Management of Persistent Vaginitis

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With vaginitis remaining a common condition that leads women to seek care, it is not surprising that some women develop chronic vulvovaginal problems that are difficult to diagnose and treat. With a differential diagnosis that encompasses vulvar disorders and infectious and noninfectious causes of vaginitis, accurate diagnosis is the cornerstone of choosing effective therapy. Evaluation should include a symptom-specific history, careful vulvar and vaginal examination, and office-based tests (vaginal pH, amine test, saline and 10% potassium hydroxide microscopy). Ancillary tests, especially yeast culture with speciation, are frequently crucial to obtaining a correct diagnosis. A heavy but normal physiologic discharge can be determined by excluding other causes. With vulvovaginal candidiasis, differentiating between Candida albicans and non-albicans Candida infection has important treatment ramifications. Most patients with C albicans infections can be successfully treated with maintenance antifungal therapy, usually with fluconazole. Although many non-albicans Candida, particularly Candida glabrata, may at times be innocent bystanders, vaginal boric acid therapy is an effective first choice for many true non-albicans Candida infections. Recurrent bacterial vaginosis, a difficult therapeutic challenge, can often be controlled with maintenance therapy. Multiple options, especially high-dose tinidazole, have been used for metronidazole-resistant trichomoniasis. With the aging of the U.S. population, atrophic vaginitis and desquamative inflammatory vaginitis, both associated with hypoestrogenism, are encountered frequently in women with persistent vaginitis.

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Financial Disclosure

Dr. Nyirjesy has been a consultant for Novadigm, Viamet Pharmaceuticals, Symbiosis, Cepheid, and Hologics. He has received research grants from Novadigm, Viamet Pharmaceuticals, Symbiosis, and Becton–Dickinson.

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ISSN: 0029-7844/14
EVALUATION OF PATIENTS WITH PERSISTENT VAGINITIS

Although most women with chronic vaginitis believe that they have recurrent yeast infections, the differential diagnosis encompasses a broad array of vulvar and vaginal conditions, including infectious, inflammatory, dermatologic, and neuropathic pain conditions. In one prospective survey of 200 patients evaluated at a tertiary care vaginitis center, 62% of whom had had symptoms for more than 1 year, Nyirjesy and colleagues found that the most common diagnoses were contact dermatitis (21%), recurrent vulvovaginal candidiasis (21%), atrophic vaginitis (15%), localized provoked vestibulodynia (13%), and physiologic discharge (9%); 18% had two or more concurrent diagnoses. Although these results may be different in other practice populations, they serve to underscore the broad differential diagnosis. It may seem daunting to evaluate a woman who has seen multiple health care providers and tried many therapies over the years without improvement, but being aware of possible causes creates a framework for evaluation and management. This review focuses on the etiology and treatment of those entities that cause primarily vaginal symptoms, but health care providers should note that many women with persistent “vaginitis” have chronic vulvar diseases, recently discussed by the American College of Obstetricians and Gynecologists. Conversely, even women with obvious vulvar diseases such as lichen sclerosus can also have vaginal processes such as candidiasis or atrophic vaginitis, which complicate management and prevent overall improvement. Thus, accurate diagnosis is the cornerstone of effective therapy. Because self-diagnosis and telephone diagnosis are frequently inaccurate, they should be avoided wherever possible, particularly in women with chronic symptoms.

Obtaining an appropriate history is the first step to proper diagnosis. When doing so, it is helpful to review patient symptoms in detail with a structured interview, which we routinely administer in our tertiary care vaginitis center. Patient symptoms can be broadly grouped into those of discharge, odor, itching, burning, irritation, or combinations thereof. Patients who report an abnormal discharge are asked about quantity, color, viscosity, and relationship to the menstrual cycle. Those reporting an abnormal odor are asked to describe it in more detail. With symptoms such as itching, burning or irritation, we try to distinguish among acute episodes, chronic discomfort, and acute exacerbations of chronic discomfort. Asking patients whether symptoms are located mainly in the vulva, vestibule, or vagina can be helpful. Furthermore, asking about chronic dyspareunia and whether it is with intromission as opposed to thrusting is quite important, because women with localized provoked vestibulodynia have pain with penetration but few daily symptoms.

Because patients have frequently received many different forms of treatment, we review what types of treatments have been administered (antifungals, antibiotics, corticosteroids, estrogen), the mode of administration (oral, topical, both), the length of therapy for each course (episodic or maintenance), and the response to each type of therapy (complete, partial, nonexistent). For example, if a woman reliably improves after each course of antifungal therapy only to recur later, she is much more likely to have vulvovaginal candidiasis than someone who describes no improvement, even short term. With contact dermatitis commonly found in this population, questions about soaps, feminine hygiene products, douching, and use of over-the-counter antifungal and numbing agents containing sensitizers such as benzocaine are important for identifying and removing possible irritants. In this population in which self-treatment is common, knowing the timing of the last dose of any treatment is important, because any recent medication hampers the clinician’s ability to do a thorough evaluation. Finally, a sexual history may lead to testing for sexually transmitted infections. Although this type of review may seem time-consuming, it only takes a few minutes and provides a concise picture of what symptoms are bothering the patient.

A general physical examination may yield a diagnosis before doing a pelvic examination. For example, finding erosive lichen planus in the mouth or hidradenitis suppurativa in the axillae makes it easier to recognize it on the vulva. Pelvic examination should begin with inspection of the vulva, including separating all the skin folds to look for abnormalities such as redness, erosions, fissures, ulcers, masses, atrophy, or alterations in the vulvar architecture such as perichoroidal scarring or resorption of the labia minora. Examination of the vestibule should also include palpation with a swab to look for tenderness, a sign of possible vestibulodynia. Similarly, vaginal evaluation should start with inspection to look for evidence of inflammation, erosions, and even synechiae before obtaining samples. Finally, because cervicitis can cause an abnormal irritating discharge, the cervix itself should be examined to assess for any mucopurulent discharge or areas of contact bleeding.

Practice guidelines by both the American College of Obstetricians and Gynecologists and the Centers
for Disease Control and Prevention stress the importance of in-office testing for vaginal pH, amines, and both saline and 10% potassium hydroxide microscopy. Frequently underused, vaginal pH testing in particular can be used to drive the entire diagnostic process. Figure 1 describes the pH-based algorithm that we use in practice. Saline microscopy can aid in diagnosing bacterial vaginosis and trichomoniasis. In addition, by assessing for increased white blood cells and abnormal cytology such as parabasal cells, saline microscopy tests for atrophic vaginitis and desquamative inflammatory vaginitis.

As shown in Table 1, these easily available tests can frequently diagnose common forms of vaginitis. However, office testing has poor performance characteristics, and ancillary tests are frequently indicated. Of those, yeast cultures with speciation of the organism play an integral part in diagnosing, treating, and ruling out vulvovaginal candidiasis. If Trichomonas vaginalis infection is suspected but not proven, the gold standard test remains either culture or the more easily available polymerase chain reaction (PCR) with the U.S. Food and Drug Administration–cleared APTIMA T vaginalis assay. We perform this latter test in all of our patients at risk for a sexually transmitted infection, those with many white blood cells on microscopy, and those in whom evaluation is consistent with recurrent bacterial vaginosis. The findings of vesicles, fissures, or ulcers should routinely lead to PCR tests for herpes simplex virus and possibly type-specific immune globulin G antibody testing. Polymerase chain reaction testing for Neisseria gonorrhoeae and Chlamydia trachomatis and bacterial cultures looking specifically for group A streptococci or Staphylococcus aureus should be considered in women with many white blood cells on saline microscopy. Although these latter two organisms may be commensals, they are also occasional causes of purulent vaginitis. Routine bacterial cultures are otherwise unhelpful and can be misleading, because normal vaginal flora such as Escherichia coli, Gardnerella vaginalis, enterococci, and group B streptococci are frequently found. For other tests for vaginal infections (ie, point-of-care enzymatic, antigen and DNA tests for candida, Gardnerella, and trichomoniasis, PCR testing for yeast and bacterial vaginosis), there is currently little evidence that they are superior to current gold standards, and in the case of PCR testing for yeast and bacterial vaginosis, they are more costly than current modalities. Finally, vulvar biopsies, and, less commonly, vaginal biopsies, should be considered for focal abnormalities, particularly if the etiology is unclear.

NORMAL VAGINAL PHYSIOLOGY AND DISCHARGE

With physiologic discharge occurring as the final diagnosis in 9% of the patients referred to our tertiary care program, understanding the normal vaginal environment is important. During a woman’s reproductive years, estrogen plays a key role in maintaining the normal vaginal environment. Before puberty, the vagina is thinned and has a high pH; culture of the vagina demonstrates a variety of organisms, including skin and fecal flora and lactobacilli. Under the influence of estrogen, the vaginal epithelium thickens. Lactobacilli become the dominant flora, which lowers the pH of the vagina to less than 4.7. Vaginal

discharge usually becomes heavier. Hormonal influences will change a discharge, with women noting a clear mucus midcycle to a thick white discharge at other times. Because many women and health care providers are taught that a thick white discharge is most frequently caused by vulvovaginal candidiasis, and despite evidence that the symptom of discharge is nonspecific, complaints of a thick white discharge often lead to repeated use of unnecessary antifungal therapy and raise fears of recurrent infection.

Diagnosing a discharge as physiologic can only be done by excluding potential causes, which will be discussed later. Furthermore, an abnormal discharge may sometimes be the result of occult urinary incontinence, which can be diagnosed by having a patient take phenazopyridine for 1–2 days and looking for a change in the color of the discharge. Even more uncommonly, a heavy discharge coming from the upper genital tract may be the result of an endometrial polyp or fallopian tube malignancy; when suspected, pelvic ultrasonography or sonohysterography should be considered. In our experience, when a discharge is physiologic, some patients require multiple visits with normal evaluations to be fully reassured.

**VULVOVAGINAL CANDIDIASIS**

With the proliferation of over-the-counter antifungal drugs, the annual market has been estimated at $275 million, and these medications number in the top 10 of all over-the-counter medications sold in the United States. The associated annual costs of vulvovaginal candidiasis in the United States in 1995, including medical and treatment expenses, travel costs, and time missed from work, were estimated to be $1.8 billion. Approximately 75% of women will develop symptomatic vulvovaginal candidiasis at least once in their lives, 50% of women will experience sporadic recurrences, and perhaps 8–10% will suffer from four or more episodes every year, the current definition of recurrent disease.

Although most people believe that a thick white discharge is the hallmark symptom of yeast infections, a woman’s perception of her discharge correlates quite poorly with vulvovaginal candidiasis, which typically causes itching, irritation, soreness, burning, external dysuria, or dyspareunia. Although findings may be minimal, examination may reveal vulvar redness, swelling, fissures, or excoriations; vaginal signs are usually limited to erythema or occasionally thrush. Office microscopy (Table 1), the first line in diagnosis, only has a sensitivity of approximately 50% and, depending on the health care provider, may have high false-positive rates. Yeast cultures with speciation should be obtained to confirm the diagnosis, certainly in women with recurrent infection and possibly in those in whom candidiasis is suspected but not proven. Repeated sampling through patient vaginal self-culture for yeast may further aid in diagnosis; in a study at a Dutch dermatology clinic, four weekly self-obtained cultures for yeast increased the number of positives from 59 at baseline to 111 in 441 women with suspected recurrent candidiasis, almost doubling the rate of diagnosis.

To develop a symptomatic infection, the prerequisite is colonization with Candida species, a common event for almost every woman. Vaginal colonization occurs through multiple routes, including local transport from the perineum and perianal areas, digital introduction, or sexual transmission. Candida colonization, usually with Candida albicans, is present in normal healthy women, up to 30% at any single time and 70% if followed longitudinally for 1 year;
for most, this is a transient asymptomatic event. After colonization, candida may be a commensal organism, but some women develop a symptomatic infection that goes away easily with standard antifungal therapy, perhaps with sporadic recurrence. In an even smaller group, as many 5%, there is a more complicated course with either failure to respond to treatment and the development of chronic infection or relatively rapid relapse after successful antifungal therapy and eventual recurrent disease.

The transition from asymptomatic colonization to symptomatic infection may be the result of intrinsic host, environmental, behavioral, or organism-related factors. Of these, diabetes, antibiotic and estrogen use, immunosuppression, and behavioral factors are familiar to most health care providers. Diabetics may be more prone to developing infections caused by Candida glabrata 18; glycosuria may be one mechanism contributing to both colonization and symptomatic infection.19 With antibiotic use, symptomatic episodes seem to occur mainly in women with preexisting colonization.20 In menopausal women, exogenous estrogen use increases the risk of both candidal colonization and infection.21 In our experience, systemic immunosuppression is rare in women with vulvovaginal candidiasis, although topical and systemic corticosteroid use may be more common. Sexual activity, particularly orogenital sex,22 and using contraception with oral contraceptives, an intrauterine device, or a diaphragm with spermicide have all been associated with increased infection.23 Although up to 20% of male partners of women with recurrent infections may harbor candida strains on their penises, actual transmission is thought to be uncommon, and treatment of the male partner to prevent vulvovaginal candidiasis is not recommended.7

In at least half of women with recurrent vulvovaginal candidiasis, there are no clear risk factors. Women with recurrent infections have increased vaginal Candida species colonization rates.24 As reviewed by Fidel,25 most affected women seem to exhibit altered local immunoregulatory mechanisms, which result in increased susceptibility to infection. In the past, it was felt that these women had a decreased immune response, but, more recently, it has been suggested that symptomatic candidiasis is the result of an increased sensitivity to yeast, leading to an inflammatory response to yeast colonization, which in turn causes symptoms.25 Finally, other host factors, including genetic factors, may be at play.26 Whatever the cause, most women with recurrent disease develop a pattern in which the infection clears with antifungal therapy only to recur within a few weeks to months, usually with the same strain of yeast.

In most women with vulvovaginal candidiasis, C albicans remains by far the most common cause of infection.25 As reviewed by Sobel,26 adherence of yeast cells to vaginal epithelium causes colonization, and subsequent germination promotes subsequent vaginitis. Virulence factors produced by Candida species, including secreted aspartate proteinases, proteases, phospholipases, and mycotoxins, may inhibit phagocytic activity and suppress the local immune system.26 In tertiary care vaginitis programs, approximately 30% of women will be infected by other species of yeast, with C glabrata and Candida parapsilosis being the most common.27

Most treatment guidelines distinguish between uncomplicated and complicated vulvovaginal candidiasis.6,7 In general, women with uncomplicated infections are otherwise healthy women with mild-to-moderate symptoms resulting from sporadic episodes of infections caused by C albicans; other women, including those with recurrent vulvovaginal candidiasis and those with non-albicans Candida infections, should be considered complicated and are more likely to fail standard antifungal therapy. Furthermore, with many women asymptotically colonized with yeast, when a woman with persistent vaginitis has a positive yeast culture, it can be difficult to distinguish between one who truly has vulvovaginal candidiasis as opposed to one who is asymptotically colonized with yeast and has a separate cause for the symptoms. An effective approach to resolve the question is to treat her and see if successful treatment, determined by a negative follow-up culture, is associated with a relief of symptoms. With C albicans infections, its eradication results in a relief of symptoms in up to 90% of cases.27 However, with C glabrata, perhaps 54% of women have no improvement of symptoms after successful eradication, and with C parapsilosis, 40% have a similar result.28

For uncomplicated disease, there are many available treatments, ranging from oral to topical, prescription to over-the-counter, and 1-day to 7-day regimens. Although each has its own advantages and disadvantages, they all have similar efficacy for C albicans infections with an expected cure rate of 80–90% in uncomplicated patients.7 However, these regimens are clearly inadequate in women with complicated disease with failure rates of 35% within just 1 month of treatment.29 Most experts agree that management begins by obtaining a positive yeast culture with speciation of the organism to confirm the diagnosis and identify the pathogen and then using that information to aggressively treat the infection.

For infections resulting from C albicans, the approach that is commonly used is maintenance
The advent of fluconazole in the early 1990s led to the replacement of ketoconazole by fluconazole as maintenance. In a study of maintenance fluconazole for recurrent vulvovaginal candidiasis, women were initially given three doses of 150 mg fluconazole, 3 days apart, to induce a negative culture. They were then randomized to weekly 150 mg fluconazole or placebo for 6 months (treatment phase), and then followed for an additional 6 months (observation phase). Of the 343 patients who were studied for efficacy, the proportions of women who remained disease-free at 6, 9, and 12 months in the fluconazole group were 91, 73, and 42.9% compared with 36, 28, and 22%, respectively, in the placebo group (P<.001). Only one patient discontinued treatment because of an adverse event (headache) attributable to fluconazole, and only one had a mild elevation in aminotransferase levels. Thus, maintenance fluconazole therapy is a well-tolerated and effective approach to treating recurrent \textit{C albicans} infections (Table 2). Although unstudied, alternate doses of fluconazole (100 or 200 mg) are also recommended, because they may be more easily accepted by prescription plans.

For women who recur after maintenance therapy (approximately 50%), many health care providers restart maintenance if the pathogen remains \textit{C albicans}. Although resistance to fluconazole seems to be fortunately rare, a recent report by Marchaim of clinically fluconazole-resistant \textit{C albicans} vulvovaginal candidiasis, possibly induced by long-term use of fluconazole, raises new concerns and underscores the need to bring the patients on maintenance therapy back to make sure that they have a negative culture and are responding to treatment appropriately.

There are some situations such as pregnancy, allergy, gastrointestinal discomfort, headaches, or cost, which prevent the use of fluconazole. Although alternate topical maintenance regimens with clotrimazole have been described and shown to be effective, those specific formulations are no longer commercially available. Current guidelines suggest using topical regimens intermittently. Regimens of miconazole 2% cream or clotrimazole 1% cream, used daily for 14 days, then twice a week for 6 months, have been used successfully in our practice (unpublished observation).

Although clinical and in vitro resistance to \textit{C albicans} is rare, the same cannot be said for non-\textit{albicans Candida} species. Vaginal boric acid at 600 mg, administered daily in a gelatin capsule for 14 days, is recommended as initial therapy and cures up to 70% of \textit{C glabrata} infections (Table 2). Apart from occasionally causing local irritation and an abnormal discharge, it is inexpensive and well-tolerated. The second line of therapy, fluconazole compounded into a 15.5% vaginal cream, given 5 g daily for 14 days, has been shown to be effective but has become prohibitively expensive. Limited experience with topical amphotericin B as a 50-mg suppository offers another option for \textit{C glabrata} infections. Finally, with \textit{C parapsilosis}, one case series described successful mycologic cure in 17 of 19 patients receiving 200 mg fluconazole twice a week for a month and six of six patients receiving 600-mg daily boric acid vaginal capsules twice daily for 2 weeks. For other non-\textit{albicans Candida} infections, evidence is limited to case reports or small case series, but the approaches used for \textit{C glabrata} or

### Table 2. Initial Treatment Options for Women With Chronic Vaginitis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>None indicated</td>
</tr>
<tr>
<td>Vulvovaginal candidiasis \textit{Candida albicans}</td>
<td>Fluconazole 150 mg orally every 3 d×3, then once/wk×6 mo</td>
</tr>
<tr>
<td>Non-\textit{albicans Candida}</td>
<td>Boric acid 600-mg capsules vaginally per d×2 wk</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>Metronidazole 0.75% vaginal gel 5 g/d×10 d, then twice/wk×4 mo</td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td>Tinidazole 2 g/d daily for 5 d</td>
</tr>
<tr>
<td>Atrophic vaginitis (vaginal treatments)</td>
<td>Estradiol 0.01% vaginal cream 2–4 g/d daily for 1–2 wk, then 1 g 1–3 times/wk</td>
</tr>
<tr>
<td>Desquamative inflammatory vaginitis</td>
<td>Conjugated estrogen (0.625 mg/g) cream 0.5 g twice/wk</td>
</tr>
<tr>
<td></td>
<td>Estradiol (0.010 mg) tablet/d×2 wk, then twice/wk</td>
</tr>
<tr>
<td></td>
<td>Estradiol (2 mg) ring every 3 mo</td>
</tr>
<tr>
<td></td>
<td>Clindamycin 2% vaginal cream, 5 g/d×4 wk</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone 10% vaginal cream, 3 g/d×4 wk</td>
</tr>
<tr>
<td></td>
<td>Estradiol (2 mg) ring every 3 mo</td>
</tr>
</tbody>
</table>

CDC, Centers for Disease Control and Prevention; NAMS, North American Menopause Society.
BACTERIAL VAGINOSIS

Affecting approximately 30% of women, bacterial vaginosis is considered the most common form of vaginitis.\textsuperscript{2} Associated sociodemographic factors include a 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.\textsuperscript{35} Bacterial vaginosis is marked by a disturbance in the vaginal microflora with a lack of the normal hydrogen peroxide-producing lactobacilli and an overgrowth of primarily anaerobic organisms. Initially thought to be caused by \textit{G. vaginalis}, more recent studies using standard culture and DNA-based technologies have shown that a broad range of bacteria, including \textit{Atopobium vaginae}, \textit{Bacteroides} \textit{Megasphaera} \textit{Leptotrichia} species, \textit{Mobiluncus} \textit{Nyirjesy} species, \textit{Eggerthella} \textit{Peptostreptococcus} \textit{Prevotella} species, \textit{Fusobacterium} \textit{Candida} \textit{C. parapsilosis} \textit{C. glabrata} \textit{G. vaginalis} \textit{Av a g i n a e} as a bystander in at least 50% of cases.\textsuperscript{28}

Through the vaginal examination will be normal apart from a discharge described as watery and gray. Diagnosis relies on finding three of four Amsel criteria. In women with disease, the biofilm consists primarily of \textit{G. vaginalis} and \textit{G. vaginalis} is not recommended because of a lack of specificity.\textsuperscript{6,7} Although commercial laboratories now offer PCR-based modalities to diagnose bacterial vaginosis using various criteria, there is no evidence of clear clinical superiority of these expensive tests over Amsel’s and Nugent criteria nor have they been shown to help in guiding therapy.

Metronidazole (oral or topical), tinidazole (oral), and clindamycin (oral or topical) are all recommended as initial treatments.\textsuperscript{6,7} They offer equivalent efficacy and can be distinguished from each other on the basis of cost, mode of administration, and adverse events. If patients fail an initial course of treatment, they can often be cured with a second course of the same therapy.\textsuperscript{7}

After treatment, a single recurrence or more may occur in up to 58% of women within 12 months.\textsuperscript{38} In a cohort of 130 Australian women treated with a 7-day course of oral metronidazole, Bradshaw and colleagues found that the risk factors for recurrence were a history of bacterial vaginosis, having a regular sex partner throughout the study, or having a female sex partner, and that hormonal contraception had a protective effect. In a molecular analysis of uncultivated organisms, they also found that women with both \textit{A. vaginae} and \textit{G. vaginalis} present initially had a much higher rate of recurrence at 1 year than those in whom \textit{G. vaginalis} alone was present (83% compared with 38%, \(P<.001\)).\textsuperscript{39}

Recent controversies about the role of the sexual partner and the possible development of vaginal biofilms as a result of \textit{G. vaginalis} infection have fueled new discussion of why women get bacterial vaginosis and why some women recur. After the early report by Gardner and Dukes\textsuperscript{40} describing \textit{G. vaginalis} as a possible cause of bacterial vaginosis, later research suggested that it was instead caused by complex changes in vaginal flora and \textit{G. vaginalis} was ignored until recently. Biofilms are a type of slime produced by bacteria, which coats certain surfaces and within which bacteria hide from and are protected from the effects of antibiotics; the best known example is the biofilm that occurs on infected foreign bodies such as central venous catheters. As reviewed by Verstraeten and Swidsinski,\textsuperscript{41} recent studies have found that 90% of women with and 10% without bacterial vaginosis have a complex polymicrobial biofilm, which can be demonstrated on electron microscopy of vaginal biopsies. In women with disease, the biofilm consists primarily of \textit{G. vaginalis} and sometimes with \textit{A. vaginae}. With standard antibiotic regimens, the bacterial load may be decreased but the biofilm may not be eliminated, thus setting the stage for recurrence after treatment. These data suggest that it is not the mere presence of \textit{G. vaginalis} that causes bacterial vaginosis, but rather biofilm-associated \textit{G. vaginalis}.
Gardner and Dukes had also hypothesized that bacterial vaginosis was sexually transmitted, but this theory was later discounted. However, as summarized by Muzny and Schwebke, data in favor of sexual transmission include evidence that bacterial vaginosis can be transmitted between female sexual partners, the data implicating the male partner from the Bradshaw study and the finding of similar flora in the male partners of women with bacterial vaginosis. The finding of polymicrobial G. vaginalis–dominant biofilm in men has added further fuel to the debate. 

Thus, bacterial vaginosis and its recurrence could be the result of one or several mechanisms: reinfection through sexual activity, failure to reestablish normal lactobacillus-dominant flora, or persistence of a vaginal biofilm. Based on these various theories, a variety of potential treatment interventions make sense. To date, treatment of partner studies, despite serious limitations, and recolonization with lactobacillus supplements, have shown no benefit and are not recommended. In an attempt to prevent reinfection, we routinely recommend consistent condom use for 3–6 months, although data supporting this recommendation are lacking. In women who have sex with women, the cleaning of shared sex toys between uses is encouraged, but routine screening or treatment of the female partner is not.

For now, the best approach seems to be maintenance therapy. To date, the only controlled study consisted of metronidazole gel twice weekly for 4 months after an initial 10-day course of therapy (Table 2). In this study of 127 evaluable women, infection recurred in 26% of metronidazole gel and 59% of placebo patients (P = .001). However, a 51% recurrence rate within 3 months and 59% rate of vulvovaginal candidiasis because of prolonged antibiotic therapy demonstrate the need for more effective therapy. Thus, an alternate regimen of 500 mg metronidazole or tinidazole twice a day for 7 days followed by 21 days of 600 mg boric acid daily followed by an additional twice weekly metronidazole gel regimen for 16 weeks was studied in 77 episodes of recurrent bacterial vaginosis. Cumulative cure at 12, 16, and 28 weeks from the initial visit was 87, 78, and 65%, respectively, with a failure rate of 50% by 36 weeks of follow-up. Although these results represent the most promising ones to date, it remains difficult to truly cure women with recurrent bacterial vaginosis.

TRICHOMONIASIS

Considered the third most common cause of infectious vaginitis, trichomoniasis is a surprisingly uncommon diagnosis at our tertiary care vaginitis center and is found in fewer than 1% of the women referred to us (unpublished observation). Although up to 50% of infected women may be asymptomatic, symptomatic women will complain of an abnormal discharge (clear to yellow–green and frothy), dyspareunia, vulvovaginal soreness and itching, and pain on urination. Physical findings include vulvovaginal erythema, discharge, and occasionally punctate hemorrhages of the vaginal mucosa and cervix. Most uncomplicated cases will be cured with treatment with either oral metronidazole or tinidazole along with treatment of the sexual partner. However, not all patients with trichomoniasis are straightforward. As noted in a review of 45 cases seen in a specialty vaginitis clinic, the most common issues pertaining to trichomoniasis in women with persistent vaginitis are missed diagnosis (31%) and metronidazole-resistant infection (33%); other cases were incident cases occurring in women being treated for other conditions. Occasionally, health care providers may also encounter women with allergic reactions to nitroimidazoles.

With a sensitivity of 60–70%, saline microscopy alone is simply not a good enough test to reliably diagnose trichomoniasis. Other tests, such as the U.S. Food and Drug Administration–cleared OSOM Trichomonas Rapid Antigen Test may provide a rapid (less than 10 minutes) result in the office. However, if T. vaginalis infection is suspected but not proven, culture or PCR is recommended. The mainstay of therapy has been metronidazole and, more recently, tinidazole. Although hypersensitivity reactions have been rare, patients who are allergic to nitroimidazoles represent a therapeutic challenge. Fortunately, oral or parenteral desensitization to metronidazole followed by treatment has been shown to be highly effective in a study of 15 patients treated and cured with such an approach. Thus, a patient with this uncommon clinical scenario should be managed in conjunction with an allergist.

Treatment failure can be related to noncompliance, reinfection, and metronidazole resistance, the latter estimated at anywhere between 1.7 and 10.1%. Thus, if a patient returns with ongoing trichomoniasis after treatment, health care providers should check to make sure that the treatment was taken and that reinfection did not occur. With resistance, the in vitro mechanisms are the result of both aerobic and anaerobic pathways. Because in vitro resistance correlates poorly with clinical outcome, metronidazole-resistant trichomoniasis is primarily a clinical diagnosis. With a resistant infection, Centers for Disease Control and Prevention guidelines recommend obtaining cultures
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for resistance testing and can offer management recommendations (telephone: 404-718-4141; web site: http://www.cdc.gov/std). A longer course of metronidazole, 500 mg orally twice daily for 7 days, then, if necessary, 2 g metronidazole or tinidazole orally daily for 5 days is recommended as initial therapy (Table 2). Beyond that, the most extensive experience is with high-dose tinidazole. In a series of 33 patients who failed courses of high-dose metronidazole, 92% were cured with high-dose tinidazole, 1 g two or three times a day orally along with 500 mg a day vaginally for 14 days.49

Apart from nitroimidazoles, the medical literature is peppered with other medications used in resistant trichomonas cases, mostly to no avail. However, experience with paromomycin, an aminoglycoside agent active against protozoas including T vaginalis, suggests that it may be one option in problematic women. Used as a 5% cream, 5 g vaginally nightly, paromomycin had a 58% cure rate, but vestibular and vulvar ulceration is a side effect that limits its use.49 Recently, the combination of high-dose (1 g three times a day) tinidazole and paromomycin cream nightly for 14 days was used successfully in two women with clinical resistance to high-dose tinidazole.50 To minimize the risk of ulceration, patients are instructed to apply a barrier such as petrolatum to the vestibule.

VULVOVAGINAL ATROPHY

As one might expect, symptomatic vulvovaginal atrophy, ie, atrophic vaginitis, is believed to be the most common cause of vulvovaginal symptoms in menopausal women.51 As summarized by the North American Menopause Society, most women with vulvovaginal atrophy may not relate their symptoms to menopausal changes. Furthermore, in 469 women with chronic vaginitis, it was diagnosed not only in women older than 50 years (48%) but also in younger women (5%).52 Thus, recognition and treatment of atrophy are part of any discussion of chronic vaginitis.

The main complaints are those of dryness, itching, burning, dyspareunia, and external dysuria. Despite the sensation of dryness, affected women may sometimes note a heavier discharge, yellow or watery, and even blood-tinged. Findings include atrophy of the labia majora or minora, vestibular and vaginal pallor, a loss of rugal folds, vaginal erythema or even petechiae, contact bleeding, and a yellow watery discharge. Laboratory findings are summarized in Table 1. Importantly, the degree of atrophic changes as measured by findings and maturation index does not correlate with symptoms.51

Expert consensus opinion51 recommends nonhormonal vaginal lubricants and moisturizers as well as continued sexual activity as initial therapy for women with vulvovaginal atrophy. However, very few controlled studies have been done to assess their effect. For most women, low-dose vaginal estrogen, used commonly in our practice, can provide adequate symptom relief (Table 2). Intravaginal dihydroepiandrosterone or hyaluronic acid may be considered as possible alternatives to estrogen, although published experience is very limited.51,52 For those women preferring systemic therapy, systemic estrogen (with or without progesterone) or ospemifene may be considered. The nuances and controversies surrounding treatment of vulvovaginal atrophy have recently been reviewed.51 Finally, it should be noted that more than 50% of women older than 50 years with chronic vaginitis may have causes that are separate from atrophic vaginitis with desquamative inflammatory vaginitis (15%) and lichen sclerosus (14%) being the most common.52

DESQUAMATIVE INFLAMMATORY VAGINITIS

First described by Gray and Barnes in 1965,54 desquamative inflammatory vaginitis is a condition that is unfamiliar to most health care providers yet is found in up to 8% of women with persistent vaginitis. Initially thought of as a possible bacterial overgrowth of an atrophic vagina55 or even a variant of lichen planus,56 the cause remains unknown. In a minority of women, it may be the result of a local toxin-induced inflammatory reaction to S aureus infection57 or even group A streptococcal infection.

The typical patient with desquamative inflammatory vaginitis is hypoestrogenic (on continuous low-dose birth control pills, postpartum and breastfeeding, or perimenopausal or postmenopausal) and notices the onset of an abnormal discharge, usually described as yellow or brown, along with burning and severe dyspareunia. Unlike vulvovaginal atrophy, examination reveals severe introital and vaginal erythema and a copious vaginal discharge. The presence of white blood cells on saline microscopy can distinguish it from atrophy. Because some patients with severe atrophic vaginitis may have white blood cells on microscopy, a lack of response to topical estrogen may also serve to distinguish between the two conditions. When we suspect desquamative inflammatory vaginitis, we routinely perform vaginal bacterial cultures, looking for group A streptococci or S aureus, and PCR for T vaginalis.

Because the cause remains unknown, various treatment regimens have been proposed. The most extensive published experience was from Wayne State University, where they studied 98 women...
treated in a nonrandomized fashion with either 2% clindamycin vaginal cream (5 g) or 10% hydrocortisone compounded vaginal cream (3–5 g) daily for 4–6 weeks. After initial treatment, 86% of women were fully controlled with the remainder partially improved. However, with longer follow-up at 1 year, 26% of treated women were cured, 58% required some sort of maintenance therapy, and 16% were only partially controlled with ongoing treatment. No conclusions could be made in terms of the relative efficacy of either drug. Anecdotally, because of the potential role of hypoestrogenism in triggering desquamative inflammatory vaginitis, most experts will use exogenous estrogen after initial treatment to decrease the chance of recurrence.

**Box 1. Possible Pitfalls in the Treatment of Women With Chronic Vaginitis**

**Evaluation**

Accepting patient self-diagnosis or telephone diagnosis

Failure to:

- get appropriate problem-focused history
- inspect vulva, vestibule, vagina, and cervix
- perform vaginal pH, amine test, and saline and potassium hydroxide microscopy
- obtain yeast culture with speciation, and, when appropriate, other ancillary laboratory tests*
- realize that one patient may have multiple causes for her symptoms

Depending on inappropriate criteria to diagnose or exclude vulvovaginal infections (eg, Pap test for bacterial vaginosis)

**Management**

Assuming that positive cultures or PCR for group B streptococci, Gardnerella vaginalis, enterococcus and Escherichia coli represent true infection

Treating for vulvovaginal candidiasis or bacterial vaginosis presumptively

Too short a course of treatment for patients with refractory or recurrent infections

Not bringing the patient back after therapy to assess her response

Forgetting that treatment with topical creams or ointments can cause symptoms similar to what the patient had in the past

*Trichomonas vaginalis* polymerase chain reaction (PCR) or culture, bacterial culture, Neisseria gonorrhoae and *Candida trachomatis* PCR, herpes simplex virus PCR and type-specific immune globulin G antibodies, vulvar or vaginal biopsies.

**FINAL CONCERNS**

Because women with chronic vaginitis are often desperate to try some sort of treatment to help their symptoms, it is easy to fall into many traps, summarized in Box 1. Some of these pitfalls such as self-diagnosis and telephone diagnosis are at times unavoidable. However, by acknowledging they exist and steering clear of them when possible, most health care providers should be able to help the vast majority of women with chronic vaginitis achieve significant control of their symptoms, a gratifying outcome for patient and health care provider alike. There remain unresolved issues with each of the conditions discussed that will require ongoing research in this often-neglected area of medicine.

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A number of research-funding agencies now require or request authors to submit the postprint (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. Within medical research, three funding agencies in particular have announced such policies:

- The National Institutes of Health (NIH)
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