

CHAPTER 35

Sexually Transmitted Diseases

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INFECTIONS OF THE EXTERNAL GENITALIA

Some STDs primarily affect the mucocutaneous tissues of the external genitalia. These include human papillomavirus infection, genital herpes, chancroid, granuloma inguinale, and lymphogranuloma venereum (LGV).

Human Papillomavirus (Condylomata Acuminata)

Condylomata acuminata, or *genital warts*, are caused by the human papillomavirus (HPV). Although recognized for centuries, HPV-induced genital warts have become one of the fastest-growing STDs of the past decade. The Centers for Disease Control and Prevention (CDC) estimates that 20 million Americans carry the virus and that as many as 5.5 million new cases are diagnosed each year.¹ The current prevalence of HPV is difficult to determine because it is not a reportable disease in all states.

A 1998 American Medical Association consensus conference on external genital warts identified four specific types of warts: *condyloma acuminata* (cauliflower-shaped lesions that tend to appear on moist skin surfaces such as the vaginal introitus or anus); *keratotic warts* (display a thick, horny layer; develop on dry, fully keratinized skin such as the penis, scrotum, or labia majora); *papular warts* (smooth surface; typically develop on fully keratinized skin); and *flat warts* (macular, sometimes faintly raised, usually invisible to the naked eye; occur on either fully or partially keratinized skin). Biopsy may be required to differentiate warts from other hyperkeratotic or precancerous lesions.²

A relation between HPV and genital (*i.e.*, cervix, vulva, and penis) neoplasms has become increasingly apparent since the early 1980s. One hundred types of HPV have been identified, more than 30 of which affect the anogenital area. Types 6 and 11 are found in most external genital warts but usually are benign, with only a low potential for dysplasia. Persons with visible genital warts may be infected simultaneously with multiple HPV types. Other HPV types of the anogenital region (*e.g.*, types 16, 18, 31, 33, and 35) have been strongly associated with cervical neoplasia.³ HPV type 16 is present in 50%

The incidence and types of sexually transmitted diseases (STDs), as reported in the professional literature and public health statistics, are increasing. However, the incidence of disease is based on clinical reports, and many STDs are not reportable or not reported. The agents of transmission include bacteria, chlamydiae, viruses, fungi, protozoa, parasites, and unidentified microorganisms. Portals of entry include the mouth, genitalia, urinary meatus, rectum, and skin. All STDs are more common in persons who have more than one sexual partner, and it is not uncommon for a person to be concurrently infected with more than one type of STD.

This chapter discusses the manifestations of STDs in men and women in terms of infections of the external genitalia, vaginal infections, and infections that have systemic effects and genitourinary manifestations. Human immunodeficiency virus (HIV) infection is presented in Chapter 10.

KEY CONCEPTS**SEXUALLY TRANSMITTED DISEASE**

- Sexually transmitted diseases (STDs) are spread by sexual contact and involve both male and female partners. Portals of entry include the mouth, genitalia, urinary meatus, rectum, and skin. All STDs are more common in persons who have more than one sexual partner, and it is not uncommon for a person to be concurrently infected with more than one type of STD.
- In general, STDs due to bacterial pathogens can be successfully treated and the pathogen eliminated by antimicrobial therapy. However, many of these pathogens are developing antibiotic resistance.
- STDs due to viral pathogens, such as the human papillomavirus (HPV) and genital herpes simplex virus infections (HSV-1 and HSV-2), are not eliminated by current treatment modalities and persist with risk of recurrence (HSV infections) or increased cancer risk (HPV).
- Untreated, STDs such as chlamydial infection and gonorrhea can spread to involve the internal genital organs with risk of complications and infertility.
- Intrauterine or perinatally transmitted STDs can have potentially fatal or severely debilitating effects on a fetus or an infant.

of cervical cancers and in 25% of low-grade cervical intraepithelial neoplasias⁴ (see Chapter 34). However, only a subset of women with HPV go on to develop cancer, suggesting that there may be variants of even the most virulent HPV, type 16, with differing oncogenic potential. Cofactors that may increase the risk for cancer include smoking, immunosuppression, and exposure to hormonal alteration (*e.g.*, pregnancy, oral contraceptives).⁵ The association with premalignant and malignant changes has increased the concern about diagnosis and treatment of this viral infection.

HPV infection begins with viral inoculation into a stratified squamous epithelium, where infection stimulates the replication of the squamous epithelium, producing the various HPV-proliferative lesions. The incubation period for HPV-induced genital warts ranges from 6 weeks to 8 months. Subclinical infection occurs more frequently than visible genital warts among men and women. Infection often is indirectly diagnosed on the cervix by Papanicolaou testing (Pap smear), colposcopy, or biopsy. Both spontaneous resolution and infection with new HPV types are common. Although reinfection from sexual partners has been considered as a reason for the high prevalence of this disease, it is now thought that reinfection with the same HPV type is infrequent. Instead, it is thought that HPV may be a lifelong infection.

Genital condylomas should be considered in any woman who presents with the primary complaint of vulvar pruritus or

who has had an abnormal Pap smear. Microscopic examination of a wet-mount slide preparation and cultures are used to exclude associated vaginitis. Acetic acid soaks may be used before inspecting the vulva under magnification, and specimens for biopsy can be taken from questionable areas. Colposcopic examination of the cervix and vagina may be advised as a follow-up measure when there is an abnormal Pap smear or when HPV lesions are identified on the vulva. Evaluation and treatment of sexual partners may be suggested, although this may be difficult considering that warts often do not become clinically apparent for several years after exposure.

The recent development and controlled trial of a vaccine to protect against HPV type 16 may eventually reduce the risk of cervical cancer associated with this strain of HPV.⁴ However, currently there is no treatment to eradicate the virus once a person has become infected. Thus, treatment goals are aimed at elimination of symptomatic warts, surveillance for malignancy and premalignant changes, and education and counseling to decrease psychosocial distress.⁶ Prevention of HPV transmission through condom use has not been adequately demonstrated.

The CDC recommends several pharmacologic agents for symptomatic removal of visible genital warts, including patient-applied therapies (podofilox and imiquimod) and provider-administered therapies (podophyllin and trichloroacetic acid).³ Podophyllin, a topical cytotoxic agent, has long been used for the treatment of visible external growths. Trichloroacetic acid is a weak destructive agent that produces an initial burning in the affected area, followed in several days by a sloughing of the superficial tissue. Imiquimod cream is a new type of therapeutic agent that stimulates the body's immune system (*i.e.*, production of interferon- α and other cytokines).

Genital warts also may be removed using cryotherapy, laser surgery, or electrocautery. Because it can penetrate deeper than other forms of therapy, cryotherapy (*i.e.*, freezing therapy) often is the treatment of choice for cervical HPV lesions. Laser surgery can be used to remove large or widespread lesions of the cervix, vagina, or vulva, or lesions that have failed to respond to other first-line methods of treatment. Electrosurgical treatment has become more widespread for these types of lesions because it is more readily available in outpatient settings and is much less expensive than laser.

Genital Herpes

Herpesviruses are large, encapsulated viruses that have a double-stranded genome. There are nine types of herpesviruses, belonging to three groups, that cause infections in humans: (1) neurotropic α -group viruses, including herpes simplex virus type 1 (HSV-1; usually associated with cold sores) and HSV-2 (usually associated with genital herpes); (2) varicella-zoster virus (causes chickenpox and shingles); and (3) lymphotropic β -group viruses, including cytomegalovirus (causes cytomegalic inclusion disease), Epstein-Barr virus (causes infectious mononucleosis and Burkitt's lymphoma), and human herpesvirus type 8 (the apparent cause of Kaposi's sarcoma).⁷

Genital herpes is caused by the herpes simplex virus. Because herpesvirus infection is not reportable in all states, reliable data on its true incidence (estimated number of new cases every year) and prevalence (estimated number of people currently infected) are lacking. From the late 1970s to early 1990s, genital herpes prevalence increased 30%. Incidence rates have

been relatively stable since 1990, with an estimated 1 million new cases occurring each year. Recent estimates in the United States indicate 50 million people (one in five adolescents or adults) are infected with genital herpes.³ Women have a greater mucosal surface area exposed in the genital area and therefore are at greater risk of acquiring the infection.

HSV-1 and HSV-2 are genetically similar, both cause a similar set of primary and recurrent infections, and both can cause genital lesions. Both viruses replicate in the skin and mucous membranes at the site of infection (oropharynx or genitalia), where they cause vesicular lesions of the epidermis and infect the neurons that innervate the area. HSV-1 and HSV-2 are neurotropic viruses, meaning that they grow in neurons and share the biologic property of latency. Latency refers to the ability to maintain disease potential in the absence of clinical signs and symptoms. In genital herpes, the virus ascends through the peripheral nerves to the sacral dorsal root ganglia (Fig. 35-1). The virus can remain dormant in the dorsal root ganglia, or it can reactivate, in which case the viral particles are transported back down the nerve root to the skin, where they multiply and cause a lesion to develop. During the dormant or latent period, the virus replicates in a different manner so that the immune system or available treatments have no effect on it. It is not known what reactivates the virus. It may be that the body's defense mechanisms are altered. Numerous studies have shown that host responses to infection influence initial development of the disease, severity of infection, development and maintenance of latency, and the frequency of HSV recurrences.

HSV is transmitted by contact with infectious lesions or secretions. HSV-1 is transmitted by oral secretions, and infections frequently occur in childhood, with most persons (50% to 90%) being infected by adulthood.⁸ HSV-1 may be spread to the genital area by autoinoculation after poor hand washing or through oral intercourse. HSV-2 usually is transmitted by sex-

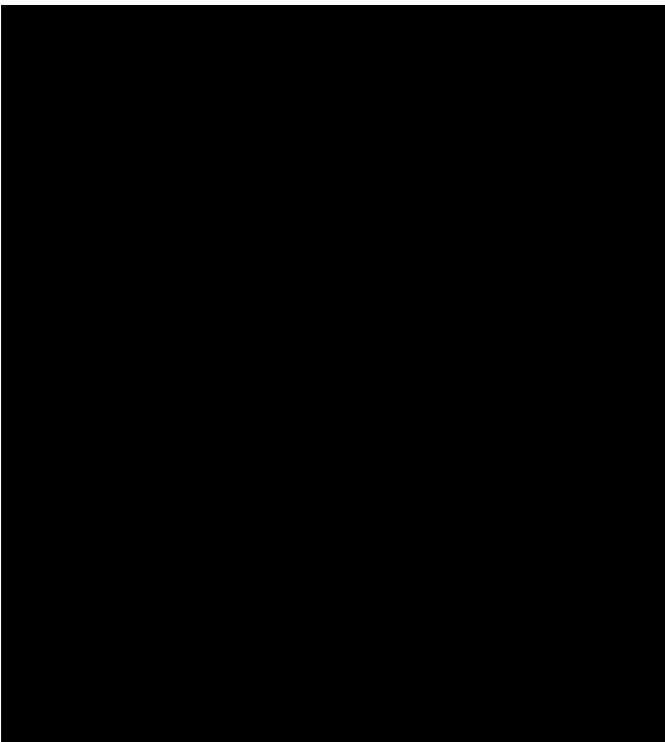
ual contact but can be passed to an infant during childbirth if the virus is actively being shed from the genital tract. Most cases of HSV-2 infection are subclinical, manifesting as truly asymptomatic or symptomatic but unrecognized infections. These subclinical infections can occur in people who have never had a symptomatic outbreak or between recognized clinical recurrences. Up to 70% of genital herpes cases are spread through asymptomatic shedding by people who do not realize they have the infection.³ This "unknown" transmission of the virus to sex partners explains why this infection has reached epidemic proportions throughout the world.

The incubation period for HSV is 2 to 10 days. Genital HSV infection may manifest as a primary, nonprimary, or recurrent infection. *Primary infections* are infections that occur in a person who is seronegative for antibody to HSV-1 or HSV-2. *Initial nonprimary infections* refer to the first clinical episode in a person who is seropositive for antibodies to the opposite HSV type (usually genital herpes in someone seropositive to HSV-1). *Recurrent infections* refer to the second or subsequent outbreak caused by the same virus type. HSV-2 is responsible for more than 90% of recurrent genital herpes infections.⁶

The initial symptoms of primary genital herpes infections include tingling, itching, and pain in the genital area, followed by eruption of small pustules and vesicles. These lesions rupture on approximately the fifth day to form wet ulcers that are excruciatingly painful to touch and can be associated with dysuria, dyspareunia, and urine retention. Involvement of the cervix and urethra is seen in more than 80% of women with primary infections.⁹ In men, the infection can cause urethritis and lesions of the penis and scrotum. Rectal and perianal infections are possible with anal contact. Systemic symptoms associated with primary infections include fever, headache, malaise, muscle ache, and lymphadenopathy. Primary infections may be debilitating enough to require hospitalization, particularly in women.

Untreated primary infections typically are self-limited and last for approximately 2 to 4 weeks. The symptoms usually worsen for the first 10 to 12 days. This period is followed by a 10- to 12-day interval during which the lesions crust over and gradually heal. Nonprimary episodes of genital herpes manifest with less severe symptoms that usually are of shorter duration and have fewer systemic manifestations. Except for the greater tendency of HSV-2 to recur, the clinical manifestations of HSV-2 and genital HSV-1 are similar. Recurrent HSV infection results from reactivation of the virus stored in the dorsal root ganglia of the infected dermatomes. An outbreak may be preceded by a prodrome of itching, burning, or tingling at the site of future lesions. Because immune lymphocytes have already developed from the primary infection, recurrent episodes have fewer lesions, fewer systemic symptoms, less pain, and a shorter duration (7 to 10 days). The frequency and severity of recurrences vary from person to person. Numerous factors, including emotional stress, lack of sleep, overexertion, other infections, vigorous or prolonged coitus, and premenstrual or menstrual distress have been identified as triggering mechanisms.

Diagnosis of genital herpes is based on the symptoms, appearance of the lesions, and identification of the virus from cultures taken from the lesions. The likelihood of obtaining a positive culture decreases with each day that has elapsed after a lesion develops. The chance of obtaining a positive culture



from a crusted lesion is slight, and patients suspected of having genital herpes should be instructed to have a culture within 48 hours of development of new lesions. Type specific (HSV-1 and HSV-2) serologic tests are available for determining past infection. Because almost all HSV-2 infections are sexually acquired, the presence of type-specific HSV-2 antibodies usually indicates anogenital infection; whereas the presence of HSV-1 antibodies does not distinguish between anogenital and orolabial infections. The CDC recommends that serologic assays for HSV-2 be available for persons who request them but does not recommend they be used for screening of the general population.³

There is no known cure for genital herpes, and the methods of treatment are largely symptomatic. The antiviral drugs acyclovir, valacyclovir, and famciclovir have become the cornerstone for management of genital herpes. By interfering with viral DNA replication, these drugs decrease the frequency of recurrences, shorten the duration of active lesions, reduce the number of new lesions formed, and decrease viral shedding with primary infections. Good hygiene is essential to prevent secondary HSV infection. Fastidious hand washing is recommended to avoid hand-to-eye spread of the infection. HSV infection of the eye is the most common cause of corneal blindness in the United States. To prevent spread of the disease, intimate contact should be avoided until lesions are completely healed.

Approximately 30% to 50% of infants born vaginally to mothers experiencing a primary HSV infection at the time of delivery will be infected, compared with only 1% of those born to women with recurrent infection.³ The risk of mortality in HSV-infected neonates ranges from 15% to 57%, and a significant number of survivors have significant sequelae.¹⁰ Active infection during labor may necessitate cesarean delivery.

Chancroid

Chancroid (*i.e.*, soft chancre) is a disease of the external genitalia and lymph nodes. The causative organism is the gram-negative bacterium *Haemophilus ducreyi*, which causes acute ulcerative lesions with profuse discharge. This disease has become uncommon in the United States, with only 143 reported cases in 1999.¹ It typically occurs in discrete outbreaks, rather than as an endemic disease in this country. It is more prevalent in Southeast Asia, the West Indies, and North Africa. A highly infectious disease, chancroid usually is transmitted by sexual intercourse or through skin and mucous membrane abrasions. Autoinoculation may lead to multiple chancres.

Lesions begin as macules, progress to pustules, and then rupture. This painful ulcer has a necrotic base and jagged edges. In contrast, the syphilitic chancre is nontender and indurated. Subsequent discharge can lead to further infection of self or others. On physical examination, lesions and regional lymphadenopathy (*i.e.*, buboes) may be found. Secondary infection may cause significant tissue destruction. Diagnosis usually is made clinically but may be confirmed through culture. Gram's stain rarely is used today because it is insensitive and nonspecific. Polymerase chain reaction (PCR) methods may soon be available commercially for definitive identification of *H. ducreyi*. The organism has shown resistance to treatment with sulfamethoxazole alone and to tetracycline. The CDC recommends treatment with azithromycin, erythromycin, ciprofloxacin, or ceftriaxone.³

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is an acute and chronic venereal disease caused by *Chlamydia trachomatis* types L1, L2, and P3. The disease, although found worldwide, has a low incidence outside the tropics. Most cases reported in the United States are in men.

The lesions of LGV can incubate for a few days to several weeks and thereafter cause small, painless papules or vesicles that may go undetected. An important characteristic of the disease is the early (1 to 4 weeks later) development of large, tender, and sometimes fluctuant inguinal lymph nodes called *buboes*. There may be flulike symptoms with joint pain, rash, weight loss, pneumonitis, tachycardia, splenomegaly, and proctitis. In later stages of the disease, a small percentage of affected persons develop elephantiasis of the external genitalia, caused by lymphatic obstruction or fibrous strictures of the rectum or urethra from inflammation and scarring. Urethral involvement may cause pyuria and dysuria. Cervicitis is a common manifestation of primary LGV and could extend to perimetritis or salpingitis, which are known to occur in other chlamydial infections.⁵ Anorectal structures may be compromised to the point of incontinence. Complications of LGV may be minor or extensive, involving compromise of whole systems or progression to a cancerous state.

Diagnosis usually is accomplished by means of a complement fixation test for LGV-specific *Chlamydia* antibodies. High titers for this antibody differentiate this group from other chlamydial subgroups. Treatment involves 3 weeks of doxycycline or erythromycin.³ Surgery may be required to correct sequelae such as strictures or fistulas or to drain fluctuant lymph nodes.

In summary, STDs that primarily affect the external genitalia include HPV (condyloma acuminata), genital herpes (HSV-2), chancroid, and lymphogranuloma venereum. The lesions of these infections occur on the external genitalia of male and female sexual partners. Of concern is the relation between HPV and genital neoplasms. Genital herpes is caused by a neurotropic virus (HSV-2) that ascends through the peripheral nerves to reside in the sacral dorsal root ganglia. The herpesvirus can be reactivated, producing recurrent lesions in genital structures that are supplied by the peripheral nerves of the affected ganglia. There is no permanent cure for herpes infections. Chancroid and lymphogranuloma venereum produce external genital lesions with various degrees of inguinal lymph node involvement.

VAGINAL INFECTIONS

Candidiasis, trichomoniasis, and bacterial vaginosis are vaginal infections that can be sexually transmitted. Although these infections can be transmitted sexually, the male partner usually is asymptomatic.

Candidiasis

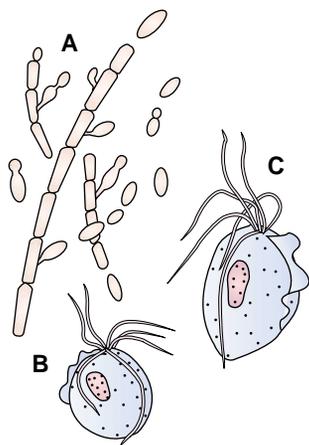
Also called *yeast infection*, *thrush*, and *moniliasis*, candidiasis is the second leading cause of vulvovaginitis in the United States. Approximately 75% of reproductive-age women in the United

States experience one episode in their lifetime; 40% to 45% experience two or more infections.⁵

The causative organism is *Candida*, a genus of yeastlike fungi. The species most commonly identified is *Candida albicans*, but other candidal species, such as *Candida glabrata* and *Candida tropicalis*, have caused symptoms. Although vulvovaginal candidiasis usually is not transmitted sexually, it is included in the CDC STD treatment guidelines because it often is diagnosed in women being evaluated for STDs.³ The possibility of sexual transmission has been recognized for many years; however, candidiasis requires a favorable environment for growth. The gastrointestinal tract also serves as a reservoir for this organism, and candidiasis can develop through autoinoculation in women who are not sexually active. Although studies have documented the presence of *Candida* on the penis of male partners of women with vulvovaginal candidiasis, few men develop balanoposthitis that requires treatment.

Causes for the overgrowth of *C. albicans* include antibiotic therapy, which suppresses the normal protective bacterial flora; high hormone levels associated with pregnancy or the use of oral contraceptives, which cause an increase in vaginal glycogen stores; and diabetes mellitus or HIV infection because they compromise the immune system. In obese persons, *Candida* may grow in skin folds underneath the breast tissue, the abdominal flap, and the inguinal folds. Vulvar pruritus accompanied by irritation, dysuria, dyspareunia, erythema, and an odorless, thick, cheesy vaginal discharge are the predominant symptoms of the infection. Accurate diagnosis is made by identification of budding yeast filaments (*i.e.*, hyphae) or spores on a wet-mount slide using 20% potassium hydroxide (Fig. 35-2). The pH of the discharge, which is checked with litmus paper, typically is less than 4.5. When the wet-mount technique is negative but the clinical manifestations are indicative of candidiasis, a culture may be necessary.

Antifungal agents such as clotrimazole, miconazole, butoconazole, and terconazole, in various forms, are effective in treating candidiasis. These drugs, with the exception of terconazole, are available without prescription for use by women who have had a previously confirmed diagnosis of candidiasis.



■ **FIGURE 35-2** ■ Organisms that cause vaginal infections. (A) *Candida albicans* (blastospores and pseudohyphae). (B, C) *Trichomonas vaginalis*.

Oral fluconazole has been shown to be as safe and effective as the standard intravaginal regimens.³ Tepid sodium bicarbonate baths, clothing that allows adequate ventilation, and the application of cornstarch to dry the area may increase comfort during treatment. Chronic vulvovaginal candidiasis, defined as four or more mycologically confirmed episodes within 1 year, affects approximately 5% of women and is difficult to manage. Subsequent prophylaxis (maintenance therapy) often is required for the long-term management of this problem.¹¹

Trichomoniasis

An anaerobic protozoan that can be transmitted sexually, *Trichomonas vaginalis* is shaped like a turnip and has three or four anterior flagella (see Fig. 35-2). Trichomonads can reside in the paraurethral glands of both sexes. Males harbor the organism in the urethra and prostate and are asymptomatic. Although 10% to 25% of women are asymptomatic, trichomoniasis is a common cause of vaginitis when some imbalance allows the protozoan to proliferate. Five million cases of trichomoniasis were diagnosed in 1999.¹ This extracellular parasite feeds on the vaginal mucosa and ingests bacteria and leukocytes. The infection causes a copious, frothy, malodorous, green or yellow discharge. There commonly is erythema and edema of the affected mucosa, with occasional itching and irritation. Sometimes, small hemorrhagic areas, called *strawberry spots*, appear on the cervix.

Diagnosis is made microscopically by identification of the protozoan on a wet-mount slide preparation. The pH of the discharge usually is greater than 6.0. Special culture media are available for diagnosis but are costly and not needed for diagnosis.

Because the organism resides in urogenital structures other than the vagina, systemic treatment is recommended. The treatment of choice is oral metronidazole (Flagyl), a medication that is effective against anaerobic protozoans.³ Metronidazole is chemically similar to disulfiram (Antabuse), a drug used in the treatment of alcohol addiction that causes nausea, vomiting, flushing of the skin, headache, palpitations, and lowering of the blood pressure when alcohol is ingested. Alcohol should be avoided during and for 24 to 48 hours after treatment. Gastrointestinal disturbances and a metallic taste in the mouth are potential adverse effects of the drug. Metronidazole has not been proven safe for use during pregnancy and is used only after the first trimester for fear of potential teratogenic effects. Sexual partners should be treated to avoid reinfection, and abstinence is recommended until the full course of therapy is completed.

Bacterial Vaginosis (Nonspecific Vaginitis)

Bacterial vaginosis is a vaginal infection that produces a characteristic fishy- or ammonia-smelling discharge yet fails to produce an inflammatory response that is characteristic of most infections.

Bacterial vaginosis represents an upheaval in the complex vaginal bacterial flora with disappearance of the normal lactobacillus species in the vagina and an overgrowth of other organisms, including *Gardnerella vaginalis* and resident anaerobic vaginal bacterial.¹² It has been suggested that the presence of anaerobes, which produce ammonia or amines from amino

acids, favors the growth of *G. vaginalis* by raising vaginal pH. Because of the presence of anaerobic bacteria and the lack of an inflammatory response, the disorder has come to be called *bacterial vaginosis*.⁵

Bacterial vaginosis is the most prevalent form of vaginal infection seen by health care professionals. Its relation to sexual activity is not clear. Sexual activity is believed to be a catalyst, rather than a primary mode of transmission, and endogenous factors play a role in the development of symptoms. The predominant symptom of bacterial vaginosis is a thin, grayish-white discharge that has a foul, fishy odor. Burning, itching, and erythema usually are absent because the bacteria has only minimal inflammatory potential. Bacterial vaginosis may be carried asymptotically by men and women.

The diagnosis is made when at least three of the following characteristics are present: homogeneous, white, noninflammatory discharge that smoothly coats the vaginal walls; production of a fishy, amine odor when a 10% potassium hydroxide solution is dropped onto the secretions; vaginal pH greater than 4.5 (usually 5.0 to 6.0); and the appearance of characteristic “clue cells” on wet-mount microscopic studies.³ *Clue cells* are squamous epithelial cells covered with masses of coccobacilli, often with large clumps of organisms floating free from the cell. Because *G. vaginalis* can be a normal vaginal flora, cultures should not be done routinely.

The mere presence of *G. vaginalis* in an asymptomatic woman is not an indication for treatment. When indicated, treatment is aimed at eradicating the anaerobic component of bacterial vaginosis to re-establish the normal balance of the vaginal flora. The CDC recommends oral metronidazole. Alternative therapies include metronidazole vaginal gel, clindamycin vaginal cream, or oral clindamycin. Treatment of sexual partners is not recommended.³

Bacterial vaginosis is associated with adverse pregnancy outcomes across all gestational ages. It has been linked to first and second trimester fetal losses, preterm delivery, low-birth-weight infants, and maternal/neonatal infections. Oral or cream clindamycin formulations can be used for treatment during the first trimester of pregnancy; oral or vaginal metronidazole can be used after the first trimester for treatment failures.

In summary, candidiasis, trichomoniasis, and bacterial vaginosis are common vaginal infections that become symptomatic because of changes in the vaginal ecosystem. Only trichomoniasis is spread through sexual contact. Trichomoniasis is caused by an anaerobic protozoan. The infection incites the production of a copious, frothy, yellow or green, malodorous discharge. Candidiasis, also called a *yeast infection*, is the form of vulvovaginitis with which women are most familiar. *Candida* can be present without producing symptoms; usually some host factor, such as altered immune status, contributes to the development of vulvovaginitis. It often can be treated with over-the-counter medications. Bacterial vaginosis is the most common cause of vaginal discharge. It is a nonspecific type of infection that produces a characteristic fishy-smelling discharge. The infection is thought to be caused by the combined presence of *G. vaginalis* and anaerobic bacteria. The anaerobe raises the vaginal pH, thereby favoring the growth of *G. vaginalis*.

VAGINAL-UROGENITAL-SYSTEMIC INFECTIONS

Some sexually transmitted diseases (STDs) infect male and female genital and extragenital structures. Among the infections of this type are chlamydial infections, gonorrhea, and syphilis. Many of these infections also pose a risk to infants born to infected mothers. Syphilis may be spread to the infant while in utero, whereas chlamydial and gonorrheal infections can be spread to the infant during the birth process.

Chlamydial Infections

Chlamydia trachomatis is an obligate intracellular bacterial pathogen that is closely related to gram-negative bacteria. It resembles a virus in that it requires tissue culture for isolation, but like a bacteria, it has RNA and DNA and is susceptible to some antibiotics. *C. trachomatis* causes a wide variety of genitourinary infections, including nongonococcal urethritis in men and pelvic inflammatory disease (PID) in women. The closely related organisms *Chlamydia pneumoniae* and *Chlamydia psittaci* cause mild and severe pneumonia, respectively. *C. trachomatis* can be serologically subdivided into types A, B, and C, which are associated with trachoma and chronic keratoconjunctivitis; types D through K, which are associated with genital infections and their complications; and types L1, L2, and L3, which are associated with LGV. *C. trachomatis* can cause significant ocular disease in neonates; it is a leading cause of blindness in underdeveloped countries. In these countries, the organism is spread primarily by flies, fomites, and nonsexual personal contact. In industrial countries, the organism is spread almost exclusively by sexual contact and therefore affects primarily the genitourinary structures.

Chlamydial infection is the most prevalent STD in the United States. Although chlamydial infections are not reportable in all states, their incidence is estimated to be more than twice that of gonorrhea. According to CDC estimates, chlamydial infections occur at a rate of 3 million new cases each year, predominantly among individuals younger than 25 years.¹ Reported rates for chlamydial infections are higher in women, largely because of the increased use of screening tests, although actual occurrence rates are thought to be the same for men and women.¹³ In the United States, costs associated with managing chlamydial infections and their complications exceed \$2 billion annually.¹³ Rates are believed to be declining because of increased efforts to screen and treat this infection.

Chlamydiae exist in two forms: (1) the elementary bodies, which are the infectious particles capable of entering uninfected cells, and (2) the initiator or reticulate bodies, which multiply by binary fission to produce the inclusions identified in stained cells. The 48-hour growth cycle starts with attachment of the elementary body to the susceptible host cell, after which it is ingested by a process that resembles phagocytosis (Fig. 35-3). Once inside the cell, the elementary body is organized into the reticulate body, the metabolically active form of the organism that is capable of reproduction. The reticulate body is not infectious and cannot survive outside the body. The reticulate bodies divide in the cell for as long as 36 hours and then condense to form new elementary bodies, which are released when the infected cell bursts.

In women, chlamydial infections may cause urinary frequency, dysuria, and vaginal discharge. The most common symptom is a mucopurulent cervical discharge. The cervix itself frequently hypertrophies and becomes erythematous, edematous, and extremely friable. Seventy-five percent of women with chlamydial infection have no symptoms; therefore, most cases are undiagnosed, unreported, and untreated.¹³ This can lead to greater fallopian tube damage and increase the reservoir for further chlamydial infections. Approximately 40% of women with an untreated chlamydial infection develop PID, and 1 in 5 of these women becomes infertile. Research has identified a possible link between three specific serotypes of chlamydiae and an increased risk for cervical cancer. The mechanism by which this occurs is unclear.¹⁴

In men, chlamydial infections cause urethritis, including meatal erythema and tenderness, urethral discharge, dysuria, and urethral itching. Prostatitis and epididymitis with subsequent infertility may develop. However, approximately 50% of men are asymptomatic. The most serious complication that can develop with nongonococcal urethritis is Reiter's syndrome, a systemic condition characterized by urethritis, conjunctivitis, arthritis, and mucocutaneous lesions (see Chapter 43).

Routine screening for adolescents and young adults has been suggested by the CDC in an effort to minimize these serious sequelae of asymptomatic infection.³ Between 25% and 50% of infants born to mothers with cervical chlamydial infections develop ocular disease (*i.e.*, inclusion conjunctivitis), and 10% to 20% having chlamydial pneumonitis.

Diagnosis of chlamydial infections takes several forms. The identification of polymorphonuclear leukocytes on Gram's stain of male discharge or cervical discharge is presumptive evidence. The direct fluorescent antibody test and the enzyme-linked immunosorbent assay that use antibodies against an antigen in the *Chlamydia* cell wall are rapid tests that are highly sensitive and specific. The positive predictive value of these tests is excellent among high-risk groups, but false-positive results occur more often in populations with lower risks. Amplified DNA probe assays, such as the PCR, ligase chain reaction

(LCR), or transcription-mediated amplification (TMA), have demonstrated specificities of near 100%.

The CDC recommends the use of azithromycin or doxycycline as the treatment of choice for chlamydial infection; penicillin is ineffective. Erythromycin or amoxicillin is the preferred choice in pregnancy.³ Antibiotic treatment of both sexual partners simultaneously is recommended. Abstinence from sexual activity is encouraged to facilitate cure.

Gonorrhea

Gonorrhea is a reportable disease caused by the bacterium *Neisseria gonorrhoeae*. In 1999, there were 360,076 reported cases of gonorrhea in the United States.¹ Of these reported cases, more than 90% involved persons between 15 and 44 years of age, with the heaviest concentration among young adults (15 to 24 years of age).¹³ There are an estimated 600,000 new cases every year.³ Although the incidence of gonorrhea has declined steadily from its peak in 1975, there was an increase in occurrence between 1997 and 1998. Improved screening efforts as well as greater use of more sensitive nonculture methods of testing may have contributed to this increase. Higher rates of occurrence among homosexual men were documented in several states, leading to a concern that an increase in unsafe sexual behavior may be occurring because of the availability of highly active antiretroviral agents for treatment of HIV infection.¹⁵

The gonococcus is a pyogenic (*i.e.*, pus-forming), gram-negative diplococcus that evokes inflammatory reactions characterized by purulent exudates. Humans are the only natural host for *N. gonorrhoeae*. The organism grows best in warm, mucus-secreting epithelia. The portal of entry can be the genitourinary tract, eyes, oropharynx, anorectum, or skin.

Transmission usually is by heterosexual or homosexual intercourse. Autoinoculation of the organism to the conjunctiva is possible. Neonates born to infected mothers can acquire the infection during passage through the birth canal and are in danger of experiencing gonorrheal conjunctivitis, with

resultant blindness, unless treated promptly. An amniotic infection syndrome characterized by premature rupture of the membranes, premature delivery, and increased risk of infant morbidity and mortality has been identified as an additional complication of gonococcal infections in pregnancy. Genital gonorrhea in young children should raise the possibility of sexual abuse.

The infection commonly manifests 2 to 7 days after exposure. It typically begins in the anterior urethra, accessory urethral glands, Bartholin's or Skene's glands, and the cervix. If untreated, gonorrhea spreads from its initial sites upward into the genital tract. In males, it spreads to the prostate and epididymis; in females, it commonly moves to the fallopian tubes. Pharyngitis may follow oral-genital contact. The organism also can invade the bloodstream (*i.e.*, disseminated gonococcal infection), causing serious sequelae such as bacteremic involvement of joint spaces, heart valves, meninges, and other body organs and tissues.

Persons with gonorrhea may be asymptomatic and may unwittingly spread the disease to their sexual partners. Men are more likely to be symptomatic than women. In men, the initial symptoms include urethral pain and a creamy, yellow, sometimes bloody discharge. The disorder may become chronic and affect the prostate, epididymis, and periurethral glands. Rectal infections are common in homosexual men. In women, recognizable symptoms include unusual genital or urinary discharge, dysuria, dyspareunia, pelvic pain or tenderness, unusual vaginal bleeding (including bleeding after intercourse), fever, and proctitis. Symptoms may occur or increase during or immediately after menses because the bacterium is an intracellular diplococcus that thrives in menstrual blood but cannot survive long outside the human body. There may be infections of the uterus and development of acute or chronic infection of the fallopian tubes (*i.e.*, salpingitis), with ultimate scarring and sterility.

Diagnosis is based on the history of sexual exposure and symptoms. It is confirmed by identification of the organism on Gram's stain or culture. An enzyme immunoassay for detecting gonococcal antigens (Gonozyne) is available but has several requirements that limit its usefulness. Detection by means of amplified DNA probes (PCR, LCR, TMA) is possible using urine and urethral swab specimens. The sensitivity of these probes is similar to that of culture, and they may be cost effective in high-risk populations.

Testing for other STDs, particularly syphilis and chlamydial infections, is suggested at the time of examination. Pregnant women are routinely screened at the time of their first prenatal visit; high-risk populations should have repeat cultures during the third trimester. Neonates are routinely treated with various antibacterial agents applied to the conjunctiva within 1 hour of birth to protect against undiagnosed gonorrhea and other diseases.

Penicillin-resistant strains of *N. gonorrhoeae* are prevalent worldwide, and strains with other kinds of antibiotic resistance continue to evolve and spread. The current treatment recommendation to combat tetracycline- and penicillin-resistant strains of *N. gonorrhoeae* is ceftriaxone in a single injection or cefixime, ciprofloxacin, levofloxacin, or ofloxacin in a single oral dose. All are equally effective and should be followed with azithromycin or doxycycline for chlamydiae. All sex partners 60 days prior to discovery of the infection should be con-

tacted, tested, and treated. Test of cure is not required with observed single-dose therapy. Patients are instructed to refrain from intercourse until therapy is completed and symptoms are no longer present.³

Syphilis

Syphilis is a reportable disease caused by a spirochete, *Treponema pallidum*. During 1999, 6657 new cases of primary and secondary syphilis were reported in the United States (2.5 per 100,000 population). This is the lowest rate ever reported, and it now appears that syphilis transmission is primarily concentrated in a few geographic areas.¹⁶ This represents a steady decline from the 50,000 cases reached in 1990 after an epidemic resurgence of this problem between 1985 and 1990. Syphilis continues to disproportionately affect minority populations. Although the 1999 rate for blacks declined by 10% from that of the previous year, it was still 30 times the rate reported in whites. The rate for Hispanics increased 20%, primarily among men. The National Plan to Eliminate Syphilis was launched in 1999 with a goal of reducing primary and secondary syphilis to fewer than 1000 cases and increasing the number of syphilis-free counties to 90% by 2005. Federal funding is available to support this effort.¹⁶

T. pallidum is spread by direct contact with an infectious, moist lesion, usually through sexual intercourse. Bacteria-laden secretions may transfer the organism during kissing or intimate contact. Skin abrasions provide another possible portal of entry. There is rapid transplacental transmission of the organism from the mother to the fetus after 16 weeks' gestation, so that active disease in the mother during pregnancy can produce congenital syphilis in the fetus. Untreated syphilis can cause prematurity, stillbirth, and congenital defects and active infection in the infant. Once treated for syphilis, a pregnant woman usually is followed up throughout pregnancy by repeat testing of serum titers.

The clinical disease is divided into three stages: primary, secondary, and tertiary. Primary syphilis is characterized by the appearance of a chancre at the site of exposure. Chancres typically appear within 3 weeks of exposure but may incubate for 1 week to 3 months. The primary chancre begins as a single, indurated, button-like papule up to several centimeters in diameter that erodes to create a clean-based ulcerated lesion on an elevated base. These lesions usually are painless and located at the site of sexual contact. Primary syphilis is readily apparent in the male, where the lesion is on the penis or scrotum. Although chancres can develop on the external genitalia in females, they are more common on the vagina or cervix, so primary syphilis may go untreated. There usually is an accompanying regional lymphadenopathy. The disease is highly contagious at this stage, but because the symptoms are mild, it frequently goes unnoticed. The chancre usually heals within 3 to 12 weeks, with or without treatment.

The timing of the second stage of syphilis varies even more than that of the first, lasting from 1 week to 6 months. The symptoms of a rash (especially on the palms and soles), fever, sore throat, stomatitis, nausea, loss of appetite, and inflamed eyes may come and go for a year but usually last for 3 to 6 months. Secondary manifestations may include alopecia and genital condylomata lata. Condylomata lata are elevated, red-brown lesions that may ulcerate and produce a foul discharge.

They are 2 to 3 cm in diameter, contain many spirochetes, and are highly infectious.

After the second stage, syphilis frequently enters a latent phase that may last the lifetime of the person or progress to tertiary syphilis at some point. Persons can be infective during the first 1 to 2 years of latency.

Tertiary syphilis is a delayed response of the untreated disease. It can occur as long as 20 years after the initial infection. Only approximately one third of those with untreated syphilis progress to the tertiary stage of the disease, and symptoms develop in approximately one half of these. Approximately one third undergo spontaneous cure, and the remaining one third continue to have positive serologic tests but do not have structural lesions.¹⁷ When syphilis does progress to the symptomatic tertiary stage, it commonly takes one of three forms: (1) development of localized destructive lesions called *gummas*, (2) development of cardiovascular lesions, or (3) development of central nervous system lesions. The syphilitic gumma is a peculiar, rubbery, necrotic lesion that is caused by noninflammatory tissue necrosis. Gummas can occur singly or multiply and vary in size from microscopic lesions to large, tumorous masses. They most commonly are found in the liver, testes, and bone. Central nervous system lesions can produce dementia, blindness, or injury to the spinal cord, with ataxia and sensory loss (*i.e.*, *tabes dorsalis*). Cardiovascular manifestations usually result from scarring of the medial layer of the thoracic aorta with aneurysm formation. These aneurysms produce enlargement of the aortic valve ring with aortic valve insufficiency.

T. pallidum does not produce endotoxins or exotoxins but evokes a humoral immune response that provides the basis for serologic tests. Two types of antibodies—nonspecific and specific—are produced. The nonspecific antibodies can be detected by flocculation tests such as the Venereal Disease Research Laboratory (VDRL) test or the rapid plasma reagin (RPR) test. Because these tests are nonspecific, positive results can occur with diseases other than syphilis. The tests are easy to perform, rapid, and inexpensive and frequently are used as screening tests for syphilis. Results become positive 4 to 6 weeks after infection or 1 to 3 weeks after the appearance of the primary lesion. Because these tests are quantitative, they can be used to measure the degree of disease activity or treatment effectiveness. The VDRL titer usually is high during the secondary stage of the disease and becomes less so during the tertiary stage. A falling titer during treatment suggests a favorable response. The fluorescent treponemal antibody absorption test or microhemagglutinin test is used to detect specific antibodies to *T. pallidum*. These qualitative tests are used to determine whether a positive result on a nonspecific test such as the VDRL is attributable to syphilis. The test results remain positive for life.

T. pallidum cannot be cultured. The diagnosis of syphilis is based on serologic tests or dark-field microscopic examination with identification of the spirochete in specimens collected from lesions. Because the disease's incubation period may delay test sensitivity, serologic tests usually are repeated after 6 weeks if the initial test results were negative.

The treatment of choice for syphilis is penicillin.³ Because of the spirochetes' long generation time, effective tissue levels of penicillin must be maintained for several weeks. Long-acting injectable forms of penicillin are used. Tetracycline or doxycycline is used for treatment in persons who are sensitive to penicillin. Pregnant patients should be desensitized and treated

with penicillin because erythromycin does not treat fetal infection. Sexual partners should be evaluated and treated prophylactically even though they may show no sign of infection. All treated individuals should be re-examined clinically and serologically at 6 and 12 months after completing therapy; more frequent monitoring (3-month intervals) is suggested for individuals with HIV infection.³

In summary, the vaginal-urogenital-systemic STDs—chlamydial infections, gonorrhea, and syphilis—can severely involve the genital structures and manifest as systemic infections. Gonorrheal and chlamydial infections can cause a wide variety of genitourinary complications in men and women, and both can cause ocular disease and blindness in neonates born to infected mothers. Syphilis is caused by a spirochete, *T. pallidum*. It can produce widespread systemic effects and is transferred to the fetus of infected mothers through the placenta.

REVIEW QUESTIONS

- Define what is meant by a sexually transmitted disease (STD) and cite the common portals of entry for STDs.
- State the significance of infection with the human papillomavirus.
- Explain the recurrent infections in genital herpes.
- Compare the signs and symptoms of infections caused by *Candida albicans*, *Trichomonas vaginalis*, and bacterial vaginosis.
- Compare the signs and symptoms of gonorrhea in the male and female.
- State the genital and nongenital complications that can occur with chlamydial infections, gonorrhea, and syphilis.



Visit the Connection site at connection.lww.com/go/porth for links to chapter-related resources on the Internet.

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