



# The role of probiotics in women with recurrent urinary tract infections

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## ABSTRACT

Urinary tract infections (UTIs) still represent a significant bother for women and result in high costs to the health system. Increasing antimicrobial resistance has stimulated interest in non-antibiotic prophylaxis of recurrent UTIs. Evidence shows that the microorganisms inhabit many sites of the body, including the urinary tract which has long been assumed to be sterile in healthy individuals, might have a role in maintaining urinary health. Studies of the urinary microbiota (UM) have identified remarkable differences between healthy populations and those with urologic diseases. The depletion of these organisms in women susceptible to UTIs raised the question of whether artificial supplementation of these microorganisms as probiotics could lower infection rates. In the literature, probiotic interventions were shown to have some efficacy in the treatment and prevention of urogenital infections. Despite previous controversy regarding the use of probiotics, as treatment for UTIs, there are increasing signs that it may be possible to use them as a first step in regulating the UM so as to reduce the risk of or as a treatment for certain urinary diseases. However, further future clinical trials, involving large numbers of patients, will be mandatory to achieve definite evidence of the preventive and curative role of probiotics in UTIs. Details about correct formulations in terms of amount of bacteria, viability and associated growth factors, will be required in order to standardize the administration schedule and achieve homogeneous and comparable results on selected patients.

**Keywords:** Lactobacillus; microbiota; probiotics; urinary tract infections.

## Introduction

Urinary tract infection (UTI) is the most frequently seen bacterial infection in polyclinic and service patients. In the United States, 11% of women over the age of 18 experience one episode of UTI a year. The incidence of UTI is most common between the ages of 18-24. The most prominent feature of UTI in women is its tendency to recur. The probability of recurrence after the first UTI episode in healthy 18-29 year-old women has been reported as 24%.<sup>[1,2]</sup> Multiple episodes can be seen within 1 year in 5% of women who had experienced an episode of UTI. The most important risk factors in women between the ages of 18-39 who had experienced UTI are sexual relationship and history of UTI.

Recurrent UTI is defined as 3 episodes within the last 12 months or 2 episodes within the last 6 months.<sup>[3]</sup>

Treatment of UTI with antibiotics causes antibiotic resistance among uropathogenic microorganisms and other bacteria in the body. Today, resistance developed by uropathogens against antibiotics is observed. Repeated treatment cures in women who experienced recurrent UTIs are effective in the development of resistance to antibiotics and adversely affect normal microbiota. Antibiotic-free protective approaches have gained popularity in recent years, especially in recurrent UTIs worldwide, as a result of resistance developing against antibiotherapy and also tendency of the patients towards antibiotic-free treatment alternatives.<sup>[4-8]</sup>

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Among these treatment approaches, probiotic applications are among the promising alternatives. In parallel with the introduction of probiotic use into the treatment modalities of UTIs, the microbiological structure of the urinary system has to be examined in more detail.

## Urinary microbiota

The structure of microbiome in humans has been a topic of immense interest in recent years.<sup>[9,10]</sup> Various studies have been performed concerning the potential roles performed by complex microbial structures in many different diseases. Although there are sufficient studies in the literature on microbiota of skin, mouth, vagina and intestines, urinary microbiota (UM) has not been investigated sufficiently. The reason for this was that until recently urine has been thought to be sterile in healthy individuals.

Thanks to 16S rRNA sequencing and advanced quantitative urine culture (EQUC) techniques developed in recent years, aerobic and anaerobic bacteria colonized in normal flora in the urinary system have been detected.<sup>[11,12]</sup> Bacterial isolation can be performed using EQUC method in 80% of the cases reported as 'no growth' in standard cultures of urine samples.<sup>[13]</sup> These bacteria in the urinary system have an important role in the health and balance of the urinary system.

In studies on urinary microbiomes, the degree of concentration of bacteria habiting in urinary systems may vary according to the sex, the method of urine collection, and the technique used to study UM. In general, *Lactobacillus* and *Streptococcus* are the most frequently observed species and many studies have been performed on them. Both microorganisms are lactic acid bacteria and have protective roles against pathogens colonized in the urogenital region.<sup>[13]</sup> Other less frequently found bacterial strains are *Alloscardovia*, *Burkholderia*, *Jonquetella*, *Klebsiella*, *Saccharofermentans*, *Rhodanobacter* and *Veillonella*. It has been reported that the urine collection method (midstream urine specimen, first voided urine specimen, suprapubic aspiration, transurethral catheterization) and the technique to identify the UM are the factors that could lead to formation of different UM profiles. UM reported in healthy women is summarized in Table 1.<sup>[12-15]</sup>

Despite the presence of many species of bacteria in the urinary system, it is of interest to note that these bacteria do not lead to a chronic UTI. Suitable nutrients for these bacteria may be found in the environment and at the same time virulence factors that may cause infection in most organisms may be detected. Stapleton explained this condition by suggesting that unchangeable host factors play a role in the colonization of these organisms.<sup>[16]</sup> So, in a sense, hosts are choosing, and containing

**Table 1. Studies demonstrating components of urinary microbiomes in healthy women, and their characteristic features**

Study population	Predominant bacteria	Sample collection method	The technique applied	References
Women aged 35-65 years (n=60)	<i>Lactobacillus</i> , <i>Gardnerella</i> , <i>Staphylococcus</i> , <i>Streptococcus</i> , <i>Enterococcus</i> , <i>Bifidobacterium</i> , <i>Atopobium</i> , <i>Enterobacteriaceae</i>	Transurethral catheter	16S rRNA gene sequencing and/or EQUC	14
Women aged 35-65 years (n=58)	<i>Lactobacillus</i> , <i>Gardnerella</i> , <i>Corynebacterium</i> , <i>Enterobacteriaceae</i> , <i>Anaerococcus</i> , <i>Bifidobacterium</i> , <i>Streptococcus</i> , <i>Staphylococcus</i> , <i>Sneathia</i> , <i>Peptoniphilus</i> , <i>Atopobium</i> , <i>Rhodanobacter</i> , <i>Trueperella</i> , <i>Alloscardovia</i> , <i>Veillonella</i>	Transurethral catheter	16S rRNA gen gene sequencing and/or EQUC	13
Women aged 27-67 years	<i>Lactobacillus</i> , <i>Prevotella</i> , <i>Gardnerella</i> , <i>Peptoniphilus</i> , <i>Dialister</i> , <i>Fingoldia</i> , <i>Anaerococcus</i> , <i>Allisonella</i> , <i>Streptococcus</i> , <i>Staphylococcus</i>	Midstream urine sample culture	16S rRNA gene sequencing	12
Female population whose age range was not indicated (n=24)	<i>Lactobacillus</i> , <i>Corynebacterium</i> , <i>Streptococcus</i> , <i>Actinomyces</i> , <i>Staphylococcus</i> , <i>Aerococcus</i> , <i>Gardnerella</i> , <i>Bifidobacterium</i> , <i>Actinobaculum</i>	Transurethral catheter	16S rRNA gene sequencing and/or EQUC	15

EQUC: Expanded Quantitative Urinary Culture

**Table 2. Properties which should be possessed by a healthy probiotic**

They should be able to adhere to the cells
They should be able to prevent or decrease adherence of pathogenic microorganisms
They should be able to secrete acids, hydrogen peroxide, and bacteriocins so as to prevent growth of pathogens
It should be safe, and should not be invasive, carcinogenic, and pathogenic
They should be able to form clusters so as to produce normal-balanced flora

microorganisms that will not harm them. Are the host and the bacteria developing all together? It is known that frequently recurrent UTIs develop in children of the women who experience clinically recurrent episodes of UTIs.<sup>[17]</sup> It is debatable whether this condition arises from a genetic predisposition or from a bacterial transfer which occurs in childhood or perhaps even at birth.

Even though the studies were limited in number, significant differences were detected between male and female UM.<sup>[18,19]</sup> This difference may be thought to be related to differences in anatomical structures, hormones and local defense mechanisms. This difference, however, is thought to play a role in susceptibility to certain diseases.

When vaginal flora is examined, it is known that microorganisms of *Lactobacillus spp.* are dominant bacteria and form UM which demonstrates antimicrobial activity. Inadequate treatment of genitourinary infections and recurrence lead to the shift of *Lactobacillus* dominance in the normal flora to the coliform uropathogens.<sup>[20]</sup>

There is a clear, and established relationship between vaginal flora and urogenital infections. Most of the microorganisms in the vagina stem from the gastrointestinal tract apart from the personal hygiene.<sup>[21]</sup> In a healthy vagina dominance of *Lactobacillus spp.* is observed.<sup>[22,23]</sup> Many scientific studies have shown that regulation of the gastrointestinal and vaginal flora with probiotic support may prevent genitourinary infections.<sup>[23]</sup>

### Definition and characteristics of probiotics

The term probiotic consists of the words “pro” in Latin and “bios” in Greek meaning life. The concept of probiotics was first introduced by Elie Metchnikoff, the Russian Nobel Prize winner in 1907. Metchnikoff notes that the microbes in the digestive system can provide positive contributions, especially in the digestive system diseases.<sup>[24]</sup> The World Health Organization has defined probiotics as “useful living microorganisms that have a positive effect on the health and physiology of a person when taken in sufficient quantities.”<sup>[25]</sup> The properties that a good probiotic should have are indicated in Table 2.<sup>[25]</sup> Probiotics can be found in foods and food supplements (in cap-

sule, tablet and powder forms). The bacteria may be present from the beginning in probiotic foods and supportive treatment agents, or may be added during the preparation of the product. Probiotics must be resistant to gastric and bile acids in order to reach the intestinal system and produce beneficial effects on the body.<sup>[26]</sup>

Since the vaginal microflora is intended to be corrected, probiotics that prevent and treat genitourinary infections should contain *Lactobacillus* species. The mechanism of action of probiotics may involve acidification of the mucosal surface, inhibition of adhesion of pathogens, production of substances such as vitamins and immunomodulators, and synergistic activity with the host's immune system.<sup>[27]</sup>

Some *Lactobacillus* species produce hydrogen peroxide and biosurfactants that acidify the vaginal mucosa. These properties as well as their microbiomimetic regulatory effects have been demonstrated.<sup>[28]</sup> All these properties make *Lactobacillus* the preferred probiotic agent for the prophylaxis and treatment of urogynecologic infections.

### Relationship between antibiotics, and probiotics

*Lactobacilli* can prevent the adherence, growth and colonization of uropathogenic bacteria.<sup>[29]</sup> It has been shown that healthy microbial populations of *Lactobacillus* species have a strong inhibitory effect on *E. coli*.<sup>[30]</sup> Infections treated using antibiotics reduce drug abuse, leading to drug resistance and render the natural barrier of the urinary system vulnerable to infections.<sup>[31-33]</sup>

Stewardson et al.<sup>[34]</sup> compared ciprofloxacin and nitrofurantoin treatments in their study and found that the ciprofloxacin group had a significant effect on intestinal microbiome which mostly contain healthy *Lactobacillus spp.* In the group of nitrofurantoin, microbiota structure demonstrated relatively lower degree of variations.

Modena et al.<sup>[35]</sup> investigated the effect of prophylactic antibiotic use on UM. UMs of prophylactic trimethoprim-sulfamethoxazole treatment, and healthy control group were compared and it was shown that the the number of pathogenic species in the antibiotic group significantly increased while microbial diversities

decreased relative to the healthy control group. These findings support the necessity of demonstrating sensitivity in selecting optimal prophylactic regimens and suggest that probiotic prophylaxis can be considered more effectively.

Although proposals for the use of only probiotics in the prophylaxis of recurrent UTI are limited it is thought that probiotics may be effective when they are part of an alternative therapy or multi-drug treatment and prophylaxis of urogenital infections.<sup>[36]</sup> Another important issue is that no serious adverse effects is seen in any of the probiotic applications.

When considered as a part of multiple treatment, antibiotics and probiotic treatment should last 2-4 hours to prevent damage to viable microorganisms in the gastrointestinal tract.

### UTI and probiotics

Most of the recurrent UTIs in women occur in the presence of uropathogenic *E. coli*. Antibiotics used in the treatment of these infections reduce the number of lactobacilli in the urinary system and may cause antibiotic resistance in the following period and destroy the existing natural barrier of the urinary system formed against infections.

In their study, Zucotti et al.<sup>[37]</sup> stated that probiotics could be a good alternative to antibiotic therapy because of their ability to bind to uroepithelial cells and inhibit pathogenic growth, and biosurfactant secretion. The same investigators have emphasized that oral *Lactobacillus* therapy can colonize these bacteria in the urinary tract following intestinal colonization.

The idea of oral probiotic application is based on the knowledge that pathogens that cause most of the urogenital infections progress from the rectum to the perineal region and then to the vagina and the mesentery. If pathogenic bacteria can achieve this, then why *Lactobacillus*, an important component of vaginal colonization, can not do it? Clinical studies have demonstrated that oral administration of *Lactobacillus* can demonstrate its effects after reaching the vagina.<sup>[38-41]</sup> In these studies, probiotic capsules containing *L. rhamnosus* and *L. fermentes* were administered orally at a dose of 10<sup>9</sup> CFU once or twice daily. In these studies the authors reported that probiotic capsules administered orally may regulate the vaginal flora and may be effective on recurrent UTIs. It has also been emphasized that oral probiotics may be more comfortable for patients than for vaginal administration, and that patient compliance with treatment may be better.

### Prevention of UTIs in women

A meta-analysis on the application of *Lactobacillus* was published.<sup>[42]</sup> A total of 294 patients from 5 published studies were evaluated and as a result vaginally administered *Lactobacillus*

probiotic chain was shown to be safe and effective in preventing recurrent UTIs in adult women (Table 3). In the analysis, it was stated that the ovules containing combinations of *L. crispatus* CTV-05 or *L. rhamnosus* GR-1 and *L. fermentum* B-54 were the most effective methods and that higher number of randomized clinical trials were needed for the evaluation of oral probiotic treatments.

Abad and Safdar reviewed 25 clinical trials in a systematic review they published in 2009 and investigated the presence of *Lactobacillus*-containing probiotics in the prevention and treatment of urogenital infections. In different studies where vaginal and oral administrations have been applied, it has been found that application times extended from 4 days to 19 months and the amount of *Lactobacillus* in the preparations used was not less than 10<sup>6</sup>/mL.

Side effects due to *Lactobacillus* prophylaxis were investigated in 7 of the studied studies, and any side effects were not observed in 4 of them and in the remaining 3 studies mild headache, and increased appetite or fever was observed. In conclusion, they found evidence that *Lactobacillus* species (particularly *L. rhamnosus* GR-1 and *L. reuteri*) may be useful in the prevention and treatment of recurrent UTIs. It is also stated that additional studies are needed to clearly define the optimal dose and duration of application.<sup>[43]</sup>

Recently, two double-blind, placebo-controlled, randomized clinical trials investigating the effects of probiotics in inhibiting recurrent UTIs have been published.<sup>[16,44]</sup> In a double-blind study, Beerepoot et al.<sup>[44]</sup> demonstrated that supplementation with 480 mg *L. rhamnosus* GR-1 and *L. reuteri* RC-14 significantly though incompletely decreased the mean number of recurrences in patients with uncomplicated UTI relative to the control. In addition, antibiotic resistance was significantly reduced in the probiotic group compared to the control group. In a recent double-blind, placebo-controlled phase 2 study, Stapleton et al.<sup>[16]</sup> investigated 100 premenopausal women who had undergone cystitis at least once within the last 12 months. These patients were divided into two groups and for 10 weeks following an episode of cystitis placebo treatment was given to 48 patients, and other 48 patients received intravaginal probiotics (Lactin-V) containing *Lactobacillus crispatus* (10<sup>8</sup> CFUs/mL). The results of this study showed that the incidence of recurrent UTIs in patients who received intravaginal *Lactobacillus* treatment decreased significantly compared to the placebo group.<sup>[16]</sup>

### Relationship between premenopausal UTI and probiotics

Most studies on probiotic application in recurrent UTI in the literature have been performed in premenopausal women. In fact, the risk factors in premenopausal women are different from those of the postmenopausal women. These risk factors include recent sexual intercourse, use of spiral or condom containing spermicide, history of UTI, and recent antibiotic use. In a mul-

**Table 3. Some studies that evaluated probiotics used in the treatment of UTIs<sup>[42]</sup>**

Agents used	Dose, and route of administration	Number of patients, and structure of the study	Efficacy in conditions of UTI	RR (95% CI) p	Reference
Antimicrobial treatment and Lactobacillus ovules	Vaginal, >1.6x10 <sup>9</sup> CFU/L. rhamnosus GR-1 and L.fermentum B-54	Randomized placebo-controlled, double-blind study including 41 pre-, and postmenopausal patients	Recurrence rate: 29% in UTI patients receiving antimicrobial treatment Recurrence rate was observed to be 21% in patients who received vaginal ovules containing <i>Lactobacillus</i> spp. following antimicrobial treatment	0.45 (0.15-1.40) p=0.2682	47
Lactobacillus rhamnosus GR-1 ve Lactobacillus reuteri B-54	Vajinal, 1x10 <sup>9</sup> CFU/L. rhamnosus GR-1 ve L.fermentum B-54	55 pre-menopausal women; randomized double-blind study	Recurrence rate was 73% in 25 patients who received once weekly doses of vaginal ovules containing L. rhamnosus GR-1 ve L.reuteri B-54; 79% decrease was observed in recurrence rates in 30 patients who received once weekly doses of intravaginal lactobacillus growth factor	Not performed	48
Lactobacillus drink, and fruit juice	Oral, 4x10 <sup>10</sup> CFU/100 mL. rhamnosus GG	324 pre-menopausal patients, randomized placebo-controlled double-blind study	The risk of UTI decreased significantly using fruit juice containing probiotic in 139 patients diagnosed as acute UTI .	1.11 (0.70-1.76) p=0.8320	49
Lactobacillus ovules	Vaginal, 10 <sup>8</sup> CFUs/ mL <i>L. crispatus</i>	100 premenopozal, Randomized placebo-controlled, double-blind study including 100 premenopausal women	Vaginal ovule containing L. crispatus, and placebo were applied for 10 weeks in patients who did not receive UTI treatment within the previous 12, and a significant decrease in disease was observed in the probiotic group	0.54 (0.24-1.23) p=0.2089	16

tivariate analysis, Scholes et al.<sup>[45]</sup> reported that frequent sexual intercourse is the most important risk factor for UTI. Other risk factors can be described as factors that cause vaginal colonization of uropathogens and decrease in the number of *Lactobacilli* which pass through ascending route into the urinary system.<sup>[46]</sup>

Though sufficient number of studies on the efficacy of probiotic applications containing especially *Lactobacillus* spp. in UTIs developed as a result of changes in the balance of vaginal flora in sexually active women have been reported in the literature, studies with postmenopausal women have not seem to be at an adequate level.

#### Dose and formulations of probiotics

In literature studies on probiotic use in UTI, duration of probiotic use ranges from 5 days to 12 months, and doses vary between 10<sup>4</sup> CFU and 10<sup>10</sup> CFU. Oral, vaginal, and liquid formulations are being used.<sup>[32]</sup>

In UTI use of mono-, and combination treatments with probiotics has been published (Table 3). These combinations have been applied with different microorganism strains and different routes of administration (vaginal, oral) and effective results have been reported.<sup>[47-49]</sup> In a recent prospective study, Montorsi et al.<sup>[50]</sup> administered a combination of 120 mg cranberry, 10<sup>9</sup>/CFU L. rhamnosus SGL 06 and 75 mg vitamin C for 3 months in female patients with recurrent UTI. In the 3rd and 6th month controls, the response rates to treatment were 72.2% and 61.1%, respectively. Researchers noted that the combination was well tolerated and effective.

In conclusion, recurrent UTIs impair quality of life significantly and antibiotic prophylaxis may increase resistance to uropathogens while being effective during treatment. Although there have been few studies on the prevention of recurrent UTIs without use of antibiotics within the past years, interest in this area has increased over the years.

The reason for this interest is the desire of the patients to be treated with natural products while the physicians are concerned about the development of resistance against antibiotics. Evidence of probiotic application in UTIs is not yet sufficient to recommend use of probiotics. Today, however, there is no doubt that UM has changed during UTI and antibiotherapy. Even the question of whether UM analysis should be done before treatment of the patients has been revived.

Most of the published studies on the use of probiotics in the treatment, and prophylaxis of UTIs have low scientific value and the treatment regimens applied are heterogeneous, time consuming. However, probiotics are preferred by the patients because they are safe and more tolerable than antibiotics.

In clinical practice, an integrality should be established between scientific evidence, clinical experience and patients' desire. Because of the lack of established treatment recommendations for recurrent UTIs up to now and/or because the proposed treatments differ in success rates across patients, probiotics seem to be further considered as a part of multimodal therapies to be applied in multifactorial diseases such as recurrent UTIs.

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