Clinical Policy Bulletin: Diagnosis of Vaginitis

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Policy

I. Aetna considers direct DNA probe assays (e.g., Affirm VIP III) for trichomonas, Candida and Gardnerella medically necessary for members with symptoms of vaginitis.

II. Aetna considers testing of pH, and testing for the presence of amines in vaginal fluids (e.g., FemExam) medically necessary for women with symptoms of vaginitis.

III. Aetna considers measurement of sialidase activity in vaginal fluid (e.g., the BVBlue test) medically necessary for the diagnosis of bacterial vaginosis in women with symptoms of vaginitis.

IV. Aetna considers screening for Trichomonas vaginalis medically necessary for women with the following risk factors: new or multiple partners; history of STDs; exchange of sex for payment; or injection drug use.

V. Aetna considers routine screening for trichomonas, Candida and Gardnerella in asymptomatic women experimental and investigational because there is a lack of scientific evidence demonstrating that such screening improves health outcomes in non-pregnant women, or in pregnant women either at high or low risk for pre-term delivery.

Background

Vaginitis (infection of the vagina) is the most common gynecologic condition encountered by physicians in the office. Patients with vaginitis almost always present with a chief complaint of abnormal vaginal discharge. The most common causes of vaginitis are trichomoniasis (Trichomonas vaginalis infection), vaginal candidiasis (Candida vaginalis), and bacterial vaginosis (BV).
Bacterial vaginosis (BV) is the commonest cause of vaginal discharge in women of child-bearing age. It is characterized by an overgrowth of anaerobic bacteria (Gardnerella vaginalis, Mycoplasma hominis; Mobiluncus species; anaerobic gram-negative rods of the genera Prevotella, Porphyromonas and Bacteroides; and Peptostreptococcus species) leading to replacement of lactobacilli and an increase in vaginal pH from less than 4.5 up to 7.0. The term vaginosis implies that infection is accompanied by little or no inflammation of the vagina.

Diagnosis of vaginitis is based on clinical symptoms, pH of the vaginal fluid and microscopic examination of the discharge. Symptoms are not present in approximately 50% of women with bacterial vaginosis infection. Bacterial vaginosis is not associated with soreness, itching or irritation. There may be an offensive and classically “fishy” smelling vaginal discharge.

Ideally, a diagnosis of BV is made if 3 out of 4 of "Amsel's criteria" are met:

- A strong fishy odor on adding alkali to vaginal fluid (positive amine test)
- Clue cells (vaginal epithelial cells heavily coated with bacilli) on microscopy
- Thin, white, homogenous discharge
- Vaginal pH greater than 4.5.

Microscopic examination may also reveal motile trichomonads or candida hyphae. The presence of Gardnerella vaginalis on culture can not be used to diagnose BV, since it is present in approximately 50% of healthy women. Culture of trichomonas and candida may be helpful if clinical symptoms are suggestive and microscopy is negative. Mixed infections are also common, with trichomonas, candida or both coexisting with BV.

Physicians have become interested in alternative, office based methods of diagnosing vaginitis. Office microscopy to detect either clue cells, trichomonas or candida may be perceived as cumbersome and inaccurate. For example, the sensitivity of microscopy in diagnosing trichomonas is estimated as low as 38% (see Table). It is also estimated that only 50% of practicing physicians can correctly diagnose routine cases of vaginal candidiasis. While the presence of clue cells to diagnose BV is considered a sensitive test, many physicians may not be adequately trained in microscopic techniques. Finally, several aspects of the diagnosis are subjective (e.g., the visual examination of the discharge, reading the pH paper, and evaluation of the odor as part of the whiff test).

DNA probes have been developed to directly detect the presence of candida, trichomonas and Gardnerella, thus providing a more objective diagnosis. Since Gardnerella is a normal part of the vaginal flora, the DNA probe test is designed to be relatively insensitive, detecting only pathogenic levels of Gardnerella. The Affirm VP III Microbial Identification System (Becton Dickinson) is a commercially available DNA probe office-based test kit that simultaneously detects the presence of Gardnerella, trichomonas and candida. The Affirm VP III was cleared by the FDA based on a 510 (k) application in June 1993. The test's sensitivity for detecting trichomonas vaginalis is high, and it can provide results in as little as 45 mins. Trichomonas can also be detected by by DNA probes amplified by polymerase chain reaction. Sample is treated with enzymes that amplify specific regions of trichomonas vaginalis' DNA. After amplification, the number of DNA fragments are quantified. Polymerase chain reaction
has proven to be the most accurate diagnostic method in recent studies. Moreover, it is currently only used in research, not clinical settings.

Other options include the use of test cards that contain pH indicators and an amine test system that can be evaluated visually, as opposed to evaluating the presence of amines by odor. The FemExam is an example of such a commercially available test system. Also available is pH paper developed specifically for evaluating vaginal secretions.

Testing for amines and pH testing is a well-established practice. In contrast, the use of DNA probe tests may be used as an alternative or a compliment to microscopic techniques.

The World Health Organization reviewed the literature on diagnostic tests for vaginitis, and found DNA techniques to be significantly more sensitive than standard wet mount microscopy, with comparable specificity for vaginal candidiasis and vaginal trichomoniasis, but somewhat less sensitive for bacterial vaginosis.

Table: Characteristics of Detection Assays: Sensitivity/Specificity (%)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Microscopy (wet mount)</th>
<th>Culture</th>
<th>Antigen detection</th>
<th>DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis</td>
<td>35-45% / 99%</td>
<td>67% / 66%</td>
<td>61-81 % / 97%</td>
<td>80% / 98%</td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td>38-82% / 100%</td>
<td>98% / 100%</td>
<td>86% / 99%</td>
<td>88-91% / 100%</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>81% / 94%</td>
<td>89% / 93%</td>
<td>93% / 93%</td>
<td>94% / 81%</td>
</tr>
</tbody>
</table>

DNA probe tests may be especially useful for primary care physicians who may be less skilled in office laboratory diagnostic techniques for vaginitis than obstetricians and gynecologists. Ferris and colleagues (1995) reported the results of a study that compared the performance of routine primary care physician-performed office laboratory diagnostic techniques for women with abnormal vaginal symptoms to the results obtained by a DNA probe test for *Trichomonas vaginalis, Gardnerella vaginalis, and Candida species* (Affirm VIP III). The investigators found that primary care physicians were not as accurate as the DNA probe test in diagnosing vaginal infections. Of 499 symptomatic women, vulvo-vaginal candidiasis was diagnosed in 20 %, vaginal trichomoniasis in 7.4 %, and bacterial vaginosis in 52.1 %. Fourteen percent of subjects had multiple vaginal infections. The sensitivity and specificity of clinician microscopically diagnosed vulvovaginal candidiasis was 39.6 % and 94 %, vaginal trichomoniasis was 75.0 % and 96.6 %, and bacterial vaginosis was 76.5 % and 70.8 %, using independent clinical examination by a medical technician as the gold standard. By comparison, the sensitivity and specificity of the DNA probe test for vulvo-vaginal candidiasis was 75.0 % and 95.7 %, vaginal trichomoniasis was 86.5 % and 98.5 %, and bacterial vaginosis was 95.4 % and 60.7 %. The DNA probe test was especially more accurate for diagnosing multiple vaginal infections. When only women with multiple vaginal infections were considered, the percentages of correct clinician diagnosis for vulvovaginal candidiasis, trichomoniasis, and bacterial vaginosis were 49.3 %, 83.6 %, and 59.7 %. For the DNA probe test, the percentages of correct
Diagnoses were 72.9 %, 92.9 % and 90.0 %, respectively. The authors concluded that primary care physicians demonstrated a high specificity but low sensitivity when identifying vaginal trichomoniasis and vulvo-vaginal candidiasis by microscopic techniques, and that the primary care physicians were not as accurate as the DNA probe test.

The screening of asymptomatic pregnant women for bacterial vaginosis to reduce the likelihood of pre-term birth is considered experimental and investigational and is not covered. The American College of Obstetricians and Gynecologists (2001) has concluded that "[t]here are no current data to support the use of ... BV screening as strategies to identify or prevent pre-term birth. ... Screening for risk of pre-term labor by means other than historic risk factors is not beneficial in the general obstetric population." ACOG guidelines on risk factors for pre-term birth state:

Although some trials have shown an association with the presence of BV and pre-term birth, most large trials designed to determine whether treatment of BV can prevent pre-term birth have failed. Currently, there are insufficient data to suggest screening and treating women at either low or high risk will reduce the overall rate of pre-term birth.

Porter and colleagues (2004) stated that treating asymptomatic, low-risk women with BV does not always prevent pre-term delivery. These authors further noted that, in general, there was no benefit to routine screening and treatment of BV. Leitch (2005) stated that BV, elevated levels of interleukin (IL)-6, IL-8, ferritin and granulocyte colony-stimulating factor are some of the secondary predictors that confirm the role of intrauterine infection in the pathogenesis of pre-term birth. Apart from BV, inflammatory markers are still not routinely used. The sensitivity of single markers in predicting pre-term birth is only moderate and serial examinations of markers, combinations of different markers and multiple marker tests have been studied, with limited results. Studies of interventions in order to prevent pre-term birth have also yielded mixed benefits, as a consequence of which the use of these markers to screen low-risk pregnancies is generally not recommended. Currently, secondary predictors of pre-term birth are used mainly to design new intervention studies tailored to specific high-risk populations and to avoid unnecessary interventions in the management of high-risk women.

The U.S. Preventive Services Task Force (USPSTF, 2008) does not recommend screening for bacterial vaginosis in pregnant women at low-risk for pre-term delivery. The USPSTF also states that current evidence is insufficient to evaluate the balance of benefits and harms of screening for bacterial vaginosis in pregnant women at high-risk for pre-term delivery. The USPSTF weighed the benefits and harms of screening for bacterial vaginosis in pregnancy by identifying new evidence addressing previously identified gaps from the 2001 USPSTF recommendation. Published literature on this topic was identified by using MEDLINE, Cochrane Library databases, the Database of Abstracts of Reviews of Effects, reference lists, and consultation with experts and was systematically reviewed. When data allowed, a series of meta-analyses (using new and 2001 report data) was done to estimate the pooled effect of treatment on pre-term delivery (less than 37 weeks, less than 34 weeks, or less than 32 weeks) and on low birth-weight and pre-term, premature rupture of membranes.

The USPSTF (Nygren et al, 2008) examined new evidence on the benefits and harms of screening and treating bacterial vaginosis in asymptomatic pregnant women. Study and patient characteristics, treatment variables, adverse pregnancy outcomes, and
internal validity quality criteria from the U.S. Preventive Services Task Force (USPSTF) and Jadad scale were abstracted. A total of 7 new randomized, controlled treatment trials and 2011 report data were combined in a series of meta-analyses to estimate the pooled effect of treatment on pre-term delivery (less than 37, less than 34, and less than 32 weeks); low birth-weight; and pre-term, premature rupture of membranes. No screening studies that compared a screened population with a non-screened population were found. Significant heterogeneity was found among the high-risk treatment trials ($p < 0.001$). It is not clear from the detailed description of the studies which factors explain the differences in pre-term delivery rates and potentially the association of treatment effect; however, both raise concern for the unintended potential for harm. The authors concluded that no benefit was found in treating women with low- or average-risk pregnancies for asymptomatic bacterial vaginosis. They stated that more research is needed to better understand these groups and the conditions under which treatment can be harmful or helpful, and to explore the relevance of bacterial vaginosis to other adverse pregnancy outcomes, such as delivery before 34 weeks.

The BVBlue test (Genzyme Diagnostics, Cambridge, MA) is used to aid in the diagnosis of BV. It detects elevated activity of vaginal-fluid sialidase, an enzyme produced by bacterial pathogens, such as gardnerella, mobiluncus, bacteroides, and prevotella. With less than 1 min of hands-on time, the test provides objective results. The solution turns blue or green if positive, yellow if negative, and is 92.8% sensitive and 98% specific versus gram stain. Studies have shown that BV may increase the risk of preterm delivery, low-birth-weight infants, endometritis, pelvic inflammatory disease, and miscarriage; and may increase the susceptibility to HIV and other STDs. While there are studies that reported the clinical value of the BVBlue test in diagnosing BV, available guidelines have not recommended its use.

Sumeksri et al (2005) compared the sensitivity of the BVBlue test for diagnosis of BV with Gram stain by using Nugent score as a gold standard. The speculum for this examination, used in the process of collecting vaginal secretions, must not be lubricated with any lubricants. The vaginal discharge was collected from the lower 1/3 of the vaginal wall. Gram stain score and the BVBlue test were conducted and compared. A total of 173 patients were enrolled in the present study. The BVBlue test was compared to the standard method for the diagnosis of BV by Gram stain using Nugent score as a gold standard. The sensitivity, specificity, accuracy, positive and negative predictive value of the BVBlue test versus the Gram stain score for diagnosis of bacterial vaginosis were 94%, 96%, 96% 86%, and 98%, respectively. The authors concluded that the BVBlue test for diagnosis of BV had high sensitivity, specificity, accuracy, positive- and negative-predictive value (94%, 96%, 96%, 86%, and 98%, respectively).

On the other hand, Yen and colleagues (2003) noted that traditionally, BV diagnosis is defined clinically by the presence of 3 of the 4 Amsel criteria. The authors stated that additional laboratory-based methods of BV diagnosis have included culture for G. vaginalis, biochemical tests for metabolic by-products of vaginal bacteria (gas chromatography), and colorimetric tests for enzymes produced by BV organisms (sialidase). The authors stated, however, that these methods remain research tools and are not widely available in clinical settings.
Furthermore, the American Academy of Pediatrics Committee on Infectious Diseases (Red Book, 2012) as well as the U.S. Preventive Services Task Force's statement on screening for BV in pregnancy to prevent preterm delivery (2008) did not mention the use of the BVBlue system (sialidase activity).

Guidelines on bacterial vaginosis from the British Association for Sexual Health and HIV (Hay, et al., 2012) state that two approaches to diagnosis are available:

Amsel’s criteria. At least three of the four criteria are present for the diagnosis of bacterial vaginosis to be confirmed: 1) thin, white, homogeneous discharge; 2) clue cells on microscopy of wet mount; 3) pH of vaginal fluid greater than 4.5; 4) release of a fishy odor on adding alkali (10% KOH).
A Gram stained vaginal smear, evaluated with the Hay/Ison criteria or the Nugent criteria.

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 (BV): predominantly Gardnerella and/or Mobiluncus morphotypes; few or absent Lactobacilli.

The Nugent score is derived from estimating the relative proportions of bacterial morphotypes to give a score between 0 and 10. A score of less than 4 is normal, 4 to 6 is intermediate, and greater than 6 is bacterial vaginosis.

The Bacterial Special Interest Group of the British Association of Sexual Health and HIV (Hay, et al., 2012) recommend using the Hay/Ison criteria in genitourinary medicine clinics. The guidelines note that commercially available tests are available such as the BVBlue, the Affirm VIP III, and a prolineaminopeptidase test card (Pip Activity TestCard, Quidel, San Diego, California) "perform adequately" when assessed against Amsel and Gram stain criteria; however, the guidelines include no recommendation for their use. The guidelines state that isolation of Gardnerella vaginalis cannot be used to diagnose bacterial vaginosis because it can be cultured from the vagina of more than half of normal women. The guidelines stated that detection of combinations of bacterial vaginosis associated bacteria by PCR may offer highly sensitive and specific diagnosis in the future but is not yet available.

The Centers for Disease Control and Prevention (2010) also recommend the gram stain as the gold standard for diagnosis of bacterial vaginosis, and recommend use of Amsel's criteria if a gram stain is not available. Similar to the BASHH guidelines, the CDC states that the BVBlue, the Affirm VIP, and the Pip Activity TestCard "have acceptable performance characteristics" compared to the gram stain, but make no recommendation for their use. The CDC states that a card test is available for the detection of elevated pH and trimethylamine, but it has low sensitivity and specificity and therefore is not recommended. The CDC also stated that PCR also has been used in research settings for the detection of a variety of organisms associated with bacterial...
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Vaginitis, but evaluation of its clinical utility is uncertain. The CDC stated that culture of *G. vaginalis* is not recommended as a diagnostic tool because it is not specific, and that cervical Pap tests have no clinical utility for the diagnosis of bacterial vaginosis because of their low sensitivity.

Guidelines on bacterial vaginosis from the New York State Department of Health (2009) recommend Amsel's criteria for diagnosis of bacterial vaginosis. The guidelines state that several commercially available tests have been developed recently and may be clinically useful; however, few published data exist on their performance. The guidelines state that PCR is not the standard for evaluation, and that culture of *G. vaginalis* is too nonspecific to be used for diagnosis of bacterial vaginosis.

Guidelines from the Centers for Disease Control and Prevention (CDC) (Workowski, et al., 2010) state that screening for *T. vaginalis* in women can be considered in those at high risk for infection (i.e., women who have new or multiple partners, have a history of STDs, exchange sex for payment, and use injection drugs).

**CPT Codes / HCPCS Codes / ICD-9 Codes**

**CPT codes covered if selection criteria are met:**

82120    Amines, vaginal fluid, qualitative

83986    Ph, body fluid, except blood

87210    Smear, primary source with interpretation; wet mount for infectious agents (eg, saline, India ink, KOH preps)

87480    Infectious agent detection by nucleic acid (DNA or RNA); Candida species, direct probe technique

87510    Infectious agent detection by nucleic acid (DNA or RNA); Gardnerella vaginalis, direct probe technique

87660    Infectious agent detection by nucleic acid (DNA or RNA); Trichomonas vaginalis, direct probe technique

87905    Infectious agent enzymatic activity other than virus (eg, sialidase activity in vaginal fluid) [BVT] test

**ICD-9 codes covered if selection criteria are met:**

041.89    Other specified bacterial infection [Gardnerella vaginitis]

112.1    Candidiasis of vulva and vagina

131.01    Trichomonal vulvovaginitis

616.10    Vaginitis and vulvovaginitis, unspecified

616.11    Vaginitis and vulvovaginitis in diseases classified elsewhere
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646.60 - Infections of genitourinary tract in pregnancy
646.64

698.1 Pruritis of genital organs

ICD-9 codes not covered for indications listed in the CPB:

V22.0 - V22.2 Supervision of normal pregnancy
V74.5 Special screening examination for venereal disease
V74.8 Special screening examination for other specified bacterial and spirochetal diseases
V81.6 Special screening examination for other and unspecified genitourinary conditions

Other ICD-9 codes related to the CPB:

623.5 Leukorrhea, not specified as infective [vaginal discharge]
623.9 Unspecified noninflammatory disorder of vagina [vaginal irritation]
625.0 Dyspareunia
625.8 Other specified symptoms associated with female genital organs [vaginal itching]
626.8 Other disorders of menstruation and other abnormal bleeding from female genital tract
788.1 Dysuria

The above policy is based on the following references:

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http://qawww.aetna.com/cpb/medical/data/600_699/0643_draft.html 01/28/2015