Nonantibiotic Prophylaxis for Recurrent Urinary Tract Infections: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Nonantibiotic Prophylaxis for Recurrent Urinary Tract Infections: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Purpose: Increasing antimicrobial resistance has stimulated interest in nonantibiotic prophylaxis of recurrent urinary tract infections. We assessed the effectiveness, tolerability and safety of nonantibiotic prophylaxis in adults with recurrent urinary tract infections.

Materials and Methods: MEDLINE®, EMBASE™, the Cochrane Library and reference lists of relevant reviews were searched to April 2013 for relevant English language citations. Two reviewers selected randomized controlled trials that met the predefined criteria for population, interventions and outcomes. The difference in the proportions of patients with at least 1 urinary tract infection was calculated for individual studies, and pooled risk ratios were calculated using random and fixed effects models. Adverse event rates were also extracted. The Jadad score was used to assess risk of bias (0 to 2—high risk and 3 to 5—low risk).

Results: We identified 5,413 records and included 17 studies with data for 2,165 patients. The oral immunostimulant OM-89 decreased the rate of urinary tract infection recurrence (4 trials, sample size 891, median Jadad score 3, RR 0.61, 95% CI 0.48–0.78) and had a good safety profile. The vaginal vaccine Urovac® slightly reduced urinary tract infection recurrence (3 trials, sample size 220, Jadad score 3, RR 0.81, 95% CI 0.68–0.96) and primary immunization followed by booster immunization increased the time to reinfection. Vaginal estrogens showed a trend toward preventing urinary tract infection recurrence (2 trials, sample size 201, Jadad score 2.5, RR 0.42, 95% CI 0.16–1.10) but vaginal irritation occurred in 6% to 20% of women. Cranberries decreased urinary tract infection recurrence (2 trials, sample size 250, Jadad score 4, RR 0.53, 95% CI 0.33–0.83) as did acupuncture (2 open label trials, sample size 165, Jadad score 2, RR 0.48, 95% CI 0.29–0.79). Oral estrogens and lactobacilli prophylaxis did not decrease the rate of urinary tract infection recurrence.

Conclusions: The evidence of the effectiveness of the oral immunostimulant OM-89 is promising. Although sometimes statistically significant, pooled findings for the other interventions should be considered tentative until corroborated by more research. Large head-to-head trials should be performed to optimally inform clinical decision making.

Key Words: urinary tract infections, prevention and control, review, meta-analysis

Abbreviations and Acronyms

RCT = randomized controlled trial

rUTI = recurrent urinary tract infection

UTI = urinary tract infection

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Editor's Note: This article is the first of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 2316 and 2317.

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URINARY tract infections are common and are among the most frequent medical conditions requiring outpatient treatment. Approximately 80% of all UTIs occur in women.[1] Approximately 20% to 30% of women with a UTI will have a recurrence. The recurrence rate varies widely from patient to patient.[2] In individuals with recurrent UTIs, ie 3 or more per year, low dose antibiotic prophylaxis for several months can be recommended.[3] However, antibiotics are the main driving force in the development of antibiotic resistance and can lead to resistance not only of the causative microorganisms but also of the commensal flora.[4] The increasing prevalence of Escherichia coli isolates (the most prevalent uropathogen) that are resistant to antimicrobial agents has stimulated interest in nonantibiotic methods for the prevention of UTIs. Increasingly patients with rUTIs are asking health care professionals about the value of taking nonantibiotic products. Therefore, health care professionals would benefit from a synthesis of the pertinent evidence from randomized trials to optimally advise their patients. In this article we review evidence from RCTs on the effectiveness, tolerability and safety of nonantibiotic prophylaxis in adults with recurrent UTIs.

MATERIALS AND METHODS

Search Strategy and Inclusion Criteria

On April 3, 2013 the electronic databases PubMed®/MEDLINE, EMBASE and the Cochrane Library were searched for relevant trials using the terms "prevention and control" OR "prophylaxis" AND "urinary tract infections" OR "cystitis" OR "pyelonephritis" OR "uti". In addition, reference lists of relevant (Cochrane) reviews were screened for relevant trials.[5–9] Only English language articles published after 1984 were included in the analysis.

Our search strategy and analysis complied with the PRISMA statement.[10] All RCTs in adults with rUTIs, mostly community dwelling women, comparing nonantibiotic prophylaxis to placebo or no treatment were included in the analysis. Recurrent UTIs were defined as at least 3 UTIs in the year preceding the start of the trial or rUTIs by the author's definition. In trials in which patients with at least 1 UTI were included, baseline results had to show a mean of at least 3 UTIs per year in all trial arms. Since the durations of post-prophylaxis effects for the various interventions were unknown, we excluded crossover trials. In addition, trials evaluating curative treatment, perioperative antibiotic prophylaxis, prevention of nosocomial infections, the effect of lifestyle interventions or the use of devices (eg urinary catheter policies, intravesical instillations) were excluded from study.

The primary outcome of interest was the proportion of patients with at least 1 symptomatic UTI. In addition, we assessed the mean number of symptomatic UTIs during followup. In most trials examined the authors reported the mean number of UTIs, the proportions without or with at least 1 UTI, or described the actual number of UTIs experienced by the participants, which then could be transformed into the corresponding means and proportions. If data on our primary outcomes were not reported or could not be calculated, we contacted the authors. To assess tolerability and safety we reported adverse and serious adverse events as a secondary outcome.

Data Extraction

All selected articles were checked independently against the inclusion criteria and study design by 2 reviewers (MAJB and NMvC or MAJB and EPvH). In cases of discordance a third reviewer was consulted (SEG). Data extraction from eligible studies was performed independently (MAJB and NMvC or MAJB and EPvH). A third reviewer was consulted to review discrepancies in data extraction (SEG or GtR).

Assessment of Methodological Quality

The internal validity of included trials was assessed by the same reviewers using the Jadad score.[11] The Jadad scale assigns scores from 0 to 5 (best quality trial) based on whether 1) the study is randomized, 2) the intervention is double-blind, 3) study withdrawals are accounted for and described, 4) the randomization procedure is adequately performed using an appropriate method such as computer generated random numbers and 5) the blinding is adequately performed using an identical looking placebo.[2] Concealment of treatment allocation was also evaluated for adequacy. If the descriptions of the procedures were such that investigators were likely to be unaware of each participant's allocation at the time of allocation, concealment was considered adequate.

Statistical Analysis

For comparison of the proportion of patients with at least 1 symptomatic UTI and the mean number of symptomatic UTIs between nonantibiotic prophylaxis and controls we used the risk ratio and the mean difference, respectively. We performed random and fixed effects meta-analyses on the risk ratios of at least 1 UTI with nonantibiotic prophylaxis compared to the control group using DerSimonian-Laird and Mantel-Haenszel weights, respectively, using Stata® software (version 10.1). Heterogeneity was assessed using the I-squared (I^2) statistic.[12] Publication bias could not be investigated due to small numbers of trials.

RESULTS

Description of Studies

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram summarizes the number of records screened and included (fig. 1).[13,14] The characteristics and methodological quality of the included studies are presented in supplementary table 1 (http://jurology.com/). We included 17 studies with data on 2,165

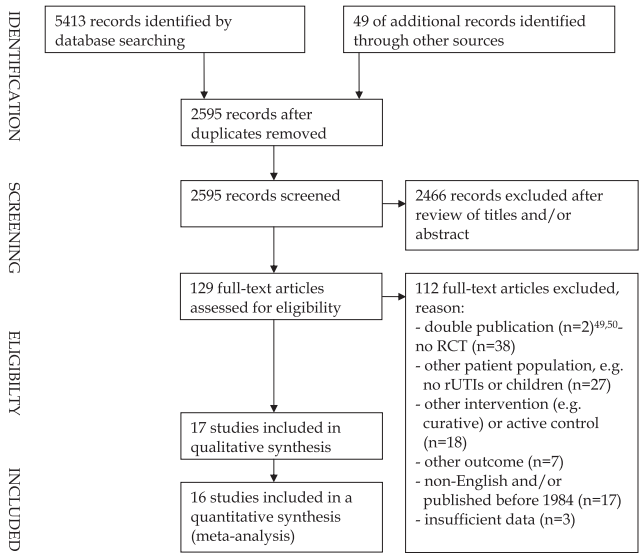

Figure 1. PRISMA flow diagram of stages in systematic review of nonantibiotic prophylaxis for rUTIs. Because of similarity of data, design and outcomes, it was concluded that 2 studies were duplicate publications.[13,14]

patients, most of whom were between 20 and 50 years old. The sample size varied between 44 and 453, with followup ranging between 20 weeks and 12 months. In most studies only women were included. In the studies by Tammen,[15] Schulman et al[16] and Magasi et al[17] about 10% to 20% of participants were men. Unfortunately the analyses were not stratified by gender. A UTI was mainly defined as symptoms suggestive of a UTI and bacteriuria. The cutoff for a microbiologically confirmed UTI varied from 10^3 to 10^5 cfu/ml. The median (IQR) quality score was 3 (2.5–4) and 7 trials (41%) were judged as having adequate allocation concealment.

Effectiveness, Tolerability and Safety of Immunoactive Prophylaxis

Various bacterial extracts have been used in the management of rUTIs. To be effective, a bacterial extract must be able to stimulate the host's immune system to produce antibodies and cytokines.[8]

Oral immunostimulant OM-89. The oral immunostimulant OM-89 (Uro-Vaxom®), an extract of 18 different serotypes of heat killed uropathogenic E. coli, stimulates innate immunity by increasing neutrophils and macrophage phagocytosis and via the up-regulation of dendritic cells. This process is likely to be mediated via toll-like receptors. Toll-like receptor 4 recognizes lipopolysaccharide, which can be found in the outer membrane of E. coli and most other gram-negative bacteria. Since various classes of uropathogens share similar antigenic structures, they can be recognized by the same pattern recognition receptor.[8] In addition, after repeated administration of OM-89, strain specific immunoglobulin G and immunoglobulin A levels increased in serum and in supernatants of cell cultures prepared from the urogenital tract of immunized mice.[18]

We included 4 studies with a total of 891 participants.[15–17,19] Participants took oral OM-89 or a placebo capsule daily. In the meta-analysis the risk ratio for the development of at least 1 UTI was significantly lower in the OM-89 group (RR 0.61, 95% CI 0.48–0.78, fig. 2), and mean number of UTIs was about half compared to placebo (supplementary table 2, http://jurology.com/).

The proportion of patients experiencing adverse events in the OM-89 group was comparable to that in the placebo group. Up to 13% of adverse events were considered treatment related. Headache and gastrointestinal complaints were reported most often. Tammen reported an allergic reaction leading to withdrawal of OM-89.[15] Other serious adverse events reported, mostly hospitalizations, were not related to the study medication.

Vaginal vaccine. Urovac is a vaginal vaccine which contains 10 heat killed uropathogenic bacteria including 6 different serotypes of uropathogenic E. coli, and 1 strain each of Proteus vulgaris, Klebsiella pneumoniae, Morganella morganii and Enterococcus faecalis. This vaccine primarily induces immunoglobulin G and immunoglobulin A in the urogenital tract, thereby reducing potential colonization of the vagina and bladder with uropathogens.[20] The exact mechanisms of protection and immunological basis are still unclear.

In a trial with 91 women primary immunization was compared to placebo.[21] Primary immunization consisted of 3 vaginal vaccine suppositories at weekly intervals (with 1 [low dose] or 2 [high dose] ampules of 2×10^9 heat killed organisms per suppository). In this study no significant differences were found in the proportion of women with at least 1 UTI and the mean number of UTIs during the 20 weeks of followup (supplementary table 2).

In 2 smaller studies the addition of booster vaccinations was evaluated.[20,22] Booster immunization consisted of 3 additional vaccine suppositories (with 1×10^9 killed organisms[20] or 2×10^9 killed organisms[22]) at monthly intervals. The time until first reinfection, the proportion of women experiencing UTI and the mean number of UTIs during followup were all in favor of the booster immunization group compared to those receiving placebo or primary immunization only (supplementary table 2). In the

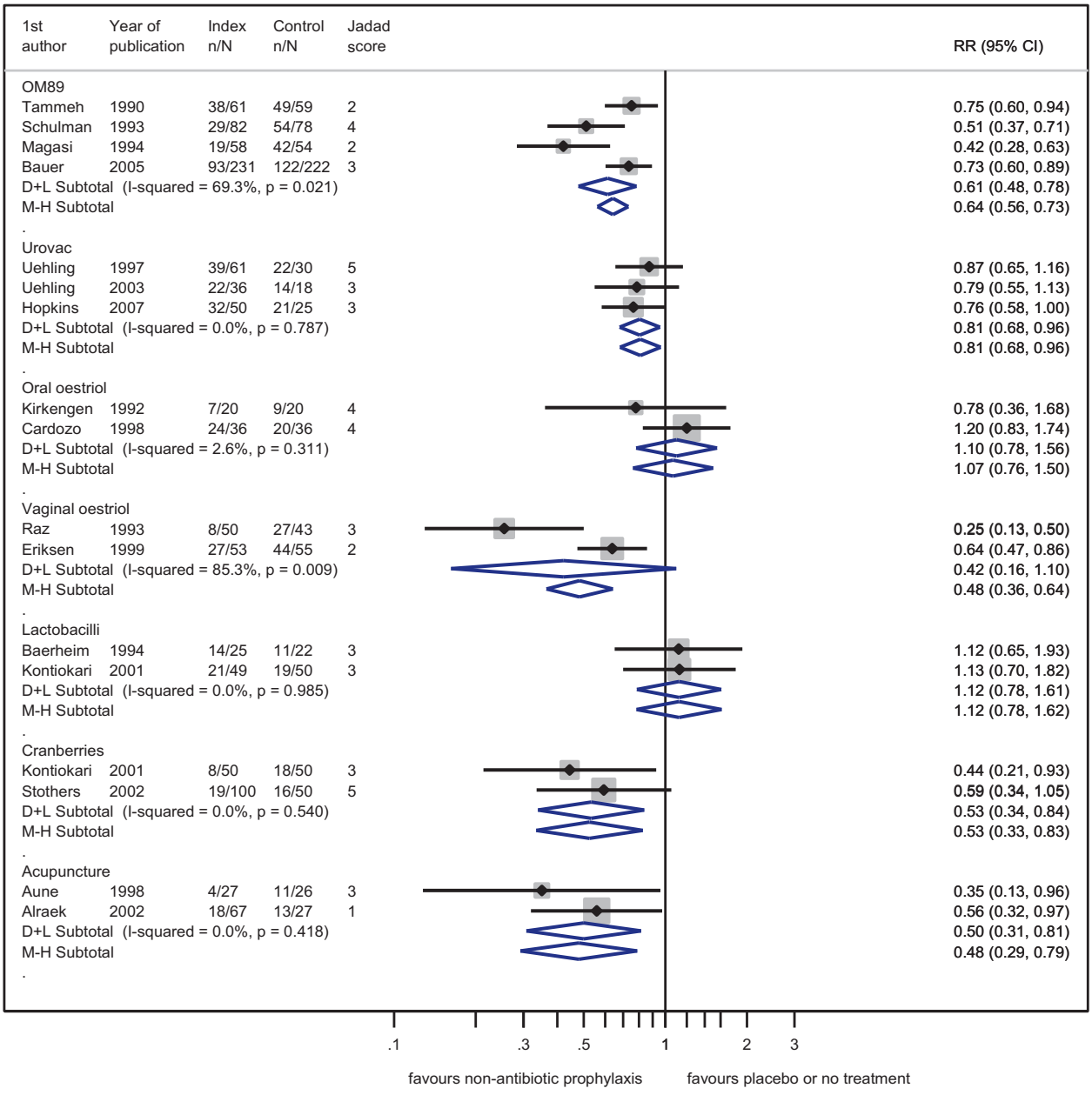

Figure 2. Forest plot showing risk ratios and 95% CIs of probability of experiencing at least 1 UTI for 17 trials on nonantibiotic prophylaxis of rUTIs, and pooled estimates using random and fixed effects methods. I-squared statistic quantifies inconsistency (percentage of variability in effect estimates that is due to heterogeneity rather than chance). Because of difference in intervention and effect size, we decided to report summary measures for comparison of acupuncture (not sham acupuncture) and control only. *D+L*, DerSimonian-Laird (random effects method). *M-H*, Mantel-Haenszel (fixed effects method).

meta-analysis of the 3 studies Urovac appeared to slightly reduce rUTI rates (RR 0.81, 95% CI 0.68–0.96, fig. 2). Up to 27.8% of the women reported vaginal irritation shortly after suppository insertion.

Effectiveness, Tolerability and Safety of Estrogen Prophylaxis

The main factors associated with rUTIs in postmenopausal women are vesical prolapse, cystocele, post-void residual volume and urinary incontinence. These abnormalities are all associated with a decrease in estrogen. Given this evidence, estrogens have been proposed as a strategy for the prevention of UTI in postmenopausal women.[9] In addition, in a placebo controlled trial the use of vaginal estrogens was associated with a significant increase in vaginal colonization with lactobacilli, which may protect the vagina against colonization with potential uropathogens.[23]

Oral estrogens. In the study by Kirkengen et al the women were treated with 3 mg oral estriol daily or corresponding placebo for 4 weeks, followed by 1 mg daily for 8 weeks.[24] The intervention in the study by Cardozo et al consisted of 3 mg oral estriol daily or placebo for 6 months.[25] Neither in the individual studies nor in the meta-analysis did oral estrogens reduce the proportion of women experiencing a UTI (supplementary table 2, fig. 2).

Cardozo et al reported breast tenderness in 7 of 36 patients (19.4%) and mild vaginal bleeding in 3 (8.3%) receiving oral estrogens.[25] Serious adverse events were hospital admission, bleeding, stroke and depression in the estrogen group, and femur fracture, sepsis, stroke and left arm paresis in the placebo group. In the study by Kirkengen et al 1 patient died of myocardial infarction.[24] In both studies the likelihood of a causal relation between each of these events and the study medication was not reported. However, oral estrogens are no longer recommended in older postmenopausal women and in those at high risk for coronary heart disease because in these groups the long-term use of oral estrogens has been found to be associated with a higher risk of venous thromboembolism, breast cancer, stroke and coronary heart disease.[26,27]

Vaginal estrogens. In a trial performed by Raz and Stamm, women were randomly assigned to 0.5 mg estriol in vaginal cream to be used each night for 2 weeks, followed by twice weekly use for 8 months.[23] In a study by Eriksen women received an estradiol-releasing vaginal ring with 2 mg estradiol (Estring®) or no treatment.[28]

Both studies showed that vaginal estrogens significantly reduced the proportion of women with a UTI (supplementary table 2). However, there was significant heterogeneity and a random effects meta-analysis revealed an insignificant pooled effect (RR 0.42, 95% CI 0.16–1.10, fig. 2).

Vaginal estrogen prophylaxis caused vaginal irritation or local discomfort in up to 20% of women. For the serious adverse events reported, a causal relationship with the study medication was deemed unlikely.

Effectiveness, Tolerability and Safety of Lactobacilli Prophylaxis

Specific lactobacilli strains can interfere with the adherence, growth and colonization of the urogenital human epithelium by uropathogenic bacteria. In particular, strains that produce antibacterial compounds, like hydrogen peroxide and biosurfactants, are believed to be important in the maintenance of a normal urogenital flora and in the prevention of infection in women. Microbiome modulating abilities of lactobacilli might also have a role, although the exact mechanisms have to be elucidated.[5,29]

Vaginal application of L. casei v rhamnosus. In the study by Baerheim et al 48 women were randomized to vaginal suppositories containing L. casei v rhamnosus twice weekly for 26 weeks or to placebo.[30] The authors did not show an advantage in terms of UTI prevention compared to placebo (supplementary table 2). Compared to the women in the placebo group (4.5%) more women in the lactobacilli group (16%) reported vaginal discharge after taking the suppositories.

Lactobacillus GG drink. The study by Kontiokari et al was an open randomized trial in 150 women who had a UTI caused by E. coli.[31] After being treated with antibacterial agents for the UTI episode, they were randomly allocated to 1 of 3 groups. The first group received 50 ml cranberry lingonberry juice daily for 6 months, the second group took 100 ml Lactobacillus GG (4×10^{10} cfu) drink 5 days weekly for 1 year and the third group received no further treatment. In the lactobacillus group 21 of 49 women (42.9%) had had a UTI at 12 months, which was similar to 19 of 50 women (38.0%) in the group without treatment (supplementary table 2). There were no adverse reactions.

Effectiveness, Tolerability and Safety of Cranberry Prophylaxis

Cranberries have been used in the prevention of UTIs for many years. The mechanism of action has not been completely elucidated, but cranberries contain A type proanthocyanidins, which in urine can inhibit the adherence of P fimbriae of E. coli to the uroepithelial cell receptors.[32]

We identified 2 studies that compared cranberry products to placebo or no treatment in women with at least 3 UTIs in the year before inclusion. In our meta-analysis cranberry products reduced UTI recurrence (RR 0.53, 95% CI 0.33–0.83, fig. 2). In the study by Kontiokari et al, for the women in the cranberry lingonberry juice group the intervention was stopped prematurely after 6 months because the manufacturer stopped producing the juice.[31] After 6 months 8 of 50 women (16%) in the cranberry group and 18 of 50 women (36%) in the control group had experienced at least 1 UTI (RR 0.44, 95% CI 0.21–0.93, supplementary table 2). There were only occasional complaints about the bitter taste of the cranberry juice.

Stothers compared cranberry juice and cranberry tablets to placebo in a double dummy double-blind study.[33] Tablets were taken twice daily and 250 ml juice was taken 3 times daily. Cranberry

juice and cranberry tablets significantly decreased the proportion of women experiencing at least 1 symptomatic UTI during the 12 months of followup (supplementary table 2). In the cranberry juice group 3 women (6%) reported gastroesophageal reflux. In the cranberry tablet group 4 women (8%) experienced mild nausea compared to 2 (4%) in the placebo group.

Effectiveness, Tolerability and Safety of Miscellaneous Prophylactic Agents

Angocin®. Albrecht et al conducted a double-blind, placebo controlled trial to verify the effectiveness and safety of Angocin Anti-Infekt N, which is an herbal medicinal product (film coated tablets) containing the active ingredients horseradish root (Armoraciae rusticanae radix, 80 mg) and nasturtium (Tropaeoli majoris herba, 200 mg).[34] For these 2 active ingredients antimicrobial effectiveness was proven in vitro based on the isothiocyanates (mustard oils). Patients were randomized to receive the study drug or placebo twice daily for 90 days.

The authors concluded that based on a per protocol analysis in 103 patients, the product Angocin was effective in the prevention of rUTIs. They found that the mean number of UTIs during the 180-day followup was 0.43 in the Angocin group compared to 0.77 in the placebo group (1-sided $p = 0.035$). The statistical significance disappeared when a 2-sided p value was calculated. However, in the intent to treat analysis on 174 patients the mean number of UTIs was 0.65 and 0.64, respectively (1-sided $p = 0.476$).

Of 84 patients in the Angocin group 36 (43%) and of 90 in the placebo group 37 (41%) reported an adverse event. Serious adverse events were reported in 1 and 2 patients in these groups, respectively. The serious adverse events were not related to the study medication.

Acupuncture. Acupuncture has traditionally been used in the treatment and prevention of many clinical conditions. We identified 2 open trials by the same group of investigators on the use of acupuncture in the prevention of recurrent UTIs in women.[35,36] In the real acupuncture group needles were inserted to the correct depth at known acupuncture points, the qi sensation was obtained and needles were manipulated by hand. In the sham acupuncture group the needles were inserted superficially, outside known acupuncture points and without manipulation. All treatments were administered twice weekly for 4 weeks.

Acupuncture significantly reduced the proportion of women experiencing a UTI (RR 0.48, 95% CI 0.29–0.79, fig. 2 and supplementary table 2). Adverse advents reported in the (sham) acupuncture groups were gastrointestinal discomfort, loose stools, a warm feeling in the legs, cold hands and feet, anxiety and depression.

DISCUSSION

Among the different forms of nonantibiotic prophylaxis described in this systematic review the oral immunostimulant OM-89 appears to be the most promising to prevent recurrent UTIs. Four trials with 891 participants showed effectiveness in reducing UTIs (RR 0.61, 95% CI 0.48–0.78) and a good safety profile. However, since some of the studies were funded by the manufacturer, we cannot rule out funding bias. In postmenopausal women there was a trend toward fewer UTI recurrences with vaginal estrogens, which was not seen with oral estrogens. Vaginal estrogens have been used for many years worldwide. However, we found that vaginal irritation occurred frequently and affected adherence.

Although there was a significant decrease in UTI recurrence with the vaginal vaccine Urovac, cranberries and acupuncture, the pooled findings for these nonantibiotic forms of prophylaxis are based on a small number of studies and are not necessarily robust.[37] Therefore, confirmation in larger studies by independent investigators seems necessary.

Vaginal application of L. casei v rhamnosus and L. rhamnosus GG drink did not appear to be effective. Various in vitro and animal studies led to the conclusion that L. rhamnosus GR-1 and L. reuteri RC-14 possess optimal properties to prevent UTIs.[29] However, identified trials using L. rhamnosus GR-1 and L. reuteri RC-14 could not be included in this review because they did not meet the predefined inclusion criteria. One trial compared vaginal suppositories with lactobacilli to vaginal suppositories with Lactobacillus growth factor,[38] and another compared the lactobacilli with trimethoprim-sulfamethoxazole.[4] One trial evaluated the effectiveness of probiotic vaginal suppositories after antimicrobial therapy for an acute UTI.[39] Another strain, L. crispatus, given as intravaginal suppositories, reduced recurrence after antimicrobial treatment of a symptomatic UTI in premenopausal women.[40]

Cranberry juice and tablets reduced the occurrence of UTIs compared to placebo. However, cranberry tablets were tolerated better. The greatest challenge in the field of cranberry research is determining the optimum dose of proanthocyanidins to prevent UTIs in vivo. Based on an ex vivo study in urine samples of volunteers who consumed cranberry powder, Howell et al concluded that 72 mg proanthocyanidins daily might offer some protection against bacterial adhesion and virulence in the urinary tract.[32]

A recent Cochrane Review concluded that cranberry products did not significantly reduce the occurrence of symptomatic UTI in women with recurrent UTIs.[6] Although investigators used the same definition for recurrent UTIs, some of the women they included in their analysis did not actually have recurrent UTIs according to the prespecified definition.[41] In another trial the end point was not UTI but the amelioration of symptoms and the reduction of the urinary uropathogen load after the treatment of a symptomatic UTI with cranberries.[42]

Two studies suggest that acupuncture might prevent recurrent UTIs.[35,36] However, these results should be interpreted cautiously due to the low quality scores (median Jadad score of 2) and small numbers. In addition, acupuncture is a complex intervention that includes a large number of variables (eg needle placement, manipulation, associated use of herbs). One has to be cautious in generalizing the findings to other variants of acupuncture which may have different effects.

Implications for Further Research

Before recommending the widespread use of a vaginal vaccine, cranberry products or acupuncture, we believe that more evidence is needed. Since UTIs can be relapsing infections and, therefore, often occur in clusters, intervention and followup periods (also after stopping the prevention method) in future trials may need to cover much longer periods to take into account the natural course of the disease. Since women are far more likely to have UTIs than men and since pathogenesis differs by gender, we recommend including only women to improve the generalizability of findings to the circumstances most often seen in daily practice. In this review in 3 trials with the oral immunostimulant OM-89, 60 of 438 included patients were men (13.7%) and unfortunately the findings were not stratified by gender.[15–17]

For most forms of nonantibiotic prophylaxis the optimum dose to prevent UTI is unknown. We are waiting for the results of the dose finding study with cranberry products that is currently under way to determine the optimal dose for future cranberry product trials.[43]

To optimally inform clinical decision making, large head-to-head trials should be performed comparing the different forms of nonantibiotic prophylaxis with each other and with antibiotic prophylaxis, which is the standard of care. Currently the effectiveness of nonantibiotic agents is substantially less than that of antibiotic prophylaxis. However, due to the lack of collateral damage, namely no increase in resistance, as well as patient preference for natural remedies, nonantibiotic prophylaxis can be an acceptable alternative to prevent recurrent UTIs.

Until now, few studies have been performed that compare nonantibiotic prophylaxis with antibiotic prophylaxis to prevent UTIs in adults with recurrent UTIs.[4,44–47] The results of a study comparing OM-89 with antibiotic prophylaxis in adults with recurrent UTIs are expected in the near future.[48]

In addition, in future trials it would be desirable to evaluate quality of life, patient preference and cost-effectiveness for each alternative. These aspects are important to consider in assessing which alternatives are worthwhile and likely to be adopted in practice.

Limitations

We did not include abstracts presented at meetings in our analysis. Usually these abstracts are preliminary, lack sufficient methodological details and are not properly peer reviewed. On the other hand, abstracts that make it to a full paper may be a selection (based on statistical significance). On balance, the magnitude of reporting and publication bias is difficult to estimate.

We excluded crossover trials from study since the variation among and the maximal duration of post-prophylaxis effects for the interventions included are unknown. Therefore, the minimal duration of washout periods for the specific interventions cannot be defined. We chose to be strict on this issue, and by excluding crossover trials ruled out biased estimates.

Systematic reviews and meta-analyses that obtain original research data on individual participants enrolled in trials have been described as the gold standard methodology. However, it cannot be viewed as preferred if one thinks in terms of cost per unit evidence obtained, but only if one has unlimited resources. In particular, what if only 60% of authors agree to share their data (which often happens)?[49] Thus, we have chosen to extract data from published studies.

To easily compare alternatives and draw conclusions, future trials should use uniform outcomes and definitions. In the trials included in this systematic review the cutoff for a microbiologically confirmed UTI varied from 10^3 to 10^5 cfu/ml. However, it is documented that as few as 10^2 cfu/ml can cause symptoms of a UTI.[28]

In earlier studies the chemical composition of available cranberry products was often not standardized and neither was the description of the dose. In addition, the bioequivalence between the juice and capsules or tablets is not clear. These factors make it difficult to compare studies and draw conclusions.[6] Likewise, obtaining consistent and reproducible results with probiotics is a challenge. Most strains of Lactobacillus and Bifidobacterium are

sensitive to room temperature, which raises concerns about storage conditions and the maintenance of cell viability.[50]

In conclusion, the findings on the use of the oral immunostimulant OM-89 are promising. Vaginal estriol can be used to prevent recurrent UTIs in postmenopausal women. Larger and better studies about the effectiveness of the vaginal vaccine Urovac (and the optimal dose), cranberry products and acupuncture are warranted.

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