent UTI*" OR "recurrent urinary tract infection*") AND ("Women"[Mesh] OR women) AND ("Non-antibiotic prophylaxis" OR "nonantibiotic prophylaxis") AND ("Placebo"[Mesh]) AND (prevention OR prophylaxis)

Results - 5

Cochrane
Search Terms - UTI nonantibiotics
Results - 29

Google Scholar
Search Terms - Non-antibiotic prophylaxis of UTI “Meta-analysis” “Non-antibiotic”
Results - 2,520

Narrowing my choices: After applying filters, I looked for titles with meta-analysis or review in the title. I then selected studies with large populations (thousands) vs. studies w/ 100s of participants. As my understanding grew, I selected studies examining specific interventions, particularly those with mixed results, to understand the nuances of these unclear findings.

Results found:
Identify at least 3 articles (or other appropriate reputable sources) that answer your specific question with the highest available level of evidence (you will probably need to look at more than 3 articles to get the 3 most focused and highest-level articles to address your question). Please make sure that they are Medline indexed.13

In addition to providing the hyperlinks, the full-length articles (PDFs) must also be attached in Brightspace.

Please post the citation and abstract for each article (to include the journal and authors’ names and date) and say why you chose it.
Please also note what kind of article it is (e.g. meta-analysis, cohort study, or independent blind comparison with gold standard of diagnosis, etc.).
At the bottom of each abstract, please comment on what your key points are from this article (including any points or concepts included in the article, but not present in the abstract – i.e. make the concepts understandable to the reader)
Please note that if the evidence is not in the abstract, you must clearly summarize the evidence in your posting.

What is the clinical “bottom line” derived from these articles in answer to your question?

1) Nonantibiotic prophylaxis for urinary tract infections: a network meta-analysis of randomized controlled trials

Abstract

Objective: Recent guidelines indicated that, in addition to antibiotics, nonantibiotic interventions serve as available preventive options for urinary tract infections (UTIs). This study aimed to compare the efficacy and safety of various nonantibiotic interventions in preventing UTIs.

Methods: The authors systematically searched databases for eligible studies. The inclusion criteria encompassed randomized controlled trials (RCTs) focusing on one or more nonantibiotic interventions for UTI prevention, with the incidence of UTIs being a key outcome measure. Subgroup analyses were performed according to age, sex, and follow-up.

Results: 50 RCTs comprising 10,495 subjects and investigating 14 interventions, were included. Nearly 80% of the RCTs utilized double-blind or triple-blind designs. In the whole group, D-mannose (risk ratio [RR] 0.34, 0.21 to 0.56), vaccine (RR 0.65, 0.52 to 0.82), probiotics (RR 0.69, 0.50 to 0.94), cranberry (RR 0.72, 0.60 to 0.87), and triple therapy (cranberry plus probiotics plus vitamin A) (RR 0.27, 0.09 to 0.87), exhibited a significant reduction in UTI incidence compared to the placebo. Probiotics (RR 0.50, 0.28 to 0.89) were the most effective in the nonadult group, while vitamin D (RR 0.46, 0.27 to 0.81) showed the highest efficacy in the long follow-up group (≥ 1 year). There was no significant difference in the incidence of adverse events between the interventions and the placebo group.

Conclusions: D-mannose, triple therapy, vaccine, probiotics, and cranberry serve as potential nonantibiotic intervention options for clinical UTI prevention.

Study design/Level of Evidence: This is a systematic review and network meta-analysis of 50 RCTs. There were 10,495 subjects across different age groups. 80% of the RCTs included were either double or triple-blinded. This represents level 1 evidence and has a low risk of bias. This was the study with the largest population I could find.

Key points: 14 different non-antibiotic interventions were included in this review. The most effective interventions included D-mannose w/ a RR of 0.34, Probiotics w/ a RR of 0.69, Cranberry products w/ a RR. of 0.72, and triple therapy (cranberry products, probiotics, and vitamin A) w/ a RR of 0.27. These data show that triple therapy can offer a 73% risk reduction of recurrence of UTIs. Data showed that probiotics were the most effective intervention for children. The interventions were all found to be safe w/ no significant difference in adverse events between interventions and placebo.

Clinical Bottom Line: These data show that nonantibiotic prophylactic interventions are an effective option for managing patients with chronic UTIs. If you have a patient who presents to your clinic multiple times a year, it is important to educate them about these prevention strategies. These strategies are typically easily accessible, will save patients pain over time, and contribute to antibiotic stewardship by reducing antibiotic use/resistance in the community.

Han, Z., Yi, X., Li, J., Liao, D., & Ai, J. (2025). Nonantibiotic prophylaxis for urinary tract infections: a network meta-analysis of randomized controlled trials. *Infection*, *53*(2), 535–546. https://doi.org/10.1007/s15010-024-02357-z

2) D-mannose vs other agents for recurrent urinary tract infection prevention in adult women: a systematic review and meta-analysis

Abstract

OBJECTIVE: We performed a systematic review and meta-analysis to determine whether D-mannose reduces urinary tract infection (UTI) recurrence (i.e. cumulative incidence) in adult women with recurrent UTI compared to other prevention agents. Secondary outcomes included side effects and compliance with D-mannose use.

DATA SOURCES: Ovid Medline 1946-, Embase 1947-, Scopus 1823-, Cochrane Library, Web of Science 1900-, and Clinicaltrials.gov were searched through 4/15/2020.

STUDY ELIGIBILITY CRITERIA: Systematic review inclusion: randomized controlled trials (RCTs), prospective cohorts, and retrospective cohorts written in English of women ≥18 years old with recurrent UTI in which D-mannose was utilized as an outpatient prevention regimen. Systematic review exclusion: lab or animal-based research, study protocols only, and conference abstracts. Meta-analysis inclusion: stated D-mannose dose, follow-up time ≥6 months, a comparison arm to D-mannose, and data available from women ≥18 years of age.

STUDY APPRAISAL AND SYNTHESIS METHODS: Two independent reviewers made abstract, full text, and data extraction decisions. Study methodologic quality was assessed using the Cochrane Risk of Bias tool. Relative risks (RRs), confidence intervals (CIs), and heterogeneity (I2) were computed.

RESULTS: Searches identified 776 unique citations. Eight publications met eligibility: 2 using D-mannose only; 6 using D-mannose combined with another treatment. Seven studies were prospective: 2 RCTs, 1 randomized cross-over trial, and 4 prospective cohort studies. One retrospective cohort study was included. Three studies met meta-analysis eligibility (1 RCT, randomized cross-over trial, prospective cohort). Pooled RR of UTI recurrence comparing D-mannose to placebo was 0.23 (95%CI: 0.14–0.37; I2=0%; D-mannose n=125, placebo n=123). Pooled RR of UTI recurrence comparing D-mannose to preventative antibiotics was 0.39 (95%CI: 0.12–1.25; I2=88%; D-mannose n=163, antibiotics n=163). Adverse side effects were reported in 2 studies assessing D-mannose only (one study (n=10) reported none; the other reported a low incidence (8/103 participants) of diarrhea). Two studies reported compliance, which was high.

CONCLUSIONS: D-mannose appears protective for recurrent UTI (versus placebo) with possibly similar effectiveness as antibiotics. Overall, D-mannose appears well tolerated with minimal side effects - only a small percentage experiencing diarrhea. Meta-analysis

interpretation must consider the small number of studies with varied study design and quality and the overall small sample size.

Keywords: D-mannose, Non-antibiotic, Nutraceutical, Prevention, Recurrent Urinary Tract Infection, Urinary Tract Infection, UTI

Study design/Level of Evidence: This meta-analysis and review include 2 RCTs, 1 randomized crossover trial, 4 prospective cohort studies, and 1 retrospective cohort study. Across these 8 studies, there were 979 total participants, a robust sample size. The meta-analysis of RCTs and prospective cohort studies represents level 1 evidence, whereas the other study included represents level 2 evidence.

Key points: Researchers found that D-mannose prevents the recurrence of UTI by binding to E.coli type 1 fimbriae, preventing bacterial adhesion to anatomical structures. The meta-analysis showed a RR of 0.23 compared to placebo, a 76% reduction in UTI recurrence. This result is similar to the findings of the 2025 Han study. D-mannose therapy had minimal side effects, and if they did occur, they were mild diarrhea. When compared to antibiotics, D-mannose had an RR of 0.39 with a CI of 0.12–1.25. This indicates uncertainty; D-mannose may be more effective, equally effective, or less effective than antibiotics for preventing UTI recurrence. Compliance to D-mannose therapy was high in the studies.

Clinical Bottom Line: These studies show that D-mannose is an effective nonantibiotic prophylactic therapy to prevent recurrent UTIs. D-mannose is safe, well-tolerated, and has significantly less side effects than prophylactic antibiotic therapy. When compared directly to antibiotic prophylaxis, the effectiveness of D-mannose is not as certain. D-mannose should be considered as a first-line therapy for non-antibiotic prophylaxis against recurrent UTI.

Lenger, S. M., Bradley, M. S., Thomas, D. A., Bertolet, M. H., Lowder, J. L., & Sutcliffe, S. (2020). D-mannose vs other agents for recurrent urinary tract infection prevention in adult women: a systematic review and meta-analysis. *American journal of obstetrics and gynecology*, *223*(2), 265.e1–265.e13. https://doi.org/10.1016/j.ajog.2020.05.048

3) Cranberries for preventing urinary tract infections

Abstract

Background: Cranberries contain proanthocyanidins (PACs), which inhibit the adherence of p-fimbriated *Escherichia coli* to the urothelial cells lining the bladder. Cranberry products have been used widely for several decades to prevent urinary tract infections (UTIs). This is the fifth update of a review first published in 1998 and updated in 2003, 2004, 2008, and 2012.

Objectives: To assess the effectiveness of cranberry products in preventing UTIs in susceptible populations.

Search methods: We searched the Cochrane Kidney and Transplant Specialised Register up to 13 March 2023 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Registry Platform (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria: All randomised controlled trials (RCTs) or quasi-RCTs of cranberry products compared with placebo, no specific treatment or other intervention (antibiotics, probiotics) for the prevention of UTIs were included.

Data collection and analysis: At least two authors independently assessed and extracted data. Information was collected on methods, participants, interventions and outcomes (incidence of symptomatic UTIs, positive culture results, side effects, adherence to therapy). Risk ratios (RR) with 95% confidence intervals (CI) were calculated where appropriate. Study quality was assessed using the Cochrane risk of bias assessment tool. Confidence in the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Main results: For this update, 26 new studies were added, bringing the total number of included studies to 50 (8857 randomised participants). The risk of bias for sequence generation and allocation concealment was low for 29 and 28 studies, respectively. Thirty-six studies were at low risk of performance bias, and 23 studies were at low risk of detection bias. Twenty-seven, 41, and 17 studies were at low risk of attrition bias, reporting bias and other bias, respectively. Forty-five studies compared cranberry products with placebo, water or no specific treatment in six different groups of participants. Twenty-six of these 45 studies could be meta-analysed for the outcome of symptomatic, culture-verified UTIs. In moderate certainty evidence, cranberry products reduced the risk of UTIs (6211 participants: RR 0.70, 95% CI 0.58 to 0.84; I^2 = 69%). When studies were divided into groups according to the treatment indication, cranberry products probably reduced the risk of symptomatic, culture-verified UTIs in women with recurrent UTIs (8 studies, 1555 participants: RR 0.74, 95% CI 0.55 to 0.99; I^2 = 54%), in children (5 studies, 504 participants: RR 0.46, 95% CI 0.32 to 0.68; I^2 = 21%) and in people with a susceptibility to UTIs due to an intervention (6 studies, 1434 participants: RR 0.47, 95% CI 0.37 to 0.61; I^2 = 0%). However, there may be little or no benefit in

elderly institutionalised men and women (3 studies, 1489 participants: RR 0.93, 95% CI 0.67 to 1.30; I^2 = 9%; moderate certainty evidence), pregnant women (3 studies, 765 participants: RR 1.06, 95% CI 0.75 to 1.50; I^2 = 3%; moderate certainty evidence), or adults with neuromuscular bladder dysfunction with incomplete bladder emptying (3 studies, 464 participants: RR 0.97, 95% CI 0.78 to 1.19; I^2 = 0%; low certainty evidence). Other comparisons were cranberry products with probiotics (three studies) or antibiotics (six studies), cranberry tablets with cranberry liquid (one study), and different doses of PACs (two studies). Compared to antibiotics, cranberry products may make little or no difference to the risk of symptomatic, culture-verified UTIs (2 studies, 385 participants: RR 1.03, 95% CI 0.80 to 1.33; I^2 = 0%) or the risk of clinical symptoms without culture (2 studies, 336 participants: RR 1.30, 95% CI 0.79 to 2.14; I^2 = 68%). Compared to probiotics, cranberry products may reduce the risk of symptomatic, culture-verified UTIs (3 studies, 215 participants: RR 0.39, 95% CI 0.27 to 0.56; I = 0%). It is unclear whether efficacy differs between cranberry juice and tablets or between different doses of PACs, as the certainty of the evidence was very low. The number of participants with gastrointestinal side effects probably does not differ between those taking cranberry products and those receiving a placebo or no specific treatment (10 studies, 2166 participants: RR 1.33, 95% CI 1.00 to 1.77; I^2 = 0%; moderate certainty evidence). There was no clear relationship between compliance with therapy and the risk for repeat UTIs. No difference in the risk for UTIs could be demonstrated between low, moderate and high doses of PACs.

Authors' conclusions: This update adds a further 26 studies, taking the total number of studies to 50 with 8857 participants. These data support the use of cranberry products to reduce the risk of symptomatic, culture-verified UTIs in women with recurrent UTIs, in children, and in people susceptible to UTIs following interventions. The evidence currently available does not support its use in the elderly, patients with bladder emptying problems, or pregnant women.

Study design/Level of Evidence: These data represent a systematic review and meta-analysis of 50 RCTs w/ 8,857 participants. These studies include populations such as woman w/ recurrent UTIS, children, elderly adults, pregannt woman, and people w/ neuromuscular bladder dysfunction. Multiple different forms of cranberry products were included, such as juice, capsules, tablets, and powders. The outcome of interest was the number of participants with symptomatic culture-verified UTIs. While there was heterogeneity amongst the studies between formulations and doses used, bias was low across the major studies. This represents level 1 evidence.

Key points: Cranberries prevent UTI in a similar way to D-mannose; they contain compounds called proanthocyanidines (PACs) that prevent E.coli from adhering to the bladder wall. Of the populations studied, cranberry intervention was found to be most effective for woman w/ recurrent UTIs (RR 0.74) and children (RR 0.46). It was found that cranberry has little benefit in elderly institutionalized, pregnant women, or adults w/ neuromuscular bladder dysfunction. Cranberry is a very safe intervention w/ possible minor GI upset. The optimal dose of PAC was found to be between 36 and 72 mg/day.

Clinical Bottom Line: For woman w/ recurrent UTI, prophylaxis with cranberry is safe and effective. The PAC content of a cranberry product will determine its effectiveness, with an optimal dosage between 36-72 mg/day. Some evidence shows that effectiveness wanes over time, so doses should be split into morning and evening doses.

Williams, G., Stothart, C. I., Hahn, D., Stephens, J. H., Craig, J. C., & Hodson, E. M. (2023). Cranberries for preventing urinary tract infections. *The Cochrane database of systematic reviews*, *11*(11), CD001321. https://doi.org/10.1002/14651858.CD001321.pub7

Overall bottom line: Non-antibiotic prophylactic therapies have shown effectiveness at preventing recurrent UTIs compared to placebo. Non-antibiotic prophylaxis is typically less effective than antibiotic prophylaxis but carries significantly less risk for side effects and antibiotic resistance. It is important for clinicians working in ambulatory care or family medicine to educate patients with recurrent UTIs on different prophylactic options. D-mannose is the most effective monotherapy (RR 0.34), whereas the most effective therapy overall is triple therapy with cranberry products, probiotics, and vitamin A (RR 0.27). To expand beyond the scope of this PICO question, it is important to identify the population when selecting a prophylactic strategy. In children, probiotics appear most effective. For post-menopausal women, vaginal estrogen appears most effective.