

## Probiotics and Women's Health

Urinary tract infections (UTI) and vulvovaginitis are the most common infectious disorders women face. During her lifetime, a woman has a 75% chance of developing vulvovaginal candidiasis. At least half of all women will suffer from one or more urinary tract infections. Following a first UTI, up to 50% of women experience recurrent infections. Bacterial vaginosis, an overgrowth of certain anaerobic microorganisms such as *Gardnerella vaginalis*, is the most common cause of vaginal itching, discomfort, and discharge. Genitourinary tract infections in women are almost invariably secondary to disruptions of the healthy vulvovaginal microbiota resulting in the growth of opportunistic pathogens. Probiotics, either consumed by mouth or administered topically, are an excellent approach to restoring and maintaining a healthy vulvovaginal microflora and supporting against infections.

### The Critical Genitourinary Role of *Lactobacillus* Species

After birth, the neonatal vagina is predominantly colonized by lactobacilli rendering the vaginal pH acidic. In childhood, vaginal pH becomes less acidic and the microbiota consists of a broad mix of aerobic and anaerobic microbes. These include *Staphylococcus epidermidis*, *Peptostreptococcus*, *Enterococcus*, *Escherichia coli*, *Eubacterium*, *Gardnerella*, and *Veillonella parvula*. Though *Lactobacillus* species are highly prevalent in the prepubertal genital tract, they are not predominant. This changes dramatically when puberty begins and estrogen levels rise. Among estrogen's numerous trophic effects are the proliferation, thickening, and maturation of the vaginal mucosa. The cornified, stratified squamous epithelial cells become rich in glycogen. *Lactobacillus* species, specifically homologous members of the *L. acidophilus* complex, come to predominate the vaginal microflora. These microaerophilic organisms utilize glucose derived from hydrolyzed glycogen secreted by the squamous epithelium and produce lactic acid. High lactic acid production by *Lactobacillus* species results in a healthy acidic vaginal pH of between 3.8 and 4.5. Chaperonin-60 sequence-based gene amplification show that the most common indigenous *Lactobacillus* species during a woman's reproductive years is the notoriously difficult to culture *L. iners*, followed by *L. crispatus*, *L. gasseri*, and *L. jensenii*. Lactobacilli present in fewer numbers include *L. acidophilus*, *L. brevis*, *L. casei*, *L. delbrueckii*, *L. fermentum*, *L. plantarum*, *L.*

*reuteri*, *L. rhamnosus*, *L. salivarius*, and *L. vaginalis*. In any given woman, the vaginal microbiota tends to be dominated by 1 or 2 *Lactobacillus* species. *Lactobacillus* populations fluctuate during the menstrual cycle peaking around the time of ovulation and dropping off during menses. Following menopause, *Lactobacillus* species become less dominant and numbers of *E. coli* increase. However, for girls and women of all ages the presence of *Lactobacillus* is essential for a healthy genitourinary tract. Lactobacilli modulate the mucosal immune response to pathogens, secrete biosurfactants to block pathogen adherence to epithelial cells and disrupt pathogenic biofilm, produce lactic acid that inhibits pathogen proliferation, generate antimicrobial toxins and bacteriocins, and many essential *Lactobacillus* species make hydrogen peroxide which kills harmful yeasts and bacteria.

### *Lactobacillus* Populations and Genitourinary Infections

Vulvovaginal candidiasis is generally caused by *Candida albicans*, but may also be due to other *Candida* species such as *C. glabrata*, *C. krusei*, and *C. tropicalis*. Reductions in *Lactobacillus* populations, loss of normal vaginal acidity, and diminished hydrogen peroxide production strongly predispose to vulvovaginal candidiasis.

Although not well understood, pathogenesis of bacterial vaginosis appears to involve a shift in vaginal microbial populations to a predominance of *Lactobacillus* strains that produce little or no hydrogen peroxide. The lack of hydrogen peroxide allows the proliferation and overgrowth of anaerobic bacteria. The most common anaerobes isolated in bacterial vaginosis are *Gardnerella vaginalis*, *Bacteroides* species, *Peptostreptococcus* species, and *Mycoplasma* species. There is evidence that the overgrowth of anaerobic pathogens in bacterial vaginosis such as *Gardnerella vaginalis* involves strains not normally found in a healthy vaginal microflora.

The fact that robust vaginal *Lactobacillus* populations confer protection against urinary tract infections has been known since 1973. Certain *Lactobacillus* strains possess the capacity to inhibit uropathogen adherence, growth, and colonization. When genitourinary *Lactobacillus* populations decline, as occurs following menopause and with vaginal dysbiosis, the risk of urinary tract infections climbs because uropathogens, primarily *E. coli* and other *Enterobacteriaceae*, are able to and colonize the vaginal and urethral epithelium.

### *Lactobacillus* and *Bifidobacterium* for Support Against UTI

Most of the clinical research on probiotics and nonsexually transmitted genitourinary tract infections in women has involved *L. acidophilus* and a patented proprietary product containing *L. rhamnosus* GR-1 and *L. fermentum* RC-14 (renamed *L. reuteri* RC-14). *Lactobacillus* probiotics were initially instilled directly into the vagina. Twice weekly applications of *L. casei* GR-1 resulted in vaginal mucosal colonization and reduced vaginal coliform populations. Weekly instillations of *L. rhamnosus* GR-1 and *L. fermentum* RC-14 significantly reduces recurrent urinary tract infections. As colonic pathogens are able to colonize the vulvovagina, probiotic lactobacilli administered orally should also be able to colonize the vagina. *L. rhamnosus* GR-1 and *L. fermentum* RC-14 given orally in a dose exceeding 1 billion CFUs daily results in vaginal *Lactobacillus* predominance. In young girls with reflux of urine from the bladder into the ureters, an oral dose of 100 million CFUs of *L. acidophilus* daily was as effective as trimethoprim/sulfamethoxazole in decreasing the incidence of urinary tract infections. In patients with leukemia, orally administered *Bifidobacterium longum*, which produces both lactic acid and hydrogen peroxide, reduced *Candida* urinary tract infections by 70%. Most studies of probiotics for bacterial vaginosis have utilized *L. acidophilus* in fermented milk, yogurt, tablets or capsules instilled intravaginally. Topical application has successfully reduced symptoms, reduced anaerobe numbers, and promoted a more healthy microbiota. In randomized trials, oral daily intake of *L. rhamnosus* GR-1 and *L. fermentum* RC-14 restores a healthy *Lactobacillus*-dominant vaginal microbiota in asymptomatic women with bacterial vaginosis. One study of *L. acidophilus* in yogurt consumed orally showed that the *L. acidophilus* colonized the vagina and reduced episodes of bacterial vaginosis when compared to consumption of pasteurized yogurt. In women with recurrent vulvovaginal candidiasis, the oral administration of *L. acidophilus* in yogurt significantly reduced the recurrence of candidiasis and decreased vaginal and rectal colonization by *Candida*. In a randomized trial of 55 women with vulvovaginal candidiasis, the antifungal fluconazole given orally with *L. rhamnosus* GR-1 and *L. fermentum* RC-14 at a dose of 1 billion CFUs twice daily for 28 days resulted in higher cure rates when compared to fluconazole treatment alone.

*References and further information available on request.*

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