

Clinical Significance of *Gardnerella vaginalis*

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Abstract

In this era of instrumentation, and lab automation, there is great improvement in the isolation and identification of microbes associated with various infectious diseases. The cause of concern is the fact that, not all microorganisms isolated from the human clinical specimens are the pathogens. Also, there are areas in human body which are normally colonized by bacteria, which are commonly termed as commensals. Isolation of such organisms from the patients with signs of infections, and to confirm their role as a pathogen appears be difficult. Therefore, it is important to understand the normal microbial flora and its changes before and after the signs of infection. Vaginal environment is known to be colonized with Lactobacilli, which is responsible for the acidic nature, and the reason for resistance against other infections. But several studies have demonstrated the presence of other bacterial flora that include *Gardnerella vaginalis* (*G. vaginalis*), both in the absence as well as during infection/inflammation. Several other reports have noted the presence of *G. vaginalis* associated with infections including the urinary tract infections. This review attempts to evaluate the potential role of *G. vaginalis* in human infections, and its clinical significance when isolated from human clinical samples.

Keywords: *Gardnerella vaginalis*; Clinical significance; Infections; Normal vaginal environment

Introduction

Gardnerella vaginalis (*G. vaginalis*) is the sole member of the genus *Gardnerella*. It was previously called as *Corynebacterium vaginalis*/*Haemophilus vaginalis*. *G. vaginalis* is a pleomorphic gram-negative bacterium showing very short bacilli (*Coccobacilli*). It is non-motile, non-spore forming, non-capsulated, catalase and oxidase negative bacterium, and can be normally present in the female genital tract. It has a complex cell wall composition, which makes it is distinct from other bacterial species [1]. They show variable staining characteristics; neither staining positively nor reacting negatively to grams stain. *G. vaginalis* is a facultative anaerobe having the ability to survive in the acidic (pH 5-6) vaginal environment along with the other vaginal inhabitant, the *Lactobacillus*. They are oxidase negative, do not produce urease enzyme and fail to reduce nitrate [1,2]. Also, 16S rRNA sequencing studies observed that *G. vaginalis* is closely related to *Bifidobacterium* species (spp.), an anaerobic bacterium [3].

Morphology and cultural characteristics of *G. vaginalis*

On culture, *G. vaginalis* grows as grey colored, tiny (1-2 mm) colonies morphologically resembling *Enterococcus* spp. as shown in Figure 1. The colonies do not emulsify easily during the smear preparation, appear as clumps and are gram-negative on grams staining

(frequently gram-variable) as shown in Figure 2. Gardner et al. were first to describe *G. vaginalis* as a causative agent of bacterial vaginosis (BV) [4]. *G. vaginalis* has been found in the vaginal environment of more than 50% of normal and healthy women [5-7]. It is frequently isolated from the cases of bacterial vaginosis along with other bacterial species that include *Atopobium vaginae*, *Mobiluncus*, *Megasphaera*, *Prevotella*, *Porphyromonas*, *Peptoniphilus*, *Bacteroides*, *Fusobacterium*, *Mycoplasma*, *Peptostreptococcus*, and other bacteria. Being normally present in the genital tract, pathogenicity/its ability to cause infections has always been in a doubt until it was found that the pathogenic strains had cytolytic properties, could form biofilms and have virulence determinants that include *prolidase* and *sialidase* activities [2,8].

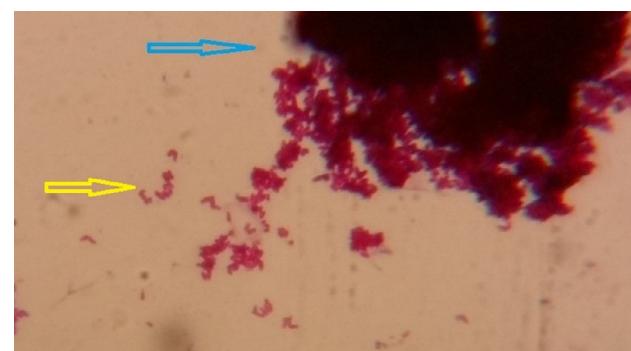


Figure 2: *G. vaginalis* on grams staining shows unemulsifiable colonies (blue arrow) and short gram-negative bacilli (yellow arrow).



Figure 1: Colonies of *G. vaginalis* as observed on blood agar.

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Isolation of *G. vaginalis* strains with pathogenic properties among cases of BV and strains without pathogenic properties in the non-BV cases confirms the role of *G. vaginalis* as a potential pathogen [7]. *G. vaginalis* has also been associated with other infections, mostly in women, that include bacteremia associated with postpartum endometritis and osteoarticular infections involving prosthetic devices. Although it was isolated from the suprapubic aspirations from women, role of *G. vaginalis* in causing urinary tract infections is still unclear. *G. vaginalis* was also isolated from men suffering from urethritis, balanitis, urosepsis, and urinary tract infections [3]. Previous research has also confirmed that there is a shift in the microbiota of the vagina from a *Lactobacillus* predominance to *G. vaginalis* and other bacterial predominance during BV [9,10]. A synergistic association of *G. vaginalis* with other vaginal microbiota (*Lactobacilli*, *Bifidobacterium* and others) was also found contributing to BV [11].

Occurrence of vaginal candidiasis, and infection with *Trichomonas* may further question the role of *G. vaginalis* in causing vaginitis. Therefore, it has been recommended that the vaginal infection caused by *G. vaginalis* alone be called *G. vaginalis* vaginitis or *Gardnerella* vaginitis differentiating it with the BV caused by other anaerobic bacteria, fungus (*Candida*) and parasites (*Trichomonas vaginalis*) [8].

This editorial attempt is to update the knowledge regarding the status of *G. vaginalis*, its pathogenic potential and clinical relevance when isolated from human clinical specimens.

Epidemiological and virulence attributes of *G. vaginalis*

Since, *G. vaginalis* could be present in the normal vaginal environment along with *Lactobacilli*, also its isolation along with other bacterial species which are known to cause BV during infection/inflammation, its role as a potential pathogen remains unclear.

A recent study had attempted to understand the evolutionary history and functional attributes of *G. vaginalis* by performing genomic analysis of few species of *G. vaginalis* and *Bifidobacterium* (also frequently isolated from cases of BV). Phylogenetic analysis using 16S rRNA, whole genome sequencing and protein families had noted revealed that *G. vaginalis* species had several similarities with the *Bifidobacterium* and found genes coding for virulence factors including the drug resistance [12]. Recent research has noted that the *G. vaginalis* isolates could be grouped as four different clades (A, B, C and D) based on sequencing of the chaperonin-60 universal target (cpn60 UT). Sialidase gene detection assay revealed variable results confirming the fact that the various strains had distinct pathogenic properties. Such studies appear very useful in characterizing the strains isolated from both symptomatic and asymptomatic patients [13].

Role of *G. vaginalis* in causing BV among BV positive, partial BV and BV negative individuals was recently evaluated using microscopy (Amsel criteria and the Nugent method), culture and polymerase chain reaction (PCR). This study had observed that *G. vaginalis* was isolated from more than 80% BV negative cases and that most isolates (79%) were belonging to clade 4 which had no Sialidase gene [14].

A study of bacterial load and clade distribution of *G. vaginalis* in vaginal secretions using two different quantitative PCR (qPCR) assays revealed the presence of low concentrations of *G. vaginalis* in non-BV cases. This research had also observed the occurrence of clades 1 and 3 among BV cases, clade 2 with intermediate BV and clade 4 with non-BV cases. And 70% of the isolates were found to belong to multi clades and there was a positive correlation of BV and multi clades [15].

Studies on clade distribution and its association with metronidazole resistance demonstrated that 100% strains belonging to the clade 3 and 4 were resistant to metronidazole whereas only 35% and 7% of clades 1 and 2 respectively were metronidazole resistant [16].

The study on the activities of clustered regularly interspaced short palindromic repeat (CRISPR)-associated (Cas) genes of *G. vaginalis* showed that the gene activities were upregulated in the patients who were not responding to the antibiotic therapy. This was attributed to the DNA repair mechanisms of the genes involved in nullifying the effects of the DNA damaging mechanisms of the antibiotics used [17].

A recent report demonstrating increased susceptibility of developing BV among women using mechanical contraceptives (copper intrauterine device) as compared to the hormonal contraception suggests the fact that the vaginal microbiota gets altered in the presence of foreign objects. Also, the bacteria could form biofilms, resist treatment and co-exist synergistically with other bacteria and can result in chronic infection/inflammation of vagina [18].

Association of increased sialidase activity with the invasive property of *G. vaginalis* was recently reported in a study which observed that there was a direct correlation with increased sialidase activity with invasiveness of *G. vaginalis*. The sialidase enzyme was noted to cleave/hydrolyze the sialic acid residues present on the glycans of mucosal surfaces, thereby contributing to the penetration of the bacteria in to the vaginal epithelial cells. Role of sialidase activity was also experimentally confirmed by using sialidase inhibitor Zanamavir, which had reduced the invasiveness by 50% [19]. One study using fluorescence in situ hybridization (FISH) and qPCR found a significant correlation of occurrence of BV with *G. vaginalis* strains containing sialidase A gene, and biofilm formation [20].

In another study which performed whole genome sequencing of three different strains of *G. vaginalis* (two isolated from cases of BV and one from normal vagina) noted that there was significant heterogeneity among the isolates both genetically and in metabolic activities. This study observed that all strains had virulence factors including genes coding for vaginolysin, fimbriae for cell adhesion, genes encoding biofilm formation, and the ability to develop multi-drug resistance. A bactericidal toxin, like the lysozyme, was also found to be produced by all the strains of *G. vaginalis*, which could be instrumental in shifting the balance of normal vaginal flora and development of BV [21].

Since the colonization of *G. vaginalis* involves contact of the bacterium to vaginal epithelial cells, a recent study applied a multidimensional approach using proteomics, bioinformatics, confocal fluorescence microscopy and monoclonal antibodies to evaluate various cell surface proteins and their potential role in the development of BV. This study had confirmed the presence of 261 proteins, some being present within the cell and many others located on the cell surface. Monoclonal antibodies against GroEL and Cna were successfully developed and detected using enzyme linked immunosorbent assay (ELISA) and immunofluorescence techniques [22].

G. vaginalis isolates from both BV and non-BV cases were studied for their antimicrobial susceptibility profile and the ability to produce vaginolysin. PCR was used to confirm the bacteria and to identify the gene coding for vaginolysin. This study had demonstrated that almost all strains (98.3% of 179 BV cases, and 100% of 25 non-BV cases) had the ability to produce vaginolysin. Most strains were susceptible to *clindamycin*, with significant resistance noted against *ampicillin* (54%), *metronidazole* (60%), *tinidazole* (60%) and *secnidazole* (72%) [23]. A study on vaginal colonization of pregnant women in Portugal

revealed higher rates of *G. vaginalis* colonization (67.5%) with only 3.9% diagnosed with BV. This study highlights the fact that mere colonization of *G. vaginalis* may not be a risk factor for BV [24].

In a recent study from India which evaluated the microbiota of vaginal secretions among HIV seropositive patients with symptoms of vaginitis, *G. vaginalis* was isolated only in 2% of the cases [25]. These findings highlight the significance of varied geographical distribution and etiopathology of *G. vaginalis*.

Colonization of other bacterial flora, replacing the resident *Lactobacilli* and increased numbers of *G. vaginalis* and other anaerobic bacteria has been noted to be common during BV. Application of probiotics to reinstate normal vaginal flora was suggested by a previous study [26].

Control and therapy of *G. vaginalis* infection

Considering the available literature, it is evident that *G. vaginalis*, along with other anaerobic bacteria may colonize the vagina. Such a colonization could disturb the vaginal environment by increasing the pH above 4.5. This in turn inhibits the growth of *Lactobacilli*, which are responsible for the acidic and healthy vaginal environment. In view of the potential of these microbes to colonize and cause acute, chronic and recurrent infections, difficulty in culturing and identifying them, and the fact that there are only limited antimicrobial agents available with reports of drug resistance, a cautious and comprehensive strategy must be employed.

Management includes the use of broad-spectrum antimicrobial agents with activity on anaerobic bacteria like clindamycin, metronidazole and tinidazole. Due to relapses and recurrent infections, a long-term course of oral antibiotics may be supplemented with intravaginal topical antibiotics (2% clindamycin) [27]. *Lactobacillus acidophilus* vaginal-probiotic containing oestriol was used in combination with oral and topical antibiotic therapy to control and prevent recurrent infection. This study results showed that there was no additional benefit of using vaginal probiotic [28].

Conclusions

In conclusion, it is evident that *G. vaginalis* can be present as a normal inhabitant of vagina along with *Lactobacillus* of healthy women. There is a possibility of shift in the numbers of normal colonizers to the potential bacteria that cause BV. Also, *G. vaginalis* has been found to develop biofilms, possess several virulence factors, become resistant to antibiotics, and be solely responsible for vaginitis. Its association with invasive infections like the bacteremia, abscesses, and urinary tract infections should be seriously considered. Role of *G. vaginalis* in the pregnant women, its role in the development of fetus requires further extensive research. Screening for the normal colonizers post puberty, after pregnancy, and post menarche could increase our understanding of the vaginal microbiota and its association with inflammation and infections. There is an increased need of understanding the vaginal microbiota among HIV seropositive women, who could be prone to frequent infections.

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