

Back to the Future: Methenamine and D-Mannose in Recurrent Urinary Tract Infections (rUTIs)

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Conflict of Interest Disclosure

- I and my mentors, Dr. Larry Danziger and Dr. Chris Schriever, have no conflicts of interest with ineligible companies to disclose



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Objectives

- Describe the epidemiology, definitions, and risk factors associated with recurrent urinary tract infections (rUTIs).
- Explain the mechanism of action and the clinical trial evidence of methenamine hippurate and D-Mannose for the prevention of rUTIs.
- List patient specific factors to select appropriate antimicrobial sparing prophylactic strategies for rUTIs.



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Acknowledgments

- Thanks to Dr. Geoffery Tsaras, MD for his constant support regarding this project and our upcoming research



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How many of you in this room have heard of methenamine hippurate or have seen it used in your practice?



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Q1 Pre-Test: Which of the following best describes the mechanism of methenamine hippurate in preventing recurrent urinary tract infections?

- A. Competitive inhibition of bacterial dihydrofolate reductase, leading to impaired thymidine synthesis in uropathogens
- B. Conversion to formaldehyde in acidic urine, resulting in nonspecific denaturation of bacterial proteins and nucleic acids
- C. Inhibition of bacterial cell wall synthesis by binding to penicillin-binding proteins in Gram-negative organisms
- D. Disruption of bacterial cell membrane integrity through concentration-dependent pore formation



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Q2 Pre-Test: Which of the following best explains why d-mannose may help prevent recurrent *E.coli* urinary tract infections?

- A. It acidifies the urine, enhancing bacterial killing
- B. It inhibits bacterial DNA gyrase, preventing replication
- C. It competitively binds bacterial FimH adhesins, reducing urothelial adherence
- D. It disrupts bacterial cell wall by inhibiting peptidoglycan synthesis



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Q3 Pre-Test: Patient Case Review

- FW, a 72-year-old postmenopausal woman presents to the ID clinic for prevention of recurrent UTIs after experiencing four culture-confirmed symptomatic infections in the past year. Prior urine cultures grew *E.Coli* and *Klebsiella pneumoniae* with increasing resistance to TMP-SMX and fluoroquinolones.
- She previously discontinued nitrofurantoin prophylaxis due to concerns about long-term adverse effects. She has no known urinary tract abnormalities. Laboratory findings were significant for an eGFR of 48 ml/min/1.73 m², and a urine pH of 5.2.
- PMH: Recurrent urinary tract infections, HTN, osteoarthritis

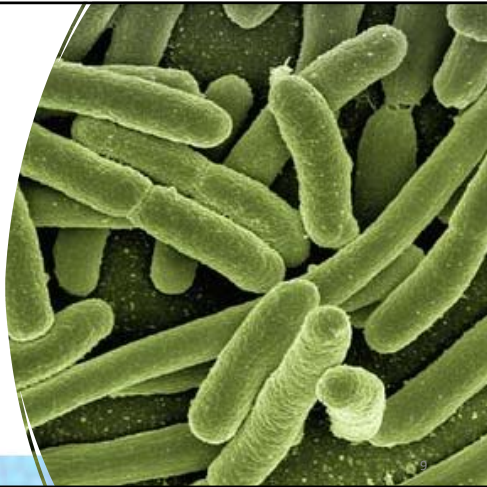


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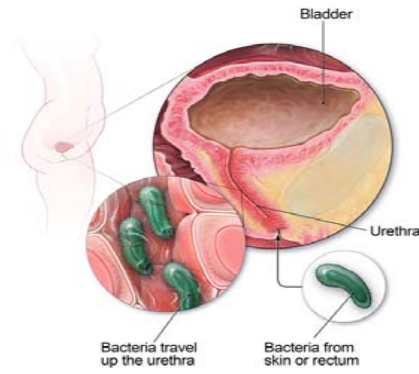
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The Infection



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3. Centers for Disease Control and Prevention. Urinary Tract Infection Basics. Updated January 22, 2024.



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Recurrent Urinary Tract Infections (rUTIs)

Definition:

- ≥ 2 episodes of symptomatic UTI in 6 months OR
- ≥ 3 episodes of symptomatic UTI in 12 months
- **Don't forget for these definitions to be met and a diagnosis to be made, this all requires symptomatic episodes (dysuria, suprapubic pain, fever, urgency, or incontinence)!!!**
- Relapse: same organism ≤ 14 days
- Reinfection: same/different organism > 14 days



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4. Ackerman AL. Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline (2025).

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Risk Factors

- Bladder diverticula, especially those that do not drain well
- Functional defects (e.g., overactive bladder and urinary incontinence)
- Intraluminal lesions (e.g., bladder stones, neoplasms, indwelling catheters, stents)
- Narrowing or scarring of the urinary tubes
- Ureteroceles, urinary fistula, and urolithiasis
- Inadequate or incomplete treatment of the initial acute cystitis
- Sexually active women, even without other predisposing conditions
- Vesicoureteral reflux



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5. Aggarwal N, Leslie SW. Recurrent Urinary Tract Infections. In: StatPearls [Internet]. Updated January 20, 2025.

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EPIDEMIOLOGY

50-60% of women will experience symptomatic acute bacterial cystitis in their lifetime

11% of adult women experience UTI in a year

20% to 40% of women who have had one previous cystitis episode are likely to experience another

Escherichia coli (E.coli), most common organism (75%-95%)

7.3 million office visits/year in US-- \$2.5 billion/yr



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4. Ackerman AL. Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline (2025).
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8. Zuo SW. Contemp Clin Trials. 2025;153:107893. doi:10.1016/j.ccl.2025.107893.

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The Problem with Recurrent Urinary Tract Infections

- rUTI is a chronic, relapsing condition that drives repeated treatment cycles
- Standard prevention has often relied on repeated antimicrobials or antimicrobial prophylaxis, which can accelerate antimicrobial resistance among common uropathogens
- rUTI causes major quality-of-life burden (pain, activity restrictions, and broader QoL impacts), making prevention and not just treatment more clinically meaningful
- This creates a stewardship gap: we need effective, antimicrobial-sparing prophylaxis options that reduce recurrence while preserving future antimicrobial utility

9. Abbott LJ. Antibiotic management of urinary tract infections in the post-antibiotic era. Clin Microbiol Infect. 2023.

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What are current preventative strategies for recurrent UTIs?

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Preventative Strategies

- **Oral Options**
 - Nitrofurantoin at 50 to 100 mg before bed (HS) daily
 - SMX-TMP at 40/200 mg HS daily
 - Trimethoprim at 100 mg HS daily
 - Cephalexin at 125 mg or 250 mg HS daily
- **Intravesical**
 - Gentamicin 20 mg in 50 ml saline daily
- **Vaginal Estrogen**
- Daily oral antibiotics (usually QHS) for 3 months (If effective/no adverse effects, then extend 6-12 months)

22. Nitrofurantoin monohydrate/macrocrystals (Macrobid) FDA Package Insert. 23. Sulfamethoxazole and Trimethoprim (Bactrim) FDA Package Insert. 24. Orion RP, Harrell LJ, Koye KS. 2009-5320-1285-1286. doi:10.1128/AAC.01188-08 25. Trimethoprim Tablets Prescribing Information, FDA Package Insert. 26. Cephalexin (Keflex) Capsules, FDA Package Insert. 27. Gentamicin Injection, FDA Package Insert. Accessed January 29, 2024. 28. Vaginal estrogen. doi:10.1097/GYN.0b013e318101010e

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Drug	Pros	Cons

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My Interest

- 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 localized cystitis worldwide
- As a PGY1, I had the pleasure of rotating with infectious diseases MD, Dr. Geoffrey Tsaras
- In his clinics, he would utilize methenamine hippurate and D-Mannose as long-term prophylaxis options for his patients and anecdotally we saw good results

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Methenamine hippurate (Hiprex)

- Not an antimicrobial! This is a urinary antiseptic
- Discovered in 1859 and introduced in 1895 as a urinary antiseptic while officially receiving its FDA approval in 1967
- Dosage: 160 mg capsules, 4 capsules 4 times daily (HCl below 30)
- Mechanism of Action: Converts to formaldehyde in acidic urine, a bacteriostatic/cidal agent based on urine concentration and pH
- Targeted Mechanism: No (non-specific)
- Systemic Antimicrobial Effect: No (only in urine)
- Resistance Development: No established plasmid mediated resistance mechanisms
- Side effects: GI, hypersensitivity (rash), bladder/stomach cancer?

Keep in mind, Alexander Flemming discovered penicillin in 1928 (the very first antibiotic) so yes, methenamine is VERY old!

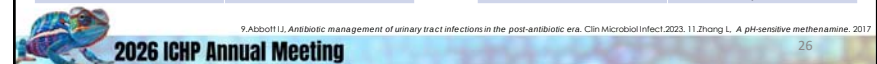
Methenamine Formaldehyde Ammonia



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What's an antiseptic again?

Feature	Methenamine	VS.	Feature	Antibiotic
Type of Agent	Chemical antiseptic		Type of Agent	Antimicrobial drug
Mechanism of Action	Converts to formaldehyde in acidic urine		Mechanism of Action	Binds specific bacterial targets (e.g., cell wall, ribosome)
Targeted Mechanism	No (non-specific)		Targeted Mechanism	Yes
Systemic Antimicrobial Effect	No (only in urine)		Systemic Antimicrobial Effect	Often yes
Resistance Development	No established plasmid mediated resistance mechanisms		Resistance Development	Common (enzymes, efflux pumps, target mutations)



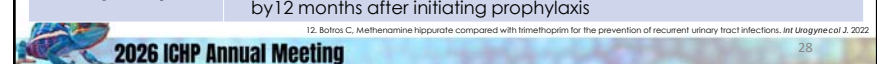
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Methenamine Hippurate Compared with Trimethoprim for the Prevention of Recurrent Urinary Tract Infections: A Randomized Clinical Trial



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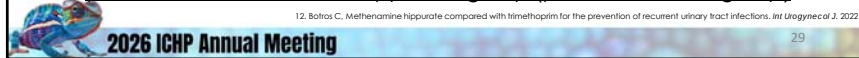
Study Design	Non-blinded randomized trial
Inclusion Criteria	• Women aged 18–99 years • Recurrent UTI, defined as: ≥2 UTIs in 6 months or ≥3 UTIs in 12 months • Culture-confirmed infection: ≥10,000 CFU/mL • Symptomatic episodes, including dysuria, suprapubic pain, fever, urgency, frequency, or incontinence • Same criteria applied to recurrences after prophylaxis
Exclusion Criteria	• Pregnant • Urinary tract abnormalities • Acute pyelonephritis • Renal insufficiency or failure • Known medication allergy
Primary Endpoint	• The primary outcome of this study was culture-proven UTI recurrence by 12 months after initiating prophylaxis



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Results

- No difference in UTI recurrence at 12 months between methenamine hippurate and trimethoprim
 - Intent-to-treat: **65.1% vs 65.1%** recurrence ($p = 1.00$)
 - Per-protocol: **65% vs 65.2%** recurrence ($p = 0.98$)
- Higher trimethoprim resistance observed among recurrent isolates in the antibiotic group:
Trimethoprim-resistant organisms: **79.5% vs 38%** (trimethoprim vs methenamine)
- Both medications significantly decreased the number of UTIs in the year subsequent to enrollment from:
4 to 1.5 UTI per year in the trimethoprim compared with 3.7 to 1.6 UTI per year in the methenamine hippurate group ($p < 0.01$ in either group)



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Strengths and Limitations

Strengths:

- Clinically relevant comparator (trimethoprim nightly)
- Long follow-up period (12 months)
- Strict, culture confirmed definition of UTI recurrence
- Antimicrobial resistance data collected

Limitations:

- Non-blinded study design
- Single-center study
- Predominantly older, postmenopausal population

Key takeaway: no difference in UTI recurrence at 12 months between methenamine hippurate and trimethoprim in both the per protocol and intention to treat groups



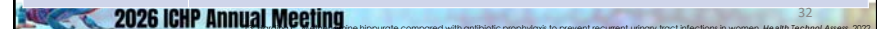
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Methenamine Hippurate Compared with Antibiotic Prophylaxis to Prevent Recurrent Urinary Tract Infections in Women: The ALTAR Non-Inferiority RCT



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Study Design	Multicentre, pragmatic, open-label, randomised, non-inferiority trial
Inclusion Criteria	• Women ≥ 18 years • Recurrent UTI, defined as: ≥ 3 symptomatic UTIs in 12 months, or ≥ 2 UTIs in 6 months, or ≥ 1 severe UTI requiring hospitalization • Eligible for prophylaxis and able to take: Nitrofurantoin, trimethoprim, or cephalexin and methenamine Hippurate • Prior prophylaxis allowed with a 3-month washout before enrollment
Exclusion Criteria	• Unable to take methenamine hippurate, including: allergy to methenamine, severe hepatic impairment (Child-Pugh C), gout, eGFR < 10 mL/min/1.73 m² • Unable to take any study antibiotics • Correctable urinary tract abnormalities contributing to rUTI • Active symptomatic UTI at enrollment (required treatment before randomization) • Pregnant, planning pregnancy, or breastfeeding
Primary Endpoint	• The primary clinical outcome was incidence of symptomatic antibiotic-treated urinary tract infection during the 12-month treatment period



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Results

- Methenamine hippurate was non-inferior to daily antibiotic prophylaxis for preventing recurrent UTIs over 12 months:
 - Difference: **0.49 UTIs/person-year (90% CI: 0.15-0.84)**, within the predefined non-inferiority margin of 1 UTI/year
- Both groups had substantial reductions in UTI frequency:
 - Methenamine: **1.38 UTIs/person per year**
 - Antibiotics: **0.89 UTIs/person-year**
- **Sustained benefit after stopping therapy:**
 - 6-month post-treatment incidence: **1.72 vs 1.19 UTIs/person-year** (methenamine vs antibiotics)
- Lower antimicrobial resistance during treatment in the methenamine group:
 - E. coli resistance on perineal swabs: **56% vs 72%** (methenamine vs antibiotics; $p = 0.05$)



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Strengths and Limitations

Strengths:

- Large, multicenter randomized controlled trial ($n = 240$) across 8 NHS sites
- Active comparator using guideline-recommended low-dose antibiotics
- Robust economic evaluation (quality of life outcomes)

Limitations:

- Progressive data loss over time
- Baseline UTI burden was high
- Reliance on patient reported outcomes
- Limited power for rare but serious adverse events

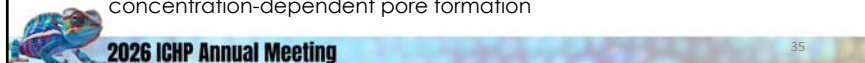
Key takeaway: Methenamine hippurate was non-inferior to daily antibiotic prophylaxis for preventing recurrent UTIs over 12 months



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Q1: Which of the following best describes the mechanism of methenamine Hippurate in preventing recurrent urinary tract infections?

- Competitive inhibition of bacterial dihydrofolate reductase, leading to impaired thymidine synthesis in uropathogens
- Conversion to formaldehyde in acidic urine, resulting in nonspecific denaturation of bacterial proteins and nucleic acids
- Inhibition of bacterial cell wall synthesis by binding to penicillin-binding proteins in Gram-negative organisms
- Disruption of bacterial cell membrane integrity through concentration-dependent pore formation



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What's D-Mannose?



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D-Mannose

- Naturally occurring simple sugar structurally similar to glucose and found in the human body as well as certain fruits (cranberries, apples) and vegetables (cabbage, broccoli)
- Dose: 1.5 - 2 g daily (available over the counter)
- Mechanism of Action: Primarily works to prevent UTIs by competitively inhibiting bacteria (like *E. coli*) from adhering to the urinary tract lining (urothelium)
 - Binds to the bacteria's **FimH adhesins**, which normally bind to mannose-containing receptors on host cells, effectively "coating" the bacteria and flushing them out in urine before they cause infection
- Side effects: Mainly GI (bloating, gas, diarrhea)

15. National Center for Biotechnology Information, PubChem 2026; 16. Scaglione, D-mannose Mechanism of Action, Front Pharmacol, 2021

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D-Mannose and rUTI: Timeline

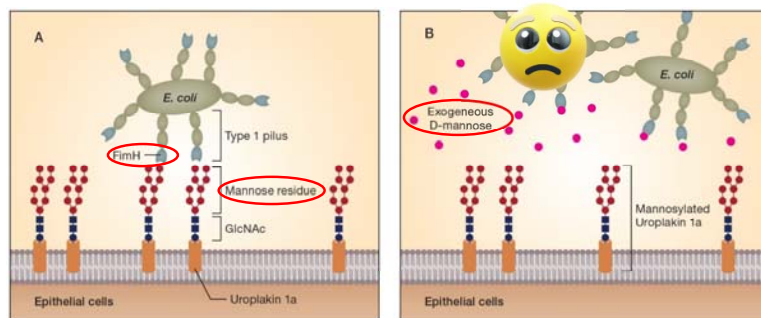
- 1888-1890**: Identified by Emil Fischer
- 1977-1980**: Initial studies established that mannose-sensitive adherence is a key mechanism for *E. coli* (specifically uropathogenic *E. coli*) to bind to epithelial cells, and that introducing D-mannose can block this interaction
- 1983-1984**: Research confirmed that D-mannose reduces *E. coli* bacteriuria in rats and inhibits the adherence of *E. coli* to human vaginal/epithelial cells
- Recent utilization has led to more clinical studies with one of the first being in 2014

29. Aronson M. urinary tract of mice with Escherichia coli. J Infect Dis. 1979 30; 32. Freudenberg K, Emil Fischer and his contribution to carbohydrate chemistry. Academic Press; 1967 33. Ofek I. Adherence of Escherichia coli to human mucosal cells mediated by mannose receptors. Nature. 1997.

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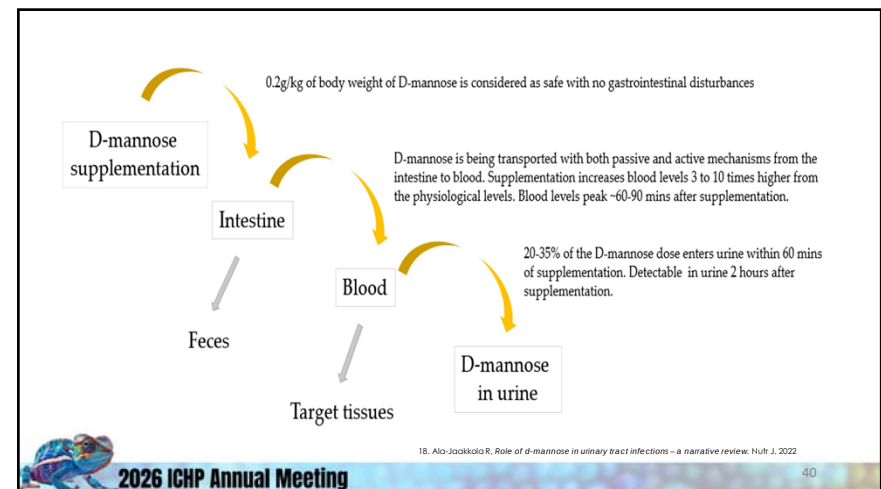


17. Wagerlechner, Why d-Mannose May Be as Efficient as Antibiotics in the Treatment of Acute Uncomplicated Lower Urinary Tract Infections. 2022

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18. Alo-Jockkolo R. Role of d-mannose in urinary tract infections – a narrative review. Nutr J. 2022

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D-Mannose Powder for Prophylaxis of Recurrent Urinary Tract Infections in Women: A Randomized Clinical Trial

19. Kranjčec B. D-mannose powder for prophylaxis of recurrent urinary tract infections in women. *World J Urol*. 2014

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Study Design	Prospective, randomized controlled study
Inclusion Criteria	• Women ≥ 18 years • History of recurrent cystitis, defined as: ≥ 2 episodes of acute cystitis in the past 6 months, and/or ≥ 3 episodes of acute cystitis in the past 12 months
Exclusion Criteria	• Pregnant, breastfeeding, or attempting to conceive • Symptoms of upper UTI: Fever $>38^\circ\text{C}$, WBC count $>12,000$ (systemic inflammatory response) • History of urinary tract anomalies • Interstitial cystitis • Diabetes • Current hormone therapy or hormonal contraception • Prior antibiotic prophylaxis
Primary Endpoint	The primary study endpoint was the number of patients in each group without recurrent UTI after 6 months

19. Kranjčec B. D-mannose powder for prophylaxis of recurrent urinary tract infections in women. *World J Urol*. 2014

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Results

- D-mannose significantly reduced recurrent UTIs compared with no prophylaxis over 6 months:
 - Recurrence: 14.6% (D-mannose) vs 60.8% (no prophylaxis) ($p < 0.001$)
- Efficacy similar to nitrofurantoin prophylaxis:
 - Recurrence: 14.6% (D-mannose) vs 20.4% (nitrofurantoin)
Difference not statistically significant
- Fewer adverse effects with D-mannose compared with nitrofurantoin:
 - Side effects were mild and did not require discontinuation

19. Kranjčec B. D-mannose powder for prophylaxis of recurrent urinary tract infections in women. *World J Urol*. 2014

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Strengths and Limitations

Strengths:

- Large sample size ($n=308$) with no dropouts
- Active antibiotic comparator (nitrofurantoin)
- Culture-confirmed UTIs with symptom criteria
- Demonstrated safety/tolerability of D-mannose over 6 months

Limitations:

- No re-entry after recurrence
- Highly selected population (excl. DM, hormonal therapy, prior prophylaxis)
- Initial ciprofloxacin treatment for all participants
- No antimicrobial resistance outcomes reported

Key takeaway: Efficacy similar to nitrofurantoin prophylaxis Recurrence: 14.6% (D-mannose) vs 20.4% (nitrofurantoin); difference not statistically significant

19. Kranjčec B. D-mannose powder for prophylaxis of recurrent urinary tract infections in women. *World J Urol*. 2014

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D-Mannose for Prevention of Recurrent Urinary Tract Infection in Adult Women: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials

20. Murali Krishna M. D-Mannose for prevention of recurrent urinary tract infection in adult women. J Infect Prev. Published online November 3, 2025.

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Study Design	Systematic review and meta-analysis
Inclusion Criteria	- Randomized controlled trials (RCTs) - Adult women with recurrent UTI - Compared D-mannose vs placebo or no treatment - Minimum follow-up of ≥ 90 days - Reported at least one clinical outcome of interest
Exclusion Criteria	- No control group - Overlapping study populations - Non-randomized study designs - Use of other active control groups
Primary Endpoint	The outcomes of interest were recurrent UTI during follow-up and adverse events

20. Murali Krishna M. D-Mannose for prevention of recurrent urinary tract infection in adult women. J Infect Prev. Published online November 3, 2025.

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Results

- No statistically significant reduction in recurrent UTIs with D-mannose compared with placebo or no treatment
 - Pooled RR 0.44 (95% CI 0.18–1.11), $p=0.082$
- No significant difference in adverse events between groups
 - RR 2.19 (95% CI 0.68–7.05), $p=0.190$
- High heterogeneity across studies
 - Recurrent UTI outcome: $I^2 = 90\%$
- Overall conclusion:
 - Evidence insufficient to confirm efficacy of D-mannose for rUTI prevention, though it appears well tolerated

20. Murali Krishna M. D-Mannose for prevention of recurrent urinary tract infection in adult women. J Infect Prev. Published online November 3, 2025.

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Strengths and limitations

Strengths:

- Only randomized controlled trials included
- Largest meta-analysis to date on D-mannose for rUTI (4 RCTs, 890 participants)
- Random effects modeling appropriately used given between study variability
- Adverse events systematically assessed

Limitations:

- Substantial heterogeneity in study design
- Only 4 RCTs included, restricting statistical power
- Three trials were not placebo-controlled, increasing risk of bias
- Variable follow-up durations (3–6 months) and dosing regimens
- No antimicrobial resistance outcomes

Key takeaway: The evidence insufficient to confirm efficacy of D-mannose for rUTI prevention, though it appears well tolerated

20. Murali Krishna M. D-Mannose for prevention of recurrent urinary tract infection in adult women. J Infect Prev. Published online November 3, 2025.

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Q2: Which of the following best explains why d-mannose may help prevent recurrent *E.coli* urinary tract infections?

- A. It acidifies the urine, enhancing bacterial killing
- B. It inhibits bacterial DNA gyrase, preventing replication
- C. It competitively binds bacterial FimH adhesins, reducing urothelial adherence
- D. It disrupts bacterial cell wall by inhibiting peptidoglycan synthesis



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Let's bring it all together^{12,13,19,20}

Key Studies	Main Takeaway
Methenamine compared with Trimethoprim (2022)	- No difference in UTI recurrence at 12 months in both the intention to treat and per-protocol groups - Higher trimethoprim resistance (79.5% vs 38% for methenamine)
Methenamine compared with antibiotic prophylaxis (ALTAR trial, 2022)	- Methenamine hippurate was non-inferior to daily antibiotic prophylaxis for preventing recurrent UTIs over 12 months <i>E. coli</i> resistance on perineal swabs: 56% vs 72% (methenamine vs antibiotics)
D-Mannose powder for prophylaxis in rUTIs (2014)	- Efficacy similar to nitrofurantoin prophylaxis: recurrence: 14.6% (D-mannose) vs 20.4% (nitrofurantoin); difference not statistically significant - Fewer adverse effects with D-Mannose compared to Nitrofurantoin
D-Mannose systematic review and meta-analysis of randomized control trials	- Overall conclusion: Evidence insufficient to confirm efficacy of D-mannose for rUTI prevention, though it appears well tolerated - Substantial heterogeneity in study design

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Drug	Pros	Cons
Nitrofurantoin	- Effective against common uropathogens (<i>E. coli</i>) - Low impact on gut flora compared with other antibiotics	- Long-term pulmonary, hepatic, and neuropathy risks - Reduced efficacy with impaired renal function - Resistance with prolonged use
SMX-TMP	- Historically effective for rUTI prevention - Convenient once daily dosing - Low cost	- High resistance rates in many regions - Hypersensitivity, cytopenias, hyperkalemia - Significant drug-drug interactions (Warfarin, ACEI, ARB)
Trimethoprim	Narrower spectrum than SMX-TMP	- Resistance patterns mirror SMX-TMP - Hyperkalemia risk
Cephalexin	- Generally well tolerated - Option for sulfa allergy	- Broader microbiome disruption - Increased <i>C. difficile</i> risk - Promotes beta-lactam resistance
Intravesical Gentamicin	- Effective against MDR organisms - Minimal systemic absorption	- Requires catheterization - Adherence and access challenges
Vaginal Estrogen	- Restores vaginal flora and lowers pH - Non-antibiotic strategy	- Delayed onset of benefit - Local irritation possible

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Has there been any data on the combination of these two agents?



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A Retrospective Evaluation Regarding Combination of Methenamine and D-Mannose Safety and Efficacy at an Academic Medical Center

- Single center research focusing on the combination of the two agents
- It will be the first study looking at the utilization of both agents together in rUTIs
- The primary objective of this study is to assess the proportion of participants experiencing at least one further episode of clinically suspected UTI requiring ambulatory care (including in-hours primary care, out-of-hours care, emergency department, or urgent care) within a 12-month period, while receiving methenamine hippurate plus D-mannose



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Q3: Patient Case Review

- FW A 72-year-old postmenopausal woman presents to the ID clinic for prevention of recurrent UTIs after experiencing four culture confirmed symptomatic infections in the past year. Prior urine cultures grew *E. Coli* and *Klebsiella pneumoniae* with increasing resistance to TMP-SMX and fluoroquinolones.
- She previously discontinued nitrofurantoin prophylaxis due to concerns about long-term adverse effects. She has no known urinary tract abnormalities. Laboratory findings were significant for an eGFR of 48 ml/min/1.73 m², and a urine pH of 5.2.
- PMH: recurrent. Urinary tract infections, Hypertension, Osteoarthritis

Given F.W.'s history and labs, which prophylactic strategy balances efficacy and safety for recurrent UTI prevention?

- Daily nitrofurantoin despite prior discontinuation
- Methenamine Hippurate, as a non antimicrobial prophylaxis
- Low-dose TMP-SMX continuous prophylaxis
- No prophylaxis, only symptomatic episodes should be treated



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Supplemental Resources

[Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline \(2025\)](#)



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Back to the Future: Methenamine and D-Mannose in Recurrent Urinary Tract Infections (rUTIs)

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