Review Article

Current Concepts

VAGINITIS

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SYMPTOMS of vaginitis are nonspecific, and neither self-diagnosis nor diagnosis by a physician is reliable without laboratory confirmation. The management of vaginitis remains largely empirical, and many assume that vaginitis is never life-threatening and that empirical therapy is always harmless. Vulvovaginitis, although frequently the result of infection, may also have noninfectious causes (Table 1); moreover, mixed infections are not uncommon.

CANDIDA VULVOVAGINITIS

The epidemiologic data on candida vulvovaginitis, a nonreportable disease, are incomplete. Prevalence estimates rely mainly on self-reported histories of diagnosis by a physician. Vulvovaginal candidiasis is routinely diagnosed without the benefit of microscopy or culture, and as many as half of the women given this diagnosis may have other conditions.[1] The widespread use of over-the-counter antimycotic drugs may make future epidemiologic studies very difficult. Although the condition is rare before menarche, by the age of 25 half of all college women will have had at least one physician-diagnosed episode of vulvovaginal candidiasis. It is less common in postmenopausal women.[2,3] In other populations, at least one episode of vulvovaginal candidiasis is reported in up to 75 percent of premenopausal women.[4]

Pathogenesis

Candida albicans is responsible for 80 to 92 percent of episodes of vulvovaginal candidiasis.[5] Recently, an increased frequency of other candida species, particularly *C. glabrata,* has been reported,[6] possibly due to widespread use of over-the-counter drugs, long-term use of suppressive azoles, and the use of short courses of antifungal drugs. Sporadic attacks of vulvovaginal candidiasis usually occur without an identifiable precipitating factor, except in patients with uncontrolled diabetes. Some, but not all, women are prone to vulvovaginal candidiasis while taking antibiotics. The risk of vulvovaginal candidiasis may be higher in women who use oral contraceptives containing high levels of estrogen.[7] Spermicide use has not been associated with vulvovaginal candidiasis, but the use of vaginal sponges and intrauterine devices has.[7]

Vulvovaginal candidiasis is not traditionally considered a sexually transmitted disease, since it occurs in celibate women and since candida is considered part of the normal vaginal flora. This does not mean that sexual transmission of candida does not occur or that vulvovaginal candidiasis is not sexually associated. There is an increase in the frequency of vulvovaginal candidiasis at the time most women begin regular sexual activity.[2,3,7] Individual episodes of vulvovaginal candidiasis do not appear to be related to lifetime numbers of sexual partners or the frequency of coitus but may be linked to orogenital sex.[7]

Diagnosis

The diagnosis of vulvovaginal candidiasis is easily established by the finding of normal vaginal pH (4 to 4.5) and positive results on saline or 10 percent potassium hydroxide microscopy (Fig. 1). Because of the poor sensitivity of these tests and the lack of specificity of clinical signs, vulvovaginal candidiasis is still possible despite negative microscopical results in patients with a compatible clinical presentation and normal pH, and a vaginal culture should be obtained. Other conditions to be considered include hypersensitivity, allergic or chemical reactions, and contact dermatitis; they rarely have an infectious cause (Table 2). Failure to recognize the frequency of local adverse reactions results in empirical prescription of additional topical agents, including high-potency steroids, that further aggravate symptoms. There are serious doubts about the accuracy of self-diagnosis of vulvovaginal candidiasis, creating concern over abuse of over-the-counter antimycotic drugs for noninfectious entities and other misdiagnosed conditions such as genital herpes.[9]

Therapy

Topical antimycotic drugs achieve cure rates in excess of 80 percent[10] (Table 3). More convenient oral azole agents also achieve high cure rates, although

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only fluconazole is approved by the Food and Drug Administration.[11] In the absence of superiority of any formulation, agent, or route of administration, patient preference should influence the selection of a drug. Side effects of single-dose fluconazole (150 mg) tend to be mild and infrequent; they include gastrointestinal intolerance, headache, and rash.[11] Oral azoles are contraindicated in pregnancy.

Uncomplicated infection, accounting for the majority of episodes, occurs in normal hosts, is infrequent, is mild to moderate in severity, and is caused by *C. albicans*. Prescription and over-the-counter antimycotic drugs, now available in short-course, often single-dose, regimens, are highly effective in uncomplicated disease. Fluconazole achieves therapeutic concentrations in vaginal secretions for at least 72 hours after the ingestion of a single 150-mg tablet.[12]

In complicated candidiasis, microbial or host factors adversely influence cure rates and vulvovaginal inflammation is moderate to severe. Predisposing host factors include uncontrolled diabetes, immunosuppression, a history of recurrent vulvovaginal candidiasis, and antibiotic therapy. Microbial determinants include candida species other than *C. albicans,* particularly *C. glabrata*, which are less susceptible to azoles.[13] Women with complicated infections are less likely to respond to short courses of antimycotic drugs and require 10 to 14 days of therapy.[11]

Recurrent Vulvovaginal Candidiasis

Defined as four or more episodes of infection per year, recurrent vulvovaginal candidiasis occurs in less than 5 percent of healthy women.[14] In only a minority is the pathogenesis — including uncontrolled diabetes and immunosuppressive therapy — apparent. Repeated vaginitis occurs with susceptible strains of *C. albicans* that persist, as evidenced by the results of longitudinal DNA-typing studies.[15] The role of sexual transmission remains unresolved.[16] A local vaginal immune mechanism may be responsible for the frequent relapses.[17] Biologic susceptibility is associated with nonsecretor status, which facilitates vaginal yeast colonization.[18] There is no evidence that women with recurrent vulvovaginal candidiasis have a vaginal flora deficient in lactobacilli.[19]

Several studies have shown the effectiveness of antifungal maintenance suppressive therapy taken for six months after an initial induction regimen has resulted in negative cultures.[10] Regimens include ketoconazole (100 mg per day), itraconazole (50 to 100 mg per day), fluconazole (100 mg a week), and clotrimazole (500-mg vaginal suppositories administered once a week). Treatment failure is not uncommon in patients with *C. glabrata* vaginitis. Moderate success can be achieved with topical boric acid (600 mg once daily for two weeks) or topical flucytosine,[13] but maintenance regimens remain unavailable. Azole resistance has only been reported in one case of vaginitis caused by *C. albicans*,[20] so in vitro susceptibility tests are rarely indicated unless compliant patients have no response to adequate therapy. Treatment should also be directed at the sexual dysfunction and marital discord that frequently accompany chronic vaginitis.

TABLE 1. CAUSES OF VAGINITIS.

Infectious vaginitis
Common causes
Bacterial vaginosis (40–50% of cases)
Vulvovaginal candidiasis (20–25% of cases)
Trichomoniasis (15–20% of cases)
Less common causes
Atrophic vaginitis with secondary bacterial infection
Foreign body with secondary infection
Desquamative inflammatory vaginitis (clindamycin-responsive)
Streptococcal vaginitis (group A)
Ulcerative vaginitis associated with *Staphylococcus aureus* and toxic shock syndrome
Idiopathic vulvovaginal ulceration associated with human immunodeficiency virus infection
Noninfectious vaginitis
Chemical or other irritant
Allergic, hypersensitivity, and contact dermatitis (lichen simplex)
Traumatic vaginitis
Atrophic vaginitis
Postpuerperal atrophic vaginitis
Desquamative inflammatory vaginitis (steroid-responsive)
Erosive lichen planus
Collagen vascular disease, Behçet's syndrome, pemphigus syndromes
Idiopathic vaginitis

TRICHOMONIASIS

Trichomoniasis affects approximately 180 million women worldwide and 2 to 3 million American women annually.[21] In most industrialized countries, the prevalence of trichomoniasis has decreased. *Trichomonas vaginalis* is identified in 30 to 40 percent of the male sexual partners of infected women. Trichomoniasis, which is associated with a high prevalence of other sexually transmitted diseases, facilitates transmission of the human immunodeficiency virus (HIV).[22] Spermicidal agents, such as nonoxynol 9, reduce the transmission of trichomonas.

Trichomoniasis in women ranges from an asymptomatic carrier state to severe, acute, inflammatory disease. If untreated in pregnancy, trichomoniasis identical to that seen in nonpregnant women is associated with premature rupture of the membranes, prematurity, and post-hysterectomy cellulitis.[23]

Diagnosis

None of the clinical features of trichomonas vaginitis are sufficiently sensitive or specific to allow a diagnosis of trichomonal infection based on signs and

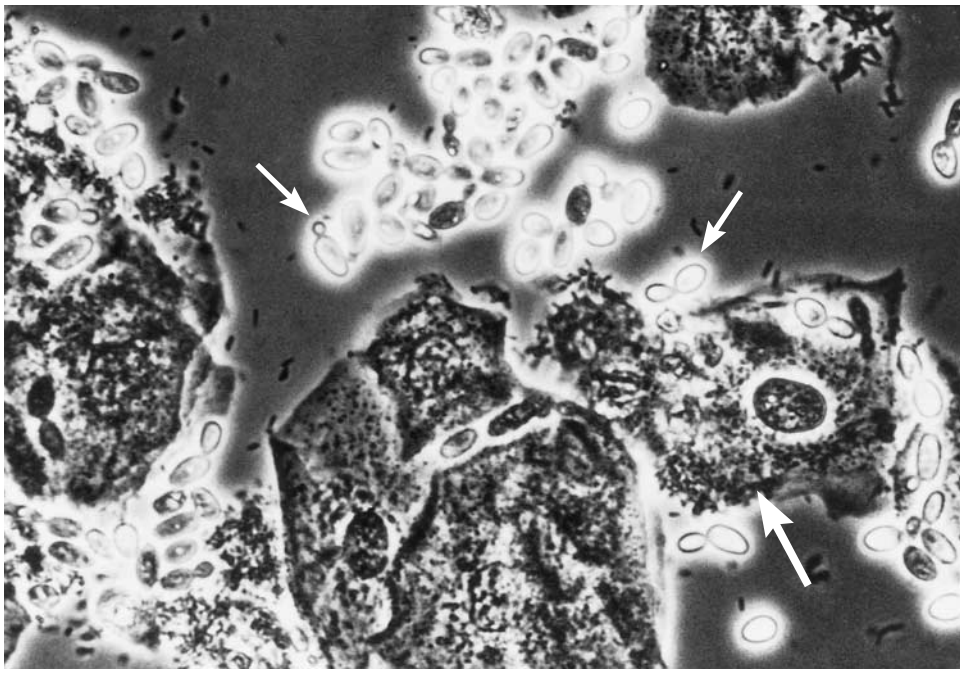

Figure 1. Polarizing Microscopy of Multiple Singlets and Budding Yeast (Small Arrows) Belonging to the Species *Candida glabrata* in a Patient with a Mixed Infection and Clue Cells (Large Arrow) in Vaginal Secretions Associated with Bacterial Vaginosis.

Clue cells are exfoliated epithelial cells to which *Gardnerella vaginalis* adhere, obscuring cell margins, and are virtually pathognomonic of bacterial vaginosis. (×20.)

TABLE 2. DIFFERENTIAL DIAGNOSIS OF VAGINITIS.*

VARIABLE	NORMAL	VULVOVAGINAL CANDIDIASIS	BACTERIAL VAGINOSIS†	TRICHOMONIASIS	ATROPHIC VAGINITIS
Symptoms	None or mild, transient	Pruritus, soreness, change in discharge, dyspareunia	Malodorous discharge, no dyspareunia	Malodorous, purulent discharge; dyspareunia	Dyspareunia, vaginal dryness
Signs	—	Vulvar erythema, edema, fissure	Adherent discharge	Purulent discharge, vulvovaginal erythema	Vestibular and vaginal thinning
pH	4.0–4.5	4.0–4.5	>4.5	5–6.0	>6.0
Amine test	Negative	Negative	Positive (~70–80%)	Often positive	Negative
Saline microscopy	PMN:EC ratio <1; rods dominate; squames +++	PMN:EC <1; rods dominate; squames +++; pseudohyphae (~40%)	PMN:EC <1; loss of rods; increased coccobacilli; clue cells (>90%)	PMN ++++; mixed flora; motile trichomonads (60%)	PMN + to ++; loss of rods; increased cocci and coliforms; parabasal cells
10% potassium hydroxide examination	Negative	Pseudohyphae (~70%)	Negative	Negative	Negative
Miscellaneous	—	Culture if microscopy negative	Culture of no value	Culture if microscopy negative	—
Differential diagnosis	Physiologic leukorrhea	Contact irritant or allergic vulvitis, chemical irritation, focal vulvitis (vulvodynia)		Purulent vaginitis, desquamative inflammatory vaginitis, atrophic vaginitis plus secondary infection, erosive lichen planus	

*PMN denotes polymorphonuclear leukocytes, and EC vaginal epithelial cells.

†For bacterial vaginosis the criteria of Amsel et al.[8] require the presence of three of four clinical signs for diagnosis: homogeneous discharge, a positive whiff–amine test, pH >4.5, and the presence of clue cells.

TABLE 3. THERAPY FOR VAGINAL CANDIDIASIS.*

DRUG	FORMULATION	DOSAGE REGIMEN
Butoconazole (Femstat)†	2% cream	5 g a day for 3 days
Clotrimazole (Gyne-lotrimin, Mycelex)†	1% cream	5 g a day for 7–14 days
	100-mg vaginal tablet	1 a day for 7 days or 2 a day for 3 days
	500-mg vaginal tablet	1 tablet
Miconazole (Monistat)†	2% cream	5 g a day for 7 days
	100-mg vaginal suppository	1 a day for 7 days
	200-mg vaginal suppository	1 a day for 3 days
	1200-mg vaginal suppository	1 suppository
Tioconazole (Vagistat)†	2% cream	5 g a day for 3 days
	6.5% cream	5 g in a single dose
Terconazole (Terazol)	0.4% cream	5 g a day for 7 days
	0.8% cream	5 g a day for 3 days
	80-mg vaginal suppository	1 a day for 3 days
Nystatin (Mycostatin)‡	100,000-U vaginal tablet	1 a day for 14 days
Ketoconazole (Nizoral)	400-mg oral tablet	Twice a day for 5 days
Itraconazole (Sporanox)	200-mg oral tablet	Twice a day for 1 day
	200-mg oral tablet	Once a day for 3 days
Fluconazole (Diflucan)	150-mg oral tablet	Single dose

*There are no significant differences in efficacy among topical and systemic azoles (cure rates, >80 percent for uncomplicated vulvovaginal candidiasis).

†The drug is sold over the counter.

‡The cure rate with nystatin is 70 to 80 percent.[10]

symptoms alone.[24-26] Vaginal pH is markedly elevated, and an increase in polymorphonuclear leukocytes is almost invariably present on saline microscopy. The wet mount is positive for motile trichomonads in only 50 to 70 percent of culture-confirmed cases.[26] Although trichomonads are often seen on Papanicolaou smears, this method has a sensitivity of only 60 to 70 percent, and false positive results are not uncommon.[26] Culture techniques have high sensitivity (95 percent) and should be considered in patients with elevated vaginal pH, increased numbers of polymorphonuclear leukocytes, and absence of motile trichomonads and clue cells or when microscopy is unavailable or yields unreliable results. Several new rapid diagnostic kits using DNA probes and monoclonal antibodies are available, with a sensitivity of 90 percent and a specificity of 99.8 percent.[27]

Therapy

The 5-nitroimidazole group of drugs — metronidazole and tinidazole — remains the basis of therapy.[24] Oral therapy is preferred, because infection of the urethra and periurethral glands provides sources for endogenous recurrence. Similar cure rates are obtained with oral metronidazole in a dose of 500 mg twice a day for seven days (cure rate, 85 to 90 percent) and a single 2-g oral dose (82 to 88 percent).[22] The cure rate increases to more than 90 percent when sexual partners are treated simultaneously. The advantages of single-dose therapy include better compliance, a lower total dose, a shorter period of alcohol avoidance, and possibly decreased candida superinfection. A disadvantage of single-dose therapy is the need for simultaneous treatment of sexual partners. Most strains of *T. vaginalis* are highly susceptible to metronidazole (minimal inhibitory concentration, 1 μg per milliliter).

In some patients, the infection is refractory to repeated courses of therapy even when all sexual partners have been treated. These rare patients may have strains of *T. vaginalis* resistant to metronidazole, which can be confirmed in vitro, and should be given the maximal tolerated dose of metronidazole (2 to 4 g daily for 10 to 14 days). There have been anecdotal reports of success in treating resistant infections with oral tinidazole; however, the drug is not readily available, and the optimal dose is unknown. Rare patients who do not have a response to nitroimidazoles can be treated with topical paromomycin (250 mg daily for two weeks).[28]

Side effects of metronidazole include a metallic taste, nausea (in 10 percent of patients), transient neutropenia (7.5 percent), an effect like that of disulfiram with alcohol, interaction with warfarin, and peripheral neuropathy. Allergy to metronidazole, although uncommon, manifests as rash, urticaria, pruritus, and rarely, anaphylaxis, which can be successfully treated by oral desensitization.[29] Metronidazole is the drug of choice in pregnancy. However, it readily crosses the placenta, and because of unsubstantiated

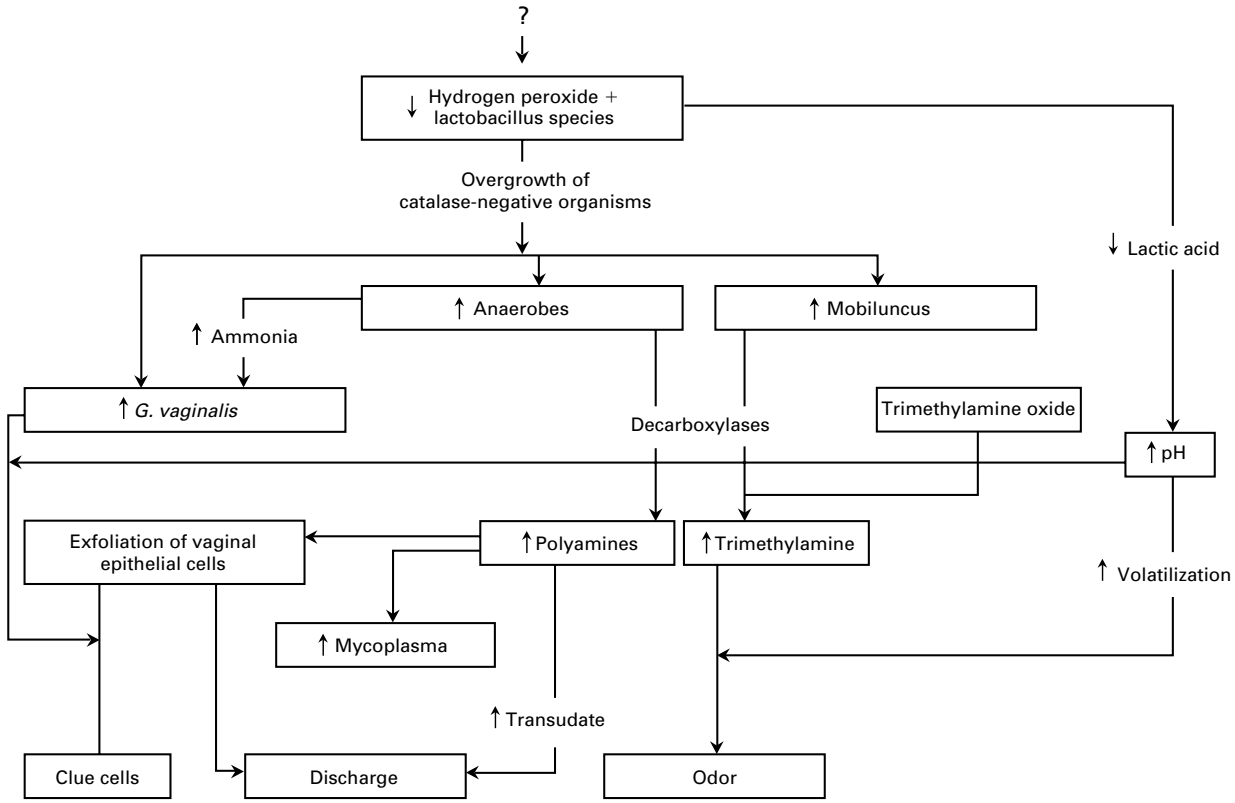

Figure 2. Proposed Pathophysiology of Bacterial Vaginosis.

The overgrowth of anaerobic microorganisms is accompanied by the production of proteolytic enzymes that act on vaginal peptides to release several biologic products, including polyamines, which volatilize in the accompanying alkaline environment to elaborate foul-smelling trimethylamine. Polyamines act to facilitate the transudation of vaginal fluid and exfoliation of epithelial cells, creating a copious discharge. Clue cells are formed when *Gardnerella vaginalis,* present in high numbers, adhere in the presence of an elevated pH to exfoliated epithelial cells.

concern about teratogenicity, some but not all consultants avoid its use in the first trimester of pregnancy.

BACTERIAL VAGINOSIS

Bacterial vaginosis is the most common cause of vaginitis in women of childbearing age. The rate of occurrence depends on the population studied: 17 to 19 percent in family-planning or student health clinics, 24 to 37 percent in sexually transmitted disease clinics, and 10 to 29 percent among pregnant women.[1,30]

Bacterial vaginosis represents a complex change in vaginal flora characterized by a reduction in the prevalence and concentration of hydrogen peroxide–producing lactobacilli[31] and an increase in the prevalence and concentration of *Gardnerella vaginalis;* mobiluncus species; *Mycoplasma hominis;* anaerobic gram-negative rods belonging to the genera prevotella, porphyromonas, and bacteroides; and peptostreptococcus species[32] (Fig. 2). The transmissible nature of bacterial vaginosis was demonstrated by Gardner and Dukes in 1955, and the microorganisms may be transferred sexually.[33] Transmission alone is not sufficient to cause disease, since most of the microorganisms are normally found in low numbers in the healthy vagina. Risk factors for bacterial vaginosis include the use of an intrauterine device, nonwhite race, and prior pregnancy.[30]

Women present with an unpleasant, "fishy smelling" discharge that is more noticeable after unprotected intercourse. The discharge is off-white, thin, and homogeneous. Pruritus and inflammation are absent, and many women with bacterial vaginosis are asymptomatic.

Diagnosis

Diagnostic criteria established by Amsel et al. (Table 2) have proved remarkably simple and useful in clinical practice.[8] Since few clinicians are adequately trained to use microscopy, overdiagnosis is common and therapy is frequently empirical. The presence of clue cells is the single most reliable predictor of bacterial vaginosis.[34] Gram's staining of vaginal secretions is even more reliable than wet mount, with a sensitivity of 93 percent and specificity of 70 per-

cent, but it is underused.[35] Although cultures for *G. vaginalis* are positive in almost all cases of bacterial vaginosis, *G. vaginalis* may be detected in 50 to 60 percent of healthy asymptomatic women. Accordingly, vaginal culture has no part in the diagnosis of bacterial vaginosis. DNA probes for *G. vaginalis* are expensive but may be useful to practitioners unable to perform microscopy.[36]

Seven studies (two case–control and five cohort studies) have reported an increased risk of preterm birth in women with bacterial vaginosis.[37,38] Studies conducted in diverse ethnic groups and economic strata detected increased relative risks of prematurity ranging from 2.0 to 6.9 that were directly attributable to bacterial vaginosis and linked to chorioamnionitis.[38,39] It is estimated that 15 to 20 percent of pregnant women in the United States have bacterial vaginosis[39]; enormous numbers of otherwise healthy women are thus at risk. In the future, it is possible that routine screening and treatment will become the standard of practice. The optimal time for this has not been defined, although two studies suggest that early screening in the first trimester may be more useful in predicting preterm delivery than later screening.[40] Hay et al. concluded that it is unusual for bacterial vaginosis to develop in pregnant women after 16 weeks of gestation.[41] Treatment trials of oral clindamycin, metronidazole alone, and metronidazole combined with erythromycin in high-risk women with asymptomatic bacterial vaginosis showed significant reductions in preterm labor.[42-44] Recommendations for routine screening and treatment await the results of further interventional studies among unselected women with bacterial vaginosis.

Causal relations have also been established between bacterial vaginosis and pelvic inflammatory disease, plasma-cell endometritis, postpartum fever, post-hysterectomy vaginal-cuff cellulitis, and postabortion infection.[30,37,45] Platz-Christensen et al. reported an association between clue cells detected on Papanicolaou smears and cervical intraepithelial neoplasia.[46] It has been suggested that bacterial vaginosis is a cofactor for human papillomavirus; however, Peters et al. failed to confirm this relation in dyskaryotic cervical smears.[47]

Therapy

Poor efficacy has been observed with triple-sulfa creams, erythromycin, tetracycline, acetic acid gel, and povidone–iodine vaginal douches.[48] There are only moderate cure rates with ampicillin (mean, 66 percent) and amoxicillin. The most successful oral therapy remains metronidazole. Most studies using multiple divided-dose regimens of 800 to 1200 mg per day for one week achieved early rates of clinical cure in excess of 90 percent and rates of approximately 80 percent at four weeks.[30,48] Although single-dose therapy with 2 g of metronidazole achieves similar immediate rates of clinical response, higher rates of recurrence have been reported.[48] Topical vaginal therapy with 2 percent clindamycin or 0.75 percent metronidazole gel has been shown to be as effective as oral metronidazole.[49] Recently, both a three-day course of topical clindamycin and daily therapy with metronidazole gel have achieved similar early cure rates.[50]

In the past, asymptomatic bacterial vaginosis was not treated, since patients often had spontaneous improvement over a period of several months. Evidence linking asymptomatic bacterial vaginosis with obstetrical and gynecologic complications has caused this policy to be reassessed, especially with the availability of topical therapy. It appears reasonable to treat asymptomatic bacterial vaginosis before pregnancy and elective gynecologic surgery.

After therapy, approximately 30 percent of patients with initial responses have a recurrence of symptoms within three months.[30] The reasons are unclear; they include reinfection, but recurrence more likely reflects vaginal relapse caused by failure to eradicate the offending organisms or to reestablish the normal protective vaginal flora dominated by lactobacillus. Management of symptomatic relapse includes prolonged therapy for 10 to 14 days, but maintenance regimens of antibiotics have largely been disappointing. New approaches include exogenous lactobacillus recolonization with selected bacteria-containing suppositories. Despite evidence of sexual transmission, no study has demonstrated reduced rates of recurrence in women whose partners were treated with metronidazole.

ATROPHIC VAGINITIS

Clinically significant atrophic vaginitis is uncommon; the majority of women with mild-to-moderate atrophy are asymptomatic.[51] With reduced endogenous estrogen, the epithelium becomes thin and lacking in glycogen, and this contributes to a reduction in lactic acid production and an increase in vaginal pH. This change in the environment encourages the overgrowth of nonacidophilic coliforms and the disappearance of lactobacillus species.

In women with advanced atrophy, symptoms include vaginal soreness, postcoital burning, dyspareunia, and occasional spotting. The vaginal mucosa is thin, with diffuse redness, occasional petechiae, or ecchymoses with few or no vaginal folds. Vulvar atrophy may also be apparent, and the discharge may be serosanguineous or watery, with a pH of 5.0 to 7.0. The wet smear shows increased polymorphonuclear leukocytes associated with small, rounded parabasal epithelial cells. The lactobacillus-dominated flora is replaced by mixed flora of gram-negative rods, although bacteriologic cultures are unnecessary. Treatment consists of topical vaginal estrogen. Nightly use of half an applicator for one to two weeks

is usually sufficient to alleviate symptoms, but symptomatic recurrence is common and may indicate a need for a systemic estrogen regimen.

Desquamative Inflammatory Vaginitis

Chronic purulent vaginitis not caused by trichomonas and in a patient without cervical and upper genital tract inflammation is uncommon. I described 51 patients, mainly perimenopausal, with diffuse exudative vaginitis, massive vaginal-cell exfoliation, purulent vaginal discharge, and occasional vaginal and cervical spotted rash.[52] Laboratory findings included an elevated pH, increased numbers of parabasal cells, and the absence of gram-positive bacilli and their replacement by gram-positive cocci on Gram's staining. A dramatic response to 2 percent clindamycin cream was reported in most patients, though some patients respond to corticosteroids only. The concept of bacterial vaginitis remains questionable, except when bacterial superinfection complicates atrophic vaginitis or a foreign body.

Noninfectious Vaginitis and Vulvitis

The symptoms of noninfectious vaginitis and vulvitis are indistinguishable from those of infectious syndromes but are most commonly confused with those of acute candida vaginitis; they include pruritus, irritation, burning, soreness, and variable discharge. Noninfectious causes include irritants (e.g., minipads, spermicides, povidone–iodine, topical antimycotic drugs, soaps and perfumes, and topical fluorouracil) and allergens that produce immunologic acute and chronic hypersensitivity reactions including contact dermatitis (e.g., latex condoms and antimycotic creams). Management includes identifying and eliminating the offending agent and should not rely on topical corticosteroids, which frequently cause local burning. Measures for local relief include sodium bicarbonate sitz baths and topical vegetable oils. A syndrome of vaginal hyperacidity due to overgrowth by lactobacilli (cytolytic vaginosis) has been described but not confirmed.

Vaginitis in HIV-Seropositive Women

Uncontrolled studies reported increased prevalence, severity, and recurrence of vulvovaginal candidiasis in HIV-seropositive women, suggesting the need for HIV serologic testing in women with recurrent symptoms.[53,54] Recent cohort studies have failed, however, to corroborate the original observations.[55] Hence, the role of HIV testing in all women with recurrent vulvovaginal candidiasis is controversial. By contrast, the prevalence of bacterial vaginosis and trichomoniasis is high in both HIV-seropositive women and seronegative controls matched for high-risk behavior. Idiopathic genital ulceration, often giant in nature, may occur in the vagina, simulating vaginitis.[56]

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