

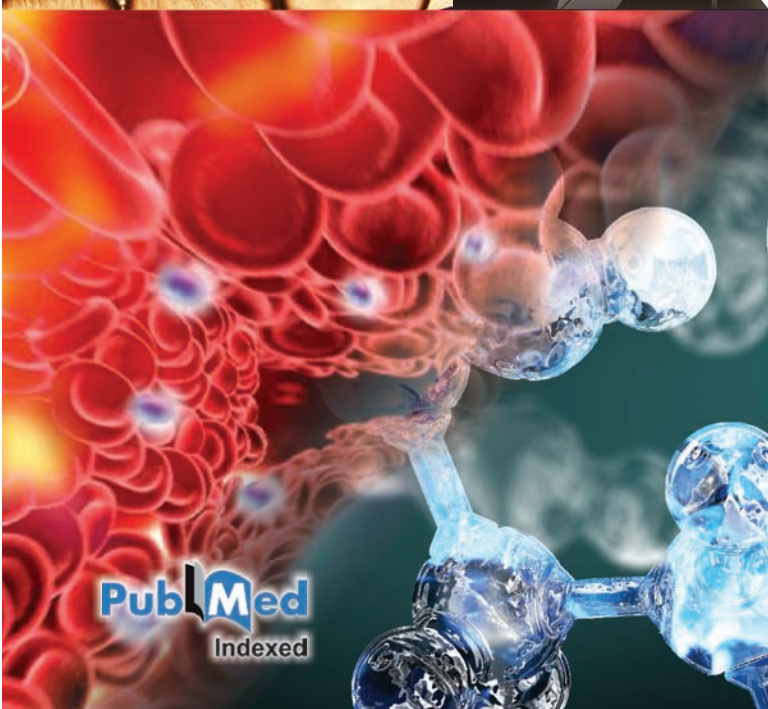
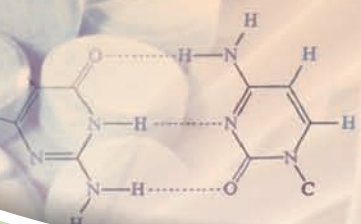
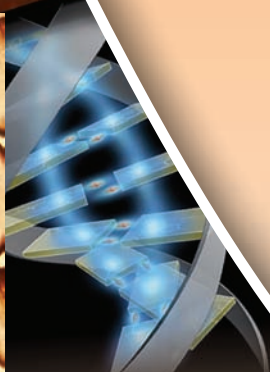
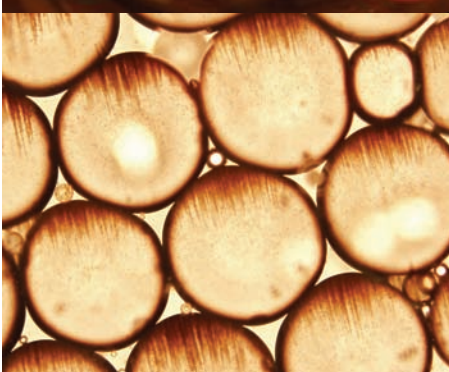


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## Bacterial vaginosis: Etiology and modalities of treatment—A brief note

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### ABSTRACT

A large women population of the world is suffering from a vaginal infection commonly known as bacterial vaginosis. The disease is associated with the decrease in the lactobacilli count in the vagina. Till date, there is a lack of full proof treatment modalities for the cure of the disease. The treatment includes the use of antimicrobials and/or acidifying agents and probiotics, either separately or in combination. This note discusses about the etiology and the various present-day modalities of treatment of bacterial vaginosis.

**KEY WORDS:** Antimicrobials, bacterial vaginosis, lactobacilli, probiotics, sexual intercourse, vagina

Bacterial vaginosis (BV) is a common vaginal infection. Although the correct etiology of the disease is not known, BV is associated with the loss of the lactobacilli colonies with a subsequent overgrowth of anaerobic polymicrobials within the vaginal lumen. Of late, its occurrence has increased many-fold and is one of the most widely studied obstetric/gynecologic infectious diseases. Before going into the details of the pathophysiology of the disease, it becomes necessary to understand the normal anatomical and physiological aspects of the vagina.

### Vagina

Vagina may be defined as an elastic lumen, which is

approximately 7.5 cm long. The elastic nature of the vagina may be attributed to the fibromuscular structure. Vaginal lumen has got three layers, viz., an outer layer of areolar tissue, a middle layer of smooth muscle, and an inner lining of stratified squamous epithelium. The lumen arises from the cervix and extends up to vaginal orifice in the perineum. The vagina runs obliquely upward and backward at an angle of 45° and lies in between the urethra and rectum. Urethra is anteriorly positioned, while rectum is posteriorly positioned to the vagina. Vagina acts as a connector between the external and internal organs of reproduction in women. In normal healthy women, the length of the anterior wall is approximately 3 inches, while its posterior wall is approximately 3.5 inches long. The vaginal opening is at the caudal end of the vulva. It is usually partially covered by the hymen, a thin membrane of connective tissue. The lubricating fluid of the vagina is secreted by the Bartholin's glands, which is located near the vaginal opening and the cervix. The pH of the vagina lies in between 3.5 and 4.5 during the period between puberty and menopause. It harbors a number of microorganisms and *Lactobacillus* is the predominant species.

Glycogen, an analogue of starch found in animals, is the main source of nutrients for the microbial flora residing in the lumen

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of the vagina. The metabolism of glycogen in the vaginal system is mediated by the estrogen hormone via estrogen receptors located in the epithelial cells covering the vaginal lumen. The activity of the estrogen receptors is dependent on the ovarian hormonal cycle. The increase in the proliferation of the epithelial cells and subsequent increase in the glycogen content during the midcycle stage of the menstrual cycle has been attributed to the increase in the estrogen levels.<sup>[1]</sup> Due to the increased proliferation rate of the epithelial cells, there is an increase in the thickness of the epithelial cell layers.<sup>[2,3]</sup> It has been observed that the quantity of the mucus, which lines the vaginal epithelia, increases as the estrogen level increases. The increased estrogen level results in the decrease in the viscosity of the mucus, which results in a watery discharge. As the menstrual cycle enters into the latter half of the follicular phase, the production of the mucus increases by 30-folds.<sup>[1]</sup> Apart from the change in the epithelial and mucosal layers, the physiology of the vagina is also dependent on the menstrual cycle. At the time of menstruation, there is an increase in the pH of the vagina to pH = 6 at day 2 with the subsequent decrease of the same to pH = 4 at day 4.<sup>[4]</sup> The dynamic changes in the environment of the vagina during the menstrual cycle leads to the drastic changes in the ecology of the vaginal microflora. In general, it is regarded that lactobacilli species is the predominant microflora responsible for maintaining the pH of the vaginal lumen.<sup>[4]</sup> A recent study on Chinese women has also supported the same.<sup>[5]</sup> But the analysis of the DNA of the microflora from the vagina of women indicates that some women harbor *Atopobium*, *Megasphaera*, and *Leptotrichia* which produces the lactic acid and not the lactobacilli species.<sup>[6]</sup>

The mucus secreted in the vagina is mainly composed of glycoprotein, mucopolysaccharides (i.e., glycogen), electrolytes, and a larger fraction of water. The mucosal layer not only provides nutrients to the vaginal microflora but also acts as receptors for them. For example, tamm horsefall protein (THP) which is present both in the human urine and vaginal region promotes adhesion of *Escherichia coli* to these regions. Although THP is not secreted by the vaginal epithelia, their presence in the vagina has been attributed to the regular contact of the external vaginal structures with the urine.<sup>[7,8]</sup> Lactobacilli undergo physicochemical interaction with the vaginal epithelia, which helps in the colonization of the lactobacilli and biofilm formation within the mucosal and the epithelial layer of the vagina.<sup>[8,9]</sup> The biofilm consists of the bacterial cell layer(s) and the secretory components from the vagina.<sup>[8,10]</sup>

The dynamic nature of the microflora is dependent on the age of the women. As the women approaches the age of 45 years, the menstrual cycle may either pause or cease forever. The condition of permanent cessation of the menstrual cycle is regarded as menopause, where there is a complete loss of follicular activity.<sup>[11]</sup> Quite often, menopause is associated with a condition where there is a remarked decrease in the vaginal secretions, especially mucus, known as post-menopausal atrophic vulvo-vaginitis. This results in the decrease in the lubrication of the vagina causing discomfort during coitus.<sup>[12]</sup> In addition, there is a decrease in the thickness of the epithelial layer thereby increasing the susceptibility of the vaginal tissue

toward infection and associated irritation.<sup>[11,12]</sup> As a result of the above conditions, there is a subsequent increase in the vaginal discomfort, dryness, burning, itching, and dyspareunia.<sup>[13]</sup> The frictional damage of the vaginal epithelia increases due to the exposure of the vaginal tissue to the moisture of the urine and is quite a common phenomenon. In addition, there is a subsequent increase in the vaginal pH in the presence of the urinary ammonia which further complicates the condition and provides an open invitation for the growth of the pathogenic microorganisms.<sup>[14]</sup>

The presence of moisture is a necessity for the proliferation of the microorganisms on any surface and the vaginal system is not an exception.<sup>[15]</sup> Sweat and transepidermal water loss is the major source of hydration of the epithelial cells. Transepidermal water loss plays an important role in the hydration of the vulva region.<sup>[15]</sup> The vaginal lumen is kept moist mainly by the vaginal secretion and to a certain extent by the urine.<sup>[16]</sup> In normal healthy women, there is an increase in the dynamic nature of the microflora with an increase in the hydration of the epithelial layer.<sup>[17]</sup> This results in the decreased permeability of the mucosal layer for the pathogenic organisms. If due to pathophysiological conditions, there is a decrease in the moisture content within the vaginal lumen and then there is a corresponding decrease in the microbial count resulting in the increase in the permeability of the barrier layer.<sup>[18]</sup> Similarly, it was found that with the increase in the moisture content around the urogenital tracts, there is a corresponding increase in the microbial activity in and around the interface of the urogenital organs and the skin.<sup>[19]</sup>

Most microbes have an optimal pH range in which they show an improved activity. Any intervention with the pH of the system may result in the growth of other microbes. The same phenomenon is also applicable for the vaginal system, which is widely populated with the lactobacilli species. The pH of the normal healthy vagina is within 3.5–4.5. The pH is mainly maintained by the production of lactic acid by the lactobacilli. Any compromise with the pH (due to pathophysiological conditions or physical activities such as insertion of contraceptive devices and intercourse) may result in the increase of the pH within the vaginal lumen, which in turn may result in the lactobacilli population and a subsequent increase in the growth of other microbe.<sup>[20]</sup> As the lactobacilli count decreases, there is a decrease in the production of lactic acid. Lactic acid has a potent anti-microbial property which helps in preventing the growth of the pathogenic microbes.<sup>[21,22]</sup> Lactobacilli also produce antimicrobial products such as bacitracin and hydrogen peroxide which further help in the prevention of the proliferation of the pathogenic microorganisms.<sup>[23,24]</sup> Lactobacilli have the capability to excrete the substances, which hinders their multiplication, from the vaginal lumen.<sup>[25]</sup> In addition, bacterial interference also plays an important role in checking the growth of the pathogens. Bacterial interference is a phenomena by which helpful bacteria utilizes the space, resources, and nutrients thereby not allowing the pathogens to proliferate.<sup>[26]</sup> This concept has been successfully used for the treatment/prevention of infections in vaginal region. Similar approaches have been used to decrease the infection rate in the nasal mucosa.<sup>[26]</sup>

The nutrient for the microbes is supplied by the vaginal secretions in addition to the secretions from the sweat, apocrine, and sebaceous glands. These secretions are composed of glycoproteins, polysaccharides, electrolytes, amino acids, nucleic acids, and fatty acids.<sup>[27]</sup> The metabolic products secreted by the microbes may influence the availability of the nutrients.<sup>[28]</sup> Fatty acids have shown antimicrobial activity (against *Streptococcus pyogenes*, *Staphylococcus aureus*, and skin micrococci) and may help in fine tuning the composition of the microbial flora.<sup>[22]</sup> They failed to produce substantial activity against gram-negative bacteria.<sup>[29]</sup> Apart from this, some peptides have also shown antimicrobial activity against various pathogenic bacteria, fungi, viruses, and protozoa.<sup>[30]</sup>

From the above discussion, it is now clear that the interaction among the host and the microbe may either create a mutually beneficial relationship (e.g., *Lactobacillus*) or may produce a deleterious effect on the host, which will lead to diseased condition and even death in severe conditions (e.g., *Candida*, *Gardnerella*, and/or trichomonas).<sup>[31]</sup> The adhesion of the pathogenic microbes to the epithelial cells is an important factor governing the colonization and/or biofilm development. This has been attributed to the competition among the natural and pathogenic microflora for the receptor sites present in the vaginal lumen.<sup>[8,32]</sup> Unfortunately, there is lack of clear understanding of the molecular basis of adherence of the lactobacilli to the epithelial cells of vagina. Some reports suggest that the adherence is mediated by the proteins present on the cell surface,<sup>[33-35]</sup> while some researchers claim that the adherence is either mediated by lipoteichoic acid<sup>[36,37]</sup> or carbohydrates.<sup>[38]</sup>

## Microflora of the Vagina

Vagina provides a biosynthetic environment that has the capability to sustain a diverse ecosystem. The microflora of the vagina can be categorized as transient and resident microflora and can easily be distinguished by newer molecular methods. The transient microflora is not capable of competing with the resident microflora in establishing a permanent residence in the vagina.<sup>[39]</sup> Knowledge about the transient and resident microflora of vagina is meager as the interpretation of the available data is very difficult. Apart from this, a large number of transient organisms continuously migrate from the exogenous source (e.g., anus and urethra).

The composition of the vaginal microflora was first described by Döderlein during the year 1892. He described the vaginal microflora as gram-positive, pleomorphic, and asporogenic bacteria, which were homogeneously distributed throughout the vaginal lumen and are often referred to as bacillus Döderlein.<sup>[40]</sup> A study where the samples were collected from college-going students and volunteers throughout the menstrual cycle indicates that the vagina is inhabited with the anaerobic and facultative microflora.<sup>[41]</sup> Similar results were also obtained from the studies on children having age varying from 2 months to 15 years.<sup>[42]</sup> Recent studies have found that lactobacilli are the dominant microflora of the vaginal system. The other microbes

include *Peptococcus* species, *Bacteroides* species, *Staphylococcus epidermidis*, *Corynebacterium* species, *Peptostreptococcus* species, and *Eubacterium* species.<sup>[43]</sup> The lactobacilli species is prevalent throughout the lifespan of women and has also been confirmed with molecular identification tools.<sup>[44]</sup> The predominance of lactobacilli is lost during various vagina diseases (e.g., bacterial vaginitis) as determined both by conventional and molecular identification techniques.<sup>[44]</sup> Among the *Lactobacillus* species, *Lactobacillus acidophilus* was considered to be the dominant microbe present in the vaginal microflora.<sup>[45]</sup> With the advent of the use of molecular identification techniques, it was found that other species (e.g., *Lactobacillus crispatus*, *Lactobacillus gasseri*, *Lactobacillus iners*, and *Lactobacillus jensenii*) may also dominate the ecosystem in the microflora.<sup>[46]</sup> The molecular identification techniques have the ability to specify the species easily in case of diverse microflora. As described earlier, vagina is a dynamic ecosystem and is a complex ecosystem having diversified species of *Lactobacillus* and other microbes. Even though the molecular identification techniques (viz., 16S r-RNA analysis, RFLP, heat shock protein) have made the life of the researchers and clinician easy, our knowledge is quite limited on the vaginal microflora. The main advantage of molecular identification techniques is its fast and efficient methods when compared with the conventional culture-based methods.

## Bacterial Vaginosis

BV is an infection that is associated with a group of pathogenic anaerobic microorganisms rather than a specific pathogen. It is a very common manifestation among the women population. Although the exact causative pathogen has not been figured out, it has been observed that there is a corresponding decrease in the population of the lactobacilli species. This results in the increase in the pH of the vaginal lumen due to the reduction in the lactic acid production. Apart from the lactic acid, the production of lactocin and H<sub>2</sub>O<sub>2</sub> also receives a setback. In general, the lactobacilli is replaced with the increased population of pathogenic gram-negative anaerobic bacteria such as *E. coli*, *Gardnerella vaginalis*, *Mycoplasma hominis*, and *Mycoplasma curtisii*.<sup>[47,48]</sup> This condition may lead to several complications, which include continuous vaginal discharge, high HIV risk, malodor (fishy smell), stomach pain, abortion, infertility, preterm birth, chorioamnionitis, and urinary tract infection.<sup>[49-51]</sup>

The microflora diversity of the vagina from the patients of BV was first reported during the year 1921 by Schröder. Till recent past, the exact causative microorganism was not known and has eluded the scientists for long, newly discovered vaginal microbes during BV were often considered as BV-causing microbes.<sup>[52]</sup> The diagnostic tests have been categorized into two categories namely clinical criteria and laboratory-based testing.<sup>[53]</sup> BV is mainly characterized by Amsel's criteria.<sup>[54]</sup> Amsel's criteria enumerates four criteria out of which at least three criteria have to be met before a woman can be declared as a patient of BV. These criteria include presence of milky homogenous watery discharge which may be gray or yellowish in color,<sup>[53]</sup> pH of vagina more than 4.5, positive amine test (fishy odor from the vaginal fluid when alkali solution is added), and the presence of clue cells.<sup>[54]</sup>

Scientists and researchers have associated BV with various factors including vaginal douching by the use of scented soaps or perfumed bubble bath and antiseptics during bath,<sup>[55]</sup> multiple sex partners and/or a new sex partner, smoking<sup>[56]</sup> and use of contraceptives (e.g., spermicides) which may increase the probability of the infection in a women.

The microflora found in the case of BV do not follow the Koch's postulates and are resistant to that approach.<sup>[52]</sup> Because the pathogenesis of BV is not clear, the management of BV is a challenging aspect for the clinicians and throughout the world, and it is becoming a very common syndrome in women in the reproductive age.<sup>[57,58]</sup> If proper care is not taken in the early phase of BV, then it may lead to secondary complications. In pregnant women, it may either cause preterm delivery or choriomnionitis.<sup>[59,60]</sup> The low weight of the infants (from BV patients) may also be accounted to the preterm birth.<sup>[50]</sup> The risk of contracting sexually transmitted diseases (e.g., HIV, syphilis, gonorrhoea, and trichomoniasis) is higher in BV patients when compared with the healthy individual.<sup>[61]</sup>

If the patients fulfill the Amsel's criteria, various diagnostic tests are used for the confirmation of the syndrome. The whiff test is the most common test that involves the addition of potassium hydroxide solution to the vaginal discharge. The presence of a strong fishy smell indicates that the patient is suffering from BV. The microscopic examination of the vaginal smear, which is analyzed for the presence of bacteria, white blood cells and clue cells, and the presence of clue cells, indicates BV. The gram staining method, introduced by Dunkelberg in the year 1965, is also a simple method for the diagnosis of BV.<sup>[62]</sup> The method helps in the confirmation of the presence of gram-positive and gram-negative bacteria in the vaginal discharge. Recently, a scoring system (on a scale of 10) based on the presence of large gram-positive rods, small gram-negative or variable rods, and small curved gram-negative to variable rods have been reported. If the score lies in between 7 and 10, then the patient is suffering from BV.<sup>[63]</sup> The various modern analytical techniques involve the use of polymerase chain reaction and oligonucleotide probes for the determination of BV. These methods are fast, reliable, and accurate.<sup>[58]</sup> Unfortunately, these techniques are not available in all the laboratories and the clinician is forced to accept the results of the afore-mentioned diagnostic tests.

## Treatment of BV

Many strategies for the treatment of BV are being used by the clinicians all over the world. The treatment protocol varies from the use of synthetic drugs to the use of probiotics. In this section, an attempt will be made to explore the different modes of treatment of BV.

### Antimicrobials in the treatment of BV

A lot of antimicrobial agents (e.g., ampicillin, penicillin, and metronidazole) have been used in the treatment of bacterial vaginitis.<sup>[57]</sup> Metronidazole have evolved as a drug of choice

for the treatment of BV and is the widely prescribed drug. It is a nitroimidazole derivative having activity against anaerobic microbes and protozoans. It has been administered either orally or locally. Tablets of metronidazole are easily available for oral administration. Formulations for the local administration of the drug include gels and suppositories.<sup>[64-67]</sup> Metronidazole and tinidazole (a chemical analogue of metronidazole) are preferred for the treatment of BV as against ampicillin. Tinidazole has a better pharmacokinetics and longer half-life than metronidazole and its recommendation for the treatment of BV is on the rise.<sup>[68]</sup> The use of ampicillin is avoided due to the emergence of ampicillin-resistant bacteria in patients with BV. It also inhibits the growth of lactobacilli.<sup>[57]</sup> The acceptance of suppositories is lower than the oral administration of the drug as they might cause irritation.<sup>[65]</sup> The insertion of suppositories into the vagina also creates problem with the patient's compliance and is worse in working women. In a recent study, it has been reported that the mode of administration of metronidazole, either orally or locally, do not have a significant difference in the eradication of the pathogenic bacteria.<sup>[67]</sup> The release of the metronidazole from the suppositories is dependent on the composition of the formulation. The release rate may be tailored by the incorporation of adjuvant. Among the metronidazole gels and lactic acid gels, for local application, lactic acid gels have been found to be more efficient and safer. The gel formulation containing a combination of both lactic acid and metronidazole has shown superior ability to recolonize the vaginal lumen with lactobacilli. The recurrence of BV is less common in patients treated with lactic acid gel when compared with patients treated with metronidazole gels.<sup>[66]</sup> This may be attributed to the hindrance and/or inhibition in the growth of the lactobacilli when metronidazole is used for the treatment and depends on the concentration of the lactobacilli.<sup>[69]</sup> Studies on the treatment of the BV have also been done with tinidazole, clindamycin, polystyrene sulfonate, and cellulose sulfate, polycarbophil-carbopol acidic vaginal gel.<sup>[15,68,70,71]</sup> Reports on clindamycin have suggested that it can be used in the treatment of BV and may be administered either orally or locally.<sup>[72]</sup> Intravaginal deliveries of clindamycin and metronidazole for the treatment of BV have shown that there was an improvement in the clinical symptoms of the patients within 21–30 days of the starting of the treatment. Unfortunately, the vagina was not recolonized with lactobacilli within the stated period.<sup>[64]</sup> The use of formulation consisting polycarbophil-carbopol and lactic acid-chitosan mucoadhesive vaginal gels has also been reported.<sup>[13,73]</sup> The polycarbophil-carbopol gels have been found to be safe.<sup>[13]</sup> Similarly, chitosan-based lactic acid delivery gels have also been found to be safe.<sup>[73]</sup>

Unfortunately, there is an increased number of reoccurrence of BV when the synthetic antimicrobials are used and may be attributed to the development of antimicrobial resistance mechanism within the microbes.<sup>[74]</sup> Hence, the researchers and clinicians are looking for alternative methods for the treatment of BV. The various chemotherapeutic agents used for the treatment of BV and their results have been compiled in Table 1.

## Probiotics in the treatment of BV

The importance of probiotics in maintaining a normal health in human and animals was described by Dr. R. Fuller during the year 1989.<sup>[79]</sup> It has recently been described as “Live microorganisms which when administered in adequate amounts confer a health benefit on the host” by the World Health Organization.<sup>[80]</sup> The lactobacilli, present in curd and different milk products, have also been categorized under probiotics. From the discussions in the previous sections, it is quite clear now that lactobacilli play an important role in the inhibition of growth, adhesion, and spread of pathogenic microbes. This has been accounted to its ability to form biofilms over the mucosal layer of the vagina and thereby compete for the nutrients and receptors with the pathogenic microbes.<sup>[40]</sup> In addition to this, they secrete lactic acid, H<sub>2</sub>O<sub>2</sub>, bacteriocins, and biosurfactants which have good antimicrobial property. Apart from the antimicrobial property of lactic acid, they help in maintaining the pH of vagina within 3.5–4.5 thereby not allowing a conducive environment for the growth of the pathogenic microbes.<sup>[20]</sup> *Lactobacillus fermentum*, *Lactobacillus casai*, *L. acidophilus*, and *Lactobacillus iners* are some of the species which have been found in vagina.<sup>[81]</sup>

### Selection Criteria for Probiotic for the Treatment of BV

The absence of *Lactobacillus* from the vagina is the specific

feature of BV.<sup>[82]</sup> The major question in the treatment of BV with the use of lactobacilli as probiotics is whether it can cure BV and can inhibit the reoccurrences. Also, which species of lactobacilli can effectively inhibit the pathogens (e.g., *Escherichia coli* and *G. vaginalis*) and at the same time allow recolonization.<sup>[83]</sup> The exact species of *Lactobacillus* for the treatment of BV may be selected based on the antipathogenic activity of the species. The consideration of following factors should also be taken into consideration before selecting the *Lactobacillus* species:<sup>[84]</sup>

1. Production of lactic acid<sup>[85]</sup>
2. Production of H<sub>2</sub>O<sub>2</sub><sup>[86]</sup>
3. Adhesion of the species to the epithelial layer<sup>[87]</sup>
4. Production of antimicrobials<sup>[88,89]</sup>

### Probiotic Treatments Available for BV

Sour milk and fermented milk were conventionally used for various health benefits. Elie Metchnikoff proposed the use of lactic acid-producing bacteria as probiotic, with scientific reasons, during the year 1907.<sup>[90]</sup> He was the first person to propose the use of *Lactobacillus* in the restoration of gastrointestinal flora.<sup>[90,91]</sup> Various commercially available *Lactobacillus*-based products for the treatment of BV include yoghurt, acidophilus milk, and available *Lactobacillus* powder and tablets.<sup>[92]</sup>

Two types of treatment methodologies are available for the treatment of BV using probiotics. The first one includes the

**Table 1: Antibiotics used for the treatment of bacterial vaginosis**

Antibiotics	Class	Result	Reference
Metronidazole and tinidazole	Antimicrobial	Resistance	[75]
Novisprin G-10	Antimicrobial α-helical octadecapeptide	May serve as template for development of topical agents to prevent BV	[76]
Clindamycin	Macrolide	Development of antimicrobial resistance among vaginal anaerobic bacteria	[74,77]
Fluconazole	Antifungal	Results showed that specific antifungal treatment can not only induce BV in BV-negative women but also cure 70% of the BV in women with BV which may be due to innate immune deficiencies like polymorphisms	[78]

**Table 2: Lactobacilli strains used for the treatment of bacterial vaginosis**

Probiotics	Results	Reference
<i>Lactobacillus</i> strains		
<i>L. gasseri</i> LN40, <i>L. fermentum</i> LN99, <i>L. casei</i> subsp. <i>rhamnosus</i> LN113, and <i>P. acidilactici</i> LN23	93% of women were cured within 2–3 days after receiving the intervention	[99]
<i>L. rhamnosus</i> GR-1 and <i>L. reuteri</i> RC-14 (Probiacac vaginal)	This intervention did not cure the BV in women with HIV but prevents the condition	[100,101]
<i>L. rhamnosus</i> , <i>L. acidophilus</i> , and <i>Streptococcus thermophilus</i>	Short-term probiotics prophylaxis with 1 capsule (Probiacac vaginal) resulted in reduction of BV recurrence and <i>G vaginalis</i> risk in a study conducted on 120 healthy Chinese women with a history of recurrent BV	[102]
<i>L. rhamnosus</i>	Promotes stabilization of vaginal ecosystem thus reducing the recurrence of BV	[103]

**Table 3: Comparison of antibiotic and probiotic therapy**

Antibiotics	Probiotics
Pharmaceutical interventions such as antibiotics are suboptimally effective and have failed to reduce the incidence of preterm birth. The failure of antibiotic therapy to prevent preterm delivery may be due to the presence of organisms already ascended the uterus or may be due to inability of the antibiotic to eradicate BV biofilms and negate their sialidase activity. <sup>[83]</sup>	Probiotics such as <i>L. reuteri</i> RC-14 and <i>L. rhamnosus</i> GR-1 incorporate themselves into pathogenic biofilms <i>in vitro</i> and cause disruption and some killing in comparison to metronidazole which although produced holes in the biofilm did not eradicate the microorganisms. <sup>[105]</sup> This process may thus explain the efficacy of lactobacilli in reducing the recurrence of UTIs, thus inducing a return of normal microbiota from a BV state. <sup>[106]</sup>

oral administration of the *Lactobacillus*, whereas the second method includes the local administration of the same in the vagina of the patient. The probiotics, when orally administered, have the natural ability to migrate to the vaginal region from the intestine via perineal and vulval skin. Studies using *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 have confirmed the phenomena.<sup>[93,94]</sup> The treatment of pregnant women, with symptoms with BV, was carried out with yoghurt containing *L. acidophilus*. Vaginal douching of the patients was done with the yoghurt continuously for a week and was repeated after every 1 week's interval. The treatment helped in improving the conditions of the patients.<sup>[95]</sup> Similar results were observed when yoghurt was locally applied in the vaginal lumen. At the cessation of the study, the vaginal pH was within the normal range and the presence of *Lactobacillus* within the lumen was also observed.<sup>[96]</sup> This kind of treatment may result in the decrease of the watery vaginal apart from its bacterial recolonization effects.<sup>[97]</sup> In a recent study, two groups of women were treated with *Lactobacillus*-based products. The first group was treated with *L. acidophilus* suppositories, whereas the second group received a combination of *L. acidophilus* suppositories and oral dose of *L. paracasai* for a period of 3 months. Both the groups showed an increase in the colonies of *Lactobacillus* with a concurrent restoration of the pH. In addition to this, the group that received combination therapy showed an increase in the restoration of the intestinal microflora.<sup>[98]</sup>

The various strains of the probiotics used for the treatment of BV and their results have been compiled in Table 2.

## Summary

With the advent of increasing cases of antibiotic-resistant pathogenic microorganisms, the use of probiotics for the treatment of BV is being extensively studied. The use of probiotics for the treatment of BV has provided a ray of hope by natural and nontoxic treatment modality.<sup>[104]</sup> Apart from the above, the probiotics may offer cost-effective treatment of BV. The antimicrobial metabolites produced by the probiotics have shown great potential not only to restrict the growth of antimicrobial resistant strains but also kill the same. Although the probiotics have shown a positive effect on the treatment of BV, not only its effect has differed from patient to patient but also its reaction time against the infection is slow. Hence, it might be a good idea to use the probiotics in conjugation with the anti-microbials which will result in the synergistic activity of both the treatment modalities. A comparison on the antibiotics and probiotics therapies has been compiled in Table 3.

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