# Approach to lymphogranuloma venereum

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## Abstract

***Objective*** To review the literature about lymphogranuloma venereum (LGV) and to provide an overview and discussion of practice guidelines.

***Sources of information*** The terms *Chlamydia trachomatis* and *lymphogranuloma venereum* were searched separately in PubMed. Empirical studies, practice reviews, and clinical guidelines were included. All reference lists were reviewed for additional articles.

***Main message*** Since 2003, there has been a resurgence of LGV among men who have sex with men in many Western countries, including Canada. Although LGV is a serovar of *Chlamydia trachomatis* (serovar L), it can invade regional lymph nodes, and consequently presents with different symptoms than the other subtypes of chlamydia (serovars A through K). Specifically, LGV transitions through 3 phases: a painless papule or ulcer at the site of inoculation; invasion of the regional lymph nodes, which can present with an inguinal or rectal syndrome; and irreversible destruction of lymph tissue. In contrast, chlamydia serovars A to K exclusively produce superficial mucosal infections. Lymphogranuloma venereum also requires a different treatment regimen than other chlamydia serovars.

***Conclusion*** In light of the current resurgence of LGV, its unique symptoms and clinical course, and its requirement for a different treatment than other chlamydia serovars, it is important for primary care providers to recognize when LGV should be included as an appropriate differential diagnosis.

### EDITOR'S KEY POINTS

- Given the resurgence of lymphogranuloma venereum (LGV) in Western countries, it is important that clinicians be aware of not only the clinical course and presentation of this infection, but also the limitations of diagnosis as outlined in current guidelines.
- Where LGV symptoms are present, clinicians should consider molecular testing of genital and extragenital samples that have positive results for chlamydia; in patients with extragenital symptoms, the use of LGV serology in conjunction with chlamydia culture could improve detection of LGV.
- Until nucleic acid amplification tests are approved for extragenital chlamydia testing, in contrast to recent Canadian recommendations, LGV serology continues to have a role in clinical practice.

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## Case

A 34-year-old man presented to an outpatient sexually transmitted infection (STI) testing clinic. He reported a 2-week history of a painful, red, swollen bump in the right inguinal region near the base of his penis. He denied fever, chills, night sweats, rashes, genital lesions, dysuria, urethral discharge, testicular pain, proctitis, rectal discharge, tenesmus, and diarrhea. He stated he had visited a walk-in clinic and received oral cloxacillin to be taken in 500-mg doses 4 times a day for 1 week but that this had provided no benefit. He reported previous unprotected receptive and penetrative oral and anal sexual contacts with male partners.

Examination revealed a 5-cm, tender, erythematous, inguinal bubo that was free of discharge and ulceration. There was no visible groove sign (ie, inflammation of the "inguinal nodes above and femoral nodes below the inguinal ligament"[1]). The genitourinary examination was otherwise unremarkable, as was the examination of his cervical lymph nodes and oropharynx. Specimens were collected to test for gonorrhea and chlamydia, including first-void urine for a nucleic acid amplification test (NAAT) and pharyngeal and rectal swabs for culture. Lymphogranuloma venereum (LGV) genotyping was requested for all specimens that had positive test results for chlamydia. Samples for serology tests for syphilis, HIV, and chlamydia

serovar L were also sent. Based on a presumptive clinical diagnosis of LGV, we prescribed 100 mg of oral doxycycline twice daily for 3 weeks, and instructed him to return to the clinic in 2 weeks for a follow-up assessment.

Follow-up showed near-complete resolution of symptoms. Serology for chlamydia serovar L had positive results, with a titre of 1:512 by microimmunofluorescence. The HIV test results were also positive. All other results were negative and, as chlamydia was not detected in the urine, pharyngeal, and rectal specimens, the laboratory did not perform LGV genotyping. We took the clinical presentation, including the response to doxycycline, and the elevated LGV serology titre to form a diagnosis of probable LGV.[1] As this diagnosis did not fulfil the public health case definition for chlamydia infection,[1] no public health reporting or follow-up occurred. Nevertheless, we did encourage the patient to refrain from sexual activity until 7 days after he had completed his treatment, and to inform all sexual partners from the previous 60 days to present for testing and empiric treatment.

*Chlamydia trachomatis* is an obligate intracellular pathogen.[2] Its 15 serovars can be classified into 3 groups based on type of infection: trachoma (serovars A, B, Ba, and C), anogenital infection (serovars D to K), and LGV (serovar L: L1, L2, and L3).[2,3] Although chlamydia infections are often asymptomatic, worldwide, trachomas are a leading cause of blindness, and anogenital chlamydia infections are the most common STI and a frequent cause of infertility and pelvic inflammatory disease.[4-7] In contrast to serovars A to K, which cause mucosal infections by infecting columnar epithelial cells, serovars L1, L2, and L3 cause systemic disease by infecting monocytes and macrophages and then invading submucosal sites and regional lymph nodes.[8,9]

In Western countries, the incidence of LGV has been increasing since 2003, primarily among HIV-positive men who have sex with men (MSM).[10-17] Part of the challenge with diagnosis is that the clinical presentation of LGV is often variable and nonspecific.[18-22] Compounding this is the fact that few laboratories can differentiate serovars D to K from L. Identifying serovar L is essential, as LGV requires a longer course of treatment compared with other chlamydia serovars to mitigate related sequelae.[23-25] Herein, our objective is to review the literature about LGV, and to provide an overview and discussion of practice guidelines.

## Sources of information

The information for this clinical review article arises from a literature search on LGV. The terms *Chlamydia trachomatis* and *lymphogranuloma venereum* were searched separately in PubMed. Empirical studies, practice reviews, and clinical guidelines were included. We reviewed all reference lists for additional articles.

## Main message

***Epidemiology.*** Lymphogranuloma venereum has not historically been identified in Western countries. However, since 2003—when clinicians identified a cluster of such infections in the Netherlands—LGV has become endemic in Canada, the United States (US), the United Kingdom (UK), and Australia.[10-17] Indeed, the Public Health Agency of Canada[11] indicates that, between 2004 and 2012 inclusively, there were 170 reported cases of LGV. As LGV is not reportable in all jurisdictions in Canada (eg, in Ontario), these numbers likely underrepresent the true burden of infection.

Because researchers identified that substance use, sex parties, anonymous sex, rectal douching, use of sex toys, fisting, and receptive anal intercourse correlated with LGV detection, initial speculation suggested rectum-to-rectum transmission.[8,14,16,21] However, subsequent analyses of stored urine samples identified a number of undiagnosed urethral LGV infections. It is possible that this reservoir of urethral infections went undetected because many previous guidelines only recommended LGV screening for rectal samples.[12] It is also possible that practitioners did not test for LGV because—unlike the textbook description of LGV[25,26]—most of the identified LGV infections were asymptomatic.[12] Moreover, subsequent reports have identified a small number of cases of pharyngeal LGV.[27-29]

***Presentation.*** Infections with chlamydia serovars D to K are typically asymptomatic. When present, symptoms tend to be consistent with localized mucosal inflammation (eg, urethritis, dysuria, proctitis, cervicitis, atypical vaginal discharge). Less commonly, these infections can ascend the genital tract and result in more severe syndromes (eg, pelvic inflammatory disease or epididymitis). In contrast, LGV symptoms are classically divided into 3 stages: local infection (primary stage), regional dissemination (secondary stage), and progressive tissue damage (tertiary stage).[5,7,8,25,26]

*Primary:* Although often unnoticed by patients, about 3 to 30 days after inoculation localized inflammation manifests at the site of exposure (often genital or rectal, but can be oropharyngeal).[8,9,12] Classically, this lesion is a transient papule, but can be a pustule or ulcer.[5,8] Direct rectal inoculation, as in the recent outbreak of LGV among MSM, can result in proctitis with symptoms of rectal pain, anorectal bleeding, mucoid or hemopurulent rectal discharge, tenesmus, and constipation.[8,9,13] The differential diagnoses for the primary lesions depend on their presentation (as papules versus ulcers), and include herpes, syphilis, genital warts, pearly penile papules, molluscum, other bacterial and fungal infections, contact dermatitis, fixed drug eruption, trauma, and Behçet syndrome. For proctitis, the list includes inflammatory bowel disease, lymphoma,

anorectal carcinoma, and other STIs (eg, gonorrhea, chlamydia serovars A to K, herpes, syphilis).

*Secondary:* About 2 to 6 weeks after the primary lesion appears, regional tissue invasion occurs and can be accompanied by constitutional symptoms (eg, fever, chills, malaise, myalgia, arthralgia).[25,26] While symptoms depend on the site of inoculation, some individuals might be asymptomatic during this stage.[5,18] With penile, urethral, or vulvar inoculation, the main presentation is an inguinal syndrome.[8] In such cases, LGV induces often unilateral, painful, firm, inguinal or femoral lymphadenopathy known as *buboes*. These lymph nodes can suppurate, ulcerate, and possibly lead to purulent discharge through cutaneous fistulas.[5-8] Concurrent inguinal and femoral lymphadenopathy can create the groove sign, which is present in 10% to 20% of cases.[12] Rectal inoculation results in proctitis and lower abdominal or low-back pain due to involvement of the pelvic and retroperitoneal lymph nodes.[12,13] In these cases lymphadenopathy is not evident on physical examination but can often be identified through imaging (eg, computed tomography or magnetic resonance imaging).[8,12,13] The differential diagnosis for localized inguinal or pelvic lymphadenopathy includes herpes, syphilis, gonorrhea, lower-limb infections, lymphoma, and pelvic malignancy.

*Tertiary:* If untreated, LGV can lead to irreversible tissue destruction and scarring.[25,26] In particular, the chronic lymphangitis and subsequent lymphatic obstruction caused by LGV can cause regional lymphedema and genital elephantiasis.[6,7] In cases of rectal involvement, perirectal abscesses, anal fistulas, and strictures are possible.

***Practice guidelines.*** Guidelines regarding LGV diagnosis and treatment from Canada,[1,7] the US,[6] the UK,[5] and Europe[4] are similar. They recommend clinicians consider LGV in the differential diagnosis when sexually active patients present with inguinal or femoral lymphadenopathy or buboes or proctitis, particularly when patients are sexually active, HIV-positive MSM.[1,4-7] When assessing patients with such symptoms, clinicians should collect samples for chlamydia NAATs or culture from the oropharynx, rectum, cervix, or urethra (via urine sample) based on patients' anatomy and sexual history, and request that the laboratory perform LGV genotyping on chlamydia-positive samples.[1,4-7] This process is also recommended for patients who are sexual partners of persons diagnosed with LGV.[1,4-7] Because the current LGV resurgence has been among MSM, the guidelines also indicate that, when screening asymptomatic MSM (especially those who are HIV-positive), clinicians should consider requesting that chlamydia-positive specimens undergo LGV genotyping.[1,4-7] The possible outcomes of this testing are negative results, positive results for chlamydia with non-LGV serovars, and positive results for chlamydia with LGV serovars.

The guidelines differ regarding the use of serology in diagnosis. The Canadian guidelines[1,7] state that "serology is not recommended, given cross-reactions with other *Chlamydia* species, and difficulties interpreting variations in titres (for example, low titres do not rule out LGV)."[7] As well, how to interpret changes in titres after treatment is unknown.[1,7,30] In contrast, the US,[6] UK,[5] and European[4] guidelines indicate that LGV serology can be used to support the diagnosis of LGV in some contexts, eg, when a laboratory cannot perform LGV genotyping. These guidelines[4-6] adopt a different approach—they indicate that while the stated shortcomings of LGV serology are valid, a microimmunofluorescence titre greater than 1:256 is suggestive of LGV. This is because LGV is invasive and can induce higher antibody titres than mucosal serovars A to K usually can.[6]

When contemplating the value of LGV serology, it is important to evaluate the limitations of available chlamydia testing. Currently, in Canada and the US, NAATs for chlamydia are only approved for genital sites (ie, tests are done on first-void urine and cervical and urethral swabs).[1,6,7] Nucleic acid amplification tests are not currently approved by the US Food and Drug Administration for extragenital sites (eg, pharyngeal, rectal), limiting diagnosis at these locations to culture.[1,6,7] This is concerning because the sensitivity of chlamydia culture from extragenital sites is poor—as low as 50%.[31] As a sizable number of chlamydia infections among MSM are exclusively rectal, many of these infections could be missed.[32,33] Moreover, research has shown that chlamydia serovars can differ by anatomic site in some individuals.[34] Indeed, "significant differences in serovar prevalence are found between rectal and urogenital specimens in men."[34] An LGV diagnosis could thus be missed even when urine NAAT results are positive for chlamydia and negative for LGV, and the extragenital test result is falsely negative. As "NAATs typically detect 20%-50% more chlamydial infections than could be detected by culture,"[31] some of these limitations could be overcome if NAATs were approved for extragenital sites.

Given the current limitations in detecting chlamydia at extragenital sites, we see a role for LGV serology in specific clinical situations. Because a negative result from a rectal chlamydia culture can be incorrect up to 50% of the time, and because only chlamydia-positive specimens undergo molecular testing for LGV, the diagnosis in MSM patients experiencing extragenital symptoms could be missed. Performing LGV serology in such a context as an adjunct to genital chlamydia NAAT and extragenital chlamydia cultures could be beneficial. However, given the limitations of LGV serology, it should be reserved for instances of high pretest probability, ie, patients from

high-risk groups such as MSM who either have symptoms suggestive of LGV or are known to have had sexual contact with persons diagnosed with LGV. Owing to the issues with interpreting LGV serology (ie, cross reactivity, variability in titre, and how to interpret titres after treatment), serology likely has no role in routine testing when the likelihood of detecting LGV is low based on LGV prevalence and clinical presentation.

For treatment, the Canadian,[1,7] US,[6] UK,[5] and European[4] guidelines recommend 100 mg of oral doxycycline twice daily for 21 days, which is longer than the treatment of non-LGV chlamydia infections (ie, 1 dose of 1 g of oral azithromycin or 100 mg of oral doxycycline twice daily for 7 days). This is based on evidence that LGV RNA can be isolated for up to 16 days during treatment.[23] An alternative regimen for LGV is 500 mg of oral erythromycin 4 times a day for 21 days, or 1 g of oral azithromycin once a week for 3 weeks.

All guidelines also recommend ongoing follow-up until signs and symptoms resolve.[1,4-7] When LGV diagnosis was through molecular testing or culture of a genital or extragenital sample with positive test results for chlamydia, the Canadian guidelines recommend repeating the chlamydia test until the results are negative, thus confirming cure of LGV. This test of cure is not possible in cases where LGV was diagnosed through serology, as the expected duration of elevated titres has not been clearly defined.[6] In these cases, follow-up should continue until signs and symptoms resolve.

For partner follow-up, the guidelines all recommend that sexual contacts from the preceding 60 days should be tested for chlamydia at all appropriate sites (ie, urethra, cervix, rectum, and pharynx); tested for other sexually transmitted infections, including HIV, syphilis, gonorrhea, and hepatitis B and C; and given empiric treatment of chlamydia infection. This treatment is 1 oral 1-g dose of azithromycin, or 100 mg of oral doxycycline twice daily for 1 week. However, because routine treatment of chlamydia does not eliminate LGV infection, in the absence of NAATs for extragenital chlamydia infections, we treat contacts of both confirmed and probable cases of LGV with full LGV treatment (100 mg of oral doxycycline twice daily for 21 days). This practice differs from the guidelines, but ensures appropriate treatment is not withheld owing to the poor sensitivity of extragenital chlamydia culture.

## Conclusion

Given the resurgence of LGV in Western countries,[10-17] it is important that clinicians are aware of both the clinical course and the presentation of this infection, and the limitations of diagnosis as outlined in current guidelines. Understanding practice guidelines,[1,4-7] including differences in these documents, can help inform clinical decision making and patient treatment. Regarding our 34-year-old male patient, the serology findings support a clinical diagnosis of probable LGV. In light of the limited sensitivity of extragenital testing for chlamydia, the absence of a culture with positive results for chlamydia does not rule out LGV. Based on such a scenario, until NAATs are approved for extragenital chlamydia testing, in contrast to recent Canadian recommendations, we believe LGV serology continues to have a role in clinical practice. Where LGV symptoms are present, clinicians should consider molecular testing of genital and extragenital samples that have positive results for chlamydia; in patients with extragenital symptoms, use of LGV serology in conjunction with chlamydia testing could help improve detection of LGV.

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**Contributors**
**Dr O'Byrne** completed the literature review, and all authors contributed to the interpretation of the literature and to preparing the manuscript for publication.

**Competing interests**
None declared

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