Diagnosis of Bacterial Vaginosis among Symptomatic Egyptian Women: Value of Assessing Bacterial Sialidase Activity

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Abstract

The development of point-of-care tests that are accurate, simple, rapid, low cost, and that do not require high levels of training for their interpretation is integral to improving the syndromic management algorithms for vaginal discharge that at present perform poorly. The present study aimed at evaluating the usefulness of assessing the bacterial sialidase activity as a rapid, sensitive and specific alternative compared to routine diagnostic methods for diagnosis of bacterial vaginosis (BV). The study included 50 female patients presenting with excessive and/or abnormal vaginal discharge. Four swabs were used to collect the vaginal discharge from each patient and were examined by culture, Amsel's criteria, Gram stain using the Nugent's score and BVBlue test to assess the sialidase activity. BV was detected in 18% of the studied women by all of the diagnostic methods. Compared to Nugent's score ≥7, the detection of sialidase by BVBlue test had 100% sensitivity and 84.6% specificity. There was a good agreement between the results of BVBlue test and clinical diagnosis using Amsel's criteria. We concluded that the determination of sialidase activity by BVBlue test can be a simple, rapid, and sensitive alternative to routine diagnostic methods that require expert manpower and sophisticated techniques.

Keywords

Vaginosis, BV, Sialidase, BVBlue, Nugent.

Introduction

Bacterial vaginosis (BV) is the most common lower genital tract infection affecting millions of sexually-active women annually (Jones et al., 2007). It is a polymicrobial syndrome characterized by a shift of the vaginal flora from the dominant Lactobacillus species to acquisition of diverse Gram-negative and variable anaerobic and facultative bacteria (Fredricks et al., 2005; Livengood, 2009; Rubins, 2011). Bacterial vaginosis is strongly associated with serious pregnancy-related outcomes including chorioamnionitis, spontaneous abortion, preterm labor (DiVico et al., 2011; Das et al., 2011; Jayakrishnan et al., 2016), pelvic inflammatory disease (Taylor et al., 2013), postpartum and postabortal endometritis (Haggerty et al., 2004). Moreover, it has been found to be associated with increased susceptibility to sexually-transmitted infections, such as Neisseria gonorrhoeae, Trichomonas vaginalis, Chlamydia trachomatis, Candida
spp., and even human immunodeficiency virus (Martin et al., 1999; Bhalla et al., 2007; Allsworth and Peipert, 2011).

The complex polymicrobial nature of BV made its diagnosis problematic with vaginal cultures, used in the past as the primary laboratory test, found to be of little value. Organisms classically incriminated in BV (e.g., *Gardenerella vaginalis*) are also recovered in 36% to 55% of asymptomatic women without clinical features (Money, 2005).

Clinical diagnosis requires the presence of at least three of the following criteria (Amsel’s criteria): (i) a vaginal pH greater than 4.5, (ii) a homogenous thin gray-white vaginal discharge, (iii) the presence of bacteria-coated epithelial cells (clue cells) in wet mount preparations of vaginal fluid, or (iv) the release of an amine (fishy) odor after addition of 10% KOH to the vaginal discharge (Tanuja et al., 2008). Although it has 90% sensitivity, diagnosis based upon clinical signs without laboratory testing has only 77% specificity (Landers et al., 2004).

Therefore, characterization of the vaginal flora by enumeration of bacterial morphotypes after Gram staining of a vaginal smear (i.e., Nugent scoring) is considered the standard method for BV diagnosis in research studies (Nugent et al., 1991). Yet, despite being highly accurate, the interpretation is subjective and the technique requires specialized training, and microscopic evaluation is not widely available for clinicians to assist in the diagnosis of BV (Hilbert et al., 2016).

The present study aimed at evaluating the usefulness of assessing the bacterial sialidase activity in diagnosing bacterial vaginosis by comparing its performance to that of the Nugent's scoring and Amsel's criteria being the routine methods used in our laboratories.

**Patients and Methods**

The study was done at the Microbiology Laboratory, Faculty of Pharmacy, Al-Azhar University and the Microbiology Laboratory, Faculty of Medicine, Ain Shams University. A total of 200 vaginal swabs was collected from 50 female patients (4 swabs/patient) suffering from excessive and/or abnormal
vaginal discharge and attending the Outpatient Gynaecology and Obstetrics Clinics of Ain Shams University and the Matareya Teaching hospitals over the period between December 2014 and May 2016. Postmenopausal women, women who had used a lubricant or a topical vaginal medication and women engaged in a sexual relation 72 hrs prior to sampling were excluded from the study.

Ethical Approval

The study was approved by the Committee of Ethics of Scientific Research, Faculty of Medicine, Ain Shams University and an informed consent was signed by participating women.

Collection of vaginal discharge

A sterile, non-lubricated speculum was gently inserted into the vagina during pelvic examination by a qualified clinician. Vaginal discharge was collected from the posterior vaginal fornix using sterile cotton swabs. Four swabs were collected for each patient. Swabs were labeled with the patient data and transported immediately (within 2 hours) to the Microbiology Laboratory for further processing. The swab submitted for anaerobic culture was inoculated into a tube of thioglycolate broth immediately after being collected.

Vaginal pH was measured, at bed side, by holding a pH strip against the speculum after finishing the examination and comparing the color to a pH chart provided by the manufacturer.

Processing of vaginal swabs

Culture

The tube containing the inoculated thioglycolate broth was incubated at 36±1°C overnight. Then, the swab was subcultured onto two Columbia blood agar plates and one MacConkey agar plate. One Columbia blood agar plate was incubated at 36±1°C under anaerobic conditions in an anaerobic jar and was examined for evidence of growth once after 72hrs incubation. The remaining plates were incubated at 36±1°C under aerobic conditions and were examined daily for evidence of growth for 72 hrs. Growing isolates were identified by their culture characteristics, morphology in Gram stain and biochemically using the Vitek 2 Compact (bioMérieux Inc.).

Examination using Amsel's criteria

The vaginal discharge was examined macroscopically and comments regarding its color, consistency, odor, and pH were recorded. Two drops of saline were then added onto two clean glass slides and one swab was gently pressed and rolled in a circular motion several times in the saline drops. Saline preparations were then examined as follows:

Amine test: A drop of 10% potassium hydroxide (KOH) was added to one saline preparation and at once whiffed for the liberation of amine (fishy) odor indicative of the presence of volatile amines such as trimethylamine. The whiff test result was recorded as either positive or negative.

Examination of wet preparation: A cover slide was put on the second drop and the saline preparation was examined using the high power (40x) of the microscope for the presence of pus cells, Clue cells (epithelial cells with hazy borders due to the presence of bacteria) and budding yeasts.

The presence of at least 3 of the following criteria was considered consistent with the diagnosis of BV: (i) vaginal pH ≥ 4.5, (ii) homogenous, milky vaginal discharge, (iii)
positive amine test; (iv) presence of clue cells in wet preparation.

Assessment of sialidase activity using the BVBlue® test kit (Gryphus Diagnostics, LLC, USA):

The BVBlue test is an enzyme activity test used to detect sialidase activity in vaginal fluid specimens using a chromogenic substrate.

One cotton swab was inserted into the BV Test Vessel and the mixture was gently mixed by swirling. The BV Test Vessel containing the swab was left to stand for 10 minutes at room temperature (20-24°C). Then, two drops of the Developer Solution were added to the BV Test Vessel containing the swab and gently mixed by swirling.

The appearance of a blue or green color indicates the presence of high levels of sialidase denoting a positive test for BV whereas the appearance of a yellow color indicates absence or low levels of sialidase denoting a negative test for BV. If the test fails to provide a blue, green, or yellow color result, the test was considered invalid and was repeated.

Examination of a Gram-stained smear using the Nugent's scoring system

One cotton swab was used to prepare a vaginal smear by gently pressing and rolling it along the middle portion of a clean glass slide then leaving it to air dry. The slide was then heat-fixed and stained with Gram stain. Slides were left to air dry and were then examined using the oil immersion (100X) objective and scanned for the presence of pus cells, bacteria, clue cells, budding yeasts and hyphae. At least 10 representative oil immersion fields were examined and the average number of Lactobacilli, Gardenerella vaginalis, and curved Gram-negative bacilli/oil immersion field was calculated. The number of each bacterial morphotype was scored separately and the total score was then calculated as described by Nugent et al., (1991).

Interpretation

Nugent's score between 1 and 3 was considered normal.
Nugent's score between 4 and 6 was considered intermediate.
Nugent's score ≥ 7 denotes a smear consistent with BV.

Statistical Analysis

Statistical analysis of the data was performed using the SPSS 15 software package under Windows 7® operating system.

Descriptive statistics

Categorical data are presented in the form of number and percent (%) whereas the continuous data are described by the mean as a measure of central tendency and by the standard deviation (SD) as a measure of variance.

Analytical statistics

The Chi-square and the Fisher-exact tests were used to determine the association between categorical parameters. A \( P \) value of \( \geq 0.05 \) was considered non-significant whereas a \( P \) value of \( <0.05 \) was considered significant.

The results of the BVBlue test, the Amsel's criteria and vaginal swab culture were compared to the results of the Nugent's scoring being the standard method. Accordingly their diagnostic performance was calculated and expressed as the sensitivity, specificity, positive predictive value (PPV),
negative predictive value (NPV) and diagnostic accuracy (DA).

Agreement between the different studied test methods was measured by the kappa coefficient. The value of kappa was interpreted as follows: Kappa < 0.2 = poor agreement; Kappa (0.21-0.4) = fair agreement; Kappa (0.41-0.6) = moderate agreement; Kappa (0.61-0.8) = good agreement; kappa (0.81-0.99) = excellent agreement.

Results and Discussion

Demographic data of the studied patients

The study included 50 females attending the Outpatient Gynaecology and Obstetrics Clinics at Ain Shams University and the Matareya Teaching hospitals. Their age ranged between 16 and 55 years (mean 35.1±10.4SD). Thirty two (32/50; 64%) of the patients were pregnant. Of the 50 studied patients, 13 (26%) complained from a foul smelling vaginal discharge whereas 37 (74%) complained from excessive abnormal discharge. Twelve patients (24%) were using vaginal douches and 58% reported previous use of intra-uterine device during the previous 2 years whereas 30% were using oral contraceptives.

Prevalence of BV among the studied patients

In the present work, 18% (9/50) of the studied women, presenting with excessive and/or malodorous vaginal discharge, gave positive results with all of the used diagnostic methods and hence were considered as BV cases. The prevalence of BV varied considerably (5 to 30%) among different studies (Bradshaw et al., 2005). Our observed prevalence was similar to those reported by Madhivanan et al., (2008), Akhter et al., (2010) and Mengistie et al., (2013) in India (19.1%), Bangladesh (21%), and Ethiopia (19.4%), respectively. However, lower prevalence of BV was reported in France (7.1%) (Dessauve et al., 2012), Turkey (7.76%) (Haltas et al., 2012) and Pakistan (10.8%) (Taj et al., 2014). On the other hand, in the studies done in Upper Egypt, higher BV prevalence rates were reported (33.3% and 33%) by Darwish et al., (2005) and Gad et al., (2014), respectively. Also, Tanuja et al., (2008) reported a higher BV prevalence rate in the urban areas (30%) compared to the rural areas (26%) of Surat. Higher rates, reaching more than 50%, were also reported in Pakistan (Nelofer et al., 2006) and India (Khatoon et al., 2013). This considerable variation in the prevalence of BV among the different studies may be attributed to the difference in the study population, their sexual and hygienic habits as well as to the different diagnostic methods used.

Diagnostic Performance of the BVBlue test compared to Nugent's score ≥ 7

Using the Nugent's scoring system, 22% (11/50) of the studied women, in the current work, were found to have a score ≥ 7 consistent with the diagnosis of BV. An intermediate score was recorded in 16% (8/50) whereas 62% (31/50) had a normal score.

Using the BVBlue test, 17 out of the 50 studied women (34%) gave positive results denoting BV whereas 33 patients (66%) had negative results. Out of the 17 BVBlue positive patients, 11 (64.7%) had a Nugent's score ≥ 7 and were considered as true BV cases. Accordingly, the sensitivity of the BVBlue test, in the current work, was found to be 100% and the specificity was 84.6%. The PPV was 64.7% whereas the NPV was 100% and the DA was 88% (Table 1). In accordance to our results, Akhter et al., (2010) and Kampan et al., (2011) reported that the BVBlue test had 100% sensitivity and
100% NPV compared to the Nugent method. Yet, unlike our results, the authors reported higher specificity (98.3%) and PPV (94.4%) for the BVBlue test.

Variable performance characteristics were reported in the studies that evaluated the BVBlue test and compared it to the results of the Nugent's score. The previously reported sensitivity for the BVBlue test ranged from 88% to 95.3% with a specificity ranging from 92.1% to 98.5% (Bradshaw et al., 2005; Khatoon et al., 2013; Gad et al., 2014).

In the current study, a good agreement was observed between the results of the BVBlue test and the Nugent's scoring (Kappa = 0.708) (Table 2). Similar results were reported by Gad et al., (2014). Excellent agreement between both tests was reported by Myziuk et al., (2003) and Kapman et al., (2010).

Diagnostic Performance of the Amsel's criteria compared to Nugent's score ≥ 7

In the present study, 26% (13/50) of the evaluated female patients had at least 3 of the required Amsel's criteria and hence were diagnosed as BV. Nine patients (9/13; 69.2%) had a Nugent's score ≥ 7 and were considered the true BV cases. Accordingly, clinical diagnosis of BV, based on Amsel's criteria, was found to have 81.8% sensitivity, 89.7% specificity, 69.2% PPV, 94.6% NPV and a DA of 88% (Table 1). Closely related results were obtained by Gad et al., (2014) who found that Amsel's criteria had a sensitivity of 88% and a specificity of 89.6% for the diagnosis of BV compared to the Nugent score. However, higher sensitivity (91% and 91%) and specificity (99% and 91%) for Amsel's criteria were reported by Bradshaw et al., (2005) and Mohammadzadeh et al., (2015), respectively. On the other hand, in the studies of Beverly et al., (2005), Dadhwal et al., (2010), Modak et al., (2011), Khatoon et al., (2013) and Taj et al., (2014), a much lower sensitivity (37%, 51.2%, 66.7%, 69%, and 68.3% respectively) with a higher specificity (99%, 98%, 94.7%, 93.1%, and 97.1% respectively) were reported.

In accordance to the results of Gad et al., (2014), we observed a good agreement between the diagnosis of BV based on Amsel's criteria and the Nugent's scoring (Kappa = 0.672).

Comparison between the results of the BVBlue test and the results of Amsel's criteria

In the present work, there was a good agreement between the results of the BVBlue test and the clinical diagnosis by Amsel's criteria (kappa=0.716) (Table 2). However, the BVBlue test was more sensitive than the Amsel's criteria, 100% versus 81.8%, when compared to the Nugent's score. Yet, the specificity of both methods was more or less the same (84.6% versus 89.7%). This finding goes in agreement with Myziuk et al., (2003).

Diagnostic performance of vaginal swab culture compared to Nugent score ≥7

Vaginal swabs yielded mixed growth in 72% of cultures (36/50). Anaerobic organisms were recovered from 40% (20/50) of vaginal swab cultures whereas Candida spp. was recovered from 34% (17/50) and 36% (18/50) of the cultures yielded growth of facultative anaerobic organisms.

As we compared the results of anaerobic culture to that of Nugent's score ≥7, we found that the vaginal swab culture had 81.8% sensitivity, 71.8% specificity, 45% PPV, 93.3% NPV and a DA of 74% (Table 1). Goyal et al., (2005) compared the isolation of anaerobes to the Nugent's score and reported that culture has 71.4% sensitivity, 84.7%
specificity, 58.8% PPV and 98.6% NPV. Pavani and Saileela (2013) demonstrated that cultures had a low sensitivity and NPV (42.55% and 84.4%, respectively) with a high specificity and PPV (92.99% and 64.51%, respectively) in diagnosing BV. Finally, Gad et al., (2014) compared vaginal swab culture to Nugent's score ≥7 and reported that culture had 90.9% sensitivity, 88% specificity, 79% PPV, and 95.2% NPV.

In the present study, a statistically significant association was observed between the isolation of *Prevotella* spp. and BV (P<0.01) (Table 3). *Prevotella* spp. was the most commonly isolated organism from patients with BV (Nugent's score ≥ 7) (6/11; 54.5%) and none of the patients (0%) with normal Nugent's score had *Prevotella* spp. isolated. Ling et al., (2013) indicated that vaginal pathogenic bacteria such as *Gardenerella vaginalis*, *Prevotella* spp., *Atopium vaginae*, *Eggerthella* and *Leptotrichia/Sneathia* are highly predictable for BV, with excellent diagnostic accuracy. Unfortunately, in the present work, we failed to isolated *Gardenerella vaginalis* by the routine culture methods followed in our laboratories.

Among patients with normal Nugent's score, the predominant isolate was *Candida* spp. (14/31, 45%). There was a statistically significant difference between patients with Nugent's score ≥ 7 and those with Nugent's score <7 regarding the isolation of *Candida* spp. (P<0.01) (Table 3). This finding recalls the previous report of Rodrigues et al., (1999) on the in-vitro, dose-dependent inhibitory effect of putrescine and cadaverine on germ tube formation by *Candida albicans* as well as on budding of strains of other *Candida* spp. The authors hypothesized that the presence of these and possibly other bacterial amines produced by anaerobes in the vaginal flora and seen in BV, may explain why candidiasis is rarely seen in these instances. Thus, finding a positive *Candida* spp. culture in the presence of BV may constitute a mixed vaginal infection but not mixed vaginitis, since positive vaginal cultures may reflect only *Candida* spp. colonization, a common finding in 10 %–15 % of healthy reproductive age women.

**Table 1** The performance characteristics of the different studied methods compared to the Nugent's scoring

| Nugent Score | Sensitivity | Specificity | PPV  | NPV  | Diagnostic Accuracy |
|--------------|-------------|-------------|------|------|--------------------|
|               | 1 - 3 (n = 31) | 4 - 6 (n = 8) | ≥ 7 (n = 11) |             |                   |                   |
| Amsel's Criteria +ve (n=12) | 1   | 3   | 9   | 81.8% | 89.7% | 69.2% | 94.6% | 88%         |
| BVBlue +ve (n=17) | 3   | 3   | 11  | 100%  | 84.6% | 64.7% | 100% | 88%         |
| Culture growing anaerobic organism (n=20) | 5   | 6   | 9   | 81.8% | 71.8% | 45%   | 93.3% | 74%         |
Table 2: Agreement between the results of the BVBlue test and those of Nugent’s score and Amsel’s criteria

| Nugent Score | BVBlue Test | Kappa coefficient |
|--------------|-------------|-------------------|
| Score ≥ 7    | 11          | 0                 |
| Score < 7    | 6           | 33                |
| BVBlue Test  | Kappa coefficient |
| Positive     | Negative    |
| ≥ 3 (+ve BV) | 12          | 1                 |
| <3 (-ve BV)  | 5           | 32                |

Table 3: Association between BV (Nugent's score ≥ 7) and the most commonly isolated organisms

| Nugent's score | Significance |
|----------------|--------------|
| Score ≥ 7      | Score < 7    |
| Prevotella spp | Positive     | Negative     |
|                | 6            | 3            |
|                | 5            | 36           |
| Bacteroids spp | Positive     | Negative     |
|                | 3            | 9            |
|                | 8            | 30           |
| Candida spp    | Positive     | Negative     |
|                | 0            | 17           |
|                | 11           | 22           |

*Fisher's Exact Test; HS= highly significant, NS=non-significant

Table 4: Comparison between BVBlue positive and BVBlue negative patients regarding the most commonly isolated organisms

| BVBlue          | P value (Significance) |
|-----------------|------------------------|
| Positive        | Negative               |
| Prevotella spp  |                         |
| Positive        | 8                       | 1                      |
| Negative        | 9                       | 32                     |
| Bacteroids spp  |                         |
| Positive        | 8                       | 4                      |
| Negative        | 9                       | 29                     |
| Candida spp     |                         |
| Positive        | 5                       | 12                     |
| Negative        | 12                      | 21                     |

*Fisher's Exact Test; bChi square test, HS= highly significant, NS=non-significant, S=significant
Association between results of BVBlue test and culture results

A statistically significant difference was observed between BVBlue positive and BVBlue negative patients regarding the isolation of Prevotella spp. (P<0.01) and Bacteroides spp. (P<0.05) (Table 4). Similarly, Briselden et al., (1992) reported that 96% of women with BV and positive sialidase activity had sialidase-positive bacteria recovered from vaginal fluid. The authors found that Prevotella spp. and Bacteroides spp. are the probable sources of sialidase in patients with BV. They could not correlate the presence of Gardnerella vaginalis, Mobiluncus spp., Peptostreptococcus spp., or Mycoplasma hominis with increased sialidase activities of greater than 7 U. By contrast, McGregor et al., (1994) correlated the sialidase activity, in women with BV, with the isolation of Gardnerella vaginalis, Mobiluncus spp., Mycoplasma hominis, Chlamydia trachomatis, and yeast. They did not specifically identify Prevotella spp. or other anaerobic bacteria associated with BV.

In the current work, no significant difference was observed between BVBlue positive and BVBlue negative women regarding the isolation of Candida spp. (P>0.05) (Table 4). Similar finding was observed by Myziuk et al., (2003).

We concluded that detection of sialidase activity can be beneficial for the diagnosis of BV in the clinic setting where microscopic capabilities are not available. The BVBlue test proved to be a simple, objective and sensitive point of care test that can be used for the rapid diagnosis of BV at physician’s office. Results are available in 10 minutes, thus the patients would benefit in terms of immediate diagnosis and treatment in the same setting instead of evaluating Gram stained smears (Nugent's method) which requires a skilled manpower, laboratory facilities and is prone to subjective errors.

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