New Microbiologica, **36**, 229-238, 2013

Bacterial vaginosis: a review on clinical trials with probiotics

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SUMMARY

Bacterial vaginosis (BV) is the most common vaginal syndrome afflicting fertile, premenopausal and pregnant women. BV is associated with important adverse health conditions and infectious complications. Therapy with oral or local recommended antibiotics is often associated with failure and high rates of recurrences. The dominance of lactobacilli in healthy vaginal microbiota and its depletion in BV has given rise to the concept of oral or vaginal use of probiotic *Lactobacillus* strains for treatment and prevention of BV. This review investigated the evidence for the use of a single strain or cocktail of probiotics, administered orally or intravaginally, either alone or in conjunction with antibiotics for the treatment of BV. Lactobacilli use in BV is supported by positive results obtained in some clinical trials. The majority of clinical trials yielding positive results have been performed using probiotic preparations containing high doses of lactobacilli suggesting that, beside strain characteristics, the amount of exogenously applied lactobacilli could have a role in the effectiveness of the product. However, substantial heterogeneity in products, trial methodologies and outcome measures do not provide sufficient evidence for or against recommending probiotics for the treatment of BV.

KEY WORDS: Bacterial vaginosis, Probiotics, Lactobacilli, Controlled clinical trials.

Received May 12, 2013 *Accepted* May 28, 2013

INTRODUCTION

The female lower genital tract, consisting of vagina and ectocervix, is an ecological niche where several aerobe and anaerobe microorganisms coexist in a dynamic balance. The homeostasis of the vaginal ecosystem results from complex interactions and synergies among the host and different microorganisms that colonize the vaginal mucosa (Mårdh, 1991; Sobel, 1997). This ecosystem is dynamic with changes in structure and composition being influenced by age, menarche, time in menstrual cycle, pregnancy, infections, methods of birth control, sexual activity, use of medication and hygiene (Srinivasan and Fredricks, 2008). In fertile, premenopausal healthy women, the vaginal ecosystem is dominated by *Lactobacillus* spp., but a diverse array of other bacteria can be present in much lower numbers. *L. crispatus, L. iners*, *L. jensenii* and *L. gasseri* are the predominant vaginal *Lactobacillus* species (Lamont *et al.,* 2011). The main frequent undesirable organisms are yeasts (*Candida albicans*, *Candida tropicalis*, *Candida krusei*), anaerobic bacteria responsible for vaginosis (*Gardnerella vaginalis*, *Mycoplasma hominis*, *Atopobium vaginae*, *Prevotella* spp., *Veillonella* spp., *Mobiluncus* spp.), uropathogens (*Escherichia coli*, *Proteus* spp., *Klebsiella* spp., *Serratia* spp.), and sexually transmitted viruses (HIV, Herpes virus) (Lamont *et al.,* 2011). Lactobacilli are involved in maintaining the normal vaginal microflora by preventing overgrowth of pathogenic and opportunistic organisms (Rönnqvist *et al.,* 2006). The principal mechanisms by which lactobacilli exert their protective functions are:

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1. stimulation of the immune system;
2. competition with other microorganisms for nutrients and for adherence to the vaginal epithelium;
3. reduction of the vaginal pH by the production of organic acids, especially lactic acid;
4. production of antimicrobial substances, such as bacteriocins, and hydrogen peroxide (Aroutcheva *et al.,* 2001).

The hydrogen peroxide microbial metabolite represents one of the most effective protective agents against pathogens. It has been observed that 70% to 95% of lactobacilli present in the vaginal flora of healthy women produce hydrogen peroxide. This percentage drops to 5% in women affected by vaginal infections (Eschenbach *et al.,* 1989).

BACTERIAL VAGINOSIS

Bacterial vaginosis (BV) represents the most common vaginal syndrome afflicting fertile, premenopausal and pregnant women, with an incidence rate ranging from 5% to 50% (Sobel, 1997). BV is a complex, polymicrobial disorder characterized by an overgrowth of strict or facultative anaerobic bacteria (*Gardnerella vaginalis*, *Atopobium vaginae, Prevotella* spp., *Mobiluncus* spp., *Mycoplasma hominis*) and a reduction of lactobacilli particularly those producing hydrogen peroxide (Fredricks *et al.,* 2005; Lamont *et al.,* 2011). Women with BV typically complain of vaginal discomfort and homogeneous malodorous vaginal discharge, which is more noticeable after unprotected intercourse, although a substantial fraction of women are asymptomatic (Klebanoff *et al.,* 2004). The overgrowth of vaginal anaerobes determines an increased production of amines (putrescine, cadaverine and trimethylamine) that become volatile at alkaline pH, i.e. after sexual intercourse and during the menstrual cycle, and contribute to the typical malodor of the vaginal discharge (Chen *et al.,* 1979). BV is frequently disregarded since the symptoms are often insignificant, however the clinical consequences could be important. In fact, the alterations in the vaginal microbiota have been associated with ascending infections and obstetric complications (Koumans *et al.,* 2002), as well as with urinary tract infections (Harmanli *et al.,* 2000). In women undergoing *in vitro* fertilization, BV may result in lower implantation rates and increased rates of early pregnancy loss (Eckert *et al.,* 2003; Verstraelen *et al.,* 2005). Increasing data also indicate that BV facilitates the acquisition of sexually transmitted diseases such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, HIV and Herpes simplex virus type-2 infection (HSV-2) (Martin *et al.,* 1999; Cherpes *et al.,* 2003; Wiesenfeld *et al.,* 2003; Sessa *et al.,* 2013). Moreover, genital tract shedding of HSV-2 (Cherpes *et al.,* 2005) and cytomegalovirus (Ross *et al.,* 2005) is significantly higher in women with BV than in BV-free women and female genital tract HIV load correlates inversely with *Lactobacillus* count (Sha *et al.,* 2005). Therefore, vaginal lactobacilli *in vivo* exert an important role in sexually transmitted infections both in relation to the protection of female health or by reducing the risk of virus transmission from an infected woman to a healthy man.

Two methods are used for BV diagnosis: the first was described by Amsel (Amsel *et al.,* 1983) and implies the presence of at least three of the following criteria:

1. thin, homogeneous vaginal discharge;
2. vaginal pH higher than 4.5;
3. 'fishy' odour of vaginal fluid after addition of 10% KOH (whiff test);
4. presence of clue cells on microscopic evaluation of saline wet preparations.

The second method, the Gram stain score of vaginal smears according to Nugent (Nugent *et al.,* 1991), involves the microscopic quantitation of bacterial morphotypes yielding a score between 0 and 10. A Gram stain score ≥7 is considered indicative of BV.

In recent years, culture-independent techniques based on the analysis of rRNA gene sequences have been developed, providing powerful tools to reveal the phylogenetic diversity of the microorganisms found within the vaginal ecosystem and to understand community dynamics (Fredricks *et al.,* 2005; Lamont *et al.,* 2011). These molecular studies indicate that the vaginal bacterial communities differ dramatically between women with and without BV. BV is associated with increased taxonomic richness and diversity. The microbiota composition is highly variable among subjects at a fine taxonomic scale (species or genus level), but, at the phylum level, *Actinobacteria* and *Bacteroidetes* are strongly as-

sociated with BV, while higher proportions of *Firmicutes* are found in healthy subjects. Several vaginal bacteria have been indicated as excellent markers of BV, either alone or in combination, including *Megasphaera*, three novel bacteria in the order *Clostridiales*, *Leptotrichia*/*Sneathia*, *Atopobium vaginae*, and an *Eggerthella*-like bacterium (Lamont *et al.,* 2011).

Therapy of BV involves oral or local administration of metronidazole or intravaginal clindamycin, and varies in efficacy (48-85% for absence of infection 4 or more weeks after treatment) (Koumans *et al.,* 2002). The long-term cure rate is low, BV recurs in up to 40% of women within 3 months after initiation of antibiotic therapy and in up to 50% of women after 6 months (Bradshaw *et al.,* 2006). There are several unpleasant side-effects and disadvantages associated with these therapies, including superinfections by pathogenic microorganisms (Sobel *et al.,* 2006) and susceptibility of lactobacilli to clindamycin (Bayer *et al.,* 1978). Moreover, vaginal pathogens, particularly *G. vaginalis* and anaerobic bacteria, are showing increasing drug resistance (McLean and McGroarty, 1996; Beigi *et al.,* 2004). The high recurrence rates resulting in repeated exposure to antibiotics and the emergence of drug-resistant strains suggest a need for alternative therapeutic tools based both on new antibacterial agents (Cruciani *et al.,* 2012) and probiotic products.

RATIONALE FOR USING PROBIOTICS IN GENITOURINARY INFECTIONS

Many studies provided evidence of the beneficial functions of the human microbiota, and prompted the selection of bacterial strains, recognized as probiotics, with health-promoting capacities for the treatment of conditions in which the microbiota, or its optimal functioning, is perturbed. Probiotics have been defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" (Joint FAO/WHO Working Group Report on Drafting Guidelines for the Evaluation of Probiotics in Food, 2002). Clinical applications of probiotics include the prevention and treatment of gastrointestinal, urogenital and respiratory infections, inflammatory bowel diseases and allergic diseases and use as adjuvants in vaccination (Kligler *et al.*, 2007; Nova *et al.,* 2007; Goldin and Gorbach, 2008; Barrons and Tassone, 2008; Vouloumanou *et al.,* 2009; Borchers *et al.,* 2009). The clinical utility of probiotics may extend to fields such as stress-related disorders (anxiety and depression) (Bravo *et al.,* 2001; Rao *et al.,* 2009) and cancer (Geier *et al.,* 2006; de Moreno de LeBlanc *et al.,* 2007). Moreover, recent studies suggested that probiotics may represent a therapeutic strategy for metabolic and cardiovascular diseases through the modulation of host metabolism and inflammation (Lye *et al.,* 2010; Wang *et al.,* 2011; Lam *et al.,* 2012). Indeed, atherosclerosis is associated with lipid accumulation and inflammation in the arterial wall, and bacteria have been suggested as the causative agents of this disease (Sessa *et al.,* 2006; Sessa *et al.,* 2007; Koren *et al.,* 2011).

The rationale for the use of probiotics in women is based on the genitourinary regulatory role played by the vaginal healthy microbiota and the need for restoration of this microbial ecosystem after insult. Lactobacilli are the commonest organisms used as probiotics. The use of lactobacilli to re-establish a physiological microbial flora of the female urogenital tract dates back to the early 1900s (reviewed by Sieber and Dietz, 1998). Since the beginning of the nineties there has been a renewed interest in the use of probiotic products in the treatment and prevention of BV and vaginitis. Since antimicrobial treatment of urogenital infections is not always effective, and problems remain due to bacterial and yeast resistance, recurrent infections, and side-effects, it is not surprising that alternative remedies are of interest to patients and their caregivers. Indeed, lactobacilli probiotics can be used over a long time without adverse effects, making them an attractive alternative to antibiotics, particularly in addressing the problem of high recurrence rates.

CLINICAL TRIALS

Studies have been carried out to assess the efficacy of a single strain or cocktail of probiotics administered orally or intravaginally in the treatment of BV (Falagas *et al.,* 2007). Two types of experimental approaches have been used in clinical trials using probiotics for treatment of BV. In the first, BV therapy was carried out using on-

ly probiotics. In the second, probiotics were administered following a conventional antibiotic therapy.

Clinical trials on probiotics use for treatment of bacterial vaginosis

The major randomized controlled trials using the first type of approach on women affected by BV are reported in Table 1. Only two studies employing different species of lactobacilli have been performed using well-characterized and well-selected strains specific for treatment of genitourinary infections (Anukam *et al.,* 2006b; Mastromarino *et al.,* 2009). Both studies used a combination of different species of lactobacilli with different biological properties on fertile non-pregnant women. *L. rhamnosus* GR-1 and *L. fermentum* RC-14 were the strains used in the first study (Anukam *et al.,* 2006b). *L. rhamnosus* GR-1 adheres strongly to uroepithelial cells and inhibits adhesion and growth of uropathogens (Reid *et al.,* 1987). *L. fermentum* RC-14 produces biosurfactant compounds (Velraeds *et al.,* 1998) and significant amounts of hydrogen peroxide, adheres to uroepithelial cells and inhibits pathogen binding (Reid and Bruce, 2001). These strains can be recovered from the vagina after oral administration (Reid *et al.,* 2001). The second study used a product containing a combination of three strains of lactobacilli (*Lactobacillus brevis* CD2, *Lactobacillus salivarius* FV2 and *Lactobacillus plantarum* FV9) (Mastromarino *et al.,* 2009). *L. salivarius* FV2 and *L. plantarum* FV9 produce anti-infective agents, including hydrogen peroxide, and are able to co-aggregate efficiently with vaginal pathogens (Mastromarino *et al.,* 2002). *L. plantarum* and *L. brevis* strains are able to adhere at high levels to human epithelial cells, displacing vaginal pathogens (Maggi *et al.,* 2000; Mastromarino *et al.,* 2002). The strains were able to temporarily colonize the human vagina (Massi *et al.,* 2004), reduce vaginal proinflammatory cytokines IL-1β and IL-6 (Hemalatha *et al.,* 2012) and showed inhibitory activity towards HSV-2 replication in cell cultures (Conti *et al.,* 2009; Mastromarino *et al.,* 2011). A single-blind comparison of intravaginal probiotics (*L. rhamnosus* GR-1 and *L. fermentum* RC-14) and metronidazole gel for the treatment of BV was carried out on a group of Nigerian women (Anukam *et al.,* 2006b). Cure of BV was based on a Nugent score ≤3 at 30 days. A BV cure rate of 65% was achieved after probiotic treatment compared to 33% of the metronidazole therapy (P=0.056). The double-blind, placebo-controlled trial (Mastromarino *et al.,* 2009) used both the Amsel criteria and Nugent scores to assess BV cure as recommended by the FDA (US Dept of

TABLE 1 - *Clinical trials on probiotics use for treatment of bacterial vaginosis (BV).*

Authors	*Size*	*Type of study/ duration*	*Intervention*	*BV cure rate*
Anukam *et al.*, 2006b	40	R, OB, AC 30 days	Daily vaginal capsule containing *L. rhamnosus* GR-1 (109 CFU) and *L. reuteri* RC-14 (109 CFU) or 0.75% metronidazole gel b.i.d. for 5 days	65% compared to 33% metronidazole (P = 0.056)
Mastromarino *et al.*, 2009	34	R, DB, PC 3 week	Daily vaginal tablet containing ≥109 CFU of *L. brevis* CD2, *L. salivarius* FV2, and *L. plantarum* FV9 for 7 days	50% compared to 6% control (P = 0.017)
Parent *et al.*, 1996	32	R, PC 4 week	1-2 daily vaginal tablet containing *L. acidophilus* ≥107 CFU and 0.03 mg estriol for 6 days	88% compared to 22% control (P <0.05)
Hallén *et al.*, 1992	57	R, DB, PC 20-40 days	Vaginal suppository containing *L. acidophilus* 10^{8-9} CFU or placebo b.i.d. for 6 days	21% compared to 0% control (P = NS)

R = randomized; DB = double blind; PC = placebo controlled; OB = observer blind. AC = active controlled. CFU = colony forming units.

Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for industry: Bacterial vaginosis-developing antimicrobial drugs for treatment 1998). The intravaginal probiotic-treated group (*L. brevis* CD2, *L. salivarius* FV2 and *L. plantarum* FV9) obtained a BV cure rate of 50% compared to 6% in the placebo-treated group with the combined test methods, whereas a 67% vs 12% cure rate was obtained when considering only the Amsel criteria. The other clinical studies were performed using different strains of *Lactobacillus acidophilus*.

A high BV cure rate (88%) was observed in a placebo-controlled study using a pharmaceutical product (containing a H_2O_2-producing *L. acidophilus* strain plus estriol) that included both pregnant and non-pregnant women (Parent *et al.*, 1996). However, the results reported in this trial may have been biased by the enrolment criteria in which only two of the four Amsel criteria were required for a positive definition of BV status. A product containing H_2O_2-producing *L. acidophilus* turned out to be ineffective for treatment of BV assessed according to Amsel criteria (Hallén *et al.,* 1992). However it is difficult to evaluate the real efficacy of the product tested in this study since 50% of the patients in the active group and 86% of the placebo group did not complete the trial.

Clinical trials on probiotics use combined with antibiotic treatment for BV

Five randomized controlled trials used lactobacilli following conventional antibiotic treatment (Table 2) to evaluate the BV cure rate after one month (Anukam *et al.,* 2006a; Petricevic and Witt, 2008) or BV recurrence after 2-6 months (Larsson *et al.,* 2008; Eriksson *et al.,* 2005; Bradshaw *et al.,* 2012). A trial in Nigeria evaluated augmentation of antimicrobial metronidazole therapy for BV by a 30-day oral probiotic treatment (*L. rhamnosus* GR-1 and *L. fermentum* RC-14) compared to placebo-treated control (Anukam *et al.,* 2006a). At the end of treatment a significantly greater number of women in the probiotic group com-

TABLE 2 - *Clinical trials on probiotics use combined with antibiotic treatment for BV.*

Authors	*Size*	*Type of study duration*	*Intervention*	*BV cure rate*
Anukam *et al.*, 2006a	125	R, DB, PC 30 days	Oral metronidazole 500 mg b.i.d. for 7 days and oral capsules containing *L. rhamnosus* GR-1 (10^9 CFU) and *L. reuteri* RC-14 (10^9 CFU) or placebo b.i.d. for 30 days starting on day 1 of metronidazole treatment	88% compared to 40% control (P <0.001)
Petricevic and Witt, 2008	190	R, OB, PC 4 weeks	Oral clindamycin 300 mg b.i.d. for 7 days, then vaginal capsules containing 10^9 CFU of *L. casei rhamnosus* for 7 days	83% compared to 35% control (P <0.001)
Larsson *et al.*, 2008	100	R, DB, PC 6 menstrual periods	Vaginal 2% clindamycin cream directly followed by vaginal capsules containing *L. gasseri* Lba EB01-DSM 14869 (10^8-10^9 CFU) and *L. rhamnosus* Lbp PB01-DSM 14870 (10^8-10^9 CFU) for 10 days, probiotic treatment repeated for 10 days after each menstruation during 3 menstrual cycles	65% compared to 46% control (P = 0.042)
Eriksson *et al.*, 2005	187	R, DB, PC 2 menstrual periods	Vaginal 100 mg clindamycin ovules for 3 days, then tampons containing 10^8 CFU of *L. gasseri*, *L. casei rhamnosus*, *L. fermentum* or placebo tampons during the next menstrual period	56% compared to 62% control (P = NS)
Bradshaw *et al.*, 2012	268	R, DB, PC 6 months	Oral metronidazole 400 mg b.i.d. for 7 days followed by vaginal pessary containing *L. acidophilus* KS400 $\geq 10^7$ CFU and 0.03 mg estriol for 12 days	72% compared to 73% control (P = NS)

R = randomized; DB = double blind; PC = placebo controlled; OB = observer blind. CFU = colony forming units.

pared to the placebo group were BV-free (Nugent score ≤3).
The study by Petricevic and Witt (2008) performed a 7-day *Lactobacillus* treatment after clindamycin therapy. Intravaginal *Lactobacillus casei rhamnosus* (Lcr35) was used in the intervention group, whereas women in the control group did not receive Lcr35 (Petricevic and Witt, 2008). The BV cure rate was evaluated by Nugent method four weeks after the last administration of medication in both groups. A significantly higher cure rate was obtained in the intervention group.
The efficacy of *Lactobacillus* supplementation after clindamycin or metronidazole treatment on the recurrence rate of BV was evaluated in three trials (Larsson *et al.,* 2008; Eriksson *et al.,* 2005; Bradshaw *et al.,* 2012). A ten-day repeated treatment with *L. gasseri* Lba EB01-DSM 14869 and *L.rhamnosus* Lbp PB01-DSM 14870 during three menstrual cycles was compared with a placebo treatment on BV-affected women enrolled according to Amsel criteria (Larsson *et al.,* 2008). The cure rate was evaluated by the Hay/Ison score (Ison and Hay, 2002). Probiotic use did not improve the efficacy of BV therapy after the first month of treatment, but it significantly reduced the recurrence rate of BV at six months from initiation of treatment.
Administration of tampons impregnated with *L. gasseri, L. casei* subsp. *rhamnosus* and *L. fermentum* or placebo tampons during the menstrual period following clindamycin treatment was exploited (Eriksson *et al.,* 2005). Cure rates assessed by Amsel criteria after the second menstrual period did not show a significant difference between the two groups. Possible explanations for the lack of effects could be the low amount of lactobacilli in tampons at the end of the study (10^6 PFU) or the unfavourable period of administration i.e. during the menstrual flow. Pessaries containing *L. acidophilus* KS400 were used in a recent trial to evaluate the efficacy of probiotics on the recurrence rate of BV following oral metronidazole treatment (Bradshaw *et al.*, 2012). A 12 day course of probiotic pessary did not achieve higher cure rates for BV compared with placebo pessary over six months of follow-up as assessed by Nugent score.
A recent prospective, randomized, placebo-controlled, double-blinded study evaluated the efficacy of vaginal probiotic capsules for BV prophylaxis in healthy women with a history of recurrent BV (Ya *et al.*, 2010). One hundred and twenty healthy Chinese women with a history of recurrent BV (≥2 BV episodes in the previous year) were assigned randomly to daily vaginal prophylaxis with 1 capsule that containing 8×10^9 CFU of *L. rhamnosus* (6.8×10^9 CFU), *L. acidophilus* (0.4×10^9 CFU) and *Streptococcus thermophilus* (0.4×10^9 CFU) or 1 placebo capsule for 7 days on, 7 days off, and 7 days on. Probiotic prophylaxis resulted in lower recurrence rates for BV (15.8% vs 45.0%; $P<0.001$) through 2 months as assessed according to Amsel criteria. Between the 2 and 11-month follow-up period, women who received probiotics reported a lower incidence of BV (10.6% vs 27.7%; $P=0.04$). However a limitation of this study was that 11-month outcomes were collected by telephone follow-up interview.

DISCUSSION

In recent years several clinical trials have been performed to investigate whether specific strains of lactobacilli, administered either orally or intra-vaginally, in combination with antibiotics or not, could be effective in the treatment or prevention of vaginal infections. The studies using lactobacilli to treat BV, albeit small in size, showed the potential of probiotics to cure BV. Although the species used in the various trials differed, three out of four studies reported a significant cure rate (Parent *et al.,* 1996; Anukam *et al.,* 2006b; Mastromarino *et al.,* 2009). When probiotics were used following antibiotic treatment, the BV cure rate was increased and recurrence rates were reduced in three out of five studies (Anukam *et al.,* 2006a; Petricevic and Witt, 2008; Larsson *et al.,* 2008).
An important issue concerns the prevention of BV recurrence in healthy women with a history of recurrent BV. Despite the important adverse health conditions associated with abnormal vaginal flora, no preventive treatments are available. The positive results obtained in the only clinical trial using lactobacilli in healthy Chinese women (Ya *et al.,* 2010) suggest the potential of probiotics for BV prophylaxis. It is noteworthy that, unlike antibiotics, lactobacilli probiotics can be

used over a long period without adverse effects.
The majority of clinical trials reporting positive results were performed using probiotic preparations containing high doses of lactobacilli (around 10^9 CFU) suggesting that, beside strain characteristics, the amount of exogenously applied lactobacilli could have a role in the effectiveness of the product. Moreover, recent observational data using prolonged repetitive courses of *Lactobacillus*-containing probiotics appear to be more promising than short courses (Ya *et al.*, 2010; Bradshaw *et al.*, 2012).
The preferred route of delivery for probiotic lactobacilli is intravaginal. However, some authors delivered lactobacilli orally to repopulate the vagina, based on the observation that pathogens can pass from the gut into the urogenital system and that orally administered *Lactobacillus* strains have been recovered from the vagina (Strus *et al.*, 2012). It is noteworthy that the capability of the lactobacilli to colonize the vagina after oral ingestion is strictly dependent on their viability and on their potential to survive gastric acid and bile salts. Furthermore, the fact that lactobacilli can reach the vagina is not to be taken for granted as the gut microbiota and the vaginal microbiota differ greatly, which excludes a direct passage of all the species and strains present in the gut. It should also be pointed out that since none of the trials on oral use of lactobacilli in BV evaluated vaginal colonization by the administered strains, it cannot be excluded that the bacteria may have exerted a systemic immunomodulating effect thus conferring an improvement of the clinical conditions. Obviously, the timing of vaginal colonization after oral administration is longer compared to direct vaginal administration. In addition, the load of lactobacilli that can be delivered orally to the vagina is clearly lower than direct vaginal administration.
In conclusion, lactobacilli use in bacterial vaginosis is supported by positive results obtained in some clinical trials. However, substantial heterogeneity in products, trial methodologies and outcome measures do not provide sufficient evidence for or against recommending probiotics for the treatment of BV. Indeed, the trials with probiotics on BV have been conducted using different bacterial species and strains, dosage regimen, route of administration, duration of treatment and population under study. All these differences could act as confounding factors hindering a real comparison among the trials and also may account for the different effectiveness of the treatments.
Larger, well-designed randomized controlled trials with standardized methodologies are needed to confirm the benefits of probiotics in the treatment of BV.

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