HHS Public Access

Author manuscript

JAMA Intern Med. Author manuscript; available in PMC 2024 August 20.

Published in final edited form as:

JAMA Intern Med. 2024 June 01; 184(6): 629–630. doi:10.1001/jamainternmed.2024.0261.

Antibiotic-sparing prevention of urinary tract infections: new evidence regarding D-mannose

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Approximately half of women experience a urinary tract infection (UTI) in their lifetime, and at least one in four women experiencing an initial episode of UTI go on to have a recurrent infection.[1] While antibiotics are the mainstay of treatment for isolated episodes of cystitis as well as suppression of recurrent episodes, much effort has been directed at identifying potential antibiotic-sparing strategies to prevent recurrent UTI, due to concern about the rise of antimicrobial resistant organisms and adverse effects associated with antibiotics.[1] Although guidelines from professional societies encourage the use of vaginal estrogen to decrease UTI recurrence in postmenopausal women, they include conflicting recommendations about other strategies for suppressing recurrent UTI, including over-the-counter supplements.[2] In particular, there is debate about the value of D-mannose, a monosaccharide compound that is hypothesized to inhibit bacterial adherence to uroepithelial cells, for preventing recurrent UTI episodes.[2]

In this issue of *JAMA Internal Medicine*, Hawyard et al[3] present the results of a randomized, double-blinded, pragmatic, primary care practice-based trial evaluating the effectiveness of oral D-mannose supplementation for recurrent symptomatic UTI in women aged 18 and over in the United Kingdom. Among the 303 women assigned to D-mannose and 295 to a fructose-based placebo, supplementation with 2 grams of D-mannose per day was not effective in reducing the primary outcome of clinically suspected recurrent UTI over 6 months. Over half of participants in both groups had a suspected recurrent UTI, including 51% assigned to D-mannose and 56% assigned to placebo (risk difference −0.05 [95% CI: −0.13 to 0.03]; P=0.26). Further, D-mannose supplementation was not superior to placebo in improving other important secondary outcomes, including the number of days of at least moderate symptoms of UTI, time to next consultation for a clinically suspected UTI, number of microbiologically proven UTIs, number of prescribed antibiotic courses for suspected UTI, or hospitalizations or serious adverse events. Overall, the trial provides compelling evidence to contest the use of D-mannose as a prevention strategy for recurrent UTI.

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In contrast to prior studies of D-mannose suggesting potential efficacy for UTI prevention, this trial benefits from a double-blinded design, recruitment of a robust sample of adult women across a wide age range, and follow-up of more than 95% of participants for the primary outcome. Study generalizability was also increased by direct recruitment of patients from over 90 general practices in England and Wales.

However, one potentially important limitation is the trial's primary outcome of clinically suspected UTI, defined as repeat clinician consultation for a possible UTI without a requirement for laboratory-based confirmation of infection. The study did not assess whether patients' consultations for possible recurrent UTI were driven by classic UTI symptoms (acute dysuria, etc.)—as opposed to the wide variety of symptoms, complaints, or suspicions for recurrent UTI that commonly arise in general practice (e.g., fatigue, non-specific pelvic discomfort, increased urinary frequency, change in urine odor, etc.). Further, many patients with clinically suspected recurrent UTI did not undergo urine culture, and only a third of suspected cases represented microbiologically confirmed UTIs.

Many of these suspected UTI episodes may not have represented true UTI, given that patients with a history of previous UTI are sometimes inclined to suspect recurrence on the basis of vague or non-specific symptoms that do not have significant clinical predictive value for acute infection.[4] The preventive benefit of D-mannose for recurrent UTI may have been obscured by a high rate of overlapping clinical inquiries by participants about symptoms that did not result from a bacterial organism and therefore would not be expected to respond to D-mannose therapy. And given that urine culture was not systematically performed, the trial cannot directly confirm or refute the hypothesis that D-mannose is effective in reducing rates of symptomatic UTI based on the gold standard definition of presence of both classic UTI symptoms and laboratory confirmed presence of a known uropathogen.

This is not the first practice-based trial of an antibiotic-sparing preventive strategy for recurrent UTI to rely on a pragmatic definition of recurrent UTI without microbiological confirmation, however.[5] Although the American Urological Association recommends that clinicians obtain urine cultures to confirm a recurrent UTI prior to initiating treatment,[1] multiple professional societies do not encourage routine urine testing for women presenting with typical UTI symptoms suggesting a recurrent episode.[2] To some extent, the ambiguity in the trial's primary outcome is merely a reflection of the uncertainty about the optimal approach to diagnosing and initiating treatment for recurrent UTI in the broader medical community. In routine practice, clinicians vary widely in their reliance on clinical tests to confirm episodes of recurrent UTI, many patients are presumptively treated for recurrent UTI who do not meet conventional diagnostic criteria,[6] and antibiotic overtreatment for both non-specific symptoms and for asymptomatic bacteriuria is common. In contrast to routine care, women with pre-existing chronic bladder syndromes were excluded from the Hayward et al. trial, decreasing the likelihood that participants were inappropriately suspected of having a recurrent UTI due to a mild or temporary flare in their chronic bladder symptoms.

Even if some of the suspected UTI cases were not true episodes of infection, these study findings have value, as they indicate that widespread D-mannose therapy is unlikely to decrease the incidence of patient consultations and clinician visits for suspected recurrent

UTI. With over $3.5 billion per year estimated expenditure on UTI care in the U.S. alone,[7] this is an important question from a healthcare system perspective, even though it may be of less interest to patients and clinicians than the question of whether D-mannose is clinically effective in suppressing microbiologically confirmed infection. However, the trial's negative findings raise an interesting question: even if D-mannose were highly efficacious in preventing UTI recurrence, how much of an impact could it realistically have on either antibiotic overuse or health system burden for UTIs, so long as other aspects of recurrent UTI diagnosis and management remain so problematic? What is the greater driver of antibiotic overtreatment for recurrent UTI in real-world settings—the lack of evidence-based antibiotic-sparing UTI prevention strategies, or the confusion about when and how clinicians should diagnose and initiate treatment if they suspect recurrent UTI?

One other challenge inherent to this type of pragmatic trial is the difficulty controlling or accurately monitoring participants' use of other over-the-counter therapies that are widely used for UTI symptoms despite inconsistent or limited evidence, including cranberry products, methenamine, and probiotics. Over a third of participants in both trial arms acknowledged using cranberry juice to manage their symptoms, for example, and it is possible that the effectiveness of D-mannose for preventing UTI recurrence might have appeared more robust if participants in both groups had refrained from using any other antibiotic-sparing interventions. However, patients trying one type of over-the-counter preventive strategy are likely to be interested in others; as a result, study findings may accurately reflect the expected effects of D-mannose supplementation in routine practice.

Given the lack of existing rigorous trials evaluating D-mannose, this pragmatic, double-blinded, randomized trial involving a robust primary care-based sample of patients provides compelling new data to challenge recommendations to use D-mannose to prevent recurrent UTI. Findings highlight the need for continued investigation into optimal diagnostic and antibiotic-sparing treatment approaches for one of the most common and challenging outpatient infectious disease syndromes.

Acknowledgments

Dr. Eva Raphael was supported by National Institutes of Health (NIH) grant K23AI166030, and Dr. Alison Huang was supported by NIH grant K24AG068601. The views expressed do not represent those of the NIH, however, and the NIH had no role in the preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication. The authors report no conflicts of interest with regard to this manuscript.

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