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The Advantages of Second Best:

Preventing Recurrent Cystitis While Sparing the Microbiome

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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 colleagues² report a comparative effectiveness study of the use of lactobacilli vs antibiotics for UTI prevention in postmenopausal women. This randomized, placebo-controlled, double-blind trial compared oral capsules containing *L rhamnosus* GR-1 and *L reuteri* RC-14 twice daily with trimethoprim-sulfamethoxazole, 480 mg, once daily. The study included 252 postmenopausal women who had experienced at least 3 self-reported, symptomatic UTIs in the year prior to enrollment and evaluated the rates of recurrent UTI and antimicrobial resistance. During 12 months of prophylaxis, the mean number of CRs of UTI in the trimethoprim-sulfamethoxazole group was 2.9 in comparison with 3.3 in the lactobacilli group ($P=.42$). Based on predetermined rules for noninferiority, lactobacilli were inferior to antibiotic prophylaxis for this primary outcome. Additionally, the mean number of MRs was significantly lower in the trimethoprim-sulfamethoxazole group (1.2) than in the lactobacilli group (1.8; $P=.02$). For both CR and MR, a higher percentage of women in the lactobacilli group experienced at least 1 event, and the median time to first recurrence was significantly shorter in the lactobacilli group. Although no significant differences were

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seen in AEs between the 2 groups, 12.2% of the lactobacilli group experienced AEs leading to withdrawal in comparison with 5.2% in the trimethoprim-sulfamethoxazole group. The leading AE category in the lactobacilli group was nausea, vomiting, or diarrhea, experienced by 21.1% of women receiving this therapy. Thus, lactobacilli therapy was clearly second-best to trimethoprim-sulfamethoxazole for the primary outcome of UTI prevention.

On the other hand, when looking at the microbial resistance outcomes, the value of the nonantibiotic approach becomes more evident. The primary outcome measure was the percentage of trimethoprim-sulfamethoxazole-resistant *E coli* isolates from the feces and urine of asymptomatic women at 1 and 12 months. After 12 months of trimethoprim-sulfamethoxazole prophylaxis, 100% of urinary isolates of *E coli* were resistant to the antibiotic. Unfortunately, 3 months after stopping antimicrobial prophylaxis, trimethoprim-sulfamethoxazole resistance in the *E coli* urinary isolates was still much higher than at study entry (approximately 60% resistance vs slightly less than 30% at baseline). Resistance to ciprofloxacin, norfloxacin, and amoxicillin also rose during the treatment period in the antibiotic group and remained higher than baseline 1 month after prophylaxis was completed. In contrast, no increase in resistance to any antibiotic was seen in the lactobacilli group during the study.

As the authors mention, this study has some limitations. Not only did the study fail to enroll the target number of 140 participants in each arm, but of women who received a study treatment, 25 in the trimethoprim-sulfamethoxazole group withdrew, and 39 in the lactobacillus group withdrew before completing 12 months of follow-up. Another important issue is that the authors were not able to demonstrate that the orally administered lactobacilli reached the vagina. The vaginal Nugent scores in the lactobacilli group did not change from baseline, nor did these scores differ from those of the antibiotic-treated group. Polymerase chain reaction failed to identify *L reuteri* in any vaginal swabs collected during this study, although *L reuteri* was found in fecal swabs in 93.4% of the lactobacilli-treated women at 12 months. The primary mechanism of lactobacilli therapy in the prevention of UTI is restoration of normal microbial vaginal flora, particularly in postmenopausal women who lose vaginal lactobacilli with declining estrogen levels. In the absence of establishing vaginal colonization with the study strains, the lactobacillus treatment group may represent placebo treatment. A final limitation of the trial is that the main outcome was self-reported UTI, and the main area of improvement in both treatment groups was comparison with the patients' self-reported UTIs in the previous year.

Given these limitations, why are the findings of this study still exciting and compelling? Modern metagenomic sequencing approaches have freed us from culture-dependent detection methods and thus have opened a window to viewing the complexity of the mixed microbial communities in the human body—the human microbiome.³ Humans rely on this microbiome for nutrition, immune development, and resistance to pathogen colonization.⁴ Unfortunately, even short-term use of antibiotics can cause long-term perturbations in the gut microbiome, and persistence of resistance genes has been documented^{5,6} even 4 years after treatment. The recent Infectious Diseases Society of America guidelines⁷ on the treatment of acute cystitis took into account this concern for “collateral damage,” or

selection for drug-resistant organisms and colonization or infection with resistant organisms, in their ranking of recommended agents.

Within the context of preserving the health of the microbiome, antibiotic-sparing approaches to UTI prevention become very appealing. In another trial,¹ *L. crispatus* vaginal suppositories showed a trend toward reduction of recurrent UTI in premenopausal women in comparison with placebo. Other clinical trials⁸ of lactobacilli to prevent recurrent UTI have been smaller and quite varied in study design and have not shown a benefit for lactobacilli over other preventive treatments or placebo. So it seems clear that, at present, lactobacilli are a second-best therapy for UTI prevention in comparison with antibiotic suppression if the main concern is the number of episodes of UTI prevented. However, if the relevant outcome is the number of doses of antibiotic use prevented, lactobacilli come out ahead. From this perspective, the “nice guys,” that is, the preventive therapy that does not damage the indigenous flora, clearly finish first.

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