Lactobacilli vs Antibiotics to Prevent Urinary Tract Infections

A Randomized, Double-blind, Noninferiority Trial in Postmenopausal Women

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**Background:** Growing antibiotic resistance warrants studying nonantibiotic prophylaxis for recurrent urinary tract infections (UTIs). Use of lactobacilli appears to be promising.

**Methods:** Between January 2005 and August 2007, we randomized 252 postmenopausal women with recurrent UTIs taking part in a double-blind noninferiority trial to receive 12 months of prophylaxis with trimethoprim-sulfamethoxazole, 480 mg, once daily or oral capsules containing 10^9 colony-forming units of *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 twice daily. Primary end points were the mean number of symptomatic UTIs per year (95% CI, –0.4 to 1.5) was outside our noninferiority margin. At least between-treatment difference of 0.4 UTIs per year (95% CI, 2.9 and 3.3, respectively. The ratio of antibiotic-resistant *E. coli* in the trimethoprim-sulfamethoxazole group and 6.8 in the lactobacilli group. In the intention-to-treat analysis, after 12 months of prophylaxis, these numbers were 2.9 and 3.3, respectively. The between-treatment difference of 0.4 UTIs per year (95% CI, –0.4 to 1.5) was outside our noninferiority margin. At least 1 symptomatic UTI occurred in 69.3% and 79.1% of the trimethoprim-sulfamethoxazole and lactobacilli participants, respectively; median times to the first UTI were 6 and 3 months, respectively. After 1 month of trimethoprim-sulfamethoxazole prophylaxis, resistance to trimethoprim-sulfamethoxazole, trimethoprim, and amoxicillin had increased from approximately 20% to 40% to approximately 80% to 95% in *E. coli* from the feces and urine of asymptomatic women and among *E. coli* causing a UTI. During the 3 months after trimethoprim-sulfamethoxazole discontinuation, resistance levels gradually decreased. Resistance did not increase during lactobacilli prophylaxis.

**Conclusions:** In postmenopausal women with recurrent UTIs, *L. rhamnosus* GR-1 and *L. reuteri* RC-14 do not meet the noninferiority criteria in the prevention of UTIs when compared with trimethoprim-sulfamethoxazole. However, unlike trimethoprim-sulfamethoxazole, lactobacilli do not increase antibiotic resistance.

**Trial Registration:** isrctn.org Identifier: ISRCTN50717094

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FOR POSTMENOPAUSAL WOMEN with at least 3 urinary tract infections (UTIs) per year, vaginal application of estrogens or low-dose oral antibiotic prophylaxis can be recommended. For various reasons, many women do not like vaginal application of estrogens and so receive antibiotic prophylaxis. An increasing prevalence of antibiotic resistance among uropathogens necessitates the development of alternative nonantibiotic methods for the prevention of recurrent UTIs (rUTIs). The disappearance of vaginal lactobacilli in postmenopausal women increases the likelihood of colonization with *Enterobacteriaceae*, which is associated with the occurrence of UTIs. Oral administration of *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 has been shown to restore the vaginal lactobacilli flora and to reduce colonization by potentially pathogenic bacteria.

We conducted a double-blind, double-dummy, randomized noninferiority trial in postmenopausal women with rUTIs, comparing 12 months of prophylaxis using either trimethoprim-sulfamethoxazole, 480 mg, once daily or oral capsules containing *L. rhamnosus* GR-1 and *L. reuteri* RC-14 twice daily.

See Invited Commentary at end of article.

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METHODS

PATIENTS

Postmenopausal women with a history of at least 3 self-reported symptomatic UTIs in the year preceding randomization were eligible for participation. Patients were living in the community and recruited through advertisements or referred by Dutch family physicians and medical specialists. Exclusion criteria were UTI symptoms at inclusion, antibiotic use in the previous 2 weeks, relevant interactions of trimethoprim-sulfamethoxazole (eg, allergy), renal failure, and renal transplant. Prophylactic treatment with probiotics, cranberries, or estrogens had to be stopped at least 2 weeks before the study and avoided during the study period. The study protocol was approved by the medical ethics committees of all 10 participating centers, and participants provided written informed consent before inclusion.

INTERVENTION

The coordinating center (Academic Medical Center, Amsterdam) prepared drug randomization lists for each study site in advance. Women were randomized to 12 months’ use of (1) trimethoprim-sulfamethoxazole, 480 mg, 1 tablet at night and 1 placebo capsule twice daily or (2) 1 capsule containing at least 10^9 colony-forming units (CFU) of Lactobacillus rhamnosus GR-1 and L. reuteri RC-14 twice daily and 1 placebo tablet at night. Masking of patients and investigators was achieved by double-dummy dosing. After discontinuation of the study medication, the women were asked to guess which intervention they had received (trimethoprim-sulfamethoxazole, lactobacilli, or do not know). Concealed randomization was ensured using computer-aided block randomization (block size remained masked), with prestratification by center and presence (yes/no) of complicating host factors. Complicated UTIs were defined as UTIs in women with functional or structural abnormalities of the urinary tract, metabolic and/or hormonal abnormalities, or impaired host responses.

ASSESSMENT

At baseline, demographic variables and clinical characteristics were collected (Table 1). Immediately before the study medication was started and monthly thereafter, until 3 months after discontinuation of the study medication, the women were asked to collect urine and feces (using a stool container with a cap-spoon combination) and to collect a vaginal swab specimen. At these times, the women also received a questionnaire addressed UTI symptoms, adverse events (AEs), infections other than UTIs, and antibiotic use. In case of a symptomatic UTI, addressing UTI symptoms, adverse events (AEs), infections other than UTIs, and antibiotic use. In case of a symptomatic UTI, patients were instructed to collect urine using a dipslide and to send this to the laboratory for culture.

Urine and stool samples were collected to measure antibiotic resistance of commensal Escherichia coli. Details are
referred elsewhere. In addition, urine samples were tested for antibacterial activity associated with trimethoprim-sulfamethoxazole or other antibacterial substances. The fecal and vaginal samples obtained at baseline and month 12 were examined for the presence of L. reuteri by real-time polymerase chain reaction, which was developed for L. reuteri in general (ie, not for L. reuteri RC-14 specifically). Nugent scores ranging from 0 to 3 (normal vaginal flora), 4 to 6 (intermediate flora), and 7 to 10 (bacterial vaginosis) were assigned to the baseline vaginal swabs and to those at month 12.

OUTCOME MEASURES

The primary clinical outcomes were the mean number of symptomatic UTIs (clinical recurrences [CRs]) during 12 months, the proportion of patients with at least 1 CR during 12 months of prophylaxis, and the median time to the first CR. A CR was defined as a UTI based on a woman's report of symptoms, usually dysuria, frequency, and/or urgency.

The primary outcome measure evaluating the development of resistance was the percentage of trimethoprim-sulfamethoxazole-resistant E. coli isolates from feces and urine of asymptomatic women at 1 and 12 months. In addition, we analyzed antibiotic susceptibility of these E. coli isolates to trimethoprim, nitrofurantoin, amoxicillin, amoxicillin-clavulanic acid, gentamicin, ciprofloxacin, and norfloxacin. An additional analysis of the primary outcomes was performed for the 3 months after discontinuation of the study medication.

Secondary outcomes were the mean number of microbiologically confirmed symptomatic UTIs (microbiologic recurrences [MRs]) during the 12 months of prophylaxis and in the 3 months after its discontinuation, the proportion of patients with at least 1 MR during these periods, and the time to the first MR. A MR was defined as a UTI based on the combination of clinical symptoms and bacteriuria (≥10^5 CFU/mL bacteria in midstream urine). If E. coli was the causative microorganism, susceptibility to the antibiotics described in the previous paragraph was determined.

Preplanned subgroup analyses focused on the mean number of CRs in women with complicated vs uncomplicated UTIs. Because the number of patients with a urinary catheter was low and unbalanced between the 2 randomization arms, we omitted the women with a urinary catheter in an additional analysis of the mean number of CRs. In patients without a urinary catheter, the prevalence of asymptomatic bacteriuria (≥10^5 CFU/mL bacteria in midstream urine) was determined at 1 and 12 months of prophylaxis.

Additional secondary outcomes included the proportion of patients experiencing serious AEs. The likelihood of a causal relationship between the study medication and serious AEs or events leading to withdrawal from the study was assessed by an independent masked data and safety monitoring board. We counted the mean number of antibiotic prescriptions for treatment of UTIs and other bacterial infections.

Success of masking was assessed by comparing the patients' guesses about treatment assignment with the actual treatment. Adherence to antibiotic and lactobacilli prophylaxis was assessed by measuring antibacterial activity in all monthly urine samples and measuring L. reuteri in feces after 12 months of prophylaxis.

To study the effect of the treatments on the change of the vaginal microflora, we determined L. reuteri and the Nugent score in vaginal swabs obtained at baseline and at month 12.

STATISTICAL ANALYSIS

We performed an intention-to-treat analysis among participants who took at least 1 dose of study medication. Analysis on main outcome measures was performed before breaking the treatment code. The primary outcome measure was the between-group difference in the mean number of CRs at 12 months.

To obtain estimates of the mean number and between-group difference in mean numbers of CRs and MRs at 12 months and at 3 months in the washout period, we used Poisson regression models for the rate of recurrences per month. The use of these Poisson models allowed for complete follow-up of each woman, even if she dropped out before the end of the study. These models included a main effect of intervention arm, as well as an offset corresponding to the observed follow-up time.

To establish noninferiority of lactobacilli prophylaxis compared with trimethoprim-sulfamethoxazole prophylaxis, the upper limit of the 95% CI for the between-group difference in the mean number of CRs at 12 months had to lie below the predefined 10% noninferiority margin. In accordance with the Consolidated Standards for Reporting of Trials and the European Medicines Agency, we report 2-sided 95% CIs of the between-treatment differences.

Furthermore, we modeled the probability of being UTI free at each time point during the 12 months of prophylaxis and in the 3-month washout period, using Kaplan-Meier estimates for both treatment arms. The significance of the difference between these Kaplan-Meier estimates was determined using the log-rank test. From these Kaplan-Meier estimates, we computed the median time to the first UTI and the probability of having at least 1 UTI after 12 months of prophylaxis and within 3 months after prophylaxis.

We performed subgroup analysis of the mean number of CRs at 12 months for women with and without complicated UTIs separately, using Poisson regression models, including main effects and the first-order interaction between the treatment group indicator variable and the indicator variable for complicated UTIs. Furthermore, in a secondary analysis, we compared the mean numbers of cumulative CRs at 12 months in women without a urinary catheter, using a similar Poisson regression model.

For all Poisson regression models, we used the Pearson χ² test for overdispersion. Because overdispersion was detected for all standard Poisson regression models, we replaced them with Poisson models with a quasi-likelihood that were capable of handling overdispersion.

For statistical analysis, we used commercial software (SPSS, version 16.0, SPSS, Inc; Stata, version 10.1, StataCorp; and R, version 2.13.1, Institute for Statistics and Mathematics), using the Epi package to obtain means with CIs, as well as differences in means with CI s and values, by linear contrasts.

PARTICIPANT FLOW

From January 1, 2005, to August 31, 2007, we recruited 252 postmenopausal women with rUTIs: 127 were randomized to the trimethoprim-sulfamethoxazole group and 125 to the lactobacilli group (Figure 1). The inclusion was planned to stop after 2 years. Baseline characteristics are reported in Table 1.

PRIMARY OUTCOMES: CRs AND DEVELOPMENT OF RESISTANCE

After 12 months of prophylaxis, the mean number of CRs was 2.9 (95% CI, 2.3 to 3.6) in the trimethoprim-sulfamethoxazole group and 3.3 (95% CI, 2.7 to 4.0) in the lactobacilli group (Table 2 and Figure 2A). The between-group difference in the mean number of CRs af-
ter 12 months was 0.4 (95% CI, −0.4 to 1.5), corresponding to a difference of 13.8%, determined as (3.3 − 2.9)/2.9 (95% CI, −13.8% to 51.7%; P = .42). The percentage of patients with at least 1 CR at 12 months was 69.3% in the trimethoprim-sulfamethoxazole group and 79.1% in the lactobacilli group. The median times to first recurrence were 6 and 3 months, respectively (log-rank P = .02; Figure 2B). The Kaplan-Meier curves from the trimethoprim-sulfamethoxazole and lactobacilli groups for CRs during the 3 months after discontinuation of the study medication did not differ significantly (log-rank P = .35) (Table 2).

After 1 month of trimethoprim-sulfamethoxazole prophylaxis, resistance to trimethoprim-sulfamethoxazole, trimethoprim, and amoxicillin increased from approximately 20% to 40% to approximately 80% to 95% in the feces and urine of asymptomatic women (Figure 3). After 12 months of trimethoprim-sulfamethoxazole prophylaxis, all urinary E coli isolates of asymptomatic women were resistant to trimethoprim-sulfamethoxazole and trimethoprim. Resistance rates for ciprofloxacin and norfloxacin in urinary E coli isolates increased from 16% to 18% at baseline to 34% 1 month after prophylaxis was stopped. Resistance did not increase during lactobacilli prophylaxis.

SECONDARY OUTCOMES

MR and Asymptomatic Bacteriuria

After 12 months of prophylaxis, the mean number of MRs was 1.2 (95% CI, 0.9−1.6) in the trimethoprim-sulfamethoxazole group and 1.8 (95% CI, 1.4−2.3) in the lactobacilli group (P = .02) (Table 2). The percentage of patients with at least 1 MR at 12 months was 49.4% in the trimethoprim-sulfamethoxazole group and 62.9% in the lactobacilli group. The median times to first MR were slightly longer than 12 months and 6 months, respectively (log-rank P = .02). The Kaplan-Meier curves from the trimethoprim-sulfamethoxazole and lactobacilli groups for the MRs in the 3 months after discontinuation of the study medication did not differ significantly (log-rank P = .11) (Table 2).

Table 3 reports causative microorganisms. In both the trimethoprim-sulfamethoxazole and lactobacilli groups, E coli was the most commonly cultured causative microorganism (76.0% vs 69.1%). Resistance percentages of these symptomatic E coli isolates were similar to or higher than those of E coli cultured from the feces or urine of asymptomatic women (Figure 3 and Figure 4).

At 1 month, 39.6% of the women (36 of 91) in the trimethoprim-sulfamethoxazole group and 44.7% of those (46 of 103) in the lactobacilli group had asymptomatic bacteriuria. At 12 months, these percentages were 38.5% (30 of 78) and 53.2% (42 of 79), respectively. Table 3 documents cultured microorganisms for the entire study period.

Uncomplicated and Complicated UTIs

The mean number of CRs after 12 months of prophylaxis in women with uncomplicated UTIs was 1.9 (95% CI, 1.4−2.6) in the trimethoprim-sulfamethoxazole group and 3.2 (95% CI, 2.5−4.2) in the lactobacilli group. In women with complicated UTIs, these numbers were 4.4 (95% CI, 3.4−5.7) and 3.4 (95% CI, 2.6−4.5), respectively. This suggests that the effect of lactobacilli compared with that of trimethoprim-sulfamethoxazole is more favorable in the presence of a complicated UTI (t test for interaction, P < .001).

At baseline, E coli from the urine of asymptomatic women with a history of complicated UTIs was more of-
### Table 2. Clinical and Microbiologic Recurrence During and After UTI Prophylaxis

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>After 12 mo of Prophylaxis</th>
<th>3 mo After Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TMP-SMX (n = 115)</td>
<td>Lactobacilli (n = 123)</td>
</tr>
<tr>
<td>Clinical recurrence</td>
<td>2.9 (2.3 to 3.6)</td>
<td>3.3 (2.7 to 4.0)</td>
</tr>
<tr>
<td>Women with ≥1, %</td>
<td>69.3 (58.9 to 77.0)</td>
<td>79.1 (69.9 to 85.7)</td>
</tr>
<tr>
<td>Median time to first, mo</td>
<td>6 (4 to 9)</td>
<td>3 (2 to 5)</td>
</tr>
<tr>
<td>Microbiologic recurrence</td>
<td>1.2 (0.9 to 1.6)</td>
<td>1.8 (1.4 to 2.3)</td>
</tr>
<tr>
<td>Women with ≥1, %</td>
<td>49.4 (38.5 to 58.4)</td>
<td>62.9 (52.4 to 71.1)</td>
</tr>
<tr>
<td>Median time to first, mo</td>
<td>&gt;12d</td>
<td>6 (4 to 12)</td>
</tr>
</tbody>
</table>

Abbreviations: ellipses, not applicable; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

a In addition to estimating the mean number of UTIs during and after prophylaxis, we modeled the probability of having no UTI at each time point during follow-up using Kaplan-Meier estimates for both treatment arms. From the Kaplan-Meier estimates we computed the median time to the first UTI as well as the probability of having at least 1 UTI after 12 months of prophylaxis and in the 3 months after prophylaxis was stopped. The 2-sided 95% CIs are reported within the parentheses.

b Significance of main effect of intervention arm, in Poisson regression model for number of UTIs per month.

c We intended to collect data from all patients in the 3 months after discontinuation of the study medication, including those who had prematurely discontinued the study medication.

d Median time to first clinical or microbiologic recurrence could not be given, since the percentage of patients with at least 1 recurrence was less than 50%.

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**COMMENT**

In a double-blind, double-dummy, randomized noninferiority trial, the mean cumulative number of symptomatic urinary tract infections (17.4%, 21.7%, and 34.8%). After 1 month of trimethoprim-sulfamethoxazole use, these differences had disappeared; both subgroups showed an increase in resistance rates to 90% to 100%.

**Adverse Events**

No significant differences in serious AEs were seen between the trimethoprim-sulfamethoxazole and lactobacilli groups (Table 4). A variety of AEs that were likely to be treatment related, including diarrhea, was responsible for the nonsignificantly higher number of withdrawals in the lactobacilli group compared with the trimethoprim-sulfamethoxazole group. One systemic allergic reaction was documented in the trimethoprim-sulfamethoxazole group.

**Changes in Vaginal Microflora**

In both groups, L. reuteri was not identified on vaginal swabs at baseline or after 12 months. Mean (SD) Nugent scores assigned to the vaginal swabs at baseline were 6.1 (2.1) and 5.8 (2.2) for the trimethoprim-sulfamethoxazole and lactobacilli groups respectively. At month 12, they were 6.1 (2.3) and 6.0 (2.1).

Further analysis of the mean number of CRs restricted to women without a urinary catheter and the results for the end points of antibiotic use and other infections, as well as masking efficacy and adherence to study medication, are provided in the eAppendix (http://www.archinternmed.com).
motic UTIs (or CRs) after 12 months of prophylaxis was 2.9 for trimethoprim-sulfamethoxazole and 3.3 for lactobacilli. The between-treatment difference was 0.4 CRs (95% CI, −0.4 to 1.5). The upper limit of the 2-sided 95% CI was outside our predefined 10% noninferiority margin. The percentage of patients with at least 1 CR at 12 months and the median time to first recurrence were also reduced with trimethoprim-sulfamethoxazole com-

Table 3. Bacteria Isolated From Urine During the First Episode of Asymptomatic Bacteriuria and the First Microbiologically Confirmed Symptomatic UTI During Prophylaxis

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Asymptomatic Bacteriuriaa</th>
<th>Microbiologic Recurrenceb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TMP-SMX (n = 102)</td>
<td>Lactobacilli (n = 109)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>42 (41.2)</td>
<td>51 (46.8)</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>5 (4.9)</td>
<td>7 (6.4)</td>
</tr>
<tr>
<td>Nonfermentors</td>
<td>17 (16.7)</td>
<td>15 (13.8)</td>
</tr>
<tr>
<td>Proteus species</td>
<td>1 (1.0)</td>
<td>9 (8.3)</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Citrobacter species</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other gram-negative bacteria</td>
<td>1 (1.0)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>18 (17.6)</td>
<td>13 (11.9)</td>
</tr>
<tr>
<td>Coagulase-negative Staphylococcus</td>
<td>12 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
<td>1 (1.0)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Other gram-positive bacteria</td>
<td>2 (2.0)</td>
<td>5 (4.6)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (2.9)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

a Defined as ≥105 colony-forming units/mL or more bacteria in midstream urine.

b Defined as UTI based on the combination of clinical symptoms and bacteriuria (≥103 colony-forming units/mL of bacteria in midstream urine).
pared with lactobacilli prophylaxis (*P* = .02). In women with complicated UTIs, trimethoprim-sulfamethoxazole prophylaxis appeared to be less effective than lactobacilli prophylaxis, possibly because baseline resistance rates in this patient group were higher. Prophylaxis with trimethoprim-sulfamethoxazole resulted in a considerable increase in trimethoprim-sulfamethoxazole, amoxicillin, and fluoroquinolone resistance among *E coli* isolated from the commensal fecal flora, from urine of asymptomatic women, and among *E coli* causing a UTI. In the 3 months after trimethoprim-sulfamethoxazole prophylaxis was stopped, resistance levels returned to values just above baseline levels. The lack of collateral damage (no increase in resistance rates) with lactobacilli instead of antibiotic prophylaxis is important. Recently, this advantage has been highlighted in the updated Infectious Diseases Society of America guidelines on the management of UTIs. An economic evaluation weighing the pros and cons of both regimens will follow in another article. Cost differences between lactobacilli and antibiotic prophylaxis may have important economic implications.

Our findings of high resistance rates after trimethoprim-sulfamethoxazole use are in concordance with earlier studies in which, after only 2 weeks of trimethoprim use, high percentages (>95%) of trimethoprim-sulfamethoxazole–resistant microorganisms were found in feces and urine. As observed by others, there was a concomitant increase in amoxicillin resistance, known to be plasmid linked, and fluoroquinolone resistance. Also at baseline, resistance to trimethoprim-sulfamethoxazole appeared to be relatively high. There is a possibility that with the use of an antibiotic comparator with a lower resistance level, the difference with lactobacilli prophylaxis would be larger.

A trial in premenopausal women with the same lactobacilli strains, administered vaginally in addition to antimicrobial therapy for a symptomatic UTI, showed, compared with sterilized skim-milk suppositories, a reduction of the rUTI rate during 6 months from 47% to 21%. In another study, the combination of *L rhamnosus* GR-1 and *L reuteri* B-54 administered vaginally once weekly

![Figure 4. Antibiotic resistance among *Escherichia coli* isolated from patients with symptomatic urinary tract infection. AMOX indicates amoxicillin; AMOX-CLAV, amoxicillin-clavulanic acid; CIP, ciprofloxacin; GEN, gentamicin; NIT, nitrofurantoin; NOR, norfloxacin; and TMP-SMX, trimethoprim-sulfamethoxazole.](image)

### Table 4. Number and Percentages of Patients Experiencing Adverse Events

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TMP-SMX (n = 115)</th>
<th>Lactobacilli (n = 123)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>66 (57.4)</td>
<td>72 (58.5)</td>
<td>1.0 (0.6-1.6)</td>
</tr>
<tr>
<td>Skin rash or urticaria</td>
<td>17 (14.8)</td>
<td>12 (9.8)</td>
<td>1.6 (0.7-3.5)</td>
</tr>
<tr>
<td>Nausea, vomiting, or diarrhea</td>
<td>18 (15.7)</td>
<td>26 (21.1)</td>
<td>0.7 (0.4-1.3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>19 (16.5)</td>
<td>18 (14.6)</td>
<td>1.2 (0.6-2.3)</td>
</tr>
<tr>
<td>Vaginal symptoms</td>
<td>19 (16.5)</td>
<td>12 (9.8)</td>
<td>1.8 (0.8-4.0)</td>
</tr>
<tr>
<td>Other</td>
<td>64 (55.7)</td>
<td>66 (53.7)</td>
<td>1.1 (0.7-1.8)</td>
</tr>
<tr>
<td>Adverse events resulting in withdrawal</td>
<td>6 (5.2)</td>
<td>15 (12.2)</td>
<td>0.4 (0.1-1.1)</td>
</tr>
<tr>
<td>Association with treatment unlikely</td>
<td>3 (2.6)</td>
<td>4 (3.3)</td>
<td>0.8 (0.2-3.6)</td>
</tr>
<tr>
<td>Association with treatment likely</td>
<td>3 (2.6)</td>
<td>11 (8.9)</td>
<td>0.3 (0.1-1.0)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>17 (14.8)</td>
<td>14 (11.4)</td>
<td>1.4 (0.6-2.9)</td>
</tr>
<tr>
<td>Association with treatment likely: systemic allergic reaction</td>
<td>1 (0.9)</td>
<td>0</td>
<td>1.1 (0.1-10.5)</td>
</tr>
<tr>
<td>Association with treatment unlikely</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UTI requiring hospitalization</td>
<td>0</td>
<td>3 (2.4)</td>
<td>0.4 (0.1-3.1)</td>
</tr>
<tr>
<td>Hospitalization for other reasons</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>8 (7.0)</td>
<td>3 (2.4)</td>
<td>3.0 (0.8-11.6)</td>
</tr>
<tr>
<td>Cardiac symptoms</td>
<td>0</td>
<td>4 (3.3)</td>
<td>0.3 (0.1-2.2)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>10 (8.7)</td>
<td>7 (5.7)</td>
<td>1.6 (0.6-4.3)</td>
</tr>
<tr>
<td>Life-threatening disease diagnosed</td>
<td>2 (1.7)</td>
<td>1 (0.8)</td>
<td>2.2 (0.2-24.1)</td>
</tr>
<tr>
<td>Serious adverse events resulting in withdrawal</td>
<td>2 (1.7)</td>
<td>1 (0.8)</td>
<td>2.2 (0.2-24.1)</td>
</tr>
<tr>
<td>Association with treatment unlikely</td>
<td>1 (0.9)</td>
<td>1 (0.8)</td>
<td>1.1 (0.1-17.3)</td>
</tr>
<tr>
<td>Association with treatment likely</td>
<td>1 (0.9)</td>
<td>0</td>
<td>1.1 (0.1-10.5)</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

* The data and safety monitoring board, masked to group assignment, judged that the following 11 withdrawals from the lactobacilli group could be associated with the use of study medication: abdominal pain and/or diarrhea (*n* = 4), itching and/or rash (*n* = 2), nausea (*n* = 1), headache (*n* = 2), dizziness (*n* = 1), and oral and vaginal candidiasis (*n* = 1). According to the data and safety monitoring board, in the TMP-SMX group, the adverse events leading to withdrawal were abdominal pain (*n* = 1), abdominal pain, headache, and petechiae (*n* = 1), and nausea, joint pain, and urticaria (*n* = 1).

* The serious adverse events leading to withdrawal were a systemic allergic reaction (*n* = 1) and the terminal stage of newly diagnosed lung cancer (*n* = 1) in the TMP-SMX group and breast cancer (*n* = 1) in the lactobacilli group. No significant differences in adverse and serious adverse events were seen between the TMP-SMX and lactobacilli groups.
as prophylaxis reduced rUTIs in premenopausal women from 6.0 to 1.6 UTIs per year. Recently, Stapleton et al\(^9\) showed that intravaginal suppositories with *Lactobacillus crispatus* reduced rUTIs after antimicrobial treatment of a symptomatic UTI in premenopausal women.

In contrast to previous trials, we were able to identify *L. reuteri* in fecal samples but not in vaginal specimens of the women taking lactobacilli. Furthermore, no effect on the vaginal Nugent score was demonstrated.\(^5\,20-22\) Therefore, we can only speculate that a more lactobacilli-dominated fecal flora exhibits a protective effect through inhibition of the growth of intestinal uropathogenic bacteria.

The major strength of our study is that we investigated nonantibiotic prophylaxis in an era of increasing antimicrobial resistance. A limitation was that our target number of 280 participants for this trial (140 in each arm) was not achieved. Nevertheless, we were able to estimate the difference between the recurrence rates fairly precisely, with an upper 95% CI limit corresponding to 1.5 additional UTIs per year for women choosing to take lactobacilli instead of trimethoprim-sulfamethoxazole prophylaxis. The results from our subgroup analysis of complicated UTIs, although plausible from a resistance perspective, remain to be corroborated.

High resistance rates at baseline and the relatively high background incidence of UTIs in our study population might have influenced our success rates. Furthermore, not all CRs could be confirmed microbiologically by urinalysis. However, if women with rUTIs have signs and symptoms consistent with those of a UTI, the likelihood of a UTI is approximately 86%.\(^23\) Indeed, 85% of the urine samples examined in our study yielded 10\(^3\) CFU/mL or more. Therefore, we believe that the number of CRs is reliable and the most relevant for patient care. Furthermore, CR has been used as an end point in previous UTI studies.\(^29\)

Another limitation of our trial is that we did not confirm by urinalysis the number of self-reported UTIs in the year before inclusion. However, the aim of the study was to compare the effectiveness between treatment arms.

In conclusion, in postmenopausal women with rUTIs, prophylaxis with *L. rhamnosus* GR-1 and *L. reuteri* RC-14 did not meet the noninferiority criteria in the prevention of UTIs when compared with trimethoprim-sulfamethoxazole. However, development of antibiotic resistance is considerably lower with use of lactobacilli. Therefore, lactobacilli may be an acceptable alternative for prevention of UTIs, especially in women who dislike taking antibiotics.

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Additional Information: Dr Gregor Reid held patents for L. rhamnosus GR-1 and L. reuteri RC-14 but has transferred the rights to Chr Hansen A/S, Denmark.


REFERENCES


INVIITED COMMENTARY

The Advantages of Second Best

Preventing Recurrent Cystitis While Sparing the Microbiome

Approximately 60% of women in the United States experience a UTI, or acute cystitis, during their lifetime. Of these, 30% go on to have multiple recurrences.1 For women who suffer from frequent recurrences, effective preventive strategies are essential to free them from this disruptive illness. Unfortunately, the use of antibiotics for UTI prevention is becoming more problematic because resistance to commonly used agents is now widespread, infection caused by Clostridium difficile is increasingly common, and our appreciation of the importance of an undisturbed microbiome in health is growing. Therefore, investigations of antibiotic-sparing approaches to UTI prevention are of great interest to physicians and patients alike.

Beerepoot and colleagues report a comparative effectiveness study of the use of lactobacilli vs antibiotics...