Infectious Vaginitis

Vaginitis is one of the most common reasons women seek medical attention and accounts for 10 million office visits annually (1). Although common in adult women, it is uncommon in prepubertal girls. The normal vaginal ecosystem is composed of a dynamic relationship between Lactobacillus spp. other normal flora and their metabolic by-products, glycogen, estrogen, and vaginal pH (2). Vaginitis occurs as a result of a shift in the vaginal flora. This shift can result either through the introduction of a pathogen or changes in the vaginal ecosystem that allow a pathogen to proliferate or push asymptomatic colonization into symptomatic infection. Despite the variety of causes of vaginitis, in approximately 90% of cases it is thought to occur secondary to a triad of infectious agents including Bacterial Vaginosis (BV), Candidiasis, and Trichomoniasis (2).

BACTERIAL VAGINOSIS

Bacterial vaginosis (BV) is a leading cause of abnormal vaginal discharge and odor and is the cause of costly obstetric and gynecologic infectious complications worldwide. Lactobacillus species are the predominant vaginal bacteria during women’s reproductive years (3, 4). A large number of commensal bacterial species also inhabit the same niche in healthy women, but at three log-fold lower numbers than those of the Lactobacillus. In addition, vaginal microorganisms that are either associated with BV, or are likely etiological agents of BV, can often be detected at low numbers in the absence of BV.

Epidemiology

BV has been studied largely among self-selected women attending a variety of clinics. Since more than 50% of women with BV are asymptomatic, large numbers of women with the condition are not included in studies of this type. The prevalence of BV in participants is similar to those found among non-pregnant women with similar demographic characteristics. The prevalence of BV in the U.S. is highest among African American women and lowest among Asian American women; highest among women with multiple sexual partners and lowest among women with no history of heterosexual contact (2, 5). BV-associated microorganisms, including Mycoplasma hominis, G. vaginalis, Mobiluncus spp., and Bacteroides fragilis are recovered from 17% to 52% of urethral cultures from male partners of women with BV. Furthermore, the same G. vaginalis biotypes are isolated from heterosexual couples (6, 7).

Pathogenesis

BV does not fulfill Koch’s postulates, i.e., no single organism is the etiological agent of this disease. While specific vaginal microorganisms are associated with BV, the current perception is that it results from a complex change in the microbial ecosystem of the vagina. BV is characterized by a substantive decrease or total elimination of the Lactobacillus species and a concomitant multi log-fold increase in the number of facultative and anaerobic Gram-positive and Gram-variable bacteria and other microbes including Gardnerella vaginalis, Bacteroides spp., Mobiluncus spp., Ureaplasma urealyticum, and Mycoplasma hominis. (4, 8-10).

Recent studies of the vaginal flora using molecular techniques have identified several novel bacterial species that are more prevalent in women with BV compared to women without BV. The first of these species to be identified was Atoxopobium vaginae, which was initially described after isolation from the vagina of a healthy woman (11). Subsequent studies using Polymerase Chain Reaction (PCR)-based detection showed that A. vaginae was more prevalent in women with BV than in healthy women, and that the sensitivity and specificity of A. vaginae detection in diagnosing BV was comparable to that of G. vaginalis detection (12-15). More recently, other fastidious vaginal microorganisms (FVM) including Eggerthella species as well as three as of yet unclassified microorganisms termed Bacterial Vaginosis Associated Bacteria (BVAB): BVAB1, BVAB2, and BVAB3, have also been shown by molecular techniques to be prevalent in women with BV (16-17).

The mechanism of how the vaginal flora changes so distinctly in BV is unknown. Lactic acid is produced by vaginal epithelial cells and vaginal microorganisms including Lactobacillus spp. Consequently, the vaginal pH in healthy women ranges between pH 3.8 to 4.2. This acidic environment is an important factor in the maintenance of the balance between the commensal and pathogenic microorganisms. Attachment and growth of lactobacilli are favored in the acidic vaginal environment while the attachment of BV-associated microorganisms is reduced (18, 19). Conversely, higher pH tends to displace lactobacilli from vaginal epithelial cell receptor sites and to maximize adherence of G. vaginalis. Risk factors for BV include douching, menstruation, and antibiotic use, all of which either directly or indirectly raise the vaginal pH above the optimum for Lactobacillus-dominated microflora. The production of hydrogen peroxide by specific species of lactobacilli also appears to play an important role in maintaining the healthy vaginal microflora (19, 20). In vitro studies have demonstrated that hydrogen peroxide-producing lactobacilli are toxic to G. vaginalis and Bacteroides spp. (17). In addition, the loss of the hydrogen peroxide-producing Lactobacillus spp. from the vaginal flora is associated with BV (21).

Cooperative interactions between BV-associated bacteria have been shown. In vitro studies by Pybus and Onderdonk (22) demonstrated a relationship between two of the predominant organisms in BV, G. vaginalis and Bacteroides spp. (22). Amino acids produced by G. vaginalis are utilized by Bacteroides to produce ammonia and short chain fatty
acids, such as succinate and isovalerate. The growth of G. vaginalis is further enhanced by the presence of ammonia, which is produced during the growth of Bacteroides. More recently, it was demonstrated that a biofilm consisting mainly of A. vaginae and G. vaginalis was present on the vaginal mucosa after metronidazole treatment (23).

Gynecological Complications

BV is related to considerable, and possibly preventable, infectious morbidity in non-pregnant women. The sequelae of BV now include endometritis, pelvic inflammatory disease, post surgical abortion infections, post-hysterectomy infection, increased risk of HIV acquisition, and possibly cervical intraepithelial neoplasia. Constituents of BV are Bacteroides spp., Mobiluncus spp., G. vaginalis and Mycoplasmas, which are all associated with laparoscopically confirmed nonchlamydial, nongonococcal pelvic inflammatory disease (PID) endometritis, salpingitis, and peritonitis (24). Women with PID are 7.5 times more likely to have BV compared with women who do not have PID. Both circumstantial and direct evidence link BV and endometritis. Research by Wolner-Hanssen and co-workers (42) identified BV 3.8 times more often among women using oral contraceptives who were examined for menorrhagia compared with women who did not report this complaint. Two studies by Larsson and co-workers demonstrate resolution of metrorrhagia following successful treatment of BV and Mobiluncus spp. (25, 26). BV has been shown to significantly increase the risk of postsurgical infection up to four times among women undergoing pregnancy termination and three- to six-times among women having abdominal hysterectomies.

Diagnosis

The diagnosis of BV is complicated by the polymicrobial nature of the condition. In a clinical setting, the most common method of BV diagnosis is based on the observation of specific signs of disease known as the “Amsel criteria”:

- Homogeneous, thin adherent gray-white discharge
- Vaginal fluid pH > 4.5
- Release of an amine odor with alkalinization of the vaginal fluid
- Presence of vaginal epithelial cells with borders obscured with adherent, small bacteria called “clue” cells

Of the four (4) Amsel criteria, only the presence clue cells is specific for BV. Discharge, odor, and elevated pH are associated with, but are not individually specific for, BV. For example, the presence of semen and Trichomonas vaginalis in the vagina also increase vaginal pH.

The Nugent score was proposed as a diagnostic test for BV that required less subjective interpretation than the Amsel criteria (27). Used mostly in a laboratory setting, the Nugent score is a semi-quantitative evaluation of vaginal Gram-positive and Gram-variable bacterial morphotypes by Gram stain that accounts for the numbers of Lactobacillus, Gardnerella vaginalis, Prevotella, and Mobiluncus species. In this way, vaginal flora is categorized as normal (Lactobacillus predominant), intermediate (mixed flora), and BV (anaerobe predominant) (28). Nugent scores have a sensitivity of up to 98.5% and a specificity of 95.6% to 100% compared to clinical criteria (32). MDL has introduced an ultrasensitive, PCR-based assay to identify pathogens that are associated with BV.

CANDIDIASIS

Epidemiology

Candidiasis accounts for 20% to 25% of cases of Infectious Vaginitis. It has been estimated that 75% of women will experience at least one (1) episode of vulvovaginal candidiasis in their lifetime (33). A study of female college graduates reported at least one (1) lifetime physician-diagnosed and treated vaginal yeast infection and 20% of women reported infection within the past year (33). Although Candida albicans can be recovered from 80% to 90% of women with vulvovaginal candidiasis, non-albicans infections are typically associated with recurrence (33). It is believed that widespread use of topical antifungal therapy in short courses may contribute to this selection of non-albicans yeast infections due to the fact that they tend to be less susceptible to these agents.

Pathogenesis

It has been proposed that mechanisms of adherence contribute to the virulence of Candida species, although the mechanism by which Candida produces disease is not well understood. In fact, there tends to be little difference between species isolated from symptomatic patients and asymptomatic carriers (33). However, filamentous forms of Candida, possessing hyphae and pseudohyphae, have been observed to penetrate vaginal epithelial cells and are thought to be an important pathologic feature.

Candida species have extraordinary phenotypic plasticity which allows them to adapt to the changing environment within its host. This ability enables Candida species to evade the host immune system, increases adhesion to human epithelial cells, and affects drug susceptibility (34). Candida species secrete extracellular hydrolytic enzymes, such as aspartyl proteinases, to disrupt host cell membranes in an attempt to facilitate adherence and tissue invasion (35).

Risk factors for candidiasis include uncontrolled diabetes mellitus, recent antibiotic therapy, immunosuppression, pregnancy, and hormone replacement therapy. Symptoms typically include perivaginal pruritus, vulvovaginal swelling, and dysuria. Tiny papules, called satellite lesions, may surround areas of erythema. Vaginal discharge, when present, is typically thick and white, although it may present as thin and loose resembling discharge associated with other disorders.
Diagnosis
Despite the commonly held belief that patients can intuitively self-diagnose yeast infections, Ferris et al., observed that vulvovaginal candidiasis was confirmed in only 33.7% of women who self diagnosed yeast infection (36). Traditional diagnosis of Candida infection is slow and complicated and relies heavily on microscopic examination, evaluation of KOH preparations, and vaginal culture. The ability to diagnose and identify candidiasis may be enhanced by the use of molecular techniques, such as Polymerase Chain Reaction (PCR).

TRICHOMONIASIS

Epidemiology
Trichomoniasis is caused by the protozoan Trichomonas vaginalis. Incidences of Trichomoniasis vary from 11% to 26% infection rates in female sexually transmitted disease (STD) clinics to as high as 50% among newly incarcerated women (36). Approximately 10% to 50% of infected women remain asymptomatic (36). Although traditionally thought of as a sexually transmitted disease, there are occasional incidences of nonvenereal transmission. It has been documented that T. vaginalis can survive in moist environments and on fomites for several hours (36).

Symptoms of infection, when present, will often be exacerbated during the menstrual cycle and may include vulvovaginal soreness or irritation, pain upon urination, painful intercourse, inflammation of the external genitalia, abdominal discomfort and a yellow/green foamy discharge which may have a fishlike odor. In women, T. vaginalis infection can cause adverse outcomes of pregnancy, cervical neoplasia, and atypical pelvic inflammatory disease. Complications in men include non-gonococcal urethritis, prostatitis, epididymitis, urethral disease, and infertility. T. vaginalis has a high association with other sexually transmitted diseases and may increase the risk of HIV transmission in both men and women. Therefore, patients found to be infected with T. vaginalis should also be screened for other STDs including Neisseria gonorrhoeae, Chlamydia trachomatis, and HIV.

Pathogenesis
Trichomonas vaginalis colonizes both the male and female urogenital tracts. This protozoan possesses four free anterior flagella and a fifth which is embedded in the undulating membrane. They are responsible for its characteristic twitching motility. The pathogenesis of T. vaginalis is due, in part, to multiple adhesion factors which provide an increased ability to cytoadhere to vaginal epithelial cells resulting in micro ulcerations.

Diagnosis
Clinically, the most common approach to diagnosis is by demonstrating the presence of the trichomonad in genital specimens by microscopic visualization in a wet mount preparation. However, this technique will only detect T. vaginalis infection in 60% of infected women (36). Due to the fact that T. vaginalis infection is associated with a shift in vaginal flora hallmarked by a reduction in Lactobacillus, an increase in anaerobes and Gardnerella vaginalis, a pH above 4.5, clue cells upon microscopic examination and a positive whiff test; many women with T. vaginalis infection will meet the diagnostic criteria for Bacterial Vaginosis. The use of molecular diagnostic methods, such as Polymerase Chain Reaction (PCR) testing, offers clinicians a highly sensitive and specific means of identification of Trichomonas vaginalis with a rapid turnaround time.

MDL has developed highly sensitive and specific Real-Time PCR based assays for the detection of the aforementioned pathogens utilizing the OneSwab® platform. Benefits of this system include:

- Real-Time PCR
- Simple & convenient sample collection
- No refrigeration required before or after collection
- Specimen viability up to five (5) days
- Test additions available up to 30 days
- 24-48 hour turnaround time
- High diagnostic specificity and sensitivity
- One vial, multiple pathogens

Table 1. Vaginal Infections: Diagnostic Clues (2, 35, 40)

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>Discharge Characteristics</th>
<th>Vaginal pH</th>
<th>Microbiology</th>
<th>Sexually Transmitted?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Vaginosis</td>
<td>Usually normal appearance of tissue. Discolored vaginal discharge which adheres to the vaginal wall. NOT accompanied by leukorrea, vulvar burning, or pruritis.</td>
<td>Color: off-white Consistency: creamy Odor: Fishy or musty odor which may increase after sexual intercourse</td>
<td>&gt;4.5</td>
<td>Polymicrobial; mostly normal flora, but can include comma-shaped, gram-variable anaerobic Mobiluncus rods, Gardnerella vaginalis, or clue cells (&gt; 20% of the epithelial cells), but few WBCs, few lactobacilli. Pap smear may indicate coccobacillary shift of flora.</td>
</tr>
<tr>
<td>Candida species</td>
<td>Vulvar pruritus, indicating spread of fungus distally onto the vulva. Hyperemic vagina, vulvar and vaginal erythema, or excoriated vulva.</td>
<td>Color: white or off-white if mixed infection present Consistency: “curdled” Odor: not malodorous unless a mixed infection is present Normal range of 3.8-4.2</td>
<td>Hyphae or budding yeast visible in 50% to 70% of cases. Fungal elements on Pap smear could indicate colonization, not infection.</td>
<td>Patients may infect the glans penis of their partners</td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
<td>Irritation and soreness of the vulva, perineum, and thighs, with dyspareunia and dysuria. “Strawberry cervix” with punctate cervical microhemorrhages visible in 25% of cases. Asymptomatic up to 50% of the time.</td>
<td>Color: greenish-yellow Consistency: Frothy and purulent Odor: foul-smelling &gt; 4.5 (70% of cases)</td>
<td>Flagellated protozoa visible on wet mount (= 60%); Pap smear sensitive for trichomonads (70%).</td>
<td>Yes</td>
</tr>
</tbody>
</table>

www.mdlab.com • 877 269 0090
References: