REVIEW

Urogenital infections in women: can probiotics help?

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Urogenital infections not caused by sexual transmission, namely yeast vaginitis, bacterial vaginosis, and urinary tract infection remain a major medical problem in terms of the number of women afflicted each year. Although antimicrobial therapy is generally effective at eradicating these infections, there is still a high incidence of recurrence. The patient's quality of life is affected and many women become frustrated by the cycle of repeated antimicrobial agents whose effectiveness is diminishing due to increasing development of microbial resistance. There is good clinical evidence to show that the intestinal and urogenital microbial flora have a central role in maintaining both the health and wellbeing of humans. Furthermore, the use of "good bacteria" to replace or augment bacterial populations is gradually achieving scientific acceptance. This application is termed probiotics: "live micro-organisms which when administered in adequate amounts confer a health benefit on the host". The role of the intestinal, vaginal, and urethral flora and probiotics in urogenital health will be the focus of this review.

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Annually, it is estimated that one billion women around the world suffer from non-sexually transmitted urogenital infections, including bacterial vaginosis, yeast vaginitis, and urinary tract infection (UTI). Although most patients respond to antimicrobial treatment, the recurrence rate is high and associated with side effects. The Centers for Disease Control in the USA show a tripling of the initial visits to physicians for non-trichomonas vaginitis from 1966 to 1999, while there was no change in the trichomonas rates. The reasons for the significant increase are not clear and could reflect sexual practices, excessive use of spermicides or antibiotics, douching, or any number of things. In terms of UTI, one of the most common reasons for a woman to visit her family physician, antibiotic treatment and prophylaxis have not altered infection rates. This may be explained in part by the fact that pathogens ascend from the rectum to the vagina then the bladder. This process is mediated by bacterial adherence (fig 1), and is not altered by antibiotic use (in that the host's cells remain susceptible to pathogen adhesion before, during and after drug use).[1] This infection process is not a hygiene issue. Indeed, the fact that the normal vaginal microflora also colonise from an intestinal origin (fig 2) means that microbial ascension *per se* is a natural process that can actually help protect the host.

COMPOSITION OF THE VAGINAL MICROFLORA

Since the vaginal microflora appears to be so critical to health and disease, what is its composition? In cases of recurrent UTI the dominant organisms are the uropathogens, generally *Escherichia coli*[2]; in recurrent bacterial vaginosis these are anaerobic Gram negative rods, generally *Gardnerella vaginalis*[3]; in recurrent yeast vaginitis these are mostly *Candida albicans*. It was long presumed that *Lactobacillus acidophilus* was the dominant member of a healthy vaginal microflora, but this is not the case. Studies using culture followed by molecular typing show *Lactobacillus crispatus* to be the most commonly isolated organism,[4] however the culture step has since been found to have limitations as not all organisms are easy to culture. Using only polymerase chain reaction (PCR) and DNA analysis it has recently been shown that *Lactobacillus iners* is the most common organism, at least in one mainly white population (fig 3).[5]

BACTERIAL VAGINOSIS

Essentially bacterial vaginosis is considered as an overgrowth of anaerobic organisms combined with a loss of the protective lactobacilli normally found in the healthy vagina. Although actual incidence figures are impossible to obtain, bacterial vaginosis is regarded as the most common cause of vaginal symptoms. This infection is commonly found in women aged 17–30 years of age,[6] but is also prevalent in older women. Bacterial vaginosis may occur in women without any

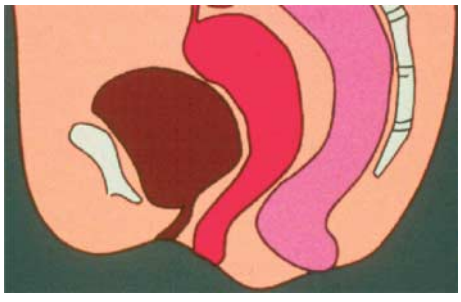

Figure 1 Anatomy of the rectum (pink region of diagram), vagina (red) and bladder (brown) in a female. The close proximity of the vagina and bladder to the rectum means that microbial colonisation of the region is continuous.

Abbreviations: PCR, polymerase chain reaction; UTI, urinary tract infection

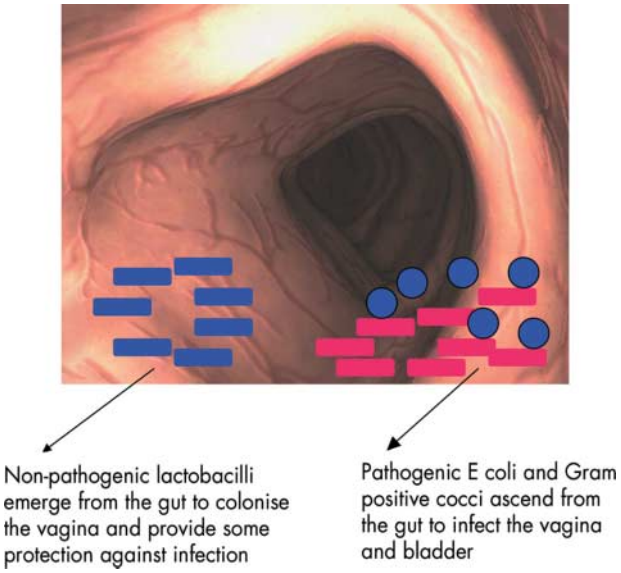

Figure 2 Bacteria emerging from the colon to colonise the vagina.

symptomatology, but it is generally associated with a homogenous white vaginal discharge. For reasons yet to be discovered, bacterial vaginosis has been found to be more common in black American women compared with white women.[7] Odour and discharge are the most common symptoms, but half the patients have vulvovaginal irritation.[8] Significant genital complications can occur including cervicitis[9] and endometritis,[10] and bacterial vaginosis patients are at greater risk of HIV infection[11] and preterm labour.[12]

Classically, the diagnosis of bacterial vaginosis has been made by finding the presence of at least 20% of "clue" cells in the squamous cell population on microscopic examination of a saline suspension of vaginal discharge, associated with two of the following[13]:

(1) Anterior fornix vaginal pH equal or greater than 4.7.

(2) Release of a fishy odour on addition of 10% potassium hydroxide to the vaginal discharge (positive "whiff test").

(3) Presence of an increased thin homogenous white vaginal discharge.

These tests represent the gold standard in diagnosing this condition, but in most clinics, this rigid regimen of bacterial vaginosis detection is not achieved. The option of culture is the method of choice in many practitioners' offices due to the ease of vaginal specimen collection and available laboratory facilities; however, this method is not very reliable for identifying some strict anaerobic bacteria. A more recent screening option is to use a simple Gram stain of a vaginal swab specimen to generate a "Nugent" score, in which the presence of mainly Gram positive rods (indicative of lactobacilli) is scored "normal" and the presence of clue cells, Gram negative rods and absence of lactobacilli is scored as "bacterial vaginosis".[13 14] This method is quite effective, although one study suggested it may not be adequate for evaluating the normal and intermediate vaginal flora in women over 40 years.[15]

Unfortunately, none of these tests are ideal, and in many cases the patient or physician may misdiagnose the problem and either treat empirically or use antiyeast therapy believing the symptoms to be due to yeast vaginitis.[16]

Currently, metronidazole is the agent of choice for the treatment of bacterial vaginosis. This therapy is only moderately effective against *G vaginalis* and *Mobiluncus spp*, is inactive against *Mycoplasma hominis* but its metabolites are highly active against anaerobes in general and the *Bacteroides spp.* There are two recommended dosage regimens for oral metronidazole: 500 mg twice daily for seven days or 2 g given in a single oral dose. Unfortunately, metronidazole is often poorly tolerated due to side effects, including gastrointestinal upset, alcohol intolerance, metallic taste, and infrequently neurological and/or haematological adverse reactions. In addition, cure rates associated with this treatment are low (as low as 61% one month after therapy)[17] and there is a high incidence of overgrowth of pathogenic bacteria after treatment. Bacterial vaginosis can be found in association with other vaginal infections, including chlamydia, trichomonas and yeast vaginitis, making diagnosis extremely difficult and treatment problematical.

The loss of vaginal lactobacilli appears to be the major factor in the cascade of changes leading to bacterial vaginosis[18] and relapses are associated with failure to establish a healthy lactobacilli dominated vaginal flora. Some physicians suggest patients douche with yoghurt, but lactobacilli found in yogurt fail to colonise the vagina[19] and are ineffective in treating or preventing bacterial vaginosis, although one small study contradicts this conclusion.[20] More recently, daily oral intake of probiotic strains *Lactobacillus rhamnosus* GR-1 and *Lactobacillus fermentum* RC-14, resulted in some asymptomatic bacterial vaginosis patients reverting to a normal lactobacilli dominated vaginal microflora (fig 4).[21 22] The mode of action has not been elucidated but might comprise:

(1) Increased ascension of probiotic and/or indigenous lactobacilli from the rectal skin to the vagina.

(2) Reduced ascension of pathogens from the rectal skin to the vagina.

(3) Enhancement of the intestinal mucosal immunity which affects vaginal immunity rendering the environment less receptive to bacterial vaginosis organisms.

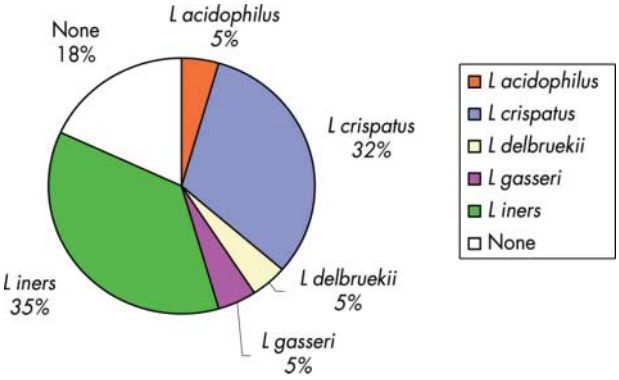

Figure 3 The most commonly isolated lactobacilli recovered from vaginal samples and determined directly by PCR and denaturing gradient gel electrophoresis.[5]

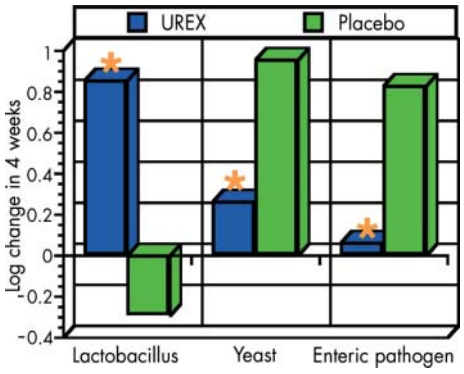

Figure 4 Effect of four weeks of daily lactobacilli (UREX = strains *L rhamnosus* GR-1 and *L fermentum* RC-14) oral probiotics versus placebo on the vaginal microflora.[22]

Such findings provide a rationale for use of proven probiotic strains to maintain vaginal health and reduce the risk of recurrent symptomatic bacterial vaginosis. In terms of eradicating symptomatic bacterial vaginosis, there is some evidence of effect. Twice daily use of hydrogen peroxide producing 10^{8-9} *L acidophilus* in a product called Vivag for six days led to a 43% improvement compared to none in the placebo group.[23] Yogurt containing *L acidophilus*, of unknown designation, was delivered in a tampon to pregnant women and shown to treat bacterial vaginosis and prevent infection at two month follow up.[24] Further studies with oral and vaginal probiotics are needed, with the former unlikely to be more effective or acceptable to patients, who need quick relief of symptoms and oral therapy takes several days for intestinal passage, vaginal ascension, and growth of the lactobacilli.

URINARY TRACT INFECTION

Lower UTI in women is regarded by some physicians as a minor inconvenience to their patients, yet this disease is responsible for significant symptomatology, morbidity, and loss of quality of life.[25] It is estimated that annually, several hundred million women suffer from UTI, with costs to health care providers amounting to over $6 billion annually worldwide.[26] This figure could even be an under-estimation given that there are three billion females in the world and the incidence of uncomplicated UTI in women as 0.5 episodes/person/year, with a recurrence rate of between 27% and 48%.[27] It is also a problem in pregnancies affecting around 5% of women, and of those 20% may acquire pyelonephritis.

Classically, 10^5 or more colony forming organisms per millilitre of urine has been regarded as the acceptable bacterial count. However, in women, counts of as low as 10^3 organisms/ml, particularly if associated with irritative bladder symptoms and the presence of increased numbers of white blood cells in the urine are now regarded as indicative of true UTI.

The usual symptoms of dysuria, frequency of micturition, and occasionally haematuria (particularly terminal) are not always present, and bacteriuria (10^5 or greater) may occur in patients who are totally asymptomatic. So called asymptomatic bacteriuria tends to increase with age, and may occur in up to 10%–15% of post-menopausal women. Gram negative organisms, particularly *E coli* (up to 85%) are the causative agents in most women suffering from UTI, followed by *Enterococcus faecalis* and *Staphylococcus saprophyticus*.

The classic studies of Stamey showed the great importance of prior vaginal colonisation with pathogenic bacteria in women suffering from UTI and the significance of the persistence or reappearance of these organisms in the causation of recurrence of infection.[28] The protective role of the normal vaginal flora, particularly lactobacilli, is gradually being accepted. Raz showed the importance of vaginal oestrogen replacement with associated lactobacilli repopulation and reduction of UTI in a cohort of post-menopausal women.[29]

It is now known that spermicidal agents can kill hydrogen peroxide producing lactobacilli, leading to enhanced vaginal colonisation by uropathogens. This is one reason for inclusion of *L rhamnosus* GR-1 in a probiotic formulation as it resists spermicides.

Treatment of the occasional lower UTI in women is well established and a simple short three day course of the appropriate antibiotic (generally trimethoprim) is adequate. Unfortunately, overuse of fluoroquinolones for simple UTI has increased resistance rates to drugs required for more serious infections.

The UTI recurrence rate, close to 50% in some cases, poses a much greater treatment challenge. Daily, low dose, long term antibiotic treatment with nitrofurantoin (50 mg at night) or other agents, is quite effective and widely used. But breakthrough infections still occur with antibiotic and antiseptic therapy,[30] due to particularly virulent pathogens, the influence of sexual practices, or other reasons. In some patients, self administration of a three day antibiotic course upon the start of symptoms and signs of UTI offers a good alternative to daily prophylaxis, leading to fewer side effects and lower risk of the development of pathogen drug resistance. Skin reactions, diarrhoea, and yeast vaginitis may be associated with the use of some antibiotics.

Although there have been great improvements in the understanding of UTI—the aetiology, diagnosis, and treatment—there is still a need to explore alternative methods in treatment and more particularly in prevention modalities. The basis for use of probiotics emerged from clinical observations in 1973, where a study of healthy women showed an association between lactobacilli presence in the vagina and no history of UTI.[31] Extensive studies of various lactobacilli strains and the properties believed to be important for protecting the host, led to selection of a two strain combination for vaginal use. This comprises distal urethral isolate *L rhamnosus* GR-1, selected primarily for its anti-Gram negative activities and resistance to spermicide, and *L fermentum* B-54, replaced more recently by RC-14, for anti-Gram positive cocci activities and hydrogen peroxide production. In order to optimise a consistent dose with a good shelf life in a formulation preferred by patients, the organisms are freeze dried and placed in gelatin capsules, with dosage at 10^9 per capsule, higher than the total microbial content of the vagina.[32] Various protocols have been explored, such as administration post-menses, one or two capsules per week, or one capsule daily for three days. The primary aim is to restore the vaginal lactobacilli microflora such that the indigenous lactobacilli recover, or the patient retains some degree of acidic pH and protection against infection.

Results from various studies indicate that the recurrence rate of UTI can be significantly reduced using one or two capsules vaginally per week for one year, with no side effects or yeast infections.[32] The rate of infection was the same as those found in studies using daily antibiotics for one year.[30] The urogenital use of lactobacilli have been a major reason for expanding earlier definitions of "probiotics" from the intestine to: "live micro-organisms which when administered in adequate amounts confer a health benefit on the host".[33]

YEAST VAGINITIS

Yeast vaginitis is a very common problem, estimated to affect around 1:5 black American women and close to 1:10 white women during any given two month timeframe,[34] with 1:12 reporting four or more episodes per year. Although there are difficulties in diagnosis and effective treatment regimens (primarily due to high recurrence rates), the aetiologies have been well studied. As with bacterial vaginosis and UTI, the intestine is the main source of the infecting fungal organisms, and overgrowth in the vagina can follow disruption of the normal flora such as with use of broad spectrum antibiotic treatment.

The clinical picture of yeast vaginitis is generally clear—the development of a white vaginal discharge characterised by its malodorous, non-homogenous caseous appearance, accompanied with vaginal and introital itch and irritation, and evidence of vaginal inflammatory reaction. The condition may, however, be overdiagnosed—Abbott showed in a small cohort of women with classic symptoms that only 34% of these patients had positive cultures.[35] This is an important issue as the availability of antiyeast medication over-the-counter means that women are self diagnosing and self medicating when they may not have a yeast infection. As these treatments can have an affect on the bacterial flora, the susceptibility to recurrent infection will likely not be reduced by repeated yeast therapy. Thus, many women find themselves taking cyclical treatment. While *Candida albicans* is the major cause of infections (around 85%), other yeast such as *Candida glabrata, Candida krusei*, and *Candida tropicalis* infect the host. What is

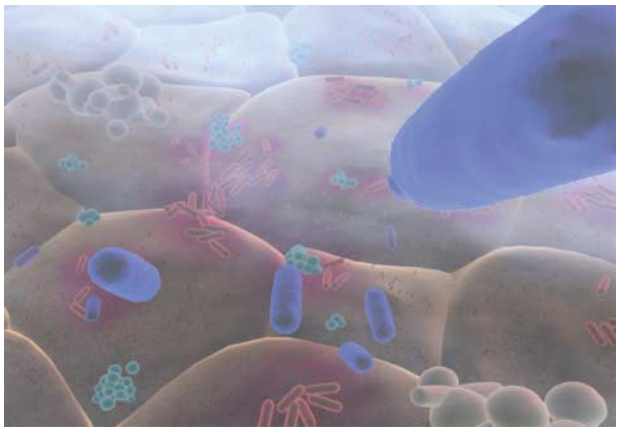

Figure 5 Depiction of lactobacilli (blue rods) released into a vaginal epithelium colonised by yeast (large, grey objects), enterococci (small round, light blue objects), and uropathogens (red/brown rods).

needed is an effective, sensitive over-the-counter self diagnostic system for detection of yeast vaginitis, matched with an appropriate treatment. This diagnostic system should not be based upon simple detection of yeast organisms, as these can be present in healthy women. Rather, it would have to measure inflammation, discharge, or a factor indicative of an infectious state.

In terms of probiotics, very few lactobacilli are able to kill or inhibit adhesion of yeast to vaginal cells or devices, although strains *L rhamnosus* GR-1 and *L fermentum* RC-14 do have some such activity.[36] There is little evidence that probiotics can effectively cure a symptomatic yeast vaginitis. Claims are often made for commercial probiotic preparations, almost none of which have any scientific verification that they are probiotics never mind having antifungal activity.[37] At best, reliable probiotic products might be an adjunct to drug therapy as a means to reduce the risk of recurrence. A crossover one year study in which 33 patients with a history of recurrent yeast vaginitis (≥5 per year) were given eight ounces of *L acidophilus* supplemented yoghurt daily for six months then switched to a yoghurt-free diet, resulted in 0.4 breakthrough infections compared with 2.5 per study term.[38] The significant reduction in number of positive cultures for candida (0.8 *v* 3.2) is consistent with a more recent use of *L rhamnosus* GR-1 and *L fermentum* RC-14 in lyophilised capsule form which showed up to one log fewer yeast recovered from the vagina during treatment compared with baseline.[22] For many years, physicians have advised patients on antibiotic treatment to take yoghurt as a means to prevent yeast vaginitis. However, unless the product is supplemented with antifungal lactobacilli, the numbers of viable organisms and the type of bacteria contained (starter dairy cultures such as *Streptococcus thermophilus* and *Lactobacillus delbreukii* var *bulgaricus* are not appropriate), no infection reduction is likely.

When lactobacilli are introduced vaginally, as depicted in fig 5, there will be an impact on the subject's microflora.[5] If this is dominated by yeast, Gram negative coliforms and anaerobes, or Gram positive cocci, then the outcome might significantly benefit the patient.

QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AT END OF REFERENCES)

1. Probiotics are defined as friendly bacteria that improve intestinal wellbeing.

A quick physician guide to probiotic use

The following are some critical points for physicians to remember and consider with respect to probiotics.

- A clear understanding of the term "probiotic" is required. The definition "live micro-organisms which when administered in adequate amounts confer a health benefit on the host" means that if a product and its strain(s) have not been proven to confer a health benefit in peer reviewed, published studies, the term probiotic does not apply.
- Currently, there are only a few recognised lactobacilli or bifidobacterial strains which meet these Food and Agriculture Organization/World Health Organization criteria. The most documented strains include *L rhamnosis* GG (Valio, Finland), *L rhamnosus* GR-1 and *L fermentu* RC-14 (Urex Biotech, Canada) followed by *L casei* Shirota (Yakult, Japan), *L acidophilus* NCFM (Rhodia USA), *L reuteri* MM53 (Biogaia, Sweden), *L plantarum* 299V (Probi, Sweden), *L johnsonnei* LJ1 (Nestlé, Switzerland), *B lactis* BB12 (Chr Hansen, Denmark), *B longum* BB536 (Morinaga, Japan), and some others. If the label does not state the strain name and number, then the product does not contain any of these organisms. In terms of urogenital health, only GR-1 and RC-14 have supportive data.
- A small study of Canadian physicians showed that 31% had any knowledge of probiotics and 24% felt that probiotics had no place in their practices.[39] This reflects a need for physicians to study more of the publications on probiotics, and a need for researchers to continue to produce evidence of probiotic efficacy, as well as their limitations. The potential impact that probiotics will have on all urogenital infections is just beginning to surface, and it behoves all physicians to examine this field of therapy to provide their patients with reasoned and truly researched guidance regarding therapeutic options, if available.
- Companies need to be encouraged to produce diagnostic kits that allow women to accurately diagnose not only bacterial vaginosis, UTI and yeast vaginitis, but also their level of vaginal "health" at any given time. In terms of infection, this will allow faster, shorter, and more effective treatment to be instigated. The use of these types of kits has already been tested quite effectively in women in the US military.[40]

2. Lactobacilli and bifidobacteria are the most commonly used probiotic organisms.

3. Lactobacilli probiotics can be used to treat urinary tract infections.

4. *L acidophilus* available on most health food store probiotics can clear bacterial vaginosis.

5. Yoghurt contains bacteria designed to reduce the risk of intestinal and vaginal infection.

6. Most vaginal and bladder pathogens, as well as the normal flora of the vagina ascend from the rectal skin.

7. All hydrogen peroxide producing lactobacilli kill *Candida albicans*.

8. FAO/WHO guidelines for probiotics make it essential that human studies proving health benefits are produced in order for a product to be referred to as a probiotic.

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ANSWERS

1. F, 2. T, 3. F, 4. F, 5. F, 6. T, 7. F, 8. T.