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Infect Dis Clin N Am
22 (2008) 637–652

INFECTIOUS
DISEASE CLINICS
OF NORTH AMERICA

Vulvovaginal Candidiasis and Bacterial Vaginosis

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For clinicians involved in women's health, vaginitis is a commonly encountered complaint and one of the most frequent reasons for patient visits to obstetrician-gynecologists [1]. Of the many causes of vaginal infections, bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC) are believed the two most common, accounting for an estimated 22% to 50% and 17% to 39% of symptomatic women, respectively [2]. Although vulvovaginal complaints, such as itching, burning, abnormal discharge, and odor, frequently may be trivialized or ignored, vaginitis has significant associated direct and indirect health care costs. In the case of VVC alone, an estimated $275 million is spent annually on over-the-counter (OTC) antifungal drugs, and they number in the top 10 of all OTC medications sold in the United States [3]. Taking into account the associated costs of VVC, such as medical and treatment expenses, travel costs, and time missed from work, Foxman and colleagues [4] estimate that the total annual cost for VVC in the United States in 1995 was $1.8 billion. In the past, BV was considered a minor nuisance infection, BV has assumed more importance as epidemiologic studies have associated it with a broad array of infectious morbidities of the female genital tract, including increased susceptibility to sexually transmitted infections, including HIV and genital herpes, and its association with adverse pregnancy outcome, in particular preterm birth.

Despite the importance of VVC and BV as common infections with significant costs and morbidities, these conditions frequently are trivialized

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The author has the following financial disclosures: KV Pharmaceuticals/Ther-Rx, consultant and speaker support; Mission Pharmacal, consultant and speaker support; and Personal Products Worldwide, consultant.

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0891-5520/08/$ - see front matter
doi:10.1016/j.idc.2008.05.002 *id.theclinics.com*

by the lay and medical communities and as a result frequently are misdiagnosed. When antifungal drugs became available for OTC use, investigators described possible benefits for afflicted women, including convenience, ability to initiate therapy rapidly, patient empowerment, and potential health care cost savings, estimated at $63.8 million from 1990 to 1994 alone [1]. Data show, however, that as few as 11% of women who have no and 34.5% of women who have a prior diagnosis of VVC can accurately recognize the classic scenario for VVC [5]. Furthermore, in a prospective study of symptomatic women about to purchase an OTC antifungal product [6], only 34% had pure VVC. Only 95 women in this study were enrolled over 2 years and patient recruitment was described as "extremely difficult." Thus, although self-diagnosis and self-treatment of vaginal infections are inaccurate in many women, most women are eager to avoid an office evaluation for vaginitis and are more than happy to self-treat.

Of equal concern, women who have vaginitis often may undergo an inadequate evaluation. Vaginitis frequently is managed by the telephone, which offers many of the advantages of self-diagnosis, with the added benefit that patients get a validation by a clinician that they do have VVC. The agreement between telephone and actual diagnosis, however, is poor [7]. Of even greater concern, when women do make the effort to be evaluated in the office by a provider, they often undergo an inadequate work-up with little use of vaginal pH testing and no or inaccurate use of a microscope to diagnose their infection [8,9].

From a practical point of view, these data indicate that clinicians always should view a prior history of vaginal infections with skepticism. Patients can describe their symptoms and response to a variety of treatments accurately, but their perceptions about what causes those symptoms may be inaccurate. Particularly with those who have a history of chronic or recurrent infections, the most important step is to ensure that the diagnosis is the correct one. Furthermore, for chronic patients, the differential diagnosis may encompass not only VVC and BV but also a wide array of vulvar and vaginal disorders [10].

Vulvovaginal candidiasis

Women who harbor *Candida* organisms in their vaginas have VVC, which has a spectrum of manifestations ranging from asymptomatic colonization to severe acute symptomatic infection [11]. Yeast colonization occurs relatively frequently, with up to 30% of healthy asymptomatic women having a positive culture for yeast at any single point of time and up to 70% if followed longitudinally over a 1-year period [12]. Some symptomatic women who have VVC may have an occasional sporadic episode, whereas others may have frequent or severe symptoms. Certain patients may develop primarily vulvar instead of vaginal manifestations of VVC. Because of the broad range of affected women, VVC now is categorized as uncomplicated

or complicated disease (Box 1) [13]. It is estimated that 80% to 90% of women who have symptomatic VVC have uncomplicated disease. In women who have complicated candidiasis, host or microbial factors distinguish the infection from an uncomplicated one; these factors have a profound impact on therapeutic outcome.

Microbiology of vulvovaginal candidiasis

C albicans is responsible for the vast majority of symptomatic episodes of VVC [11]. Of the non-*albicans* yeast species, *C glabrata* is considered the most common [14–16]. Because vaginal yeast cultures are not done routinely in the management of uncomplicated VVC, however, the relative contribution of other species of yeast to the burden of VVC is difficult to measure. In a review of vaginal yeast isolates obtained by polymerase chain reaction (PCR) from 1316 women across the United States, *C albicans* accounted for 80.2% of the positives, *C glabrata* 14.3%, *C parapsilosis* 5.9%, and *C tropicalis* 8.0% [17], but these numbers may have been affected by provider bias. Other less frequent causes of VVC include *C krusei* [18], *C lusitaniae*, and *Saccharomyces cerevisiae* [19].

Pathogenesis and risk factors for vulvovaginal candidiasis

With complicated and uncomplicated VVC, there are two elements that are important in the development of a symptomatic episode. The first consists of vaginal colonization by *Candida* species, followed in turn by the

Box 1. Classification of vulvovaginal candidiasis

Uncomplicated
- Sporadic or infrequent episodes *AND*
- Mild to moderate symptoms or findings *AND*
- Suspected *C albicans* infection *AND*
- Normal, nonpregnant woman

Complicated
- Recurrent (≥4 per year) episodes *OR*
- Severe symptoms or findings *OR*
- Suspected or proven non-*albicans Candida* infection *OR*
- Abnormal host (diabetes, severe medical illness, immunosuppression, other vulvovaginal conditions, or pregnancy)

Data from Centers for Disease Control and Prevention, Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. MMWR Recomm Rep 2006 4;55(RR-11):54.

transformation from the asymptomatic state to a symptomatic infection. *Candida* enters the vagina through any of several different sources, including local spread from the perineum and gastrointestinal (GI) tract, digital introduction, and sexual transmission. Estrogen is believed crucial in the maintenance of colonization [20]. Whatever the mechanism of entry, colonization is a common event. Once it occurs in women who have recurrent VVC (RVVC), colonization may be the result of a persisting single strain of *Candida* or introduction of new strains of *C albicans* or other species [21].

Epidemiologic data suggest that, by age 25, half of all college women experience at least one episode of VVC and that an important risk factor is the initiation of sexual activity [22]. Among college women, VVC is more common among African American women than white women [22]. A variety of other factors is important in the development of VVC and RVVC. Familiar factors include diabetes, antibiotic and estrogen use, immunosuppression, and behavioral factors. Diabetic patients are less likely to respond to antimycotic therapy [14], and they may be more prone to developing infections caused by *C glabrata* [23]. Some women who have RVVC exhibit an impaired tolerance for glucose despite having a similar incidence of overt or preclinical diabetes than controls [24]. Recent antibiotic use is reported by some women as a predictable precipitating factor for isolated and RVVC [25], but it is believed that these symptomatic episodes occur primarily in women in whom colonization preceded the course of antibiotics [26]. Although anecdotal experience suggests that estrogen may play a role in the pathogenesis of VVC, epidemiologic data are conflicting and their causal role is controversial [27]. In a few women, RVVC may be the result of systemic immunodeficiency caused by illness or systemic therapy with corticosteroids or similar drugs. In HIV-infected women, vaginal colonization with *Candida* is substantially increased, but the frequency of RVVC is increased only modestly, with attack rates of VVC significantly lower than oropharyngeal candidiasis [28]. In clinical practice, immunosuppression seems to be a rare cause of VVC, and a work-up for an underlying illness is indicated only if other elements in a patient's history or examination suggest a need for it.

A variety of behavioral factors is proposed as a cause of VVC and RVVC. Sexual factors, in particular orogenital sex [22], may contribute to the introduction of microorganisms or may facilitate symptomatic disease because of microtrauma to the vulva and the vestibule. Although sexual intercourse alone may not be associated with increased *Candida* colonization [29], contraceptive practices may contribute to VVC; oral contraceptives [30], use of a diaphragm and spermicide [29], and the use of an intrauterine device [30] all are associated with an increased risk for infection. Spinillo and colleagues have identified douching as a risk factor in women who have RVVC caused by *C glabrata* [31].

In approximately half of women who have RVVC, no risk factors for VVC can be identified. Although women who have RVVC have increased *Candida* colonization rates [32], it is not known whether or not this enhanced colonization is vagina specific or occurs elsewhere, such as in the GI tract. In some cases, colonization may be explained by genetic predispositions, such as being nonsecretors of Lewis antigens, glycoproteins that potentially may inhibit the binding of *Candida* to vaginal mucosa [33]. Depressed or reduced protective local immunoregulatory mechanisms and cytokine elaboration, some mediated by certain genetic polymorphisms [34], may result in increased susceptibility to RVVC. Alternatively, other investigators have found that symptomatic VVC may be the result of an abnormal heightened or increased sensitivity to yeast [35]. The findings that vaginal epithelial cells collected from healthy women exhibit anti-*Candida* activity in vitro and that such activity is reduced in cells of women who have RVVC suggest that yet other innate host factors play a role in preventing yeast infections [36].

Presentation and diagnosis of vulvovaginal candidiasis

The clinical symptoms of VVC are nonspecific, and clinicians should keep in mind that a broad variety of infectious and noninfectious diseases can cause similar symptoms. Contrary to common perception, many women who have VVC do not notice any change in their vaginal secretions. Vulvovaginal itching, irritation, soreness, burning, or dyspareunia are the more common symptoms of VVC [2]. Occasionally, VVC causes external dysuria because of the burning that occurs when urine hits inflamed vulvar tissues [37]. On vulvar examination, patients may exhibit redness, swelling, fissures, or excoriations, and vaginal signs of erythema or a thick curdy discharge may be found [37].

Women who have vaginal symptoms should undergo standard office testing, consisting of vaginal pH measurement, amine or whiff test, saline, and 10% potassium hydroxide microscopy. Although vaginal pH generally is not affected by VVC and remains less than 4.5 in premenopausal women, the finding of a normal pH helps to exclude BV, trichomoniasis, atrophic vaginitis, or some sort of mixed infection. With saline microscopy, examiners should look closely for blastospores or pseudohyphae. The background vaginal flora may appear otherwise normal or somewhat decreased, and white blood cells generally are absent. The addition of 10% potassium hydroxide solution to patient specimens makes it easier to visualize fungal elements.

Microscopy is the mainstay in the diagnosis of VVC, yet studies show that microscopy has a sensitivity of at best 50% and misses a substantial percentage of women who have symptomatic VVC [15,38]. Given the limitations of standard office tests, yeast cultures should be obtained in women who describe the correct symptoms for VVC and in whom office tests are

negative. Furthermore, in women who have complicated VVC, cultures with speciation of the organism can guide the choice of antifungal therapy. Although PCR testing for yeast is commercially available [17], its usefulness is limited by the need to obtain PCR for the full spectrum of organisms that can cause VVC and the added expense relative to culture. Finally, although a positive yeast culture may represent a woman who is asymptomatically colonized, a positive culture in the setting of vulvovaginal symptoms yields the correct diagnosis in approximately 90% of women [15]; conversely, some women who have vulvovaginal symptoms and a positive yeast culture may find, once the yeast is eradicated, that the yeast was an innocent bystander and their symptoms are due to some other problem.

Treatment of vulvovaginal candidiasis

An episode of VVC should be categorized as complicated or uncomplicated (see Box 1). For patients who have uncomplicated VVC, the broad range of available therapies is summarized in Table 1. Current choices are for the most part limited to azole medications, fungistatic drugs that inhibit cell wall metabolism. Azoles are available as topical (creams or suppositories) or oral therapy, vary from 1 to 7 days of treatment, and can be obtained with or without a prescription. Some of the short courses achieve effectiveness by increasing the dose of the drug (eg, miconazole and tioconazole), whereas others do so by maintaining therapeutic drug levels over 4 or 5 days (eg, single-dose butoconazole cream or oral fluconazole). The practical implications of these differences in formulation remain unclear.

Table 1
Therapy for uncomplicated vulvovaginal candidiasis

Drug	Formulation	Dose	Duration	Prescription status
Butoconazole	2% single dose cream	5 g daily	1 day	Prescription
	2% cream	5 g daily	3 days	OTC
Clotrimazole	1% cream	5 g daily	7 days	OTC
	2% cream	5 g daily	3 days	OTC
	100 mg vaginal suppository	100 mg daily	7 days	OTC
	200 mg vaginal suppository	200 mg daily	3 days	OTC
	500 mg vaginal suppository	500 mg daily	1 day	Prescription
Fluconazole	150 mg oral tablet	150 mg daily	1 day	Prescription
Miconazole	2% cream	5 g daily	7 days	OTC
	4% cream	5 g daily	3 days	OTC
	100 mg vaginal suppository	100 mg daily	7 days	OTC
	200 mg vaginal suppository	200 mg daily	3 days	OTC
	1200 mg vaginal suppository	1200 mg daily	1 day	OTC
Terconazole	0.4% cream	5 g daily	7 days	Prescription
	0.8% cream	5 g daily	3 days	Prescription
	80 mg vaginal suppository	80 mg daily	3 days	Prescription
Tioconazole	6.5% cream	5 g daily	1 day	OTC

In terms of therapeutic efficacy, most commonly defined as clinical cure (resolution of signs and symptoms) and mycologic cure (negative follow-up fungal culture), women who have uncomplicated VVC have cure rates of 80% to 90% with the treatment regimens listed in Table 1. Topical therapy causes local burning in 5% to 10% of patients and tends to be messier. With the advent of ketoconazole, oral therapy has been available for more than 20 years. Because of liver toxicity with ketoconazole, widespread use of oral therapy occurred only after the approval of fluconazole, which for the most part has mild self-limited side effects of GI intolerance and headache. More serious adverse events, primarily rash and liver toxicity, occur rarely. In terms of efficacy, a review of 19 randomized controlled trials found that oral and topical therapies have similar short- and long-term clinical cure rates and short-term mycologic cure rates [39]. Although the reviewers noted a marginally superior long-term mycologic cure rates (odds ratio 1.29; 95% CI, 1.05 to 1.60) with oral therapy, the significance of this finding is unclear. Oral therapy may be associated with a slightly slower improvement in symptoms [40]. Because fluconazole is a category C drug in pregnancy, most clinicians treat pregnant patients with topical therapy to limit the amount of drug exposure. Because the success rate with the treatment of uncomplicated VVC is so high, lack of response implies an incorrect diagnosis. Therefore, persistent symptoms mandate a re-evaluation, which should include a vaginal yeast culture.

Women have complicated VVC for microbial or host factors. Regardless of the reason, women who have complicated VVC exhibit a poorer response to standard courses of antifungal therapy and require more aggressive therapy. This concept has been validated in several prospective randomized studies, which consistently show that the criteria for complicated disease in Box 1 are indicators of treatment failure [14,41]. Categories of complicated VVC and recommendations for therapy are discussed later.

Severe vulvovaginal candidiasis

In most studies of VVC, the severity of the infection is not addressed as a predictor of outcome. When measured, however, patients who have a severe episode are consistently less likely to respond to standard antifungal therapy [14,41]. In a prospective study of 556 women who had severe or RVVC randomly assigned to a single-dose or a two-dose (every 3 days) regimen of oral fluconazole (150 mg), the two-dose treatment group had significantly higher clinical cure rates on day 14 (94 versus 85%) and day 35 (80 versus 67%) ($P < .05$) [14]. Therefore, patients who have severe symptoms or extensive findings should receive a longer course of therapy. In patients who prefer topical therapy, it seems reasonable to recommend at least 7 to 14 days treatment.

Recurrent vulvovaginal candidiasis

RVVC is defined as four or more episodes of VVC in the preceding year, with at least one of these episodes well documented with culture [13]; most

cultures are positive for *C albicans*. Seventy percent of women who have RVVC who receive a conventional course of treatment with an antifungal agent can expect to have another episode within 6 months [42]. For the most part, self-treatment of repeated episodes permits rapid initiation of antimycotic therapy, but it does little to prevent the next attack. The most effective approach to treatment, particularly with *C albicans* infections, seems to be maintenance antifungal therapy. Treatment options, which have been studied and shown to be effective, include ketoconazole (100 mg orally daily) [42], clotrimazole (500 mg suppositories weekly) [43], and fluconazole (150 mg orally once weekly) [16]. Because of liver toxicity associated with use of ketoconazole, the latter two agents, especially fluconazole, are now preferred as maintenance regimens.

In the case of fluconazole, an induction phase of three doses of fluconazole (150 mg given every 3 days) is followed by a maintenance regimen of fluconazole (150 mg once a week). In a randomized study of 6 months of weekly fluconazole, 9% of the fluconazole compared with 64% of the placebo group suffered a relapse of their infection [16]. None of the women stopped treatment because of adverse events. For women unable to take fluconazole, less extensive experience with repeated dosing of topical azoles suggests that it also is effective. Although maintenance therapy serves to control and in many cases prevent future symptomatic episodes, the finding that 57% of disease-free women in the fluconazole study recurred within the next 6 months underscores the limitations of current treatment options. For women who do have recurrences, even longer courses of maintenance therapy (eg, 1 year) may be required to suppress their infections. Controlled studies to date have failed to demonstrate a benefit to treating a partner [44]. Other approaches, such as hormonal manipulation with depot medroxyprogesterone [45], use of yogurt [46], lactobacillus therapy [47], desensitization to *Candida* antigen [48], and a low carbohydrate diet lack sufficient data to support recommendation of their use.

Non-albicans Candida *infections*

Although clinical and in vitro resistance to *C albicans* fortunately is rare, non-*albicans Candida* species are less likely to respond to azole antifungal therapy [14,18,49]. Vaginal boric acid (600 mg), administered daily in a gelatin capsule for 14 days, cures up to 70% of *C glabrata* infections [50]. It is inexpensive and well tolerated, with the most common side effects local irritation and a change in the vaginal discharge. Topical flucytosine, compounded as a 15.5% vaginal cream and administered as 5 g daily for 14 days, is described for resistant *C tropicalis* infections [51] and shown to eradicate the majority of *C glabrata* infections that fail to respond to boric acid [50]. Finally, limited experience with topical amphotericin B, as stand-alone therapy in 50-mg suppository form [52] or in combination with flucytosine as a cream [53], both for 14 days, offers other options for *C glabrata* infections.

Bacterial vaginosis

Although BV in the past frequently has been ignored, it is considered the most common form of vaginitis and affects approximately 30% of women [54]. Because most women who have BV exhibit no or minor symptoms, there is a tendency to overlook this condition. Sociodemographic factors associated with BV include younger age, being non-Hispanic black or Mexican American, having less than a high school education, living at or near the federal poverty level, and douching [54]. Sexual risk factors, such as being sexually active, age of first sexual intercourse, and having multiple male lifetime sexual partners, particularly over the past year, all are risk factors for BV [54]. In lesbian women, female partners of women who have BV have a higher incidence of BV [55]. Despite the sexual risk factors associated with BV, however, BV is considered sexually associated but not sexually transmitted [56].

In the past 20 years, BV has been found to be a risk factor for a broad range of infectious morbidities in women, and this infection has rightfully gained increasing attention. In nonpregnant women, BV is associated with many disorders of the female reproductive tract, including urinary tract infections, increased risk for infection after gynecologic surgery, cervicitis, pelvic inflammatory disease, and an increased susceptibility to HIV and gonococcal, chlamydial, trichomonal, and genital herpes infections [57–61]. In pregnant women, BV is associated with spontaneous abortion, preterm birth, and postpartum endometritis [13,62].

Presentation and diagnosis of bacterial vaginosis

Patients who have BV, when symptomatic, complain mainly of an abnormal vaginal discharge and a fishy odor. An estimated 50% of women who have BV, however, are asymptomatic. On examination, few if any signs of vulvovaginal erythema are found. The most prominent finding may be an abnormal watery gray discharge. BV is diagnosed by finding three of four Amsel's criteria: abnormal discharge, vaginal pH greater than 4.5, positive amine test, and more than 20% of the epithelial cells being clue cells. Culture has no role to play in diagnosing this condition, but vaginal Gram's stain, the Nugent score [63], is considered the gold standard. A maximum score of 10 is obtained when no gram-positive rods (representing lactobacilli—4 points), many gram-negative or variable rods (*G vaginalis* and anaerobic species—4 points), and many curved gram-variable rods (*Mobiluncus* morphotypes—2 points) are found; scores of 7 or higher are considered consistent with BV. Compared with the gold standard, Nugent scoring by vaginal Gram's stain, Amsel's criteria have a sensitivity of 92% [64].

Microbiology of bacterial vaginosis

BV is a polymicrobial infection, a disturbance in the normal vaginal microflora marked by a lack of the normal hydrogen peroxide producing

lactobacilli and an overgrowth of primarily anaerobic organisms. The vaginal microbial ecosystem itself, however, is in a constant state of flux that remains poorly understood. Schwebke and colleagues [65] evaluated Gram's stains in healthy women over a 6-week period and found significant, but transient, fluctuations in vaginal flora. Only 22% of the 51 patients maintained consistently normal Gram's stains during the study period, and many women had changes consistent with BV, which resolved without treatment. A broad array of variables encountered by most women on a frequent basis affected vaginal flora: menses, sexual activity, spermicide use, vaginal intercourse, and nonuse of condoms. The factors that may lead one woman to develop true BV as opposed to a transient change in vaginal flora that resolves on its own remain unknown.

When Gardner and Dukes [66] published their landmark study of BV, they described a new organism, eventually named *Gardnerella vaginalis*, and attempted to show that it fulfilled Koch's postulates. As the years passed and anaerobic culture techniques were used to learn more about this infection, this condition became regarded primarily as an anaerobic one, where *G vaginalis* and the genital mycoplasmas were cofactors, but where a broad range of other bacteria, including *Bacteroides* spp, *Peptostreptococcus* spp, *Fusobacterium* spp, *Prevotella* spp, and *Mobiluncus* spp played an important role [67]. In the past few years, with the advent of molecular microbiologic techniques, such as 16S rDNA PCR, understanding of the microbiology of BV has continued to expand, and it is now accepted that a wide variety of other uncultured organisms, including *Atopobium vaginae*, BV-associated bacteria (BVAB) 1, BVAB 2, BVAB 3, *Megasphera* spp, *Eggerthella* spp, and *Leptotrichia* spp. Several excellent articles summarize the most recent findings on the vaginal flora associated with BV [68,69].

As discussed previously, Gram's stain remains the gold standard for diagnosing BV in research studies and it permits evaluation of subgroups of women who have BV. These studies indicate that not all forms of BV are the same, and that women who have more severe abnormalities on Gram's stain are more likely to have other morbidities. For example, in a study of more than 6800 pregnant women, Hauth and colleagues [70] found that those who had a Nugent score of 9 or 10 were at greater risk for preterm birth than women who had BV and had a lower Nugent score and women who did not have BV by Nugent criteria. Pereira and colleagues [71] reported significant variations in microflora of pregnant women with BV and found that pregnant women with BV who had *Mobiluncus* morphotypes on Gram's stain tended to be older, non-Hispanic black, to have more lifetime sexual partners compared with women who had BV, and to be given a clinical diagnosis of BV by their health care providers than those who did not have *Mobiluncus* on Gram's stain. These different subgroups of BV also exhibit variability in measures of local vaginal cytokine levels [72].

Treatment of bacterial vaginosis

Table 2 summarizes the various therapies available for BV. In general, providers can think of treatment as topical or oral. In general, the least expensive therapy is generic oral metronidazole, but it may cause significant GI intolerance [73]. Newly approved, tinidazole causes less nausea and anorexia than metronidazole, particularly with the 5-day regimen [74], but has the same potential for disulfiram-like reactions as metronidazole. Both drugs should be used with caution in patients on warfarin or lithium. Topical therapy has the advantage of avoiding systemic side effects, such as GI intolerance, which is particularly common with metronidazole. Although clindamycin use may be associated with in vitro antimicrobial resistance [57], the listed alternatives seem to have comparable clinical efficacy and safety [13]. As with the treatment of VVC, treatment of BV should be individualized to patients after considering multiple clinical factors.

The current consensus is that all treatments of BV provide equivalent efficacy and can be distinguished from each other on the basis of cost, mode of administration, and adverse events. There are emerging data to suggest, however, that different subgroups of BV may vary in their response to antibiotics. Nyirjesy and colleagues [75] performed a retrospective analysis of women who had BV who were enrolled in three different clinical trials who had received metronidazole gel or single-dose clindamycin cream. In women who had *Mobiluncus* morphotypes on pretherapy Gram's stain, they found a lower *Mobiluncus* score at the test-of-cure visit in the group who received the clindamycin therapy ($P = .047$); more significantly, the cure rates by clinical and Gram's stain criteria were higher in the clindamycin group ($P = .04$). These differences did not occur in women who did not have *Mobiluncus* morphotypes on baseline Gram's stain. It is unknown whether or not these differences are particular to *Mobiluncus* species themselves or whether or not these morphotypes are markers for uncultivated bacterial species. Further studies are warranted to confirm and expand on these initial findings.

Table 2
Therapy for bacterial vaginosis

Oral	
Metronidazole	500 mg twice daily for 7 days
Tinidazole	1 g daily for 5 days
	2 gm daily for 2 days
Clindamycin	300 mg twice daily for 7 days[a]
Topical	
Clindamycin	2% cream, 5 g daily for 7 days
	2% single dose cream, 5 g daily for 1 day
	100 mg ovules daily for 3 days
Metronidazole	0.75% gel, 5 g daily for 5 days

[a] Seldom used in clinical practice.

In pregnancy, the two main issues are the role of treatment of BV in pregnancy, and, just as importantly, whether or not BV treatment in pregnancy affects other problems, such as preterm birth. Despite earlier concerns, neither clindamycin nor metronidazole has known teratogenic effects [76]; data on use of tinidazole in pregnancy are lacking. In later pregnancy, use of clindamycin is discouraged because of a possible increase in low-birth-weight infants and neonatal infections [13]. BV is associated with a 1.5-fold to 3-fold increase in preterm birth [62]. The mechanism of action most likely is related to infection that ascends into the uterus and later causes labor, rupture of membranes, and birth. It is less clear, however, if treatment of BV has any material impact on this increased risk, and the issue of treatment remains controversial. As reviewed recently by Iams and colleagues [77], there may be evidence to suggest a benefit to treating with clindamycin before 20 weeks' gestation in pregnancy.

Recurrent bacterial vaginosis

After treatment of BV, recurrence may occur in up to 30% of women within 3 months [78]. Several studies from an Australian cohort of women have shed further light on the issue of recurrence [79,80]. After a 7-day course of therapy with oral metronidazole, Bradshaw and colleagues [79] followed a group of 130 women. By 12 months, 58% had at least one recurrence of BV. Risk factors associated with recurrence were a prior history of BV, having a regular sex partner throughout the study, or having a female sex partner. Inconsistent condom use was not associated with recurrence, and hormonal contraception had a protective effect. In a molecular analysis of uncultivated organisms, these investigators found that women in whom *Atopobium vaginae* and *G vaginalis* were present initially had a much higher rate of recurrence at 1 year than those in whom *G vaginalis* alone was present (83% versus 38%, $P < .001$) [80].

These data, along with others, suggest that recurrence of BV may be the result of persistence of pathogenic bacteria or re-infection from exogenous sources, including a sexual partner. Potentially, recurrence also could be the result of a failure of the normal lactobacillus-dominant flora to re-establish itself. These theories suggest a variety of potential treatment interventions to prevent recurrence. To date, treatment of partner studies and recolonization with lactobacillus supplements generally show no benefit [78]. One study in Peru, which compared metronidazole gel to ovules containing 500 mg of metronidazole with nystatin (100,000 units), found a lower recurrence rate (52% versus 33%, $P = .01$) at 104 days with the ovule treatment [81]. Although this study may indicate that a higher dose of metronidazole eradicated persistent pathogens more effectively, study limitations and the concomitant use of nystatin may be important confounding factors. Maintenance antibiotic therapy, in the form of metronidazole gel twice weekly after an initial 10-day course of therapy, may

represent a promising avenue for treating women whoh ave recurrent BV, as it worked better than placebo (70% versus 39%) in a placebo-controlled double-blind randomized study [82]. The relatively high (an additional 27%) recurrence rate within 3 months of stopping therapy and the high rate of VVC as a complication of prolonged antibiotic therapy, however, demonstrate the great need for more effective therapy for BV.

Summary

VVC and BV represent common infections that frequently are trivialized and misdiagnosed. There remains a clear need for better diagnostic modalities not only in terms of home testing for patients who self-diagnose and -treat but also for health care providers. Although treatment of uncomplicated cases is straightforward and associated with high cure rates, issues of recurrence and resistance continue to plague many women. As understanding of pathophysiology for both conditions continues to move forward, better approaches to therapy hopefully will be available to more chronic patients in the near future.

References

[1] Lipsky MS, Waters T, Sharp LK. Impact of vaginal antifungal products on utilization of health care services: evidence from physician visits. J Am Board Fam Pract 2000;13:178–82.
[2] Anderson MR, Klink K, Cohrssen A. Evaluation of vaginal complaints. JAMA 2004;291: 1368–79.
[3] Marrazzo JM. Vulvovaginal candidiasis. BMJ 2003;326:993–4.
[4] Foxman B, Barlow R, D'Arcy H, et al. Candida vaginitis: self-reported incidence and associated costs. Sex Transm Dis 2000;27:230–5.
[5] Ferris DG, Dekle C, Litaker MS. Women's use of over-the-counter antifungal medications for gynecological symptoms. J Fam Pract 1996;42:595–600.
[6] Ferris DG, Nyirjesy P, Sobel JD, et al. Over-the-counter antifungal drug misuse associated with patient-diagnosed vulvovaginal candidiasis. Obstet Gynecol 2002;99:419–25.
[7] Allen-Davis JT, Beck A, Parker R, et al. Assessment of vulvovaginal complaints: accuracy of telephone triage and in-office diagnosis. Obstet Gynecol 2002;99:18–22.
[8] Wiesenfeld HC, Macio I. The infrequent use of office-based diagnostic tests for vaginitis. Am J Obstet Gynecol 1999;181:39–41.
[9] Ledger WJ, Polaneczky MM, Yih MC, et al. Difficulties in the diagnosis of Candida vaginitis. Infectious Diseases in Clinical Practice 2000;9:66–9.
[10] Nyirjesy P, Peyton C, Weitz MV, et al. Causes of chronic vaginitis: analysis of a prospective database of affected women. Obstet Gynecol 2006;108:1185–91.
[11] Sobel JD, Faro S, Force RW, et al. Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. Am J Obstet Gynecol 1998;178:203–11.
[12] Beigi RH, Meyn LA, Moore DM, et al. Vaginal yeast colonization in nonpregnant women: a longitudinal study. Obstet Gynecol. 2004;104:926–30.
[13] Centers for Disease Control and Prevention, Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. MMWR Recomm Rep 2006;55(RR-11):51–6.
[14] Sobel JD, Kapernick PS, Zervos M, et al. Treatment of complicated Candida vaginitis: comparison of single and sequential doses of fluconazole. Am J Obstet Gynecol 2001;185:363–9.

[15] Nyirjesy P, Seeney SM, Grody MHT, et al. Chronic fungal vaginitis: The value of cultures. Am J Obstet Gynecol 1995;173:820–3.
[16] Sobel JD, Wiesenfeld HC, Martens M, et al. Maintenance fluconazole therapy for recurrent vulvovaginal candidiasis. N Engl J Med 2004;351(9):876–83.
[17] Trama JP, Adelson ME, Raphaelli I, et al. Detection of Candida species in vaginal samples in a clinical laboratory setting. Infect Dis Obstet Gynecol 2005;13(2):63–7.
[18] Singh S, Sobel JD, Bhargava P, et al. Vaginitis due to Candida krusei: epidemiology, clinical aspects, and therapy. Clin Infect Dis 2002;35(9):1066–70.
[19] Richter SS, Galask RP, Messer SA, et al. Antifungal susceptibilities of Candida species causing vulvovaginitis and epidemiology of recurrent cases. J Clin Microbiol 2005;43(5): 2155–62.
[20] Hillier SL, Lau RJ. Vaginal microflora in postmenopausal women who have not received estrogen replacement therapy. Clin Infect Dis 1997;25(Suppl 2):S123–6.
[21] Vazquez JA, Sobel JD, Demitriou R, et al. Karyotyping of Candida albicans isolates obtained longitudinally in women with recurrent vulvovaginal candidiasis. J Infect Dis 1994;170:1566–9.
[22] Geiger AM, Foxman B. Risk factors for vulvovaginal candidiasis: a case-control study among university students. Epidemiology 1996;7:182–7.
[23] DeLeon EM, Jacober SJ, Sobel JD, et al. Prevalence and risk factors for vaginal Candida colonization in women with type I and type II diabetes. BMC Infect Dis 2002;2:1–11.
[24] Donders GG, Prenen H, Verbeke G, et al. Impaired tolerance for glucose in women with recurrent vaginal candidiasis. Am J Obstet Gynecol 2002;187:989–93.
[25] Spinillo A, Capuzzo E, Acciano S, et al. Effect of antibiotic use on the prevalence of symptomatic vulvovaginal candidiasis. Am J Obstet Gynecol 1999;180:14–7.
[26] Pirotta MV, Garland SM. Genital Candida species detected in samples from women in Melbourne, Australia, before and after treatment with antibiotics. J Clin Microbiol 2006; 44(9):3213–7.
[27] Reed BD, Gorenflo DW, Gillespie BW, et al. Sexual behaviors and other risk factors for Candida vulvovaginitis. J Womens Health Gend Based Med 2000;9:645–55.
[28] Ohmit SE, Sobel JD, Schuman P, et al. A longitudinal study of mucosal Candida colonization and candidiasis among HIV-seropositive and at-risk HIV-seronegative women. J Infect Dis 2003;188:118–27.
[29] Hooten TM, Roberts PL, Stamm WE. Effect of recent sexual activity and use of diaphragm on vaginal flora. Clin Infect Dis 1994;19:274–8.
[30] Barbone F, Austin H, Louv WC, et al. A follow-up study of methods of contraception, sexual activity, and rates of trichomoniasis, candidiasis, and bacterial vaginosis. Am J Obstet Gynecol 1990;163:510–4.
[31] Spinillo A, Capuzzo E, Egbe TO, et al. Torulopsis glabrata vaginitis. Obstet Gynecol 1995; 85:993–8.
[32] Giraldo P, von Nowaskonski A, Gomes FA, et al. Vaginal colonization by Candida in asymptomatic women with and without a history of recurrent vulvovaginal candidiasis-Obstet Gynecol 2000;95:413–6.
[33] Chaim W, Foxman B, Sobel JD. Association of recurrent vaginal candidiasis and secretory ABO and Lewis phenotype. J Infect Dis 1997;176:828–30.
[34] Giraldo PC, Babula O, Gonçalves AK, et al. Mannose-binding lectin gene polymorphism, vulvovaginal candidiasis, and bacterial vaginosis. Obstet Gynecol 2007;109(5):1123–8.
[35] Fidel PL Jr, Barousse M, Espinosa T, et al. An intravaginal live Candida challenge in humans leads to new hypotheses for the immunopathogenesis of vulvovaginal candidiasis. Infect Immun 2004;72(5):2939–46.
[36] Barousse MM, Steele C, Dunlap K, et al. Growth inhibition of Candida albicans by human vaginal epithelial cells. J Infect Dis 2001;184:1489–93.
[37] Eckert LO, Hawes SE, Stevens CE, et al. Vulvovaginal candidiasis: clinical manifestations, risk factors, management algorithm. Obstet Gynecol 1998;92:757–65.

[38] Bergman JJ, Berg AO, Schneeweis R, et al. Clinical comparison of microscopic and culture techniques in the diagnosis of Candida vaginitis. J Fam Pract 1984;18:549–52.
[39] Nurbhai M, Grimshaw J, Watson M, et al. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). Cochrane Database Syst Rev 2007 Oct 17;(4):CD002845.
[40] Seidman LS, Skokos CK. An evaluation of butoconazole nitrate 2% site release vaginal cream (Gynazole-1) compared to fluconazole 150 mg tablets (Diflucan) in the time to relief of symptoms in patients with vulvovaginal candidiasis. Infect Dis Obstet Gynecol 2005; 13(4):197–206.
[41] Sobel JD, Brooker D, Stein GE, et al. Single oral dose fluconazole compared with conventional topical therapy of Candida vaginitis. Am J Obstet Gynecol 1995;172:1263–8.
[42] Sobel JD. Recurrent vulvovaginal candidiasis: a prospective study of the efficacy of maintenance ketoconazole therapy. N Engl J Med 1986;315:1455–8.
[43] Davidon F, Mould RF. Recurrent genital candidosis in women and the effect of intermittent prophylactic treatment. Br J Vener Dis 1978;54:176–83.
[44] Fong IW. The value of treating the sexual partners of women with recurrent vaginal candidiasis with ketoconazole. Genitourin Med 1992;68:174–6.
[45] Dennerstein GJ. Depo-Provera in the treatment of recurrent vulvovaginal candidiasis. J Reprod Med 1986;31:801–3.
[46] Hilton E, Isenberg HD, Alperstein P, et al. Ingestion of yogurt containing Lactobacillus acidophilus as prophylaxis for candidal vaginitis. Ann Intern Med 1992;116(5):353–7.
[47] Pirotta M, Gunn J, Chondros P, et al. Effect of lactobacillus in preventing post-antibiotic vulvovaginal candidiasis: a randomised controlled trial. BMJ 2004;329(7465):548.
[48] Rigg D, Miller MM, Metzger WJ. Recurrent allergic vulvovaginitis; treatment with Candida albicans allergen immunotherapy. Am J Obstet Gynecol 1990;162:332–6.
[49] Sood G, Nyirjesy P, Weitz MV, et al. Terconazole cream for non-Candida albicans fungal vaginitis: results of a retrospective analysis. Infect Dis Obstet Gynecol 2000;8:240–3.
[50] Sobel JD, Chaim W, Nagappan V, et al. Treatment of vaginitis caused by Candida glabrata: use of topical boric acid and flucytosine. Am J Obstet Gynecol 2003;189(5):1297–300.
[51] Horowitz B. Topical flucytosine for chronic recurrent Candida tropicalis infections. J Reprod Med 1986;31:821–4.
[52] Phillips AJ. Treatment of non-albicans Candida vaginitis with amphotericin B vaginal suppositories. Am J Obstet Gynecol 2005;192(6):2009–12.
[53] White DJ, Habib AR, Vanthuyne A, et al. Combined topical flucytosine and amphotericin B for refractory vaginal Candida glabrata infections. Sex Transm Infect 2001;77(3):212–3.
[54] Allsworth JE, Peipert JF. Prevalence of bacterial vaginosis: 2001–2004 National Health and Nutrition Examination Survey data. Obstet Gynecol 2007;109(1):114–20.
[55] Marazzo JM, Koutsky LA, Eschenbach DA, et al. Characterization of vaginal flora and bacterial vaginosis in women who have sex with women. J Infect Dis 2002;185:1307–13.
[56] American College of Obstetricians and Gynecologists. Vaginitis ACOG Practice Bulletin No. 72. Obstet Gynecol 2006;107:1195–206.
[57] Beigi RH, Austin MN, Meyn LA, et al. Antimicrobial resistance associated with the treatment of bacterial vaginosis. Am J Obstet Gynecol 2004;191:1124–9.
[58] Koumans EH, Kendrick JS, CDC Bacterial Vaginosis Working Group. Preventing adverse sequelae of bacterial vaginosis: a public health program and research agenda. Sex Transm Dis 2001;28:292–7.
[59] Torok MR, Miller WC, Hobbs MM, et al. The association between Trichomonas vaginalis infection and level of vaginal lactobacilli, in nonpregnant women. J Infect Dis 2007;196(7): 1102–7.
[60] Schwebke JR, Desmond R. A randomized trial of metronidazole in asymptomatic bacterial vaginosis to prevent the acquisition of sexually transmitted diseases. Am J Obstet Gynecol 2007;196(6):517, e1–6.

[61] Schwebke JR, Weiss HL. Interrelationships of bacterial vaginosis and cervical inflammation. Sex Transm Dis 2002;29:59–64.
[62] Goldenberg RL, Culhane JF, Iams JD, et al. Epidemiology and causes of preterm birth-Lancet 2008;371(9606):75–84.
[63] Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of Gram stain interpretation. J Clin Microbiol 1991;29:297–301.
[64] 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.
[65] Schwebke JR, Richey CM, Weiss HL. Correlation of behaviors with microbiologic changes in vaginal flora. J Infect Dis 1999;180:1632–6.
[66] Gardner HL, Dukes CD. Haemophilus vaginalis vaginitis: a newly defined specific infection previously classified non-specific vaginitis. Am J Obstet Gynecol 1955;69(5):962–76.
[67] Ness RB, Hillier SL, Richter HE, et al. Douching in relation to bacterial vaginosis, lactobacilli, and facultative bacteria in the vagina. Obstet Gynecol 2002;100:765–72.
[68] Fredricks DN, Fiedler TL, Thomas KK, et al. Targeted PCR for detection of vaginal bacteria associated with bacterial vaginosis. J Clin Microbiol 2007;45(10):3270–6.
[69] Kalra A, Palcu CT, Sobel JD, et al. Bacterial vaginosis: culture- and PCR-based characterizations of a complex polymicrobial disease's pathobiology. Curr Infect Dis Rep 2007;9(6): 485–500.
[70] Hauth JC, MacPherson C, Carey C, et al. Early pregnancy threshold vaginal pH and gram stain scores predictive of subsequent preterm birth in asymptomatic women. Am J Obstet Gynecol 2003;188:831–5.
[71] Pereira L, Culhane J, McCollum K, et al. Variation in microbiologic profiles among pregnant women with bacterial vaginosis. Am J Obstet Gynecol 2005;193:746–51.
[72] Culhane JF, Nyirjesy P, McCollum K, et al. Variation in vaginal immune parameters and microbial hydrolytic enzymes in bacterial vaginosis positive pregnant women with and without mobiluncus species. Am J Obstet Gynecol 2006;195:516–21.
[73] Paavonen J, Mangioni C, Martin MA, et al. Vaginal clindamycin and oral metronidazole for bacterial vaginosis: a randomized trial. Obstet Gynecol 2000;96:256–60.
[74] Livengood CH III, Ferris DG, Wiesenfeld HC, et al. Effectiveness of two tinidazole regimens in treatment of bacterial vaginosis: a randomized controlled trial. Obstet Gynecol 2007;110: 302–9.
[75] Nyirjesy P, McIntosh MJ, Steinmetz JI, et al. The effects of intravaginal clindamycin and metronidazole therapy on vaginal mobiluncus morphotypes in patients with bacterial vaginosis. Sex Transm Dis 2007;34:197–202.
[76] Diav-Citrin O, Shechtman S, Gotteiner T, et al. Pregnancy outcome after gestational exposure to metronidazole: a prospective controlled cohort study. Teratology 2001;63:186–92.
[77] Iams JD, Romero R, Culhane JF, et al. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. Lancet 2008;371(9607):164–75.
[78] Wilson J. Managing recurrent bacterial vaginosis. Sex Transm Infect 2004;80:8–11.
[79] Bradshaw CS, Morton AN, Hocking J, et al. High recurrence rates of bacterial vaginosis over the course of 12 months after oral metronidazole therapy and factors associated with recurrence. J Infect Dis 2006;193(11):1478–86.
[80] Bradshaw CS, Tabrizi SN, Fairley CK, et al. The association of Atopobium vaginae and Gardnerella vaginalis with bacterial vaginosis and recurrence after oral metronidazole therapy. J Infect Dis 2006;194(6):828–36.
[81] Sanchez S, Garcia PJ, Thomas KK, et al. Intravaginal metronidazole gel versus metronidazole plus nystatin ovules for bacterial vaginosis: a randomized controlled trial. Am J Obstet Gynecol 2004;191(6):1898–906.
[82] Sobel JD, Ferris D, Schwebke J, et al. Suppressive antibacterial therapy with 0.75% metronidazole vaginal gel to prevent recurrent bacterial vaginosis. Am J Obstet Gynecol 2006;194: 1283–9.