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Recurrent vulvovaginitis

Anna M. Powell, MD, Clinical instructor [a, b, *], Paul Nyirjesy, MD, Professor, Director [b]

[a] Department of Obstetrics and Gynecology, Medical University of South Carolina, Charleston, SC, USA
[b] Department of Obstetrics and Gynecology and Medicine, Drexel Vaginitis Center, Drexel University College of Medicine, Philadelphia, PA, USA

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Vulvovaginitis (VV) is one of the most commonly encountered problems by a gynecologist. Many women frequently self-treat with over-the-counter medications, and may present to their health-care provider after a treatment failure. Vulvovaginal candidiasis, bacterial vaginosis, and trichomoniasis may occur as discreet or recurrent episodes, and have been associated with significant treatment cost and morbidity. We present an update on diagnostic capabilities and treatment modalities that address recurrent and refractory episodes of VV.

Introduction

Complaints pertaining to vulvovaginal symptoms are among the most common presenting symptoms a gynecologist will encounter. Vulvovaginitis (VV) is associated with significant direct and indirect health-care costs and may affect 15–39% of women. Many women self-treat, and over-the-counter (OTC) antifungal creams are among the most commonly purchased OTC medications. VV can be linked with significant morbidity and affects women of all ages. Furthermore, vulvovaginal infections have been associated with other morbidities of the female genital tract, including increased susceptibility to and transmission of human immunodeficiency virus (HIV) infection, infertility, and poor pregnancy outcomes [1]. The most common causes of infectious VV are vulvovaginal candidiasis (VVC), bacterial vaginosis (BV), and trichomoniasis.

* Corresponding author. Department of Obstetrics and Gynecology, 245 N. 15th Street, MS 495, 16th Floor, New College Building, Philadelphia, PA 19102, USA. Tel.: +1 215 762 8292 (Business), +1 267 773 9075 (Home); Fax: +1 215 762 1470.
E-mail address: powell.am@gmail.com (A.M. Powell).

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Although many providers may think of vulvovaginal infections as fairly straightforward and easy to treat, treatment failures and recurrent infections occur commonly. Patients faced with such infections are frequently offered repeated courses of the same ineffective regimens. However, for most women with chronic or recurrent vaginal infections, there are approaches to evaluation and treatment which can yield more satisfactory outcomes. In this article, we will review the current literature about the etiology, diagnosis, treatment, and management of recurrent or refractory infections.

Vulvovaginal candidiasis

While women are led to believe that they can accurately self-diagnose VVC, only 11% who have never had an episode of VVC and 34% who have can accurately recognize the written description of VVC [2]. In 2002, Ferris and colleagues prospectively investigated a cohort of 95 women who had self-diagnosed VVC and were about to purchase an OTC antifungal for self-treatment. After proper evaluation, only 34% had VVC while an additional 20% had VVC with another infection, most frequently BV. Women in the study who experienced a prior episode of VVC were no more likely to correctly identify their infection than women with first-time symptoms, and the women who did correctly identify their symptoms were no more confident about their self-diagnosis than others [3]. It is estimated that up to 50% of women using OTC products for self-diagnosed VVC may eventually need to visit a clinician because of improper diagnosis and therapy [3]. Thus, VVC is frequently misdiagnosed and mismanaged due to inaccurate self-diagnosis and self-treatment. The absence of rapid, simple, and inexpensive home diagnostic tests may further impede proper identification.

The initial approach to a patient with symptoms of VVC (itching, burning, and abnormal discharge) includes thorough history and physical examination, with attention paid to risk factors including antibiotic use, prior episodes of VVC, immunosuppression, and diabetes mellitus. Office tests, including vaginal pH, saline and 10% potassium hydroxide (KOH) smears are crucial to making an initial diagnosis. In patients with suggestive symptoms but negative microscopy, a yeast culture is also helpful, as hyphae or blastospores are only identified with microscopy in about 50% of cases [4]. In patients whose initial tests are negative, and who are unable to return easily for evaluation, diagnosis may be significantly aided by providing patients with swabs with transport medium for self-sampling to be directly sent to a laboratory [5]. Furthermore, a positive yeast culture permits speciation of the causative organism, which in turn may have important implications for antifungal therapy. Although culture also allows access to the organism for antifungal susceptibility testing, such testing is rarely used in clinical practice unless patients experience repeated clinical or mycologic treatment failure. Where available, drug sensitivities can be considered for fluconazole, miconazole, itraconazole, amphotericin B, and capsofungin but may be of limited usefulness [6]. Diabetics and pregnant women may have different profiles of drug resistance from the nondiabetic nonpregnant patient [6]. Although polymerase chain reaction (PCR) testing for yeast has been available for a number of years and may yield more rapid results than culture, disadvantages of PCR testing include little data about performance compared to culture, variations in quality between laboratories, an inability to detect less common types of yeast, and significantly increased costs. There is no indication for *Candida* PCR in most clinical settings.

First-line therapy for an acute episode of vaginitis is generally very effective and can be accomplished with the use of an oral or topical azole, with topical medications preferable in pregnancy. A

Table 1
Classification of VVC [42].

Uncomplicated vulvovaginal candidosis
• Sporadic and infrequent infections AND
• Mild to moderate symptoms or findings AND
• Suspected *C. albicans* infection AND
• Nonpregnant, nondiabetic woman
Complicated vulvovaginal candidosis
• Four or more recurrences per year OR
• Severe symptoms or findings OR
• Suspected or proven Non-*albicans Candida* infection OR
• Impaired host immune system (diabetes, immunosuppression, pregnancy, other vulvovaginal conditions)

classification system, in use for the past decade to separate simple from complicated episodes of VVC, may guide the clinician in determining length of treatment (Table 1). Acute episodes typically respond to imidazoles or polyenes with success rates reported up to 75% within 4–6 weeks after treatment [4]. Recurrent vulvovaginal candidiasis (RVVC) is defined as four or more episodes of symptomatic acute *Candida* vaginitis in a 12-month period [7] and occurs in approximately 5% of all women who have an initial episode of VV [5]. Forty to 50% of women will have a *recurrence* of VVC after an initial episode but only 5–8% will have *recurrent* VV [8]. Although many women with VVC may have an identifiable etiology like recent antibiotic use or poorly controlled diabetes, one-third to one-half of RVVC cases have no clear cause [7].

Prior to the onset of a symptomatic episode, yeast must establish colonization, which requires adherence to the vaginal epithelial cells and is often mediated by mannoproteins. Virulence factors produced by *Candida* species such as aspartate proteinases, proteases, phospholipases, and mycotoxins may inhibit phagocytic activity or suppress the local immune system [4,6,8]. In women with RVVC, some refractory infections may be due to azole-resistant *Candida albicans*. In a high volume vaginitis clinic, 25 patients were found to have resistant *C. albicans* infections, with minimum inhibitory concentrations of fluconazole resistance $\geq$2 μg/mL [9]. While awaiting susceptibility testing, the patients were treated with a 14-day course of intravaginal nystatin or boric acid. Further therapy was determined by antimicrobial susceptibility. Low-dose fluconazole resistance was generally responsive to 150–200 mg fluconazole twice weekly, whereas other patients required therapy using itraconazole or ketoconazole.

The previous comments notwithstanding, most RVVC cases are thought to be due to genetics, behavior, or intrinsic host biology. It is postulated that susceptible women are more prone to recolonization, inciting a proinflammatory cytokine cascade in the presence of even small amounts of yeast [7]. Certain risk factors, such as recent antibiotic use, hormonal contraception, diets of excessive sugar, may trigger episodes of VVC. Unfortunately, many women with RVVC have no consistently identifiable risks. No clear benefit has been established in treating a male partner. This has prompted a search for other etiologies, including a genetic basis, to explain the underlying pathology of recurrences.

C. albicans is the most common fungal species present in the vaginal microbiome, and its interactions with vaginal epithelial cells mitigate the body's immune response to its presence. Deficiencies in epithelial cell recognition of candidal cell wall moieties or in the innate immune response elaboration may cause an overactive or, conversely, an ineffective immune response to the presence of these organisms. Polymorphisms of epithelial cell surface receptors affecting dectin-1 or mannose-binding lectin can have deleterious effects on antifungal cytokine elaboration [9]. As a result, RVVC could be considered a chronic condition which requires prolonged suppressive treatment to achieve symptom relief or resolution.

One suppressive regimen involves giving three doses of fluconazole 3 days apart to achieve a negative yeast culture, then maintaining the patient on once weekly fluconazole 150 mg for 6 months [10]. Fluconazole's pharmacokinetic properties lend themselves to maintenance use for RVVC. This antifungal exhibits a prolonged half-life in the vagina and achieves a high inhibitory concentration for at least 96 h. Furthermore, a possible synergistic effect with acetic acid produced by vaginal microorganisms adds to its activity. Adjusting the maintenance regimen to twice weekly is a possibility for breakthrough symptoms after the 96-h window [7]. Another described regimen uses individualized decreasing doses of fluconazole

Table 2
Maintenance therapy regimens for recurrent vulvovaginal candidiasis.

	Regimen	Efficacy
Sobel 2004 Study design: randomized control trial	Induction with 150 mg fluconazole oral q72 hours × 3 doses then once weekly × 6–12 months	91% treatment group symptom-free at 6 months; 43% relapse-free at 12 months.
Donders 2008 "ReCiDif Regimen" Study design: prospective cohort trial	• 200 mg fluconazole 3 × in 1st week. (Monthly testing for recurrence done prior to initiation of next treatment phase) • 200 mg fluconazole weekly × 8 weeks • 200 mg once bi-weekly × 4 months • 200 mg once monthly × 6 months	90% patients symptom-free at 6 months; 77% relapse-free at 12 months.

to achieve symptom resolution (Table 2) [11]. With this regimen, 77% of patients were disease free at the end of 1 year. Other treatment options include ketoconazole 100 mg orally daily or clotrimazole 500 mg suppositories weekly. Limiting factors of ketoconazole therapy are headaches and rare cases of nonviral hepatitis [4]. Patients on maintenance therapy who experience breakthrough symptoms may have an early inflammatory response to regrowth of yeast. Treatment of an additional relapse may require additional fluconazole maintenance weekly for 12 months [7]. Depending on the maintenance regimen, relapse rates may range from 23% to 50% [11,12]. Most women will experience relapse within 1–2 months of stopping therapy, but others may delay until 10 months after therapy [10].

Boric acid is considered an effective second-line drug for recurrent or refractory *Candida* vaginitis. Vaginal use is well tolerated, but it may be fatal if ingested or systemically absorbed in large quantities and is relatively contraindicated in pregnancy [12]. Boric acid powder (600 mg) is delivered intravaginally in a gelatin capsule or suppository and inhibits hyphal formation and virulence factors, including CDR1 drug efflux activity and biofilm formation [13].

While most relapses are caused by the same *C. albicans* strain, occasionally this can be attributed to a new strain of *C. albicans* or a non-*albicans Candida* species. Non-*albicans Candida* infections should be considered when there is a poor response to a course of azoles. Of these, *C. glabrata* is the most common, but it is thought to be a weaker pathogen with poorer adherence to vaginal tissue [6]. It is more commonly identified in non-Whites and type 2 diabetics. Treatment is most successful with vaginal 600 mg boric acid suppositories nightly for 14 days, although occasionally other modalities like 17% flucytosine cream or amphotericin B suppositories may be required.

Bacterial vaginosis

BV represents a pathogenic shift of the vaginal flora with a polymicrobial overgrowth of facultative and anaerobic organisms. It is considered the most common cause of vaginitis worldwide. The presence of BV puts a woman at risk for acquiring other sexually transmitted infections (STIs) including gonorrhea, chlamydia, and HIV, as well as for adverse pregnancy outcomes such as preterm birth [1]. The most common presenting symptom is vaginal discharge and a fishy odor, usually worse after intercourse and menses. Normal vaginal flora is dominated by lactobacilli which produce hydrogen peroxide to keep organisms that do not produce catalase in check. In women with BV, this normal flora is replaced by a broad range of primarily anaerobic bacteria, including species such as *Gardnerella vaginalis*, *Atopobium vaginae*, and *Mobiluncus* species. Most clinical cure rates are reported within a short time after treatment cessation and few studies report long-term BV cure rates. Practitioners struggle with the treatment of repeat episodes of BV; recurrence rates are cited as high as 30–50% within 2–3 months [14]. As new theories circulate regarding the pathogenesis of bacterial vaginosis, it is helpful to consider the risk for recurrence in terms of reinfection, recurrence, and resistance.

Accurately diagnosing BV is critical because too often recurrent BV (RBV) is approached and treated empirically, often leading to delay of appropriate therapy. Diagnosis can be made using either Amsel's criteria, consisting of a thin, grayish vaginal discharge, a positive “whiff” test with the application of 10% potassium hydroxide (KOH), >20% clue cells on wet mount and pH > 4.7, or a Nugent score based on Gram stain. Amsel's criteria are more specific while the Nugent score is more sensitive, and these tests concur in 80–90% of cases. One advantage of Nugent scoring is high intra- and interobserver reliability and reproducibility; however, most point-of-care testing will involve the use of Amsel's criteria. Clue cells correlate best with Gram stain results and are thought to be the most reliable feature in making a diagnosis of BV. A vaginal pH > 4.5 is considered the most sensitive criterion [14]. Several commercial point-of-care tests have been developed to aid diagnosis in clinical and research settings, some of which have compared favorably to Amsel's criteria and Gram stain [15]. The OSOM BV Blue test® (Gryphus Diagnostics, AL, USA) is a Food and Drug Administration (FDA)-approved point-of-care test that detects elevated vaginal fluid sialidase enzyme activity and has shown an 88–97.6% sensitivity and 95–97.5% specificity compared to Gram stain with similar results compared to Amsel's criteria [16]. The BD Affirm™ VP III (BD Diagnostic Systems, NJ, USA) *G. vaginalis* (GV) DNA hybridization assay is a DNA hybridization test that detects high concentrations of *GV*, along with the presence of certain *Candida* species, and *Trichomonas vaginalis.* [15] Although this test is touted as an office test, it requires having the machine to run samples in the office and thus is more commonly available as a send-out

laboratory. Although molecular diagnostic techniques have shown the complexity of the vaginal microbiome in women with BV [15], the authors feel that they remain primarily a research tool and are much more expensive than Amsel's criteria.

BV is strongly associated with sexual activity. Male partners of women with BV who do not use condoms frequently have *Gardnerella* detectable in the genitourinary tract. Biotyping is able to identify the same species in both sexual partners in 90% of cases [17]. Schwebke and Desmond report a higher likelihood of BV cure in women who abstained from sex or consistently used condoms, and who refrained from douching [18]. Previous randomized, controlled trials investigating partner treatment have not documented any significant benefit but have been criticized for significant methodological flaws [19]. With recent data showing that male partners often share the biofilm of women with recurrences, alternative partner treatment strategies may eventually be in order. Evidence points to a moderate protective effect on incident BV with consistent condom use [14].

In women with RBV, another putative cause may be the development of a vaginal biofilm community containing several organisms that create a field difficult to penetrate with antibiotics. Swidsinski et al. (2005) showed that GV is able to form an adherent biofilm on vaginal epithelium, and further work has illustrated that GV may be just the first species whose presence facilitates further growth of other species normally associated with BV [20]. The biofilm contains organisms including but not limited to GV, *A. vaginae*, *Bacteroides*, *Corynebacterium*, *Prevotella*, *Ruminococcus*, and *Streptococcus.* [20,24] Bacterial density within the biofilm is on the order of 10^{10}–10^{12} cells per gram compared to 10^{6}–10^{8} cells per gram of dispersed GV found in vaginal fluid washings. Yeoman et al. suggest that different GV strains have substantially different metabolic and virulence potentials [21]. Vaginal biopsies of women with BV analyzed with FISH (fluorescent in situ hybridization) demonstrated a dense biofilm in confluent or patchy layers covering at least 50% of the vaginal epithelial surface.

In a longitudinal study of 20 women with BV treated using standard metronidazole dosing compared to 40 controls, vaginal biopsies demonstrated that the biofilm is temporarily suppressed during antibiotic administration but quickly regains activity once completed [22], typically within 10–12 weeks. A similar course of recurrence was observed after the study was repeated with moxifloxacin, a fluoroquinolone which is not currently the standard of care for BV treatment [17,23]. Further evaluation of the natural course of vaginal biofilms will be needed to investigate treatment modalities to prevent recurrence of BV. Interestingly, McMillan et al. investigated the effects of lactobacilli application on biofilms containing *GV* and *A. vaginae*, as well as uropathogenic *Escherichia coli* (UPEC) [12]. *Lactobacillus reuteri* R-14 and *L. rhamnosus* GR-1 were applied and noted to cause a more uniform pattern of cell death than treatment of the same biofilm with metronidazole, which produced holes in the biofilm. This study further underlines the theory that metronidazole alone may be insufficient for effective BV treatment.

The 2010 sexually transmitted disease (STD) guidelines from the Centers of Disease Control (CDC) [25] recommend the following treatment regimens standard for BV: metronidazole 500 mg twice daily for 7 days, 0.75% metronidazole vaginal gel for 5 days, or 2% clindamycin vaginal cream for 7 days [24]. Oral metronidazole and vaginal clindamycin have similar cure rates at 1 month (60–90%). Oral tinidazole, administered as 2 g/day as a single dose for 2 days or 500 mg twice daily for 5 days [25], seems equivalent to oral metronidazole and intravaginal clindamycin cream. A study of 593 women with BV showed no statistical difference in the cure rate between standard oral dosing of metronidazole, tinidazole 500 mg twice daily orally for 7 days, or tinidazole 1 g daily for 7 days [26]. One concern regarding the use of clindamycin for the treatment of BV is that it has gram-positive coverage with potential activity against lactobacilli. However, a retrospective analysis of three studies investigating 2% clindamycin vaginal cream (single dose and multidose) to 0.75% metronidazole vaginal gel reviewed baseline lactobacillus scores obtained by Gram stain for each treatment modality and found similar significant improvement in the presence of lactobacillus morphotypes at 21–30 days after treatment across all treatment groups [27].

The ultimate goal of any treatment is to restore a normal vaginal environment by promoting the growth of indigenous *Lactobacillus* species and decreasing the growth of abnormal flora [27]. The use of probiotics to achieve this goal makes sense, but studies to date have been fairly limited and involve formulations which are not yet commercially available. While Vujic et al. demonstrate that 6 weeks of

probiotic treatment versus placebo may aid in restoration of normal vaginal flora [28], other studies [29,30] suggest an adjuvant role for probiotics without replacement of metronidazole. Anukam et al. supplemented a 7-day treatment course of metronidazole for BV with an oral formulation of *Lactobacillus GR-1* and *RC-14* versus placebo for 30 days, and demonstrated an initial cure rate of 88% versus 40% ($P < 0.001$) with a significant recovery of lactobacilli in vaginal swabs from the study group post treatment [29]. Nevertheless, data about probiotics are so sparse as to prevent recommending them in women with RBV.

Thirty percent of women with an initial response to BV therapy will relapse within 3 months, and 58% within 12 months [16]. Recurrence risk factors include having a regular sex partner, having a female sex partner, not using hormonal contraception, and a prior history of BV [16]. Practitioners may treat a symptomatic relapse with either oral or vaginal metronidazole or clindamycin, which may be same or different from prior treatment. RBV is defined as three or more documented episodes in 12 months, and women with RBV should be offered long-term maintenance therapy with metronidazole gel [7]. A maintenance therapy regimen using 0.75% vaginal metronidazole gel twice weekly for 4 months after treatment of an acute BV episode was evaluated in a multicenter double-blinded prospective randomized control trial [7]. While the probability of remaining in clinical remission was initially 70%, a clinical recurrence was seen in half of the patients by 3 months, and the probability of clinical cure at 7 months post maintenance therapy was 34–37%, which was still significantly greater than the placebo group. Rare adverse events were encountered, including secondary VV. A single-center uncontrolled pilot study showed promising results with the addition of 600 mg vaginal boric acid capsules for 21 days added to an oral regimen of metronidazole or tinidazole taken for 7 days. The study looked at a total of 58 women with 77 episodes of BV, and showed a cumulative disease-free rate at 12 months of 87%; however, the study was limited by non-blinding, a lack of control or placebo agent, and variable duration of therapies [31]. Only 22% of the study population was treated for two or more episodes of BV during the 4-year study period [31]. There have been no studies, to our knowledge, of maintenance therapy trials using clindamycin.

High resistance to metronidazole and clindamycin has been found in isolates of GV in cases of RBV [32]. This suggests that antibiotic resistance as well as relapse is responsible for recurrence. Sixty-eight percent of GV strains [32] were found to be resistant to metronidazole while 76% were sensitive to clindamycin. Among strains isolated from women with RBV, 58.8% were resistant to metronidazole. The authors reported switching to the use of clindamycin 300 mg twice daily for 7 days as their primary BV regimen. Austin et al. investigated antimicrobial susceptibilities of vaginal microbes in women with BV pre- and post treatment with either intravaginal metronidazole or clindamycin [33]. Clinical cure rates were similar for both treatment groups: at 7–12 days, 79% and 88% for metronidazole and clindamycin, at 35–45 days, 62% and 55%, and at 70–90 days, 58% and 55%. The presence of *A. vaginae* may relate to poor treatment outcomes [34]. Ferris et al. examined species composition of vaginal flora before and 1 month after metronidazole treatment using a PCR assay targeting *A. vaginae* and found concentrations of the bacteria highest for patients who failed treatment or responded incompletely. Other studies have also reported *A. vaginae* metronidazole resistance [35].

Trichomonas vaginalis

Trichomoniasis is caused by the protozoan *T. vaginalis*. *T. vaginalis* infection is often subclinical, and no specific symptom is diagnostic [36]. Symptoms in women range from asymptomatic carriers to severe vaginitis or cervicitis [37]. It is a common pathogen associated with increased risk of HIV acquisition and transmission, preterm delivery, and upper genital tract infection [37]. *T. vaginalis* infection can persist in the female urogenital tract for long periods of time, and up to one-third of asymptomatic women will develop symptoms within 6 months [38]. A nationally representative cohort from the National Health and Nutrition Examination Survey (NHANES) study between 2001and 2004 demonstrated that 3.1% of US women of reproductive age are infected, with an annual incidence of at least 1.1 million [39]. Whether trichomoniasis should be a nationally notifiable condition in the United States remains an ongoing debate [40]. Prevalence is particularly high in non-Hispanic black women, incarcerated individuals, HIV-infected women, and among STD clinic patients [39,41].

There are no official guidelines for *T.vaginalis* testing. Wet mount and microscopy can be performed in the clinical setting with high specificity but only 60–70% sensitivity. Culture has been considered the gold standard laboratory test but takes up to 5 days for results [36]. Vaginal specimens may be evaluated with point-of-care- FDA-approved tests: OSOM *Trichomonas* Rapid Test (Genzyme Diagnostics, Cambridge, MA, USA) and the Affirm VP III (BD Diagnostic Systems, Sparks, MD, USA), with sensitivities of 82–94% and specificities of 98.8–100% [37]. The OSOM *Trichomonas* Rapid Test is an immunochromatographic capillary flow assay that can be read within 10 min of placement into a buffered sample. More recently, an alternative to in-office testing is the APTIMA test (Gen-Probe INC, San Diego, CA, USA), which uses transcription-mediated amplification to detect species-specific16S ribosomal RNA. As this test has demonstrated superiority over traditional wet mount and culture, it is considered by most experts to be the new gold standard for diagnosing trichomoniasis [36].

Uncomplicated infections may be treated with either one-time metronidazole 2 g orally or one-time tinidazole 2 g orally. Metronidazole and tinidazole are nitroimidazoles which have a 5-nitro group that is reduced into a nitro radical within the target organism. Tinidazole has a longer half-life and slower elimination rate and is thought to have superior tissue distribution [37]. Cure rates for single-dose regimens are 90–95% (metronidazole) and 86–100% (tinidazole) and increase if the sexual partner is treated simultaneously [24,42]. HIV-positive women with trichomoniasis should be treated with metronidazole 500 mg twice daily for 7 days [43] as infections were cleared more effectively with this regimen.

Tinidazole is 10 times as expensive as metronidazole for single-dose regimens, significantly limiting its use. Single-dose regimens may result in improved patient compliance but higher rate of side effects, including nausea, vomiting, headache, insomnia, rash, and dry mouth. Because of poor efficacy, topical metronidazole gel is not recommended at all for treatment [24]. A recent randomized dose-ranging study of combination metronidazole 750 mg/miconazole 200 mg vaginal suppository twice daily for 7 days versus oral metronidazole 2 g single dose showed no significant differences in cure rates and supports the possibility of this unavailable product as an alternative to oral nitroimidazole [44]. Partner testing and treatment is recommended; detection of trichomonas in male partners may require several diagnostic modalities, as detection rates with culture alone or culture and wet mount ranged only from 22 to 45%. A combination of urine, urethral culture, and urine PCR showed 71.7% diagnostic concordance [45]. Because partner infection rates are very high (70–80%), the sexual partner should likely receive treatment despite negative diagnostic modalities. Recurrent *T. vaginalis* infections may be caused by partner reinfection, metronidazole resistance, or a treatment failure. Assuming adequate partner treatment has taken place, nitroimidazole resistance should be investigated.

Metronidazole resistance is classified as aerobic or anaerobic. Aerobic resistance can develop in vivo at therapeutic levels of metronidazole, and is mitigated by the downregulation of the ferredoxin- and oxygen-scavenging pathways. Reduced levels of ferredoxin result in lowered activation of metronidazole and decreased intracellular transport of the drug [42]. Anaerobically resistant strains can be induced in vitro by cultivating trichomonads with increasing but sublethal drug concentrations for a period of 12–21 months, which causes decreased or absent pyruvate ferridoxinoxidoreductase (PFOR) activity [42]; downregulation of this pathway may prevent the activation of metronidazole. Prevalence of low-level metronidazole resistance has been reported to be 4.3% in one prospective cohort utilizing patients from STD clinics in six US cities [46]. Thirty-two percent isolates from a study of 175 isolates from women with refractory infections sent to the CDC for susceptibility testing showed high resistance to metronidazole [47]. However, metronidazole in vitro resistance should not be confused with treatment failure, as many metronidazole-resistant strains may still be eliminated with standard dosing; correlation with clinical outcomes remains unclear.

In cases of true treatment failure, a culture is recommended for susceptibility testing. In such cases where the single regimen of metronidazole fails, 500 mg orally twice daily for 7 days or tinidazole 2g once is recommended [24]. Partners of persons with refractory trichomoniasis should also be evaluated and treated with an extended dose. Tinidazole or metronidazole may then be used 2 g orally daily for 7 days. The next step up in treatment may be tinidazole 1 g orally twice daily for 7 days [48–50]. For persistent infections, increasing dosage and duration of metronidazole or tinidazole with or without intravaginal metronidazole may also be used. Several case series have reported success with tinidazole 1 g orally two or three times daily combined with 500 mg daily intravaginally for a total of 14 days with

Table 3
Summary of testing modalities for infectious vulvovaginitis to aid office diagnosis.

	Office tests	Gold standard diagnosis	FDA-approved Point-of-care testing
Vulvovaginal candidiasis	pH: <5.0 Whiff: negative Wet mount: buds or hyphae with KOH preparation	Culture	n/a
Bacterial vaginosis	pH: ≥4.7 Whiff: positive Wet mount: >20% clue cells diagnostic	Gram stain	OSOM BV Blue or AFFIRM VP
Trichomoniasis	pH:≥4.7 Whiff: positive Wet mount: mobile trichomonads, leukocytes	Culture	OSOM Rapid Trichomonas test, APTIMA *T. vaginalis* assay

a 79% cure rate [50]. A course of 5% intravaginal paromomycin, an aminoglycoside antibiotic, applied nightly for 14 days has also yielded favorable results in combination with high oral doses of tinidazole (1g three times daily for 14 days) in two patients with resistant infections [48]. As a stand-alone therapy in 13 patients, however, paromomycin only cured 58% and caused localized irritation and ulceration [51].

Trichomoniasis detection rates will likely improve, and more data will be necessary to determine the true significance of the low versus high level of nitroimidazole resistance. Until new data shed light on better alternative treatments, the recommendation to continue using nitroimidazoles in most situations will remain.

Conclusions

Recurrent vaginitis should be treated as a chronic condition that may require acute and long-term treatment (Table 3). For VVC, the use of yeast culture and antibiotic susceptibility testing may guide treatment in refractory cases. BV severity and persistence appears to be a function of its manifestation as a biofilm, which metronidazole alone may be insufficient to treat completely. New point-of-care tests in development may significantly improve the ability to diagnosis and treat trichomoniasis.

Practice points

- Recurrent or refractory infections attributed to VVC, BV, or trichomoniasis may cause significant morbidity.
- Newer diagnostic modalities are on the horizon but few new point-of-care testing has been validated or FDA approved. Basic office testing (vaginal pH, amine test, saline, and 10% KOH microscopy) remains the cornerstone of evaluation. Adjunctive tests such as trichomonas PCR testing and yeast cultures may be helpful in selected cases [15].
- Maintenance regimens for each particular cause of infectious VV may be required to control symptoms and prevent long-term recurrences.

Research agenda

- Point-of-care testing for rapid diagnosis of VVC.
- Improved strategies for BV biofilm elimination.
- Further development of maintenance regimens for RBV.

Conflict of interest

Dr. Nyirjesy has received research support from Genesis Biotechnology Group and Medicis Corporation and has worked as a consultant for Medicis and Hologic Corporations.

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