

REVIEW ARTICLE

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Inflammatory Vaginitis

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VAGINAL SYMPTOMS ARE REMARKABLY COMMON. IN THE UNITED STATES, vaginal infections are among the 25 most common medical reasons for which women consult a physician, resulting in 5 million to 10 million office visits per year.¹⁻³ Vaginal infections affect a woman's quality of life by causing frustration, anxiety, sexual dysfunction, and vulvovaginal discomfort. In addition to direct health care costs associated with the management of vaginal infections, there are indirect costs related to adverse reproductive health consequences.^{3,4} An abnormal vaginal microbiome, or vaginal dysbiosis, which characterizes bacterial vaginosis and desquamative inflammatory vaginitis, has been linked to adverse pregnancy outcomes, pelvic inflammatory disease, an increased risk of sexually transmitted infections, and other reproductive health problems, such as a poor outcome of in vitro fertilization (IVF).⁵⁻⁷

This review focuses on bacterial vaginosis and desquamative inflammatory vaginitis because both are common, underrecognized disorders, and important new data about them have emerged. Not discussed in this review are trichomoniasis and vulvovaginal candidiasis, two other common causes of vaginal symptoms.

VAGINAL MICROBIOME

Natural fluctuations in the vaginal microbiome occur during the reproductive cycle and throughout a woman's life. During a woman's reproductive years, the vaginal microbiome appears to be principally influenced by the effects of estrogen on vaginal epithelial cells, the predominance of lactobacilli, and low pH. The vaginal microbiome can also be transiently influenced by several other factors, such as use of antimicrobial agents, sexual activity, and menses, all of which challenge our understanding of the dynamic patterns of vaginal flora.⁴ On the basis of genomic investigations, the vaginal microbiome has been classified into at least five community state types (CSTs).^{4,8} Four CSTs are dominated by a lactobacillus (lactic acid-producing) species: *Lactobacillus crispatus*, *L. gasseri*, *L. iners*, or *L. jensenii* (Table 1). One type (CST IV) is characterized by low concentrations or an absence of lactobacilli and high concentrations of obligate or facultative anaerobic flora. This CST is associated with both bacterial vaginosis and desquamative inflammatory vaginitis. *L. crispatus*, *L. gasseri*, and *L. jensenii* usually occur as a single or predominant microorganism in the vaginal microbiome, whereas *L. iners* commonly occurs as a component of a polymicrobial vaginal flora, often transitioning to bacterial vaginosis.⁹ *L. crispatus* excludes other organisms through low pH due to robust lactic acid production together with hydrogen peroxide and specific host antimicrobial proteins called defensins.⁸

The presence of hydrogen peroxide-producing lactobacilli is associated with reduced levels of vaginal proinflammatory cytokines.¹⁰ Low pH associated with

Table 1. Diagnostic Findings in Vaginal Secretions from Women with Healthy Vaginal Flora, Women with Bacterial Vaginosis, and Women with Desquamative Inflammatory Vaginitis.

Variable	Healthy Vaginal Flora	Bacterial Vaginosis	Desquamative Inflammatory Vaginitis
pH	<4.7	≥4.7	≥4.7
Amine odor	Negative	Positive	Negative
Clue cells	Absent	Present	Absent
Epithelial cells	Mature squamous cells	Mature squamous cells	Immature parabasal cells
Neutrophils	Absent	Absent	Present
Flora	Sparse monomorphic bacilli	Abundant polymorphic coccobacilli	Abundant polymorphic cocci and bacilli
Microbiome	Lactobacilli	<i>Gardnerella vaginalis</i> , <i>Atopobium vaginae</i> , others	<i>Escherichia coli</i> , group B streptococci, others
CST*	I, II, V	III, IV	IV

* Community state type (CST) I is dominated by *Lactobacillus crispatus*, CST II by *L. gasseri*, CST III by *L. iners*, and CST V by *L. jensenii*; CST IV is composed of a polymicrobial mixture of strict and facultative anaerobes.⁸

lactobacilli may be an evolutionarily selected trait to defend against sexually transmitted and other infections,¹¹ since a low-pH environment markedly inhibits bacterial growth. Hydrogen peroxide-producing lactobacilli predominate in normal vaginal flora, typically accounting for 70 to 90% of the total microbiome in a healthy vagina.^{12,13} Figure 1A and 1B show, respectively, the physical appearance of normal vaginal secretions on speculum examination and rodlike bacteria on a microscopic examination of a wet-mount preparation of normal vaginal fluid. Table 1 compares the characteristics of vaginal secretions among healthy women, women with bacterial vaginosis, and those with desquamative inflammatory vaginitis.

BACTERIAL VAGINOSIS

A link between *Haemophilus vaginalis* and abnormal vaginal discharge was first described in 1955.^{4,14} Subsequently, *H. vaginalis* was renamed *Gardnerella vaginalis*, and the syndrome was renamed non-specific vaginitis¹⁴ or anaerobic vaginosis because anaerobic organisms, in addition to *G. vaginalis*, were observed. Currently, the condition is called bacterial vaginosis.⁴ The search for a single etiologic agent has continued, with investigations of mobiluncus species in the 1980s and 1990s¹⁵⁻¹⁷ and, in the 2000s, investigations of *Atopobium vaginae*¹⁸⁻²⁰ and the discovery of Clostridiales-type bacteria.²¹ However, most investigators have concluded that bacterial vaginosis is a polymicrobial

disorder of the vaginal microbiome that is characterized by the absence of vaginal lactobacilli.

Bacterial vaginosis is one of the most common vaginal ecosystem-related microbiologic syndromes among women of childbearing age. An estimated 7.4 million cases of bacterial vaginosis occur each year in the United States. The prevalence rates are in the range of 15% among pregnant women, 20 to 25% among young women seen at student health clinics, and up to 30 to 40% among women seen at sexually transmitted disease clinics. The prevalence rates for bacterial vaginosis vary strikingly among ethnic groups and countries.²² Rates are generally higher in black and Hispanic populations and lower in white and Asian populations. The reasons for the large differences in prevalence rates according to race or ethnic group and geographic region are unknown. Two reviews provide excellent overall summaries of bacterial vaginosis and the literature on the disorder.^{22,23}

Despite advances in our understanding of bacterial vaginosis, it remains an enigmatic condition.²⁴ A recent natural history study showed that incident bacterial vaginosis is associated with an initial decrease in the abundance of *L. crispatus* and a subsequent increase in the abundance of *Prevotella bivia*, *G. vaginalis*, *A. vaginae*, and megasphaera type 1 (anaerobes commonly found in bacterial vaginosis).⁹ Dramatic differences in metabolite compositions and concentrations of microbial origin in bacterial vaginosis have also

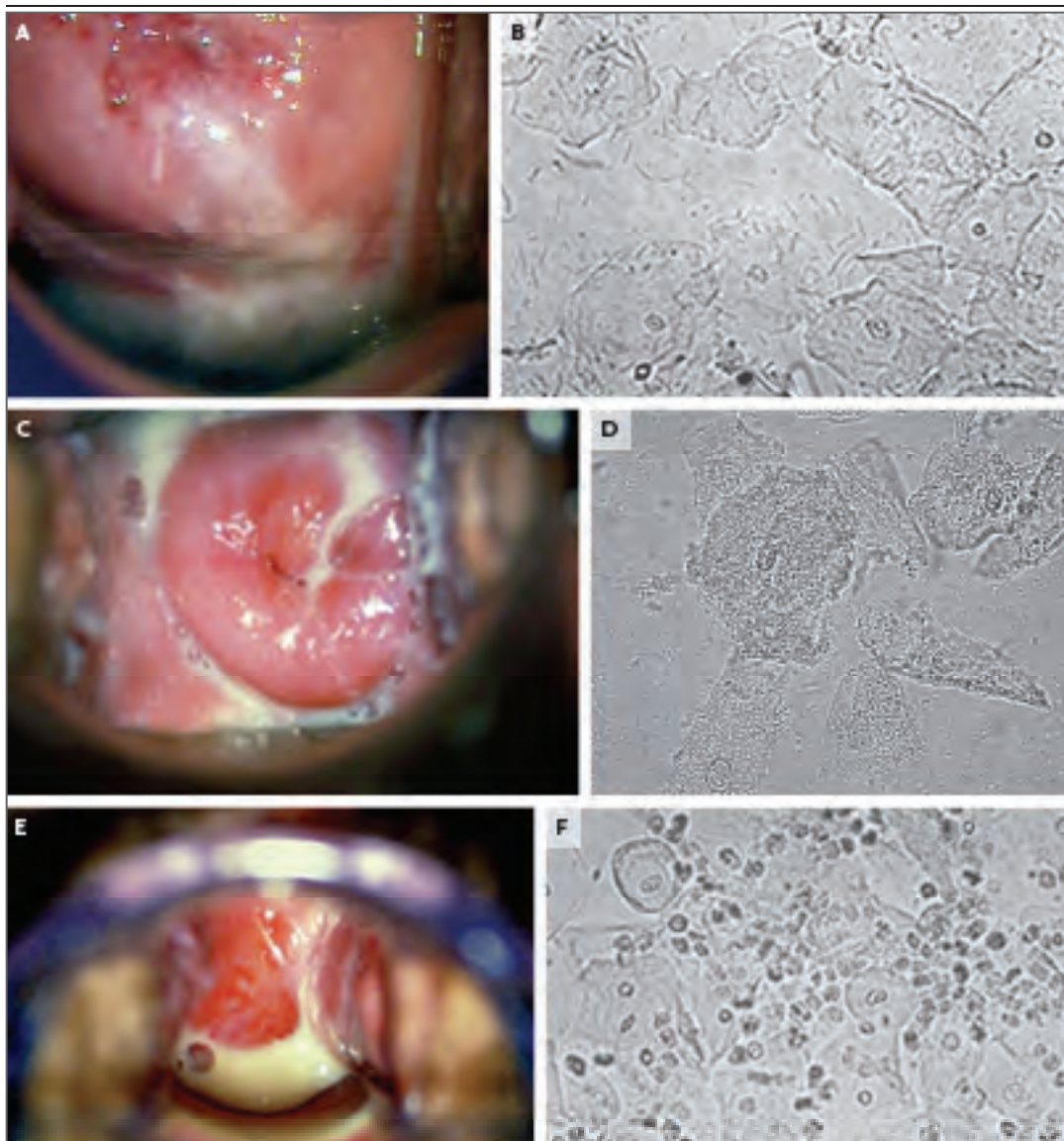


Figure 1. Features of Healthy Vaginal Flora, Bacterial Vaginosis, and Desquamative Inflammatory Vaginitis.

Panel A shows healthy cervicovaginal mucosa and a small amount of vaginal discharge, findings that are consistent with a predominance of lactobacilli. Physiological cervical ectopy and clear cervical mucus are evident. In Panel B, microscopic examination of a wet-mount preparation shows rodlike bacteria, which are consistent with lactobacilli. No leukocytes are present. Panels C and D show the features of bacterial vaginosis: heavy, milky, homogeneous vaginal discharge with bubbles (Panel C), which are consistent with gaseous by-products of anaerobic bacteria, and vaginal epithelial cells covered by coccobacilli on microscopic examination (Panel D), a feature of clue cells. No leukocytes are present. Panels E and F show the features of desquamative inflammatory vaginitis: heavy, yellowish vaginal discharge and inflamed cervicovaginal mucosa (Panel E), with microscopic examination showing a high number of leukocytes (with a predominance of mononuclear leukocytes) and round parabasal cells (Panel F), findings that are consistent with inflammation.

been identified by means of a global metabolomics approach.²⁵

Bacterial vaginosis is characterized by a milky, homogeneous, malodorous vaginal discharge

(Fig. 1C) that causes vulvovaginal discomfort and vulvar irritation. The disorder is also characterized by the absence of clinically significant vaginal inflammation as indicated by an absence

of neutrophils. Several studies have shown that inflammatory cytokines are increased in the vaginal discharge of patients with bacterial vaginosis, suggesting leukocyte inhibition despite a proinflammatory milieu.^{8,22,26} Bacterial vaginosis–associated odor is typically a fishy smell (i.e., a positive whiff test after the addition of one drop of potassium hydroxide to vaginal discharge on a glass slide). This smell is caused by the release of organic acids or polyamines on alkalinization of vaginal fluid, which are by-products of anaerobic bacterial metabolism (e.g., putrescine and cadaverine).²⁷ The polymicrobial load is increased by a factor of up to 1000, as compared with normal, lactobacilli-dominated vaginal flora. Thus, bacterial vaginosis represents an abnormal vaginal ecosystem, both qualitatively and quantitatively.

The absence of a clear disease counterpart in males has made it difficult to determine whether bacterial vaginosis is sexually transmitted. A systematic review of randomized trials of treatment for male sexual partners to prevent recurrent bacterial vaginosis in women showed that none of the trials had sufficient power to determine the role of the male partner in the recurrence of bacterial vaginosis.²⁸ Another review concluded that, as compared with placebo, antibiotic treatment for the sexual partners of women treated for bacterial vaginosis had no effect on rates of clinical or symptomatic improvement among the women or on the rate of recurrence of bacterial vaginosis for up to 12 weeks after treatment.²⁹ However, bacterial vaginosis and sexually transmitted infections have many characteristics in common, and several findings are consistent with a strong association between incident bacterial vaginosis and sexual activity.^{29,30} Thus, there may be either unmeasured confounders in these studies or a transmissible microbial component of bacterial vaginosis that has not yet been identified.

DIAGNOSIS

The validation of two standardized, reproducible diagnostic tests for bacterial vaginosis that are based on the use of vaginal swabs has been an important development. One test is laboratory-based Gram's staining for vaginal flora³¹; the other is a bedside, wet-mount microscopic test for vaginal clue cells.³² Clue cells are epithelial squamous cells covered by coccobacilli in the

absence of rods (Fig. 1D); an absence of rods indicates an absence of lactobacilli. These tests have been introduced into clinical practice and are widely used to determine whether bacterial vaginosis is present. A vaginal pH of less than 4.7 provides an easy-to-read cutoff value for distinguishing between normal flora and bacterial vaginosis and is used to rule out bacterial vaginosis (Table 1).

A recent study validated the use of an investigational molecular nucleic acid amplification test that has been approved by the Food and Drug Administration for the diagnosis of bacterial vaginosis and other vaginitis syndromes.³³ Quantitative polymerase chain-reaction assays for the diagnosis of bacterial vaginosis are based on detection of the predominant bacterial vaginosis–associated organisms, such as *G. vaginalis*, *A. vaginae*, and *mobiluncus* species. In the study, involving 1740 symptomatic patients, the performance of the nucleic acid amplification test for detecting bacterial vaginosis, as compared with the reference method (the combined results of vaginal Gram's staining and wet-mount microscopy), was acceptable (sensitivity, 90.5%; specificity, 85.8%).³³ However, the test requires additional validation.

PATHOGENESIS

Bacterial vaginosis can be considered a biofilm infection, with a dense polymicrobial biofilm consisting primarily of *G. vaginalis* adhering to the vaginal epithelium.³⁴ An *A. vaginae* biofilm is always present with a *G. vaginalis* biofilm,²² and higher bacterial loads of *G. vaginalis* and *A. vaginae* increase the probability of biofilm formation. The vaginal biofilm appears to create a favorable anaerobic environment for other obligate anaerobic bacteria.²² An important finding related to upper genital tract complications is that half of women with bacterial vaginosis also have a bacterial vaginosis–associated biofilm covering the endometrium.³⁵ That this biofilm ascends to the endometrium may explain the links among adverse pregnancy outcomes, pelvic inflammatory disease, and bacterial vaginosis. However, the exact role of biofilm in relation to infectious diseases of the upper genital tract remains uncertain.³⁶ For instance, the endometrial cavity is not sterile in most women, and the presence of low levels of bacteria in the uterus is not associated with clinically significant inflammation.³⁷

The striking increase, by a factor of 1000, in potentially virulent bacteria in women with bacterial vaginosis, as compared with women who have healthy vaginal flora, may explain the association of bacterial vaginosis with upper genital tract infection.

BACTERIAL VAGINOSIS AND OTHER SEXUALLY TRANSMITTED INFECTIONS

Bacterial vaginosis is associated with not only the acquisition but also the transmission of other sexually transmitted infections, especially human immunodeficiency virus (HIV) infection.^{38,39} In women with bacterial vaginosis, CD4 T cells are recruited to the lower genital tract mucosa.^{40,41} Among HIV-infected women, the quantity of HIV in vaginal secretions from women with bacterial vaginosis is increased substantially, as compared with HIV in vaginal secretions from women without bacterial vaginosis.⁸ The bacterial vaginosis–associated vaginal microbiome also inactivates the topical microbicide tenofovir, which is used for the prevention of HIV transmission.⁴² *Chlamydia trachomatis* infection is strongly associated with bacterial vaginosis.^{43,44} Chlamydia-associated cervicitis increases the amount of cervical secretions. This increase, in turn, may change the vaginal ecosystem, favoring the growth of anaerobic microorganisms. Thus, controlling *C. trachomatis* infection rates may prevent bacterial vaginosis, perhaps explaining why efforts to control *C. trachomatis* have had a disproportionately positive effect on reducing rates of pelvic inflammatory disease.⁴⁵

OVERALL DISEASE BURDEN

Bacterial vaginosis has a large variety of sequelae in the upper genital tract, including increased risks of preterm birth, first-trimester miscarriage in women undergoing IVF, amniotic-fluid infection, chorioamnionitis, endometritis after childbirth or abortion, and infections after hysterectomy, as well as pelvic inflammatory disease, both in general and after abortion.^{23,46} The attributable proportion of these sequelae has not been universally quantified. Overall, bacterial vaginosis is associated with only a modest increase, by a factor of 2, in the risk of preterm birth. Although this risk has been consistently observed in multiple populations, the vast majority of women with bacterial vaginosis do not deliver preterm. The risks of endometritis after cesarean section,⁴⁷

vaginal-cuff cellulitis after hysterectomy,⁴⁸ and postpartum endometritis⁴⁹ are increased by up to a factor of 6 among women with bacterial vaginosis.

Several studies have assessed the value of screening for and treating bacterial vaginosis in the prevention of preterm birth. The results have been highly variable, and antimicrobial treatment of bacterial vaginosis in pregnancy does not universally reduce adverse pregnancy outcomes.^{50,51} Treatment of bacterial vaginosis in early pregnancy (at <20 weeks of gestation) may be more effective in preventing preterm birth than treatment in later pregnancy.⁵² Since microorganisms associated with bacterial vaginosis can ascend into the endometrium before pregnancy, they may infect the chorioamnion during pregnancy.^{53,54}

Genetic factors may be an important component in the pathogenesis of preterm birth associated with bacterial vaginosis. In one study, the risk of preterm birth was increased by a factor of 6 among women with both bacterial vaginosis and a single-nucleotide polymorphism (SNP) for tumor necrosis factor α but was increased by a factor of only 2 among women with either feature alone.⁵⁵ Among women with other inflammatory SNPs, preterm birth rates were increased by a factor of 2 to 5 for women who had bacterial vaginosis as compared with those who did not have bacterial vaginosis.⁵⁶

The link between bacterial vaginosis and pelvic inflammatory disease has been more consistently replicated than the association of bacterial vaginosis with adverse pregnancy outcomes. Laparoscopic studies have shown that microorganisms that are prevalent in high concentrations in the vagina in women with bacterial vaginosis are also observed in the endometrium and fallopian tubes in women with proven pelvic inflammatory disease.⁵⁷

TREATMENT

Table 2 summarizes the guidelines from the Centers for Disease Control and Prevention for the treatment of bacterial vaginosis.⁵⁸ The guidelines consist of various regimens of oral or vaginally applied metronidazole or clindamycin. Oral metronidazole, topical metronidazole, and topical clindamycin are equally effective, although oral metronidazole has more side effects.⁵⁹ The presence of *A. vaginae*, which is often resistant to metronidazole, predicts a high risk of recurrence,

suggesting that metronidazole is not an ideal empirical agent.⁶⁰ The exact relationship of bacterial vaginosis–associated biofilm with treatment failure is not known. It is plausible, however, that biofilm infection is difficult to eradicate by means of antimicrobial therapy. The role of probiotics as supplementary agents in the treatment of bacterial vaginosis is under study.²² In one trial, oral lactobacilli combined with metronidazole was more effective than metronidazole alone in resolving bacterial vaginosis.⁵⁹

DESQUAMATIVE INFLAMMATORY VAGINITIS

Desquamative inflammatory vaginitis is a newly recognized clinical syndrome characterized by persistent purulent vaginal discharge and vaginal erythema, often with submucosal cervicovaginal petechiae (Fig. 1E).^{61,62} Inflammation is the cardinal feature of this disorder, which has also been called idiopathic inflammatory vaginitis. Donders and colleagues have recently reviewed the literature on this inflammatory vaginitis, which they call “aerobic vaginitis.”⁶³ However, the term “desquamative inflammatory vaginitis” holds priority and was first introduced in 1965 by Gray and Barnes.⁶² The term “aerobic vaginitis” was introduced in 2002 in reference to a disease entity caused by an abnormal vaginal microbiome genomically defined as CST IV.⁶³ The published literature on desquamative inflammatory vaginitis is still surprisingly limited, consisting mainly of retrospective case series or short reviews.^{61,63,64}

CAUSE

The exact cause of desquamative inflammatory vaginitis is unknown but appears to be a dysbiosis of the normal vaginal microbiome associated with inflammation. In desquamative inflammatory vaginitis, the vagina is colonized with facultative bacteria, not the obligate anaerobic bacteria that colonize the vagina in bacterial vaginosis. The microflora in desquamative inflammatory vaginitis typically consist of *Escherichia coli*, *Staphylococcus aureus*, group B streptococcus, or *Enterococcus faecalis*.⁶³ The microbiome associated with desquamative inflammatory vaginitis is less well understood than the bacterial vaginosis microbiome. Desquamative inflammatory vaginitis may also represent a systemic inflammatory syndrome that produces vaginal inflammation, resulting

Table 2. Treatment Guidelines for Bacterial Vaginosis.*

Treatment	Regimen
Recommended treatments	
Metronidazole	500 mg orally twice a day for 7 days
Metronidazole 0.75% gel	One applicator (5 g) intravaginally once a day for 5 days
Clindamycin 2% cream	One applicator (5 g) intravaginally at bedtime for 7 days
Alternative treatments	
Tinidazole	2 g orally once a day for 2 days
Tinidazole	1 g orally once a day for 5 days
Clindamycin	300 mg orally twice a day for 7 days
Clindamycin ovules	100 mg intravaginally at bedtime for 3 days

* The guidelines are from the Centers for Disease Control and Prevention.⁵⁸

in abnormal vaginal flora. As with bacterial vaginosis, understanding the mechanism underlying the loss of vaginal lactobacilli should shed light on the pathogenesis of desquamative inflammatory vaginitis.

SYMPTOMS AND SIGNS

Clinical manifestations of desquamative inflammatory vaginitis include purulent vaginal discharge and a strong inflammatory reaction. The vaginal discharge is homogeneous and yellowish, with no fishy smell (Table 1). Vulvar irritation and vaginal mucosal erythema with ecchymotic lesions or erosions are present in severe cases (Fig. 1E). Symptoms may last for a long time and fluctuate, suggesting a chronic or recurrent natural history.

EPIDEMIOLOGY

In the few studies that have systematically analyzed the prevalence of desquamative inflammatory vaginitis among pregnant or nonpregnant women, the rates have ranged from 2 to 20%.⁶³ One important limitation of epidemiologic studies has been the lack of standardized biomarkers for the diagnosis of desquamative inflammatory vaginitis. Lack of diagnostic precision is compounded by the fact that the existence of this condition has not been accepted universally by clinicians. In our experience, highly symptomatic desquamative inflammatory vaginitis is relatively rare, whereas a less symptomatic form of vaginal dysbiosis, characterized by reduced numbers of lactobacilli, increased numbers of facul-

Table 3. Treatment Recommendations for Desquamative Inflammatory Vaginitis.*

Treatment	Regimen
Recommended treatments	
Clindamycin 2% cream	Intravaginally daily at bedtime for 1 to 3 wk; consider maintenance therapy once or twice a week for 2–6 mo
Topical glucocorticoid	
Hydrocortisone, 300–500 mg	Intravaginally daily at bedtime for 3 wk; consider maintenance therapy once or twice a week for 2–6 mo
Clobetasol propionate	Intravaginally daily at bedtime for 1 wk (duration not evidence-based)
Additional recommended treatments†	
Fluconazole	150 mg orally once a week as maintenance therapy
Topical vaginal estrogen	Twice a week

* The recommendations are from Reichman and Sobel.⁶⁵ Official treatment guidelines for desquamative inflammatory vaginitis have not been developed.

† Additional recommended treatments are for use in combination with clindamycin or one of the glucocorticoids.

tative bacteria, and inflammation, is much more common. To what extent this dysbiosis translates into symptomatic disease remains to be determined.

DIAGNOSIS

Microscopic examination of wet-mount preparations of vaginal secretions reveals an increase in inflammatory cells and parabasal epithelial cells (Table 1 and Fig. 1F), and vaginal flora are usually abnormal, with an elevated pH.⁶³ The point-of-care diagnosis is based on the presence of an increased number of leukocytes and parabasal epithelial cells. Microscopic examination of wet-mount preparations is the preferred diagnostic method for desquamative inflammatory vaginitis, since Gram's staining of vaginal flora does not discriminate between bacterial vaginosis and desquamative inflammatory vaginitis. The use of routine vaginal cultures is not recommended.

DISEASE BURDEN

The disease burden caused by desquamative inflammatory vaginitis has not been well studied. The disorder has been linked to an increased risk of preterm birth, premature rupture of mem-

branes, chorioamnionitis, and other adverse pregnancy outcomes, such as miscarriage.⁶³ Dysbiosis in women with desquamative inflammatory vaginitis might increase the risk of neonatal group B streptococcal infection or urinary tract infection caused by *E. coli*. Desquamative inflammatory vaginitis is also likely to be important in upper genital tract infection such as pelvic inflammatory disease, although this has not been definitively proved.

TREATMENT

Recommended treatment approaches for desquamative inflammatory vaginitis are presented in Table 3.⁶⁵ These treatment options have not been properly tested in randomized clinical trials. Metronidazole is not effective in desquamative inflammatory vaginitis, and treatment failure with metronidazole in women with bacterial vaginosis may suggest desquamative inflammatory vaginitis. Clindamycin is active against the broad spectrum of facultative bacteria linked to desquamative inflammatory vaginitis and also has an antiinflammatory effect. In clinical practice, topical clindamycin, often used as prolonged maintenance therapy, seems to be an effective treatment approach for severe forms of desquamative inflammatory vaginitis. Maintenance therapy once weekly is commonly used to reduce the risk of recurrences or flare-ups.

An observational study suggested that topical application of 2% clindamycin, with or without 10% hydrocortisone, is useful in the treatment of severe desquamative inflammatory vaginitis.⁶⁶ Women with desquamative inflammatory vaginitis characterized by a heavy parabasal-cell component may benefit from intravaginal application of estrogens as maintenance therapy.⁶⁷ Official treatment guidelines for desquamative inflammatory vaginitis have not been developed or implemented.

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

The human vaginal ecosystem is highly dynamic. The vaginal microbiome can affect host physiology, and host physiology can affect the vaginal microbiome. Research is needed for a better understanding of the interactions among the vaginal microbiome, host physiology, reproduction,

and host defense. Recent genomic research has increased our knowledge of the vaginal microbiome. Future research based on genomic, proteomic, and metabolomic techniques may ultimately have a major effect on women's reproductive health. **The mechanisms that initiate and maintain colonization with vaginal lactobacilli, especially *L. crispatus*, in women of reproductive age need to be elucidated.** New biomarkers for an abnormal vaginal microbiome are needed for clinical practice.

Microorganisms of the vaginal microbiome alter the innate immune response and barrier properties of the human vaginal epithelium. Substantial increases in vaginal pH and disruption

of immune barriers enhance susceptibility to sexually transmitted infections,⁶⁸ and this, in turn, increases the disease burden caused by an abnormal vaginal microbiome. Understanding the mechanisms that initiate and maintain a healthy vaginal microbiome will be essential for the development of improved treatments for bacterial vaginosis and desquamative inflammatory vaginitis, as well as effective topical microbicides for the prevention of HIV infection and other sexually transmitted infections.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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