Updated Overview of Bacterial Vaginosis; Pathogenesis, Diagnosis and Treatment

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Abstract

Background: The amniotic sac, commonly called membranes, is a thin tough transparent pair of membranes. The inner of these membranes is called amnion that encloses the fetus. The outer part is called chorion and it’s a part of placenta that allows fetal nutrition. Bacterial vaginosis is a polymicrobial, superficial vaginal infection involving reduction in the amount of hydrogen- peroxide producing lactobacillus and an overgrowth of anaerobic and Gram- variable bacteria e.g. Gardnerella vaginalis, Mycoplasma hominis and other anaerobes. The majority of cases are asymptomatic while symptomatic cases present by malodorous grayish vaginal discharge. Its prevalence in pregnancy is 15 - 30 % and can be diagnosed by Amsel's criteria that include presence of homogenous vaginal discharge, pH of vagina > 4.5, presence of clue cells in vaginal discharge and positive whiff test. According to Amsel, if 3 of the 4 criteria are positive, bacterial vaginosis is diagnosed

Keywords: Bacterial Vaginosis

Background

Bacterial vaginosis (BV), also known as vaginal bacteriosis, is a vaginal disease characterized by increased vaginal discharge with fishy smell. The discharge is usually white or gray in color may be associated with dysuria. Itching is an uncommon symptom. Occasionally the condition may be asymptomatic. Bacterial vaginosis increases the risk of infection by a number of other sexually transmitted infections including human immune deficiency virus (HIV). It also increases the risk of preterm labor among pregnant women (1).

Healthy vaginal microbiota consists of species which do not cause symptoms, infections, or negatively affect pregnancy. It is dominated mainly by Lactobacillus species. Bacterial Vaginosis is defined as disequilibrium in the vaginal microflora with decline in the number of lactobacilli with increase of a number of bacteria including Gardnerella vaginalis creating a biofilm which allows other opportunistic bacteria to thrive (2). There is a change in the bacterial prevalence in the vagina, illustrated in table (I). Bacterial vaginosis is so named because it is not a vaginitis, as no polymorphonuclear leucocytes (PML) are present in the vaginal discharge of patients with bacterial vaginosis so ,the disease is not an inflammatory process (3).
Some studies suggest that the absence of PML in bacterial vaginosis could be a consequence of the inhibitory effect of succinic and acetic acids which are detected in high concentrations in the vaginal fluid of women with bacterial vaginosis and in culture supernates of *Prevotella* and *Mobiluncus* spp. So, bacterial vaginosis is a real infection (3). An additional point in support of vaginosis being a real infection is its high response to antibiotic therapy (4).

**The most prevalent organisms in bacterial vaginosis:**

1. **Gardnerella vaginalis**
   
   *Gardnerella vaginalis* (*G. vaginalis*) is classified as a species of *Haemophilus bacteria*. Under the microscope it appears as a Gram-negative rod, although it has been reported to have a Gram-positive cell wall structure. *G. vaginalis* grows as small, circular, convex, gray colonies on Chocolate agar and blood agar. In clinical sample of BV, it is associated microscopically with clue cells, which are vaginal epithelial cells heavily coated with bacteria (5).

2. **Mycoplasma hominis**
   
   Mycoplasma hominis is a bacteria present in the vagina that is thought to be a cause of bacterial vaginosis and pelvic inflammatory disease. The primary habitats of human and animal mycoplasmas are the mucous surfaces of respiratory tract, urogenital tract, eyes, alimentary canal and the mammary glands. It is a cell wall deficient bacteria. They are resistant to antibiotics that target cell wall synthesis, such as penicillin (5).

3. **Bacteroids species**
   
   *Bacteroides* species are Gram negative, non-spore forming, obligatory anaerobes, and may be either motile or non-motile that have been isolated from the vagina. One of the metabolic features of this group is the production of succinic acid from the fermentation of glucose. (3).

**Table (I):** Flora in bacterial *Vaginosis*. (3).

<table>
<thead>
<tr>
<th>Increased Prevalence</th>
<th>Increased Concentration (Fold)</th>
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<tr>
<td><em>G. vaginalis</em></td>
<td>17</td>
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<tr>
<td><em>Bacteroides</em></td>
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<tr>
<td><em>Peptostreptococcus</em></td>
<td>10</td>
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<td><em>M. hominis</em></td>
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<table>
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<tr>
<th>Decreased Prevalence</th>
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<td>Facultative <em>Lactobacillus</em></td>
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**Epidemiology:**

Bacterial vaginosis is the most common infection of the vagina in women of reproductive age. The percentage of women affected at any given time vary between 5% and 70%. BV is common in parts of Africa and least common in Asia and Europe. In the United States about 30% of those between the ages of 14 and 49 are affected. Rates vary considerably between ethnic groups within a country (6).

**Risk factors of bacterial vaginosis**

Risk factors include douching, which alters the vaginal flora and predisposes women to developing BV. Douching is strongly discouraged by the U.S. department of health and human services and various medical authorities (7).

New or multiple sex partners are considered risk factor. However, it is not considered a sexually transmitted infection. Antibiotics use and intrauterine device are risk factors (8).
Sexual activity and bacterial vaginosis
The Center for Disease Control (CDC) defines sexually transmitted infections (STIs) as "a variety of clinical syndromes and infections caused by pathogens that can be acquired and transmitted through sexual activity." But the CDC does not specifically identify BV as sexually transmitted infection (9). It is possible for sexually inactive persons to develop bacterial vaginosis (10).

Pathogenesis
Bacterial vaginosis was named because bacteria are the etiologic agent in this infection and an associated inflammatory response is lacking. BV is the most common cause of vaginal discharge and the most common infection encountered in the outpatient gynecologic setting. An increase in vaginal discharge and vaginal malodor caused by a change in the vaginal flora characterizes BV. The vaginal discharge of BV is characteristically described as a thin, gray, homogeneous fluid that is adherent to the vaginal mucosa (11).

Bunyan, et al. (12) have demonstrated the relationship of Gardnerella vaginalis with other bacteria in causing BV. BV is known to be a synergistic polymicrobial infection. Some of the associated bacteria include Lactobacillus species, Prevotella, and anaerobes, including Mobiluncus, Bacteroides, Peptostreptococcus, Fusobacterium, Veillonella and Eubacterium species. Mycoplasma hominis, Ureaplasma urealyticum, and Streptococcus viridans may also play a role in BV. Atopobium vaginae is now recognized as a pathogen associated with BV.

In BV, the vaginal flora becomes altered through unknown mechanisms, causing an increase in the local pH. This may result from a reduction in the hydrogen peroxide–producing lactobacilli. Lactobacilli are large rod-shaped organisms that help maintain the acidic pH of healthy vaginas and inhibit other anaerobic microorganisms through elaboration of hydrogen peroxide. Normally, lactobacilli are found in high concentrations in the healthy vagina. In BV, the lactobacilli population is reduced greatly, while populations of various anaerobes and G. vaginalis are increased (13).

G. vaginalis forms a biofilm in the vagina. This biofilm may be resistant to some forms of medical treatment. This predominant G. vaginalis biofilm has been shown to survive in hydrogen peroxide (H₂O₂), lactic acid and high levels of antibiotics. When the biofilm was subjected in the laboratory to enzymatic dissolution, susceptibility to H₂O₂ and lactic acid were restored. These findings may lead to future development of novel therapies involving enzymatic degradation of biofilms. No such products are currently on the market (14).

Diagnosis of bacterial vaginosis:
Clinical symptoms
The most common symptom experienced by nearly all women affected with bacterial vaginosis is vaginal discharge. This discharge frequently happens after sexual contact, and it comes with a fishy odor that can be nauseating to the smell. The discharge itself is thin grayish in color. The malodour is often noticed after coitus where the alkaline seminal fluid has resulted in the release of volatile amines and fatty acids (15). The amount of discharge may be scanty, moderate or profuse and it is usually adherent to vaginal wall. The discharge coats the walls of the vagina, and is usually without significant irritation, pain, or erythema (redness) (4).
Vaginal examiantion: Findings on vaginal examination include the following:

Typical BV discharge characteristics include the following:
1. Most often gray, thin, and homogeneous
2. Adherent to the vaginal mucosa
3. May not visualize pooling of discharge in the posterior fornix because of adherence to the vaginal mucosa
4. May observe small bubbles in the discharge fluid
5. An increased light reflex of the vaginal walls may be observed, indicating a very wet appearance (16).

Lack of significant vulvovaginal inflammation
- Typically, the labia, introitus, cervix, and cervical discharge appear normal.
- Evidence of cervicitis should prompt a workup for concomitant infection with Neisseria gonorrhoeae, Chlamydia trachomatis, or herpes simplex virus (HSV) (17).

Investigations for diagnosis of bacterial vaginosis
1. Amsel criteria
   To make a diagnosis of bacterial vaginosis, a swab from inside the vagina should be obtained. The discharge sample is subjected to three tests, two positive results in addition to the discharge itself are enough to diagnose BV. If there is no discharge, then all three criteria are needed (18).

   These tests aim at finding of
   - A characteristic "fishy" odor on wet mount. This test, called the whiff test, is performed by adding a small amount of potassium hydroxide to a microscopic slide containing the vaginal discharge. A characteristic fishy odor is considered a positive whiff test and is suggestive of bacterial vaginosis.
   - Loss of acidity. To control bacterial growth, the vagina is normally slightly acidic with a pH of 3.8–4.2. A swab of the discharge is put onto litmus paper to check its acidity. A pH greater than 4.5 is considered alkaline and is suggestive of bacterial vaginosis.
   - The presence of clue cells on wet mount. The test for clue cells is performed by placing a drop of sodium chloride solution on a slide containing vaginal discharge. If present, clue cells can be visualized under a microscope. They are so named because they give a clue to the reason behind the discharge. These are epithelial cells that are coated with bacteria (18).

   In clinical practice BV can be diagnosed using the Amsel criteria:
   - Thin, white, yellow, homogeneous discharge
   - Clue cells on microscopy
   - pH of vaginal fluid >4.5
   - Release of a fishy odor on adding alkali—10% potassium hydroxide (KOH) solution.(18)

At least three of the four criteria should be present for a confirmed diagnosis. The modified Amsel Criteria is equally diagnostic of BV as the Amsel's. The modified Amsel Criteria says two instead of the three out of the four criteria is diagnostic of BV (19).

Gardnerella vaginalis is the main culprit in BV. Gardnerella vaginalis is a short rod, therefore, it is a coccobacillus. The bacteria that have covered the squamous epithelial cells making the epithelial cells have obscured ends are not bacilli, they are coccobacilli. Hence, the presence of clue cells and gram variable coccobacilli are indicative or diagnostic of Bacterial Vaginosis (20).
Microscopic evaluation of the bacterial flora:

The bacterial flora may be examined microscopically for evidence of changes in the overall bacterial predominance. The healthy vagina has a predominance of lactobacilli (large Gram-positive rods). The flora of a patient with BV changes to become dominated by coccobacilli, reflecting an increase in the growth of *Gardnerella vaginalis* and other anaerobes (22). An alternative diagnostic criterion of bacterial vaginosis is to use a Gram-stained vaginal smear, with either

a) Hay/Ison criteria (23) or
b) Nugent criteria (24).

A. **The Hay/Ison criteria are defined as follows:**

- **Grade 1 (Normal):** Lactobacillus morphotypes predominate.
- **Grade 2 (Intermediate):** Mixed flora with some Lactobacilli present, but Gardnerella or Mobiluncus morphotypes also present.
- **Grade 3 (Bacterial Vaginosis):** Predominantly Gardnerella and/or Mobiluncus morphotypes. Few or absent Lactobacilli.

**a) Nugent Criteria:**

Nugent's criteria are used to quantify or grade bacteria via Gram stain of vaginal samples. In brief, Nugent's criteria evaluate 3 types of bacteria via Gram stain: *Lactobacillus*, *Bacteroides/Gardnerella*, and *Mobiluncus*. They are each graded on a scale of 1-4 (1+ is < 1 cell per field, 2+ is 1-5 cells per field, 3+ is 6-30 cells per field, and 4+ is >30 cells per field). In this system, *Lactobacillus* and *Bacteroides/Gardnerella* are given scores between 0-4, but *Mobiluncus* is only graded from 0-2. Total scores are then calculated and used as follows: 0-3 (Normal), 4-6 (intermediate vaginosis), and 7-10 (bacterial vaginosis) (22). In this scale, a score of 0-10 is generated from combining three other scores. This method is time consuming and requires trained staff, but it has high interobserver reliability (20).

2) **Vaginal cultures:**

Obtaining routine vaginal cultures in patients with BV has no utility, because this is a polymicrobial infection and some women may have asymptomatic carriage of *G. vaginalis* organisms. Although *G. vaginalis* has been demonstrated to grow in up to 100% of vaginal cultures of women with BV, it has also been cultured in up to 70% of asymptomatic women.
However, obtaining cultures to exclude other infectious etiologies (eg, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae*) is appropriate. In recurrent cases that have not resolved with standard regimens, cultures may be appropriate (21).

3) Special diagnostic methods for diagnosis of bacterial vaginosis:

a) Papanicolaou smear:

In the USA a (Pap smear) is made with endo and ectocervical material. In Sweden and elsewhere it also includes sampling the vaginal fluid and have found high sensitivity and specificity (90 and 97%) predictive values for Papanicolaou smear diagnosis of bacterial vaginosis, while those in USA have not. The issue is not the Papanicolaou stain itself, but the source of the sample (26).

b) Diagnostic tests based on detection of bacterial products:

Some methods of diagnosis of bacterial vaginosis are based on the detection of metabolic products of microorganisms (Trimethylamine, succinic acid, proline aminopeptidase enzyme and sialidases enzymes) unique to vaginal fluid of women with bacterial vaginosis. These types of diagnostic tests have several potential advantages over culture or Gram stain methods: they are objective, can be adapted for batch processing, and if properly modified are rapid and require no special equipment (27).

c) Gas liquid chromatography:

Gas liquid Chromatography is another tool available for diagnosis of bacterial vaginosis, it would not be practical in most setting because clinics and many hospital laboratories are not equipped with Gas liquid Chromatography (28).

d) Polymerase chain reaction:

It is a powerful method of in vitro DNA synthesis for detecting vaginal microbes. It is a rapid and sensitive for amplifying species-specific DNA. It is possible to determine the presence of Gardnerella Vaginalis in stored genital tract samples by PCR, suggesting that this could be developed in to an objective method that could be useful for certain applications. Moreover, bacterial PCR correlates better than Nugent or Amsel criteria (29).

e) DNA probe:

This test is recommended to be used in conjunction with the pH and amine test for diagnosis of bacterial vaginosis to increase the specificity and positive predictive value (28).

**Treatment of bacterial vaginosis:**

Treatment of bacterial vaginosis is important for several reasons. First, bacterial vaginosis affects 8% to 23% of women during their reproductive years and is the most common etiology of vaginal symptoms that prompt women to seek medical care. Second, bacterial vaginosis has been strongly associated with numerous adverse sequelae related to the upper genital tract, especially in pregnant women, who experience a higher rate of preterm delivery and low birth weight infants in presence of bacterial vaginosis (30).

Some studies suggested avoiding douching, avoiding sex, or limiting the number of sex partners to lower the risk of vaginosis. Probiotics may help prevent re-occurrence. While there is tentative evidence, it is not strong enough to recommend their use for this purpose (31). Treatment includes

a) **Antibiotics:**

Treatment is typically with the antibiotics metronidazole or clindamycin. They can be either given by mouth or applied inside the vagina. Other antibiotics that may work include macrolides, lincosamides, nitroimidazoles, and penicillins.
About 10% to 15% of people, however, do not improve with the first course of antibiotics and recurrence rates of up to 80% have been documented (32). This inability to prevent recurrences reflects our lack of knowledge on the origins of BV. *Atopobium vaginae* has been recently reported to be associated with BV in around 80% of the cases and might be involved in the therapeutic failures (12). Recurrence rates are increased with sexual activity with the same pre-/posttreatment partner and inconsistent condom use although estrogen-containing contraceptives decrease recurrence. When clindamycin is given to pregnant women symptomatic with BV before 22 weeks of gestation the risk of pre-term birth before 37 weeks of gestation is reduced (33).

b) **Probiotics:**
Probiotics are live bacteria that may confer a health benefit on the host. In the past, there were other definitions of probiotics. The first use of the term “probiotic” as microorganisms that have effects on other microorganism was expressed as follows: Substances secreted by one microorganism that stimulate another microorganism (34).

Obiero, et al., (35) found tentative but insufficient evidence for probiotics as a treatment for BV. Tan, et al., (36) reached the same conclusion. Richardson, et al., (37) found some evidence supporting the use of probiotics during pregnancy to improve neonatal outcome.

**Management of sex partners:**
The results of some clinical trials indicate that a woman's response to therapy and the likelihood of relapse or recurrence are not affected by treatment of her sex partner(s), therefore, routine treatment of sex partners is not recommended. (38).

Other studies concluded that Antibiotic treatment of male partners could re-establish the normal microbiota of the male urogenital tract. BV associated bacteria in or on the male genitals may promote relapse, reinfection of, women with BV. Treating the male partner is an effective and safe intervention and offers the advantage of preventing the recurrence of infection (39).

**Prognosis and complications**
Although previously considered a mere nuisance infection, untreated bacterial vaginosis may cause complications such as endometritis, salpingitis, pelvic inflammatory disease. BV leads to an increased risk for acquiring HIV. Post gynecologic procedure infections, such as vaginal cuff cellulitis (post hysterectomy) and post abortion infection may also occur (37).

Bacterial vaginosis increases complications of pregnancy, including premature rupture of membranes, premature labor, chorioamnionitis, and postpartum endometritis (40).

The prognosis for uncomplicated cases of bacterial vaginosis is generally excellent. Uncomplicated bacterial vaginosis that is assessed promptly typically resolves with standard antibiotic treatment. Infections such as candida vaginitis or *Atopobium vaginae* in patients whose symptoms do not resolve after treatment of BV is Suspected. The prognosis of complicated cases of bacterial vaginosis varies.


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