Vulvovaginal Disease: An Evidence-Based Approach to Medical Management

Case Study and Commentary, Jeff Andrews, MD, FRCSC

Vulvovaginal discharge complaints are very common, accounting for more than 10 million U.S. office visits annually and countless phone contacts [1]. Annual medication costs for these complaints are estimated at more than $700 million, with about half this amount spent on over-the-counter (OTC) preparations [2].

The diagnosis of initial vulvovaginal discharge complaints is usually straightforward, and in a majority of cases the diagnosis will be bacterial vaginosis, vulvovaginal candidiasis, or trichomoniasis. Patients with recurrent and resistant infections pose a greater diagnostic challenge. Most challenging are patients with a symptomatic problem without evidence of any of the common causes. An algorithmic approach, incorporating symptoms, signs, vaginal pH, and microscopy, can aid clinicians in making the diagnosis.

CASE STUDY
Initial Presentation

A 33-year-old woman calls the clinic reporting vaginal itching and burning, with increased white discharge. She tried OTC products, which did not help. She is asking for a phone-in prescription. She thinks she has bacterial vaginosis because that is what she had the last time after an OTC antifungal did not work.

• What are the most common causes of abnormal vaginal discharge?

Bacterial Vaginosis

In U.S. women seeking health care for abnormal vaginal discharge, the most common cause is bacterial vaginosis [3]. The prevalence of bacterial vaginosis has been reported at 5% in asymptomatic college students, 12% in screened pregnant women, and 30% in women screened prior to termination of pregnancy [3,4].

Bacterial vaginosis is a clinical syndrome characterized...
by the replacement of the normal dominant H2O2-producing \textit{Lactobacillus} species in the vagina with high concentrations of anaerobic bacteria (eg, \textit{Gardnerella vaginalis, Mobiluncus sp, Prevotella sp}). \textit{Mycoplasma hominis} and \textit{Ureaplasma urealyticum} can also be found with bacterial vaginosis [5,6]. Bacterial vaginosis was initially described as not associated with inflammation (vaginosis, not vaginitis); however, there is a recognized subset of patients with bacterial vaginosis who have a relative increase in white cells [1,3,4,7–10]. Bacterial vaginosis is not classified as a sexually transmitted infection. It can arise and remit spontaneously in sexually active and non–sexually active women. However, bacterial vaginosis is associated with sexual factors, including early age at first intercourse, higher number of lifetime sexual partners, recent new sex partner, female sex partner, and douching within prior 7 days. There is evidence that the presence of bacterial vaginosis increases the risk of contracting \textit{Neisseria gonorrhoeae} if there is exposure to that organism [11]. There is evidence that the presence of bacterial vaginosis in pregnancy is associated with increased risk of complications. Current guidelines recommend treating symptomatic bacterial vaginosis during pregnancy [12–14]. Women with asymptomatic bacterial vaginosis who are at high-risk of preterm birth should be treated with an oral antibiotic [15,16]. There is a lack of evidence regarding asymptomatic bacterial vaginosis in low-risk pregnancy and screening is not recommended [17–23].

**Vulvovaginal Candidiasis**

Vulvovaginal candidiasis is the second most common cause of vaginal discharge. Vulvovaginal candidiasis is caused by abnormal colonization of the vagina and/or the vulva by yeast cells. By far the most common yeast is \textit{Candida albicans}, accounting for 80% to 95% of infections. \textit{Candida glabrata} is responsible for 5% of infections overall but 16% of recurrent yeast vulvovaginitis. Fewer than 5% of yeast infections are caused by \textit{C. tropicalis, C. parapsilosis, C. krusei, C. kefyr, C. gilliermondii, or Saccharomyces cerevisiae} [24,25]. \textit{Candida} is often present in women with no symptoms and is probably part of the normal vaginal flora under conditions of normal pH. A change in the vaginal environment is necessary before the yeast exerts a pathological action. The precise conditions required for pathogenesis are not known; decrease in peroxidase-producing lactobacilli appear to be important and the presence of a gene polymorphism associated with a diminished production of mannose-binding lectin is important in women with recurrent vulvovaginal yeast infections. Broad-spectrum antibiotics are a known precipitant of vulvovaginal candidiasis [6,24,26,27]. Acute vulvovaginal candidiasis refers to uncomplicated infections of brief duration, typically caused by \textit{C. albicans} [4,28,29].

Recurrent vulvovaginal candidiasis is present in less than 5% of women of childbearing age. Recurrent vulvovaginal candidiasis is defined as 4 or more episodes of candidiasis in a 1-year period [4,30]. Complicated vulvovaginal candidiasis includes recurrent infection, severe infection (with additional complications such as secondary infection and ulceration), non-\textit{albicans} infection, infection in pregnant women, infection in immunocompromised women, infection in women with uncontrolled diabetes mellitus, and infection in women who are bedridden [4,24,28,29,31,32].

**Trichomoniasis**

The third most common cause of abnormal vaginal discharge is trichomoniasis. \textit{Trichomonas vaginalis} is a flagellated protozoa, which is sexually transmitted and can cause infection in the vagina, urethra, and paraurethral glands [33–36].

Other causes of abnormal vaginal discharge include physiologic variant of normal, mucopurulent endocervicitis, mixed infection, and desquamative inflammatory vaginitis.

- What are the clinical features of these common entities?

Bacterial vaginosis is often asymptomatic. Symptomatic women usually complain of an offensive, fishy-smelling vaginal discharge and frequently have burning or irritation of the outer vagina and vulva. On examination, the usual finding is a thin, white/grey, homogenous discharge coating the walls of the vagina, often excessive and sometimes with small air bubbles [8,14].

Vulvovaginal candidiasis is clinically associated with itching; however, no symptoms or signs, either alone or combined, are specific for the diagnosis. Other infections, particularly bacterial vaginosis (which is more common), can present in a similar way, and it is not always possible to distinguish between these infections on the basis of history and examination alone. The onset of symptoms tends to be rapid, and there is a common association with the week after menstruation. Dyspareunia and dysuria may be reported. In severe cases, patients may have soreness, burning, excoriation, and pain. On examination, erythema is a classic finding, usually localized to the vagina and vulva, but it may extend to the labia majora and perineum; the border of this is clear and emphasized. Fissuring of the vagina, edema, erosion, and secondary infection may be present. Vaginal discharge is often described as white and “cottage cheese–like” but may be watery or purulent. It is usually odorless. Excoriation, erosion, and secondary infection may be seen [4,8].

Trichomoniasis infections are asymptomatic in 10% to 50% of women. The most common symptoms include vaginal discharge, vulvar itching, dysuria, and offensive odor. On examination, no abnormalities are found in 5% to
15% of women. Vaginal discharge is present in up to 70% of infected women and varies in consistency from thin and scanty to profuse and thick. The classic frothy, yellow-green discharge occurs in 10% to 30% of women. Only 2% of infected women have the “strawberry” appearance of the cervix on visual examination [8,33].

- Can the case patient be safely and effectively treated over the phone?

Although managing vaginal discharge complaints without a clinical visit may be attractive to patients and providers, the probability of wrong diagnosis is high. Self-treating is inaccurate and ineffective, because it is based on self-diagnosis. In a study of women who purchased an OTC antifungal, only one third had vulvovaginal candidiasis, 50% required therapy for a different infection, and 15% had no infection [37]. Self-diagnosis and telephone diagnosis are inaccurate [12,38,39]. But from the patient perspective, going to the office/clinic is inefficient, time-consuming, costly, and interferes with work.

An alternative between treating over the phone and a time-consuming office visit is for the patient to have a brief encounter with the office/clinic nurse. The patient would complete a brief check-off questionnaire, go to a room, insert 2 swabs about 8 cm into the vagina, and place the swabs inside a vial. The nurse would do a pH test with 1 swab, and add 0.5 mL of saline to the vial. The patient would leave and await a phone call. When time allows, the clinician would perform a microscopic saline prep test (with or without potassium hydroxide [KOH]). If the criteria were met for a diagnosis, then the patient would receive a phone prescription. If a diagnosis could not be made, patient would be contacted to have an appointment with the clinician.

- What is the suggested workup of a patient with vulvovaginal symptoms?

Figure 1, Figure 2, and Figure 3 present an algorithm for the approach to diagnosis. The focused examination begins with the vulva; many patients have vulvar manifestations. During the examination, a vaginal pH is measured and a specimen for microscopy is obtained. If supplies are available in the examination room, one method is to prepare a slide with 1 drop of saline and 1 separate drop of KOH; then obtain the specimen from the posterior fornix with a plastic spatula and do a direct emulsion on the slide, perform a whiff test from the KOH mix, apply cover slips, and then carry the slide to a microscope. A second choice would be to obtain the specimen with a saline-moistened swab and place that in 2 to 3 drops of saline in a vial. The vial is then carried to the microscope and slides are prepared there; in this scenario the whiff test must be done on a separate, undiluted specimen of vaginal discharge. The whiff test attempts to detect a fishy odor of vaginal discharge before or after addition of 10% KOH. A positive whiff test makes candidiasis less likely (negative likelihood ratio, 0.31 [95% confidence interval, 0.12–0.79]) but is positively associated with trichomoniasis (positive likelihood ratio, 1.9 [95% confidence interval, 1.3–2.7]) [8]. A positive whiff test is 1 of the 3 diagnostic criteria for bacterial vaginosis (Table 1).

In selected cases (eg, resistant or recurrent infection), vaginal cultures for yeast and bacteria may be obtained. Sometimes these cultures may be obtained and sent only following microscopic examination, if needed. Polymerase chain reaction tests can also be performed for trichomonads or yeast. In at-risk cases, cultures for gonorrhea and chlamydia may be sent; in low-risk cases, the swab may be obtained at examination and sent only if an unexplained leukorrhrea is found on microscopic evaluation. Identification of *Mycoplasmal/Ureaplasma* would require either special culture media or use of polymerase chain reaction.

Laboratory Testing

Determining vaginal pH may be a helpful component of evaluating the vaginal secretions of a patient with lower genital tract complaints. Normal pH (< 4.5) essentially rules out the diagnosis of bacterial vaginosis and prompts search for yeast. A pH above 4.5 suggests bacterial vaginosis, trichomoniasis, or mucopurulent endocervicitis (chlamydia).

Microscopy of the saline prep of discharge is done at low power (100×) to allow microscopic scanning of the slide. This will help identify motile parasites or hyphae but is of inadequate power to detect clue cells or yeast buds or *Mobiluncus*. High power (400×) is useful to definitively assess the presence of clue cells, white blood cells (WBCs), motile trichomonads, and budding yeasts. The clinician inspects at least 10 fields before determining that the specimen lacks pathogens. Inspect the epithelial cells first and then the spaces in between the cells to assess the vaginal flora. A finding of leukorrhea (> 1 leukocyte per epithelial cell) prompts a careful look for motile trichomonads and for yeast and consideration of chlamydia.

Case Continued

The patient is not treated over the phone and is asked to come to the clinic. On examination, she has a normal-appearing outer vulva, with a slightly erythematous vestibule, and an excessive amount of white/yellow thick discharge. The cervix appears normal. The pH is 4 and whiff test is negative. A saline preparation is done and cultures obtained.
VULVOVAGINAL DISEASE

Wet prep shows qualitatively increased WBC numbers but not outnumbering epithelial cells. No clue cells, no yeast buds or hyphae, and no trichomonads are seen. Lactobacilli rods are seen and rods account for more than 50% of the bacterial organisms. Some of the rods are significantly longer than what is usually seen.

- How is the proper diagnosis made?

There are definitive criteria for making a diagnosis of bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis. In addition, various components of the history, examination, and laboratory testing for vulvovaginal discharge suggest and increased or decreased likelihood of a particular diagnosis (Table 1, Table 2, and Table 3).

Bacterial Vaginosis Diagnosis

The diagnostic “gold standard” for bacterial vaginosis is based on Amsel’s criteria of at least 3 of the following: (1) thin, white, homogenous discharge; (2) clue cells on microscopy (vaginal epithelial cells heavily coated with bacilli); (3) vaginal fluid pH greater than 4.5; and (4) release of a fishy amine odor on adding alkali (10% KOH) [13]. Recent studies have supported that 2 of the 4 criteria approximates the test accuracy of 3 of the criteria [40].

An alternate diagnostic standard is a Gram-stained vaginal smear evaluated with the Ison/Hay [41] or Nugent criteria [42]. According to Ison/Hay, predominance of lactobacillus morphotypes is normal; a mixture of flora is intermediate; and a predominance of Gardnerella and/or Mobiluncus morphotypes with few or absent lactobacilli is bacterial vaginosis. The Nugent score grades the relative proportions of bacterial morphotypes between 0 and 10; less than 4 is normal, 4 to 6 is intermediate, and greater than 6 is bacterial vaginosis. Research studies have employed different diagnostic standards and therefore the study populations are heterogenous.

For women who continue to have recurrent or unresolved vaginal symptoms that had been thought to be bacterial vaginosis and are not explained by candidiasis or sexually transmitted infections such as trichomoniasis, clinicians should re-evaluate for less common causes such as atrophic vaginitis, chemical/irritant vaginitis, allergic vaginitis, Behçet’s syndrome, desquamative inflammatory vaginitis, or erosive lichen planus vaginitis.

Vulvovaginal Candidiasis Diagnosis

Investigations are not always necessary on the first presentation if the signs and symptoms are consistent with uncomplicated vulvovaginal candidiasis. The definitive criteria for diagnosis are the presence of buds and hyphae on saline prep of the discharge or a positive culture of yeast.

If the vaginal fluid is in the normal pH range of 4.0 to 4.5, this may be indicative of vulvovaginal candidiasis. A higher pH (> 5.0) is suggestive of bacterial vaginosis or trichomoniasis. High vaginal swabs should be used to collect discharge from the anterior fornix or lateral wall of the vagina and assessed by saline prep and may be sent to the laboratory for microscopy and/or Gram stain and/or culture. Microscopy (saline prep) looking for budding yeast spores and/or pseudohyphae detects only about 70% of cases [36,43]. Culture is useful for identification of resistant species and is reserved for complicated or recurrent infections. If the saline prep shows many white cells with no yeast forms or hyphae, then cultures could be sent for yeast and also to rule out chlamydia and gonorrhea [24,33,44].

Severe vulvovaginal candidiasis is characterized by marked vulvar redness, swelling, excoriation, and fissure formation [28].

The definition of complicated vulvovaginal candidiasis is (1) at least 4 episodes/year with symptoms of increasing severity; (2) severe symptoms or findings; (3) suspected or proven non-albicans infection; (4) vulvovaginal candidiasis plus comorbidities (diabetes, pregnancy, severe illness, or immunosuppression).

Trichomoniasis Diagnosis

The definitive criteria for diagnosis are the presence of motile trichomonads on saline prep of the discharge or a positive culture of trichomoniasis. Microscopy of a saline prep will diagnose 40% to 80% of infected women. Culture will diagnose up to 95% of infected women. Cervical cytology may detect T. vaginalis as an incidental finding, with a sensitivity of 60% to 80% but a false-positive rate of 30%; therefore, diagnosis should be confirmed by culture or direct observation of vaginal secretions.

Case Continued

The patient’s pH is normal and no yeast forms are seen. There are no positive findings in support of vulvovaginal candidiasis, and the normal pH decreases the likelihood; however, saline prep is negative in 30% of cases of vulvovaginal candidiasis, so a culture for yeast is sent to the laboratory. With normal pH, no malodor, no clue cells, and lactobacilli predominant on the saline prep, bacterial vaginosis has been effectively ruled out. No trichomonads are seen; however, saline prep is apparently negative in 20% to 60% of cases, so a culture is sent to the laboratory. Cultures are also sent for gonorrhea and chlamydia.

This patient’s assessment does not meet the diagnostic criteria for bacterial vaginosis, vulvovaginal candidiasis, or trichomoniasis. There is the impression of leukorrhea,
but the number of WBCs does not exceed epithelial cells. The patient is advised that she might be in the process of improving from a recent yeast infection, which she had self-treated successfully with OTC cream.

The patient returns 1 week later complaining of the identical symptoms of vaginal itching and burning, with increased yellowish-white discharge. The examination is repeated, beginning again with the vulva. Although vulvar disease does not cause increased abnormal discharge, itching and burning can be symptoms of vulvar conditions such as contact dermatitis (allergic), lichen sclerosus, squamous cell hyperplasia, lichen planus, plasma cell vulvitis, and psoriaform disorders. In some patients, atrophic vaginitis is a consideration. Other conditions to consider include physiologic discharge, recurrent yeast, and vulvar vestibulitis. Physiologic discharge is characterized by complaint of excessive discharge without other symptoms.

Test for pH is 5.5. There is no malodor and amine whiff test is negative. Microscopy reveals increased WBCs, numerous parabasal cells, and less than 50% rods representing lactobacilli.

• What other conditions could account for this patient’s symptoms?

Unusual conditions that could account for this patient’s symptoms include desquamative inflammatory vaginitis, cytologic vaginosis, and lactobacillosis.

Desquamative Inflammatory Vaginitis

Desquamative inflammatory vaginitis is sometimes referred to as aerobic vaginitis. The symptoms of desquamative inflammatory vaginitis are burning and dyspareunia. The signs of desquamative inflammatory vaginitis are vaginal and vestibular erythema and irritation with profuse yellowish discharge; when severe, this may look like symmetric “peeled” epithelium, with edema. The amine whiff test is negative. The pH is usually elevated above 4.5. On microscopy, there are numerous WBCs and inflammatory cells, with the ratio of WBC to epithelial cells in excess of 1. Numerous parabasal cells are seen (>10%). No yeast or trichomonads are seen.
Lactobacilli are absent, and many gram-positive cocci are seen (usually streptococci or *Escherichia coli*). Cultures are negative for trichomoniasis, yeast, chlamydia, and gonorrhea. Although streptococci may be cultured, this does not mean that desquamative inflammatory vaginitis is caused by streptococci. Some authorities argue that desquamative inflammatory vaginitis may be the vaginal expression of lichen planus.

Desquamative inflammatory vaginitis is a diagnosis of exclusion. The differential includes cervicitis, and visual examination of the cervix is important. Parabasal cells are not seen with cervicitis; culture for chlamydia is recommended [45].

**Cytologic Vaginosis and Lactobacillosis**

Cytologic vaginosis is not recognized by all experts. Cytologic vaginosis is very similar to lactobacillosis, with the single differentiator being that with lactobacillosis, long-chain lactobacilli are seen on microscopy. Therefore, these 2 conditions will be described in tandem.

The symptoms are pruritis, dyspareunia, and vaginal dysuria with variable discharge. History is notable for cyclic increase of symptoms in the luteal phase of the menstrual cycle. The vulva may appear slightly red with vaginal discharge, which may be either thin and watery or thick and curdlike. The amine whiff test is negative. The pH is usually low-normal: 3.5 to 4.7. On microscopy, few WBCs, many desquamated epithelial cells, and a remarkably large number of lactobacilli, with possible “false clue cells” (coating of epithelial cells with lactobacilli) are the features of cytologic vaginosis. Lactobacillosis is distinguished by long chains of bacilli, which are filamentous or serpiginous. Typical lactobacilli are between 5 and 15 microns in length; whereas the lactobacilli in these symptomatic patients ranged between 40 and 75 microns in length. Cultures are negative for trichomoniasis, yeast, chlamydia, and gonorrhea.

Some experts say that lactobacillosis and cytologic vaginosis do not exist and that patients should do nothing and wait for self-correction. Therapeutic interventions used at specialty clinics include bicarbonate of soda lavage and antibiotics. Bicarbonate sitz bath is used for 15 minutes 2 to 3 times in the first week; then 1 to 2 times weekly as needed. Bicarbonate douche is prepared by mixing 1 to 2 tablespoons of baking soda with 4 cups of warm water; a douche bag,
available at most pharmacies, is used to infiltrate the vagina with the solution. The douche lavage is used twice weekly for 2 weeks. Prescribed antibiotics are amoxicillin and clavulanate 500 mg thrice daily for 7 days or doxycycline 100 mg twice daily for 10 days [12,46].

**Case Continued**

With negative culture results in hand, and the findings at today’s visit, the physician is favoring the diagnosis of desquamative inflammatory vaginitis.

- **What is the treatment of desquamative inflammatory vaginitis?**

Empiric treatment is 2% clindamycin vaginal cream for 14 days; no randomized controlled trials have been reported. Most subspecialty experts advocate a combined course of intravaginal clindamycin with intravaginal hydrocortisone: either Anusol suppositories inserted in the vagina or from a compounding pharmacy hydrocortisone 100 mg/g in clindamycin 2% emollient cream base; insert 5 g (applicator full) nightly for 14 nights [45].

- **What is the treatment of the more common causes?**

**Treatment of Bacterial Vaginosis**

**Oral Agents**

For patients with a diagnosis of bacterial vaginosis, treatment is indicated for symptomatic women, for women undergoing surgical procedures that involve the vagina, and some pregnant women. Women who do not volunteer symptoms, discovered to have bacterial vaginosis, may elect to take treatment if offered. Asymptomatic women may report a beneficial change in their discharge following treatment.

Oral metronidazole, intravaginal metronidazole, and intravaginal clindamycin are equally effective at curing bacterial...
### Table 1. Bacterial Vaginosis (BV): Impact of Signs and Symptoms on Likelihood of Diagnosis

<table>
<thead>
<tr>
<th>Component</th>
<th>Evaluation</th>
<th>BV Rule-in (Increased Likelihood)</th>
<th>BV Rule-out (Decreased Likelihood)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Large Change in Likelihood</td>
<td>Moderate Change in Likelihood</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td>Odor</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>No odor</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sign</strong></td>
<td>Profuse discharge</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Yellow discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thin, homogenous vaginal discharge</td>
<td>Diagnostic criteria 1/3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whiff test positive</td>
<td>Diagnostic criteria 1/3</td>
<td></td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>&gt; 4.5</td>
<td>Diagnostic criteria 1/3</td>
<td></td>
</tr>
<tr>
<td><strong>Wet preparation</strong></td>
<td>Bacilli with corkscrew motility</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal lactobacilli</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clue cells</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Three diagnostic criteria are needed for BV (recent literature suggests that 2 criteria may be sufficient). The presence of bacilli with corkscrew motility on saline prep is a strong diagnostic clue. The absence of a fishy odor or negative amine whiff test argues against BV. The dominance of lactobacilli on saline prep argues against BV. (Adapted from Anderson MR, Klink K, Cohrssen A. Evaluation of vaginal complaints. JAMA 2004;291:1368 and Landers DV, Wiesenfeld HC, Heine RP, et al. Predictive value of the clinical diagnosis of lower genital tract infection in women. Am J Obstet Gynecol 2004;190:1004–10.)

### Table 2. Vulvovaginal Candidiasis (VVC): Impact of Signs and Symptoms on Likelihood of Diagnosis

<table>
<thead>
<tr>
<th>Component</th>
<th>Evaluation</th>
<th>Candidiasis Rule-in (Increased Likelihood)</th>
<th>Candidiasis Rule-out (Decreased Likelihood)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Large Change in Likelihood</td>
<td>Moderate Change in Likelihood</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td>Patient belief she has one</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cheesy discharge consistency</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Itching</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absence of odor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Watery discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sign</strong></td>
<td>Thick, curdy, or flocculent white discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fishy odor, whiff test</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>&gt; 4.5</td>
<td></td>
<td></td>
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<tr>
<td><strong>Wet preparation</strong></td>
<td>Clue cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absence of buds and/or hyphae</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Buds and/or hyphae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture</td>
<td>Positive</td>
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Note: Diagnostic criteria for VVC are the identification of buds/hyphae on saline prep or a positive culture. The character of the discharge is a strong diagnostic clue. The presence of a fishy odor or positive amine whiff test argues against VVC. (Adapted from Anderson MR, Klink K, Cohrssen A. Evaluation of vaginal complaints. JAMA 2004;291:1368 and Landers DV, Wiesenfeld HC, Heine RP, et al. Predictive value of the clinical diagnosis of lower genital tract infection in women. Am J Obstet Gynecol 2004;190:1004–10.)
vaginosis (cure rates of 70%–80% after 4 weeks in controlled trials) [47]. For women who are not pregnant, choice of treatment is based on patient preference. Patients tend to prefer fewer doses. The single-dose option is clindamycin 2% sustained-release vaginal cream 5 g (Clindesse) [48]. Clindamycin 2% cream may be given as 1 full applicator (5 g) intravaginally at bedtime for 7 days. Metronidazole gel 0.75% may be given as 1 full applicator (5 g) intravaginally once a day for 5 days (Metrogel). Oral treatments include metronidazole 500 mg orally twice daily for 7 days; metronidazole 750 mg extended-release tablets once daily for 7 days; clindamycin 300 mg orally twice daily for 7 days. An alternative is a single oral dose of 2 g, which may improve compliance but may be less effective at 4-week follow-up (35%–50% with 7-day treatment vs. 20%–33% with single-dose treatment). Tindamax (tinidazole) was approved by the U.S. Food and Drug Administration in 2007 for treatment of bacterial vaginosis. Due to cost, it should be considered a second-line treatment. Tindamax may be prescribed as 1 g orally daily for 5 days or as 2 g orally daily for 2 days [49–52].

For pregnant women, the route of delivery is oral [13,14,47]. The recommended regimen for oral metronidazole is 500 mg twice daily for 7 days. An alternative is clindamycin 300 mg orally twice daily for 7 days. Although there is no evidence of teratogenicity of metronidazole in pregnancy, large single doses are avoided [53,54].

Other Treatments
Current evidence-based medicine guidelines recommend that vaginal douching, use of shower gel, and use of antiseptic agents or shampoo in the bath should all be avoided, since the effectiveness of these counter-measures is uncertain. A recent multicenter cross-sectional study of 1200 women assessed douching practices and found that recent douching increased the risk of bacterial vaginosis twofold (odds ratio, 2.1 [95% confidence interval, 1.3–3.1]) [55]. There is insufficient evidence regarding the relative benefits and harms of vinegar douche (to lower pH as a preventive for recurrent bacterial vaginosis) to make a recommendation. Similarly, new commercial products that may alter vaginal pH have not undergone sufficient study to report benefit for prevention of bacterial vaginosis. There are not sufficient studies of vaginal wash (30 mL) or douche with 3% hydrogen peroxide to determine if this is beneficial or harmful.

Studies of live-culture yogurt or Lactobacillus acidophilus have not found benefit; one explanation is that these lactobacilli are not hydrogen peroxide–producing [6]. Evidence does not support the use of oral or vaginal lactobacilli for prevention of vulvovaginal Candidiasis [56–58].

About 15% to 30% of patients who had bacterial vaginosis have a recurrence within 3 months of treatment. Since bacterial vaginosis can be asymptomatic, recurrence often cannot be differentiated from treatment failure. No clinical trials have compared specific, comprehensive strategies for recurrent bacterial vaginosis. Due to evidence of a higher recurrence rate with single-dose oral treatment, prolonged duration of therapy for recurrent bacterial vaginosis is recommended; options are suppressive therapy with oral metronidazole for 10 days or with metronidazole gel 0.75% for 10 days.

### Treatment of Vulvovaginal Candidiasis

**Oral Agents**
First-line treatment for uncomplicated acute vulvovaginal

### Table 3. Trichomoniasis: Impact of Signs and Symptoms on Likelihood of Diagnosis

<table>
<thead>
<tr>
<th>Component</th>
<th>Evaluation</th>
<th>Trichomoniasis Rule-in (Increased Likelihood)</th>
<th>Trichomoniasis Rule-out (Decreased Likelihood)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Large Change in Likelihood</td>
<td>Moderate Change in Likelihood</td>
</tr>
<tr>
<td>Sign</td>
<td>Yellow discharge ✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whiff test ✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>&lt; 4.5 ✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wet prep-ration</td>
<td>Absence of trichomonads ✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture</td>
<td>Positive Diagnostic criteria ✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VULVOVAGINAL DISEASE

candidiasis is an imidazole: butoconazole (2% sustained-release cream, Femstat), clotrimazole (500 mg vaginal suppository, Lotrimin/Mycelax), miconazole (1200 mg vaginal suppository, Monistat), or terconazole (6.5% ointment, 3 days, Terazol). These are 80% to 90% effective, and most are available as OTC 1-day treatments. Three-, 7-, and 14-day treatments confer no advantage. The efficacy of topical imidazoles is not dependent on the duration of treatment but is related to the total dose of drug received. A single high-dose is as effective as a lower divided dose over several days [30,59]. Prescribed imidazoles are not more effective than OTC imidazoles. A systematic review found that for every 3 women treated with topical imidazoles, 1 additional subject had resolution of symptoms compared to the placebo in the short term (number needed to treat, 3). No particular topical imidazole was found to be superior to any other [4,32].

An alternate treatment is the oral triazoles: fluconazole (150 mg, Diflucan) and itraconazole (200 mg, Sporanox). With triazoles, one must consider potential enzyme-mediated drug interactions, including oral diabetes drugs. Oral fluconazole and itraconazole are as effective as topical imidazoles, although fluconazole is better tolerated. A systematic review of 17 randomized controlled trials found no significant difference in effectiveness between imidazoles and triazoles [32,59,60]. Oral ketoconazole (Nizoral) is not usually indicated for uncomplicated vulvovaginal candidiasis: topical imidazoles for 6 to 12 days; oral triazole on day 1 and day 4 [29]. Evidence has shown that it is not beneficial to treat a male sex partner for acute vulvovaginal candidiasis or recurrent vulvovaginal candidiasis [4,26,32].

Topical Agents

Another class of antimicrobial drugs that target fungi are the polyene compounds, such as nystatin and amphotericin B (50 mg daily for 14 days). Topical nystatin is not recommended for uncomplicated vulvovaginal candidiasis but may be useful after treatment failure. Nystatin is more effective against certain resistant strains of yeast such as C. krusei and C. glabrata (C. glabrata can also be managed with extended 2-week course imidazoles) [61,62]. Nystatin vaginal cream is not commercially available in the United States; vaginal tablets may be prescribed (100,000 U) 1 or 2 times a day for 2 weeks. For severe infections, the dose of 500,000 U of vaginal nystatin may be increased to every 12 hours. Treatment failure in uncomplicated vulvovaginal candidiasis is unusual. Possible reasons for apparent treatment failure are wrong diagnosis (reevaluate), resistant organism (consider culture), mixed infection (10% of infections are mixed), and poor compliance (consider using fluconazole or itraconazole) [61].

For vulvovaginal candidiasis in pregnancy, a recent Cochrane review of 10 trials concluded that topical imidazoles are more effective than topical nystatin in the treatment of pregnant women and that longer courses of treatment (7 days) may be necessary [28,63].

Treatment of Recurrent or Severe Infections

For recurrent yeast, topical imidazoles or oral triazoles can be used as prophylaxis if the timing of the yeast infection is well-understood. For persistent or resistant yeast, a culture may be helpful in guiding drug selection. Treatment of recurrent infection consists of an initial induction period of 6 to 12 days of daily treatment with an imidazole cream or oral triazole on the first day and fourth day, followed by a maintenance or prevention period of weekly topical imidazole or oral triazoles for 3 to 6 months. These regimens are based on empirical data and expert opinion, with the exception of 1 randomized placebo-controlled trial [4,12,28,30,61,64–66]. Longer-course therapy is suggested for severe vulvovaginal candidiasis: topical imidazoles for 6 to 12 days; oral triazole on day 1 and day 4 [29]. Evidence has shown that it is not beneficial to treat a male sex partner for acute vulvovaginal candidiasis or recurrent vulvovaginal candidiasis [4,26,32].

Other Treatments

There is insufficient evidence to provide recommendations regarding povidone-iodine antiseptic in topical intravaginal formulations, douching, garlic, tea tree oil, and yogurt [6,26,67]. The ingestion of yogurt containing live lactobacilli for the prevention of vulvovaginal candidiasis is controversial. While some studies have shown beneficial effects, there are no randomized controlled trials and at least 1 study suggested that yogurt may actually increase the recurrence of vulvovaginal candidiasis, and so it is not recommended at present [26,55,57,58]. Commercially available yogurt (even with live culture) do not contain peroxide-producing lactobacilli.

There is limited evidence to support the use of boric acid suppositories per vagina in the event of failed azole therapy. The pH of boric acid is about 5.2. The suppositories are compounded: fill 0-gel capsule halfway (600 mg boric acid). For the initial treatment, a 600-mg capsule is inserted vaginally daily for 14 days. For prophylaxis in patients with frequent recurrent vulvovaginal candidiasis, long-term maintenance is with boric acid capsules inserted into the vagina twice weekly [55,68,69].

Gentian violet has been used for a long time because of its antifungal and antimicrobial properties. A 0.25% or 0.5% aqueous solution may be applied at home daily or may be painted in the physician’s office as a 1.0% solution (once weekly for up to 3 times). Semi-permanent purple staining on clothing may occur. Some patients develop a vulvar irritation following application [4,55].

5-flucytosine is a pyrimidine developed for use as an anticancer drug. Although not effective against cancer, it is fungicidal and is apparently deaminated within the yeast cell to 5-fluorouracil, which is incorporated into RNA and interferes with cell development. However, not all strains of C. albicans are susceptible, and drug resistance develops. The
drug is highly effective against imidazole-resistant strains of \textit{C. tropicalis}. A compounding prescription is written: 500 mg – 1 g/5 g compounded in hydrophilic cream base; insert 5 g per vagina once daily at bedtime for 14 nights [68].

**Treatment of Trichomoniasis**

Oral antimicrobial treatment for trichomoniasis is recommended due to the high incidence of infection of the urethra and paraurethral glands and the greater effectiveness (95%) of oral treatment compared with vaginal treatment [33,70]. Recommended treatment regimens are metronidazole 500 mg orally twice daily for 5 to 7 days or metronidazole 2 g orally as a single dose. The single-dose treatment may improve compliance and is less expensive. Partners should be treated concurrently with index patient [33,70].

A second-choice therapy is tinidazole (Tindamax), recommended as a first-line agent along with metronidazole for the treatment of trichomoniasis by the Centers for Disease Control and Prevention. Tinidazole is given as 2 g orally as a single dose (4 × 500-mg tablets). However, tinidazole has no additional benefits over metronidazole, has been less extensively studied, and is much more expensive [33].

During pregnancy, the recommended oral metronidazole 400 mg twice daily for 5 days. There is no evidence of teratogenicity from the use of metronidazole in women during the first trimester of pregnancy [33]. However, single high-dose metronidazole should be avoided, both during pregnancy and while breastfeeding, due to lack of safety data [33].

**Treatment of Mixed Infections**

Ten percent to 15% of women with vaginitis complaints have mixed infections; treatment should cover both. Typical combination therapy is single-dose fluconazole for vulvovaginal candidiasis plus topical therapy for bacterial vaginosis. Oral metronidazole or tinidazole would be drugs of choice for trichomoniasis and bacterial vaginosis.

**SUMMARY**

Vulvovaginal discharge complaints are common and a source of annoyance and discomfort for many women. An evidence-based diagnostic algorithm, based on the likelihood ratio test properties of common components of the evaluation will support an efficient and accurate diagnostic process.

**References**


VULVOVAGINAL DISEASE


CME EVALUATION: Vulvovaginal Disease: An Evidence-Based Approach to Medical Management

DIRECTIONS: Each of the questions below is followed by several possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. The following are diagnostic features of which condition: abnormal vaginal discharge, elevated vaginal pH, positive whiff test, and clue cells.
   A. Trichomoniasis
   B. Yeast vaginitis
   C. Bacterial vaginosis
   D. Desquamative inflammatory vaginitis
   E. Cytologic vaginosis

2. Which of the following is NOT an evidence-based treatment for bacterial vaginosis?
   A. Metronidazole
   B. Clindamycin
   C. Tinidazole
   D. Lactobacillus acidophilus
   E. No treatment

3. Which of the following statements is FALSE?
   A. Trichomoniasis during pregnancy should be treated with oral metronidazole 400 mg twice daily for 5 days
   B. Asymptomatic bacterial vaginosis during pregnancy should not be treated
   C. Topical imidazoles are the treatment of choice for vulvovaginal candidiasis during pregnancy
   D. A vaginal yeast infection during pregnancy is defined as a complicated vulvovaginal candidiasis
   E. The male partner should not be treated in cases of female candidiasis or bacterial vaginosis but should be treated in cases of female trichomoniasis

4. Which of the following statements is TRUE?
   A. Microscopy looking for budding yeast spores and/or pseudohyphae detects only about 30% of cases of vaginal candidiasis
   B. Of women who purchased an over-the-counter antifungal, two thirds did in fact have a yeast infection
   C. Trichomoniasis infection is asymptomatic in up to 50% of women
   D. Microscopy of a saline preparation will miss 20% to 60% of women with a trichomoniasis infection
   E. Lactobacilli normally comprise one third of the bacteria in the vagina
   F. The cure rate for bacterial vaginosis at 4 weeks after evidence-based therapy is 95%

5. Management of recurrent vulvovaginal candidiasis should include all of the following EXCEPT
   A. Prophylactic topical imidazole
   B. Obtaining a culture for yeast
   C. Bioactive live culture yogurt
   D. Prophylactic oral triazoles
   E. Prolonged therapeutic regimens
EVALUATION FORM: Vulvovaginal Disease: An Evidence-Based Approach to Medical Management

Participants may earn 1 credit by reading the article named above and correctly answering at least 70% of the accompanying test questions. A certificate of credit and the correct answers will be mailed within 6 weeks of receipt of this page to those who successfully complete the test.

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1. A  B  C  D  E
2. A  B  C  D  E
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   __ Excellent   __ Good   __ Fair   __ Poor

2. This article was fair, balanced, free of commercial bias, and fully supported by scientific evidence.
   __ Yes   __ No

3. Please rate the clarity of the material presented in the article.
   __ Very clear   __ Somewhat clear   __ Not at all clear

4. How helpful to your clinical practice was this article?
   __ Very helpful   __ Somewhat helpful   __ Not at all helpful

5. What changes will you make in your practice as a result of reading this article?
   ________________________________________________________________
   ________________________________________________________________
   ________________________________________________________________
   ________________________________________________________________

6. What topics would you like to see presented in the future?
   ________________________________________________________________
   ________________________________________________________________
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   ________________________________________________________________
   ________________________________________________________________

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