CLINICAL PRACTICE

Acute Vulvovaginitis

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 24-year-old sexually active woman presents with a 3-day history of vaginal pruritus and increased vaginal discharge. One year before presentation, she had the same symptoms, which resolved with use of an over-the-counter antifungal agent. She uses oral contraceptives for birth control. The physical examination reveals vulvar erythema and normal-appearing vaginal discharge. How should she be evaluated and treated?

THE CLINICAL PROBLEM

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Vaginitis is a common reason for visits to a health care provider, accounting for 6 million visits per year. Symptoms associated with vaginitis can cause substantial distress, resulting in time lost from work and altered self-esteem. It is estimated that over a billion dollars is spent annually on both self-treatment and visits to a medical provider.[1] In addition, women with bacterial vaginosis and trichomoniasis have an increased risk of infection with human immunodeficiency virus (HIV) because the levels of protective lactobacilli are decreased and inflammation is present; this increased risk is independent of behavioral factors, further supporting the benefit of the accurate diagnosis and treatment of vaginitis.[2,3]

NORMAL VAGINAL FLORA

Lactobacilli are both the predominant bacteria in the vaginal tract and the regulator of normal vaginal flora. Lactobacilli make lactic acid, which maintains the normal vaginal pH of 3.8 to 4.5, and inhibit the adherence of bacteria to vaginal epithelial cells. Approximately 60% of vaginal lactobacilli strains produce hydrogen peroxide, which inhibits the growth of bacteria and destroys HIV in vitro.[4] Estrogen improves lactobacilli colonization by enhancing vaginal epithelial-cell production of glycogen, which breaks down into glucose and acts as a substrate for the bacteria.

Although lactobacilli are the dominant bacteria, other bacteria are also present in the vagina, including streptococcal species, gram-negative bacteria, *Gardnerella vaginalis,* and anaerobes. *Candida albicans* can also be found in normal flora as a commensal agent in 10 to 25% of asymptomatic women.[5]

ACUTE VAGINITIS

The three most common types of acute vaginitis are bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis.

Bacterial Vaginosis

Bacterial vaginosis is the most common cause of acute vaginitis and accounts for 15 to 50% of the cases in symptomatic women, depending on the population stud-

ied.[6] Bacterial vaginosis reflects a shift in vaginal flora from lactobacilli-dominant to mixed flora, including genital mycoplasmas, *G. vaginalis,* and anaerobes such as peptostreptococci, and prevotella and mobiluncus species. Vaginal cultures do not adequately capture the complexity of vaginal flora in bacterial vaginosis; a recent study used molecular methods to identify a cluster of noncultivable bacteria related to clostridium in affected women.[7]

Risk factors for bacterial vaginosis include having more than one sexual partner, having changed partners in the previous 30 days,[8,9] having a female sexual partner,[10] and douching at least monthly or within the previous 7 days.[3] A lack of hydrogen peroxide–producing lactobacilli is also a recognized risk factor for bacterial vaginosis, and it may explain in part the higher risk of this infection among black women, which is independent of other risk factors.[11,12] Social stressors (such as homelessness, threats to personal safety, and insufficient resources) have also been reported to increase the risk.[11]

In addition to causing bothersome symptoms, bacterial vaginosis is associated with an increased risk of many upper genital tract infections, including endometritis after cesarean section, vaginal delivery, or abortion; wound infection; increased infection after vaginal and abdominal hysterectomy; pelvic inflammatory disease; preterm delivery; and chorioamnionitis. Women with bacterial vaginosis also have an increased risk of spontaneous abortion and a decreased probability of successful in vitro fertilization.[13-16]

Vulvovaginal Candidiasis

Although most women with acute vaginitis assume that candida is the cause, this is true in only 15 to 30% of cases. Approximately 75% of women will receive a diagnosis of vulvovaginal candidiasis at least once, and of those, about 50% will have a recurrence.[17,18] Most cases of acute vulvovaginal candidiasis are caused by *C. albicans.* Risk factors include pregnancy, being in the luteal phase of the menstrual cycle, nulliparity, the use of spermicides[5,8,19] (but not low-dose oral contraceptives), and young age (the risk is highest from the ages of 15 to 19 years and then decreases).[5] Recent therapy with broad-spectrum antibiotics such as tetracycline, ampicillin, and oral cephalosporins is also a risk factor, presumably because it eliminates the protective vaginal flora, especially lactobacilli.[5,20] Whereas *C. albicans* is a commensal agent in many asymptomatic women, symptomatic infection correlates with vaginal infiltration by polymorphonuclear neutrophils and a high vaginal fungal burden.[21]

Recurrent vulvovaginal candidiasis (four or more documented episodes in 1 year) occurs in less than 5% of the population. Altered local immune response, such as a hyper-IgE–mediated response to a small amount of candida antigen, may predispose women to recurrences.[22] Whereas *C. albicans* is still the most common fungus isolated in women with recurrent vulvovaginal candidiasis, an increased prevalence of non-albicans species, especially *C. glabrata,* may be found in up to 15% of women with recurrent infections.[23]

Trichomonas vaginalis

T. vaginalis, an intracellular parasite that is sexually transmitted, is the cause of acute vaginitis in 5 to 50% of cases, depending on the population studied. It is the most common sexually transmitted infection in the United States, with an estimated 5 million new cases annually.[24] Risk factors for trichomoniasis include a change in sexual partners, intercourse twice weekly or more, three partners or more in the past month, and another coexistent sexually transmitted disease.[25] Trichomoniasis is associated with upper genital tract infections such as those described for bacterial vaginosis, including infections after delivery, surgery, and abortion; pelvic inflammatory disease; and preterm delivery.[24]

STRATEGIES AND EVIDENCE

DIAGNOSIS

Symptoms and Signs

Classically, bacterial vaginosis is associated with a thin, whitish-gray, fishy-smelling discharge; vulvovaginal candidiasis with a thick, white, curdy discharge without odor; and trichomoniasis with a copious yellow discharge that may have a foul odor. Multiple studies, however, have demonstrated that symptoms such as pruritus and the characteristics of the discharge do not reliably predict the cause of acute vaginitis; the amount and color of vaginal discharge are among the least reliable features for predicting the cause of vaginitis (Table 1).[27] In addition, studies demonstrate that women are not able to accurately

Table 1. Typical Features of Vaginitis.

Condition	Symptoms and Signs*	Findings on Examination*	pH	Wet Mount	Comment
Bacterial vaginosis†	Increased discharge (white, thin) Increased odor	Thin, whitish-gray homogeneous discharge, sometimes frothy	>4.5	Clue cells (>20%) Shift in flora Amine odor after adding potassium hydroxide to wet mount	Greatly decreased lactobacilli Greatly increased cocci, bacilli, small curved rods
Candidiasis	Increased discharge (white, thick)‡ Pruritus Dysuria Burning	Thick, curdy discharge§ Vaginal erythema	<4.5	Hyphae or spores	Can be mixed infection with bacterial vaginosis, *T. vaginalis*, or both, and have higher pH
Trichomoniasis¶	Increased discharge (yellow, frothy) Increased odor Pruritus Dysuria	Yellow, frothy discharge with or without vaginal or cervical erythema	>4.5	Motile trichomonads Increased white cells	More symptoms at higher vaginal pH

* Although these features are typical, their sensitivity and specificity are generally inadequate for diagnosis.
† For a diagnosis of bacterial vaginosis, a report of increased discharge has a sensitivity of 50% and a specificity of 49%; odor, a sensitivity of 49% and a specificity of 20%; and a pH above 4.7, a sensitivity of 97% and a specificity of 65%, as compared with the use of a Gram's stain.[6]
‡ Forty percent of patients presenting with symptoms of vaginitis report increased (white) discharge, but this discharge is not related to *C. albicans* in many studies.[5]
§ A report of thick, curdy discharge has a positive predictive value of 84% but a sensitivity of only 18%.[5]
¶ A report of a yellow discharge has a sensitivity of 42% and a specificity of 80%; a frothy discharge on examination has a sensitivity of 8% and a specificity of 99%.[26]

diagnose the cause of their vaginitis, even women who have previously had vulvovaginal candidiasis.[28]

Physical examination should include a careful inspection of the external genitalia, vaginal sidewalls, and cervix, as well as of the discharge, although the limitations of these features in making a diagnosis should be kept in mind. Fissures and excoriations on external genitalia occur in about a quarter of the cases of candida vulvovaginitis but are unlikely in cases of bacterial vaginosis or trichomoniasis. Erythematous punctuations on the cervix, so-called strawberry cervix, are associated with trichomoniasis, but occur rarely (2 to 5% of cases).[6,28]

Vaginal pH should be measured by touching a cotton-tipped swab to the sidewall of the vagina midway between the introitus and the cervix and then touching the swab to commercially available pH paper (expanded in the range of 4.0 to 5.5 pH); pH should not be tested by sampling the vaginal pool in the posterior fornix, since its pH may be elevated by the presence of cervical mucus. The normal vaginal pH of 4.0 is not altered in vulvovaginal candidiasis. An elevated pH of 4.5 or higher occurs in 97% of women with bacterial vaginosis and is also typical of trichomoniasis. Although concomitant bacterial vaginosis or trichomoniasis will elevate the vaginal pH in a patient with candidal vulvovaginitis, a normal pH rules out bacterial vaginosis or trichomoniasis. Blood or semen in the vaginal vault may also elevate the vaginal pH.

Microscopical Evaluation

Microscopical evaluation of vaginal fluid is the mainstay of diagnosis of acute vaginitis. Bacterial vaginosis is a clinical diagnosis, requiring at least three of the following four features: vaginal pH greater than 4.5; thin, watery discharge; wet mount showing more than 20% clue cells (i.e., vaginal squamous epithelial cells with copious adherent coccobacilli); and positive "amine" odor test (performed by adding 10% potassium hydroxide to a drop of vaginal discharge on the slide and smelling for the distinctive odor that results from released volatilized amines). Wet mounts in women with bacterial vaginosis also characteristically have altered background flora with multiple cocci, variably shaped bacteria, and few, if any, rod-shaped lactobacilli (Fig. 1). Vulvovaginal candidiasis is diagnosed by the presence of hyphae visible on a potassium hydroxide wet mount[4] (Fig. 2). The microscopical diagnosis of trichomoniasis is made by viewing mobile trichomonads on wet mount; increased polymorphonuclear cells are

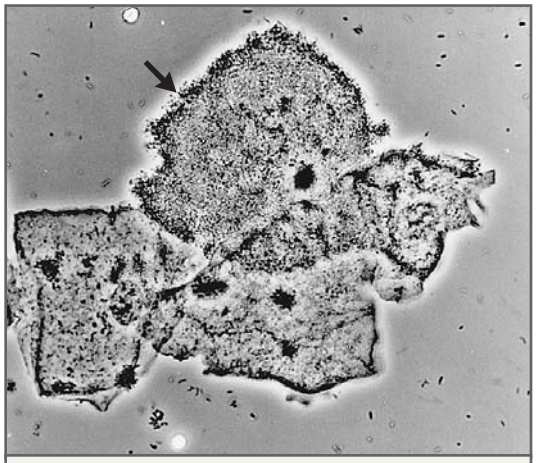

Figure 1. Vaginal Wet Mount Showing Clue Cell (Arrow) and Normal Epithelial Cells.

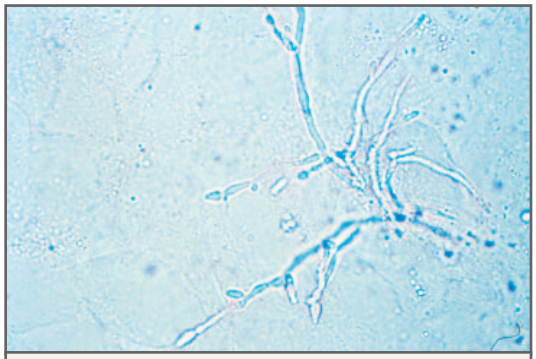

Figure 2. Vaginal Wet Mount Revealing Hyphae.

often present (Video 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org). Table 2 reviews the sensitivity and specificity of these and other findings for the various conditions.

Vaginal culture for *C. albicans* is useful if a wet mount is negative for hyphae but the patient has symptoms and discharge or other signs suggestive of vulvovaginal candidiasis on examination.[5] Fungal culture may also be useful in cases of recurrent vulvovaginal candidiasis to rule out non–*C. albicans* species; culture is infrequently useful in women who have recently treated themselves with an antifungal agent (up to 90% have a negative culture within 1 week after treatment). Vaginal culture for bacteria is not useful, since anaerobes, coliforms, and *G. vaginalis* can all be found in normal vaginal flora.

Point-of-Care Tests

Several point-of-care tests are available (Table 2), which may be useful particularly when a microscope is not available. The role of these tests in the routine management of vaginitis is unclear, in part owing to cost.

TREATMENT

Bacterial Vaginosis

Treatment for bacterial vaginosis consists of anaerobic therapy. Seven days of oral metronidazole therapy is as efficacious as 5 days of vaginal administration, with a symptomatic cure rate of approximately 80% and a microbiologic cure rate of 70% at 1 month in placebo-controlled, randomized trials.[32] Randomized trials have also demonstrated that a 7-day course of 2% vaginal clindamycin cream is as effective as oral metronidazole[33] and that a single dose of an extended-release preparation of clindamycin cream yields similar results.[34] Single-dose oral metronidazole is no longer approved as an alternative regimen for bacterial vaginosis because of a failure rate of 50%.[35]

For cases of recurrent bacterial vaginosis (three or more episodes in the previous year), one double-blind, randomized trial demonstrated that after 10 days of daily induction therapy with vaginal metronidazole the twice-weekly use of 0.75% metronidazole gel for 16 weeks maintained a clinical cure in 75% of patients at 16 weeks and 50% at 28 weeks.[36]

Vulvovaginal Candidiasis

Uncomplicated vulvovaginal candidiasis is defined as infrequent (three or fewer episodes per year), with mild-to-moderate symptoms, probably caused by *C. albicans*, and occurring in an immunocompetent host. Approved treatments for this condition include a variety of topical antifungal agents typically used for 1 to 3 days, and one oral agent, fluconazole (150 mg), in a single dose. Both topical and oral azole drugs result in relief of symptoms and negative cultures in 80 to 90% of patients, and no agent has clear superiority in randomized trials.[37] Patient preference, response to prior therapy, and cost should thus guide the choice of therapy.

The over-the-counter availability of vaginal antifungal therapy makes self-treatment a reasonable option for many women. However, it must be recognized that symptoms suggestive of uncomplicated vulvovaginal candidiasis may reflect an alternative diagnosis. One study of women

Table 2. Diagnostic Tests Available for Vaginitis.

Test	Sensitivity	Specificity	Comment
	%		
Bacterial vaginosis*			
pH >4.5	97	64	
Amsel's criteria	92	77	Must meet 3 of 4 clinical criteria (pH >4.5, thin watery discharge, >20% clue cells, positive "whiff" test [amine odor present with addition of base]), but similar results achieved if 2 of 4 criteria met
Nugent criteria			Gram's stain morphology score (0–10) based on lactobacilli and other morphotypes; a score of 0–3 indicates normal flora, a score of 4–6 intermediate flora, and a score of 7–10 bacterial vaginosis; high interobserver reproducibility
Papanicolaou smear	49	93	
Point-of-care tests			
QuickVue Advance pH+ amines	89	96	Positive if pH >4.7
QuickVue Advance *G. vaginalis*†	91	>95	Tests for proline iminopeptidase activity in vaginal fluid; if used when pH >4.5, sensitivity is 95% and specificity is 99%
OSOM BV Blue†	90	>95	Test for vaginal sialidase activity
Candida‡			
Wet mount			
Overall	50	97	
Growth of 3–4+ on culture	85		*C. albicans* a commensal agent in 10–25% of women
Growth of 1+ on culture	23		
pH ≤4.5			pH may be elevated if mixed infection with bacterial vaginosis or *T. vaginalis* present
Papanicolaou smear	25	72	
T. vaginalis§			
Wet mount	45–60	95	Increased visibility of microorganisms with a higher burden of infection
Culture	85–90	>95	
pH >4.5	56	50	
Papanicolaou smear	92	61	False positive rate, 8% for standard Pap test and 4% for liquid-based cytologic test
Point-of-care test			
OSOM	83	98.8	Requires 10 min to perform; tests for *T. vaginalis* antigens

* For details, see Eschenbach et al.[6] and the guidelines of the American College of Obstetricians and Gynecologists (ACOG).[29]
† Proline iminopeptidase and sialidase are enzymes produced by many bacteria associated with bacterial vaginosis.
‡ For details, see Eckert et al.[5] and Shurbaji et al.[30]
§ For details, see Soper,[24] the ACOG guidelines,[29] and Krieger et al.[31]

seen at a clinic for sexually transmitted diseases found that self-treatment of the symptoms listed on the package insert of an over-the-counter medication for candidiasis would correctly treat only 28% of the patients; 53% had bacterial vaginosis, infection with *T. vaginalis*, gonorrhea, or chlamydia.[5] In another study involving women purchasing over-the-counter antifungal therapy,

only 34% had vulvovaginal candidiasis and no other vaginal infection.[28] If a patient chooses self-treatment, she should be advised to come in for examination if the symptoms are not eliminated with one course of over-the-counter therapy.

Complicated vulvovaginal candidiasis refers to infection in women who are pregnant, immunocompromised, or debilitated or who have uncontrolled diabetes, severe symptoms, infection with candida species other than *C. albicans,* or recurrent episodes (four or more in 1 year). In pregnancy, treatment for 7 to 14 days with topical azoles is recommended, and oral agents should be avoided. In a randomized, placebo-controlled trial involving women with severe vulvovaginal candidiasis, a second dose of fluconazole (150 mg) given 72 hours after the first increased the cure rate from 67 to 80%.[38] A randomized, controlled trial of women with recurrent candidal vulvovaginitis demonstrated that, after a 10-day course of oral fluconazole (150 mg) daily, 90% of women remained symptom-free during a 6-month suppressive course of weekly fluconazole (150 mg), and symptomatic episodes were reduced by 50% during the subsequent 6 months in these women as compared with those randomly assigned to a placebo for suppression.[39]

Infections with candida species other than *C. albicans* are often azole-resistant; however, one study of terconazole for non–*C. albicans* fungal vaginitis resulted in a mycologic cure in 56% of patients and a symptomatic cure in 44%.[40] A trial in which women used vaginal boric acid capsules (600 mg) daily for a minimum of 14 days resulted in a symptomatic cure rate of 75% for those with non–*C. albicans* infections.[23]

Trichomoniasis

Oral nitroimidazole therapy is recommended for infection with *T. vaginalis.* A randomized trial comparing a single orally administered dose of metronidazole (2 g) and tinidazole (2 g) indicated that tinidazole is equivalent or superior to metronidazole, resulting in cure rates of 90 to 95%.[41] The prevalence of low-level resistance to metronidazole in patients with infection with *T. vaginalis* is 2 to 5%; in case series, prolonged treatment with higher doses of metronidazole and tinidazole has been successful. Because *T. vaginalis* is sexually transmitted, treatment of the patient's partner is important and increases cure rates.

AREAS OF UNCERTAINTY

Oral or vaginal lactobacilli are often used as alternatives to treat vulvovaginal symptoms, but studies in women with bacterial vaginosis or candida vulvovaginitis have not provided evidence of their efficacy.[42]

It remains controversial whether screening and treating asymptomatic pregnant women for bacterial vaginosis are routinely warranted. Three of four placebo-controlled trials involving women at increased risk for preterm delivery demonstrated a reduction in this outcome after treatment with oral or vaginal clindamycin[43-45]; trials involving the use of oral or vaginal clindamycin in the first trimester or early in the second trimester in low-risk women have also shown lower rates of preterm birth, spontaneous abortion, and postpartum infection.[46-48] One trial involving women at low risk who were treated late in the second trimester or in the third trimester of pregnancy with oral metronidazole (2 g, repeated 48 hours later and then followed by two 2-g doses repeated 14 days later) failed to demonstrate an improvement in pregnancy outcome.[49] The Centers for Disease Control and Prevention (CDC) does not routinely recommend screening and treating pregnant women who are at low risk for asymptomatic bacterial vaginosis. Available evidence does not support the use of screening for trichomoniasis during pregnancy; in one randomized trial, asymptomatic pregnant women treated with oral metronidazole (the same regimen as in the trial above) late in the second trimester or in the third trimester had more preterm deliveries than those receiving a placebo.[50]

GUIDELINES

The CDC has issued guidelines for the treatment of acute vaginitis (Table 3).[37] The recommendations presented here are consistent with those guidelines.

CONCLUSIONS AND RECOMMENDATIONS

In a patient such as the one described in the vignette, likely causes of the symptoms include bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis. Further history, including the characteristics of the discharge, should be ob-

Table 3. Treatment Recommendations for Acute Vaginitis.*

Disease	Drug	Dose	Cost†
Bacterial vaginosis‡	Metronidazole (Flagyl)	500 mg orally twice a day for 7 days§	$
	0.75% Metronidazole gel (Metrogel)	One 5-g application intravaginally daily for 5 days¶	$$$
	2% Clindamycin cream (Cleocin vaginal)	One 5-g application intravaginally every night for 7 days	$$$
	2% Extended-release clindamycin cream (Clindesse)‖	One application intravaginally¶	$$
	Clindamycin**	300 mg orally twice daily for 7 days	$$$
Vulvovaginal candidiasis, uncomplicated			
Intravaginal therapy¶	2% Butoconazole cream (Mycelex-3)	5 g per day for 3 days††	$$
	2% Sustained-release butoconazole cream (Gynazole)	One 5-g dose	$$$
	1% Clotrimazole cream (Mycelex-7)	5 g for 7–14 days††	$
	Clotrimazole (Gyne-Lotrimin 3)	Two 100-mg vaginal tablets per day for 3 days	$
		One 100-mg vaginal tablet per day for 7 days	$
	2% Miconazole cream	5 g per day for 7 days††	$$
	Miconazole (Monistat-7)	One 100-mg vaginal suppository per day for 7 days††	$$
	Miconazole (Monistat-3)	One 200-mg vaginal suppository per day for 3 days††	$$
	Miconazole (Monistat-1 vaginal ovule)	One 1200-mg vaginal suppository††	$
	6.5% Tioconazole ointment (Monistat 1-day)	One 5-g dose††	$
	0.4% Terconazole cream (Terazol 7)	5 g per day for 7 days	$$$
	0.8% Terconazole cream (Terazol 3)	5 g per day for 3 days	$$
	Terconazole vaginal	One 80-mg vaginal suppository per day for 3 days	$$$
	Nystatin vaginal	One 100,000-U vaginal tablet per day for 14 days	$$$
Oral therapy	Fluconazole (Diflucan)	One 150-mg dose orally	$
Vulvovaginal candidiasis, complicated‡‡			
Intravaginal therapy¶	Azole	7–14 days	$$
Oral therapy§§	Fluconazole (Diflucan)	Two 150-mg doses orally 72 hr apart	$$$
Trichomoniasis	Metronidazole (Flagyl)	One 2-g dose orally	$
		500 mg orally twice daily for 7 days	$
	Tinidazole (Tindamax)	One 2-g dose orally¶¶	$$

* Recommendations are based on the CDC 2006 Guidelines for Treatment of Vaginitis.[37]
† A single dollar sign indicates a cost of less than $15, two dollar signs a cost of $15 to $29, and three dollar signs a cost of $30 or more.
‡ Oral therapy is recommended for pregnant women.
§ Drug may cause gastrointestinal upset in 5 to 10% of patients; a disulfuram reaction is possible; alcohol should be avoided for 24 hours after ingestion. In the absence of a clear indication for a particular type of therapy (e.g., for women who are pregnant), the patient's preference, the response to prior therapy, and cost should guide the choice of therapy.
¶ Vaginal treatments cause local vaginal irritation in 2 to 5% of patients.
‖ This agent is approved by the Food and Drug Administration but is not listed in the CDC 2006 Guidelines.[37]
** This agent is listed as an alternative treatment in the CDC 2006 Guidelines.[37]
†† This agent is available over the counter.
‡‡ Complicated vulvovaginitis refers to disease in women who are pregnant, women who have uncontrolled diabetes, women who are immunocompromised, or women who have severe symptoms, non–*Candida albicans* candidiasis, or recurrent episodes (four or more per year).
§§ Oral therapy is not recommended for pregnant women.
¶¶ Drug may cause gastrointestinal upset in 2 to 5% of patients; disulfuram reaction is possible; alcohol should be avoided for 72 hours after ingestion.

tained, but such information cannot be relied on for a definitive diagnosis. Pelvic examination should be performed, with a determination of the vaginal pH; a normal pH is inconsistent with the presence of bacterial vaginosis or trichomoniasis. Microscopical evaluation is often diagnostic. (Point-of-care tests are an alternative, especially if microscopical examination is not available.) In a patient who has findings consistent with the presence of candidiasis, mild-to-moderate symptoms, no complicating coexisting illnesses, and no history of frequent recurrences, I would recommend a short course of an over-the-counter topical antifungal agent or a single dose of fluconazole (150 mg). If the findings were consistent with the presence of bacterial vaginosis, I would recommend topical clindamycin cream or metronidazole vaginal gel; oral therapy with either agent is a possible alternative. For trichomoniasis, oral azole therapy is warranted, and treatment of the patient's partner is required. If the patient prefers not to be seen in the clinic, a course of over-the-counter treatment for vulvovaginal candidiasis could be tried, but the patient should be seen if her symptoms do not resolve with this therapy.

No potential conflict of interest relevant to this article was reported.

A video showing motile trichomonads is available with the full text of this article at www.nejm.org.

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