OBG MANAGEMENT

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Practical strategies for acute and recurrent vaginitis

Self-diagnosis and treatment are out, and meticulous, in-office diagnosis is in—and there is new hope for women with chronic candidiasis: maintenance fluconazole.

IN THIS ARTICLE

SANDRA'S CASE

"Last hope" to end recurrent infections

Sandra, 46, makes an appointment to discuss her recurrent vaginal infections. In the past year, she has had numerous episodes of itching, burning, and abnormal discharge and has used "everything" to treat them. She has tried an array of antifungal and antibiotic preparations, but has experienced only transient relief. She says you are her last hope to break the cycle of recurrent infections.

How do you respond?

Although vaginitis is usually considered a minor nuisance, many women experience chronic symptoms that persist or recur after treatment. For patients such as Sandra, chronic vaginitis is a constant source of frustration and a serious threat to quality of life.

Careful diagnosis is the first and most important step to eradicate vaginitis, and this article describes the essential components—as well as common pitfalls. In some cases, high-dose therapy or maintenance regimens may be indicated; these strategies are also described in detail.

The usual suspects

Vaginitis is defined as inflammation of the vagina marked by pain, itching, and/or a purulent discharge. Depending on the population, the most common causes of infectious vaginitis are:

- bacterial vaginosis (BV) (22%–50% of symptomatic women),
- vulvovaginal candidiasis (VVC) (17%–39%), and
- trichomoniasis (4%–35%).[1]

However, vaginitis in 7% to 72% of women remains undiagnosed.[1] Their symptoms may be caused by atrophic vaginitis, vulvar dermatological conditions, vulvodynia, or other entities.

The hazards of self-diagnosis

Although a wide range of pathogens can cause vaginitis and symptoms are often nonspecific, the trend in the past decade has been for women to diagnose and treat themselves for VVC. The reasons: availability of over-the-counter (OTC) antifungals, ability to rapidly initiate antimycotic therapy, empowerment of women, and the likelihood of reducing direct and indirect healthcare costs.[2]

Unfortunately, recent studies suggest that self-diagnosis may not be as beneficial as we thought. Ferris and colleagues[3] studied 601 women in a variety of medical and community sites in Georgia and found that only 11% without and 34.5% with a prior diagnosis of VVC could accurately recognize it or bacterial vaginosis.

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Self-diagnosis is not as helpful as we thought. Even with a prior diagnosis, only a third of women identified it

A later prospective study[4] of 95 symptomatic women purchasing OTC antifungal agents found that only 34% had pure VVC; treatment with a topical antifungal would have been inappropriate or inadequate in the rest, many of whom had bacterial vaginosis.

A more recent longitudinal study[5] of women who submitted yeast cultures every 4 months for a year found no correlation between antecedent *Candida* colonization and subsequent antifungal use.

Avoid telephone diagnosis, too. Although telephone conversations are useful for patient triage and treatment in many clinical situations, diagnosis of vaginal symptoms by telephone correlates poorly with the actual diagnosis.[6]

If it's really VVC, it should respond to antifungals. Over-the-counter antifungals are as effective as their prescription counterparts, so women with VVC should respond to OTC therapy. If a woman reports a lack of response, question the initial diagnosis and offer a thorough evaluation instead of recommending further treatment as the initial step.

Even the pros can be wrong

In a review of 52 medical records of women referred to a tertiary-care vaginitis center, Wiesenfeld and Macio[7] found that vaginal pH testing was performed at only 3% of office visits and that 42% of referring physicians failed to perform microscopy as part of their evaluation.

In a study of 61 women diagnosed with VVC after clinical examination and microscopy in a university-based outpatient gynecology clinic, Ledger et al[8] found that 49% had a negative yeast culture and polymerase chain reaction.

Office-based tests, even when they are performed in the best of circumstances by personnel focused on vaginal symptoms, have relatively low sensitivity: 92% for bacterial vaginosis, 62% for *Trichomonas*, and a mere 22% for yeast.[9]

The right test matters

Given the nonspecific nature of vulvovaginal symptoms and the limitations of office-based testing, a few tests are nevertheless useful for patients with chronic symptoms or an unclear diagnosis.

Yeast cultures. When VVC is suspected, cultures increase sensitivity and allow for speciation of the organism. Speciation is crucial to choosing the proper antifungal drug (*see page 26*).

***Trichomonas* cultures.** Because a wet mount has low sensitivity in diagnosing trichomoniasis, *Trichomonas* cultures are useful in selected patients (with >90% sensitivity), such as women with a previous diagnosis of trichomoniasis, those at risk for sexually transmitted disease (STD), or those with microscopy showing BV or leukorrhea.

When *Trichomonas* cultures are unavailable, the OSOM *Trichomonas* Rapid Test (*Genzyme Diagnostics, Cambridge, Mass*) has better sensitivity than microscopy to detect *Trichomonas vaginalis*.

Herpes cultures and antibodies. Because genital herpes often presents with mild or nonspecific symptoms, a herpes simplex virus (HSV) culture and type-specific immunoglobulin-G HSV antibodies should be ordered when the patient presents with fissures or ulcers of the vulva.

Forget the gram stain. Given the relatively high sensitivity (92%) of Amsel criteria to diagnose bacterial vaginosis and the difficulty of obtaining Nugent scores on gram stains of vaginal secretions, the value of gram stains outside of research settings for women with suspected bacterial vaginosis is unclear.

Vulvar biopsies. Many women who complain of vaginitis actually have vulvar disorders.

Be prepared to obtain vulvar biopsies if necessary.

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INTEGRATING EVIDENCE AND EXPERIENCE

High-dose treatment (and maybe condoms) improved cure rate

Although metronidazole gel 0.75% is a standard BV therapy in the United States, much higher doses in combination with nystatin are common in other countries such as Peru. They proved more effective in a recent randomized trial, suggesting that high doses or more prolonged courses of therapy may be beneficial when standard treatment fails.

In the single-blind trial, Sanchez and colleagues[24] compared 5 nights of metronidazole gel 0.75% (37.5 mg per dose) to the same duration of treatment with intravaginal ovules containing 500 mg metronidazole and 100,000 U nystatin.

Patients were asked to return 14, 42, and 104 days after treatment; 138 (91%) of 151 women returned at least once.

At every follow-up, the women treated with the ovules had significantly lower recurrence rates (4%, 17%, and 33% for the ovules, compared with 20%, 38%, and 52% for the gel).

Was use of condoms related? Although participants were not randomized for condom use, recurrent infection was more likely among women whose partners did not use them.

The trial's strengths and limitations

This study is notable for its long follow-up, blinding of the evaluator and biostatistician, and diagnostic methods (both Amsel and Nugent criteria).

The trial addressed the question of whether early recurrence is due to persistent pathogenic flora or failure to repopulate the vagina with hydrogen-peroxide–producing lactobacilli. The improved cure rate with the higher dose of intravaginal metronidazole ovules suggests that it more effectively eradicated abnormal flora than the lower dose.

However, the condom finding suggests that exposure to some factor associated with the partner also plays an important role.

The main limitation was the variability of elapsed time for follow-up visits. For example, the range for the first visit was 10 to 132 days; as a result, some women had a first evaluation that was much later than others.

Further, because participants were Peruvian, the applicability to a US population with potentially different demographics or sex practices is unclear.

Watch for complicated VVC

Women who harbor *Candida* organisms in their vaginas have VVC. At one end of the spectrum are women who are asymptomatically colonized. It is not necessary to treat these women or make an effort to identify the organisms. At the other end of the spectrum are symptomatic women, who have been traditionally treated with a variety of antifungal therapies, now available in multiple formulations.

Many experts now believe VVC should be classified as complicated or uncomplicated (**TABLE 1**) to help identify women in whom therapy is likely to fail. Uncomplicated VVC has cure rates of 80% to 90%.[10] In contrast, several studies suggest that women with complicated VVC have lower short-term cure rates with either topical clotrimazole or oral fluconazole.[10,11]

Most women with recurrent VVC fall into the complicated category. For the most part, these are normal, healthy women who experience substantial discomfort and disruption of their daily well-being and sexuality because of recurrent infections. Self-treatment permits rapid initiation of antimycotic therapy,

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Bacterial vaginosis recurs in up to 30% of women within 3 months, and greatly disrupts well-being

TABLE 1

Criteria for candidiasis diagnosis

UNCOMPLICATED (meets all criteria)
Cure rate of 80% to 90%
Sporadic or infrequent episodes
Mild to moderate symptoms or findings
Suspected *Candida albicans* infection
Normal, nonpregnant woman
COMPLICATED (meets 1 or more criteria)
Cure rates vary widely
Recurrent (4 or more episodes per year)
Severe symptoms or findings
Suspected or proven non-albicans *Candida* infection
Abnormal host
• diabetes
• severe illness
• immunosuppression
• other vulvovaginal conditions
Pregnancy

Adapted from Sobel JD, et al.[26]

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6 months of maintenance fluconazole is recommended

but does nothing to prevent the next symptomatic episode.

Which *Candida* sp is it?

When standard antimycotic therapy fails, the species of infecting organism seems to be particularly important. Women with *Candida glabrata* colonization have markedly lower cure rates than women colonized with *C albicans*.[11] Thus, a crucial first step in treating women who have complicated VVC is obtaining a yeast culture. A positive culture helps corroborate the diagnosis, increases the sensitivity of the evaluation, and allows speciation of the organism and proper selection of therapy.

Non-albicans species less likely to respond to standard azole therapy. *Candida glabrata* is the second leading cause of VVC, but is less responsive to standard therapies. For example, cure rates of perhaps 50% can be expected with a 7-day course of terconazole cream.[12]

When azole therapy is ineffective, intravaginal boric acid in 600-mg capsules can be used every night for at least 14 days and will be effective in about two thirds of patients.[13] However, some patients have accidently ingested these boric acid capsules and died (apparently this dose of boric acid is lethal when taken orally). Thus, it is crucial that patients be warned specifically about this hazard.

In a series of 30 patients with no response to azole therapy and subsequent boric acid, Sobel and colleagues achieved a cure rate of 90% with a 14-day course of flucytosine cream 17%, given in 5-g nightly doses.[13]

Watch for false negatives in women on azole therapy. In general, the *C albicans* organism tends to be sensitive to azole therapy. Thus, if a woman with *C albicans* infection is cultured while on therapy, the odds are very high that she will have a negative yeast culture.

Maintenance fluconazole

Maintenance therapy with ketoconazole for recurrent VVC was first proposed in 1986, but was never widely adopted due to concerns about liver toxicity.

More recently, maintenance fluconazole was found to be effective in a double-blind, placebo-controlled study.[14] After treating the initial infection with 3 doses of fluconazole (150 mg every 3 days), researchers randomized women to a 6-month course of weekly fluconazole (150 mg) or placebo. During the 6-month treatment phase, relapse was noted in 9% of the fluconazole group and 64% of the placebo group. However, of the 126 fluconazole-

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treated women who were disease-free at the end of the treatment phase, 72 (57%) experienced relapse during the next 6 months.

Fluconazole for 6 months. Although about 50% of women have a relapse after stopping treatment, most can at least successfully control and prevent symptomatic episodes as long as they are using fluconazole in maintenance doses. Most experts recommend a 6-month course of maintenance therapy.

Alternatives to fluconazole. Extensive clinical experience has shown fluconazole to be safe and well tolerated in most women. However, women who are unable or unwilling to take it may benefit from repeated dosing of topical azoles, which also appear to be effective (although reported experience is less extensive than with fluconazole).

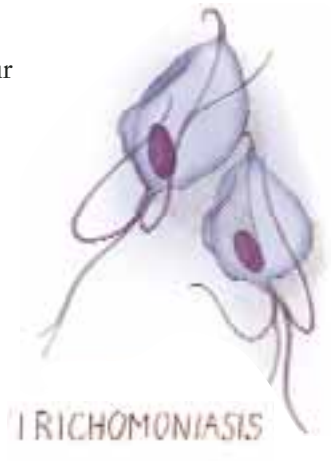
Vaginal trichomoniasis

This common STD has an estimated annual incidence of 3 million cases in the United States alone. Symptomatic women may complain of abnormal discharge, itching, burning, and/or postcoital bleeding. Physicians evaluating these women should be aware that microscopy has much lower sensitivity than many would expect, and that further testing may be necessary to establish a clear diagnosis (ie, cultures or the OSOM *Trichomonas* Rapid Test).

Treating uncomplicated infection

In the United States, trichomoniasis treatment consists of metronidazole or tinidazole; either may be given as a single 2-g dose. Although tinidazole has a somewhat longer half-life and slightly better activity against *T vaginalis*, both drugs appear to be effective and metronidazole is substantially cheaper. They also have similar side effects, including a possible disulfiram-like effect, although the incidence of adverse gastrointestinal (GI) effects may be lower with tinidazole.

Metronidazole allergy or resistance



Though rare, either can occur with trichomoniasis. Allergic patients should be referred for desensitization and later treated with metronidazole; both intravenous (IV) and oral regimens have been used successfully. We lack data on cross-reactivity between tinidazole and metronidazole. Metronidazole resistance is thought to occur in 1 in 2,000 to 3,000 cases.[15] If resistance is suspected, interview the patient carefully to exclude medication noncompliance and reinfection from an untreated partner. In a series of 33 cases, high-dose tinidazole (at least 1 g twice daily for 14 days) was well tolerated and effective in more than 90% of resistant cases.[16] Susceptibility testing of the resistant isolate by a reference laboratory may help guide drug choice and dosing.

Other options, such as topical paromomycin cream, which has been studied only in small series, may have local side effects such as vulvovaginal ulceration, and should be considered a last resort.[16]

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Microscopy can have low sensitivity for trichomoniasis—further testing may be necessary

New approaches to BV

BV is a polymicrobial infection marked by a lack of hydrogen-peroxide–producing lactobacilli and an overgrowth of facultative anaerobic organisms. Organisms found with greater frequency and numbers include *Gardnerella vaginalis*, *Mycoplasma hominis*, *Bacteroides* spp, *Peptostreptococcus* spp, *Fusobacterium* spp, *Prevotella* spp, *Mobiluncus* spp, and other anaerobes.[17]

Diagnostic criteria

Women with symptomatic vaginosis complain of abnormal vaginal discharge and a fishy odor.

BV is diagnosed by finding at least 3 of the following Amsel criteria:

TABLE 2

Bacterial vaginosis treatment options

DRUG	FORMULATION	DOSE PER DAY	DURATION
Clindamycin	2% cream 2% single-dose cream 100-mg ovules 300 mg oral	5 g 5 g 100 mg 300 mg bid	7 days 1 day 3 days 7 days
Metronidazole	0.75% gel 500 mg oral	5 g 500 mg bid	5 days 7 days

- abnormal gray discharge
- vaginal pH of more than 4.5
- positive amine test
- more than 20% of epithelial cells are clue cells

Susceptibility to other infections

In nonpregnant women, BV has been linked to infections of the reproductive tract, including pelvic inflammatory disease, postprocedural gynecologic infections, and acquisition of HIV.[5] Treating BV prior to abortion or hysterectomy appears to substantially lower the risk of postoperative infection.[18] Treatment also helps resolve concurrent mucopurulent cervicitis.[19] However, we lack evidence that BV treatment decreases the risk of pelvic inflammatory disease or HIV.

First-line treatment

The number of approved treatment options has increased (**TABLE 2**). Although clindamycin may have greater in vitro resistance,[5] all the listed agents have comparable clinical efficacy and safety.[20-22] Topical agents often cost more than generic oral metronidazole, although the latter is often associated with GI symptoms.

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Twice-weekly intravaginal metronidazole greatly reduces relapse

When BV recurs

After treatment, bacterial vaginosis recurs in as many as 30% of women within 3 months.[23] A number of explanatory theories have been proposed:

- persistent pathogenic bacteria
- reinfection from exogenous sources, including a sexual partner
- failure of normal lactobacillus-dominant flora to reestablish itself

In support of the first theory, Sanchez and colleagues[24] found a lower risk of recurrence after treatment with high-dose (500 mg) intravaginal metronidazole plus nystatin, compared with standard metronidazole gel. (*See "High-dose treatment [and maybe condoms] improved cure rate," on page 25.*)

The same study suggested a possible link to exposure to exogenous pathogens: Women who used condoms after treatment had a lower risk of recurrence than women who did not. However, other randomized trials evaluating treatment of the partner have shown no benefit in preventing recurrent BV.

Similarly, recolonization with lactobacillus supplements using nonvaginal strains failed to show a clear benefit.[23]

Benefits of maintenance therapy

Some women with recurrent BV appear to improve with low-dose maintenance antibiotic therapy. In a recent study of low-dose metronidazole gel (0.75%),[25] women with recurrent BV were given a 10-day course to clear that episode, then randomized to maintenance metronidazole (1 applicator twice a week) or placebo for 4 months. Seventy percent of the treatment group remained free of infection, compared with only 34% of the placebo group. After an additional 4 months of observation, 39% of the treat-

ment group remained free of BV compared with 18% of the placebo group.

Although these findings demonstrate significant improvement with maintenance therapy, the relapse rate remained relatively high. A high rate of VVC was also noted: Almost 60% of women required antifungal therapy at some point during the study.

Vaginitis: A way of life

SANDRA'S CASE

At minimum, symptom control

After careful evaluation and vaginal cultures, you diagnose Sandra with candidiasis infection with the *C glabrata* species and prescribe 600-mg capsules of intravaginal boric acid—taking care to warn her that they are for intravaginal use only, not to be taken orally—which completely relieve her symptoms for several months.

Although the candidiasis eventually recurs, the symptoms are not as severe and resolve again with more boric acid capsules.

For patients like Sandra, vaginitis may be an inescapable fact of life.

Fortunately, as our understanding of vulvovaginal conditions has improved, more effective evaluation and treatment enable us to establish clearer diagnoses and choose therapies that—at a minimum—keep symptoms under control. ■

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For some women, recurrent vaginitis is an inescapable a fact of life, but we can choose therapies that control symptoms

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