



The Syndromic Approach to Sexually Transmitted Genital Ulcer Disease (GUD)

Learning Objectives:

Upon completion of this content the learner will be able to:

1. List the common etiologies of GUD.
2. List the distinguishing characteristics of the genital lesions produced by different STDs, specifically genital herpes, primary syphilis, chancroid, lymphogranuloma venereum (LGV), and granuloma inguinale (GI).
3. Conduct the appropriate diagnostic work-up to differentiate the etiology of GUD.
4. List effective antimicrobial treatment for the common STD etiologies of genital ulcers.
5. Apply syndromic management based on risk factors and local epidemiology when lab results are not available.

The Syndromic Approach to Genital Ulcer Disease Curriculum Module Contributors

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GENITAL ULCER DISEASE (GUD)

I. GENERAL CONSIDERATIONS

Genital ulcer disease is one of the major STD syndromes and may affect sites other than the genitalia, such as anal and perianal sites. Syndromic management is often the most practical approach to patients with GUD, given the limitations of both clinical and laboratory diagnosis. The syndromic approach is particularly useful for patients at high risk for disease, who may be lost to follow-up, and in resource-poor settings. This chapter outlines the approach to a patient in the U.S. with a genital ulcer. Separate chapters in the National Network of STD/HIV Prevention Training Centers' core clinical curriculum contain more detailed information on genital herpes, syphilis, and chancroid.

II. DIFFERENTIAL DIAGNOSIS

- A. STD-related etiologies and organisms:
 - 1. Genital herpes: Herpes Simplex Virus Type 1 and Type 2
 - 2. Primary syphilis: *Treponema pallidum*
 - 3. Chancroid: *Haemophilus ducreyi*
 - 4. Lymphogranuloma venereum (LGV): *Chlamydia trachomatis* serovars L1-L3
 - 5. Granuloma inguinale (Donovanosis): *Klebsiella* (formerly *Calymmatobacterium*) *granulomatis*
- B. Non STD-related etiologies:
 - 1. Non-STD infectious causes of GUD: Candidiasis/balanitis, pyoderma secondary to *Phthirus pubis* or *Sarcoptes scabiei*, common skin infections (e.g., Staph), *entamoeba histolytica*.
 - 2. Non-infectious causes of GUD: aphthous ulcers (aphthosis major), Behcet's syndrome, fixed drug eruption, "Reiter's" syndrome, trauma/abrasions, squamous cell carcinoma (SCC) in situ, invasive squamous cell carcinoma, Erythema multiforme (EM)/Steven's Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN).
- C. No etiology is found in 20% to 50% of GUD cases, most likely related to the sensitivity of the laboratory tests (affected by self-medication, duration of lesion, technology of the test).

III. EPIDEMIOLOGY

- A. General GUD:
 - 1. Epidemiology is key. It is important to know the demographic and behavioral characteristics of the patient. Travel history, particularly

travel abroad or domestic travel within regions with high rates of syphilis or chancroid, are important to cover.

2. Past medical and current medical history is important, especially when considering both infectious and non-infectious etiologies of GUD. For instance, patients with a fixed drug eruption may have had symptoms before in association with a certain medication. In addition, certain medications (i.e., sulfonamides, seizure medications) and even viral infections (i.e., recurrent HSV) are associated with erythema multiforme.
 3. Globally, the most frequent cause of STD-related GUD is genital herpes, followed by syphilis, then chancroid. While lymphogranuloma venereum (LGV) has recently emerged (or been increasingly recognized) in the U.S. and Western Europe, the presentation encountered most frequently in recent years has been the presentation of proctitis, rather than GUD. Therefore, it is not clear that GUD (or the classic inguinal/genital presentation) due to LGV has increased. Granuloma inguinale (GI, or donovanosis) is almost never encountered in the U.S.
 4. More than one disease is sometimes present in a patient with genital ulcers and, therefore, a thorough workup (when resources permit) at the time of presentation may help prevent confusion later.
 5. Multiple studies have demonstrated that the presence of GUD increases the risk of HIV infectiousness and susceptibility, resulting in an estimated 2-5-fold increase in HIV *transmission* rates with GUD.
- B. Genital herpes:
1. The majority of genital and perianal herpetic outbreaks in the U.S. are caused by HSV-2, though 10-50% of first episodes are due to HSV-1.
 2. In the general U.S. population, 16.2% of persons ages 14-49 has HSV-2 antibodies. Among whites, 8.7% of men and 15.9% of women are HSV-2 positive, and among blacks, 29% of men and 48% of women are seropositive (F Xu, MD, PhD, MR Sternberg, PhD, SL Gottlieb, MD, SM Berman, MD, LE Markowitz, MD Seroprevalence of Herpes Simplex Virus Type 2 Among Persons Aged 14–49 Years — United States, 2005–2008. *MMWR*, 2010;59 (15):456-459). Seropositivity increases with age. Importantly, the majority of persons with antibodies to HSV-2 do not report a history of genital herpes.
 3. HSV-2 seroprevalence rates show a correlation with level of sexual activity (e.g., number of lifetime sexual partners).

4. HSV-2 is more common in HIV-infected persons and adults of lower socioeconomic status.

C. Syphilis:

Caused by *Treponema pallidum*. The primary lesion of syphilis, called a “chancre”, is the stage characterized by genital ulcer disease. Multiple chancres are possible though much less common. A syphilitic chancre occurs at the site of inoculation, which is dependent upon the type of sexual activity engaged in by the patient. Therefore, a primary chancre may be found at the oral, anal or perianal site (and other sites as well). Rates of syphilis continue to rise, particularly among men who have sex with men (MSM), and most significantly among MSM co-infected with HIV and black MSM.

D. Chancroid:

1. Infection caused by *Haemophilus ducreyi*.
2. Very low incidence in the U.S. Most current cases in the U.S. are acquired from foreign sources.
3. Demographic and behavioral factors associated with a higher incidence of chancroid include: lower socioeconomic status, commercial sex work or contact with commercial sex workers, male gender (male: female ratio is 10:1), and uncircumcised men.
4. Chancroid infection is endemic in regions of Africa, southeast Asia, India, South America and the Caribbean.

E. Lymphogranuloma venereum:

1. Caused by *Chlamydia trachomatis* serovars L1, L2, and L3. These serovars infect predominantly monocytes and macrophages and pass through the epithelium to regional lymph nodes, and can then disseminate.
2. Endemic in parts of Africa, Southeast Asia, India, South America, and the Caribbean.
3. Recent increase in incidence (versus recognition) of LGV in the U.S. and Western Europe associated with MSM, many of whom are HIV co-infected. Presentation is most often proctitis as opposed to GUD.
4. Epidemiology in developing countries has not been well characterized due to clinical difficulty distinguishing LGV from chancroid, which also causes bubo formation, and insensitivity of laboratory confirmation.

- F. Granuloma inguinale (Donovanosis):
1. Caused by *Klebsiella granulomatis*, (formerly *Calymmatobacterium granulomatis*)
 2. The disease occurs rarely in the United States, although it is endemic in some tropical and developing areas, including India; Papua, New Guinea; the Caribbean; central Australia; and southern Africa.
 3. Though generally sexually transmitted, transmission by fecal contamination of abraded skin and autoinoculation have been suggested.

IV. CLINICAL MANIFESTATIONS

General considerations:

- A. The clinical manifestations of STD-related GUD depend on the etiologic agent involved. See Table 1 on the following page.
- B. None of these signs are pathognomonic (absolutely distinctive) due to overlap and atypical presentations, except perhaps for the presence of multiple vesicles which are generally present only with HSV infection.
- C. Relying solely on clinical manifestations to determine the etiology of GUD is neither sensitive nor specific, which is why laboratory confirmation is important. Co-infections can be present in up to 10% of cases of GUD.
- D. Lesions may occur anywhere in the ano-genital area, including the cervix, the vagina, the penis, around the anus and inside the rectum.
- E. HIV co-infected patients may have more variable signs and symptoms.

Table 1: Clinical Features of Genital Ulcers Most Commonly Seen in U.S.

	Genital Herpes	Primary Syphilis	Chancroid	LGV
Etiologic agent	HSV-1 & HSV-2	<i>T. pallidum</i>	<i>H. ducreyi</i>	<i>C. trachomatis</i> L1, L2, L3
Incubation period	2-7 days	10-90 days (avg. 21 days)	3-10 days (avg. 4-7 days)	3 days-6 weeks
Initial lesions	Papule → vesicle*	Papule	Papule or pustule	Papule, pustule, or vesicle
Presenting lesion	Vesicles	Chancre	Ulcer/bubo	Ulcer/bubo
Number and distribution of lesions	Multiple*, may coalesce. Bilateral in primary; unilateral in recurrent.	Usually one	Single or multiple	Usually single, transient
Diameter	1-2 mm	5-15 mm	Variable	2-10 mm
Edges	Erythematous	Sharply demarcated, elevated, round, or oval	Undermined, ragged, irregular	Elevated, irregular
Depth	Superficial	Superficial or deep	Excavated, deep	Superficial or deep
Base	Serous, erythematous, nonvascular	Smooth, non-purulent, relatively nonvascular	Necrotic, generally purulent, bleeds easily	Variable, nonvascular
Induration	None	Usually present	None	Occasionally present
Pain	Common, often with prodrome of tingling*	Uncommon*	Common, severe	Variable
Lymphadenopathy	Usually present in primary infection, and absent in recurrences	Firm, non-tender, bilateral	Tender, may suppurate, usually unilateral	Tender, may suppurate, usually unilateral

Adapted from Ballard (in K Holmes)

*Useful in differential diagnosis

V. DIAGNOSTIC APPROACH**A. Patient history:**

1. Lesion history: prodrome, initial presentation (especially presence of vesicles), duration of lesion, pain, other systemic symptoms, use of systemic or topical remedies, any history of similar symptoms in the past or partners with similar symptoms.
2. Medical history: HIV status, skin conditions, drug allergies, medications.

3. Sexual history: gender of partners, number of partners (new, anonymous), venue for meeting partners, commercial sex exposure, partners with symptoms or signs, partners with known HSV or recent syphilis diagnosis, HIV status of partners.
 4. Travel history
- B. Physical exam:
1. Lesion: examine for appearance, distribution, number, size, induration, depth, and tenderness.
 2. Genital exam: examine genital and perianal area for other lesions. Anoscopy is appropriate in patients with rectal exposure (if resources and experience permit).
 3. Lymph node(s): note number and location of enlarged nodes, size, tenderness, presence of bubo.
 4. General exam: thorough examination of oral cavity and skin of torso, palms and soles, and neurologic exam, including cranial nerves.
- C. Laboratory testing:
1. General approach. After a thorough sexual history and physical exam of the patient presenting with GUD, the provider should consider the complete differential diagnosis and conduct laboratory testing based on clinic testing capability and probability of disease.
 - a) ALL patients with GUD should receive a serologic test for syphilis (i.e., ideally a non-treponemal syphilis serology test [RPR or VDRL] or, for sites utilizing reverse sequence testing, a treponemal-specific serology test.).
 - b) If HSV is suspected, a culture or PCR-based test for HSV should be performed. Consider HSV type-specific serology if history is suggestive of a recurrent lesion or no lesion amenable to culture.
 - c) All patients presenting with GUD should be offered counseling and testing for HIV, and screened for other STDs (e.g., chlamydia and gonorrhea).
 - d) In the U.S., routine testing of all patients with GUD for chancroid is not indicated. Consider, if the patient gives a history of travel to an area where chancroid is prevalent, or if the lesion does not respond to treatment in a patient with negative syphilis serologies.

- e) In the U.S., consideration should be given to LGV in patients with a clinically compatible presentation. Specific LGV diagnostic testing is not currently available. Genital specimens (i.e., lesion or urethral swab) may be tested for *C. trachomatis* with culture, direct immunofluorescence or nucleic acid amplification testing (NAAT). NAATs are not currently FDA-approved for rectal testing though specimens can be sent to one of several large laboratories that have performed the appropriate verification studies for NAATs-based tests at extra-genital sites that are needed to direct clinical management. Positive chlamydial serology (complement fixation titer > 1:64) lends further support for a diagnosis of LGV, though none of the aforementioned tests are able to distinguish LGV from non-LGV *C. trachomatis*.
2. Genital herpes: If vesicles are present, the most likely diagnosis is HSV infection. A history of vesicles, recurrent lesions, exposure to HSV, or the presence of painful, superficial lesions are also all suggestive of HSV infection. The following is a summary of tests available for the diagnosis of genital herpes. See HSV module for more detail on each test.
- a) Culture: Test of choice in patients with vesicles or moist ulcers. The sensitivity of culture is highest for moist lesions.
 - b) Antigen detection: Direct fluorescent antibody test (DFA) or ELISA, near equal to culture if moist lesions. Most can distinguish type. May be better for healing lesions than culture.
 - c) Type-specific serology: Ideal as a guide in diagnosis for culture-negative recurrent lesions or when no lesions amenable for culture are present, but history suggests herpes.
 - d) Cytology (Tzank or Pap): insensitive; not recommended for use in the diagnosis of HSV.
 - e) PCR: More sensitive than culture and increasingly used in many settings that have conducted the appropriate Clinical Laboratory Improvement Amendment (CLIA) verification studies.
3. Syphilis: When the chancre appears, darkfield (DF) microscopy can be performed for *Treponema pallidum*. If darkfield is not available, or is negative, perform stat non-treponemal serology test for syphilis. A quantitative non-treponemal test should also be done. See syphilis module for detailed information on laboratory testing for syphilis.

- a) Darkfield microscopy: Ideal, provides immediate diagnosis; but requires experience and unavailable in many settings.
- b) Serologic testing:
 - 1) Non-treponemal tests (RPR, VDRL): Ideally done on a stat basis. A negative test does not rule out syphilis. Only 75-85% sensitive in primary syphilis. If high clinical suspicion and negative non-treponemal test, treat for syphilis and repeat non-treponemal test in 2-4 weeks. More likely to be positive if the lesion has been present for more than 7 days.
 - 2) Treponemal tests (TP-PA, FTA-ABS): More sensitive than the non-treponemal tests in primary syphilis. However, usually reactive for life, even after adequate treatment. Used to confirm a reactive RPR or VDRL. Increasingly used as the initial syphilis serology test in settings conducting reverse sequence syphilis testing. As is the case for non-treponemal testing, if high clinical suspicion and negative treponemal test, treat for syphilis and repeat test in 2-4 weeks.
- 4. Chancroid: The presence of large, suppurative, tender lymph nodes (buboes) accompanying a painful, purulent ulcer is highly suggestive of chancroid. See Chancroid module for more detailed information on diagnostics.
 - a) Gram stain: Neither sensitive nor specific for detecting *Haemophilus ducreyi* in a smear of lesion exudate. Requires considerable experience to read with accuracy. Typical appearances include "school of fish," "railroad ties," clumps or whorls.
 - b) Culture: Gold standard. 40-80% sensitive at best because *H. ducreyi* is an extremely fastidious organism. Requires special, enriched medium that is not commercially available. If a patient's history suggests potential exposure to *H. ducreyi*, contact the local public health laboratory about the availability of this test.
 - c) Syndromic therapy without definitive diagnostic testing will be necessary in most settings as it is not advisable to delay therapy if media is not immediately available. A probable diagnosis of chancroid, for both clinical and surveillance purposes, can be made if all of the following criteria are met: 1) the patient has one or more painful genital ulcers; 2) the patient has no evidence of *T. pallidum* infection by darkfield examination of ulcer exudate or by a serologic test for syphilis performed at least 7 days after onset of ulcers; 3) the clinical presentation, appearance of genital ulcers and, if

present, regional lymphadenopathy are typical for chancroid; and 4) a test for HSV performed on the ulcer exudate is negative. If more than one case of probable chancroid is noted, it is important to notify public health authorities to facilitate the availability of appropriate diagnostics tests as well as an outbreak investigation.

5. Lymphogranuloma venereum. Diagnosis is usually made serologically and by exclusion of other causes of GUD or inguinal lymphadenopathy.
 - a) Serology:
 - 1) Complement fixation test (CF): CF titers usually appear within the first two weeks following infection. A titer $\geq 1:64$ is supportive of a diagnosis of LGV, but not diagnostic, because cross-reaction occurs with non-L serovars of *Chlamydia trachomatis*. A titer of $>1:256$ is strongly supportive, whereas a titer of $<1:32$ excludes except in the early stages of disease.
 - 2) Microimmunofluorescent test (MIF): More type-specific and more sensitive, but often unavailable. An MIF-derived IgG over 1:256 with appropriate clinical presentation, or a 4-fold rise to broadly crossreactive LGV serovar-specific antigens supports a diagnosis of LGV.
 - b) Culture: Isolation of *Chlamydia trachomatis* L₁L₂L₃ from lesion or lymph node is the definitive diagnostic test. Isolate must be typed with specific monoclonal antibodies to differentiate the serotypes. L₂ is the most common serovar.
 - c) Nucleic Acid Amplification Tests (NAATs): NAATs are not currently approved for rectal testing though they are approved for urine, vaginal, cervical and urethral sites. Current NAAT tests are unable to distinguish between LGV and non-LGV types of *C. trachomatis*. However, a positive NAAT for chlamydia with a compatible clinical picture would lend support for this diagnosis.
6. Granuloma inguinale (Donovanosis or GI):
 - a) *Klebsiella granulomatis* is a Gram-negative coccobacillus that is not routinely cultured.
 - b) The diagnosis is made by the identification of intracellular “Donovan bodies” on a biopsy or smear of lesion exudate using a Wright’s stain. Lesions are slowly destructive and granulomatous.

VI. TREATMENT

A. General approach:

A diagnosis based only on medical history and physical exam is often inaccurate in diagnosing GUD. Providers, however, often need to treat before laboratory results are available. A decision regarding presumptive treatment depends on clinic testing capability, probability of disease, and potential for loss to follow-up.

2. Reasons to treat prior to laboratory results:

- a) Decrease ongoing transmission. (e.g., If high suspicion of syphilis or risk of loss to follow-up, then empiric treatment is critical to decrease transmission.)
- b) Lessen the severity of symptoms. (e.g., Prompt therapy of primary herpes decreases duration of symptoms.)

B. Primary syphilis:

Benzathine Penicillin G 2.4 MU IM is the treatment of choice. (See syphilis module for more detailed discussion of treatment, including alternative therapies for penicillin-allergic patients.)

Recommended presumptive treatment if high clinical suspicion, high-risk sexual behavior, including MSM with multiple partners or commercial sex exposure, or risk of loss to follow-up.

C. Genital herpes:

Several antiherpetic medications are available, which are equivalent in efficacy, but different in their bioavailability. Treatment regimens differ for stage of disease and HIV co-infection. (See HSV module for current CDC Treatment Guidelines.)

D. Chancroid:

Azithromycin 1 G orally single dose **OR**
Ceftriaxone 250 mg IM single dose **OR**
Ciprofloxacin 500 mg orally BID x 3 days **OR**
Erythromycin base 500 mg orally TID x 7 days

In HIV-infected patients, healing may take longer, and longer courses of therapy may be required. Because data are limited concerning the therapeutic efficacy of the recommended ceftriaxone and azithromycin regimens in HIV-infected patients, these regimens should be used for such patients only if follow-up can be ensured. Repeat aspiration of fluctuant lymph nodes/bubos through healthy skin may be necessary, even after initiation of appropriate therapy, to prevent spontaneous rupture

of inguinal/femoral glands. For this reason, I and D may be preferred to needle aspiration in order to prevent multiple subsequent procedures (see chancroid module for more information.)

E. LGV:

Recommended:

Doxycycline 100 mg orally BID x 21 days

Alternates:

Erythromycin base 500mg orally QID x 21 days

F. Granuloma Inguinale:

Recommended:

Doxycycline 100 mg orally BID x 21 days*

Alternates:

Azithromycin 1 g orally once a week x 3 weeks* **OR**

Ciprofloxacin 750mg orally BID x 21 days* **OR**

Erythromycin base 500 mg orally QID x 21 days* **OR**

Trimethoprim-Sulfamethoxazole 1 double-strength tablet (160mg/800mg) orally BID x 21 days*. See 2010 CDC Treatment Guidelines

*Granuloma inguinale heals slowly from the edges of the lesions. Therapy should be continued at least 3 weeks or until all lesions have completely healed. Relapse can occur 6-18 months after apparently effective therapy.

G. Counseling and patient education:

1. Risk reduction counseling should be offered to all GUD patients.

a) Assess patient's behavior-change potential and individualize the patient's prevention plan.

b) Discuss prevention strategies. Educate that GUD can occur in both male and female genital, anal, or perianal areas that are covered or protected by a latex condom, as well as in areas that are not covered. Correct and consistent use of latex condoms can reduce the risk of GUD and other STDs.

2. Disease education:

a) Provide disease-specific educational materials.

b) Herpes education: due to the chronicity of genital herpes, specific herpes counseling and education is important. Given the volume of information that needs to be imparted to the newly diagnosed herpes patient, it is generally advisable to bring the patient back at

least once to ensure that all points are covered and that questions have been answered. See the Patient Counseling and Education section of the HSV module.

VII. FOLLOW-UP AND MANAGEMENT OF PARTNERS

- A. Patients should be reevaluated in one week. Check test results and status of lesions. For information regarding clinical resolution of herpes, syphilis, and chancroid, see the treatment sections in the respective modules. LGV and GI patients should be followed clinically until signs and symptoms have resolved. Treat appropriately any initially untreated infections, if test results return positive.
- B. If all tests were negative (syphilis serologies, HSV test, *H. ducreyi* culture), repeat RPR or VDRL, reevaluate clinical manifestations. If there is significant lymphadenopathy, consider LGV. If there are suppurative lymph nodes, also consider chancroid, even if culture is negative. If ulcer(s) is/are deep, persist/s, or worsen/s despite therapy for syphilis, chancroid, and HSV, consider possibility of resistant *H. ducreyi*, malignancy, aphthosis majore and, much less likely in the United States, Behcet's syndrome. If lesions persist, but are superficial, consider fixed drug eruption, circinate balanitis (Reiter's syndrome), candidiasis, or scabies. If lesions recur and remain culture-negative, consider HSV type-specific serology.
- C. Refer to infectious disease or dermatology if lesion(s) persist/s after evaluation and treatment for STD etiologies, and diagnosis is still uncertain.
- D. Partner management:
 1. Partners should be assessed according to the diagnosis of the index patient and as described in each appropriate section of this module. (See HSV, syphilis, and chancroid modules.)
 2. LGV contacts within 60 days of onset of index patient's symptoms should be examined, tested for urethral, rectal or cervical chlamydial infection, and treated.
 3. If GI is diagnosed, all sex partners of patient within the 60 days prior to onset of symptoms should be examined and offered therapy.

VIII. COMPLICATIONS

- A. Complications and sequelae of untreated infections have been described for syphilis, HSV, and chancroid lesions in their specific modules.
- B. Untreated LGV can cause lymphatic obstruction, leading to elephantiasis of the genitalia, and rectal involvement can cause strictures and fistula formation.
- C. Untreated GI can cause genital elephantiasis and deformity, as well as urethral, anal, and vaginal stenosis. Hematogenous spread to internal organs and bones has been described. Neonatal GI can be fatal and may be averted with early treatment in pregnancy or by cesarean section. An association has been noted between genital carcinoma and GI, however it is uncommon, and a causative role for GI has not been established.

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