



---

# Difficult-to-Manage Vaginitis

---

P. JANET SAY, MD\* and CLAUDIA JACYNTHO, MD†

\*Auckland Sexual Health Service, Auckland, New Zealand; and  
†Hospital dos Servidores do Estado do Rio de Janeiro, Health's  
Ministry Souza Marques University, Rio de Janeiro, Brazil

## Introduction

Vulvovaginitis a common condition with up to 10 million office visits a year in the United States. Management and prevention is complicated by incomplete understanding of the pathogenesis of the various conditions associated with vulvovaginitis. It is common for patients to have visited many healthcare providers as well as using numerous over-the-counter preparations (OCP). The presence of more than one infection may give mixed signs and symptoms. Therefore, stringent microbiologic diagnosis is necessary but not always available. There continues to be major gaps in knowledge about the complex vaginal ecosystem and the interaction between different bacteria and the local immunity in this specialized reproductive site. Standardized therapy has not been fully defined in unique situations such as the management of pregnant women, postmenopausal women, women with diabetes (candidiasis), and women with human immunodeficiency virus (HIV) infection. Complimentary and alternative

agents are often used, but their values have not been elucidated in properly controlled trials.

## Epidemiology

Only two thirds of patients with vaginal discharge have an infectious cause. Cervicitis from sexually transmitted infections, ie, gonorrhea, chlamydia, and herpes, should be excluded by taking a sexual history and performing appropriate tests. A discharge may be present with many other conditions, including yeast, trichomoniasis, bacterial vaginosis, desquamative inflammatory vaginitis, large macerated vaginal condyloma acuminata, retained tampons, foreign bodies, contraceptive diaphragms or sponges, cervical polyps, or vaginal and cervical tumors.

The commonly used colored and perfumed agents in the form of soaps, toilet paper, bubble baths, panty liners, and douching fluids as well as Nonoxynol 9 lead to chemical vulvovaginitis. Allergic reactions may follow the use of latex condoms, local antifungal agents, and preservative agents, eg, paraben derivatives and chlorhexidine in lubricants. Other dermatoses such as psoriasis, seborrheic dermatitis, eczema, and lichen sclerosus

Correspondence: P. Janet Say, MD, Auckland Sexual Health Service, Green Lane Clinical Centre, Private Bag 92024, Auckland, New Zealand. E-mail: pjsay@gladstoneclinic.co.nz

may primarily cause vulvitis but also may be associated with secondary candidal infection. Patients may perceive their physiological discharge as abnormal. As well as the monthly modal variations, normal vaginal discharge may change throughout the female life cycle. Despite exclusion of pathology, some patients will need careful reassurance.

Atrophic vaginitis secondary to hypoestrogenization may lead to thinning of the vaginal epithelium (25 layers to less than 10 layers). There may be inflammation, bacterial superinfection, vaginal soreness, and dyspareunia along with a watery discharge that responds to local estrogen therapy. Menopausal women may experience a rare but severe infectious vaginitis caused by *Streptococcus pyogenes* (group A Strep), however, this condition is more often seen in children.

Other rare conditions include bullous diseases, lichen planus, and the controversial other vaginitides, cytolytic vaginosis, and lactobacillosis.

There are numerous causes for vulvovaginitis in the prepubertal child. Simple causes include foreign bodies such as toilet paper. Sexually transmitted infections should alert the clinician to the possibility of sexual abuse and the need for referral to a multidisciplinary, specialized agency. Other infections that are not sexually transmitted include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and group A *Streptococcus*. Vaginal discharge also may be part of a systemic viral illness.

### ***Clinical Diagnosis***

Women with bacterial vaginosis often present with vaginal wetness, discharge, and odor. However, the majority of women do not report any signs and symptoms even with direct questioning.<sup>1</sup> Anderson et al conducted a literature review on the sensitivity and specificity of symptoms, signs, and office laboratory procedures for assessment of vaginitis. Eighteen articles were reviewed. The authors concluded that the cause of vaginal complaints may be easily diagnosed when

typical findings appear on microscopy, but there was poor correlation with individual symptoms and signs. The existing diagnostic approach fails to diagnose 30% of women with vaginal symptoms.<sup>2</sup>

### ***A Diagnostic Dilemma***

Many patients with recurrent vulvovaginal symptoms have, in desperation, sought help from multiple health providers and may have used medications that preclude accurate microbiologic diagnosis. Recurrent vulvovaginal candidiasis (RVVC) tends to be cyclical. Local antimycotics may impair cultural diagnosis for up to 1 month unless quantitative methods are used. Intravaginal clotrimazole has an inhibitory effect on trichomonas. Broad-spectrum antibiotics may confuse the picture with effects on local bacterial flora. Instructing the patient to use self-applied swabs (SAS) such as self-administered vaginal swabs when symptoms recur and prior to treatment can be useful.<sup>3</sup>

Direct microscopy is fundamental, and a good clinician can diagnose most cases of vaginitis with a microscope. Cotton wool swabs absorb white cells, but wet mounts and smears taken using plastic loops are more representative of the elements present in the vaginal discharge. A loopful (10  $\mu$ L) of secretion is mixed in with a small drop of saline on a glass slide (wet mount). Another loopful may be smeared across a slide for Gram stain. Direct wet mount microscopy and/or phase-contrast microscopy is useful for identifying the presence of motile flagellates, clue cells, mixed bacteria, *Mobiluncus* species, yeasts (blastospheres or mycelium), and polymorphonuclear leukocytes. An assessment can be made of the maturation index, an indication of estrogenization, assessing the numbers of polygonal flat superficial vaginal epithelial cells and their proportion to round or oval parabasal cells. A Gram stain of vaginal secretions can aid in the diagnosis of bacterial vaginosis using the Nugent's criteria in which a quantitative point system of 7 to 10 is diagnostic.<sup>4</sup> Vaginal pH is a useful

adjunct to the diagnosis; the sample should be taken from the lateral wall of the upper third of the vagina and ideally not mixed with mucous, blood, semen, or topical preparations. Polymerase chain reaction (PCR) is available for *Trichomonas vaginalis* diagnosis (mostly used for research purposes in the United States). It has no defined role in the clinical diagnosis of vulvovaginal candidiasis (VVC). However, as a research tool, it has confirmed the presence of continuously persistent, small numbers of yeasts in RVVC patients despite ongoing antifungal therapy.<sup>5</sup>

### Bacterial Vaginosis

#### EPIDEMIOLOGY AND PATHOGENESIS

Bacterial vaginosis (BV) is the most common cause of vaginitis in adult women. Bacterial vaginosis is associated with the loss of normal lactobacilli and a polymicrobial overgrowth that includes *Gardnerella vaginalis*, anaerobic Gram-negative rods and cocci, *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Mobiluncus curtisii*, and *M. mulieris* as well as *Streptococcus agalactiae* (group B streptococcus).

Factors associated with bacterial vaginosis include foreign bodies such as retained

tampons, vaginal sponges, douching, sex toys, multiple partners, as well as a recent change in sexual partner(s). Receptive cunnilingus has been described as a risk factor, in women who have sex with women, with strong concordance among couples suggesting a possible sexually transmitted infection, although this is still questioned. In a recent study of 890 women with BV and 890 controls, it was found that smoking was a major factor along with lack of condom and oral contraceptive use.<sup>6</sup> The pathogenesis of BV is still enigmatic. Table 1 describes some factors that may be involved in the pathogenesis of BV.

The flour paste, gray, sometimes frothy discharge coating the vaginal walls is possibly a breakdown product of cervical mucous as many of the BV-associated organisms produce sialidase (eg, *Mobiluncus*, *M. hominis*, *Gardnerella*, *Prevotella*, and *Bacteroides fragilis*). Interestingly, *T. vaginalis* also produces sialidase. Lactobacilli probably produce sialidases but this is much less than those produced by BV-related bacteria. This is most likely part of a mechanism to ensure normal cervical mucous turnover.<sup>7</sup>

*Lactobacillus crispatus* and *jensenii* are present vaginally and are both hydrogen peroxide-producing lactobacilli (HPPL+). Hydrogen peroxide limits growth of

TABLE 1. Some Factors Involved in the Pathogenesis of Bacterial Vaginosis

Host Factors	Microbiologic Factors	Biochemical Changes
Foreign bodies: tampons sponges intrauterine devices, sex toys	Possible association with an initiating infectious agent such as STI	Enzymes: mucinases and sialidoses break down cervical mucous
Sexual activity: new/multiple sexual partners, oral sex, douching	Lactobacilli: fall in numbers, rise in pH, lack of HPPL+ strains, selection of other bacteria, eg, <i>Escherichia coli</i>	Inflammatory response: (? Gardnerella toxin) leads to an increase in cytokines, proteases, and collagenases
Increased risk: smoking lack of condom and oral contraceptive use	HPPL+/myeloperoxidase/chlorine system a bleach-like action that can be limited in bacterial vaginosis	Polyamines produced by anaerobes may cause exfoliation: clue cells
Other possible predisposing factors: cervical cap spermicides, antibiotics	Gardnerella leads to rise in pH	

HPPL, hydrogen peroxide-producing lactobacilli.

catalase-producing bacteria keeping out many exogenous organisms. Some bacteria such as *Escherichia coli* and other catalase-negative organisms are resistant to the effects of the hydrogen peroxide.<sup>8</sup> The loss of HPPL+ strains from the vaginal ecosystem may be triggered by an as-yet unknown mechanism or be caused by the overwhelming effect of the introduction of high numbers of exogenous bacteria.

A study of the influence of the normal menstrual cycle on vaginal tissue, discharge, and microflora showed that *Lactobacilli* increased over the menstrual cycle, and the concentration of non-*Lactobacilli* species, including *Prevotella*, was high at menses and then decreased over the cycle.<sup>9</sup> More recent studies have shown that sexual intercourse and antibiotic use increase the risk of losing colonization by HPPL+ strains.

The effects of contraceptive methods on the vaginal microflora have been studied prospectively showing that women who use a cervical cap or diaphragm have a higher incidence of *E. coli* vaginal colonization and an abnormal vaginal Gram stain with Nugent's criteria. The use of a spermicide in the previous week was associated with an abnormal Nugent score, colonization by *E. coli*, and other bacteria. There was also a falloff in lactobacilli, but they quickly returned to baseline levels.<sup>10</sup>

Lactobacilli ensure the acidity (pH 4.0–4.5) of the vaginal milieu by producing lactic acid. *Gardnerella vaginalis* produces amino acids, which are broken down by anaerobic bacteria to produce volatile amines. This results in a rise in the pH. An unpleasant odor occurs, particularly after sexual activity. Odor is a symptom significantly associated with the presence of BV. Lactobacilli, by their production of lactic acid, also have a growth autoinhibitory effect by lowering the vaginal pH. Another property of *Lactobacilli* is their ability to autoaggregate through attachment to vaginal epithelial cells and coaggregate to other organisms such as *E. coli*, group B streptococcus, *G. vaginalis*, and *C. albicans*.

An HPPL+/myeloperoxidase/chloride system produces a potent antibacterial oxidant, which acts at a higher pH (between 5 and 6). It seems that abnormal numbers of bacteria start to appear and increase before the disappearance of HPPL+ strains.

Replacement of lost HPPL+ strains by probiotics (eg, *L. crispatus*) is currently under trial for the treatment and prevention of recurrent bacterial vaginosis (RBV). A recent trial showed that cyclically administered *L. crispatus* intravaginally after a 2-g metronidazole treatment led to colonization by this HPPL+ strain in the majority of women compared with placebo<sup>11</sup>; however, further placebo-controlled studies will be required to confirm these findings.

Studies on cytokine upregulation in BV suggest that this condition is associated with an inflammatory response. *Gardnerella's* cytotoxin can produce an inflammatory cascade and this, along with the breakdown of the mucous plug, may allow colonization of the upper reproductive tract and help explain the occurrence of pelvic inflammatory disease (PID) or chorioamnionitis of pregnancy.

Recently, *Atopobium vaginae*, an anaerobic coccobacillus resistant to metronidazole, has been described in increasing numbers in patients with BV.<sup>12</sup> This organism was characterized in 1999 and has been isolated from a tuboovarian abscess. It produces large amounts of lactic acid and was originally misidentified as a *Lactobacillus* species. It is sensitive to penicillin, cephalosporins, clindamycin, and vancomycin but resistant to gentamicin as well as metronidazole.

#### BACTERIAL VAGINOSIS TREATMENT

A 7-day course of oral metronidazole results in cure rates of 80% at 4 weeks; however, recurrence rates of 15% to 30% were recorded within 3 months in a study in which the mean follow-up time was 6.9 years.

#### RECURRENT BACTERIAL VAGINOSIS

Sobel has suggested, in the absence of a precise definition, that RBV could be defined as 3 or more attacks per year.<sup>11</sup> At present,

RBV is thought to be a relapsing condition. As many as 50% of women with BV may be asymptomatic. Many symptomatic women, posttreatment, may still have significant abnormalities of vaginal flora; the severity of these abnormalities is an indication of how early the symptoms will relapse.<sup>13</sup> There may be a failure of recolonization of HPPL+ strains, or perhaps RBV is a “reinfection” from the partner resulting from an as-yet unknown precipitating infectious cause. Male partners are not usually treated because this is not considered a sexually transmitted infection, although urethral smears of the partner(s) often show the typical morphotypes of BV. Selective antibiotic resistance has also been suggested as a factor. As Sobel states, the pathogenesis of BV is still unclear so that the cause of RBV is also bound to be less predictive.

### ***Clinical and Laboratory Diagnosis***

Symptomatic women report discharge and odor. Vaginal irritation is described in up to 45% of patients but is not associated with overt inflammation, although 30% of women will have polymorphs in significant numbers in vaginal secretion. BV is defined by 3 or 4 of Amsel’s criteria, ie, clue cells (at least one in 5 vaginal epithelial cells with edges obscured by bacteria), vaginal pH greater than 4.5, amine odor spontaneously or after addition of 10% KOH to vaginal fluid, and a thin homogenous discharge.

The laboratory diagnosis is further categorized using Nugent’s criteria involving examination of the Gram stain looking for morphotypes, which are assigned a score. A score of 7 or more is equated with BV (grade 3), 4 to 6 is regarded as intermediate (grade 2), and 0 to 3 is considered normal (grade 1). A Gram stain grade 3 smear was 100% sensitive and almost 90% specific as a diagnostic tool in a study of 308 Gram stain analyses.<sup>14</sup> Grade 2 readings correlated with BV in 37.2% of 94 occasions. Grade 1 was recorded 231 times and was often seen

after clindamycin treatment, being associated with BV only once. The intermediate grade 2 category is suggested as a Gram stain diagnosis and is not useful clinically. This is not just because of the specificity and positive predictive value, but also because women with grade 2 usually fail to respond to clindamycin treatment.

In addition to the wet prep, other screening tests are available for BV. These include Proline Iminopeptidase (PIP)—the Femexam *G. vaginalis* PIP activity test card, the BV Blue Test, which measures vaginal fluid sialidase activity, and the Osmetech Microbial Analyzer (OMA). The sensitivity and specificity of the OMA was 81.45% and 76.1% compared with Amsel’s criteria and 82.9% and 77.3% compared with Gram stain. The BV Blue Test had a sensitivity versus Amsel’s criteria of 97% and specificity of 99% and a positive predictive value of 97%. The Proline test compared with Amsel’s criteria had a sensitivity of 84% and a specificity of 92% for BV, similar to that of a Gram stain. Vaginal infections are often mixed and the BV Blue Test does not rule out the presence of yeast, *T. vaginalis* or other organisms. These tests should not be used in women who have recently douched, had sex or used spermicides, vaginal lubricants, or feminine deodorant sprays within 72 hours before testing. A recent paper showed the acceptability of a self-sampling technique to collect vaginal smears for Gram stain diagnosis of BV.<sup>15</sup>

### **BACTERIAL VAGINOSIS AND UPPER GENITAL TRACT INFECTION**

Bacterial vaginosis is associated with mucopurulent endocervicitis. Up to 50% attending a sexually transmitted disease clinic and diagnosed with a mucopurulent endocervicitis had coexistent BV. Bacterial vaginosis-associated *Prevotella* and *Peptostreptococcus* species have been found in fallopian tube tissue and endometrial biopsies of patients with acute PID. Plasma cell endometritis has been found on endometrial biopsy in association with BV. Further

studies on the issue of whether BV is associated with endometritis and infertility are necessary.

Postoperative infections, including post-abortion PID, posthysterectomy cuff cellulitis, and postcesarean endomyometritis, are associated with asymptomatic BV. Preoperative antibiotic prophylaxis can reduce these complications.

#### **COMPLICATIONS OF BACTERIAL VAGINOSIS IN PREGNANCY**

The Vaginal Infection in Pregnancy Study (VIP) has reported an increased risk (up to 40%), of preterm birth in women with BV, with 15% to 20% of pregnant women having BV.<sup>11</sup> In randomized, placebo-controlled treatment trials, patients at high risk for preterm delivery who were treated with oral metronidazole all showed considerable reduction in the instance of preterm labor associated with BV.

Unfortunately, similar results have not been forthcoming in low-risk pregnant women with asymptomatic BV. Because of adverse events in trials using topical clindamycin, this preparation is not recommended in this situation. Ugwumadu's trial supported the use of oral clindamycin in the second trimester leading to reduction in late miscarriage and preterm delivery.<sup>16</sup> Because of statistical inconsistencies in these trials, the issue of routine screening is unresolved.

#### **MISCARRIAGE AND BACTERIAL VAGINOSIS**

Bacterial vaginosis is strongly associated with second-trimester miscarriage as well as other adverse pregnancy outcomes. One study showed that treatment with oral clindamycin, 300 mg twice daily for 5 days, reduces the incidence of second-trimester loss. The relationship among BV, endometritis, failure of implantation, and first-trimester loss is unclear. There are no treatment studies to investigate the possible benefit of antibiotics on reducing the incidence of first-trimester

loss. Spontaneous clearance of BV does not occur in most pregnant women.<sup>17</sup>

#### **TREATMENT OF RECURRENT BACTERIAL VAGINOSIS**

Generally, treatment of a recurrence of BV is the same as the first episode or it can be switched from macrolides to nitromidazoles, or vice versa. With frequent recurrences, oral or intravaginal metronidazole was recommended for 3 days at the onset of menstruation for 3 to 6 months, and then antifungal treatment was offered if there was a history of candidiasis. Clindamycin therapy appears to have better activity against *Mobiluncus*, *G. vaginalis*, and *M. hominis* than metronidazole, but metronidazole does not affect *Lactobacilli*. Cure rates with 500 mg metronidazole orally twice daily for 7 days have been equivalent to clindamycin vaginal cream for 3 to 7 days and metronidazole vaginal gel once a day for 5 days. Wilson has reviewed combined approaches, including single-dose metronidazole combined with vaginal lactate tablets, as well as another regimen consisting of tinidazole (2-g single oral dose) followed by acidic vaginal gel for 3 weeks. A further approach suggested could be replacement *Lactobacilli* to maintain the normal vaginal pH and cover with prophylactic treatment to control overgrowth of bacteria.<sup>13</sup> Prophylactic twice-weekly metronidazole has been used by some women with recalcitrant BV.

#### **TREATMENT IN PREGNANCY**

Metronidazole or clindamycin have been recommended for high-risk pregnant women who are symptomatic or asymptomatic. Metronidazole is given 3 times per day (250 mg 3 times per day for 7 days)<sup>18</sup> or as a single 2-g oral dose. Clindamycin has been dosed as 300 mg orally twice a day for 7 days. Similar regimens can be used in pregnant women who are symptomatic with the addition of metronidazole gel 0.75% (one full application of 5 g intravaginally twice a day for 5 days). However, studies have not agreed

on the need for treatment in the low-risk patient population.

Treatment of BV has still not been adequately evaluated as a method for preventing morbidity in pregnancy or the puerperium or morbidity in postgynecologic surgery.

#### **TREATMENT OF ASYMPTOMATIC WOMEN IN OTHER SITUATIONS**

Although often implemented, the use of BV therapy in asymptomatic women before inserting intrauterine devices is still controversial because there are insufficient studies regarding the risk of upper genital tract infection and the use of prophylaxis.

Until studies reveal the role of ascending infection (and there is clear evidence to show that removal of BV limits HIV acquisition), most asymptomatic women should be told of the diagnosis. Treatment may be offered despite no clear recommendations. This question is relevant, because women with HIV and asymptomatic BV have BV-associated PID.

### ***Recurrent Vulvovaginal Candidiasis***

Recurrent vulvovaginal candidiasis (RVVC) is defined as 4 or more episodes of symptomatic disease per year.<sup>5</sup> After menarche, the incidence of candidiasis increases and peaks over the 30- to 40-year-old age group. In perimenopausal and postmenopausal women, RVVC occurs in association with estrogen replacement and tamoxifen treatment.<sup>19</sup> Other exogenous factors include imbalance of reproductive hormones, contraceptives, pregnancy, hormone replacement therapy, antibiotic use, diabetes mellitus, and immunosuppression (AIDS, steroids). A recent prospective study of 65 women on maintenance antifungal therapy assessed the risk factors of RVVC, and this showed increased recurrence with the use of panty liners or pantyhose and the consumption of cranberry juice or acidophilus-containing products, as well as a history of bacterial vaginosis.<sup>20</sup>

Predisposition for candida colonization may follow hypersensitivity to colored and perfumed agents, including Nonoxynol 9, vaginal douching products, panty liners, soap products, toilet paper, and additives to bath water, eg, bath bombs.<sup>21</sup>

#### **PATHOGENESIS**

Fidel et al have spent decades investigating the host defences against vaginal candidiasis. Research in animal models and clinical studies have shown that there are natural innate protective mechanisms associated with susceptibility to this infection, eg, variations in human vaginal epithelial cells inhibiting the growth of *Candida albicans*. Recently, however, the use of a live challenge model in asymptomatic humans revealed that protection against VVC coincided with a noninflammatory innate presence of the yeast, whereas symptomatic infection correlated with a neutrophil infiltrate in the vaginal lumen and increased growth of candida. Symptomatic vaginitis is therefore caused by an aggressive innate response.<sup>5</sup>

### ***Clinical Disease***

Sobel's classification of VVC<sup>21</sup> includes uncomplicated and complicated vaginitis. Ninety percent of patients have uncomplicated VVC with mild to moderate infrequent episodes of vaginitis resulting from *C. albicans*, and over 90% respond to all azoles (given systemically or topically) regardless of the duration of therapy. Patients with complicated VVC may not respond to short-course azole therapy and often require more prolonged antifungal treatment (see Table 2).

#### **LABORATORY DIAGNOSIS**

Patients may have to be reviewed on more than one occasion, especially when antifungals have been used recently and/or swabs are culture-negative for yeasts. The use of self-administered swabs is recommended to confirm the diagnosis at symptomatic recurrence and pretreatment. It is now understood that recurrent candidiasis is generally associated with the same strain of candida as

**TABLE 2. Classification of Vulvovaginal Candidiasis**

Uncomplicated VVC
• Sporadic or infrequent VVC
• Mild to moderate VVC
• Likely to be <i>Candida albicans</i>
• Nonimmunocompromised women
Complicated VVC
• Recurrent VVC
• Severe VVC
• Non- <i>C. albicans</i> candidiasis
• VVC in women with uncontrolled diabetes, debilitation, or immunosuppression or those who are pregnant

Reprinted from Sobel.<sup>21</sup>

VVC, vulvovaginal candidiasis.

the initial infection. It may also be present in the rectal site and is commonly associated with the same strain in sexual partners. Recurrent vulvovaginal candidiasis is the result of a vaginal relapse of a persistent yeast infection. It has been shown that in between acute symptomatic exacerbations, women may carry yeast in numbers that may be only detected by PCR. High vaginal swabs may provide positive cultures if there are greater than or equal to  $10^3$  blastospores/mL in the vaginal secretions. Cultures should be done whenever possible to identify the species of yeast and ensure there is not a mixed infection. New chromogenic agar media for the differentiation of candida species may be directly plated to exclude this situation. Culture ensures that isolates can be tested for mean inhibitory concentration (MIC) using the guidelines of The National Committee for Clinical Laboratory Standards (NCCLS) microbroth dilution methods with interpretive break points.<sup>22</sup>

Routine sensitivities are not generally indicated for *C. albicans* isolates. Often, the non-*C. albicans* species are more likely to be resistant in vivo. In the non-*C. albicans* yeasts, it is useful in some cases to predict the sensitivities. For example, if *C. krausei* is isolated, it is inherently resistant to fluconazole, *C. tropicalis* is variably sensitive to fluconazole, and *C. glabrata* may be dose-dependent but develop more resistance during therapy.

#### MANAGEMENT OF RECURRENT VULVOVAGINAL CANDIDIASIS

The management of recurrent *C. albicans* includes initial induction therapy to achieve mycologic remission before initiating a maintenance (pulse) regimen. A multicenter, double-blind study of initial induction therapy in 560 women with RVVC has shown that an initial dose of 150 mg fluconazole with a repeat dose 3 days apart was adequate to achieve control.<sup>23</sup> Sobel's recent, multicenter, prospective, randomized study on maintenance fluconazole therapy for recurrent vulvovaginal candidiasis used open-label remission induction with fluconazole. This study of 387 women, half on placebo, used 3 150-mg fluconazole doses given 72 hours apart as induction followed by 150-mg pulses weekly. Disease-free women at 6 months were 90.8% (35.9% placebo), at 9 months 73.2% (27.8%), and at 12 months 42.9% (21.9%). Median time to clinical recurrence was 10.2 months as compared with the placebo group of 4 months.<sup>24</sup>

Other recommendations for the management of recurrent *C. albicans* with suppression therapy include a longer duration of initial induction therapy. The optimal maintenance regimen is unknown but these include 400 mg clotrimazole vaginal suppositories once a week or 100 to 150 mg fluconazole orally once weekly or less frequently. The Centers for Disease Control and Prevention guidelines\* have included ketoconazole at a lower dosage (ie, 100 mg daily orally with monitoring for hepatotoxicity) and itraconazole (400 mg once monthly or 100 mg daily) ensuring adequate absorption. Swallowing itraconazole capsules with acidic beverages, eg, non-diet cola, ensures adequate acidity for absorption. All these regimens may prevent relapse in up to 50% of women but generally need to be continued for at least 6 months.

\*Of note: a new sexually transmitted disease treatment guideline will be available in 2006.

In *C. albicans*-infected women, symptomatic occurrences are suppressed as long as there is compliance with treatment. If a relapse occurs, the initial induction therapy may have to be repeated before continuation of maintenance therapy. Sobel has recommended, in proven rerecurrences with identical organisms, that the induction regimen followed by maintenance should be given for up to 12 months.

Fluconazole-resistant *C. albicans* is very rare, although it has been described frequently in the immunosuppressed, particularly HIV-positive patients, with specifically oropharyngeal and esophageal candidiasis.

#### **DRUG INTERACTIONS IN ORAL AZOLES**

Triazoles such as itraconazole and fluconazole, with a half-life of 4 or 5 days, may interact with other drugs significantly. They are inhibitors of cytochromes (CYP) P3A4. These catalytic chemoproteins metabolize through P-450 enzymes, and their reduced activity may lead to an increase in the bioavailability of the interreacting drug and therefore increased toxicity. Cardiac dysrhythmia may be associated with high-dose fluconazole and itraconazole when combined with astemizole, cisapride, and the new H1-antihistamines.

### ***Difficult-to-Manage Vulvovaginal Candidiasis and Recurrent Vulvovaginal Candidiasis***

#### **PREGNANCY**

Topical azoles in the form of creams and pessaries are often used in pregnancy. Nystatin pessary or vaginal cream (100,000 units) was classically used for a 14-day course. Recently, imidazoles such as clotrimazole cream (1%) are inserted for 7 days. In recurrent cases, 500-mg clotrimazole pessaries may be used intravaginally every 1 or 2 weeks

for symptom control. Oral antifungal therapy is used at times in pregnancy; however, it is a class C drug and therefore not recommended. Teratogenic effects have occurred in several patients on long-term and high-dose fluconazole.<sup>25</sup> Some women describe their RVVC after a specific pregnancy, whereas others with RVVC have found it to improve during pregnancy.

#### **HIV**

Recurrent vulvovaginal candidiasis was once thought to be a marker for HIV positivity in women. This was to be expected with the immunosuppression and use of broad-spectrum antibiotic treatments for opportunistic infections. However, recent studies have not always confirmed its increased frequency in this group, nor have they confirmed differences in clinical and microbiologic findings or response to standard therapy between HIV-positive and -negative women. There have been studies showing increased HIV shedding in patients with VVC and decreases in HIV1 RNA after successful therapy for candidiasis.

#### **DIABETIC WOMEN**

Patients with uncontrolled diabetes may have only partial response to suppression and maintenance therapy with systemic antimycotics. Relapse is common and a long-term management schedule for these difficult-to-treat patients is essential from the start. Diabetic women are more prone to non *C. albicans* infections, particularly *C. glabrata*.

#### **IATROGENIC ASSOCIATED RECURRENT VULVOVAGINAL CANDIDIASIS**

Patients on long-term, intermittent antibiotics and high-dose steroid therapy may present with recalcitrant RVVC. A long-term strategy of management should be considered, including limiting these therapies whenever possible and dealing with the underlying disorder.

#### MANAGEMENT OF NON-CANDIDA ALBICANS VULVOVAGINAL CANDIDIASIS

Whereas over 85% to 90% of VVC is caused by *C. albicans*, other causes (in order of incidence) include *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, and *C. guilliermondii*. The most common of the non-*C. albicans* species is *C. glabrata*. *C. glabrata* is seen as a very small yeast without mycelium on microscopy of wet preparations of vaginal discharge. *C. glabrata* tends to be resistant to fluconazole. *C. krusei* has both blastospores (budding yeast cells), and pseudomycelium on microscopy and is also resistant to fluconazole. Patients with saccharomyces have poor response to oral azoles. It is important to confirm the identity of the yeast and to rule out mixed infections using chromogenic agar plates.

One treatment that is ideal for the non-albicans species is boric acid powder. It consists of compounding 600 mg in a gelatin capsule and is inserted vaginally daily for 14 days. Cure rates of approximately 70% have been noted. With recurrence, a repeat course for 14 days could be tried and then twice-weekly boric acid for several months if needed. Boric acid absorption from the vagina has been reported on blood boron analysis as less than 10 µg/L, but long-term use leading to systemic toxicity has not been investigated. Another agent to consider is intravaginal 100,000 units/g Nystatin cream per day for 3 to 6 months. Use of aqueous gentian violet 1% is not encouraged because it is an aniline dye. A vaginal cream of flucytosine (a 17% solution) for 14 days has been described as useful. It has also been mixed with amphotericin B for use in refractory *C. glabrata* infections.<sup>26</sup>

#### NEW DEVELOPMENTS IN ANTIFUNGAL TREATMENT

Voriconazole is a new triazole that has fungistatic activity against yeasts, including *C. albicans* resistant to fluconazole and *C. glabrata*. New agents include rilopirox (a topical agent) and eberconazole (another

imidazole) that may be effective against *C. krusei* and *C. glabrata*.<sup>27</sup>

Combination therapy, eg, terbinafine and other antifungals, have not shown antagonism. Although synergy was not achieved, there was a decrease in MIC in one or both drugs. Drug-resistant genes in *C. albicans* are under investigation as are immunotherapeutic therapies such as vaccines, immunomodulators, and activated transferrin.

### Trichomoniasis

#### EPIDEMIOLOGY

Vaginal trichomoniasis is the most common nonviral sexually transmitted infection of the genitourinary tract with approximately 120 million women worldwide diagnosed with this infection every year.

Reports based on the literature show highly divergent prevalence rates of trichomonas in different countries and even in different geographic regions. There are approximately 3 million cases of trichomonas in the United States annually, and it accounts for approximately one fourth of vaginitis cases.<sup>28</sup>

The prevalence of trichomonas in a population attending a gynecology clinic in the developed city of Brasilia was 6% (similar to the United States).<sup>29</sup> The prevalence was 10.3% of the general female population in the rural hinterland of the Brazilian northeast, where the infrastructure is precarious in comparison to other areas in Brazil.<sup>30</sup>

The prevalence of trichomonas in Brazil is constantly high (up to 37%) in sex workers. There appears to be extremely low rates in rural areas in Bangladesh (0.8%) and in a family planning clinic in Hanoi, Vietnam (1.3%).

The current consensus is that trichomonas infection is almost exclusively acquired through sexual intercourse or contact. Trichomonas has been relatively trivialized and has received only scant attention. More recently, trichomonas has been associated with premature birth and HIV transmission.

### RISK FACTORS

Women colonized with *T. vaginalis* are significantly more likely to be black, cigarette smokers, users of illicit drugs, unmarried, less educated adolescents, having problematic partner relationships and of low socio-cultural and economic groups.<sup>21</sup>

Several sexual behavioral factors associated with trichomonas include having a greater number of sexual partners both lifetime and in the last year, 5 years or more of sexual activity, a history of gonorrhea or other sexually transmitted infections, and early coitarche. Trichomonas is the most common sexually transmitted infection in older women. Chronic asymptomatic infection can persist for several decades.

### PATHOGENESIS

*T. vaginalis*, a motile flagellated protozoan, attaches to mucous membranes and ingests other bacteria. If symptomatic, it causes a green, sometimes frothy discharge with a high pH and fishy odor. Only a few protozoa are necessary for trichomonas transmission to a mature female. There are several serotypes of *T. vaginalis* with different pathogenic potential. The morphology of *T. vaginalis* depends on various factors, including the temperature, the pH, and the redox potential of the infected sites (the vagina, the urethra, and the Bartholin's and Skene's glands).

The mechanisms by which *T. vaginalis* causes disease remain to be elucidated. Trichomonas ranges from an asymptomatic condition to an inflammatory disease, depending on the host response and other factors not completely understood.

### CLINICAL AND LABORATORY DIAGNOSIS

Simple microscopy, pH determination, and amine tests usually confirm the diagnosis of trichomonas. It is important to remember that multiple causes of vaginitis may be concomitant. A careful history and physical examination may help differentiate them. Because trichomonas is a sexually transmitted infection, specific tests should be performed

for other sexually transmitted infections, including cervical swabs for upper genital tract infections such as gonorrhea and chlamydia and examination for herpes as well as for other causes of vaginitis. In only 2% of cases, the classic strawberry cervix is visible. This has to be differentiated from changes associated with hypoestrogenization or desquamative inflammatory vaginitis. The typical signs and symptoms of trichomonas are listed in Table 3. However, trichomonas may not present with typical signs and symptoms in many women.

The diagnosis of trichomonas is confirmed by wet mount microscopy visualizing the typical trichomonads, motile oval flagellates, along with the usual high numbers of polymorphonucleocytes. In chronic cases, only a few trichomonads may be seen, but this is variable, and in these situations, culture is recommended and, if available, PCR.

The Papanicolaou test is the most readily available cytologic method for screening cellular abnormalities and sexually transmitted pathogens in most developing countries. However, it is inadequate for the diagnosis of trichomoniasis, although like wet mounts, it has low sensitivity but high specificity for detecting vaginal trichomonas. The wet mount should be taken after the menstrual period optimally, from the posterior vaginal wall.<sup>31</sup> If the vaginal pH is 5 or more, the wet mount

**TABLE 3. Signs and Symptoms of Trichomonas**

- 
- Soreness in and around the vagina and vulva, at times localized to the vestibule
  - External dysuria
  - Dyspareunia
  - Inability to tolerate speculum insertion
  - Discomfort in the pelvis (rare)
  - Frothy, fishy smelling, greenish-yellow discharge
  - Elevated vaginal pH (often up to 6.0)
  - Positive whiff test
  - Punctate hemorrhages (petechial strawberry cervix)
  - Erythema of the vestibule and labia minora
  - Erythema in the Bartholin's and Skene's duct openings
  - Bleeding with intercourse
  - Double capillary loops on colposcopy
  - Superficial "scalded" rash on upper thighs
-

is negative and symptoms and signs of BV have been excluded, a specific culture is indicated to grow *T. vaginalis*. The In Pouch Trichomonas vaginalis culture system (BioMed Diagnostics, Santa Clara, CA), which consists of culture medium in a clear plastic envelope, is comparable in sensitivity with Diamond's medium.

The PCR is the most sensitive test and many in-house PCRs are available; however, there are variable sensitivities between the tests, which may be based on technical variations or be related to strain variability. At this point in time, the PCR is used for research in the United States. A vital stain, acridine orange, has been used to show the presence of typical trichomonads by DNA staining; unfortunately, it has a high incidence of false-positives as well as false-negatives. In Brazil, scientists are developing a new diagnostic test for human trichomoniasis using FLUTAX, a fluorescent toxoid that stains the microtubule structure in living trophozoites of *T. vaginalis* in urine and vaginal discharge.<sup>32</sup>

#### MALE DIAGNOSIS

The signs and symptoms in men include a thin whitish discharge or occasionally a purulent yellow discharge from the penis and painful or difficult urination. However, most men do not experience any symptoms. The urethra is the main site of infection in men, but only small numbers of protozoans may be present, possibly as a result of the presence of zinc ions in healthy prostatic secretion. The role of trichomonas in causing prostatitis remains unclear, but it has been isolated from the epididymis. Recently, semen has been shown to be the best specimen to confirm diagnosis.<sup>33</sup> Urethral swab cultures or spundown first urine samples (30 mL) are examined by microscopy for protozoans, and are then cultured. Modified Diamond's media may have to be incubated for up to 10 days to ensure a positive culture in the presence of few trophozoites.

#### DIFFERENTIAL DIAGNOSIS

Lactational/postpuerperal hypoestrogenization can mimic trichomonas. The symptoms are similar: discomfort with urination, vaginal itching and dryness, dyspareunia, and vaginal discharge. The vaginal mucous membranes are bright red and the vaginal pH becomes more alkaline ( $\text{pH} \geq 5$ ). Microscopic examination of the vaginal discharge shows decreased lactobacilli, decreased superficial cells, and increased basal and parabasal cells. Women with desquamative inflammatory vaginitis can present with a purulent discharge and dyspareunia. The yellow discharge has a high pH. Macular spots may be present on the cervix, and microscopy reveals increases in polymorphs and parabasal cells. Perimenopausal women with hypoestrogenization may have a watery discharge with a high pH, few epithelial cells, and parabasal cells on microscopy. The discharge of BV has an alkaline pH; however, there are generally no obvious inflammatory cells. The presence of clue cells or mixed organisms, particularly *Mobiluncus* species on Gram stain, with a lack of lactobacilli, using Amsel's criteria confirms the diagnosis.

#### TREATMENT OF INITIAL TRICHOMONAS INFECTION

The CDC guidelines for sexually transmitted infection treatment recommend the oral nitroimidazoles as first-line treatment. Metronidazole is readily available in the United States and approved by the Food and Drug Administration for use throughout all trimesters of pregnancy. The CDC 2002\* recommended regimens of metronidazole include 2-g single dose or 500-mg twice a day for 7 days. These regimens have cure rates of 92% to 95%, and when treatment of sex partners is ensured, this may be increased.<sup>34</sup> Alcohol consumption with metronidazole can trigger cramps, nausea, vomiting, severe headaches, and flushing.

\*Of note: a new sexually transmitted disease treatment guideline will be available in 2006.

Recently, tinidazole has been approved in a 2-g single dose for the treatment of trichomonas.

#### **RECURRENT TRICHOMONIASIS— DIFFICULT TO TREAT**

Distinguishing between reinfection and relapse of trichomonas is not always possible. Recurrent trichomonas is most often the result of reinfection from an untreated partner. Total resistance to the nitroimidazoles is very rare; partial resistance has more often been described. Metronidazole may be broken down *in vivo* in the local vaginal milieu by other bacteria if they are present in large numbers.

#### **THE MALE CONNECTION**

Spontaneous cure in men is often seen, with the trichomonads and their symptoms disappearing in a few weeks without treatment. However, a few men carry the infection for several months. Men can transmit the disease to their sexual partners even when symptoms are not present. All male partners who are not allergic to nitroimidazoles should be treated to stop reinfection. Single doses of nitroimidazoles are generally inadequate to eradicate trichomonas from males; thus, a week of treatment is recommended.

It is wise to screen for trichomonas in a male with recurrent nongonococcal urethritis (NGU), negative for chlamydia and *Ureaplasma*. Approximately 5% to 10% of patients with NGU have trichomonas diagnosed.<sup>21</sup>

The majority of trichomonas in Brazil is related to a third party. Female promiscuity is not tolerated in Brazilian rural culture. In a study of 341 women in rural Brazil, almost 90% were married and only 3% reported condom use. However, their husbands or partners had sexual intercourse with other women, including sex workers.

The Cochrane Review analyzed randomized or quasirandomized trials of different treatment strategies in women with trichomonas.<sup>35</sup> The quality of the trials was assessed and 54 had data extracted by 2 reviewers

independently using standard criteria. Treating the partner can be effective in decreasing reinfection rates. Further research should focus on developing effective partner treatment strategies to prevent reinfections and reduce the prevalence of trichomonas.

#### **RESISTANCE TO THE 5 NITROIMIDAZOLES**

Metronidazole and other nitroimidazole drugs (such as ornidazole, tinidazole, nimorazole, carnidazole) have been used as antitrichomonal agents for more than 30 years.

Treatment options are limited when patients fail to respond to metronidazole. Those with reduced *in vitro* susceptibility to metronidazole respond to high-dose, but poorly tolerated, regimens of metronidazole. For patients who fail to respond to the initial metronidazole treatment, the 2002 CDC guidelines advise retreatment with 500 mg metronidazole twice a day for 7 days and then 2 g metronidazole per day for 3 to 5 days, if necessary. If treatment fails again, increasing doses of metronidazole may still be tried and metronidazole susceptibility testing considered.

Alternative regimens have included 500 mg tinidazole orally 4 times per day together with 500 mg intravaginally twice a day for 14 days or 1 g orally 3 times a day and 500 mg vaginally 3 times a day for 14 days. The tinidazole plasma elimination half-life is approximately twice that of metronidazole (67 hours vs. 12–14 hours). Analysis of trichomonads recovered from patients refractory to metronidazole show that some trichomonas strains are more susceptible to tinidazole. The optimal or minimal dose of tinidazole for cases that are clinically resistant to metronidazole is by no means established. Topical paromomycin was effective in 7 (58%) of 12 patients treated, but frequent local vulvovaginal adverse reactions preclude extensive use.<sup>36</sup>

In a 3-year period, 612 patients (244 females and 368 males) suspected of sexually transmitted infection were examined

clinically and microbiologically at the Institute of Dermatovenereology in Belgrade. *Trichomonas* infection was found in 90 (36.88%) of 244 tested females and in 126 (32.34%) of 368 males. The patients detected for trichomonas were treated according to the CDC protocol; 3 patients (1.39%, 2 males and one female) were not cured but trichomonas was eliminated by metronidazole in a dose of 3 g daily for 2 days.<sup>27</sup>

The limiting factor in most patients is side effects to oral metronidazole, mainly dose-limiting nausea. In a few cases, investigators resorted to high-dose intravenous metronidazole, although this treatment may be associated with seizures and encephalopathy. High-dose therapy with metronidazole, particularly when long term treatment is used, is also associated with other important complications, including pancreatitis, neutropenia, and peripheral neuropathy.

Another nitroimidazole derivative, ornidazole, has been described as causing hepatotoxic damage resembling acute cholestatic hepatitis. Four trials compared oral metronidazole treatment with oral and intravaginal treatment together and found the combined regimen more effective. Six trials compared tinidazole with ornidazole. The ornidazole group had a higher incidence of side effects, most notably fatigue. There is little clinical experience with other agents such as mebendazole and furazolidone.

In conclusion, most trials in women using single-dose treatment with any nitroimidazole drug resulted in parasite cure rates above 90%. Although rarely severe, side effects seem to be relatively common and dose-related. Every effort should be made to treat partners. From the limited evidence reviewed here, there seems to be little difference between the various nitroimidazoles.

#### **METRONIDAZOLE ALLERGY**

In the presence of hypersensitivity or severe intolerance to metronidazole, and therefore usually to the other nitroimidazoles, there are less effective treatment options.<sup>21</sup> Intravaginal administration of 5 g paromomycin

once per day for 14 days had a 58% cure rate in resistant trichomoniasis, but was frequently associated with excoriation and ulceration.<sup>36</sup> Other alternatives include clotrimazole vaginally, douching with zinc sulfate (1%), or povidone-iodine. Arsenic pessaries (acetarsol) at a dosage of 500 mg daily for 10 days in metronidazole-resistant *T. vaginalis* was used in the 1930s and has been reintroduced in the United Kingdom.<sup>37</sup>

Allergy to metronidazole is rare; however, when it occurs, it generally manifests as an immediate hypersensitivity reaction with urticaria, rash, pruritus, vasodilatation, flushing, and bronchospasm. A desensitizing incremental dosing protocol has been described, beginning with low intravenous subtherapeutic doses increased up to the treatment dose. Despite this, severe and life-threatening hypersensitivity reactions have been described during desensitization, which may preclude its use in pregnant women. Also, serum sickness and Stevens-Johnson syndrome have been reported.

#### **CROSS-RESISTANCE AMONG 5 NITROIMIDAZOLE DRUGS**

Cross-resistance among the group of 5 nitroimidazole drugs is common. The incidence of drug resistance in trichomonas appears to be on the rise and improved surveillance of treatment failures is urged.<sup>38</sup> Alternative therapies, including herbal remedies, have not been investigated adequately.

#### **PREGNANCY AND LACTATION—COMPLICATIONS AND DIFFICULT TO TREAT**

Cotch et al evaluated prospectively the association between *T. vaginalis* and the risk of adverse pregnancy outcome in a large cohort of ethnically diverse women (13,816 women). The prevalence of *T. vaginalis* by culture was 12.6%. After considering other recognized risk factors, including coinfections, pregnant women infected with *T. vaginalis* at midgestation were statistically significantly more likely to have a low-birth-weight infant, to deliver preterm, and to have a preterm

low-birth-weight infant. Compared with whites and Hispanics, trichomonas accounts for a disproportionately larger share of the low-birth-weight rate in blacks.<sup>39</sup>

The National Institute of Child Health and Human Development 2001 screened pregnant women for trichomonas by culture and treated them with metronidazole. Preterm delivery occurred in 19% of the metronidazole group and 10.7% of the placebo group. They concluded that treatment of pregnant women with asymptomatic trichomonas does not prevent preterm delivery, and therefore routine screening and treatment of asymptomatic pregnant women for this condition cannot be recommended.<sup>40</sup> The same authors in 2003 showed that metronidazole treatment of women with trichomonas significantly increased the risk of preterm birth compared with placebo. Another trial has supported these findings, which suggest that treatment of trichomonas during pregnancy is associated with adverse infant outcomes and that this detrimental effect might be the result of metronidazole. It is important to remember that further investigation of these issues is needed secondary to limitations in many trials.

Metronidazole is excreted in breast milk. A single 2-g dose administered to a nursing mother would result in a concentration of 25 mg/L metronidazole in her breast milk. It is advised that mothers stop breast feeding for 24 hours after ingesting metronidazole.

### ***Complications: Pelvic Inflammatory Disease***

Trichomonas is now the object of serious investigation attempting to clarify its role in such conditions as PID. Trichomonas has been associated with postoperative vaginal cuff cellulitis after hysterectomy. A preoperative or perioperative antibiotic that includes coverage specifically against trichomonas has not been studied. One of the 3 potential mechanisms of the pathogenesis of PID is the presence of trichomonas acting

as a vector for intracellular organisms in a similar way to spermatozoa.

### **HIV TRANSMISSION AND TRICHOMONAS INFECTION**

Data suggest a 2- to 5-fold increased risk for HIV among persons who are concurrently infected with genital ulcer diseases (eg, herpes simplex virus type 2) and nonulcerative inflammatory diseases (eg, gonorrhea, *Chlamydia trachomatis*, trichomoniasis, and BV). Treatment of HIV-positive patients with these diseases is the same as in HIV-negative patients. Trichomonas is now being recognized as a sexually transmitted agent able to amplify the transmission of HIV by possibly increasing viral shedding in the genital tract, and therefore result in increased HIV infectivity. Trichomonas is particularly prevalent among HIV-infected women with high-risk sexual behaviors. "Recurrent" trichomonas is high among this group of HIV-infected women, but it may represent reinfection. More intensive screening and counseling interventions focusing on trichomonas prevention in those with HIV infection are as necessary as an HIV prevention strategy.

### **DESQUAMATIVE INFLAMMATORY VAGINITIS**

Other forms of vaginitis such as desquamative inflammatory vaginitis (DIV) exist. Desquamative inflammatory vaginitis can be difficult to diagnose and treat. This form of vaginitis is a condition of unknown etiology, presenting with a thin yellow discharge (at times bloody), a high vaginal pH, and superficial dyspareunia. This unusual recurrent vaginitis is associated with polymorphonuclear leukocytes, increased parabasal cells, and mostly Gram-positive cocci on microscopy.

### ***Summary***

The 3 common forms of vaginitis seen in healthcare providers' offices include bacterial vaginosis, yeast, and trichomonas

infections. These conditions have a variety of treatments that are generally successful. Occasionally, resistant or recurrent infections are found and treatment can be more difficult in these situations. It is important to carefully inspect the gross appearance of the vulva, the wet mount, and perform laboratory studies to be confident of the diagnosis when formulating a treatment plan for vaginitis.

## References

- Klebanoff MA, Schwabke JR, Zhang J, et al. Vulvovaginal symptoms in women with bacterial vaginosis. *Obstet Gynecol.* 2004; 104:267–272.
- Anderson MR, Klink K, Cohn A. Evaluation of vaginal complaints. *JAMA.* 2004;291:1368–1379.
- Garland SM, Tabrizi SN. Diagnosis of sexually transmitted infections (STI) using self collected non-invasive specimens. *Sex Health.* 2004;1:121–126.
- Nugent RP, Krohn MA, Hillier S. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. *J Clin Microbiol.* 1991;29:297–301.
- Fidel PL. History and new insights into host defense against vaginal candidiasis. *Trends Microbiol.* 2004;12:220–227.
- Smart S, Singal A, Mindel A. Social and sexual factors for bacterial vaginosis. *Sex Transm Infect.* 2004;80:58–62.
- Wiggins R, Hicks SJ, Soothill PW, et al. Mucinas and sialidases: their role in the pathogenesis of sexually transmitted infections in the female genital tract. *Sex Transm Infect.* 2001;77:402–408.
- Antonio MAD, Hawes SE, Hillier SL. The identification of vaginal *Lactobacillus* species and the demographic and microbiological characteristics of women colonized by these species. *J Infect Dis.* 1999;180:1950–1956.
- Eschenbach DA, Thwin SS, Patton DL, et al. Influence of the normal menstrual cycle on vaginal tissue, discharge, and microflora. *Clin Infect Dis.* 2000;30:901–907.
- Gupta K, Hillier SL, Hooton TM, et al. Effects of contraceptive methods on the vaginal microbial flora: a prospective evaluation. *J Infect Dis.* 2000;181:595–601.
- Sobel DJ, Clinical A. Update in treatment of bacterial vaginosis, highlights of a clinical roundtable, 9/01. *Supplement Ob Gyn News International Medical News Group.* 2004.
- Ferris MJ, Maszta A, Aldridge KE, et al. Association of *Atopobium vaginae*, a recently described metronidazole resistant anaerobe, with bacterial vaginosis. *BMC Infect Dis.* 2004;4:1–8.
- Wilson J. Managing recurrent bacterial vaginosis. *Sex Transm Infect.* 2004;80:8–11.
- Taylor-Robinson D, Morgan DJ, Sheehan M, et al. Relation between Gram-stain and clinical criteria for diagnosing bacterial vaginosis with special reference to Gram grade II evaluation. *Int J STD AIDS.* 2003;14:6–10.
- Boskey ER, Atherly-Trim SA, O'Campo PJ, et al. Acceptability of a self-sampling technique to collect vaginal smears for gram stain diagnosis of bacterial vaginosis. *Womens Health Issues.* 2004;1: 14–18.
- Ugwumadu A, Manyonda I, Reid F, et al. Effect of early, oral clindamycin on late miscarriage and pre term delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomised control trial. *Lancet.* 2003;361:983–988.
- Hay PE. Bacterial vaginosis and miscarriage. *Curr Opin Infect Dis.* 2004;17:41–44.
- Joesoef MR, Schmid GP, Hillier SL. Bacterial vaginosis: review of treatment options and potential clinical indications for therapy. *Clin Infect Dis.* 1999;28(Suppl 1):S57–S65.
- Reed BD, Gorenflo DW, Gillespie BW, et al. Sexual behaviors and other risk factors for candida vulvovaginitis. *J Womens Health (Larchmt).* 2000;9:645–655.
- Patel DA, Gillespie B, Sobel JD, et al. Risk factors for recurrent vulvovaginal candidiasis in women receiving maintenance antifungal therapy: results of a prospective cohort study. *Am J Obstet Gynecol.* 2004;190:644–653.
- Hillier S, Sobel J. Vaginal infections. In: Morse SA, Ballard RC, eds. *Atlas of Sexually Transmitted Diseases & AIDS*, 3rd ed. St. Louis: Mosby; 2003:159–179.
- National Committee for Clinical Laboratory Standards Reference Method for Broth Dilution Anti Fungal Susceptibility Testing of Yeasts. Approved Standard. NCCLS Document M 27-A, Wayne, PA; 17. No. 9; 1997.
- Sobel JD, Kapernick PS, Zervos M, et al. Treatment of complicated candida vaginitis: comparison of single and sequential doses of fluconazole. *Am J Obstet Gynecol.* 2001;185:363–369.
- Sobel JD, Wiesenfeld HC, Martens M, et al. Maintenance fluconazole therapy for recurrent vulvovaginal candidiasis. *N Engl J Med.* 2004;351:876–883.
- Pursley TJ, Blomquist IK, Abraham J, et al. Fluconazole-induced congenital abnormalities in three infants. *Clin Infect Dis.* 1996;22: 336–340.
- White DJ, Habib AR, Vanthuyne A, et al. Combined topical flucytosine and amphotericin B for refractory vaginal *Candida glabrata* infections. *Sex Transm Infect.* 2001;77:212–213.
- Rubin AI, Bagheri B, Scher RK. Six novel antimycotics. *Am J Clin Dermatol.* 2002;3:71–81.
- Brown D. Clinical variability of bacterial vaginosis and trichomoniasis. *J Reprod Med.* 2004;49:781–786.
- Lobo TT, Feijo G, Carvalho SE, et al. A comparative evaluation of the Papanicolaou test for the diagnosis of trichomoniasis. *Sex Transm Dis.* 2003;30:694–699.
- Soares VL, Mesquita A, Cavalcante FG, et al. Sexually transmitted infections in a female population in rural northeast Brazil: prevalence, morbidity and risk factors. *Trop Med Int Health.* 2003;30:595–603.
- Soszka S, Kazanowska W, Kuczynska K, et al. *Trichomonas vaginitis* at different life stages of women. *Wiad Parazytol.* 1990;36: 211–217.
- Lecke SB, Tasca T, Souto AA, et al. Perspective of a new diagnostic for human trichomoniasis. *Mem Inst Oswaldo Cruz—Rio de Janeiro.* 2003;98:273–276.
- Krieger JN, Aldrete JF. *Trichomonas vaginalis* and trichomoniasis. In: Holmes KK, et al., eds. *Sexually Transmitted Diseases*, 3rd ed. New York: McGraw-Hill; 1999:587–604.
- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. *MMWR Morb Mortal Wkly Rep.* 2002;51:44–45.
- Forna F, Gulmezoglu AM. Interventions for treating trichomoniasis in women. *Cochrane Database Syst Rev.* 2003;2:CD000218.
- Sobel JD, Nyirjesy P, Brown W. Tinidazole therapy for metronidazole resistant vaginal trichomoniasis. *Clin Infect Dis.* 2001;33: 901–1346.
- Patlman RS. Recalcitrant vaginal trichomoniasis. *Sex Transm Infect.* 1999;75:127–128.
- Dunne RL, Dunn LA, Upcroft P, et al. Drug resistance in the sexually transmitted protozoan *Trichomonas vaginalis*. *Cell Res.* 2003;13:239–249.
- Cotch MF, Pastorek JG II, Nugent RP, et al. *Trichomonas vaginalis* associated with low birth weight and preterm delivery. The Vaginal Infections and Prematurity Study Group. *Sex Transm Dis.* 1997;24:353–360.
- Klebanoff MA, Carey JC, Hauth JC, et al. Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic *Trichomonas vaginalis* infection. *N Engl J Med.* 2001;345:487–493.