Fannyhessea vaginae (Atopobium vaginae)

The vagina represents a distinct ecosystem whereby homeostasis of environmental conditions is maintained by the resident microflora. This homeostasis is a dynamic process influenced by several factors, including age, menstrual cycle, pregnancy, birth control, infections, sexual frequency and number of partners, and hygienic habits. Lactobacilli are believed to constitute the majority of the normal flora and are postulated to regulate the vaginal environment through the production of hydrogen peroxide, lactic acid, bacteriocins, and other antimicrobial agents that prevent the overgrowth of commensal bacteria with *L. crispatus* or *L. jensenii* accounting for 95% and 94% of the hydrogen peroxide-producing normal flora of Caucasian women, respectively (1). Despite the predominance of several bacterial species; *Staphylococcus*, *Escherichia*, *Gardnerella*, *Streptococcus* and *Peptostreptococcus* are also present within the normal flora. Fluctuations within the levels of vaginal lactobacilli result in a disruption of this delicate balance and are believed to be the causative factor behind Bacterial Vaginosis (BV).

Bacterial Vaginosis

Bacterial Vaginosis (BV) presents as the most common cause of homeostatic disruption in women of reproductive age. The etiology of this syndrome remains unknown despite a better understanding of its pathogenesis. BV is characterized by disturbed vaginal microflora where the predominant lactobacilli are depleted and there is an overgrowth of *Gardnerella vaginalis* and other anaerobic bacteria, such as *Bacteroides fragilis*, *Mobiluncus mulieris* and *Mobiluncus curtisii* (2-5). Often, the initial symptom of BV is increased vaginal odor that may only be apparent following sexual intercourse. Less common symptoms include increased vaginal discharge, vulvar irritation and painful urination (6). Diagnosis is dependent upon patient history, vaginal examination, microscopic evaluation and clinical evaluation. The presence of “clue” cells, vaginal epithelial cells having bacteria adherent to their surface edges, upon microscopic evaluation of a vaginal smear is considered to be a specific criterion for the diagnosis of BV (**Figure 1**) (6). Treatment consists of antibiotic courses (metronidazole or clindamycin) as well as topically and orally administered lactobacilli cultures to aid their re-establishment within the vagina. Left untreated, BV may lead to adverse conditions such as pelvic inflammatory disease, preterm birth, and postpartum endometritis (7-9). Abnormal vaginal microflora has also been associated with increased susceptibility to HIV (10-12), *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections (13). Though not regarded as a sexually transmitted disease, sexual habits, including increased numbers of sexual partners and the use of intrauterine devices as a method of birth control, serve as predisposing factors for the onset and transmission of BV (6).

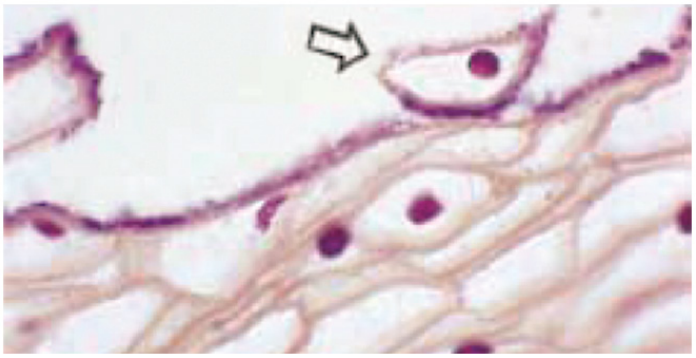

Figure 1. Vaginal epithelial cells demonstrating *F. vaginae (A. vaginae)* and *G. vaginalis* Biofilm formation in BV. Red stain specifically identifies *A. vaginae* and *G. vaginalis*. Arrow identifies a clue cell (2).

Fannyhessea vaginae (Atopobium vaginae)

A recent Australian publication reported increased incidences of both *Gardnerella vaginalis* and *Fannyhessea vaginae (Atopobium vaginae)* in the vaginas of virgin women, with transmission occurring through oral sex or hand-genital contact (14). Statistically, there has been no predilection for the occurrence of BV in one racial group over another (6).

Mounting evidence has demonstrated a direct link between the presence of *F. vaginae (A. vaginae)* and BV. The genus *Atopobium* is a relatively new designation created to account for the phylogenetically distinct *Lactobacillus minutus*, *Lactobacillus rimae* and *Streptococcus parvulus* bacterial species. All strains within the genus are anaerobic, Gram-positive elliptical cocci-shaped bacteria. Prior to the isolation of the novel *Atopobium* isolate, *F. vaginae (A. vaginae),* from the vaginal flora of a healthy woman in Sweden in 1999, members of this genus had heretofore only been detected in dental and pelvic abscesses, abdominal wounds and human feces (8,10). The clinical significance of *Atopobium* had been ill-defined until 2003, when the bacterium was isolated from a tuboovarian abscess from a woman in Germany. The inability to designate pathological roles for this bacterial species is, in large part, due to the fastidious nature of its growth, which severely impedes detection by standard culturing methods.

Table 1. Concomitant infection with *F. vaginae (A. vaginae)* and *G. vaginalis* in BV (15).

Recurrence, Nugent score	*G. vaginalis* detected (n = 89)			*G. vaginalis* not detected (n = 7)		
	A.vaginae detected (n = 52)	*A. vaginae* not detected (n = 37)	*P*	*A.vaginae* detected (n = 1)	*A. vaginae* not detected (n = 6)	*P*
BV						
7-10	43 (83)	14 (38)	<001	0	0	…
0-6	9 (17)	23 (62)		1	6	
Abnormal vaginal flora	46 (89)	19 (51)	<001	1	1	.29
0-3	6 (11)	8 (49)		0	5	

The presence of *F. vaginae (A. vaginae)* has recently been demonstrated to serve as a useful diagnostic marker for BV (**Table 1**) (15-17). A study comprised of 358 women experiencing either abnormal vaginal odor or discharge evaluated the roles of *Gardnerella vaginalis* and *F. vaginae (A. vaginae)* in BV recurrence following metronidazole therapy (15). Of this group, 50% were found to have normal vaginal flora, 10% were intermediate and 39% had BV as assessed by the Nugent Score criteria. Real-Time PCR analyses demonstrated the presence of *Gardnerella vaginalis,* often viewed as a diagnostic marker of BV, in 99% of the BV group. However, 66% of the women with normal flora were also found to harbor *G. vaginalis*; therefore, questioning its negative predictive power and its use as a diagnostic marker (**Table 2**). *F. vaginae (A. vaginae)*, however, was determined to be highly specific for BV affected individuals, with 96% detection levels observed within the BV group and only 12% within the normal flora group (**Table 2**) (15).

Table 2. Incidence of *Fannyhessea vaginae (Atopobium vaginae)* in BV. The presence of *Fannyhessea vaginae (Atopobium vaginae)* serves as a better indicator of BV than does *Gardnerella vaginalis*.

Statistics	*F. vaginae (A. vaginae)*	*Gardnerella vaginalis*
Sensitivity with relation to BV	96%	99%
Specificity with relation to BV	77%	35%
Prevalence associated with abnormal vaginal flora	88%	41%
NPV	96%	99%
PPV	74%	50%

An inextricable link between *G. vaginalis* and *F. vaginae (A. vaginae)* has become apparent from the analyses of these BV cases in that *A. vaginae* is rarely ever present in the absence of *G. vaginalis* regardless of Nugent Score, suggesting a synergistic effect exists between the two bacteria (15-16). This association was also made apparent through the analysis of vaginal biofilms, whereby *G. vaginalis* and *F. vaginae (A. vaginae)* were found to comprise greater than 90% of the film (**Figure 1**). The detection of high levels of both species correlates with a significant increase in antibiotic failure and the recurrence of BV, while the absence of either species is highly predictive of a negative BV diagnosis (15).

Treatment

Due to the large number of bacterial species present within the vagina, treatment courses for BV-affected individuals must be broad-based. Currently, clindamycin and metronidazole are the two most commonly prescribed antibiotics. Metronidazole has been chosen as the preferred treatment because of its ability to increase the colonization rate of hydrogen peroxide-producing lactobacilli (17). However, some cases do not resolve with a single course of treatment (6). This may in part be due to a preference in prescribing metronidazole and the decreased level of metronidazole-susceptibility observed with the few strains of *F. vaginae (A. vaginae)* which have been isolated (**Figure 2**) (6, 18).

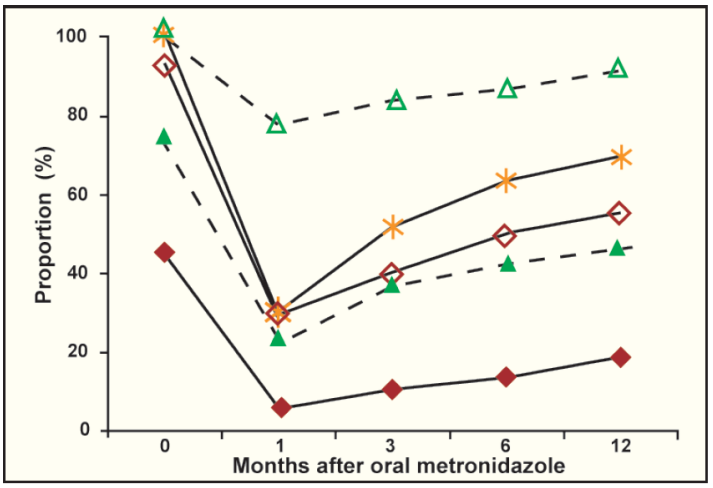

Figure 2. Incidence of metronidazole failure and recurrence of BV. Proportion of women with detectable *F. vaginae (A. vaginae)* (AV) and *Gardnerella vaginalis* (GV) over a twelve month course following oral metronidazole therapy. Legend: Nugent Score of 4-10 (∗); detectable AV (◇); high AV load (◆); detectable GV (△); high GV load (▲).

Table 3. Treatment Recommendations. CDC's 2015 Sexually Transmitted Diseases Summary of 2015 CDC Treatment Guidelines (20).

Recommended Regimens
Metronidazole oral[a] 500 mg orally twice a day for 7 days ***OR***
Metronidazole gel 0.75%[a] one applicator (5 g) intravaginally, once a day for 5 days ***OR***
Clindamycin cream 2%[a, b] one applicator (5 g) intravaginally at bedtime for 7 days
Recommended Regimens (Alternatives)
Tinidazole 2 g orally once daily for 2 days ***OR***
Tinidazole 1 g orally once daily for 5 days ***OR***
Clindamycin 300 mg orally twice daily for 7 days ***OR***
Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days
★Treatment is recommended for all symptomatic pregnant women

[a] The recommended regimens are equally efficacious.

[b] These creams are oil-based and may weaken latex condoms and diaphragms. Refer to product labeling for further information.

With the increased rate of drug therapy failure in mind, screening patients for the presence of *G. vaginalis* and *F. vaginae (A. vaginae)* both pre- and post-therapy might be advantageous. Medical Diagnostic Laboratories (MDL) has developed a highly sensitive Real-Time PCR assay for the detection of *F. vaginae (A. vaginae)*: **Test 142 *Fannyhessea vaginae (Atopobium vaginae)* by Real-Time PCR.** This testing is currently available utilizing the ***OneSwab***® and ThinPrep® specimen collection platforms.

Exhaustive analyses confirmed the specificity of the Real-Time Assay for *F. vaginae (A. vaginae)* with no observed cross-reactivity against a panel of 51 other human pathogens of bacterial, fungal, and viral origin, including other members of the *Atopobium* genus and organisms closely related by 16S rDNA sequences. This Real-Time PCR assay was used to analyze 96 cervicovaginal swab samples submitted to our clinical laboratory for detection of organisms associated with BV. Of those samples, 28 (29%) were positive for *F. vaginae (A. vaginae)*. Of the 28 positive samples, 23 were concomitantly infected with *G. vaginalis*, two with both *G. vaginalis* and *M. mulieris* or *M. curtisii*, one with both *G. vaginalis* and *B. fragilis*, and two contained *F. vaginae (A. vaginae)* alone (**Table 4**) (19). This test provides an accurate and expeditious evaluation of human cervicovaginal samples for the presence of *F. vaginae (A. vaginae)* that will dramatically aid the diagnosis of BV.

Table 4. Incidence of *F. vaginae (A. vaginae)* in BV. The presence of *F. vaginae (A. vaginae)* serves as a better indicator of BV than does *Gardnerella vaginalis*.

	BV
No pathogens detected	59
F. vaginae (A. vaginae)	2
Gardnerella vaginalis	7
Mobiluncus mulieris	2
F. vaginae (A. vaginae) + *Gardnerella vaginalis*	23
F. vaginae (A. vaginae) + *Gardnerella vaginalis* + *Mobiluncus mulieris*	2
F. vaginae (A. vaginae) + *Gardnerella vaginalis* + *Bacteroides fragilis*	1
TOTAL	***96***

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PATIENT **MDL #** **10100031**

DOE, BVPANEL N **FINAL**
13 JONQUIL CT ADDRESS 2
PARAMUS, NJ 07653
DOB: 01/01/2000 (Age 24)
Gender: Female
Ethnicity: Not provided
Patient ID: N/A
Home #: 732-307-0308

SPECIMEN

Type	Source	Collected	Received	Reported
Thin-Prep	Cerv/End	03/13/2024	03/14/2024	N/A

CLIENT **NPI:** 1710448105

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759 Bacterial Vaginosis Panel (with Lactobacillus Profiling) by QPCR

Indicative of Abnormal microflora.
Suggestive of Bacterial Vaginosis.
Lactobacillus species not detected.

REPORT HISTORY

See Bacterial Vaginosis/ Aerobic Vaginitis Trend Report for prior Date of Service

03/14/2024

Bacteria Detected	POSITIVE	Indicator	Abundance
749 *Sneathia sanguinegens*		BV	31.62%
164 BVAB2		BV	29.27%
125 *Bacillus fragilis*		BV	12.36%
754 *Mobiluncus mulieris*		BV	12.36%
764 BVAB1		BV	4.53%
165 Megasphaera type 2		BV	2.93%
142 *Atopobium vaginae*		BV	2.92%
765 BVAB3		BV	1.67%
752 *Prevotella bivia*		BV	0.88%
748 *Streptococcus anginosus*		BV	0.88%
165 Megasphaera type 1		BV	0.29%
753 *Mobiluncus curtisii*		BV	0.29%

Pathogens **Not Detected**

750 *Bifidobacterium breve* *
132 *Gardnerella vaginalis* *

*This test was developed and its performance characteristics determined by the laboratory. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

Medical Director, Jing-Jing Yang, M.D.

MDL#: **10100031** 03/25/2024

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