GENITAL ULCER DISEASE (GUD)

This chapter from the Canadian Guidelines on Sexually Transmitted Infections 2006 Edition has undergone revisions and has been updated as of October 2007. The chart below summarizes the most significant changes made to the chapter and cross-references the corresponding page numbers in the current hard copy version of the guidelines.

Section	Page	Current Wording/Problem	Update/Clarification
Special Considerations under *Children*	**68**	New statement required on the management of contacts named in suspect child sexual abuse cases	Addition of a new bullet in blue box All persons named as suspects in child sexual abuse cases should be located and clinically evaluated; prophylactic treatment may or may not be offered and the decision to treat or not should be based on history, clinical findings and test results. (See Sexual abuse in Peripubertal and Prepubertal Children).

GENITAL ULCER DISEASE (GUD)

Etiology

Definition

- Ulcerative, erosive, pustular or vesicular genital lesion(s), with or without regional lymphadenopathy, caused by a number of sexually transmitted infections (STIs) and non–STI-related conditions.

STIs

- For most young, sexually active patients with genital ulcer disease (GUD), etiology is related to an STI. Most often it is due to herpes simplex virus type 1 or 2 (HSV-1 or HSV-2), causing genital herpes.[1] More than one etiology may be found if a careful evaluation is conducted.[2] Other STI causes of GUD are as follows:
  - *Treponema pallidum* spp., causing primary syphilis.
  - *Haemophilus ducreyi*, causing chancroid.
  - *Chlamydia trachomatis* serotype L1, 2 or 3, causing lymphogranuloma venereum (LGV).
  - *Klebsiella granulomatis*, causing granuloma inguinale (donovanosis).

Non–STI-related infections or conditions

- Non–STI-related infections or conditions causing GUD may also be seen (see Differential Diagnosis, below).
- Even after a complete diagnostic evaluation, at least 25% of patients with GUD have no laboratory-confirmed diagnosis.[3]

Epidemiology

- The cause of GUD can be related to a number of factors, such as geographical area where sexual intercourse has taken place; socioeconomic factors; gender of sexual partners; number of partners; HIV status and local prevalence; drug use; commercial sex; and circumcision.[4]
- GUD constitutes at most 5% of visits to physicians for a possible STI.[5]
- About 70 to 80% of genital ulcers are due to HSV-1 or HSV-2.
- Genital ulcers in sexually active persons can be associated with two or more pathogens.[2]
- Women and men with GUD are at increased risk of acquiring and transmitting HIV.[6]
- Syphilis and LGV are rare causes of GUD in Canada, but should be considered in persons having sex while travelling to endemic areas or among men who have sex with men (MSM). When identified, the potential for a localized discrete outbreak exists. Rarely, granuloma inguinale and chancroid should also be considered.
- Syphilis incidence is increasing in Canada, with regional outbreaks of infectious syphilis occurring in recent years, including Vancouver, the Yukon, Calgary, Edmonton, Toronto, Ottawa, Montreal and Halifax.[7–9]
- Chancroid has been sporadically associated with focal urban epidemics in North America, particularly among cocaine users. Sex workers are the usual reservoir.

- Rectal LGV outbreaks are now occurring among MSM in Europe, with recent reports of cases in North America. Co-infection with HIV and hepatitis C virus are seen at a high rate,[10–11] including in Canada.[12]
- HIV infection increases the transmission of STI genital ulcers, and the reverse is also true.[13]

Risk factors

- The following are risk factors for STI-related GUD[14]:
  - Sexual contact with:
    - MSM.
    - A person with GUD.
    - A new partner.
    - A partner who is from or has travelled to an endemic area.
    - Sex workers and their clients.
    - An anonymous sexual contact (e.g., from the Internet, bathhouse, rave/circuit party).
    - A person who is infected with HIV.
  - Travel to endemic areas.
  - Living in region(s) in Canada experiencing outbreaks (e.g., syphilis).
  - Previous genital lesions or STI.
  - Drug use in self and/or partner.

Prevention

- Sexual activity of any mucosal type — oral, anal or genital — can be associated with sexually transmitted ulcers. Patients presenting with concerns about STIs and/or birth control should be given information on the efficacy of barrier methods in preventing STI/HIV transmission and provided safer sex counselling (see *Primary Care and Sexually Transmitted Infections* chapter).
- Identify barriers to prevention practices and the means to overcome them (see *Primary Care and Sexually Transmitted Infections* chapter).
- In the case of bacterial GUD caused by an STI, patients and contacts should abstain from unprotected intercourse until treatment of both partners is complete. For genital herpes, see *Genital Herpes Simplex Virus Infections* chapter.

Manifestations

- Diagnosis is often inadequate when based solely on history and physical examination, because of the lack of sensitivity and specificity of lesion(s), even in so-called “classic” cases.[3]
- Concurrent infection with HIV can change the clinical features of genital ulcers; the therapeutic regimen may also be different.

Table 1. Manifestations

STI	Site	Appearance	Other signs/symptoms
Herpes simplex virus[15]	• For both sexes, anywhere in the "boxer short" area • Men: glans, prepuce, penile shaft, anus, rectum (for MSM) • Women: cervix, vulva, vagina, perineum, legs and buttocks	• Grouped vesicles evolving toward superficial circular ulcers on an erythematous base • Smooth margin and base • Enlarged, nonfluctuant and tender inguinal lymph nodes most common in primary infection	• Ulcers usually painful and/or pruritic • Genital pain • Constitutional symptoms, such as fever, malaise and pharyngitis, are common with primary infection
Primary syphilis (see *Syphilis* chapter)	• At site of inoculation, although most individuals with syphilis fail to notice primary chancre[16]	• Papule evolving to a painless chancre • Indurated with serous exudates • Single ulcer in 70% of cases • Smooth margin and base	• Firm, enlarged, non-fluctuant, non-tender lymphadenopathy is common
Chancroid	• At site of inoculation	• Single or multiple necrotizing and painful ulcers • Two or more in 50% of cases	• Often painful swelling and suppuration of regional lymph nodes, with erythema and edema of overlying skin
Lymphogranuloma venereum[17]	• At site of inoculation	• Self-limited single painless papule, which may ulcerate, followed some weeks later by tender inguinal and/or femoral lymphadenopathy, mostly unilateral, and/or proctocolitis. Recent outbreaks in MSM have been characterized primarily by proctocolitis • If not treated, fibrosis can lead to fistulas and strictures and/or obstruction of the lymphatic drainage, causing elephantiasis	• Signs/symptoms of urethritis
Granuloma inguinale	• At site of inoculation	• Single or multiple progressive ulcerative lesions • Highly vascular (beefy red appearance) • Bleeds easily on contact • Two or more in 50% of cases • Hypertrophic, necrotic and sclerotic variants • Relapse can occur 6–18 months after apparently effective therapy	• Painless

MSM = men who have sex with men

Diagnosis

Table 2. Diagnostic features of STI-related GUD

Disease	% of STI-related GUD	Incubation period
Herpes (recurrent genital herpes more frequent than primary genital herpes)	95%	2–7 days for primary genital herpes
Primary syphilis	>1%	3–90 days
Chancroid	<1%	5–14 days
Lymphogranuloma venereum	<1%	3–30 days
Granuloma inguinale	<1%	1–180 days

GUD = genital ulcer disease
STI = sexually transmitted infection

Differential diagnosis

Table 3. Infectious, non–STI-related causes of genital ulcers[18]

Fungal	Viral	Bacterial
• Candida • Deep fungi (rare)	• Cytomegalovirus (rare) • Varicella or herpes zoster virus (rare) • Epstein-Barr virus (rare)	• *Staphylococcus* spp. • *Streptococcus* spp. • *Salmonella* spp. • *Pseudomonas* spp. • Mycobacteria • Parasite (e.g., scabies)

Table 4. Non-infectious skin and mucosal conditions and diseases[19]

Bullous dermatoses	Non-bullous dermatoses	Malignancy
• Non-autoimmune – Contact dermatitis – Erythema multiforme (almost always HSV-related) – Toxic epidermolysis • Auto-immune – Pemphigus – Cicatricial pemphigoid	• Nonspecific vulvitis/balanitis • Aphthae or aphthous ulcers, aphthosis • Lichen planus, erosive lichen planus • Lichen sclerosus • Behcet's disease • Pyoderma gangrenosum • Fixed drug eruption • Lupus erythematosus • Crohn's disease • Vasculitis	• Squamous-cell carcinoma • Vulvar intraepithelial neoplasia • Less common: – Extramammary Paget's disease – Basal-cell carcinoma – Lymphoma/leukemia – Histiocytosis X

HSV = herpes simplex virus

- Other causes of ulcerative lesions of the skin and mucosa:
  - Trauma (less common)
  - Idiopathic: 12 to 51% of genital ulcers have no definite cause in research settings. Referral to an expert when no etiology is found may diminish this fraction.[4]

Specimen collection and laboratory diagnosis

- The minimum testing for all cases of GUD should include a viral identification test for HSV and a syphilis serology.
- Inform laboratory in advance when special procedures need to be followed. Consultation with an experienced colleague may be warranted.
- Biopsies, cultures, smears and serology should be ordered as appropriate for evaluation of all vulvar ulcers.

Herpes simplex virus

- See *Genital Herpes Simplex Virus Infections* chapter.
- Herpes testing is important for all lesions, initial and recurrent, even in classic cases, because of false-positive clinical diagnosis. Retesting following a positive test is almost always of limited value. Typing is important to aid in the discussion of the natural history, help assess partners and help discuss preventive agendas.
- Viral identification
  - Viral identification by either viral culture or nucleic acid amplification tests (NAAT), or, if not available, by antigen test.
  - Culture should be carried out on at least three unroofed pustules/vesicles or wet ulcers *unless* HSV infection has been previously confirmed by a laboratory test. The specimen must be transported in a special viral transport medium.

  - NAATs are considered superior, but their availability is limited (see *Laboratory Diagnosis of Sexually Transmitted Infections* chapter).
- Type-specific serology
  - In the presence of a potential case of genital herpes and two negative viral identification tests, or if there is difficulty organizing testing when lesions are present or lesions are rare, type-specific serology can help confirm possible genital herpes cases.[20] If both HSV-1 and HSV-2 serology are negative 12 weeks after the first manifestation, genital herpes is not likely.
  - It should be noted that the availability of type-specific serology is limited in Canada.

T. pallidum
- See *Syphilis* chapter.
- Identification: dark-field examination or direct fluorescent antibody test on swab from ulcers. Contact your local laboratory regarding these tests, as they are not widely available.
- Serology
- Syphilis serology should include a non-treponemal test (e.g., rapid plasma reagin [RPR], Venereal Disease Research Laboratory [VDRL]) or treponemal-specific enzyme immunoassay (ELISA). As treponemal tests are far more sensitive in primary syphilis than non-treponemal tests, many authorities advocate proceeding directly to treponemal tests when primary syphilis is suspected. Although EIA is highly sensitive, the test can lack specificity therefore if the treponemal-specific ELISA is positive, confirmation by a second treponemal-specific test is required (e.g. TP-PA, MHA-TP, FTA-ABS).
  - If non-treponemal syphilis serology is found, positive confirmation by treponemal-specific test (e.g., *Treponema pallidum* particle agglutination [TP-PA], microhemagglutination for *Treponema pallidum* [MHA-TP] or fluorescent treponemal antibody absorption [FTA-ABS]) should be sought if not already ordered (see *Syphilis* chapter).
  - Serologic tests should be repeated 2-4 weeks after the original negative test if syphilis is a possibility.
  - Dark-field examination or fluorescent antibody for *T. pallidum* of lesions, if available.

Other causes
- If history, risk factors and physical findings warrant testing for other less common causes of GUD, special laboratory tests may be needed to properly assess the etiology of ulcerative disease. Consider testing for chancroid, LGV and granuloma inguinale.
- *H. ducreyi* (chancroid)
  - See *Chancroid* chapter.
  - Bacterial culture on specific culture medium (special arrangement to be made in advance).
  - NAAT where available (e.g., polymerase chain reaction [PCR]).
  - Gram stain may also be useful (see *Laboratory Diagnosis of Sexually Transmitted Infections* chapter).
- *C. trachomatis* serovar L1, L2 or L3 (LGV)
  - See *Lymphogranuloma Venereum* chapter

  - Identification of *C. trachomatis* by culture, NAAT or serology, followed by confirmation of LGV serovars through DNA sequencing or restriction fragment length polymorphism (RFLP).
- *Klebsiella granulomatis* (granuloma inguinale)
  - Identification of dark-staining Donovan bodies on crushed or biopsy specimen.

Caution
- Except for genital herpes, most Canadian clinicians have limited experience with STI-related genital ulcers. Early referral to a colleague experienced in this area should be considered, particularly if the case involves the following:
  - Travel.
  - MSM.
  - HIV-infected individuals.
  - Immunocompromised patients.
  - Systemic disease.
- Atypical and/or non-healing lesions may require a biopsy and should be referred to a colleague experienced in this area.[21]

Management[22]

If test results are not yet available
- Treatment considerations:
  - Empiric treatment for chancroid, LGV and syphilis should be discussed with a local expert or public health official only if follow-up is uncertain and if risk factors for these diseases are present.
  - Treatment at the time of presentation should be considered for genital herpes for almost all cases of GUD, especially if the symptoms are typical.
- See *Chancroid, Lymphogranuloma Venereum* and *Syphilis* chapters for more information.

If results are available for RPR, VDRL, TP-PA, MHA-TP/dark-field examination/fluorescent antibody test
- Positive (motile corkscrew spirochetes present): treat for syphilis (see *Syphilis* chapter).
- Dark-field examinations, fluorescent antibody tests *and* tests for HSV infection and *H. ducreyi* are negative or not performed: treat as syphilis if there is a recent history of contact with infectious syphilis or clinical suspicion is strong and follow-up cannot be ensured.
- Otherwise:
  - Consider therapy for HSV if laboratory tests are negative and presentation is typical of HSV infection (see *Genital Herpes Simplex Virus Infections* chapter).
  - Treat for chancroid if presentation suggests chancroid (see *Chancroid* chapter).

Treatment[23]

- For treatment recommendations for syphilis, HSV, chancroid and LGV, see appropriate chapters.
- Treatment of ulcerative STIs in HIV co-infected patients may represent a treatment challenge.[24] See relevant chapters on treatment of specific infections, or, if not experienced in this area, consult an experienced colleague.

Granuloma inguinale[3,25–29]

- Preferred:
  - Doxycycline 100 mg PO bid for 21 days (based on studies of older preparations of tetracyclines) *[C-III]*.
  - Trimethoprim-sulfamethoxazole double strength PO bid for 21 days *[C-III]*.
- Alternatives:
  - Ciprofloxacin 750 mg PO bid for 21 days *[C-III]*.
  - Erythromycin 500 mg PO qid for 21 days *[C-III]*.
  - Azithromycin 500 mg PO daily or 1 g weekly for a minimum of 21 days *[C-III]*.

Consideration for Other STIs

- See *Primary Care and Sexually Transmitted Infections* chapter.
- Obtain specimen(s) for the diagnosis of chlamydial and gonococcal infections and other STIs when appropriate (including LGV, chancroid and granuloma inguinale if there has been travel to regions where these infections are endemic).
- HIV testing and counselling are recommended (see *Human Immunodeficiency Virus Infections* chapter). Patients with syphilis, LGV and chancroid are at especially high risk for concurrent HIV infection.[3] Timing of HIV testing is important, as genital ulceration is a marker for HIV risk. Baseline testing at the initial visit and repeat HIV testing in 12 weeks should be considered.
- Immunization against hepatitis B in those with no immunity against this virus is also recommended (see *Hepatitis B Virus Infections* chapter).
- Discuss HPV vaccine with women as per the recommendations outlined in the Canada Communicable Disease Report, Volume 33 ACS-2, (2007) *National Advisory Committee on Immunization (NACI) statement on Human papillomavirus vaccine.*

Reporting and Partner Notification

- Conditions that are reportable according to provincial and territorial laws and regulations need to be reported to the local public health authority (see chapters of specific infections for reporting requirements).
- Partner notification is vitally important for the rare bacterial ulcerative conditions discussed in this section in order to prevent an outbreak.
- When treatment is indicated for a diagnosis of syphilis, chancroid, LGV and granuloma inguinale, all partners who have had sexual contact with the index case should be located, clinically evaluated and treated appropriately.[3] For more information on partner notification and treatment by infection, see *Chancroid, Lymphogranuloma Venereum* and *Syphilis* chapters.
- Local public health authorities are available to assist with partner notification and appropriate referral for clinical evaluation, testing, treatment and health education.

Follow-up

- A follow-up visit should be arranged for re-evaluation.
  - For chancroid and granuloma inguinale, if the patient is compliant with the prescribed treatment, symptoms resolve *and* there is no risk of re-exposure to an untreated partner, repeat diagnostic testing is not routinely recommended.

  - For LGV, see *Lymphogranuloma Venereum* chapter.
  - For genital HSV infection, no test of cure is necessary.
  - For syphilis, see *Syphilis* chapter.
- Timing for HIV testing should be considered at this stage. Most patients presenting with an acute genital ulcer will be too early in the window to have reactive serology related to an HIV infection.

Special Considerations

Children

- Sexual abuse needs to be considered when GUD is found in children beyond the neonatal period. Consultation with a colleague experienced in such cases should be sought (see *Sexual Abuse in Peripubertal and Prepubertal Children* chapter).
- All persons named as suspects in child sexual abuse cases should be located and clinically evaluated; prophylactic treatment may or may not be offered and the decision to treat or not should be based on history, clinical findings and test results (See *Sexual abuse in Peripubertal and Prepubertal Children* chapter).
- Reporting sexual abuse:
  Sexual abuse of children must be reported to the local child protection agency.
  Local public health authorities may be helpful in evaluating both the source of the infection and potential transmission in the community.
- Whenever possible, it is strongly recommended that the child should be evaluated at or in conjunction with a referral centre (see Appendix F and G).

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