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Ingestion of Yogurt Containing *Lactobacillus acidophilus* as Prophylaxis for Candidal Vaginitis

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■ *Objective:* To assess whether daily ingestion of yogurt containing *Lactobacillus acidophilus* prevents vulvovaginal candidal infections.

■ *Design:* Crossover trial for at least 1 year during which patients were examined for candidal infections and colonizations while receiving either a yogurt-free or a yogurt-containing diet. Patients served as their own controls.

■ *Setting:* Ambulatory infectious disease center in a teaching hospital providing tertiary care.

■ *Patients:* Thirty-three women with recurrent candidal vaginitis were eligible after recruitment from community practices and clinics and through advertising. Twelve patients were eliminated for protocol violations. Of the remaining 21 patients, 8 who were assigned to the yogurt arm initially refused to enter the control phase 6 months later. Thus, 13 patients completed the protocol.

■ *Interventions:* Women ate yogurt for 6 months of the study period.

■ *Measurements:* Colonization of lactobacilli and candida in the vagina and rectum; candidal infections of the vagina.

■ *Main Results:* Thirty-three eligible patients were studied. A threefold decrease in infections was seen when patients consumed yogurt containing *Lactobacillus acidophilus*. The mean (± SD) number of infections per 6 months was 2.54 ± 1.66 in the control arm and 0.38 ± 0.51 per 6 months in the yogurt arm ($P = 0.001$). Candidal colonization decreased from a mean of 3.23 ± 2.17 per 6 months in the control arm to 0.84 ± 0.90 per 6 months in the yogurt arm ($P = 0.001$).

■ *Conclusion:* Daily ingestion of 8 ounces of yogurt containing *Lactobacillus acidophilus* decreased both candidal colonization and infection.

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Candidal vaginitis is a common cause of gynecologic infections in the United States, with an increased incidence seen in pregnant women, diabetic women, and women receiving antibiotic or corticosteroid therapy (1-6). However, some women do not have these risk factors but experience chronic vulvovaginal candidal infections (3, 5, 7). The current therapies are often inadequate and many patients fail treatment; however, reports on systemic prophylaxis have been promising (8, 9). Success with folk remedies, such as topical and systemic yogurt administration, has been reported anecdotally (10-12). No controlled studies have been done to evaluate yogurt as therapy or prophylaxis for this condition. We did a study to evaluate whether the regular ingestion of yogurt containing *Lactobacillus acidophilus* would decrease the number of episodes of vaginal candidiasis.

Methods

Patients

Women with recurrent vaginal candidiasis were recruited from community practices and the gynecology clinic of the Long Island Jewish Medical Center in New Hyde Park, New York. Patients excluded from the study included those with multiple vaginal pathogens, those who were receiving immunosuppressive or chronic antibiotic therapy, those who had ingested more than 16 ounces of yogurt weekly before the study, or those who were less than 16 years of age.

Study Design

Informed consent for participation in the research project was obtained from all patients. At the initial evaluation, a questionnaire was administered to each patient. The questionnaire covered pertinent gynecologic, dietary, personal, sexual, menstrual, and chronic medical problems, as well as family history. The vaginitis history included the number of episodes per year; the relation of the episodes to menses, sexual activity, and season of the year; the number of episodes diagnosed by a physician; and the presence or absence of microbiologic confirmation. The dietary history focused on the quantity of yogurt and other dairy products consumed. The patients were not instructed to alter dietary or sexual practices.

At admission to the study, each patient had a physical examination. Posterior fornix and vaginal wall specimens obtained using preweighed swabs were directly inoculated onto Sabouraud, chocolate, and Thayer-Martin media (Becton Dickinson Microbiology Systems [BBL], Cockeysville, Maryland). An additional swab was placed into 0.5 mL of nonbacteriostatic saline for quantification of yeast and lactobacilli. Slides were prepared for Gram staining, potassium hydroxide (10%) digestion, and fluorescent antibody detection of trichomonads. The vaginal pH was determined. During the first pelvic exam-

ination and when clinically indicated, viral cultures and specimens for the detection of chlamydia were obtained. Rectal cultures for candida and lactobacilli were obtained. All specimens were hand-carried to the laboratory for immediate processing. Before enrollment, the patients were observed for a maximum of 3 months for evidence of candidal vulvovaginitis.

Patients served as their own controls. Initially, patients were randomly assigned to one of two arms: In one arm, patients were instructed not to eat yogurt for 6 months, with crossover to 8 ounces of yogurt daily for the next 6 months. In the other arm, patients began on the yogurt diet and crossed over to a yogurt-free diet. Eight months into the study, a change was made in the protocol to begin all patients on the control arm. This change was made because some patients who started on the yogurt arm refused to cross over to the control arm. A patient requiring antibiotics during the study was told to double her daily yogurt consumption while on therapy during the yogurt phase.

Patients were seen at monthly intervals for at least 1 year; data relating to symptoms of vaginitis, sexual activity, last menstrual period, and changes in medications and diet were recorded. Patients were examined and microbiologic sampling was repeated at each visit. If the patient had symptoms of intercurrent vaginitis, she was examined, and a culture was done within 72 hours. Miconazole, nystatin, or other topical antifungal agents were given as treatment for intercurrent vaginitis. No colonizations were treated. No systemic antifungal agents were used during the study. If a visit was missed, interviews were done at the subsequent visit to assess intercurrent symptoms. A supply of yogurt was given to the patients at each visit. Women were instructed to refrigerate the yogurt and obtain new supplies if the yogurt reached the expiration date.

Laboratory Analysis

Yogurts from different manufacturers were analyzed to establish the presence of *Lactobacillus* species. Undiluted yogurt and dilutions of yogurt ranging from 10^{-2} to 10^{-7} were plated on selective Rogosa agar (BBL, Cockeysville, Maryland). A yogurt was chosen for the study (Colombo plain, Methuen, Massachusetts) that yielded greater than 10^8 colony-forming units (CFU) per millilitre of *L. acidophilus*. (Note: Currently, Colombo plain yogurt does not contain *L. acidophilus*.) This process was repeated during the study to ensure viability of *L. acidophilus* in the same yogurt over time until 2 weeks after the expiration date. All testing revealed greater than 10^8 CFU/mL of viable *L. acidophilus*.

Specimens obtained at all examinations were plated on *Lactobacillus* agar (Rogosa) with 10^{-2}, 10^{-4}, and 10^{-6} dilutions of vaginal washings and then incubated anaerobically at 37 °C. for 2 to 5 days. Cultures were examined for the presence of *L. acidophilus* and other *Lactobacillus* species. Rectal cultures were similarly treated. *Candida* isolates were speciated and quantified. *Candida albicans* was identified by germ tube formation, blastospores, chlamydospores, and biochemical reactions elicited with both API-20C (Analytab Products, Hicksville, New York) and the Vitek AMS yeast card (Vitek System, Hazelwood, Maryland). Anaerobic cultures were incubated in Gas-Pak-type jars (BBL). Qualitatively, all specimens were examined for aerobic and facultative anaerobic bacteria, fungi, trichomonads, and, when infection was suspected, chlamydiae and herpes simplex virus. All Gram-stained vaginal smears were evaluated for the presence of inflammatory cells and microbiota. Anaerobic bacteria were identified with API-ANIDENT (Analytab, Inc., Hicksville, New York). Lactobacilli were identified on the basis of 14 biochemical reactions in addition to colonial and microscopic morphology. These reactions included catalase production; and acid production on yeast-supplemented deMan-Rogosa-Sharpe agar from cellobiose, glucose, galactose, gluconate (observed for both acid and gas production), lactose, maltose, mannitol, melezitose, salicin, sorbitol, sucrose, and trehalose. Esculin hydrolysis was determined. Reaction profiles were generated by a program based on *Bergey's Manual of Systematic Bacteriology* (13) and Johnson and colleagues' "Taxonomy of the *Lactobacillus acidophilus* Group" (14). The phenotypic reactions elicited by the tests in our study served to identify groups of closely related bacteria that corresponded with results obtained from reference strains. Because *L. acidophilus* does not produce D-lactic acid, the absence of this isomer in addition to esculin hydrolysis served to distinguish this species from *Lactobacillus brevis*.

Lactobacillus acidophilus hydrogen peroxide production was determined using the method of Eschenbach and colleagues (15).

Clinical vaginitis was defined by the presence of erythema and an exudative discharge in association with symptoms of pruritus or pain. Candidal vaginitis was defined by the presence of clinical vaginitis with a Gram stain positive for budding yeast, pseudohyphae, an acidic vaginal pH, and a positive culture for *Candida* species. Candidal vaginal colonization was defined by a vaginal culture positive for *Candida* species with no clinical evidence of vaginitis. Candidal stool colonization was defined by a rectal culture positive for *Candida* species. Chronic candidal vaginitis was defined by at least five reported episodes of Candida vaginitis per year.

Statistical Analysis

Only patients with microbiologically confirmed candidal vaginitis were included in the analysis. The nominal time at risk was 6 months for each woman in the study but excluded the following time periods: the 2 weeks at the beginning of each study arm to allow for the wash-in and wash-out effect of the yogurt; the time during which protocol was violated (eating yogurt in the control phase or not eating yogurt for 4 consecutive days in the yogurt phase); and the 2 weeks following the completion of antibiotic therapy. A woman who lost 8 weeks on either arm was excluded from all analyses. A paired *t*-test was used to compare the mean number of infections developing during the control arm with the number developing during the yogurt arm of the study. A chi-square test was used to assess the relation between the presence of *Candida* species in the stool and in the vagina during any examination.

The effect of various epidemiologic factors on the incidence of vaginitis was tested by a series of analyses of variance and hierarchical multiple regressions in which the interaction of each factor with the presence or absence of eating yogurt was tested for significance.

The incidence of candidal vaginitis was calculated as the number of infections divided by the time at risk. All statistical tests were two-tailed.

Results

Eighty-three women who reported a history of chronic candidal vaginitis were recruited for the study and entered the observation period preceding the study. Twenty-seven had no evidence of vaginitis. Twenty-three had infections due to other causes (16 patients, unidentified pathogens; 3 patients, herpes simplex virus; 2 patients, *Trichomonas* species; 1 patient, *Gardnerella* species; and 1 patient, *Neisseria gonorrhoeae*).

Thirty-three women were entered into the study. Twenty women did not complete the protocol: Twelve women were excluded for protocol violations (6 failed to keep appointments, 2 were on long-term antibiotic therapy, 2 regularly failed to eat yogurt, and 2 were subsequently found to have mixed infections [*Trichomonas* and *Candida* infections]). Of these 12 women excluded from the study, 10 had been started on the "no yogurt" arm. All had documented yeast infections before entry. One patient on the "no yogurt" arm had *L. acidophilus* stool colonization. Eight women who had been assigned initially to the yogurt arm completed the first 6 months of the trial but refused to enter the control arm because of clinical improvement (all 8

women had positive vaginal candidal infections on entry; 4 became colonized with *L. acidophilus*; and during the 6-month follow-up period, 2 had single episodes of vaginal yeast infections).

Thus, 13 women completed the protocol, completing all required follow-up examinations in each arm. Because of the systematic attrition noted early in the study, 11 of the 13 women were begun on the control arm.

The 13 women ranged in age from 24 to 50 years (mean age, 35 years). Three patients reported five candidal infections per year, two reported 6 to 8 per year, and eight reported that they had chronic infections. Age at the onset of yeast infections ranged from 19 to 30 years (mean age at onset, 23 years). None of the women had diabetes mellitus. Nine patients (69%) reported a history of using birth control pills; three were taking these pills during the course of the study.

The primary dependent variable was the number of infections in the 6 months on either study arm. The mean number of infections per 6 months was 2.54 ± 1.66 in the control arm and 0.38 ± 0.51 infections per 6 months in the yogurt arm ($P = 0.001$). (Figure 1; Table 1).

A second dependent variable used in our study was candidal colonization regardless of clinical evidence of infection. (This measure was assessed by laboratory personnel who were blinded to the patient's current study arm and clinical data.) The mean number of positive *Candida* colonizations was 3.23 ± 2.17 per 6 months in the control arm and 0.84 ± 0.90 per 6 months in the yogurt arm ($P < 0.001$) (*see* Figure 1 and Table 1).

To ensure that the results had not been affected by changes in patient behavior, the analyses were repeated using only examinations after "clean" time periods (that is, periods during which patients experienced no change in diet, birth control method, or sexual partner). The results of these analyses were essentially unchanged. All patients who crossed over from "no yogurt" to yogurt reported subjective relief.

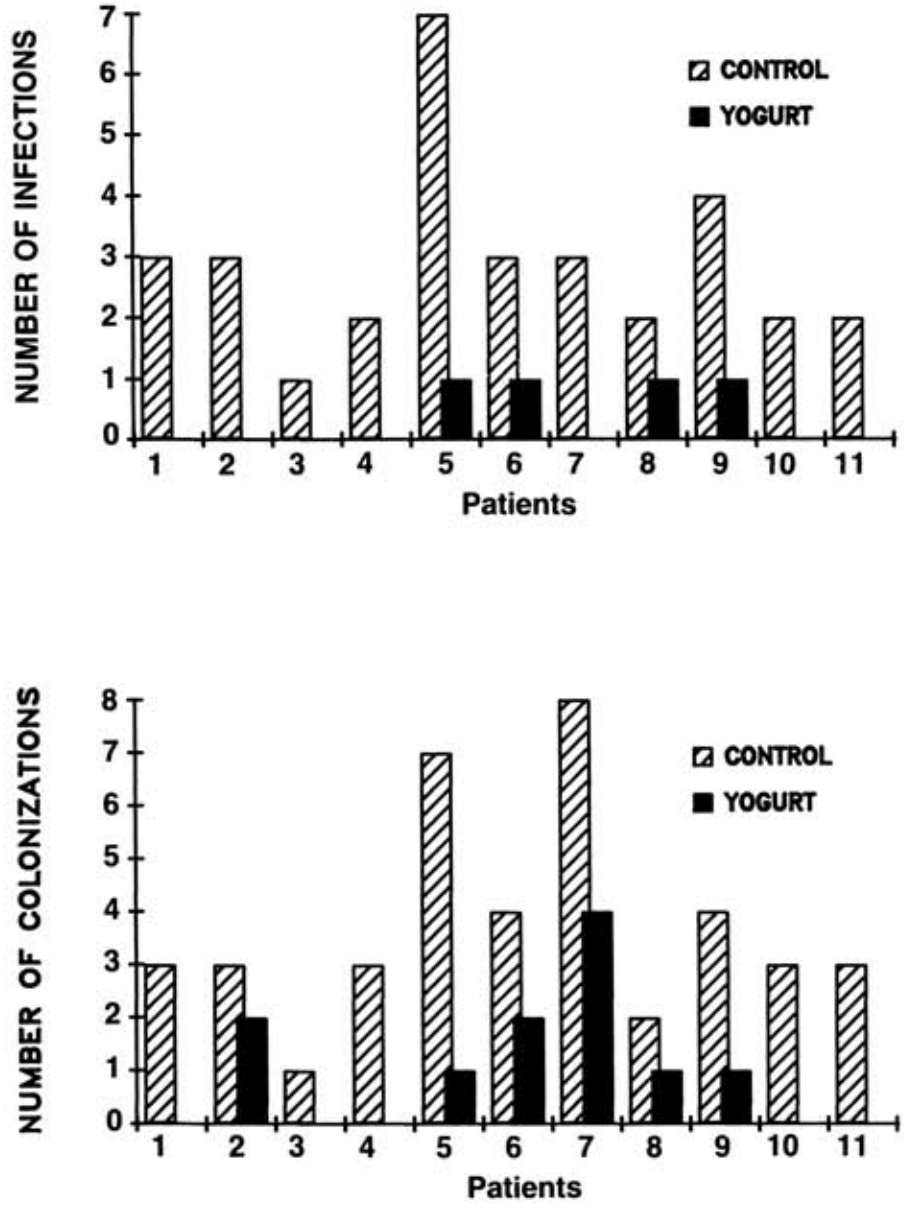

Figure 1. *Candida* infections and colonizations. Top. Number of *Candida* infections per 6 months in individual patients. **Bottom.** Number of colonizations per 6 months in individual patients.

Table 1. Effect of Yogurt on Candidal Infections and Colonizations*

Variable	Control Arm	Yogurt Arm	*P* Value†
Infections per 6 months, *n*	2.54 ± 1.66	0.38 ± 0.51	< 0.001
Colonizations per 6 months, *n*	3.23 ± 2.17	0.84 ± 0.90	0.001
Examinations in which infection was detected, %	0.33 ± 0.19	0.13 ± 0.19	0.002

* All values are expressed as mean ± SD.
† Calculated by paired *t*-test.

Before entering the yogurt arm, 10 women had positive stool or vaginal cultures, or both, for *L. acidophilus* 23% of the time (25 positive cultures in 110 visits). While on the yogurt arm, 11 women had positive stool and vaginal cultures for *L. acidophilus* 31% of the time (24 positive cultures in 78). The different number of visits reflects additional evaluations when patients were symptomatic. Yogurt-derived *L. acidophilus* showed moderate production of H_2O_2.

A clear relation emerged between the presence of *L. acidophilus* in the rectum and its presence in the vagina. When *L. acidophilus* was absent in the stool (119 specimens), the probability that it would be present in the vagina was only 15.5%. By contrast, when *L. acidophilus* was present in the stool (26 specimens), the probability that it would be present in the vagina was 54.8% ($P < 0.001$).

Discussion

Women who experience recurrent candidal vulvovaginitis can choose from myriad topical and systemic therapies, none of which appears to be "the answer." Vaginal instillation of yogurt and *L. acidophilus*-containing milk products have been tried in an uncontrolled fashion with varying degrees of purported success (10-12). We studied the use of ingested yogurt containing viable *L. acidophilus* cultures as preventive therapy for candidal vaginitis.

In our study, we found a decrease in the incidence of candidal vulvovaginitis during the yogurt arm. An understanding of the pathogenesis of chronic candidal vaginal infections may help explain the ability of yogurt to decrease the occurrence of such infections. However, the reasons for persistent infection are unclear.

Persistent candidal colonization may play a role in the association between a gastrointestinal candidal reservoir with vaginal colonization, infection, and reinfection, but this is controversial. Identical *Candida* strains in the mouth, anus, and vagina, suggestive of auto-inoculation, have been demonstrated in some studies (16-18). Other studies have shown that gastrointestinal colonization has little to do with vaginal recurrences, either because the vaginal microflora are not directly linked to changes in the gastrointestinal microflora or because a vaginal reservoir exists that is responsible for reinfection (19-21). Recurrence has also been attributed to host factors or interactions of candida with other possible pathogens (22, 23).

We evaluated the effect of the ingestion of yogurt containing *L. acidophilus* on gastrointestinal *Lactobacillus* colonization. Because there is evidence that lactobacillui can inhibit the growth of candida, we attempted to assess the effect of colonization on gastrointestinal and vaginal candidal load or pathogenicity, or both (24-26).

Despite conflicting data about the ability of diet and *L. acidophilus* supplementation to alter the gastrointestinal microbiota, we anticipated an increase in *L. acidophilus* colony counts in stool and vaginal specimens after yogurt ingestion and a subsequent decrease in vaginal yeast colony counts (25-31). We chose a yogurt that had a high *L. acidophilus* content, because the evidence suggested that *L. acidophilus* had improved survival on passage through the acidic gastric pH when compared with other *Lactobacillus* species (25). Although *Lactobacillus* colonization increased when patients were on the yogurt arm, the difference was not significant. An association between the presence of *Lactobacillus* species in the rectum and vagina was seen, and yogurt ingestion had a marked effect on the incidence of candida infection in the vagina and rectum.

Certain lactobacilli may serve a function in the normal vaginal ecosystem. Eschenbach and colleagues (15) reported that hydrogen peroxide-producing lactobacilli were inhabitants of the normal vagina, whereas anaerobic or non-H_2O_2 producers were associated with vaginosis (32). In our study, *L. acidophilus* strains in yogurt were found to produce hydrogen peroxide. Additionally, anaerobic lactobacilli predominated in the infected women and in the women on the non-yogurt arm.

The attrition rate in our study was high because participation involved some inconvenience to the patient. The degree of systematic attrition was unexpected, however, and was due to the refusal of patients who had experienced relief with yogurt to enter the control arm. This may have introduced bias. However, analysis of these women showed a rapid decrease in infections while on yogurt as compared with patients who began the study on the control arm. In addition, given the chronic nature and prolonged history of vaginitis in these women, this alteration of the study design should not have had any effect on the outcome.

Neither the patients nor the interviewer were blinded to the patient's treatment assignment, again introducing a potential bias. This was not seen as a major problem for two reasons: the magnitude of the effect of yogurt was quite large, more than could be reasonably attributed to bias; and the laboratory results were reported by personnel who had no knowledge of the patients' study arm. To further exclude the effect of observer bias, we analyzed candidal colonization exclusive of clinical findings and found a significant effect with a marked decrease in candidal growth when the patients were eating yogurt. A comparative, double-blinded study in which yogurt with live lactobacillus cultures is compared with irradiated or pasteurized yogurt would be desirable.

It appears that the gastrointestinal strain of *L. acidophilus* colonized the vaginal tract of our patients. Those interested in using dairy products to recolonize their

gastrointestinal tracts should be wary of claims of dairy product manufacturers. When various brands of yogurt were tested, some did not contain the advertised lactobacilli (33).

All of the women enrolled carried a diagnosis of chronic candidal vaginitis, yet candidal infections were documented in only 41%. Some of the misdiagnoses included treatable problems (gonorrhea, bacterial vaginosis and *Trichomonas* infection), emphasizing the importance of making a specific etiologic diagnosis in patients with chronic vaginitis.

In summary, our prospective study of women with recurrent candidal vulvovaginitis found that the daily ingestion of 8 ounces of yogurt containing *L. acidophilus* decreased both candidal colonization and infection. The mechanism of action may be multifactorial; lactobacilli or a particular *Lactobacillus* species may have a direct effect on candidal growth and survival.

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