CHAPTER 44

Genital Ulcer Disease

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A genital ulcer is defined as a discrete mucosal or cutaneous discontinuity involving the genitals, perineum, or surrounding tissues. Genital ulcer disease (GUD) is an important risk factor for sexual acquisition and transmission of human immunodeficiency virus (HIV), and serious long-term sequelae can result from all causes of GUD. The etiologies of GUD vary geographically and are strongly associated with behavioral, demographic, and socioeconomic factors, in addition to the prevalence of HIV infection. Genital herpes is the most common cause of GUD worldwide, followed by syphilis, chancroid, lymphogranuloma venereum (LGV), and granuloma inguinale (also known as donovanosis). These causes of sexually transmitted GUD will be discussed here, with the exception of syphilis, which is described in detail in Chapter 43. Nonsexually transmitted causes of GUD such as systemic viral illnesses, aphthous ulcers, autoimmune disease, and *Schistosoma hematobium* infection are less common and are associated with specific risk factors, including geographic location, medical comorbidities, demographics, and behavioral factors.

Herpes simplex virus type 2 (HSV-2) is recognized as the leading global cause of GUD, with seropositivity up 50% in certain populations in the United States and over 70% among sexually active adults in many regions of sub-Saharan Africa. While syphilis and chancroid remain important contributors to GUD in some resource-limited settings, these are now significantly less prevalent than they were a decade ago. This important shift from bacterial to viral causes of GUD may be secondary to improved syndromic management, increased antibiotic use, and behavioral change. Additionally, advances in laboratory testing facilitate the detection of viral pathogens that might previously have gone undetected.

In returning travelers and recent immigrants with GUD who have engaged in unprotected sex, one must consider HSV, as well as causes of genital ulceration rarely observed in developed countries. The classic presentation of genital herpes is with multiple vesicles or ulcerative lesions on examination. The presence of a single ulcer should prompt work-up for other causes of GUD in addition to HSV. A careful history, including the timing and geographic location of the encounter, may also suggest a specific etiology. Incubation periods vary from several days in the case of chancroid and HSV to several weeks with LGV, and certain ulcerative diseases such as donovanosis are highly prevalent in certain parts of the world and rarely reported in others (**Table 44.1**). Systemic symptoms, such as fever and general malaise, may be present with primary HSV, syphilis, chancroid, LGV, and donovanosis but are observed most frequently in individuals with genital herpes and secondary syphilis. Inguinal adenopathy can also be observed with any of the GUD syndromes discussed in this chapter, as well as with primary syphilis. Additionally, the duration of symptoms may provide clues to diagnosis. While the clinical course of bacterial GUD is measured in weeks to months, genital herpes typically resolves spontaneously within days to weeks and recurs weeks to months later (**Table 44.1**).

TABLE 44.1 Overview of Characteristics of Genital Ulcer Disease (excluding syphilis; see Chapter 43)

	Geographic Region	Incubation Period	Appearance of Genital Lesions	Systemic Symptoms	Duration of Symptoms
Herpes simplex virus (HSV)	Worldwide	3-5 days	Multiple small, vesicles, pustules or ulcers; large ulcer after small lesions coalesce; adenopathy usually in primary	Yes (primary, not recurrent)	Lifetime recurrence of episodes lasting 5-10 days; primary infection lasts 2-6 weeks
Chancroid	Sub-Saharan Africa, Asia	3-5 days for papules 1-2 weeks for ulcers	Single or multiple ulcers	Yes	Several weeks for ulcers; adenopathy may last 1-3 months
Lymphogranuloma venereum (LGV)	Africa, Southeast Asia, South America, Caribbean; Europe and North America among MSM	3-12 days for ulcers; 10-30 days for adenopathy	Painless blister (single or multiple) that ulcerates; tender inguinal adenopathy; proctitis/proctocolitis	Yes	Several weeks to months
Granuloma inguinale (donovanosis)	Papua New Guinea, Southern Africa, India, Brazil, Caribbean	4-6 weeks	Single or multiple tender and vascular ulcers; inguinal inflammation may occur	Rarely	Several months

MSM, Men who have sex with men.

TABLE 44.2 Laboratory Evaluation of Sexually Active Patients with Genital Ulcer Disease

Lesions typical of genital herpes[a]
PCR, direct FA, or culture for HSV
Screening tests for other STDs (syphilis, HIV, chlamydia, and gonorrhea)
Other genital ulcers
PCR, DFA, or culture for HSV
Type-specific HSV serology
Darkfield microscopy or direct FA test for *Treponema pallidum*
Syphilis serology
Selected cases
Culture or PCR for *Haemophilus ducreyi* (if available)
PCR and serology for *Chlamydia trachomatis* (LGV) (if available)
Culture for pyogenic bacteria

[a]For example, a cluster of vesicular or pustular lesions, or multiple superficial ulcers.
DFA, Direct fluorescent antibody test; *HIV*, human immunodeficiency virus; *HSV*, herpes simplex virus; *LGV*, lymphogranuloma venereum; *PCR*, polymerase chain reaction; *STDs*, sexually transmitted diseases.

Since presentations of GUD vary and have substantial overlap, clinical diagnosis is both insensitive and nonspecific, making it important to supplement the clinical history and examination with diagnostic laboratory testing, especially among HIV-1-infected individuals (**Table 44.2**). However, even with an extensive evaluation, a definitive diagnosis will not be made in as many as 25% of cases due to the lack of sensitive and specific laboratory testing. As the dominant risk factors for acquisition of GUD are those associated with all sexually transmitted infections (STIs) (multiple sex partners, intercourse with a new partner or high-risk partner, and failure to use condoms), laboratory testing for other STIs should be incorporated into routine work-up of GUD. HIV testing is particularly important to incorporate into the STI work-up; higher rates of chancroid and HSV-2 infection are observed in HIV-1-infected individuals, and these two infections have been strongly associated with HIV-1 transmission and acquisition.

HERPES SIMPLEX VIRUS (HSV)

Epidemiology

Genital herpes, which can be caused by either of the herpes simplex viruses (HSV-1 and HSV-2), is now the most prevalent cause of GUD worldwide. HSV is a lifelong, incurable infection, believed to be indefinitely contagious to sex partners. Genital HSV increases the risk of acquiring HIV almost three-fold, likely due to the mucosal and epithelial disruption and recruitment of $CD4^+$ T cells to the genital area that result from HSV infection. Globally, HSV-2 is the most common cause of genital herpes, with seroprevalence ranging from ~20% among adults in the general population in the United States and parts of Western Europe to 50-70% in sub-Saharan Africa. Among commercial sex workers in parts of Africa and Southeast Asia, rates may be as high as 90%, and around 60% of HIV-negative men who have sex with men (MSM) in South America may be HSV-2-seropositive.

HSV-1, which also causes orolabial herpes (cold sores), is an increasingly common cause of genital herpes, most notably in the United States and Northern Europe, perhaps as a result of the declining rates of HSV-1 acquisition in childhood. In some populations HSV-1 now causes the majority of primary genital herpes. While the seroprevalence of HSV-1 ranges from >50% in developed countries to nearly 100% in developing countries, the frequency of genital HSV-1 infection in most parts of the world is not known, as serology does not reveal the anatomic location of HSV-1 infection.

Most people with genital herpes are unaware of their infection. The proportion of HSV-2-seropositive individuals who report being aware of a history of genital herpes has ranged

from only 9% in the general population up to 34% among women attending a sexually transmitted diseases clinic in the United States. As a result, most cases of genital herpes are acquired from sex partners who are unaware of being infected themselves. Women have a higher risk of genital HSV acquisition than men, likely due to greater mucosal surface area in women and the fact that younger women frequently have male sexual partners who are older and thus more likely to be infected with HSV-2.

Pathogenesis

HSV entry occurs via the genital mucosa or a break in the genital skin. During primary infection, the virus enters sensory neurons and migrates to the sacral dorsal root ganglion, where it establishes latency. Primary infection is controlled, and viral dissemination may be prevented, by a cytotoxic T lymphocyte response. During HSV reactivation, which can be triggered by immunosuppression, ultraviolet light, trauma, fever, and possibly stress, the virus travels down the axon and multiplies within epithelial cells, producing similar but less severe lesions to those found during primary infection.

Clinical Manifestations and Diagnosis

There are three types of genital HSV infection: primary, nonprimary first episode, and recurrent. Primary infection is defined by the presence of HSV (of either type) in the genital tract of an individual seronegative for both HSV-1 and HSV-2. Nonprimary first episode is defined by the presence of HSV-2 in the genital tract of an individual with only HSV-1 antibodies or, rarely, the presence of HSV-1 in an individual with only HSV-2 antibodies. Recurrent infection is defined as the presence of either type of HSV in the genital tract of an individual with antibodies autologous to the genital type. Prior HSV-1 antibodies do not significantly reduce the risk of infection with HSV-2 but do reduce the likelihood of symptomatic HSV-2 infection.

Primary genital HSV infection is characterized by bilateral multiple small vesicular or pustular lesions that may coalesce into large ulcerated areas, which persist for 4-15 days and then crust over. Over 75% of patients experience a second crop of lesions during primary infection, which begin between day 4 and day 10. Complete healing of all lesions takes a mean of 16.5 days in men and 19.5 days in women. Local symptoms, including itching, pain, dysuria, tender inguinal lymphadenopathy, and urethral and/or vaginal discharge, occur frequently. Among women, 70-90% have HSV cervicitis during primary infection. Nearly 70% of women and 40% of men report systemic symptoms, including fever, malaise, myalgias, and headache, during primary infection. Less commonly, aseptic meningitis and/or disseminated HSV infection can occur, including HSV hepatitis. HSV proctitis and anorectal infection may also occur, especially among MSM.

Manifestations of recurrent genital herpes are generally confined to the mucosa or skin. Most people with HSV recurrence experience some degree of prodromal symptoms, which may include tingling, burning, and/or pain. During recurrence, lesions are generally unilateral, cover a much smaller area than those of primary infection, and last 4-5 days. The median number of recurrences in the first year of infection is five in men and four in women. Recurrence rates decrease by a median of one episode per year. Recurrence of genital HSV-1 is much less frequent, averaging only one episode per year, and only 60% of patients with genital HSV-1 have a recurrence within the first year.

"Atypical" presentations of genital HSV are common. Vesicles and ulcers may be absent, with fissures, furuncles, erythema, or pain instead. Lesions caused by HSV may be mistakenly attributed to other infectious agents (e.g., *Candida*), trauma, insect bites, allergic reaction, "irritation," or hemorrhoids, or may appear in an atypical location such as the thigh. Thus, all genital lesions, especially recurrent lesions present in the S2 or S3 dermatomes, should be evaluated for HSV.

Since clinical diagnosis of genital herpes is neither sensitive nor specific, patients presenting with genital lesions should undergo virologic testing to determine the diagnosis (**Table 44.2**). In patients presenting with multiple vesicular lesions and/or history consistent with

genital herpes, initiation of presumptive therapy while awaiting laboratory results is advisable. Polymerase chain reaction (PCR) is four times more sensitive than viral culture and has become the standard of care in the developed world. Antigen detection via direct fluorescent antibody testing is also sensitive and specific for identifying HSV on a smear taken from vesicular fluid or an ulcer base. Viral culture is another option, but the sensitivity declines rapidly within a few days of onset, as lesions begin to heal. A Tzanck test to look for cytopathic changes associated with herpetic lesions is unreliable and not advised. Since antibodies to HSV generally appear within several weeks after infection and persist indefinitely, type-specific serologic tests can be useful in confirming a diagnosis of HSV but cannot distinguish between new and pre-existing infection. All patients with new genital herpes infection should be tested for HIV; testing for other STIs should also be considered.

Treatment and Prevention

All patients with first-episode genital herpes should be treated with oral antivirals to reduce the risk of severe local spread as well as the likelihood and severity of systemic symptoms (**Table 44.3**). Episodic antiviral therapy shortens the duration of symptoms, while suppressive therapy can reduce the recurrence rates by 70-80% among patients with frequent outbreaks. Treatment of recurrences should be initiated within 24-48 hours of symptom development, as efficacy declines after that window. See **Table 44.3** for details on treatment of genital HSV infection.

TABLE 44.3 Treatment of Genital HSV Infection

First episode of genital herpes

Acyclovir 400 mg orally three times a day (or 200 mg orally five times a day) for 7-10 days

or

Famciclovir 250 mg orally three times a day for 7-10 days

or

Valacyclovir 1.0 g orally twice a day for 7-10 days

Severe infection that requires parental therapy

Acyclovir 5-10 mg/kg body weight i.v. every 8 h for 2-7 days or until clinical improvement is observed, followed by oral antiviral therapy to complete at least 10 days total therapy

Episodic treatment of recurrent herpes

Acyclovir 400 mg orally three times a day for 5 days (or 800 mg orally twice a day for 5 days, or 800 mg three times a day for 2 days)

or

Famciclovir 125 mg orally twice a day for 5 days (or 1 g orally twice a day for 1 day, or 500 mg orally once followed by 250 mg twice daily for 2 days)

or

Valacyclovir 500 mg orally twice a day for 3 days (or 1 g orally once a day for 5 days)

Suppressive therapy[a]

Acyclovir 400 mg orally twice a day

or

Famciclovir 250 mg orally twice a day

or

Valacyclovir 500 mg (<10 episodes/year) or 1000 mg (>10 episodes/year) orally once a day

[a]The need to continue suppressive therapy should be discussed periodically (e.g., annually).
Adapted from specific product package inserts; standard guidelines for therapy of genital herpes in otherwise healthy adults (not pregnant); and Centers for Control and Prevention, 2010. Sexually transmitted diseases treatment guidelines 2010. MMWR 51(RR-06):11–12.

Methods of preventing genital HSV infection include condoms and use of suppressive antiviral therapy in the infected partner. For both men and women, the use of condoms is associated with ~50% decrease in HSV-2 acquisition, and daily suppressive antiviral therapy administered to the HSV-2 infected partner can reduce risk of HSV-2 transmission among monogamous couples by approximately one-half. Patients with genital herpes should be counseled that viral shedding, which can result in transmission to sex partners, is common even in the absence of symptoms.

CHANCROID

Epidemiology

The global prevalence of chancroid has decreased dramatically during the last decade. Nonetheless, chancroid remains an important cause of genital ulcers in certain resource-limited areas. Sentinel surveillance in various parts of sub-Saharan Africa and Asia has reported decreases in prevalence from 48 to 95% throughout the 1980s and 1990s, leading to discussion of the feasibility of eradication. Chancroid is uncommon in developed countries. For example, only 85 cases were reported from 2009 to 2013 in the United States. In developed countries, chancroid occurs in localized epidemics in populations having high sex-partner change rates. Chancroid is closely linked to commercial sex work, substance abuse, and economic deprivation, relying heavily on core groups for transmission and persistence within populations. Other risk factors include male gender, lack of circumcision, and HIV-1 seropositivity. HIV-1 infected individuals have longer duration of symptoms and may not respond well to treatment, further increasing their risk of transmitting HIV-1, chancroid, or both.

Pathogenesis

Haemophilus ducreyi, the cause of chancroid, is a small, Gram-negative bacillus. The organism is nutritionally fastidious, slow growing, and difficult to isolate. Bacteria enter genital mucosa via superficial abrasions that occur during sexual intercourse, and infect epithelial cells. This results in an inflammatory papule that rapidly evolves into a pustule and later ulcerates. The predominant immune response to *H. ducreyi* is a Th1 cell-mediated response, with CD4 T-cell infiltration of ulcers. Although antibodies are produced to several outer membrane proteins, their specificity and contribution to acquired immunity is not known.

Clinical Manifestations and Diagnosis

Symptoms usually appear 3-5 days after exposure but can occur up to 2 weeks after sexual contact. A tender papule or pustule characterizes the first stage and precedes ulcer formation by several days to up to 2 weeks. Individuals may be infectious during this period. Ulcers may be single or multiple, erythematous, and usually 1-2 cm in diameter, although the appearance can vary, especially in the setting of HIV infection. Chancroid was historically called the "soft chancre," reflecting the fact that the edges of ulcers are not indurated when compared with syphilis. The ulcer shape may be round, oval, or irregular, and the base is typically covered with purulent exudate. Some cases are mild, with nonspecific-appearing lesions. Most ulcers occur on the penis, especially under the foreskin in uncircumcised men, and near the introitus in women. Sores can also develop in the perianal area or rectum. Infection with *H. ducreyi* is usually painful but may be asymptomatic or painless in women, which may delay diagnosis and treatment.

Approximately 50% of male patients with untreated chancroid will also have inguinal lymphadenopathy, which is more commonly unilateral than bilateral and develops 1-2 weeks after the appearance of ulcers. Overlying cutaneous erythema and fluctuance are often present and help to distinguish chancroid from syphilis or herpes, which do not present with the characteristic "bubo." If untreated, lymph nodes may rupture and drain spontaneously, leaving open, ulcerated sores. Despite the locally aggressive nature of the infection, fever and disseminated infection rarely occur. Ulcerative lesions may persist for several weeks in the absence of treatment, and adenopathy can persist for 1-3 months. Complications from

TABLE 44.4 Recommended Regimens for Treatment of Chancroid

Azithromycin 1.0 g orally in a single dose
Ceftriaxone 250 mg intramuscularly in single dose
Ciprofloxacin 500 mg orally twice a day for 3 days
Erythromycin 500 mg orally 3 times a day for 7 days

From: Centers for Control and Prevention, 2010. Sexually transmitted diseases treatment guidelines 2010. MMWR 51 (RR-06), 11–12.

genital ulcers and buboes include phimosis, inguinal scarring, superinfection, and development of fistulas after bubo rupture.

The diagnosis of chancroid can be challenging, since culturing *H. ducreyi* requires special culture medium and assay sensitivity is <75%. Multiplex PCR has been developed to test specimens for *H. ducreyi*, syphilis, and HSV, but it is primarily available for surveillance and research purposes. Gram-stain sensitivity ranges from 10 to 90% and shows small, pleomorphic, Gram-negative rods. Serology is not helpful in most cases, because it is unable to distinguish past from present infection and is usually not available.

Treatment and Prevention

Several studies in the last decade have documented the efficacy of single-dose treatment of chancroid with ceftriaxone or azithromycin and with 3-day regimens of ciprofloxacin or other fluoroquinolones. The 2010 Centers for Disease Control and Prevention recommendations are shown in **Table 44.4**. Resistance has been documented against penicillin, ampicillin, and tetracycline; all regimens have somewhat reduced efficacy in HIV-infected persons. Fluctuant lymph nodes should be aspirated as often as necessary to prevent spontaneous rupture, and an examination should be carried out 7 days after starting treatment. If there is no obvious improvement, it is important to consider other diagnoses. Testing for syphilis and HIV-1 at time of ulcer and 3 months later is recommended in all cases. Condom use and good personal hygiene, including washing with soap and water after sexual exposure, have been shown to reduce transmission of chancroid. However, condoms do not cover all areas that may be affected by chancroid and may not ensure complete protection. Partners of persons with chancroid should be treated, regardless of whether they have symptoms, if there has been sexual contact within the 10 days preceding onset of symptoms.

LYMPHOGRANULOMA VENEREUM (LGV)

Epidemiology

LGV is a systemic, chronic, sexually transmitted infection that is endemic in parts of Africa, Southeast Asia, South America, and the Caribbean. It disproportionately affects individuals in lower socioeconomic strata and those with multiple sexual partners. Although historically considered rare in North America, Europe, and Australia, several recent outbreaks of LGV proctitis have been described among MSM on these continents, specifically among populations with high HIV prevalence. Additionally, there is increasing evidence that LGV is often asymptomatic. As a result, it is frequently underdiagnosed in high-risk populations.

Pathogenesis

LGV is caused by *Chlamydia trachomatis* serovars L1, L2, L3, and recently discovered L2b, thought to be responsible for many of the recent outbreaks in Europe. Compared with the more prevalent oculogenital strains (Chapter 42), these serovars grow rapidly and are more cytolytic in cell culture. While both humoral and cellular immune responses occur, past infection does not confer immunity. Delayed hypersensitivity is considered to be responsible

for the chronic, relapsing lymphadenopathy and lymphatic obstructions that are the hallmarks of untreated infection.

Clinical Manifestations and Diagnosis

LGV has both acute and chronic manifestations. One week to several months after the initial exposure, small blisters or papules appear on the mucous membranes and skin around the genital area. These may spread to involve the groin or anus and can develop into ulcerative lesions similar to those caused by chancroid, syphilis, or herpes. Although discomfort increases as the infection progresses, the sores are not usually painful and may go unnoticed. Primary infection may also include urethritis or cervicitis, similar to infection with other *C. trachomatis* serovars. Systemic spread results in regional lymphadenopathy that is usually erythematous, tender, and fluctuant and may be associated with fever and other systemic symptoms that evolve over 2-4 weeks. In MSM and women, this stage may also present as acute hemorrhagic proctocolitis, and symptoms may include fever, rectal pain, tenesmus, rectal discharge, and bleeding.

The majority of individuals recover spontaneously. However, some will develop chronic inflammation if not treated with antibiotics. Late complications include indurated, matted nodes with sinus tracts, nonhealing genital ulcers, abscesses, and rectal strictures. Rarely, squamous cell carcinoma or lymphatic obstruction occurs, with elephantiasis of the genitals or lower extremities. Although PCR of urine, bubo pus, or rectal discharge for chlamydia species can aid in the diagnosis, a positive test does not distinguish serovars L1, L2, L3, and L2b from other chlamydia strains. As such, a clinical diagnosis is often made after exclusion of other causes of inguinal adenopathy.

Treatment and Prevention

The recommended regimen for LGV is doxycycline 100 mg orally twice a day for 3 weeks. Alternate regimens include erythromycin 500 mg four times daily for 3 weeks or possibly azithromycin once weekly for 3 weeks, although clinical data in support of azithromycin are lacking. Ulcers should begin to clear within 1 week after initiating treatment and heal completely within 3-5 weeks. Partners with whom a patient has had sexual contact in the 30 days prior to onset of symptoms should be examined, tested for chlamydial urethritis and cervicitis, and treated appropriately.

GRANULOMA INGUINALE

Epidemiology

Granuloma inguinale, also known as donovanosis, is a rare STI that is most commonly diagnosed in the Indian subcontinent, Papua New Guinea, isolated areas of Australia, Southern Africa, Brazil, and parts of the Caribbean. Most cases in the United States are imported from such endemic areas, and a mean of only 11 cases was reported annually in the 1990s.

Pathogenesis

Klebsiella granulomatis, the cause of granuloma inguinale, is a small, pleomorphic, Gram-negative coccobacillus that typically appears intracellularly in macrophages ("Donovan bodies"). The histologic picture and course suggest that the clinical manifestations are due largely to a cell-mediated immune response.

Clinical Manifestations and Diagnosis

Granuloma inguinale presents with one or more indolent, mildly tender ulcerative lesions in the inguinal region. Lesions typically appear vascular with hypertrophic granulation-like tissue and may bleed on contact. Inguinal masses are due more frequently to subcutaneous extension of inflammatory tissue than to lymphadenopathy. Rarely, lesions spread with an appearance similar to that of squamous cell carcinoma and lead to penile autoamputation. Although systemic symptoms do not occur, disseminated osteolytic lesions have been described. Diagnosis is made by visualization of dark-staining Donovan bodies in biopsied

tissue. *K. granulomatis* recently has been sustained in culture for the first time, which may lead to improved characterization of the organism.

Treatment and Prevention

A 3-week course of doxycycline or trimethoprim-sulfamethoxazole is the recommended treatment for donovanosis. Alternative regimens include 3-week courses of ciprofloxacin, erythromycin, or azithromycin. Since relapse can occur months after therapy is completed, longer durations may be indicated in severe cases, and patients should be monitored for resolution of clinical symptoms. While the utility of treating sexual partners has not been established, it is recommended that individuals who have had sexual contact within 60 days prior to symptomatic disease be examined and offered treatment.

FURTHER READING

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