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Editorial

The Inundated Commensals- Bacterial Vaginosis

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Preface

Bacterial vaginosis is a condition engendered from overgrowth and imbalance of composition of normal vaginal bacterial flora. Although contemplated to originate from *Gardnerella vaginalis*, contemporary terminology of bacterial vaginosis illuminates effusive progression of diverse bacteria naturally inhabiting the vagina to engender the condition. Bacterial vaginosis is additionally nomenclated as "shift in flora", "*Gardnerella vaginalis*" or "clue cells" [1].

Bacterial vaginosis is not a sexually transmitted disease (STI) as it represents an exuberance of normal vaginal bacteria as a sexually transmitted disease (STI) is generated by bacterial flora which are not endogenous to the vagina [1,2].

Bacterial vaginosis is associated with complications such as pelvic inflammatory disease, infertility, postoperative infections, induction of premature labour or low birth weight babies [1,2].

Disease pathogenesis

Lactobacillus spp is preponderant within vaginal microbiota. Bacterial vaginosis emerges due to an imbalance of natural vaginal bacterial flora with characteristic alteration of commonly discerned bacterial subtypes along with an elevated bacterial count. Multitudinous microbes infecting vaginal canal in young females induces excessive, malodorous vaginal discharge [1,2].

Bacterial vaginosis displays a depletion in *Lactobacillus* spp along with augmentation of poly-microbial vaginal microbiota especially obligate and/or facultative anaerobes. Although inadequately deciphered, mechanism of occurrence of bacterial vaginosis or lack of *Lactobacillus* spp proves to be a detriment for several sexual and reproductive functions [2,3].

As bacterial vaginosis is accompanied by declining quantities of *Lactobacilli*, bacterial vaginosis is posited to commence with *Gardnerella vaginalis* infection. The organism creates a biofilm which permits proliferation of adjunctive, opportunistic bacteria within the vagina.

Although *Gardnerella vaginalis* is frequently incriminated in engendering bacterial vaginosis, the condition is poly-microbial and organisms such as *Prevotella, Mobiluncus*, pepto-streptococci, *Mycoplasma hominis* and *Ureaplasma urealyticum* are implicated [2,3].

Bacterial vaginosis and concurrent, enhanced possibility of impending sexually transmitted infections (STIs) is due to colonization of adjunctive vaginal pathogens within upper genital tract. Bacterial vaginosis also engenders enzymes which decimate infection resisting ability of host leukocytes or enhanced release of endotoxins which activate production of cytokines and prostaglandins within the vagina. Irrespective of concordant clinical symptoms, bacterial vaginosis demonstrates elevated levels of genital, pro- inflammatory cytokines [2,3].

Enhanced vaginal pH exceeding > 4.5 can create adherence of *Gardnerella vaginalis* to innumerable vaginal squamous epithelial cells with consequent morphologic emergence of classic "clue cells". Mucus coating of cervico-vaginal epithelium is the preliminary defence and accrual site of resident vaginal microbiota. Also, cervico-vaginal mucus (CVM) lubricates and protects underlying squamous epithelium which circumvents viral acquisition and transmission. As in respiratory and gastrointestinal tract, resident microbiota can alter the configuration of mucus within female genital tract [3,4].

Association of bacterial vaginosis with enhanced acquisition and transmission of human immune deficiency virus (HIV) exemplifies impact of vaginal bacteria upon tissue integrity, inflammation, elevation of pro- inflammatory cytokines/chemokines and recruitment and activation of HIV target cells [3,4].

Cervico-vaginal mucus (CVM) microstructure is predominantly identical and intact in symptomatic and asymptomatic individuals. Also, adhesive nanoparticles and viral (HIV) particles are mobile within the mucus in symptomatic and asymptomatic bacterial vaginosis, thus implying a diminished barrier to viral influx [4].

Lactic acid delineates an immunomodulatory influence upon cervico-vaginal epithelial cell lines along with augmentation of anti-inflammatory cytokine interleukin 1 receptor antagonist (IL-1RA), decreased pro- inflammatory cytokines and declining response to Toll-like receptor induced inflammation. Thus, lactic acid concentration is an indicator of composition of vaginal microbiota and is concordant with vaginal pH. However, lactic acid concentration does not directly influence viral adhesion. Enhanced vaginal pH is associated with augmented viral motility [3,4].

Constituent bacteria of bacterial vaginosis are associated with enhanced levels of mucin degradative enzymes such as sialidase, glycosidase, mucinase or prolidase. It is posited that *Gardnerella vaginalis* produces sialidase which degrades cervico-vaginal mucus (CVM) in animal models. Mucus degrading enzymes generated in bacterial vaginosis can decimate mucus barrier function and reduce adherence to viral (HIV) particles in order to amplify viral movability. Alternatively, depleted adhesion or viral interactions are concurrent to elevated levels of mucin degrading enzymes [3,4].

Disease characteristics

Females with bacterial vaginosis delineate an elevated possibility of acquiring sexually transmitted infections (STIs) Although not an infectious disorder, mode of bacterial transmission in bacterial vaginosis remains obscure. Bacterial dissemination occurs amongst individuals via sexual intercourse, a manoeuver which may alter composition of natural vaginal bacterial flora [4].

Typically, the condition appears on account of decimated quantification of normal, hydrogen peroxide producing *Lactobacilli* in concurrence with effluence of anaerobic bacteria [5].

Bacterial vaginosis is commonly discerned within women of reproductive age group wherein around 5% to 70% subjects are incriminated. Around 30% women between 14 years to 49 years are affected [4,5].

Although frequently delineated in African subcontinent, the disorder is infrequent within Asia and Europe. Disease incrimination is proportionately variable within diverse ethnic groups. Roughly 51% of non white women of African- American descent and approximately 32% of Mexican Americans are implicated. Bacterial vaginosis is prevalent in around 30% of American Caucasians and approximately 44% of sub-Saharan Africans [4,5].

Factors incriminated in possible emergence of bacterial vaginosis are repetitive vaginal douching, multiple sexual partners, recent administration of antibiotics, spermicidal preparations or diverse medications, previous pregnancy, cigarette smoking and insertion of intrauterine device. Furthermore, bacterial vaginosis can appear in subjects unexposed to sexual intercourse. Unmarried girls, early age

of first intercourse and commercial sex professionals are frequently affected by bacterial vaginosis. Accruing a sexual partner enhances possible occurrence of bacterial vaginosis by 60%. Vaginal douching is dissuaded [4,5].

Screening of asymptomatic women for bacterial vaginosis is not recommended. However, investigation and treatment of symptomatic women is beneficial [4,5].

As a frequent cause of anomalous vaginal discharge in young females, bacterial vaginosis is commonly associated with squamous intra-epithelial lesions (SIL) secondary to human papilloma virus (HPV) infection. The disorder is uncommon in postmenopausal women except in individuals treated with hormonal replacement therapy.

Untreated bacterial vaginosis is associated with complications of pregnancy. Bacterial vaginosis augments probable emergence of subsequent chlamydia (1.9 times) or gonorrhoea (1.8 times) infection. Subjects with bacterial vaginosis and concomitant HIV infection frequently transmit the virus to sexual partners, in contrast to individuals devoid of bacterial vaginosis. Bacterial vaginosis elevates viral (HIV) shedding by six times [4,5].

In women with bacterial vaginosis, augmented bacterial diversity and decimated *Lactobacilli* quantification depict a 60% or 4 times elevated possibility of acquiring human immune deficiency virus-1 (HIV-1) infection, in contrast to women with abundance of vaginal *Lactobacillus crispatus*. A 3 times increased female to male transmission of HIV is observed in seropositive females with bacterial vaginosis, which may not be due to enhanced vaginal exudation of HIV RNA [4,5].

Bacterial vaginosis enhances possible infection with herpes simplex 2 virus (HSV2) besides reactivation of human papilloma virus (HPV) infection. Bacterial vaginosis is indicative of persistence of human papilloma virus (HPV) thereby warranting therapy of asymptomatic women with bacterial vaginosis co-infected with human papilloma virus (HPV) [5].

A multitude of obstetric and sexual health complications accompany bacterial vaginosis. Pregnancy with bacterial vaginosis is associated with two times amplified possibility of preterm birth, especially within early second trimester and three to five times enhanced probability of spontaneous abortion within first trimester. Additionally, incidence of chorio-amnionitis, premature rupture of membranes (PROM), adverse neonatal outcomes, postpartum endometritis, pelvic inflammatory disease (PID) and urinary tract infection (UTI) is elevated. Bacterial vaginosis is also associated with tubal factor infertility [5].

Prevalence of bacterial vaginosis is augmented in infertile women (45.5%), in contrast to fertile women (15.4%). Females with bacterial vaginosis subjected to *in vitro* fertilization depict reduced percentage of implantation and amplified proportion of early pregnancy loss [5].

Clinical elucidation

Approximately 50% of incriminated subjects are asymptomatic. Fishy or ammonia-like, malodourous, excessive vaginal discharge is discerned. Typically, the fish-like, vaginal discharge is thin, greyish or white [5,6].

Majority of women with bacterial vaginosis demonstrate a copious, malodorous vaginal discharge following sexual intercourse. Additional clinical symptoms are represented by dysuria, dyspareunia and vaginal pruritus. Cogent history pertaining to disease incurring risk factors along with history of preceding episodes of bacterial vaginosis infection is mandated [5,6].

Clinical evaluation of bacterial vaginosis is often achieved by Amsel criterion. A minimal of three of four diagnostic criterion are required to clinch the diagnosis.

The Amsel criterion are configured by

- A thin, white to yellowish, homogenous vaginal discharge
- Clue cells as discerned upon microscopy
- pH of vaginal fluid exceeding > 4.5
- Occurrence of fish-like odour following addition of alkaline, 10% potassium hydroxide (KOH) to the specimen [5,6].

Modified and definitive Amsel criterion necessitate concurrence of two of four aforementioned factors. Sensitivity and specificity of Amsel criterion are 70% and 94%, respectively [5,6].

Alternatively, gram's stain of vaginal fluid is visualized in order to ascertain the predominant bacterial strain. The technique is referred to as "Nugent" process.

Nugent score is a gold standard for categorizing bacterial vaginosis. Nugent score is frequently employed for screening and adoption of pertinent inclusion/exclusion criterion of women with bacterial vaginosis in clinical trials. As a relatively subjective methodology, Nugent score depicts a sensitivity of 85% and specificity of 100% for discerning poly-microbial vaginal microbiota. Nugent score is also efficacious in classifying poly-microbial bacterial species, in contrast to 16S ribosomal deoxyribonucleic acid (rDNA) sequencing [5,6].

Cytological elucidation

Characteristic features of bacterial vaginosis can be obtained upon microscopic assessment of wet mount of vaginal fluid. Bacterial vaginosis typically demonstrates "clue cells" which are cervical epithelial cells embedded with elongated, rod-shaped bacteria. Specifically, clue cells are squamous epithelial cells superimposed with clusters of cocci or bacilli which extend upon cellular periphery, thereby engendering a velvety bacterial coat and a shaggy cellular appearance. The cell in it's entirety may not be coated with bacteria [7].

Lactobacilli are depleted and concurrent inflammatory cells are absent, except when accompanied by an adjunctive infectious process. Miniature coccobacilli configure a granular, bluish or sandy backdrop upon assessment of conventional Papanicolaou smears. Liquid based cytological smears depict a clean background, in contrast to conventional smears [6,7].

Differential diagnosis

Competent physical examination can aid the demarcation of concomitant vaginal conditions and eliminate identical clinical representations as herpes simplex virus infection. Speculum examination can exclude cervicitis and microscopic assessment of wet mount of vaginal discharge can suitably discern candida or trichomonas infection. Culture of cervical swabs can detect the occurrence of chlamydia or gonorrhoea [7,8].

Investigative assay

Comprehensive physical and pelvic examination is required to evaluate the characteristics of vaginal discharge. Identical disease representation and clinical manifestations due to candidiasis, cervicitis, chlamydia, gonorrhoea, herpes simplex virus or trichomonas infection require exclusion [7].

Assessment of cervical friability and cervical motion tenderness is critical in order to eliminate concordant obstetric conditions. Evaluation of pyrexia, pelvic pain and pertinent history of sexually transmitted infections is crucial in order to exclude associated, serious diseases. Cervical swabs are obtained to eliminate infection with chlamydia or gonorrhoea [8].

Papanicolaou smear demonstrates a sensitivity of 80% and specificity of 87% in detecting bacterial vaginosis. Exemplification of clue cells is accompanied by augmented sensitivity and specificity of the technique. Clue cells are a significant, reliable diagnostic feature of bacterial vaginosis which are suitably discerned with microscopic examination of vaginal fluid [7,8].

Exclusion of candida or trichomonas infection is necessitated. As several cervico-vaginal infections are concomitant and simultaneously discerned, entire specimen of vaginal fluid requires scanning and evaluation in order to detect clue cells or adjunctive infections. Assessing pH of vaginal fluid can aid discernment of bacterial vaginosis. Vaginal pH is determined by pH paper with pertinent comparison with colour controls. Vaginal pH exceeding > 4.5 is denominated [7,8].

Bacterial vaginosis is indicated clinically and confirmed by microscopic evaluation of cervical swab or wet mount of vaginal discharge. "Whiff test" to determine a malodorous, fish-like vaginal discharge is indicative of bacterial vaginosis. Whiff test is performed by adding miniature quantities of potassium hydroxide to microscopic slide containing the vaginal discharge. Enunciation of a characteristic, fishy odour is indicative of bacterial vaginosis [7,8].

Presence of "clue cells" on wet mount is diagnostic. A drop of sodium chloride solution is placed upon the wet mount with microscopic examination of slide for visualization of characteristic clue cells. Typically, a minimum of two aforesaid, representative evaluations along with characteristic vaginal discharge is considered adequate to confirm bacterial vaginosis. In the absence of malodorous vaginal discharge, a comprehensive assessment of aforesaid parameters is necessitated [8].

Therapeutic options

Roughly 30% instances of bacterial vaginosis can undergo comprehensive resolution without therapy. Employment of standardized antibiotic therapy may not rehabilitate an optimal or protective vaginal microbiota [7,8].

Bacterial vaginosis can be treated with clindamycin or metronidazole. Oral ingestion or vaginal application of aforesaid medications is efficacious. The medications can be safely employed in pregnant women. Nearly 10% to 15% of women may be unresponsive to initial course of antibiotics and necessitate additional or repetitive therapy. Therapeutic strategies are recommended for symptomatic subjects although asymptomatic bacterial vaginosis may be at a similarly elevated possibility of infection with human immune deficiency virus (HIV) [7,8].

Treatment of sexual partners of women with bacterial vaginosis remains unnecessary as clinical symptoms, reoccurrence and therapeutic outcomes are unaffected. Pregnant, symptomatic females with bacterial vaginosis require clindamycin prior to 22 weeks of gestation in order to decimate possible premature induction of labour preceding 37 weeks of gestation [7,8].

Reoccurrence of bacterial vaginosis can occur in nearly 80% of females following therapy. Subjects with relapsing bacterial vaginosis may necessitate a repeat course of antibiotics. Probiotics are not advantageous for treating or circumventing bacterial vaginosis [7,8].

Lactobacillus		Score	Gardnerella		Score	Mobiluncus		Score
4	+	0	4	+	4	4	+	2
3	+	1	3	+	3	3	+	2
2	+	2	2	+	2	2	+	1
1	+	3	1	+	1	1	+	1
0		4	0		0	0		0

0 – 3 "Gram stain score indicates normal bacterial vaginal flora.
4 – 6 "Gram stain score reveals altered vaginal flora that is not consistent with bacterial vaginosis".
7 – 10 "Gram stain score is consistent with bacterial vaginosis"

Figure 1: *Nugent scoring of bacterial vaginosis [9].*

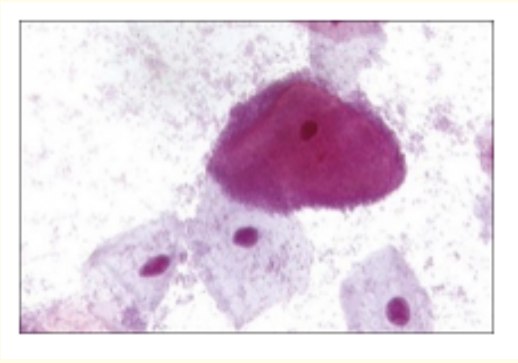

Figure 2: *Bacterial vaginosis with clue cells comprised of cervical epithelial cells embedded with rod-shaped bacteria [10].*

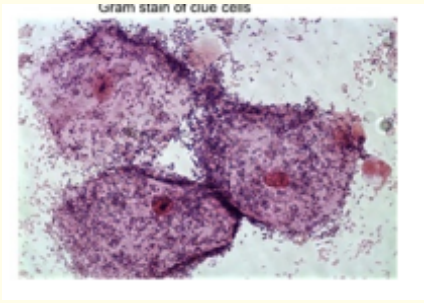

Figure 3: *Bacterial vaginosis delineating intense accumulation of vaginal bacterial flora upon clue and vaginal epithelial cells as manifested with Gram's stain [11].*

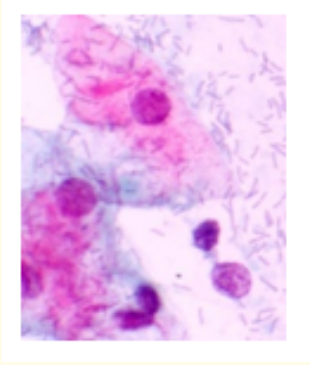

Figure 4: *Lactobacillus appearing in clusters and singular dispersion with superimposition upon vaginal epithelial cells [12].*

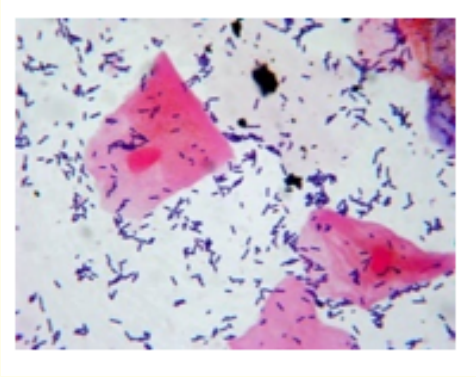

Figure 5: *Bacterial vaginosis depicting vaginal epithelial cells with superimposed lactobacilli and altered bacillary species [13].*

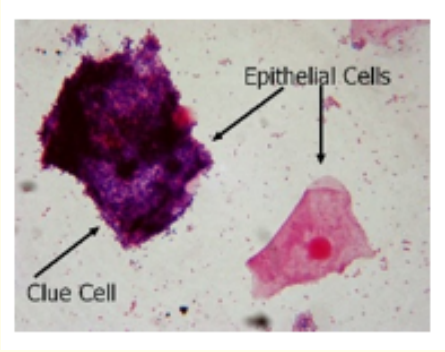

Figure 6: *Clue cells are diagnostic of bacterial vaginosis and delineate epithelial inundation of altered vaginal microbiota [13].*

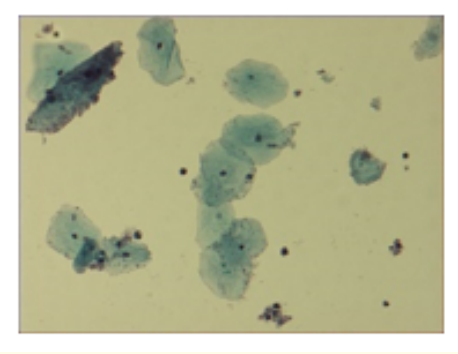

Figure 7: *Gardnerella spp infesting vaginal epithelium with consequent emergence of bacterial vaginosis [14].*

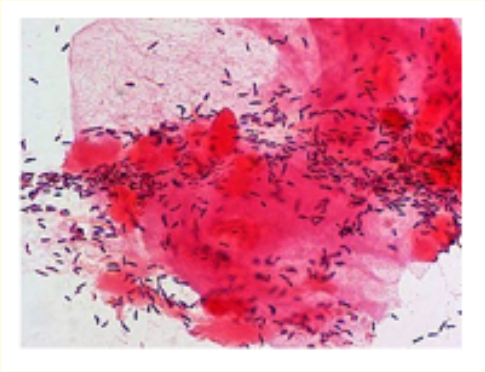

Figure 8: *Gram's stain of bacterial vaginosis demonstrating aggregates, cords and clusters of rod-like bacilli and cocci superimposed upon vaginal epithelial cells [15].*

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9. Image 1 Courtesy: Research Gate.
10. Image 2 Courtesy: Basic medical key.
11. Image 3 Courtesy: Quizlet.com.
12. Image 4 Courtesy: Pathology outlines.
13. Image 5 and 6 Courtesy: Pinterest.

14. Image 7 Courtesy: Medbullets.com.

15. Image 8 Courtesy: UNSW embryology.

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