

Study/Reference	Stapleton AE, Au-Yeung M, Hooton TM, Fredricks DN, et al. Randomized, Placebo-controlled Phase 2 Trial of a Lactobacillus crispatus Probiotic Given Intravaginally for Prevention of Recurrent Urinary Tract Infection. Clinical Infectious Diseases 2011;52(10):1212–1217	
Purpose	It was this study’s goal to assess the ability of Lactin-V to reduce the incidence of recurrent UTI and to confirm the safety of the intravaginal probiotic.	
Study Design/ Methodology	This study was a single-center, randomized, double-blind, placebo-controlled, phase 2 trial, grant funded study, co-sponsored by the National Institute of Diabetes/Digestive/Kidney Diseases and the NIH’s Office of Research in Women’s Health.	
	Primary Outcome(s):	Secondary Outcome(s):
	The primary objective of this study was to evaluate Lactin-V’s ability to reduce the incidence of cystitis and produce high-levels of vaginal colonization with L. crispatus in healthy premenopausal women with recurrent UTIs.	Secondary objectives were to evaluate patterns of vaginal colonization with L. crispatus and to confirm the safety of the intravaginal probiotic.
Population	Inclusion criteria:	Exclusion Criteria:
	<ul style="list-style-type: none"> • Premenopausal women between the ages of 18–40 • Current, symptomatic, uncomplicated cystitis, defined as: <ul style="list-style-type: none"> ○ 1 or more typical UTI symptoms (dysuria, frequency, or urgency) <li style="text-align: center;">and ○ Pyuria <li style="text-align: center;">and ○ A positive urine culture with one or more uropthaogens or Lactobacillus species present as a single infecting organism. 	<ul style="list-style-type: none"> ▪ Patients were excluded if they had: <ul style="list-style-type: none"> • Complicated cystitis or uncomplicated pyelonephritis; • A history of urologic abnormality or renal calculi; • A recent sexually transmitted infection (STI) or BV or a history of recurrent BV; • Risk factors for STI and human immunodeficiency virus (HIV) infection; • Within 2 months of post-pregnancy or were lactating • Entered menopause; • Diabetes, HIV infection, or other immunocompromied state; • Had drug or alcohol abuse; • Persistent symptoms and/or pyuria after treatment of the initial acute UTI.
Size	A 100 young, healthy, women were randomized in equal proportions.	
Treatment Groups	In this study, all enrolled received antibiotics for an acute urinary tract infections, and were then randomized in equal proportions to receive either a Lactin-V intravaginal suppository or placebo, self-administered without an applicator, for five consecutive days, then once a week for 10 weeks.	
Intervention	Measurements to determine these outcomes included a structured interview, including a review of adverse events, and a structured physical examination, which included: Assessment of the appearance of external genitalia; Pap-like exam; Vaginal wet mount and assessment of vaginal discharge Urinalysis, urine dipstick for leukocytes, nitrite, and blood; as well as test to quantify the amount of WBCs in the urine. Urine and vaginal cultures were collected. In addition, a vaginal swab specimen for quantitative PCR evaluation for L. crispatus was conducted at visit 3 and 4 to assess the degree of vaginal colonization.	
Statistics	Data analysis consisted of evaluation of study means, medians, and frequency counts. The effect of the intervention was described using relative risks and 95% confidence intervals (CIs). Intent-to-treat analysis was performed in conjunction with per-protocol analyses were performed to assure similar results were seen.	
Results (Efficacy/ Safety)	General Results	
	<ul style="list-style-type: none"> • The median age was 21 years in both groups and median number of lifetime UTIs was 4.5 in all patients. 75% of women in both groups had never been married, and almost all (99%) were sexually active and had an equal median rate of sexual activity in the month prior to enrollment; 10% of women had used a spermicidal-containing birth control method in the past month. 	
	Primary Outcome	Secondary Findings

	<ul style="list-style-type: none"> • Seven (15%) of the women receiving Lactin-V had at least 1 UTI compared with 13 (27%) of the women receiving placebo (RR, .5; 95% CI, .2–1.2). • The prevalence of E. coli induced UTIs was similar in the 2. • Most women receiving Lactin-V achieved high-level vaginal colonization with 39/42 (93%) having high-level colonization at the final visit. • Only 30/44 68% of patients receiving placebo were found to have high-level colonization of L. crispatus at final evaluation (P = .004). • Women who received Lactin-V and achieved a high-level L. crispatus vaginal colonization pattern throughout the course of the study had a significant reduction in the risk of rUTI, whereas when this high-level colonization pattern occurred in women who received placebo, it was not protective (RR for Lactin-V, .07; RR for placebo, 1.1; P, .01). 	<ul style="list-style-type: none"> • Adverse effects were reported by 56% of Lactin-V patients and by 50% placebo patients. • The most common adverse effects reported vaginal discharge, itching or moderate abdominal discomfort. • One participant was reported to placebo group discontinued treatment due to adverse effects. No significant differences in rates of pyuria between the 2 groups were reported, with the rate of pyuria at 3 weeks being 13% and 22% for the treatment and placebo groups, respectfully. The rate of pyuria at 4 weeks was 32% and 33% for the treatment and placebo groups, respectfully. • No episodes of pyelonephritis were reported in either group.
Conclusions	Author Conclusions	Overall Conclusions
	<p>Authors conclude that Lactin-V treatment in women with rUTI resulted in robust and prolonged colonization with Lactobacillus crispatus, with a trend of reducing the incidence of recurrent UTI by 50%. The protective effects of Lactin-V were even greater in those women who achieved the most robust colonization with L. crispatus and reflect an apparent treatment advantage for Lactin-V over natural recovery of the vaginal flora after an episode of rUTI. Larger efficacy trials of this preventive method are warranted.</p>	<p>UTI-causing microorganisms are gaining resistance to traditional antibiotic treatment; therefore, a clear need for preventative UTI therapy is evident. No statistically significant difference in the rate of rUTI was found in this study. Those women receiving Lactin-V had a lower rate of rUTI and a higher rate of vaginal colonization with L. crispatus, indicating Lactin-V may have a potential therapy benefit. However, 68% of placebo treated women also achieved a high level of L. crispatus vaginal colonization, yet there was no reduction in the incidence of rUTI in this group. Due to the study's limitations, further evaluation of L. crispatus colonization, specifically colonization with the Lactin-V strain, and its ability to reduce the reoccurrence of UTI is needed.</p>
Comments	Strengths	Weaknesses
	<ul style="list-style-type: none"> • Sufficient background evidence to support study purpose • Randomized controlled trial • No potential conflict of interest 	<ul style="list-style-type: none"> • Relatively small sample size • Formal statistical analysis was not performed on some of the major outcome measures. • The study provided no explanation on which statistical tests were utilized. • High potential of Type II error