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A Practical Update on Sexually Transmitted Infections: Advances in Diagnosis and Treatment

Highlights From a Symposium

Course Co-Directors

Jack D. Sobel, MD
Wayne State University
Harper Hospital
Detroit

Phillip G. Stubblefield, MD
Boston University School of Medicine

Jonathan M. Zenilman, MD
Johns Hopkins School of Medicine
Baltimore

Ob.Gyn. News®

Group Publisher/
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Art Director
Louise A. Lynch

Production Specialist
Rebecca Slebodnik

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Faculty Disclosure

Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. They must also disclose any discussion of investigational or unlabeled uses of products.

Dr. Eschenbach is a consultant to 3M Pharmaceuticals. **Dr. Marrazzo** discusses the use of intravaginal *Lactobacillus crispatus* capsules for the treatment of bacterial vaginosis. **Dr. Rompalo** receives grant/research support from GlaxoSmithKline and is on the speaker's bureau for GlaxoSmithKline, and Pfizer Inc. **Dr. Sobel** has received clinical grants from 3M, Pfizer Inc., and Ortho-McNeil. He discusses the investigational use of fluconazole and 17.4% topical flucytosine cream for treating *Candida glabrata*, and 10% hydrocortisone for treating erosive lichen planus. **Dr. Stubblefield** has nothing to disclose. **Dr. Zenilman** receives grant/research support from Osmetech PLC, is a consultant to Merck and Co., and is on the speaker's bureau for GlaxoSmithKline and Pfizer Inc.

Introduction

Jack D. Sobel, MD
Phillip G. Stubblefield, MD
Jonathan M. Zenilman, MD

The intent of this supplement is to provide a practical update on advances in diagnosis and treatment of the three most common causes of infectious vaginitis—diseases that practicing women's health care providers encounter daily—bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), and trichomoniasis. We are delighted that some of the leading specialists in sexually transmitted disease research were able to provide these insights into the etiology of lower genital tract infections, new treatment modalities for them, and the challenges of managing recurrent disease. Dr. Jeanne M. Marrazzo starts off these pages with a discussion of the bacterial flora in the normal vaginal environment and how endogenous and exogenous elements can disrupt this delicate microbial ecosystem. Dr. Anne M. Rompalo reviews the revised Centers for Disease Control and Prevention treatment guidelines for trichomoniasis and discusses how to document and manage metronidazole-resistant cases. In his presentation on BV, Dr. David A. Eschenbach explains why empiric treatment of the disease can cause more harm than good. He also summarizes the many associations between BV and upper genital tract infections. Dr. Jack D. Sobel provides not one but two discussions relating to VVC. The first is an update on management of routine and recurrent VVC. The second discussion is designed to aid practicing women's health care providers in making a differential diagnosis of VVC from noninfectious causes of vulvovaginitis. The following presentations were based on a continuing medical education conference held April 5-6, 2003, in Washington, D.C., and jointly sponsored by Boston University School of Medicine and Ob.Gyn. News.

Normal Vaginal Flora

Jeanne M. Marrazzo, MD, MPH

When a patient comes to a women's health care provider's office with a vaginal complaint, the likelihood that she has already tried to self-treat using one or more of the many types of over-the-counter (OTC) preparations available is high. In 2002, women in the United States spent $250 million on prescription yeast medication, an additional $250 million on OTC yeast products, $100 million on douching preparations, and $60 million on so-called genital cosmetics (such as deodorants), according to the Consumer Healthcare Products Association.

In a discussion of what constitutes normal vaginal flora, it is important to note that what is meant is a vaginal environment that has not been adulterated by such products as well as by prescribed medications. OTC douches may contain powerful surfactants and disinfectants. One popular vaginal cream includes a topical anesthetic; another contains an antihistamine. A homeopathic vaginal suppository on the market contains nonviable *Candida* organisms along with plant extracts. It is clear from the impressive sales figures that large numbers of women are spending substantial amounts of money to alter their normal vaginal flora.

Vaginal PH Is a Key Indicator

Because the other presentations in this supplement center on various pathologic conditions in the vagina, it is important to lay the groundwork here with an explanation of what characterizes a normal, healthy vagina.

A healthy vagina is highly acidic, with a pH less than 4.7. The vaginal acidity is achieved primarily by lactic acid, which is produced by human lactobacilli. The low pH has two effects. It encourages the growth of acidophilic organisms, primarily lactobacilli, and it inhibits the growth of other organisms. These other organisms may be either resident commensal flora or exogenous invaders. An elevated vaginal pH is associated with loss of hydrogen peroxide (H_2O_2)-producing lactobacilli, presence of bacterial vaginosis (BV) and trichomoniasis, acquisition of gonorrhea, and enhanced transmission of human immunodeficiency virus (HIV).

Adequate estrogen is essential for achieving low vaginal

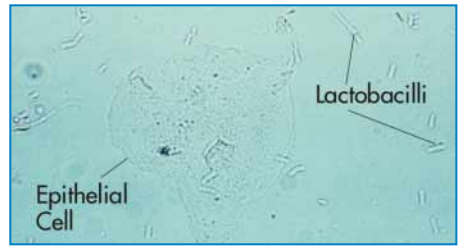
pH. Estrogen is needed to maintain an adequate squamous epithelial cell layer of the vaginal mucosa. The cell layer must be sufficiently thick (≥20 cells) to serve as a glycogen source for the lactobacilli to produce lactic acid. Although lactic acid can be produced from glucose even in the absence of lactobacilli, this action alone would not achieve sufficient vaginal acidity. The presence of lactobacilli is required to achieve a pH less than 5.

Menstrual fluid has a pH similar to that of blood, which is in the range of 7.35 to 7.45. Menses in effect introduce a pH challenge to the vaginal environment. There are typically a transient increase in pH and changes to the lactobacilli population after exposure to this alkaline fluid.[1]

Douches and the exogenous products discussed earlier have varying effects on the vaginal environment.[2] However, they typically deplete lactobacilli, especially if used repeatedly and in high concentrations. Spermicides, such as nonoxynol-9, have a similar effect.[3]

Fortunately, many of the antimicrobial agents more commonly used to treat cervicitis, vaginitis, and sexually transmitted infections, including doxycycline, azithromycin, clotrimazole, and fluconazole, do not adversely affect *Lactobacillus* levels when used short term. Use of oral or vaginal metronidazole may in fact increase the amount of lactobacilli, apparently because of the agent's targeted effect on the anaerobes. Intravaginal clindamycin, in contrast, may cause a transient decrease in lactobacilli, but this effect is not sustained.[4]

FIGURE



Lactobacilli appear as large gram-positive rods when examined via saline-wet preparation microscopy.

Host of Organisms Populate Vaginal Environment

Lactobacilli should constitute 95% of the flora found in the vagina. Ideally, they should be present at levels of at least 10^5 colony-forming units per milliliter. (See the **Figure** for an example of how lactobacilli appear in normal vaginal fluid as seen via wet preparation microscopy.) The remaining 5% of flora is composed of an array of facultative anaerobes (*Staphylococcus epidermidis*, corynebacteria, groups A and B streptococci, *Gardnerella vaginalis*, *Mobiluncus* species), anaerobes (*Peptostreptococcus* species, *Peptococcus* species, *Eubacterium* species, *Prevotella* species), aerobes (*Escherichia coli*, *Staphylococcus aureus*), *Mycoplasma hominis*, *Ureaplasma urealyticum*, and fungi (*Candida* species).[5] It should be emphasized that these organisms are normal colonizers and not pathogenic when their numbers are kept in check by a healthy *Lactobacillus* population. This appears to be true even with organisms such as *G. vaginalis*, the organism associated primarily with BV, which can be found in approximately half of asymptomatic women. This is why doing a routine culture usually is not helpful in diagnosing the cause of vaginitis in women.

Similarly, *Candida* is found in 15% to 43% of nonpregnant women, and finding pseudohyphae or yeast cells in vaginal fluid via microscopy or culture in the absence of symptoms does not define vulvovaginal candidiasis (VVC).

The lactobacilli found in the vagina have specific adherent properties that let them attach to the vaginal epithelium and colonize. Lactobacilli typically found in the gut, when transferred to the vagina, do not thrive. Neither do the bovine species of lactobacilli that are found in yogurt and other OTC products. *Lactobacillus crispatus* is thought to be the key player in the vagina, but other species, such as *Lactobacillus jensenii* and *Lactobacillus iners*, are being investigated as well.[6] Most vaginal lactobacilli produce H_2O_2, which interacts with host peroxidases to produce an oxidant that has viricidal and bacteriocidal effects. However, some women have lactobacilli that do not produce H_2O_2. These lactobacilli still appear to provide benefit, however: Women with non–H_2O_2-producing lactobacilli have been shown to have lower BV prevalence than women with no lactobacilli.[7]

If lactobacilli are so essential to vaginal well-being, an obvious question is: Why not recolonize women who lack these organisms? This is apparently the thinking behind the *Lactobacillus* products found in many health food stores. A study by Hughes and Hillier[8] looked at some of these products, such as yogurt-based douches and acidophilus powders, and found that not only are these bovine strains of *Lactobacillus* but they may be contaminated with enterococci, *E. coli*, and other organisms found in a cow's gastrointestinal tract. As mentioned previously, only human strains of lactobacilli appear to have the adherent qualities needed to flourish in the vagina.

This author participated in a still-ongoing study of an intravaginal capsule containing human *L. crispatus* that was given to women with BV along with metronidazole.[9] The data are still under analysis, but results were mixed. Among the insights gained from this study are that the vaginal microenvironment is truly complex and that tinkering with these regulators can have unanticipated consequences. Attempts are now under way to formulate a *Lactobacillus* preparation that does not alter the commensal bacteria.

Aging, Pregnancy, and Other Factors That Change Composition of Vaginal Flora

The environment of the vagina is very dynamic and is constantly responding to both endogenous and exogenous stimuli. Some of these, such as menstrual fluid, OTC products, and antibiotics, have already been discussed. Hor-

monal fluctuations and sexual practices can also cause transient alterations in the balance of flora in the vagina.[10]

As women begin menopause and their estrogen levels start to decline, shifts in the vaginal flora become evident. *Lactobacillus* levels drop, particularly of H_20_2-producing lactobacilli. Levels of *Mobiluncus* and other anaerobes increase. Interestingly, despite the drop in lactobacilli, menopausal and postmenopausal women do not appear to have increased prevalence of BV.[11]

During pregnancy, the vaginal flora do not differ substantially, save for an increase in *Candida*.[12] Racial differences in vaginal bacteria, such as African American women having fewer H_20_2-producing lactobacilli, may become exaggerated during pregnancy. It is now well known that BV increases the risk of adverse outcomes during pregnancy, but it has also been shown that the presence of H_20_2-producing lactobacilli alone is itself predictive of lower likelihood of delivering preterm.[13]

Sexual intercourse can affect the vaginal environment in a number of ways. Semen, like menstrual fluid, is an alkaline agent, with a pH of nearly 7.5. Intercourse is also associated with increased exposure to perineal residents such as group B streptococci, *E. coli*, and enterococci. Use of diaphragms is known to increase *Candida* colonization but does not appear to affect other flora. Frequent oral sex also may affect the vaginal environment; the practice is associated with increased prevalence of BV and VVC.

Diagnosing Vaginitis More Accurately

It is hoped that this discussion of how endogenous and exogenous factors may disrupt the balance of vaginal flora will aid physicians in diagnosing the root causes of their patients' vaginal complaints (**Table**). The most useful test a caregiver can administer, and one that is too frequently overlooked, is a vaginal pH test. In addition, measurement of vaginal amines also can be extremely valuable in narrowing the differential diagnosis. An amines test measures volatile amines that are the by-products of anaerobic metabolism. Elevated pH and amine values are associated with both BV and trichomoniasis.

Other common errors physicians may make in misdiagnosing vaginitis include insufficient microscopy skills (or not using a microscope at all to examine vaginal secretions), not recognizing the poor sensitivity of wet mounts for diagnosing VVC and trichomonal infections, relying on bacterial cultures for diagnosing vaginitis, and overlooking the possibility of mixed infections or that the patient may have used OTC products that can obscure diagnosis.

TABLE

Problems in Accurate Diagnosis of Vaginitis

- Failure to do microscopy
- Poor quality microscopy
- Insensitivity of wet preparation for *Trichomonas*, yeast
- Failure to do pH/amine test
- Inappropriate reliance on vaginal bacterial cultures
- Mixed infections present, undetected
- Use of over-the-counter products for self-treatment that obscure diagnosis

One final observation to make regarding vaginal flora is to call attention to an important change in the revised *Sexually Transmitted Diseases Treatment Guidelines* issued by the Centers for Disease Control and Prevention last year.[14] The guidelines use strong language to recommend that vaginal spermicides containing nonoxynol-9 not be used. Not only have several studies shown these products to be ineffective in preventing gonorrhea, chlamydia, or HIV, but nonoxynol-9 is now known to be a surfactant that disrupts vaginal cell membranes, especially when used frequently or at high concentrations, and can cause microscopic ulcerations and abrasions that can enhance transmission of disease.

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Diagnosis and Treatment of Routine and Resistant Trichomoniasis

Anne M. Rompalo, MD, ScM

According to the World Health Organization (WHO), trichomoniasis is the most common sexually transmitted infection (STI) worldwide. The agency estimated 1999 incidence at 174 million cases, but it acknowledges that data are limited.[1] The two regions in which disease rates are highest are South and Southeast Asia, with 76 million new cases annually, and sub-Saharan Africa, with 32 million cases. WHO estimates North America's incidence at just over 8 million. In the United States, trichomoniasis is second to chlamydia in estimated annual incidence of STIs.

Trichomoniasis is a parasitic disease caused by the protozoan *Trichomonas vaginalis*. It is associated with sexual intercourse and is not generally spread by fomites. It is frequently seen in combination with gonorrhea and bacterial vaginosis (BV). Rates are fairly evenly distributed among sexually active women of all ages.

Trichomoniasis has been characterized for decades, if not longer, as a nuisance disease. However, new evidence suggests that it may be more of a health threat than previously realized. A study by the Vaginal Infections and Prematurity Study Group showed that trichomoniasis may be associated with adverse pregnancy outcomes such as premature rupture of the membranes and preterm delivery.[2] It has also been associated with increased human immunodeficiency (HIV) virus transmission in women.[3]

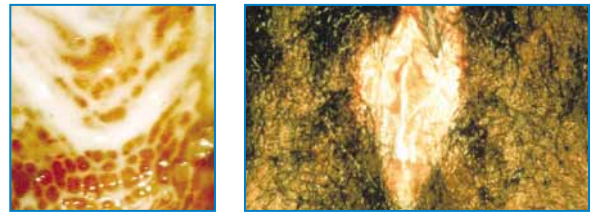
Diagnosing Trichomoniasis via Wet Preparation and Other Methods

Women are the primary carriers of the disease. Urine is thought to be toxic to the trichomonad, which is why most men appear to clear the disease rapidly when exposed. A 1963 study of men who had sex with women infected with trichomoniasis showed that 70% of the men were infected within 2 days, but only 47% were infected 2 weeks later.[4]

The majority of men are asymptomatic, but occasionally they may present with nongonococcal urethritis—an inflammation of the urethra with symptoms akin to chlamydial or gonococcal infection. The fact that most men are asymptomatic poses problems when health care providers try to treat partners of exposed women. Men who are experiencing no symptoms may balk at having to take medication.

In women, the classic presentation of trichomoniasis is a malodorous, diffuse, yellow-green discharge with vulvar irritation (**Figure 1**). The discharge and symptoms can worsen after menses. Left untreated, symptoms can persist for years. Chronic infection can cause desquamation of the vaginal epithelium and leukocytic inflammation.

FIGURE 1



Trichomoniasis classically presents with a yellow-green, malodorous discharge. However, a large percentage of infected women may be asymptomatic.

Although the frothy discharge accompanied by pruritus and burning are the most common symptoms, trichomoniasis sometimes is detected in asymptomatic women. Some of these women may present with the so-called strawberry cervix and no discharge. The strawberry hemorraghea is seen only in about 5% of cases. Its pathogenesis is not well understood.

Trichomoniasis is usually diagnosed via microscopy of vaginal secretions. However, this method has only 60% to 70% sensitivity, at best. When seen on a wet preparation under a microscope, *T. vaginalis* appears ovoid, about the size of a white blood cell, approximately 10 to 20 µm wide (**Figure 2**). It has four free anterior flagella and a fifth flagellum embedded in an undulating membrane that extends around the anterior two-thirds of the cell. Its characteristic jerky movement helps microscopists distinguish it from an epithelial cell or white blood cell.

Culture is the most sensitive commercially available method of diagnosis. However, it is not routinely used because it takes approximately 2 to 7 days to obtain results. To date, the U.S. Food and Drug Administration (FDA) has not approved any polymerase chain reaction (PCR) tests for *T. vaginalis*. This author participated in a study to evaluate a new PCR test.[5] In this observational study of 337 women seeking care at an STI clinic, the sensitivity of the PCR test was 84%, compared with 52% for wet preparation and 78% for culture. (Specificity of the PCR test was 94%.) These findings appear to indicate that trichomoniasis may be undertreated using standard algorithms for metronidazole therapy.

It should be noted, also, that in addition to *T. vaginalis*, two related species can infect humans. *Trichomonas tenax* is

found in the mouth, and *Pentatrichomonas hominis* is found in the intestine. When patients who are highly unlikely to have *T. vaginalis*, such as an elderly woman in a nursing home, have positive urine cultures, contamination of the specimen by these other species may be one possible explanation. However, only *T. vaginalis* infects the genitourinary tract.

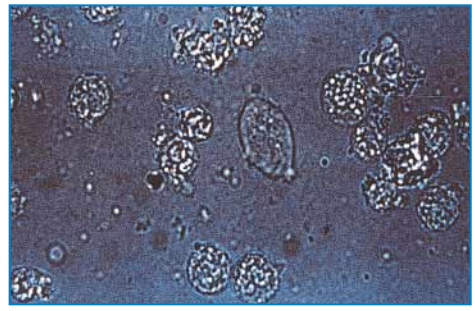
Treating Trichomoniasis

Routine Cases

The revised 2002 treatment guidelines from the Centers for Disease Control and Prevention (CDC) recommend metronidazole 2 g orally as a single dose or 500 mg orally for 7 days.[6] Randomized controlled trials that have tested these regimens have found cure rates as high as 90% to 95%. Treating sex partners may result in even higher cure rates and is to be encouraged. Metronidazole vaginal gel is less efficacious than the oral form, with cure rates of less than 50%. The vaginal gel does not seem to be able to achieve therapeutic levels in the urethra or perivaginal glands.

The FDA has not approved any therapy other than metronidazole for treatment of trichomoniasis.

FIGURE 2



Trichomoniasis, caused by *Trichomonas vaginalis* (shown), is usually diagnosed via microscopy of vaginal secretions. However, this method has only 60% to 70% sensitivity. Culture is more sensitive but is rarely used in the clinical setting.

Difficult-to-Treat Patients

For routine trichomoniasis infection, it is unnecessary for either men or women to return for follow-up treatment if they become asymptomatic. But what about the returning symptomatic female patient? Does she have a new, recurrent, persistent, or resistant infection? Treating the woman's sex partner during her initial infection may help the caregiver document possible cases of resistant disease.

About 5% of cases of trichomoniasis worldwide are estimated to be resistant to standard metronidazole therapy. Most cases are of low-level resistance in women and can be treated with increasing doses of metronidazole. Lossick and Kent[7] in 1991 published several possible regimens. Dosing ranged from 20 g to 40 g, administered over 1 to 2 weeks. They noted that optimal treatment for men is not known. The CDC recommends, in cases where initial treatment with oral metronidazole fails, re-treating patients with metronidazole 500 mg twice daily for 7 days.[6] If that fails, stepping up to a single 2-g dose of metronidazole daily for 3 to 5 days can be tried. High-level metronidazole resistance occurs in about 1 in 2,000 to 1 in 3,000 cases.

Patients with laboratory-documented infection who do not respond to the 3- to 5-day treatment regimen and who have not been reinfected should be managed in consultation with a specialist. Since therapy is limited for such cases, diagnosis should be confirmed with culture and sensitivity testing. Because very few laboratories do such testing, guidance is available from the CDC.

Symptoms of metronidazole-resistant cases of trichomoniasis are indistinguishable from routine ones. However, symptoms can persist for months or even years. Unfortunately for such patients, few alternatives to metronidazole have proved successful. A 1998 study by Nyirjesy et al[8] found topical paromomycin 6.25% cream to be useful. This medication, however, is associated with a high degree of vulvovaginal irritation and toxicity and is not widely available.

Tinidazole appears to have a good safety profile and better patient tolerability than paromomycin. A study by Sobel et al[9] demonstrated a 92% cure rate in 24 patients using a regimen of oral and vaginal tinidazole for a minimum of 14 days. Although the medication has not been approved by the FDA for this use, it can sometimes be obtained through a compassionate-use request. Tinidazole is available in Canada.

In difficult-to-treat cases, not only should sex partners be treated but both patient and partner should be counseled to avoid sex until both are cured.

The patient who is allergic to or cannot tolerate nitroimidazoles can be desensitized, then treated with the therapeutic regimen. Pregnant patients can be treated with the 2-g oral dose of metronidazole. A metaanalysis by Burtin et al[10] has shown no teratogenic or mutagenic effects from therapeutic dose ranges. Although trichomoniasis has been associated with several adverse outcomes of pregnancy, treating asymptomatic infection has not been shown to lessen the association.[11] HIV-infected patients should be treated the same as HIV-negative patients.

New on the Horizon: 'Sick Trich'

Some recent research has reported on an interesting phenomenon that has been named "sick trich," in which *T. vaginalis* itself is infected by a double-stranded (ds) RNA virus. This causes an upregulation of the synthesis of surface expression of a highly immunogenic protein, p270.[12] Infection by this dsRNA virus is also associated with differential qualitative and quantitative expression of cysteine proteinases. These proteinases in turn are linked to tricho-

Continued on page 15

New Findings in Routine and Recurrent Vulvovaginal Candidiasis Treatment

Jack D. Sobel, MD

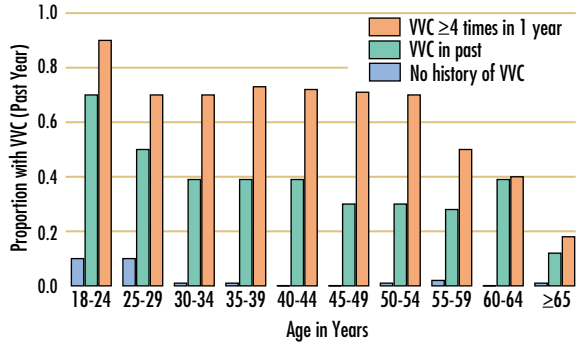
The availability of over-the-counter (OTC) medications to treat candidiasis has made it difficult to determine true current incidence rates of the disease, because so many women self-diagnose and self-treat their infections. However, based on data obtained before OTC antifungal medications became available, 75% of women have at least one episode of vulvovaginal candidiasis (VVC) sometime in their lives, 40% to 45% have more than one episode, and approximately 5% have recurrent VVC.[1]

Recurrent VVC is defined as four or more episodes of documented VVC per year. It is likely that multiple factors contribute to the etiology of recurrent disease. These will be discussed in more detail shortly. The majority of recurrent cases are idiopathic, which can be frustrating for both patient and clinician.

Women are most likely to have VVC when they are between 15 and 30 years of age. In women who have only sporadic VVC, incidence declines over the next 20 to 30 years, for unknown reasons. It is thought that, perhaps, some type of immunity develops or that monogamous behavior may be responsible for the lower attack rates. In contrast, women with recurrent VVC do not experience lower incidence until past age 55 (**Figure 1**).[2]

FIGURE 1

Vulvovaginal Candidiasis (VVC) Incidence by Age, VVC History



Source: Foxman B et al. *Sex Transm Dis.* 2000;27:230-235.

Although peak incidence occurs with onset of sexual activity, candidiasis is not classified as a sexually transmitted infection (STI). It is not associated with number of sexual partners, age of first onset of sexual activity, recent change in sexual partners, or other markers seen in classic STIs such as chlamydia and gonorrhea. *Candida albicans* is the dominant pathogen in VVC; it is responsible for more than 85% of cases.[3] There is no evidence of increasing frequency of non–*C. albicans* species, such as *Candida glabrata*, but if the patient is infected with one of these more unusual species, treatment must be altered to fit the pathogen.

Pathogenesis of Recurrent VVC Has Two Phases

As Dr. Marrazzo points out in her discussion elsewhere in this supplement, *Candida* are among the many organisms that comprise normal vaginal flora, and finding yeast cells on cultures of vaginal fluid in the absence of symptoms does not define VVC.

The pathogenesis of recurrent VVC is typified by two phases. The first is colonization of the vagina. At this stage, the patient is a carrier but is not symptomatic. Host factors that enhance susceptibility to *Candida* colonization include infection by human immunodeficiency virus (HIV), uncontrolled diabetes mellitus, and use of corticosteroids, antibiotics, or hormone replacement therapy. Behavioral factors that may facilitate colonization include frequency of sexual intercourse, orogenital sex, and use of oral contraceptives, contraceptive sponges, or an intrauterine device. Certain blood serotypes and African American ethnicity are also associated with increased risk of colonization.

The second phase in the pathogenesis of recurrent VVC is the transformation from colonization to symptomatic disease. Risk factors for the transformation phase are somewhat different from those for colonization. The major known host factors that facilitate transformation are antibiotics use, diabetes, sexual activity, and, possibly, carbohydrate excess in the diet.

Approximately 25% to 30% of women attribute their yeast infections to taking antibiotics. HIV infection is a much less prominent factor in transformation than it is in colonization. It results in a minor increase in symptomatic disease. When it does so, the clinical spectrum of the disease is identical to that in women without HIV. Recurrent VVC should not be seen as a sentinel sign of HIV infection.

Dietary factors such as consuming excessive amounts of sugar have been associated anecdotally with recurrent VVC, but an association has now been confirmed by both prospective and retrospective studies. In a recent case-control study, Donders et al[4] measured glucose metabolism in 62 women without diabetes with recurrent VVC. After ingesting 75-g glucose, women with recurrent VVC had a 15% increase of glucose circulating in their blood, compared with the control group, for at least 2 hours. The authors suggested that glucose tolerance in women with re-

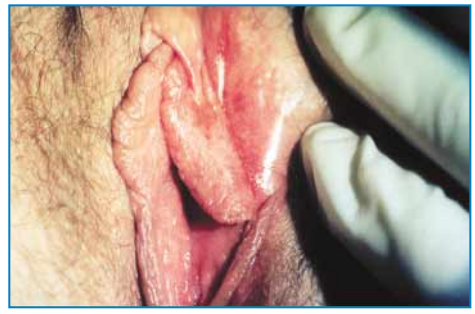
current VVC is discretely impaired. It is thought that glucose may facilitate *Candida* adhesion to vaginal epithelial cells, but this has not been demonstrated.

All 'Recurrent' Cases of VVC Are Not *Candida*

Many of the patients seen by the women's health care provider for recurrent VVC are women who have been referred by family practitioners and other nonspecialists. In this author's experience, approximately three quarters of the patients referred for recurrent VVC do not in fact have the condition. The most common misdiagnosis is bacterial vaginosis.

Genital herpes is also frequently misdiagnosed as VVC, a fact that is not well reported in the herpes literature. What typically occurs is that a patient develops pruritus, burning, soreness, and irritation. Her physician incorrectly diagnoses her as having VVC and prescribes an antifungal cream, and she shows improvement in 4 to 5 days. However, with herpes, she will also get better in 4 to 5 days. Most physicians expect herpes to manifest as a vesicle, a blister, or an ulcer. However, herpes can also appear as a fissure, which can be mistaken for *Candida* fissures (**Figure 2**). When the patient with misdiagnosed herpes experiences subsequent outbreaks, her physician may think she has recurrent VVC.

FIGURE 2



Genital herpes is frequently misdiagnosed as recurrent vulvovaginal candidiasis, especially when it presents with fissures, as seen here, rather than the more classic vesicular lesions.

Other conditions that can be mistaken for VVC include idiopathic vestibulitis syndrome, contact or irritant dermatitis, atrophic vulvovaginitis, physiologic leukorrhea, dermatoses such as lichen sclerosus, and, more rarely, desquamative inflammatory vaginitis. (Some of these conditions are discussed in more detail in the accompanying article on vulvovaginal symptoms as manifestations of systemic diseases.) Thus, the first step in treating recurrent VVC is to confirm the diagnosis. One cannot make a diagnosis of VVC on visual inspection alone. If a patient says she has used several different antifungal formulations and is not responding to them, she may in fact be communicating that she does not have a *Candida* infection.

Guidelines have been developed to help physicians designate VVC as either uncomplicated or complicated.[5] Uncomplicated cases are mild to moderate in degree of severity. Outbreaks are infrequent or sporadic. The pathogen is likely to be *C. albicans*, and pseudohyphae are seen via microscopy. The host is normal and not pregnant. VVC is considered to be complicated if it is moderate to severe, if it recurs four or more times per year, if it is non–*C. albicans* species, if budding yeast are seen via microscopy, or if the host is abnormal (e.g., has uncontrolled diabetes, is pregnant, or is immunocompromised).

Treating Recurrent VVC

Ninety percent of the patients who seek treatment for VVC have uncomplicated VVC. These women can be treated with short-course therapy with any of the many topical azole agents available. Cure rates exceed 90% in this group.

Patients with complicated VVC need prolonged therapy. This approach was validated in a study in which this author participated, comparing a single dose of fluconazole with two sequential doses.[6] In this study, women were categorized as having either severe or recurrent candidiasis. The two groups were separately randomized to receive either a single oral 150-mg dose of fluconazole followed by placebo or two sequential oral 150-mg doses of fluconazole 72 hours apart. (Because fluconazole maintains therapeutic concentrations in vaginal tissue for 72 to 96 hours, the two-dose treatment was equivalent to 1 week of therapy.) The two-dose regimen achieved significantly higher ($P = 0.015$) cure rates by day 14 in women with severe disease. Logistic regression analysis showed that this benefit may not apply to women infected with non–*C. albicans* species. Species such as *C. glabrata* have reduced susceptibility to azole agents. The only available agents that appear to be effective against *C. glabrata* are boric acid and flucytosine.

This physician authored a study of 73 women infected with *C. glabrata* who had failed treatment with azole medications.[7] The women were put on a regimen of 600 mg of boric acid per day, inserted vaginally, for either 14 or 21 days. Two thirds of the women were cured, and there was no significant difference in cure rates between the 14-day or 21-day regimen.

The patients who were not cured by boric acid were given 17.4% topical flucytosine cream to use once daily for 14 days. The flucytosine cream is not available commercially and must be prepared by a formulating company. It is very expensive. Of the 30 women who used the flucytosine cream, 27 were cured, two failed, and one was lost to follow-up.

Maintenance Therapy for Recurrent VVC

Numerous studies on treating women with recurrent VVC have shown that many women who are cured later

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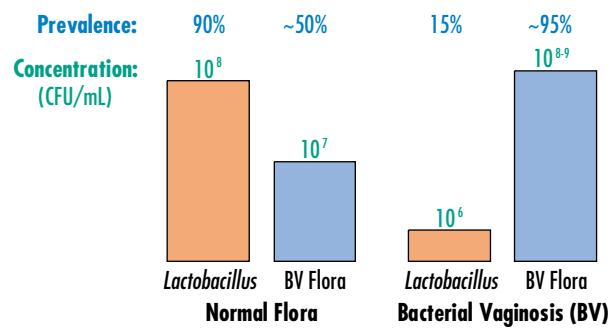
Overview of Bacterial Vaginosis and Its Role In Upper Genital Tract Infection

David A. Eschenbach, MD

Lactobacilli are the dominant microorganisms in normal vaginal flora, as Dr. Marrazzo discusses elsewhere in this supplement. In women with bacterial vaginosis (BV), both prevalence and concentrations of *Gardnerella vaginalis* and anaerobic bacteria are increased and lactobacilli are decreased. This author participated in a 2002 study that demonstrated that, in women with normal flora, lactobacilli are present in concentrations of about 10^8 colony-forming units (CFU)/mL and BV flora are present in concentrations of about 10^7 CFU/mL.[1] In contrast, the vaginal flora of women with BV show lactobacilli at 10^6 CFU/mL concentrations and BV flora at 10^8 to 10^9 CFU/mL (**Figure 1**).

Factors known to predispose women to BV are (1) lack of lactobacilli or lack of hydrogen peroxide (H_2O_2)-producing lactobacilli, (2) new sexual partner, (3) lesbian partner with BV, (4) douching, (5) antibiotic treatment, (6) coexisting sexually transmitted infection (STI) such as trichomoniasis, and (7) African American ethnicity.

FIGURE 1



CFU = colony-forming units
Adapted from Marrazzo JM et al. *J Infect Dis.* 2002;185:1307-13.

BV is not considered an STI in the classic sense of chlamydia or gonorrhea, and treating male partners does not appear to help prevent recurrence in women. However, research done on lesbian partners seems to indicate that BV is transmitted through insertive sex toys and receptive oral-anal sex.[1] This implies that something is being transmitted sexually, whether it is a phage that kills lactobacilli or some other microorganism that has yet to be identified. Research done in 1955 when Gardner and Dukes[2] first characterized BV showed that introducing *G. vaginalis* into the vagina usually does not produce BV, but introducing flora from women with BV into the vagina of someone without BV will induce BV symptoms 73% of the time.

Recognizing and Treating BV

Diagnosis of BV is made clinically using Amsel criteria.[3] Three of the following four criteria must be met:

- Vaginal fluid has pH ≥4.7;
- Discharge has a homogenous appearance;
- A positive amine odor is evident when potassium hydroxide is added to vaginal fluid ("whiff" test);
- Clue cells (squamous epithelial cells covered with bacterial rods or cocci, giving them a granular border) are present via wet preparation microscopy of vaginal fluid.

The importance of doing a pH test cannot be overemphasized. A normal pH reading tells the practitioner that the patient has either normal flora or candidiasis; an elevated pH reading indicates possible BV, trichomoniasis, or cervicitis.

Research has shown that microscopy by the average practicing physician in the United States is not very accurate.[4] For practitioners who do not feel confident of their microscopy skills, a DNA hybridization test is available, as well as alternative office-based tests that measure pH and amines. These tests may be expensive, but they are better than an unskilled microscopist in detecting BV.

Recommended treatment for BV, according to the latest revision of the Centers for Disease Control and Prevention guidelines, is to use metronidazole 500 mg twice daily orally for 7 days, metronidazole gel 0.75% intravaginally (5-g applicator) once daily for 5 days, or clindamycin cream 2% intravaginally (5-g applicator) for 7 days.[5] Alternative regimens for BV—metronidazole 2 g orally in a single dose, clindamycin 300 mg orally twice daily for 7 days, or clindamycin ovules 100 g intravaginally for 3 days—have lower efficacy against BV.

Dangers of Treating BV Empirically

Dr. Sobel emphasizes the importance of confirming a diagnosis of vulvovaginal candidiasis before treating it in his presentation on that subject in this supplement. The same is equally true for BV (**Figure 2**). Medications used improperly can upset the delicate balance of flora in the normal vagina and actually introduce disease in a population that is otherwise normal. This author participated in a dose-finding study for clindamycin cream that evaluated changes in the vaginal flora.[6] In this study, quantitative vaginal cultures for facultative and anaerobic bacteria and genital mycoplasmas were performed on women with clinical signs of BV who were treated with various con-

centrations of clindamycin cream or placebo. The cultures were obtained at baseline and approximately 1 week and 1 month after completion of therapy. In patients treated with active medication, concentrations of lactobacilli increased and concentrations of other bacteria species decreased overall, which was desirable. However, concentrations of undesirable *Enterococcus* species and *Escherichia coli* increased, apparently filling the microbial void left by the drop in other bacteria. These two organisms are not particularly sensitive to clindamycin cream. A study from the Netherlands that examined changes in vaginal flora after administration of clindamycin cream to women at high risk of spontaneous preterm birth showed that using the antimicrobial agent on women with normal flora was actually harmful.[7] Sixteen women in the study who had normal flora at baseline had intermediate flora after clindamycin treatment.

FIGURE 2

Bacterial vaginosis typically presents with a homogenous, skim milk–like discharge. Diagnosis should not be based on appearance alone but in conjunction with pH and amines tests and wet preparation microscopy of vaginal fluid.

Treating Recurrent BV

A study by Sobel et al[8] showed that treatment of BV with oral metronidazole or topical clindamycin yields high success rates initially, but within 90 days symptoms have returned in a substantial portion of women. What are the options, then, for women with recurring BV? A number of new approaches are being tested.

In her discussion on vaginal flora, Dr. Marrazzo discusses an ongoing study in which she is involved that is looking at ways to recolonize the vaginas of women with BV with strains of human *Lactobacillus crispatus*. Dr. Sobel has studied using metronidazole gel twice weekly to prevent recurrent BV.[9]

BV and Upper Genital Tract Infection

As will be discussed in more detail below, BV is associated with increased risk of postpartum endometritis following either cesarean or vaginal delivery, postcesarean wound infection, postabortion pelvic inflammatory disease (PID), postabdominal hysterectomy cuff cellulitis, and preterm delivery.

BV has some qualities that make it more likely to invade the upper genital tract than other microorganisms. It has the ability to produce sialidase, which appears to impair the body's local immunoglobulin A.[10] It is important for ob.gyns. to recognize that the cervical mucus does not provide an impermeable barrier and that there is probably a constant, low-level travel of microorganisms from the vagina to the uterus, fallopian tubes, and abdomen. Introducing exogenous matter into the vagina, whether medications or pathogens, is not like putting something on the skin. In women, there is direct communication from the vagina through the cervix into the uterus and abdominal cavity.

In women with lactobacilli-dominant flora, most of the harmful organisms are nonpathogenic or are neutralized before they can do harm. This is evidently not the case in women with abnormal flora.

Work by Watts et al[11] and Newton et al[12] showed that women with BV have a twofold increase in postpartum endometritis—a sixfold increase if they have a cesarean delivery—compared to women with normal flora. A study by Larsson et al[13] showed that PID following abortion was reduced threefold by metronidazole therapy in women who had BV.

The etiology of PID, which includes endometritis, salpingitis, pelvic peritonitis, and related infections, is assumed to occur by the ascent of microorganisms from the vagina into the upper genital tract. PID has been considered primarily a sexually transmitted disease caused in large part by gonorrhea and chlamydia; however, work by Hillier et al[14] found BV-associated microorganisms present in women with PID.

Several studies conducted in the 1990s have shown that women with BV have three to four times the risk of posthysterectomy cuff cellulitis than women with normal flora. Evidence for pretreating women with BV prior to surgical procedures such as hysterectomy is strong, but the optimal time to begin therapy has not yet been determined.

Studies that have looked at BV in patients undergoing in vitro fertilization have found that women with BV have the same conception rates as women with normal flora but a higher pregnancy-loss rate in the first trimester. It should be noted that the rate of BV or intermediate flora in women undergoing in vitro fertilization is approximately 35% to 40%. This relatively high rate is probably due to the antibiotics patients receive as part of their treatment.

A number of studies have documented an association between BV and preterm delivery. However, a large study of nearly 2,000 women by Carey et al[15] found that metronidazole therapy did not have any impact on preventing preterm delivery. This finding does not mean that BV does not cause preterm delivery, only that this antimicrobial regimen given at this time in the pregnancy did not work.

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Noninfectious Vulvovaginal Symptoms as Manifestations of Systemic Diseases

Jack D. Sobel, MD

Every women's health care provider learns in medical school that the three most common causes of infectious vaginitis are, in order of prevalence, bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), and trichomoniasis. What is often overlooked, however, is just how frequently women who present with vulvovaginal symptoms do not have any of the above diseases.

In an unpublished study in which this author participated, several thousand women at a Midwestern university completed a daily questionnaire about their vulvovaginal symptoms for 2 months. An interesting finding from this survey was that approximately one third of respondents described transient vulvovaginal symptoms that disappeared after 1 to 3 days. Women sometimes self-treated with a variety of over-the-counter medications, and most of the time their symptoms did not result in a visit to a practitioner. It is important for women's health care providers to understand how common mild to moderate vulvovaginal symptoms are, especially in a younger population.

This discussion will focus initially on patients who present with vulvovaginitis but who have normal vaginal pH, which effectively rules out BV and trichomoniasis, and who test negative for *Candida* via wet preparation microscopy or culture.

Full Dermatologic History Is Essential

Before the women's health care provider begins the clinical examination of the patient, he or she must take a complete history. Knowing whether a patient has dermatologic disorders, allergies, oral pathology, or chronic disease may aid the practitioner in making a diagnosis. If a patient says, for example, that she has systemic lupus erythematosus or Sjögren's syndrome, foremost on the physician's mind should be whether the condition might have vulvar or vaginal manifestations. An examination of the patient's skin also may reveal important clues. Eczematous lesions in the antecubital region, for example, may be an indication that a patient has eczema, which may be an explanation for her vulvar pruritus. Inspecting the mouth and oral cavity may uncover chronic mucocutaneous candidiasis, Behçet's syndrome, oral lichen planus, or other conditions that also manifest in the genitalia.

Lastly, before inserting the speculum, the physician should inspect the entire vulvar and vestibular region thoroughly. Fissures, lesions, and ulcerations that may lie hidden behind skinfolds or obscured by pubic hair will not be discovered in a cursory check.

Contact Dermatitis and Irritant Dermatitis

Among noninfectious causes of vaginitis (**Table**), the most common are contact dermatitis or chemical dermatitis, resulting from exposure to soaps, deodorants, perfumes, or other products that provoke an allergic or irritant reaction. Questioning the patient about use of exogenous agents, including spermicides, lubricants, panty liners, and feminine hygiene products, or about wearing synthetic or tight-fitting clothing will usually help the physician decide whether the woman's vaginal symptoms may be due to chemical dermatitis or an allergic reaction.

TABLE

Noninfectious Causes of Vulvovaginal Symptoms

- Irritant/chemical
- Contact dermatitis/allergic
- Atrophic (estrogen)
  - Postmenopausal
  - Postpartum
- Vulvar dermatosis
  - Lichen sclerosus, lichen simplex
- Systemic dermatosis
  - Eczema, atopic dermatitis
  - Psoriasis
- Collagen vascular disease
- Idiopathic vulvovestibulitis syndrome

Atrophic Vaginitis

Atrophic vaginitis, or, more specifically, atrophic vestibular disease, is underdiagnosed and understudied, particularly in premenopausal women. Up to 40% of postmenopausal women experience symptoms of atrophic vaginitis, which is caused by a decrease in circulating estrogen. In premenopausal women, estrogen production can be interrupted by radiation therapy, chemotherapy, immunologic disorders, and oophorectomy. Postpartum estrogen declines may also cause vaginal atrophy.

In atrophic vaginal disease, the vaginal epithelium becomes thin and atrophic from lack of estrogen, with markedly reduced secretions. This may result in dyspareunia. The woman may experience pruritus or burning, accompanied by a watery discharge.

Other Vulvar Dermatoses: Case Studies

Behçet's Syndrome

A patient was referred to this physician because of recurrent genital ulceration. Upon physical examination, a large, deep ulcer on her vulva was apparent. Questioned about her history of oral diseases, she mentioned that she experienced recurrent ulcers in her mouth. She was subse-

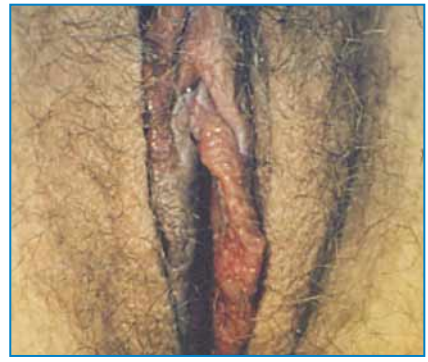
quently diagnosed as having Behçet's syndrome, a chronic inflammatory disorder of unknown etiology characterized by deep, painful, penetrating, and recurring oral and genital ulcers. The ulcers can be either single or multiple, do not form a vesicle, and last for weeks. They can occur on the vulva or in the vagina.

There are no laboratory tests for confirming Behçet's syndrome; diagnosis must be made clinically. Fortunately, it is relatively uncommon in the United States. Prevalence is highest in Japan, the Middle East, and certain Mediterranean regions. Management depends on the frequency and severity of recurrences. Patients are typically treated with intralesional corticosteroids as palliative therapy. These do not prevent recurrences. Thalidomide is sometimes used for systemic treatment.

Recurrent Erythema Multiforme

A patient was referred as having recurrent VVC because every few weeks she would experience rawness and soreness, accompanied by edema, in her labia that had an erosive component (**Figure 1**). When questioned, she acknowledged that she also had soreness in her pharynx. Examination of her palate revealed the typical finding of recurrent erythema multiforme. Recurrent erythema multiforme is sometimes drug induced, but it is most commonly associated with herpes simplex virus infection. It is usually treated with acyclovir, along with corticosteroids during the acute phase.

FIGURE 1



This patient was referred for recurrent vulvovaginal candidiasis because she experienced soreness, erythema, and edema every few weeks. When questioned about pain anywhere else, she acknowledged that these recurrences were frequently accompanied by soreness in her pharynx. Inspection of her mouth revealed oral lesions of recurrent erythema multiforme.

Psoriasis and Atopic Dermatitis With Vulvar Involvement

Another patient presented with pruritus vulvae and erythematous focal lesions that were lateral to the vagina and vulva, with a silvery sheen. These types of lesions are characteristic of psoriasis. Psoriatic involvement of the vulva is quite common. When examining the patient, the practitioner can look for signs of psoriasis elsewhere, such as knees and other extensor surfaces. Diagnosis can be confirmed by biopsy. Cases are typically managed by dermatologists using topical corticosteroids and systemic agents.

Similarly, atopic dermatitis can also present with pruritus vulvae. Once again, the practitioner can look for signs of eczematous lesions elsewhere on the body. A patient was referred to the author for recurrent VVC because she had pruritus and irritation. However, she had lesions in the perineal area that were typical of severe atopic dermatitis.

Atopic dermatitis is managed with topical corticosteroids or one of the newer nonsteroidal immunomodulatory agents.

Erosive Lichen Planus

The usual expression of lichen planus is cutaneous. Occasionally, the condition affects solely the mucosal membranes of the mouth and genitalia. In the mouth, the lesions are erosive and typically present on the buccal and gingival surfaces, surrounded by a white area (**Figure 2A** on page 14). Oral lichen planus causes soreness in the mouth and sometimes the pharynx and esophagus. There may be gingival irritation as well.

In the genital area, the vestibule is far more likely to be the site of involvement than the vagina. The erosive lesions are similar to those seen in the mouth (**Figure 2B** on page 14). There are no obvious, well-demarcated ulcers but instead a focal, multifocal, or diffuse erosion. The condition typically causes severe dyspareunia.

If the patient has florid lichen planus of the mouth, diagnosis of genital involvement is straightforward. However, occasionally a patient will present with vaginal or vulvar symptoms with no prior diagnosis of skin or oral involvement. In these cases, diagnosis is much more difficult. Biopsy is not essential to diagnosis, but, if done, should reveal loss of surface epithelium and deeper inflammatory infiltrate.

Typically, patients with erosive lichen planus have purulent discharge. A Gram stain or wet preparation examination of the discharge would likely reveal vast numbers of both polymorphonuclear neutrophil (PMN) leukocytes and mononuclear cells.

Both oral and genital manifestations of erosive lichen planus are extremely difficult to treat. For the women's health care provider, management of the disease depends on whether the erosive involvement is in the vagina or the vestibule. For the vagina, potent topical corticosteroids are required, but until the recent introduction of a clobetasol gel, such products were not commercially available for intravaginal use. Corticosteroids designed for rectal use are not strong enough. This physician has had success in treating patients by having creams containing from 10% to 15% hydrocortisone formulated. The vagina typically responds dramatically, provided the patient has adequate vaginal estrogenization. Topical estrogen may be required for optimal healing effect.

Erosive lichen planus of the vestibule is far more problematic to treat. Patients typically cannot tolerate topical corticosteroids on the raw, eroded skin surface. The typical approach is to begin management with very-low-dose corticosteroids, accompanied by topical estrogen, and to try to increase the corticosteroid's strength as the patient heals.

Desquamative Inflammatory Vaginitis

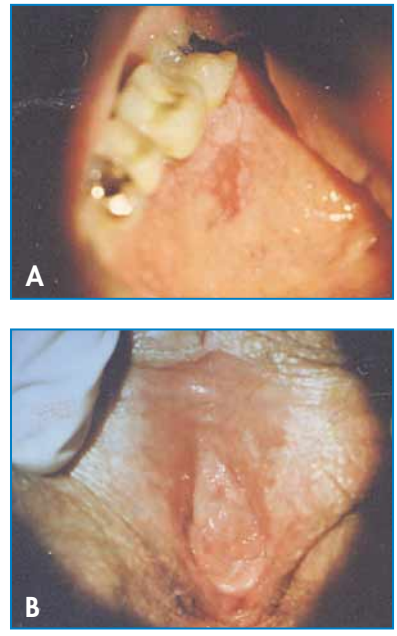
Occasionally, women will present with a vaginitis that is purulent, but they have no evidence of lichen planus in either the mouth or the genitalia. Typically, these are postmenopausal women already on hormone replacement therapy (HRT). They complain of a chronic discharge, which is greenish yellow, as well as burning, pruritus, and pain in the vagina, vestibule, or vulva. They experience not only dyspareunia but also postcoital burning. A test of the vaginal discharge will indicate pH above 6.0, and wet preparation microscopy will show numerous PMNs and mononuclear and parabasal cells. Bacteriologist Herman Gardner first described this syndrome several decades ago, naming it desquamative inflammatory vaginitis (DIV).[1] He termed it "desquamative" because of the eroded appearance of the vagina and the large number of parabasal cells representing a desquamation of the epithelium.

An inspection of the vagina may reveal anular erythematous lesions. They may give the vagina a spotted appearance, similar to the strawberry cervix. Sometimes the erosions are much more diffuse.

Distinguishing DIV from erosive lichen planus can be difficult. In fact, many patients first diagnosed with DIV are later rediagnosed as having the latter disease. It is possible that they are the same entity and that patients with DIV are women who have no oral, skin, or vulvar manifestations of the disease.

This author participated in a study in which DIV was treated with 2% clindamycin suppositories, resulting in clinical improvement in more than 95% of patients.[2] Because the patients did not get better with topical metronidazole or systemic antibiotics, it was thought that DIV may be caused by a clindamycin-specific microorganism, such as *Mycoplasma genitalium*. However, it is now known that topical clindamycin has an antiinflammatory effect in addition to its antimicrobial capabilities. Later work by Andersen et al[3] has shown that 60% to 70% of patients get better with corticosteroid suppositories. The fact that DIV responds to corticosteroids argues against its having an infectious etiology.

FIGURES 2A, 2B



Oral erosive lichen planus may present (A) with diffuse erosive lesions on the buccal surface, accompanied by gingival symptoms and soreness in the esophagus and pharynx. In the genital area (B), involvement usually centers on the vestibule, not the vagina. Lesions are similar to those seen in the mouth.

Lichen Sclerosus

A patient presented with hypopigmented skin changes lateral to the labia, along with telangiectasia, atrophy, and loss of labia minora. This agglutination of the labia minora, typically accompanied by erythematous atrophy or vestibular erosion, is typical of lichen sclerosus. In advanced disease, the clitoral hood may be ablated, and there is scarring and fibrosis of the surrounding tissue.

The vulvar component responds to corticosteroid treatment. However, erosion and inflammation in the vestibule do less well with corticosteroids. Because many of the women who present with lichen sclerosus are postmenopausal, they are often on HRT. Treating them with corticosteroids gives them two risk factors for candidiasis. Therefore, the physician must ascertain whether exacerbation of pruritus is due to the natural history of lichen sclerosus or possible superimposed VVC infection.

Graft vs. Host Disease

Patients who have received bone marrow grafts or other types of transplants frequently develop vulvovaginal symptoms. Because they are on long-term immunosuppressive therapy, they are often treated empirically for VVC. Although the most common sites for graft vs. host disease are the skin, gut, and liver, vulvovaginal manifestations can occur. The disease may present as erosions that resemble lichen sclerosus or lichen planus. These patients are managed by treating the graft vs. host disease in consultation with an oncologist.

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Diagnosis and Treatment of Routine and Resistant *Trichomoniasis*

Continued from page 7

monal adherence to the vaginal epithelium, cytotoxicity, and degradation of basement membrane components.

This author participated in a cross-sectional study in an STI clinic to determine the prevalence and clinical significance of the dsRNA virus–infected *T. vaginalis*.[13] The dsRNA virus was isolated in 21 of the 28 cases of trichomoniasis (22 women and 6 men). The virus was not associated with the presence of discharge, dysuria, or genital pruritus, irritation, or odor. Women were more commonly infected than men (86% vs. 33%). Patients with the dsRNA-infected *Trichomonas* were significantly older than patients without it (median age, 38 years vs. 23 years; $P=0.003$). However, it should be emphasized that this was a small study, with few male subjects. Although this new dsRNA virus may have important implications for virulence and pathogenesis of *T. vaginalis*, much more data are needed before conclusions can be made on its significance.

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New Findings in Routine and Recurrent Vulvovaginal Candidiasis Treatment

Continued from page 9

relapse. Even in women without recurrent vaginitis, the offending *Candida* species can be cultured again approximately 4 weeks after successful treatment (i.e., successful treatment defined as having an early posttreatment negative culture as well as cessation of symptoms). This is rarely due to reinfection. Instead, the organisms appear to have learned how to adapt. Such organisms are now being referred to as adaptive strains of *C. albicans* that are genetically selected to adapt to fluconazole. The existence of such strains may explain why so many women experience recurrent VVC.

Not only are the women who have recurrent disease more likely to become colonized after initial treatment, they are also more likely to develop symptoms. They appear less able to tolerate the organism in their vaginas than women with uncomplicated disease. Thus, a study was done to see if maintenance therapy could prevent these women from becoming colonized. This was a randomized, double-blind, multicenter study comparing fluconazole with placebo as maintenance prophylactic therapy of 284 women with recurrent VVC. Initial findings are discussed here, although the study has not yet been published.

Patients were initially given three doses of fluconazole 72 hours apart to induce clinical remission. At day 14, all patients were asymptomatic and 95% had negative cultures. However, polymerase chain reaction analysis showed that the women were still colonized with the microorganisms; there were simply too few of them to be detected by culture. The women then began fluconazole 150 mg or placebo once a week as maintenance therapy for 6 months. After they concluded the maintenance therapy, they were observed for an additional 6 months.

During the 6-month maintenance period, 128 of the 142 women taking fluconazole remained in remission, compared with only 51 of 142 women taking placebo. At the end of 12 months, approximately 40% of the women who had been on fluconazole had relapsed. However, a 60% cure rate in this difficult-to-treat population is worth noting.

Serial cultures performed throughout the study did not show emergence of resistance to fluconazole or emergence of non–*C. albicans* species. Fluconazole appeared to be ex-

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tremely safe, with no discontinuations due to adverse effects. In conclusion, fluconazole appears to be a safe and reasonable means of managing, if not curing, recurrent VVC.

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BV and HIV

Several cohort studies have shown that women with BV have higher acquisition rates of human immunodeficiency virus (HIV) than women with normal flora. The elevated pH and decreased number of H_2O_2-producing lactobacilli in the vagina that characterize BV may be two possible mechanisms by which BV may aid in HIV seroconversion. BV is also associated with lowered levels of secretory leukocyte protease inhibitors, both of which are believed to contribute to HIV resistance. BV is associated with increased levels of interleukin 1-β cytokines, which are known to upregulate HIV replication. Lastly, *G. vaginalis* and *Mycoplasma hominus* both have been shown to stimulate HIV expression in vitro.

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