Lymphogranuloma Venereum (LGV)

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LYMPHOGRANULOMA VENEREUM (LGV)

Etiology

- Caused by *Chlamydia trachomatis*, serovars L1, L2, L3.
- LGV can be transmitted through vaginal, anal or oral sexual contact.

Epidemiology

- In general, an uncommonly reported sexually transmitted infection (STI) in Canada.
- Endemic in parts of Africa, Asia, South America and the Caribbean[1], thought to account for 2–10% of genital ulcer disease in areas of India and Africa.[2]
- **A relatively rare disease in industrialized countries; until recently, the majority of cases were acquired in endemic areas.**
- However recent outbreaks in men who have sex with men (MSM) starting in the Netherlands in 2003,[3] with reports of cases in Belgium,[4] France,[5] Germany, Sweden,[4] the U.K.,[6] the U.S.,[7,8] and Canada.[9]
- LGV is not nationally notifiable in the U.S. or Canada. Since the issuing of LGV alerts, cases have started to surface in the U.S.,[7,8] and in Canada.[9]
- Recent outbreaks among MSM have been associated with concurrent HIV, other STIs, hepatitis C and participation in casual sex gatherings such as "leather scene" parties and high-risk activities such as "fisting".[3,4]
- **LGV may enhance the transmission and acquisition of HIV, other STIs and blood-borne pathogens.**
- Nationally notifiable *C. trachomatis* is not broken down into LGV and non-LGV serovars. As such, the national LGV rate is unknown; however, a national enhanced surveillance system was initiated in February 2005 by the Public Health Agency of Canada in partnership with provincial and territorial public health departments.

Prevention

- Condoms or other barrier methods[10] for vaginal, anal and oral sex.
- Extragenital inoculation is possible;[1] therefore, unprotected oral sex is not a safer-sex activity for the prevention of LGV.
- Minimize or avoid sexual activities associated with mucosal damage: for example, fisting, which could facilitate transmission.[11] Avoid sharing of sex toys and clean toys prior to use.
- See *Primary Care and Sexually Transmitted Infections* chapter.

Manifestations

- Unlike other *C. trachomatis* serovars (A-K), LGV strains are more invasive, preferentially affecting the lymph tissue.[3]
- Commonly divided into three stages (see Table 1).[1]

Table 1. Manifestations

Primary LGV	• Incubation period of 3–30 days. • Small (1–6 mm), painless papule at site of inoculation (vulva, vagina, penis, rectum, oral cavity, occasionally cervix) that may ulcerate. • Self-limited and may go unnoticed in up to 50% of people.[1]
Secondary LGV	• Begins within 2-6 weeks of primary lesion.[2] • Often accompanied by significant systemic symptoms, such as low-grade fever, chills, malaise, myalgias, arthralgias; occasionally accompanied by arthritis, pneumonitis or hepatitis/perihepatitis; rarely associated with cardiac involvement, aseptic meningitis and ocular inflammatory disease.[2] • Abscesses and draining sinuses are possible (<⅓ of patients). • Involves the lymph nodes and/or anus and rectum.
Secondary LGV causing lymphadenopathy	• Inguinal/femoral is the most common form and is characterized by painful inguinal and/or femoral lymphadenopathy (unilateral in ½ to ⅔ of cases), referred to as buboes. • "Groove sign": inguinal nodes above and femoral nodes below the inguinal ligament (once considered pathognomonic for LGV). • Other lymphadenopathy may occur depending on site of inoculation (e.g., cervical lymphadenopathy following inoculation during oral sex).
Secondary LGV causing anorectal symptoms	• Characterized by acute hemorrhagic proctitis. • Symptoms of proctocolitis. • Bloody, purulent or mucous discharge from the anus, as well as constipation, are common presenting symptoms.[3,9,10,12]
Tertiary LGV (chronic LGV occurring in 10-20% of untreated cases)	• More common in females than males. • Chronic inflammatory lesions lead to scarring: – Lymphatic obstruction causing genital elephantiasis.[1,2,13] – Genital and rectal strictures and fistulae. • Possible extensive destruction of genitalia (esthiomene).

Diagnosis

- The diagnosis of LGV is not always straightforward. The symptoms and signs of LGV significantly overlap with other STIs, other infections, drug reactions and malignancies. The diagnosis is often based on the history and clinical picture and is supported by laboratory testing, although in Canada confirmatory testing for LGV is now readily available in some laboratories (see *Laboratory testing*, below). For surveillance purposes, only cases positive by LGV confirmatory tests are considered confirmed cases.[9] It may be appropriate, however, for less strict clinical, epidemiologic and laboratory criteria to be used for the clinical management of cases and contacts.

Diagnostic procedures

- Anoscopy/sigmoidoscopy/proctoscopy
  - Pattern similar to ulcerative colitis.
  - Granular or ulcerative proctitis.
- Bubo aspiration
  - Buboes in LGV usually contain a small amount of milky fluid.
  - May require injection of 2–5 mL of sterile saline for aspiration.
  - Buboes should be aspirated through healthy skin.

Laboratory testing

- Routine tests for *C. trachomatis* may be positive in patients with LGV, but generally do not include typing to distinguish LGV serovars from non-LGV serovars. Definitive diagnosis of LGV requires serovar-specific (confirmatory) testing using DNA sequencing or restriction fragment length polymorphism (RFLP). Clinicians will therefore need to request that testing be done for LGV specifically, as most laboratories will not automatically perform serovar typing.
- The availability and type of testing for LGV varies by laboratory. Some local laboratories are able to do confirmatory testing for LGV, while others will need to involve the National Microbiology Laboratory (NML) via their provincial laboratory. Please check with your local laboratory for more information on how to collect and transport specimens. Where possible, suspected cases of LGV should have both swab and sera samples submitted for laboratory testing. Serology and confirmatory testing (DNA sequencing and RFLP) are available at the NML.
- **Due to issues of cross-reactivity and difficulty with interpretation of test results, serological testing should not be used for diagnostic purposes in the absence of culture or NAAT.**

Table 2. Laboratory testing

Type of test	Test specifics	Differentiate between LGV and non-LGV serovars
Tests for *C. trachomatis* (not specific to LGV serovars)		
Culture	Culture for *C. trachomatis*	• No • Positive specimens may be sent for RFLP or DNA sequencing to identify LGV serovars
NAAT	PCR, TMA and SDA	• No • Positive specimens may be sent for RFLP or DNA sequencing to identify LGV serovars
Serology	Testing modalities vary by laboratory: • MIF test for *C. trachomatis:* high-titre (titre ≥1:256) • CF test for *C. trachomatis*: positive (titre >1:64) – MIF is a more specific test for LGV than CF – Cross-reactivity may be an issue with CF	• No • Because of the invasive nature of LGV, serology titres are in general significantly higher in LGV vs. non-LGV *C. trachomatis* infections • High-titre serology is suggestive of LGV infection but is not definitive; low-titre serology does not eliminate possibility of past or current LGV infection
LGV-specific tests (confirmatory)		
DNA sequencing	Definitively identifies LGV serovars	• Yes • Samples that test positive for *C. trachomatis* with NAAT or culture can be sent for DNA sequencing*
RFLP	Definitively identifies LGV serovars	• Yes • Samples that test positive for *C. trachomatis* with NAAT or culture can be sent for RFLP testing*

CF=complement fixation
LGV=lymphogranuloma venereum
MIF=microimmunofluorescence
NAAT=nucleic acid amplification test
PCR=polymerase chain reaction
RFLP=restriction fragment length polymorphism
SDA=strand displacement amplification
TMA=transcription-mediated amplification

* For laboratories sending samples to NML for confirmatory testing (DNA sequencing or RFLP), please note that it is the original sample that has to be submitted to NML. These samples will be tested by PCR for *omp*1, and this PCR product is what needs to be sent for sequencing by the NML.

Specimen collection

- Table 3 describes types of specimens that may be collected for the laboratory tests described above, for the diagnosis of LGV by stage of infection.

Table 3. Specimen collection

Stage of Infection	Sample Type	Tests	Comments
Primary	Swab of lesion	Culture or NAAT	Because the invasive nature of LGV has not yet manifested in the primary stage of the infection, serology at this stage is unlikely to be helpful
Secondary and tertiary	Bubo aspirate	Culture or NAAT	Identification of *C. trachomatis* in bubo fluid is highly suggestive of LGV, even prior to or without identification of LGV serovars
	Rectal, vaginal, oropharyngeal, or urethral swab	Culture or NAAT	NAAT is not officially approved in Canada for use with rectal or oropharyngeal swabs. Repeat testing is advised to confirm a positive test
	Urine	NAAT	
	Serology	MIF test CF test	See *Table 2*

CF=complement fixation
LGV=lymphogranuloma venereum
MIF=microimmunofluorescence
NAAT=nucleic acid amplification test

- **For samples being sent to the NML, the following storage and shipping recommendations apply:**
  - Dry swabs should be stored and shipped frozen.
  - Swabs stored in chlamydia transport media should be kept frozen at –80°C if culture will be done, or at –20°C if culture will not be done.
  - Urine samples should be stored and shipped frozen.
  - See *Laboratory Diagnosis of Sexually Transmitted Infections* chapter for more information on collecting and shipping specimens.

Management

- Treatment with appropriate antibiotic regimen (see *Treatment* section, below).
- Aspiration of buboes may help symptomatically; however, incision/drainage or excision of nodes is not helpful and may delay healing.

Treatment

- Suspected cases should be treated empirically for LGV while awaiting test results.

Table 4. Treatment of lymphogranuloma venereum

First Line	**Doxycycline** 100 mg PO bid for 21 days *[B-II]*
Alternative	**Erythromycin** 500 mg PO qid for 21 days* *[C-III]*
Possible	**Azithromycin** 1g PO once weekly for 3 weeks† *[C-III]*

* Erythromycin dosage refers to the use of erythromycin base. Equivalent dosages of other formulations may be substituted **(with the exception of the estolate formulation, which is contraindicated in pregnancy)**; erythromycin (NOT the estolate formulation) should be used in pregnancy.

† While some experts believe azithromycin to be effective in the treatment of LGV, clinical data are lacking.

Treatment of partners

- Sexual partners from the last 60 days prior to symptom onset or date of diagnosis if asymptomatic should be contacted, tested and treated empirically (regardless of whether signs/symptoms are present) as follows:
  - **Azithromycin** 1g PO in a single dose *[C-III]*

  OR
  - **Doxycycline** 100 mg PO bid for 7 days *[C-III]*
- Should test results confirm an LGV infection, treat as recommended for cases above.

Consideration for Other STIs

- Because of rates of co-infection, testing for HIV, syphilis, HSV, gonorrhea, hepatitis B and hepatitis C is recommended in patients with LGV (see chapters on individual infections for more information on testing).
- Testing for chancroid and donovanosis (granuloma inguinale) should also be considered in patients with LGV, especially if there has been travel to regions where these infections are endemic.
- Immunization for hepatitis B should be offered to non-immune patients (see *Hepatitis B Virus Infections* chapter for more information).
- The opportunity to provide safer-sex counselling should not be missed.

Reporting and Partner Notification

- An enhanced surveillance system was initiated by the Public Health Agency of Canada, in partnership with the provinces and territories, in February 2005.
  - LGV should be reported by local public health authorities to the appropriate regional and provincial/territorial authorities, who have, in turn, agreed to report LGV to the Sexual Health and STI Section of the Public Health Agency of Canada.
  - Case definitions for national enhanced surveillance as of August 2005 are as follows.[9]

Table 5. Case definitions

Probable case	Positive result on culture, NAAT or serologic testing for *C. trachomatis* plus the presence of proctitis OR inguinal or femoral lymphadenopathy OR a sexual partner with LGV
Confirmed case	Presence of *C. trachomatis* serotype L1, L2, L3 confirmed by DNA sequencing or RFLP

LGV=lymphogranuloma venereum
NAAT=nucleic acid amplification
RFLP=restriction fragment length polymorphism

- Any sexual partners from the last 60 days prior to symptom onset or date of diagnosis (if asymptomatic) should be contacted, tested and empirically treated regardless of clinical findings and without waiting for test results. (see *Treatment* section).

Follow-up

- **Patients should be followed until chlamydial tests are negative (test of cure) and the patient has clinically recovered.[3] Serology should not be used to monitor treatment response, as the duration of antibody response has not been defined.**
  - Test of cure should be performed at 3–4 weeks after the completion of effective treatment to avoid false-positive results due to the presence of non-viable organisms (especially if using NAAT).
- Surgery may be required to repair genital/rectal damage of tertiary LGV.

Special Considerations

- Based on limited data, HIV appears to have little effect on the clinical presentation, although atypical presentations in HIV-positive patients have been rarely reported.[14]
- Disease duration may be prolonged in HIV-positive patients.[14]
- In pregnancy, erythromycin (non-estolate preparations) should be used for the treatment of LGV.