Breaking the cycle of recurrent urinary tract infections in women: a network meta-analysis of superior preventive measures

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Abstract

Recurrent urinary tract infections (rUTI) impose a substantial burden, particularly on vulnerable populations, such as women. The importance of effective prevention strategies is crucial in reducing the incidence of rUTI. While various preventive measures are available, there remains a gap in knowledge regarding their effectiveness and safety in clinical practice. This study aims to evaluate various interventions' performance in reducing the risk of rUTI and safety compared to placebo in healthy women. This network meta-analysis (NMA) was conducted according to the Systematic Reviews and Meta-Analyses Preferred Reporting Items for Systematic Reviews and Meta-Analyses NMA Checklist. A systematic search was performed in Scopus, PubMed, CENTRAL, EBSCO, Hindawi, and ProQuest up to June 14th, 2024. Studies that met our eligibility criteria are qualitatively assessed using the Cochrane Risk of Bias Tool 2. Data analysis was conducted using Rstudio v.4.3.1 with the DerSimonian-Laird random-effects model. The p-value was calculated to rank treatments. There were 6325 samples obtained from 40 journals. Fosfomycin-trometamol is the best intervention in preventing rUTI in women [p=0.9965; relative risk (RR)=0.09; 95% confidence interval (CI) 0.05-0.17]. Cranberry extract (p=0.62; RR=0.38; 95% CI 0.24-0.60) and nitrofurantoin (p=0.617; RR=0.38; 95% CI 0.27-0.53) have the most evidence with acceptable RR. Combinations of lactobacillus, cranberry, and D-mannose resulted in the lowest count of adverse effects (p=0.7623; RR=0.9; 95% CI 0.06-13.82). Cranberry extract and nitrofurantoin are highly effective in preventing rUTIs in women. Despite the promising performance of fosfomycin-trometamol, further research is needed to confirm its effectiveness. The composition of lactobacillus, cranberry, and D-mannose appears as the safest option to prevent rUTI.

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Introduction

Urinary tract infections (UTIs) are responsible for more than 404.61 million cases, 236,790 deaths, and 520,200 disability adjusted life years worldwide in 2019, with approximately 150 million cases being diagnosed annually.[1,2] This has caused a substantial burden, particularly in vulnerable populations. In terms of epidemiology, it is reported that women have a higher risk of developing UTIs, as 50-60% of them experience at least one episode of UTI throughout their lifetime.[3] Moreover, UTIs in women have a high recurrence rate of 25-35% within 3-6 months, particularly increasing during the first 2 months after treatment.[4] This matter certainly causes serious concern due to its detrimental impact on work productivity, family responsibilities, quality of life, as well as sexual well-being, leading to significant setbacks and sparking alarms about its far-reaching consequences in public health.[5]

Recurrent UTI (rUTI) is defined as the occurrence of two episodes of UTI in 6 months or three episodes in 12 months. The most frequent uropathogens involved are from *Enterobacteriaceae,* specifically *Escherichia coli* and *Klebsiella pneumonia.*[6] The currently available medication includes repeated courses of antibiotics, with higher doses and a more prolonged course of treatment as

infections recur. Although focusing on the causative pathogen is likely to eradicate bacteriuria, frequent and extended use of antibiotics may damage commensal bacteria, leading to gut and vaginal microbiota dysbiosis as well as bacterial resistance.[7] Additionally, the use of antibiotics is associated with various adverse effects, such as nausea, diarrhea, headache, candidiasis, and vaginal burning.[5] To date, there are numerous substances developed to treat UTIs as well as to prevent their recurrences, namely a combination of Lactobacillus strain, cranberry, and D-mannose, *E. coli* extract, D-mannose, cranberry, and acupuncture.[7,8] Nevertheless, direct comparisons between each treatment are nowhere to be found. Thus, this paper aims to provide a comprehensive review and meta-analysis regarding the effectiveness of various prevention strategies for rUTI as well as to propose future recommendations for their application in clinical use.

Materials and Methods

This network meta-analysis (NMA) was undertaken adhering to the guidelines outlined in the Systematic Reviews and Meta-Analyses NMA Checklist of Items and guided by the Cochrane Handbook for Systematic Reviews of Interventions.[9,10]

Search strategy

The literature search was carried out on six databases, namely Scopus, PubMed, CENTRAL, EBSCO, Hindawi, and ProQuest, up to June 14th, 2024. The literature search was carried out with keywords using Boolean operators as detailed in Table 1.

Study eligibility criteria

Prior to the literature search, criteria for inclusion and exclusion were established to ensure homogeneity in the selected studies. The inclusion criteria comprised studies meeting the following conditions: i) clinical trial studies using randomized controlled trial (RCT); ii) patients positively diagnosed with UTI; iii) peer-reviewed journals; iv) studies with any UTI intervention treatment; and v) studies including at least one parameter analyzed in this study, namely: frequency of rUTI and adverse event. Exclusion criteria included: i) irretrievable full-text articles; ii) incompatible language; iii) non-human clinical trials; and iv) incomplete outcome reporting. The authors individually assessed study eligibility, resolving any discrepancies through discussion.

Outcome measures

This research examines several prevention approaches for rUTI correction by assessing the outcomes of the frequency of rUTI and adverse events. The study focused on evaluating outcomes related to the rUTI prevention approach. This study assessed the indications for the rUTI preventive approach by measuring the relative risk (RR). Additionally, this study investigated the adverse events that occurred. These outcomes provided a comprehensive understanding of the best effectivity of each preventive method. All results are retrieved based on their availability in each included study. All authors independently extracted the outcomes from the included papers for quantitative analysis, with any disagreements resolved through discussion.

Quality assessment

Five authors (RM, SRR, YGPP, JAW, and MVA) independently conducted a methodological quality assessment to evaluate the risk of bias of each eligible study using the Cochrane Collaboration's Risk of Bias 2 (RoB 2) tool.[11] Disagreements of judgments were resolved by a group discussion. The RoB 2 is a revised tool consisting of five bias domains explicitly designed to

Table 1. Literature search terms for included studies.

Database	Keywords
Scopus	(((Recurrent Urinary Tract Infection) OR (Recurrent UTI)) AND (Prevention) AND ((Antibiotic) OR (D-mannose) OR (Cranberry) OR (Vaccine)) AND ((Randomized controlled trial) OR (RCT)))
PubMed	#1 "Urinary Tract" [MeSH Terms] #2 (("Urinary Tract"[Title/Abstract]) OR ("UTI"[Title/Abstract])) #3 #1 OR #2 #4 "Recurrent" [Title/Abstract] #5 #3 AND #4 #6 "Prevention"[Title/Abstract] #7 #5 AND #6 #8 ("Antibiotic"[Title/Abstract]) OR ("D-mannose"[Title/Abstract]) OR ("Cranberry"[Title/Abstract]) OR ("Vaccine"[Title/Abstract])) #9 #7 AND #8 #10 Humans[MeSH Terms] #11 #9 AND #10 #12 "random*" OR "RCT" OR "trial*" OR "randomized controlled trial*" OR "clinical trial"#13 #11 AND #12
EBSCO	(((Recurrent Urinary Tract Infection) OR (Recurrent UTI)) AND (Prevention) AND ((Antibiotic) OR (D-mannose) OR (Cranberry) OR (Vaccine)) AND ((Randomized controlled trial) OR (RCT)))
CENTRAL	(((Recurrent Urinary Tract Infection) OR (Recurrent UTI)) AND (Prevention) AND ((Antibiotic) OR (D-mannose) OR (Cranberry) OR (Vaccine)) AND ((Randomized controlled trial) OR (RCT)))
Hindawi	(((Recurrent Urinary Tract Infection) OR (Recurrent UTI)) AND (Prevention) AND ((Antibiotic) OR (D-mannose) OR (Cranberry) OR (Vaccine)) AND ((Randomized controlled trial) OR (RCT)))
ProQuest	#1 mesh.Exact("Urinary Tract") #2 noft("Urinary Tract" OR "UTI") #3 noft("Recurrent") #4 noft("Antibiotic" OR "D-mannose" OR "Cranberry" OR "Vaccine") #5 noft("clinical trial" OR "RCT") #6 (#1 OR #2) AND #3 AND #4 AND #5

UTI, urinary tract infection; RCT, randomized controlled trial.

consider the risk of bias of randomized trials arising from: i) the randomization process; ii) deviations from intended interventions; iii) missing outcome data; iv) the measurement of the outcome; and v) the selection of the reported result. The risk of bias on each domain was rated as low-risk, high-risk, or some concerns (unclear) for the algorithms that incorporated several domain-specific signaling questions. Judgment levels from all domains were later deduced as an overall risk of bias for each study. A study is considered low risk of bias if all domains show low risk. If at least one domain was rated as unclear, studies were judged as having some concerns. Studies were judged to be at high risk of bias if at least one domain presented a high risk or there were some concerns in multiple domains that could significantly lower the confidence in the study results. Subsequently, the data extracted from cohort studies were entered into the "bias" section of a Microsoft Excel 2021 spreadsheet. The spreadsheet was then uploaded to the ROBVIS website to visually present the assessment results using the traffic light system.[12]

Statistical analysis

The NMA was performed using both Frequentist methods, employing the netmeta package in Rstudio version 4.3.1. This research also utilizes pooled RR to report the incidence of rUTI based on the reported type in each study. All outcome measures were assessed with a 95% confidence interval (CI). The statistical method employed was the inverse variance model, and the choice between fixed or random effect models depended on the heterogeneity observed for each outcome. Heterogeneity was analyzed using I^2 statistics, with cut-off criteria of 0%, 25%, 50%, and 75% indicating insignificant, low, moderate, and high heterogeneity, respectively. The DerSimonian-Laird random-effects model was used to accommodate unavoidable heterogeneity, while differences between each study contained in the direct and indirect analysis evidence were assumed. Most of the results of the NMA are presented in the Frequentist method, including forest plot, net league table, and net-split forest plot. The pooled effect size and heterogeneity assessment results from each comparison are obtained from the pairwise forest plot. Furthermore, a higher p-value indicates rank treatments.

Results

Study characteristics

We conducted a systematic search, resulting in a total of 12,800 articles, which were retrieved from 7 databases. After screening based on the year and the type of article, also with the automation tools available on the databases, we screened 1662 articles. Among those studies, 1457 studies were excluded because they were irrelevant and were not non-clinical trials or RCT studies. Hence, 112 studies were unable to be retrieved, resulting in 93 studies left. 43 of those article candidates were reported as duplicates, whereas 13 other studies' data were not eligible for study (samples in UTI, not rUTI), and 8 were considered qualitative studies. A total of 29 studies were included in this study to be examined further. The flow diagram in Figure 1 provides detailed

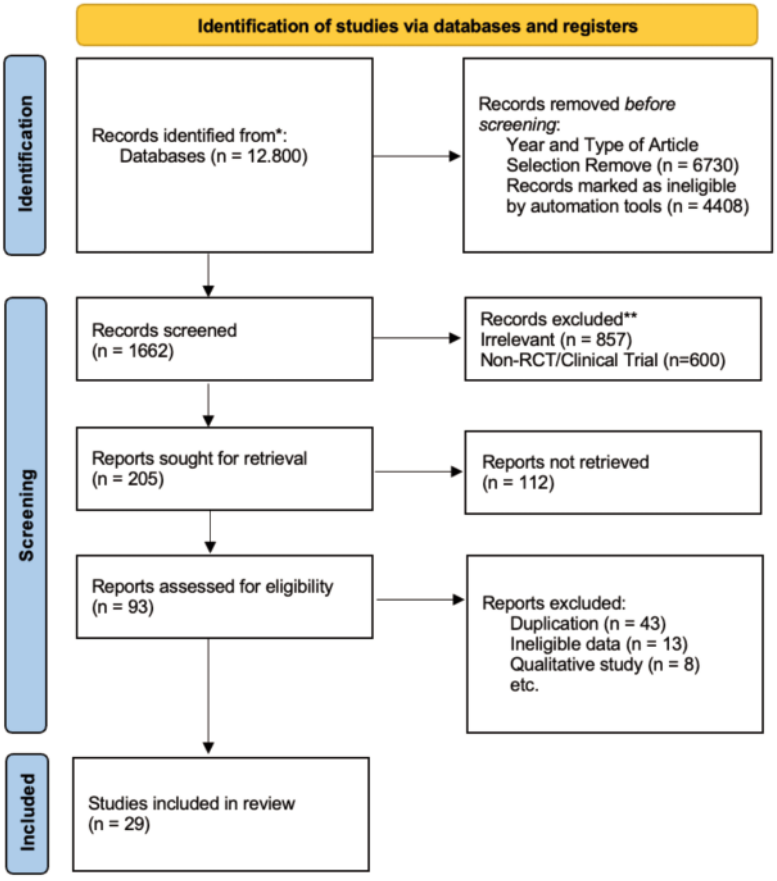

Figure 1. The study selection process is presented on a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart. RCT, randomized controlled trial.

information on the study selection process.

Risk of bias assessment

The quality of overall studies can be considered acceptable (Figure 2). According to the judgement, 6 studies were rated as high risk of bias; 9 studies were rated as some concern risk of bias; and 8 studies were low risk of bias.

Effectivity

A network plot illustrating all treatment comparisons is shown in Figure 3. Overall, there are 14 nodes, each corresponding to a different treatment. The most studied comparison was cranberry juice *vs.* placebo, examined in 4 studies. This was followed by comparisons involving vaccines, cranberry extract, and nitrofurantoin, each studied in three studies, all of which were compared to a placebo. Figure 4 presents all treatment comparisons, displaying each RR value and CI. Figure 5 summarizes the results, using placebo as the reference point for all treatment comparisons. These Figures indicate that Fosfomycin-trometamol was the most effective method for reducing the recurrence rate of UTIs with RR 0.09 (95% CI 0.05-0.17). All other interventions were also effective in reducing rUTI with statistical significance, except for the vaccine, cranberry juice, and a combination of lactobacillus, cranberry, and D-mannose. The vaccine, with or without a booster, was associated with an increased rate of rUTI (RR>1) but lacked statistical significance, as its CI crossed the line of no effect. Cranberry juice and the combination of lactobacillus, cranberry, and D-mannose were associated with a decreased rate of rUTI but were not statistically significant, RR 0.90 (95% CI 0.71-1.14) and 0.49 (95% CI 0.23-1.03), respectively. Notably, cranberry extract and nitrofurantoin were the most extensively studied interventions and demonstrated acceptable risk reduction with statistical significance, RR were 0.38 (95% CI 0.24-0.60) and 0.38 (95% CI 0.27-0.53), respectively.

Adverse effect

Figure 6 presents the network plot for the adverse effects outcome. Results for the findings shown in Figure 7 are presented as a net league table, and in Figure 3 as forest plots. All of the treatments could give an adverse effect; however, the adverse effects that we reported in this study were generalized.

In this NMA, 18 RCTs were included and evaluated for their number of adverse effects, as shown in Figure 3. The authors included treatments such as cranberry, vaccine, antibiotics, devices, and biopolymers. To ensure that the information used was relevant and minimally biased, we also include a placebo as our standard of care for UTI.

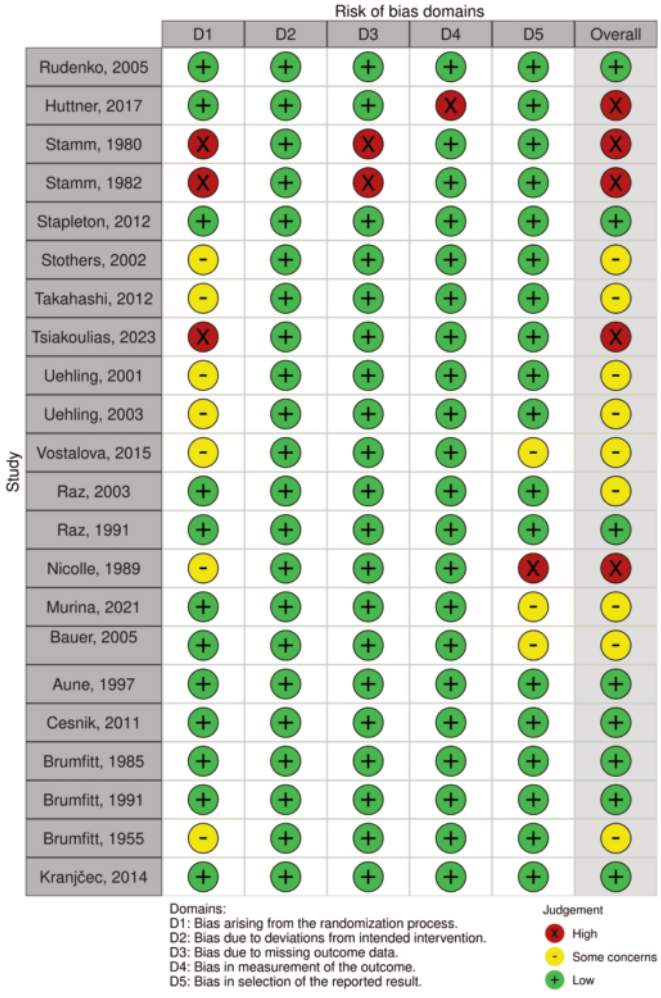

Figure 2. Risk of bias assessment.

Comparison of rUTI prophylaxis shows that all treatments had a chance to develop an adverse effect compared to placebo (no treatment), as shown in Figures 7 and 8. The estimate is located at the intersection of the column-defining treatment and the row-defining treatment. Data presented as RRs (95% CI). Significant results are in darker shades of colors (dark red or dark blue). In the upper triangle, comparison of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right *vs*. the medication on the top left in the diagonal; *e.g.*, RR 0.82 (95% CI 0.63-1.07) indicates a significant reduction in the incidence of adverse effects for the vaccine compared with placebo or no vaccination. In the bottom triangle, comparison of treatments should be read from left to right. An RR below 1 favors the medication on the top left *vs*. the medication on the bottom right in the diagonal; *e.g.*, RR 0.897 (95% CI 0.058-13.815) indicates a non-significant reduction in the incidence of lactoflorene cist (LP+C+DM) compared with the placebo/no treatment. Combinations of lactobacillus, cranberry, and D-mannose resulting in the lowest count of adverse effects have the most evidence [RR 0.9 (95% CI: 0.06-13.82)], with a significant risk ratio of 0.9. Therefore, they can decrease the adverse effect by 10% compared to being treated with a placebo. However, fosfomycin-trometamol

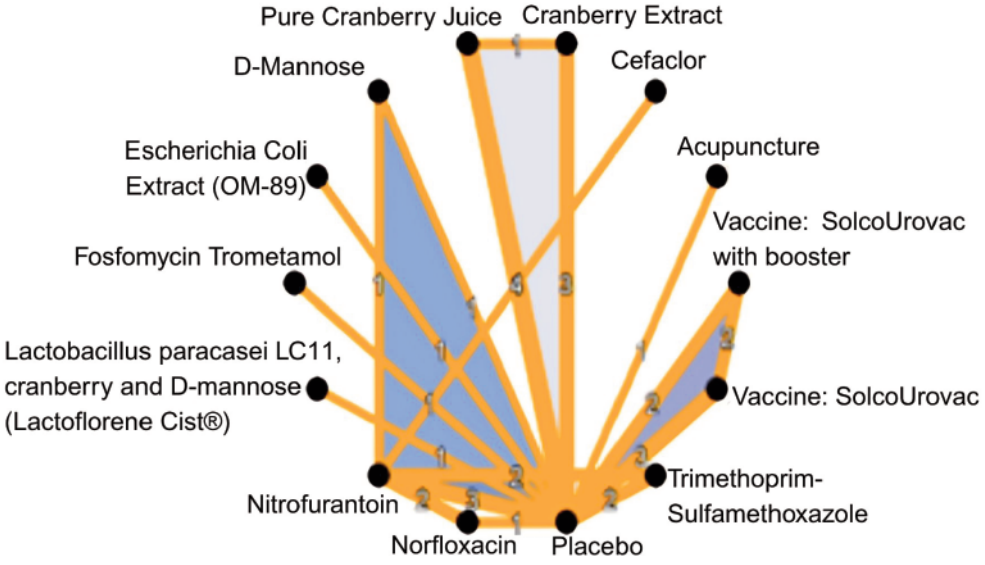

Figure 3. Network plot of evidence for urinary tract infection recurrence.

A	.	.	.	.	.	.	.	.	.	0.346 [0.154; 0.774]	.	.	.
1.081 [0.283; 4.129]	C	.	.	.	.	.	.	0.840 [0.304; 2.317]	.	.	.	.	.
0.901 [0.358; 2.269]	0.834 [0.261; 2.662]	CE	0.900 [0.400; 2.025]	.	.	.	.	.	.	0.355 [0.224; 0.562]	.	.	.
0.385 [0.166; 0.893]	0.356 [0.119; 1.067]	0.427 [0.261; 0.699]	CJ	.	.	.	.	.	.	0.918 [0.721; 1.169]	.	.	.
1.417 [0.551; 3.644]	1.311 [0.409; 4.197]	1.572 [0.807; 3.062]	3.680 [2.129; 6.364]	DM	.	.	.	0.714 [0.391; 1.306]	.	0.240 [0.146; 0.392]	.	.	.
0.446 [0.195; 1.020]	0.413 [0.139; 1.222]	0.495 [0.305; 0.804]	1.159 [0.858; 1.566]	0.315 [0.186; 0.532]	Ec	.	.	.	.	0.775 [0.646; 0.929]	.	.	.
3.724 [1.381; 10.043]	3.445 [1.021; 11.626]	4.132 [1.987; 8.594]	9.673 [5.174; 18.087]	2.628 [1.231; 5.613]	8.347 [4.556; 15.292]	FT	.	.	.	0.093 [0.052; 0.165]	.	.	.
0.708 [0.236; 2.130]	0.655 [0.177; 2.420]	0.786 [0.328; 1.883]	1.840 [0.838; 4.041]	0.500 [0.204; 1.225]	1.588 [0.734; 3.431]	0.190 [0.074; 0.490]	LP+C+DM	.	.	0.488 [0.231; 1.032]	.	.	.
0.908 [0.378; 2.177]	0.840 [0.304; 2.317]	1.007 [0.573; 1.769]	2.358 [1.556; 3.574]	0.641 [0.363; 1.132]	2.034 [1.385; 2.989]	0.244 [0.125; 0.476]	1.281 [0.563; 2.917]	N	1.475 [0.895; 2.431]	0.396 [0.281; 0.558]	0.883 [0.441; 1.767]	.	.
1.407 [0.518; 3.825]	1.302 [0.421; 4.022]	1.562 [0.743; 3.282]	3.656 [1.932; 6.919]	0.993 [0.470; 2.098]	3.154 [1.700; 5.852]	0.378 [0.165; 0.864]	1.987 [0.765; 5.159]	1.551 [0.948; 2.535]	No	0.056 [0.004; 0.852]	.	.	.
0.346 [0.154; 0.774]	0.320 [0.110; 0.933]	0.384 [0.245; 0.601]	0.898 [0.706; 1.142]	0.244 [0.149; 0.399]	0.775 [0.646; 0.929]	0.093 [0.052; 0.165]	0.488 [0.231; 1.032]	0.381 [0.271; 0.535]	0.246 [0.136; 0.444]	P	1.502 [0.852; 2.647]	0.868 [0.661; 1.141]	1.182 [0.672; 2.078]
0.603 [0.228; 1.596]	0.558 [0.172; 1.804]	0.669 [0.330; 1.357]	1.566 [0.863; 2.842]	0.425 [0.205; 0.881]	1.351 [0.761; 2.400]	0.162 [0.073; 0.358]	0.851 [0.337; 2.150]	0.664 [0.368; 1.198]	0.428 [0.200; 0.920]	1.744 [1.011; 3.009]	T+S	.	.
0.304 [0.130; 0.713]	0.281 [0.093; 0.849]	0.337 [0.199; 0.571]	0.790 [0.549; 1.137]	0.215 [0.122; 0.377]	0.682 [0.491; 0.946]	0.082 [0.043; 0.155]	0.429 [0.193; 0.953]	0.335 [0.217; 0.518]	0.216 [0.113; 0.414]	0.880 [0.670; 1.156]	0.504 [0.274; 0.928]	V	1.051 [0.583; 1.896]
0.315 [0.120; 0.825]	0.291 [0.088; 0.961]	0.349 [0.175; 0.699]	0.818 [0.458; 1.461]	0.222 [0.108; 0.457]	0.705 [0.404; 1.233]	0.085 [0.039; 0.185]	0.444 [0.178; 1.111]	0.347 [0.185; 0.650]	0.224 [0.101; 0.494]	0.911 [0.537; 1.544]	0.522 [0.244; 1.116]	1.035 [0.602; 1.778]	V+B

Figure 4. Net league table of head-to-head comparisons. A, acupuncture; C, cefaclor; CE, cranberry extract; CJ, pure cranberry juice; DM, *D-mannose; Ec, Escherichia coli extract (OM-89); FT, fosfomycin trometamol; LP+C+DM,* Lactobacillus paracasei LC11, cranberry and D-mannose (Lactoflorene Cist®); N, nitrofurantoin; No, norfloxacin; P, placebo; T+S, trimethoprim-sulfamethoxazole; V, vaccine: SolcoUrovac (Solco Basel); V+B, vaccine: SolcoUrovac with booster.

has the most adverse effects by having a risk ratio of 82808.98.

Discussion

Clinical experience

Based on our clinical experience, in our hospital, there is an antibiotic guideline in each in-hospital treatment room. The guideline itself was arranged based on the clinical evidence on each ward. Antibiotics that were used in the hospital were different in each room sometimes. This guideline was aimed at minimizing antibiotic resistance. In Indonesia, we usually would use cotrimoxazole (trimethoprim-sulfamethoxazole) to treat UTI; however, in this study, it is shown that this medicine was not as effective as the others, and also had the second most side effects after fosfomycin. The availability of fosfomycin itself was limited in our teaching hospital since it is used if the patient is unresponsive to the first-line antibiotics. Based on our hospital guideline, fosfomycin was categorized as category B, which means it is shown in studies within animals, and it does not show risk to the fetus; however, there are no controlled studies on pregnant women. Cotrimoxazole was used to treat *Staphylococcus saprophyticus* and Enterobacter strains. While the most strains found in our hospital were *E. Coli* (80%), usually treated with levofloxacin and cefepime for complicated UTI in severe cases inward patients. There are other antibiotics, such as ciprofloxacin (used to treat *Klebsiella* and *Pseudomonas*), and for treating severe inward UTI patients, we usually use gentamicin (*Klebsiella*), ampicillin (*Enterobacter*), and cefoperazone sulbactam (*Staphylococcus, Saprophyticus*, *Acinobacter baumannii*, and *Proteus mirabilis*).[13]

Our impression of the current UTIs was good; there is a very low number of rUTIs at our hospital, which is caused by both parties, the patient and the physicians. We, as the physicians, will give the patients antibiotics based on our hospital's antimicrobial guidelines. By that, the treatment will be personalized based on where the patients were treated (inward rooms and outward clinic). A thorough education by the physician is also important for the outpatient (discharged and polyclinic patient). The patient's compliance, together with the family support, plays a crucial role in treating this disease and preventing it from returning to the patient. However, there are also severe rUTI cases, since our teaching hospital is an A-grade facility, meaning that referred patients usually come to us for more comprehensive treatment.

We are very hopeful that there will be a new antibiotic that could treat severe cases of UTI (recurrent, resistant, *etc*.) and a more specific spectrum of antibiotics to treat specific bacterial strains in patients. A campaign of antibiotic usage was needly to do since in our cases, patients tend to buy antibiotics by themselves from some unlicensed pharmacies. Cost-effective antibiotics were also expected to maximize the treatment on every layer of the community.

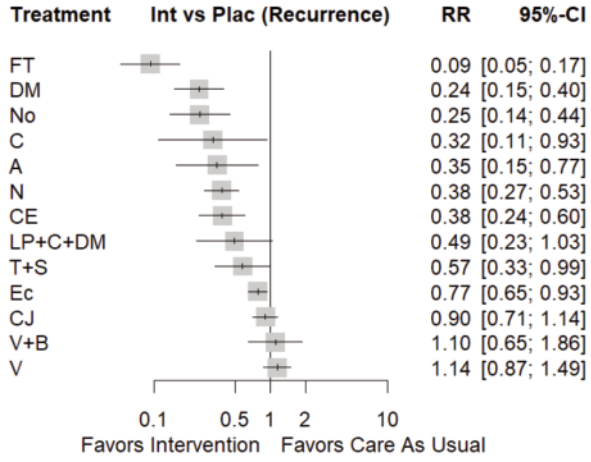

Figure 5. Forest plots for effectiveness in reducing recurrence, comparing each prophylaxis with placebo. RR, relative risk; CI, confidence interval; FT, fosfomycin trometamol; DM, D-mannose; No, norfloxacin; C, cefaclor; A, acupuncture; N, nitrofurantoin; CE, cranberry extract; LP+C+DM, *Lactobacillus paracasei* LC11, cranberry and D-mannose (Lactoflorene Cist®); T+S, trimethoprim-sulfamethoxazole; Ec, *Escherichia coli* extract (OM-89); CJ, pure cranberry juice; V+B, vaccine: SolcoUrovac with booster; V, vaccine: SolcoUrovac (Solco Basel).

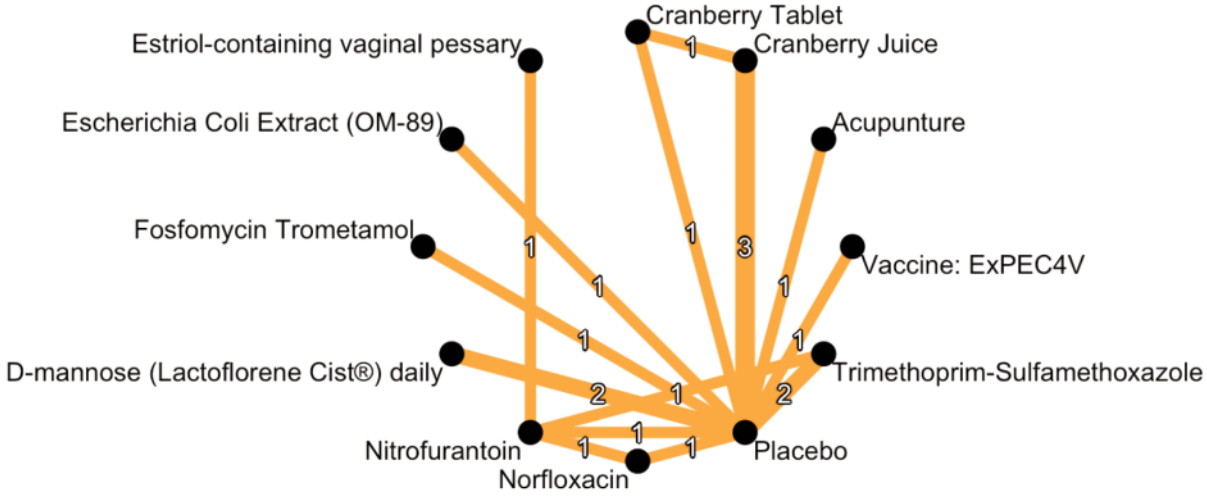

Figure 6. Network plot of evidence for adverse effect.

A	.	.	.	.	.	.	.	.	1.101 [0.466 to 2.600]	.	.
0.742 [0.257 to 2.142]	CJ	0.600 [0.151 to 2.377]	.	.	.	.	.	.	1.617 [0.836 to 3.126]	.	.
0.646 [0.177 to 2.36]	0.871 [0.324 to 2.339]	CT	.	.	.	.	.	.	1.250 [0.356 to 4.385]	.	.
0.506 [0.092 to 2.8]	0.683 [0.137 to 3.395]	0.784 [0.134 to 4.593]	E	.	.	.	0.988 [0.502 to 1.946]	.	.	.	.
1.084 [0.441 to 2.667]	1.462 [0.743 to 2.876]	1.678 [0.614 to 4.588]	2.141 [0.477 to 9.616]	Ec	.	.	.	.	1.015 [0.777 to 1.326]	.	.
0.000 [0.000 to 0.000]	0.000 [0.000 to 0.000]	0.000 [0.000 to 0.000]	0.000 [0.000 to 0.001]	0.000 [0.000 to 0.000]	FT	.	.	.	82808.984 [5227 to 1311828]	.	.
1.226 [0.070 to 21.541]	1.654 [0.100 to 27.298]	1.899 [0.104 to 34.532]	2.422 [0.108 to 54.191]	1.131 [0.073 to 17.642]	92272.868 [1892.687 to 4498514.605]	LP+C+DM	.	.	0.897 [0.058 to 13.815]	.	.
0.500 [0.104 to 2.406]	0.675 [0.158 to 2.888]	0.775 [0.151 to 3.966]	0.988 [0.502 to 1.946]	0.462 [0.121 to 1.765]	37659.339 [1767.213 to 802521.109]	0.408 [0.020 to 8.475]	N	1.024 [0.401 to 2.613]	5.000 [0.261 to 95.876]	1.67 [0.25 to 11.12]	.
0.644 [0.146 to 2.84]	0.869 [0.223 to 3.383]	0.998 [0.212 to 4.698]	1.273 [0.420 to 3.855]	0.594 [0.172 to 2.050]	48492.264 [2377.328 to 989135.664]	0.526 [0.026 to 10.442]	1.288 [0.536 to 3.096]	No	1.000 [0.239 to 4.184]	.	.
1.101 [0.466 to 2.6]	1.484 [0.797 to 2.763]	1.704 [0.646 to 4.492]	2.173 [0.496 to 9.531]	1.015 [0.777 to 1.326]	82808.984 [5227.307 to 1311827.990]	0.897 [0.058 to 13.815]	2.199 [0.591 to 8.181]	1.708 [0.510 to 5.718]	P	0.195 [0.023 to 1.64]	0.82 [0.63 to 1.07]
0.457 [0.075 to 2.798]	0.616 [0.111 to 3.414]	0.708 [0.109 to 4.575]	0.903 [0.169 to 4.818]	0.422 [0.084 to 2.125]	34390.560 [1415.856 to 835332.451]	0.373 [0.016 to 8.831]	0.913 [0.197 to 4.224]	0.709 [0.139 to 3.620]	0.415 [0.084 to 2.047]	T+S	.
0.904 [0.368 to 2.221]	1.219 [0.621 to 2.394]	1.400 [0.513 to 3.821]	1.786 [0.398 to 8.013]	0.834 [0.574 to 1.213]	68037.231 [4241.975 to 1091252.210]	0.737 [0.047 to 11.494]	1.807 [0.473 to 6.898]	1.403 [0.407 to 4.832]	0.822 [0.632 to 1.068]	1.98 [0.39 to 9.96]	V

Figure 7. Net league table of head-to-head comparisons. A, acupuncture; CJ, cranberry juice; CT, cranberry tablet; E, estriol-containing vaginal pessary; Ec, *Escherichia coli* extract (OM-89); FT, fosfomycin trometamol; LP+C+DM, D-mannose (Lactoflorene Cist) daily; N, nitrofurantoin; No, norfloxacin; P, placebo; T+S, trimethoprim-sulfamethoxazole; V, vaccine.

Effectivity

Fosfomycin-trometamol exhibits superior efficacy compared to other interventions. The mechanism of action of fosfomycin involves the inhibition of the enzyme pyruvyl transferase, which plays a critical role in the synthesis of peptidoglycan in bacterial cell walls. This inhibition disrupts the integrity of the bacterial cell wall, leading to lysis and cell death. Fosfomycin-trometamol is highly effective in the majority of uncomplicated UTIs caused by *E. coli*. Furthermore, fosfomycin has a low-resistance rate, with a global resistance ratio of approximately 1%. At high concentrations, fosfomycin-trometamol demonstrates the ability to eradicate bacteria before they have the opportunity to mutate, highlighting their important role in preventing UTI recurrence.[14-16] Cranberry juice intervention has been shown to reduce the likelihood of rUTI, although the reduction is not statistically significant. The proanthocyanidins present in cranberry juice inhibit the adhesion of uropathogens, such as *E. coli*, thereby preventing the recurrence of UTIs. However, Obi *et al.* (2021) reported that cranberry juice effectively reduced the incidence of rUTIs by 50% to 80% in female samples.[17] Similarly, Takahashi *et al.* (2013) demonstrated that cranberry juice could prevent the recurrence of UTIs in women over a 24-week period.[18] Nevertheless, when compared to antibiotics, cranberry juice is less effective.[19] Therefore, cranberry juice may serve as an adjunctive therapy alongside antibiotics for rUTIs, provided that its concentration and formulation are appropriately considered. Vaccine and booster vaccine interventions did not demonstrate significant effectiveness in reducing the incidence of rUTIs. In this study, most vaccines utilized the vaginal mucosal vaccination method.[20,21] However, Hopkins *et al.* (2007) reported that vaginal mucosal vaccines were significantly effective in reducing rUTIs by enhancing immunity.[22] Therefore, further studies with larger sample sizes are needed to evaluate the effectiveness of vaccines and booster vaccines in rUTIs.

Adverse effects

In this study, a placebo was found to be an intervention that did not cause adverse effects. This is because a placebo does not exert any physiological effects on the patient's body compared to other interventions, thereby not inducing side effects. Additionally, psychological and expectation factors, wherein patients believe the intervention they receive has an effect on their body, can influence

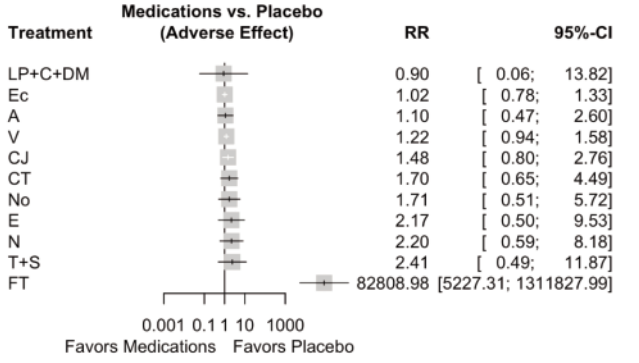

Figure 8. Forest plots for effectiveness and acceptability, comparing each psychotherapy with treatment as usual. RR, relative risk; CI, confidence interval; LP+C+DM, D-manose (Lactoflorene Cist) daily; Ec, *Escherichia coli* extract (OM-89); A, acupuncture; V, vaccine; CJ, cranberry juice; CT, cranberry tablet; No, norfloxacin; E, estriol-containing vaginal pessary; N, nitrofurantoin; T+S, trimethoprim-sulfamethoxazole; FT, fosfomycin trometamol.

their psychological state, leading to a reduction in symptoms and complaints. This may also alter the patients' expectations, subsequently changing their perception of adverse effects.[23]

Aside from placebo, interventions involving lactobacillus, cranberry, and D-mannose demonstrated a lower likelihood of adverse effects compared to other interventions. The study by Murina *et al.* (2021) indicated that these interventions did not result in any adverse effects. However, further studies with larger sample sizes are needed to validate these findings in future research.[7] Although fosfomycin-trometamol demonstrates superior effectiveness compared to other interventions, it is associated with the highest incidence of adverse effects. Two types of adverse effects were observed in this intervention: mild dyspnea and moderate allergic skin reactions. Mild dyspnea is believed to be unrelated to fosfomycin and trometamol. Both adverse effects can be managed with corticosteroid therapy.[15]

Strengths and limitations

This study's strength lies in being the first systematic review and NMA exploring the effectiveness of various preventive measures against rUTIs. This study also investigates the adverse events of each intervention. Moreover, this study covers a wide range of areas and includes a sufficient number of samples for all analyses. However, limitations for this study are that the demographics of the participants were all different from the study design and outcome measure. In addition, further large-scale randomized studies are necessary to validate the findings from this NMA. Moreover, there are no studies evaluating nitrofurantoin and cranberry directly, whereas both interventions have the most evidence with the same efficacy on preventing rUTIs.

Conclusions

Cranberry and nitrofurantoin are effective for preventing rUTIs, with the most substantial evidence supporting their use. Fosfomycin-trometamol is the most effective, but further research is needed to confirm this. In terms of safety, a combination of lactobacillus, cranberry, and D-mannose is the safest, with the least adverse effects.

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