BMJ Best Practice

Lymphogranuloma venereum

Straight to the point of care

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Summary

Primary manifestation of lymphogranuloma venereum infection is painless penile or vulvar inflammation and ulceration at the site of inoculation; often not noticed by the patient.

Secondary stage typically occurs weeks after development of the primary lesion; presents as painful, unilateral, inguinal or femoral lymphadenopathy (often referred to as "inguinal syndrome").

Proctocolitis has emerged as a more typical presentation in men who have sex with men (particularly those who are HIV-positive).

Chronic inflammation can lead to scarring and fibrosis causing lymphedema of the genitals, or formation of strictures and fistulae if anorectal involvement.

Identification of *Chlamydia trachomatis* from the swab of a genital ulcer or aspiration of a bubo is definitive diagnosis.

Doxycycline is the preferred first-line treatment; macrolides are an alternative treatment option (e.g., in pregnant or lactating women, or patients with allergies to tetracyclines).

Large buboes may be aspirated, but incision and drainage or surgical excision of buboes may complicate healing.

Definition

Lymphogranuloma venereum (LGV) is a STI caused by *Chlamydia trachomatis* genovars/serovars L1, L2, or L3 (collectively termed the "LGV biovar"), which are endemic to the tropics, but now emerging in developed regions. Infection occurs through contact with mucous membranes or abrasions in the skin of the genital region.

Epidemiology

L1, L2, and L3 genovars/serovars of *Chlamydia trachomatis* are endemic to tropical regions of Southeast Asia, Latin America, the Caribbean and Africa. Historically, LGV has been considered a rare disease in developed countries of temperate climates; however, in urban areas of Europe and North America, outbreaks of LGV proctocolitis have been reported among men who have sex with men (MSM), often in association with transmission of syphilis, HIV, and hepatitis C.[9] [10] LGV occurs rarely in the US but as it is not a notifiable STI, current incidence rates are difficult to ascertain.

LGV may occur at any age, but the peak incidence is between 15 and 40 years, the ages when sexual activity is at its peak.[11] LGV is more commonly reported in men because early signs are more apparent in men, but it is thought that men and women are probably equally affected.[11] Studies among MSM who reported receptive anal intercourse in Germany, the UK, and Netherlands have shown that LGV may be asymptomatic in about one quarter of cases.[12] [13]

Reporting from endemic regions suggest that LGV is less common than herpes simplex virus or syphilis as a predominant cause of genital ulcer disease, and less common than chancroid as a cause of inguinal lymphadenopathy.[14] [15] [16]

Etiology

Infection with *Chlamydia trachomatis* occurs through contact with mucous membranes or abrasions in the skin. Sexual transmission is the most common route, but extragenital sites may be affected when inoculated by nonsexual contact, accidental laboratory inhalation, or when transmitted by exposure to fomites.

Pathophysiology

Chlamydiae are obligate intracellular bacteria. The infective form of *Chlamydia trachomatis* is the elementary body, which may enter cells by phagocytosis or endocytosis. The organism binds to epithelial cells via the major outer-membrane protein, the OmcB protein, and heparin sulfate receptors.[17]

While other chlamydial infections tend to be confined to the site of inoculation, LGV genotype-specific *C trachomatis* extends directly to the draining regional lymph nodes, where they proliferate as reticulate bodies within lymphocytes and monocytes. Reticular bodies revert to elementary bodies and the inclusion bodies containing them rupture within the host cell. Consequently, the cell lyses, releases its infective contents and the lifecycle perpetuates with cell-to-cell spread.[18] Epithelial cells, when infected, produce inflammatory cytokines and an initial neutrophilic response. In vitro studies demonstrate that interferon-gamma inhibits replication, but does not terminate the lifecycle.[19]

Inguinal and femoral nodes are the most frequently observed nodes initially involved in heterosexual men. In women and men who have sex with men, lower abdominal pain and back pain are common presenting symptoms associated with involvement of deep pelvic and lumbar lymph nodes. In women, these nodes become involved due to lymphatic spread from the cervix and posterior vaginal wall. Within the lymph nodes, inflammation occurs locally and an inflammatory mass forms when surrounding tissue becomes involved. As the lymphatic inflammation becomes suppurative, abscesses may coalesce or become necrotic. The buboes (inflamed, tender, swollen lymph nodes) that form can rupture spontaneously and create fistulae or sinus tracts. Lymphatic architecture is remodeled by scarring and fibrosis. Subsequent obstruction may

lead to genital elephantiasis. Systemic manifestations may occur by direct extension through sinus tracts or bacteremic spread.[20]

Classification

Clinical classification[1]

Three stages of LGV have been identified: primary, secondary, and tertiary.

Primary stage:

- Characterized by painless penile or vulvar inflammation and ulceration at the site of inoculation (may be genitals or anus), which spontaneously heals within a few days; this is often not noticed by the patient.

Secondary stage:

- The classic inguinal presentation has become a less common finding, but occurs weeks after development of the primary lesion and presents as painful, unilateral, inguinal or femoral lymphadenopathy, possibly with buboes (often referred to as "inguinal syndrome").
- When acquired through direct exposure to the rectal mucosa, proctocolitis is another presentation with key symptoms including anorectal pain, rectal bleeding or mucopurulent discharge, diarrhea or constipation, abdominal cramping, reduced anorectal aperture, or tenesmus.
- Patients may present with fever, malaise, back or abdominal pain, or arthralgias. Less commonly a "groove sign of Greenblatt" (describes the characteristic sausage-shaped swellings of the inguinal lymph node above the inguinal ligament and the femoral lymph node below the inguinal ligament, where the inguinal ligament forms a groove in between the swellings) may be seen.

Tertiary stage:[2]

- Characterized by chronic and progressive edema, which results in enlargement, scarring, and ultimately destructive ulceration of the genitalia.
- This is the most common presentation in women due to a lack of symptoms in primary and secondary stages in women.
- Sequelae of chronic infection may result in fibrosis, and formation of sinus tracts and strictures of the anogenital tract as abscesses rupture. In women, this may progress to esthiomene (fibrotic genital elephantiasis), or fistulae involving the urethra, vagina, uterus, or rectum. In men, a physical finding known as saxophone penis or penoscrotal elephantiasis has also been described.

Case history

Case history #1

A 30-year-old male with HIV presents with a 3-week history of progressive anorectal pain, abdominal cramping, rectal bleeding, and diarrhea. He reports that he has been examined by a physician at a different institution who suggested that he might have inflammatory bowel disease. A prescription of metronidazole was given, but his symptoms continued to progress. He has not had fevers, weight loss, malaise, or fatigue. He travels frequently to Amsterdam, the Netherlands, where he reports that he had anal-receptive intercourse with a male partner within the last 3 months and often does not use condoms.

He does not have inguinal lymphadenopathy. He has a narrowing at the anorectal verge and exquisite tenderness.

Case history #2

A 27-year-old male presents with a 2-week history of progressively enlarging masses in his right groin. The masses are inflamed and he reports fever, arthralgias, and malaise. He does not report ulcerations, pyuria, or dysuria. He returned from southeast Asia 4 weeks previously. He admits to using cocaine and having unprotected vaginal intercourse with a female sex worker before returning to the US. His right inguinal and femoral lymph nodes (above and below the inguinal ligament) are oval, approximately 3 cm in dimension, immobile, and tender to palpation. The overlying skin is thick and indurated.

Other presentations

Extragenital manifestations are rare, but LGV can present as pharyngitis, ulceration in the tongue or pharynx, or with cervical lymphadenopathy.[3] [4] [5] LGV has been detected by nucleic acid amplification tests in the pharynx and urethra of asymptomatic carriers.[6] Disseminated disease occurs as a result of bacteremic spread producing conditions including arthritis, hepatitis, pericarditis, pneumonia, or meningoencephalitis.[7] Erythema nodosum is also occasionally associated.[8] Sequelae of chronic infection may result in fibrosis and formation of sinus tracts and strictures of the anogenital tract as abscesses rupture. In women this may progress to esthiomene (fibrotic genital elephantiasis) or fistulae involving the urethra, vagina, uterus, or rectum. In men, a physical finding known as saxophone penis or penoscrotal elephantiasis has also been described.[2] Late complications are rare but have been observed more frequently following proctocolitis.

Approach

Diagnosis is based on clinical suspicion, careful history taking and physical examination, and exclusion of other etiologies, with a definitive diagnosis confirmed by appropriate microbiologic testing if available.

Primary stage of LGV

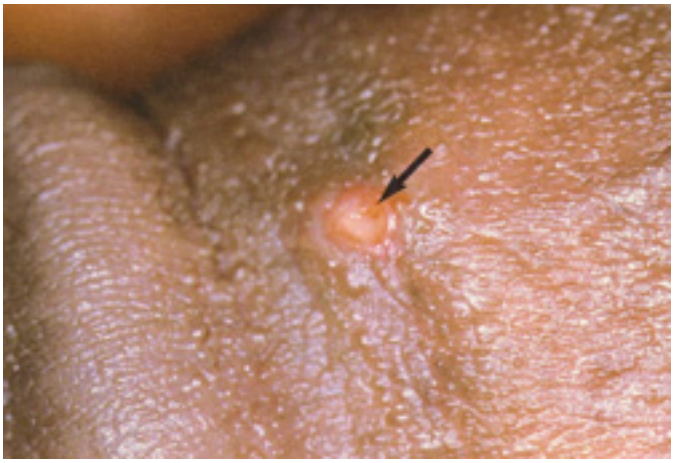
The primary stage is characterized by painless penile or vulvar inflammation and ulceration at the site of inoculation, which spontaneously heals within a few days. This is often not noticed by the patient and they rarely present at this stage.[1]

History:

- Age, sex, history of STIs, HIV status, history of unprotected sexual intercourse (either anal or vaginal), risky sexual behavior, and history of sexual contact with a resident of an endemic area are key components of the history.

Physical examination:

- Inflammation and ulceration may be seen on the genitals or anus; however, as the ulcers heal within a few days, patients rarely present at this stage.



Penile ulceration, a primary manifestation of lymphogranuloma venereum

Courtesy of Ronald Ballard; reproduced with permission from The Diagnosis and Management of Sexually Transmitted Infections in South Africa, 3rd ed., Johannesburg, South African Institute for Medical Research, 2000

Secondary stage of LGV

Secondary stage typically occurs weeks after development of the primary lesion and presents as painful, unilateral, inguinal or femoral lymphadenopathy, possibly with buboes (often referred to as "inguinal syndrome"). This is the most common presentation.[1] Patients may also present with symptoms of proctocolitis or bacteremic spread.

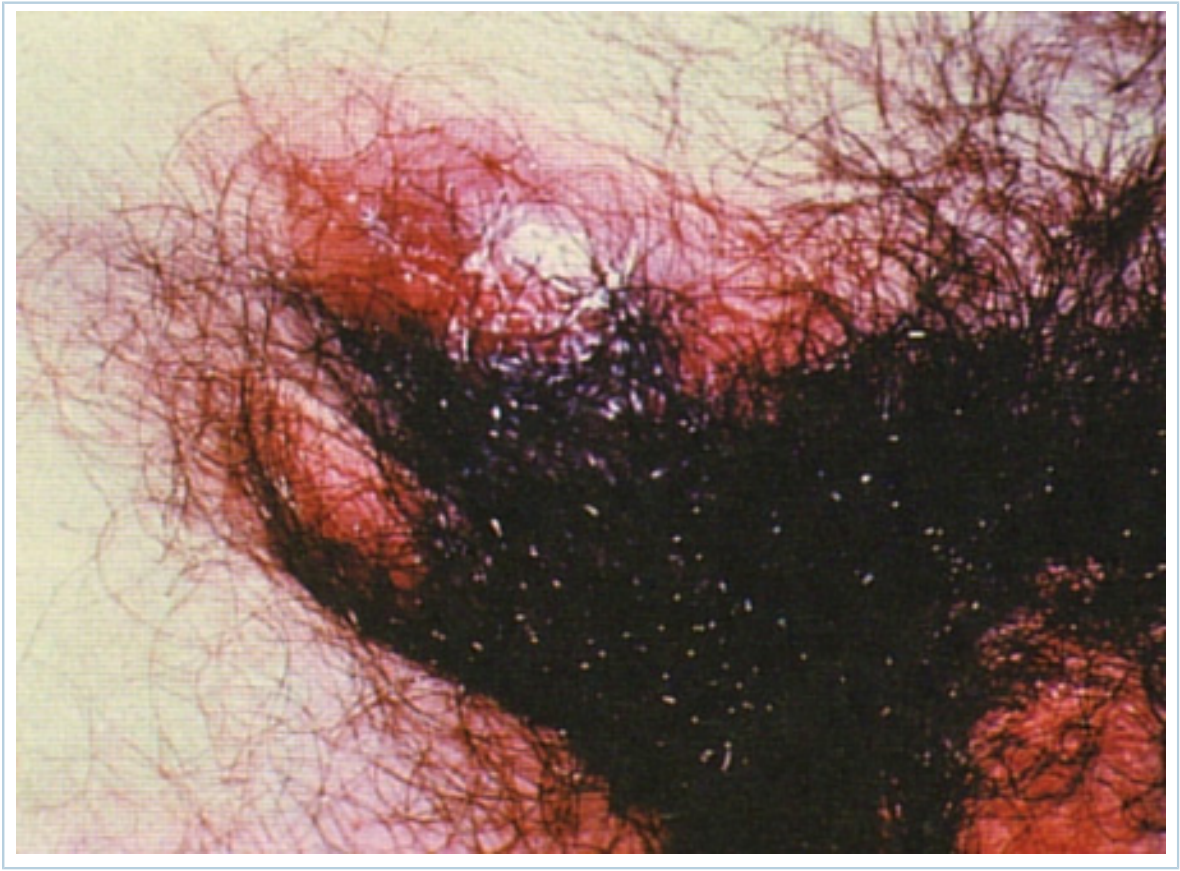
History:

- Age, sex, history of STIs, HIV status, history of unprotected sexual intercourse (either anal or vaginal), risky sexual behavior, and history of sexual contact with a resident of an endemic area are key components of the history.
- Patients may commonly complain of fever, malaise, arthralgias, or lower abdominal or back pain.

- Patients with proctocolitis may complain of anorectal pain, rectal bleeding, mucopurulent discharge, diarrhea or constipation, abdominal cramping or tenesmus.
- Patients with bacteremic spread may complain of symptoms associated with the organ system affected (e.g., arthralgia, respiratory compromise, or hepatic pain and/or jaundice).

Physical examination:[7] [8] [24]

- Patients with the classic presentation will present with pain and swelling in the groin. Less commonly a "groove sign of Greenblatt" (the characteristic sausage-shaped swellings of the inguinal lymph node above the inguinal ligament and the femoral lymph node below the inguinal ligament, where the inguinal ligament forms a groove in between the swellings) may be seen. Erythema nodosum is also occasionally associated.



Inguinal and femoral lymphadenopathy, a secondary manifestation of lymphogranuloma venereum

Courtesy of Ronald Ballard, reproduced with permission from The Diagnosis and Management of Sexually Transmitted Infections in South Africa, 3rd ed., Johannesburg, South African Institute for Medical Research, 2000

- When acquired through the rectal mucosa, proctocolitis is another presentation. Digital rectal examination may be difficult due to tenderness, but will often reveal perianal ulcerations, rectal bleeding, mucopurulent discharge, and a reduced anorectal aperture.
- Disseminated disease occurs as a result of bacteremic spread producing conditions including arthritis, hepatitis, pericarditis, pneumonia, or meningoencephalitis.
- In women, a pelvic exam can be performed to visualize the cervix and to obtain swabs for testing.

Tertiary stage of LGV

Tertiary stage is characterized by chronic and progressive edema, which results in enlargement, scarring and ultimately destructive ulceration of the genitalia. This is the most common presentation in women due to a lack of symptoms in primary and secondary stages in women.[1]

Sequelae of chronic infection may result in fibrosis, and formation of sinus tracts and strictures of the anogenital tract as abscesses rupture. In women, this may progress to esthiomene (fibrotic genital elephantiasis), or fistulae involving the urethra, vagina, uterus, or rectum. In men, a physical finding known as saxophone penis or penoscrotal elephantiasis has also been described.[2]

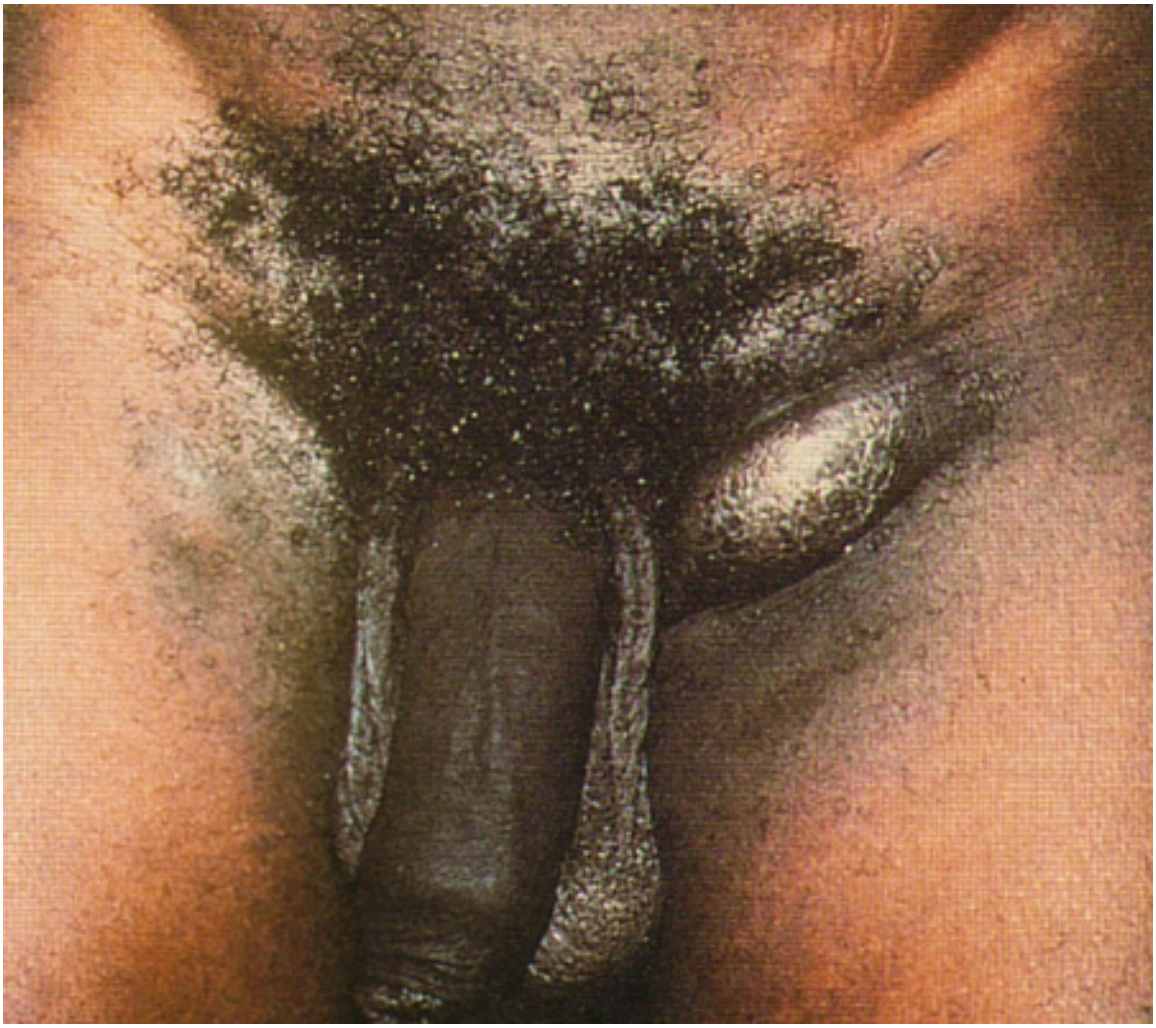
Late complications are rare and have been observed more frequently following proctocolitis. While women are more prone to develop late symptoms and complications, men tend to develop symptoms acutely. Furthermore, the cervix may remain infected indefinitely in females; males are not likely to be infectious after the primary lesion has resolved.[22]

History:

- Age, sex, history of STIs, HIV status, history of unprotected sexual intercourse (either anal or vaginal), risky sexual behavior, and history of sexual contact with a resident of an endemic area are key components of the history.

Physical examination:

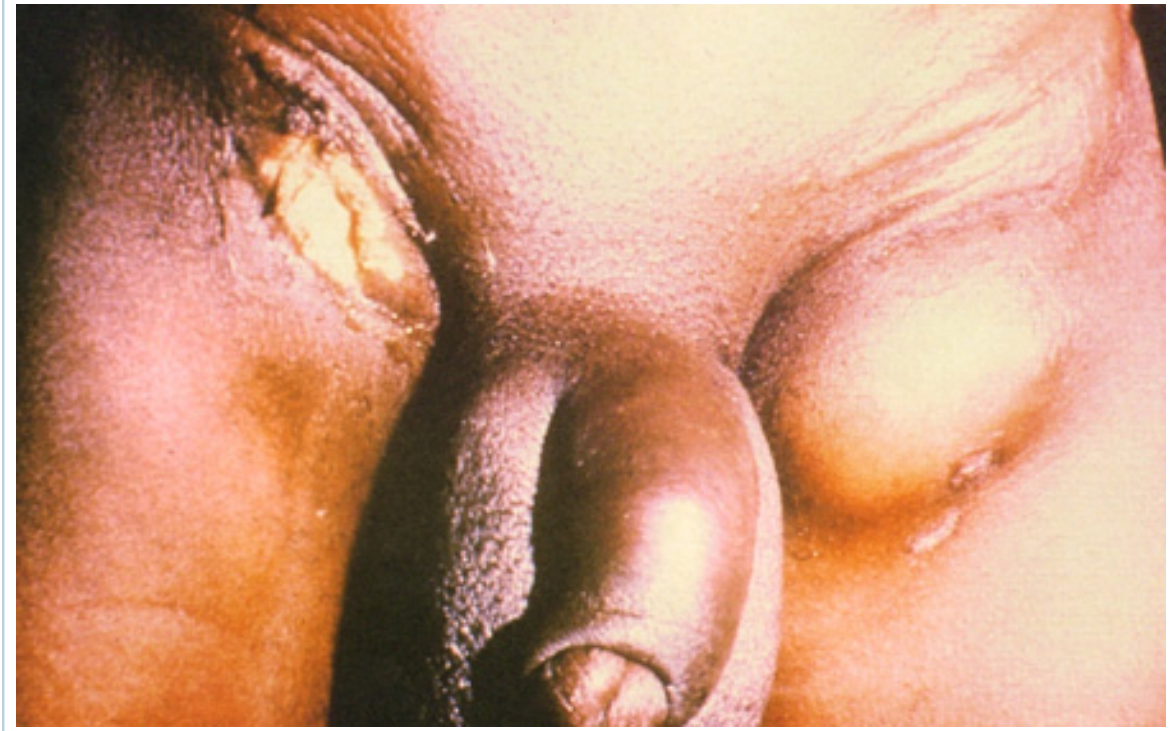
- In the tertiary stages of presentation, clinical characteristics are marked by chronic and progressive edema, which result in enlargement, scarring and ultimately destructive ulceration of the genitalia.



Chronic inflammation from inguinal buboes leading to scarring and fibrosis, a tertiary manifestation of lymphogranuloma venereum

Courtesy of Ronald Ballard, reproduced with permission from The Diagnosis and Management of Sexually Transmitted Infections in South Africa, 3rd ed., Johannesburg, South African Institute for Medical Research, 2000

- Less common findings include anogenital strictures, fistulae, or sinus tracts; genital elephantiasis; saxophone penis or esthiomene.



Lymphedema of the genitals with abscess and fistula formation

Courtesy of Ronald Ballard, reproduced with permission from The Diagnosis and Management of Sexually Transmitted Infections in South Africa, 3rd ed., Johannesburg, South African Institute for Medical Research, 2000

Laboratory evaluation

Diagnosis must be confirmed by appropriate microbiologic testing, regardless of the stage of disease. Identification of LGV serotypes of *Chlamydia trachomatis* is the definitive diagnosis. *C trachomatis* can be distinguished from other species of Chlamydiae by 16S ribosomal ribonucleic acid sequence analysis.[25] On the basis of antigenic specificity confirmed by monoclonal antibodies and molecular sequencing of the major outer-membrane protein, 18 subspecies of *C trachomatis* have been identified, designated by the letters A through L.[26] LGV is caused by genovars/serovars L1, L2, and L3. L2 is the most common of the genovars/serovars that cause LGV.

Swabs are taken from genital ulcers, the cervix, and if symptoms of proctocolitis are present, the rectum. If a patient presents with classic symptoms (inguinal lymphadenopathy) or is otherwise asymptomatic, then urethral swabs or urine specimens are collected.

Molecular techniques have a greater sensitivity compared with culturing and so are preferred first; culturing is not necessary if molecular techniques are available. Nucleic acid amplification testing (NAAT) for *C trachomatis* detects all genovars, including LGV genovar-specific *C trachomatis* , but cannot distinguish between them. Although not cleared by the Food and Drug Administration for analysis of rectal or oropharyngeal specimens, the Centers for Disease Control and Prevention (CDC) recommends testing by NAAT for patients presenting with proctitis or extragenital infections.[27]

A definitive diagnosis can only be made with LGV-specific testing, such as PCR-based genotyping. Specimens that are NAAT-positive may be sent for confirmation of a LGV-specific genovar by real-time polymerase chain reaction (RT-PCR); however, results may take several weeks to return. A presumptive diagnosis of LGV can be made with a positive NAAT from a patient with proctocolitis or clinical suspicion

while awaiting LGV-specific testing. RT-PCR assays are available through the CDC or state public health laboratory, if not available locally.

Radiologic imaging may have a role in the evaluation of deep pelvic anatomy during the later stages of presentation.

Those with signs and symptoms of proctocolitis may be referred for anoscopy or proctosigmoidoscopy. A high white blood cell count on Gram stain from anoscopy/proctosigmoidoscopy in high-risk patients with proctocolitis may support a diagnosis of LGV.[21] Colonoscopy may be considered if inflammatory bowel disease is suspected. LGV is generally confined to the distal sigmoid colon and rectum, whereas Crohn disease may present anywhere in the gastrointestinal tract.[24] Histologically, however, no pathognomonic features of LGV have been described, and findings with LGV may overlap with findings of inflammatory bowel disease, such as crypt abscess and focal granuloma formation.[28]

Serologic testing with either complement fixation or microimmunofluorescence may be useful if direct detection has not been successful or if molecular testing is not available. Isolation of *C trachomatis* from culture of fluid aspirate or swabs of genital or rectal ulcers is the most specific study; however, techniques vary with laboratory and are not widely available as they are more labor intensive and less sensitive than other molecular techniques.

Genovar typing is an emerging test that may be used with reference testing for epidemiologic purposes.

The Frei test, derived from chlamydial antigens, is now obsolete. A positive test does not differentiate past from present chlamydial infection or infection with other chlamydial species.

STI testing

Patients who are being tested for LGV should also be tested for other STIs (e.g., syphilis, HIV, gonorrhea, herpes, and hepatitis). Patients whose HIV tests are negative should be offered HIV pre-exposure prophylaxis (PrEP).[29] [30]

DIAGNOSIS

History and exam

Key diagnostic factors

inguinal lymphadenopathy (common)

- During the secondary stage, tender lymphadenopathy is the classic presentation. One third will have bilateral node involvement.[33]

nonspecific symptoms of proctocolitis (uncommon)

- Symptoms such as anorectal pain, rectal bleeding or mucopurulent discharge, diarrhea or constipation, abdominal cramping, reduced anorectal aperture, or tenesmus are nonspecific symptoms of proctocolitis. Men who have sex with men at high risk for LGV with these symptoms should be screened.[21]

groove sign of Greenblatt (uncommon)

- Twenty percent of affected men will have both femoral and inguinal node involvement. The groove is created by the inguinal ligament.[2]

genital elephantiasis, saxophone penis, esthiomene (uncommon)

- Late stages may occur several years after initial infection. These findings are a result of progressive lymphangitis, chronic edema, and sclerosing fibrosis of the subcutaneous tissues.[22]

Other diagnostic factors

fever, malaise, arthralgias (common)

- Nonspecific symptoms that may accompany lymphatic spread indicating a systemic response to infection.

lower abdominal or lower back pain (common)

- Nonspecific symptoms that may indicate deep iliac node involvement.[22]

genital or anal ulcer (uncommon)

- Primary ulcers usually appear 3 to 30 days after exposure. In women and men who have sex with men, these lesions occur in the vagina or rectum and frequently evade detection.[31] [32]

nonspecific symptoms of bacteremic spread (uncommon)

- Arthritis, hepatitis, pericarditis, pneumonia, and meningoencephalitis are all nonspecific signs that may accompany bacteremic spread, indicating a systemic response to infection.

erythema nodosum (uncommon)

- Erythema nodosum is occasionally associated with LGV.[8]

anogenital sinus tracts, strictures, or fistulae (uncommon)

- Sequelae of chronic infection may result in fibrosis, and formation of sinus tracts and strictures of the anogenital tract as abscesses rupture.

Risk factors

Strong

other STIs

- Those at risk for other STIs are also at risk for LGV. Having concurrent gonorrheal proctitis and genital ulcerative disease, including anogenital herpes and syphilis, were also found to be strong independent risk factors.[21]
- No recent studies clearly distinguish these risk factors or include patients other than men who have sex with men; however, the association with other STIs most likely is related to risky sexual behavior.

risky sexual behavior

- Participating in risky sexual behavior (including sex with anonymous or casual partners and unprotected intercourse) is a strong independent risk factor.[21]

HIV-seropositivity

- No studies have shown that susceptibility to LGV is affected by immune status or prior HIV infection; however, the inflammatory or ulcerative nature of STIs may augment transmissibility and susceptibility to HIV.[22]
- In a case-control study comprising solely of a group of men who have sex with men (MSM) following an outbreak of LGV in The Netherlands, HIV seropositivity was the strongest associated factor (when compared with a control group of MSM without anorectal chlamydia).[21]
- In a meta-analysis of 13 studies from 2000 to 2009, the prevalence of HIV among LGV cases in the MSM population ranged from 67% to 100%. MSM with LGV were over 8 times more likely to have HIV than those who had non-LGV chlamydia infection.[23]

age (20 to 40 years)

- Transmission most frequently occurs during ages of highest sexual activity.
- Although LGV is not common at younger ages, infants may be infected by their mother during delivery and passage through the vaginal canal.[22]

Weak

unprotected intercourse in an area endemic for LGV

- Although recent studies of risk factors for LGV include only men who have sex with men in an outbreak setting, the same risk factors are likely relevant for heterosexual women and men, particularly those who live in or travel to an endemic area. LGV cases reported in nonendemic areas are typically travelers who visit endemic areas.[22]

male

- Although no studies suggest that males are at higher risk for acquiring LGV, men are more likely to manifest LGV with an acute presentation.[22]
- Outbreaks of anorectal LGV in nonendemic areas have been described in men who have sex with men.[9] [12] [21] [24]

Tests

1st test to order

Test	Result
genital or lymph node specimens for nucleic acid amplification testing (NAAT) • A presumptive diagnosis of LGV can be made with NAAT using urine and lymph node specimens as well as swabs of the urethra, rectum, cervix, and genital ulcers.[27] If NAAT is not available locally, the state health department can forward samples to the Centers for Disease Control and Prevention (CDC). Although not FDA-cleared for analysis of rectal or oropharyngeal specimens, the CDC recommends NAAT testing for patients presenting with proctitis or extragenital infections.[27]	**positive for *Chlamydia trachomatis* (LGV and non-LGV genovars may be detected, but commercially available NAATs cannot distinguish between them)**
swab via anoscopy for Gram staining • Men who have sex with men who report receptive anal intercourse, particularly those who are HIV-positive, may warrant empiric treatment with this finding while awaiting other confirmatory tests.[21]	**anorectal Gram stain showing greater than 10 WBC/high-power field is suggestive of LGV**
fluid or swab for LGV-specific molecular testing • Definitive diagnosis can only be made with LGV-specific testing, such as PCR-based genotyping. • Specimens that are NAAT positive should be sent for confirmation by RT-PCR; however, results may take several weeks to return. Rectal swabs can be sent for PCR analysis. • If this test is not available locally, the state health department can forward samples to the CDC.	**positive for LGV-specific *C trachomatis* genovars**
STI testing • Patients who are being tested for LGV should also be tested for other STIs (e.g., syphilis, HIV, gonorrhea, herpes, hepatitis B, and hepatitis C). Patients whose HIV tests are negative should be offered HIV pre-exposure prophylaxis (PrEP).[29] [30]	**positive or negative for STI**

Other tests to consider

Test	Result
endoscopy with histopathology • Those with signs and symptoms of proctocolitis may be referred for anoscopy or proctosigmoidoscopy. Colonoscopy may be considered if inflammatory bowel disease is suspected. Histologically, no pathognomonic features of LGV have been described, and findings with LGV may overlap with findings of inflammatory bowel disease, such as crypt abscesses and focal granuloma formation.[24] [28]	**lesions in LGV are generally confined to the rectum and distal sigmoid colon, whereas Crohn colitis can have a more varied colonic distribution; histopathology with LGV may reveal acute and chronic inflammation with less distortion of crypt architecture than is usually seen with inflammatory bowel disease**
serum for complement fixation • A complement fixation with a high titer in the absence of symptoms does not confirm LGV, and a low titer does not exclude LGV.	**a titer greater than 1:64 or a 4-fold rise between acute and convalescent specimens is suggestive of active LGV**
serum for microimmunofluorescence (MIF) • Serotype-specific MIF has a higher sensitivity (>90%) and specificity than complement fixation, but similarly, it cannot distinguish past from present infection. MIF is not widely available.[34]	**a titer greater than 1:128 is strongly suggestive, but patients with LGV often have titers greater than 1:256**
CT of abdomen and pelvis • Imaging of the abdomen and pelvis is ordered when deep pelvic and rectosigmoid involvement is suspected.	**may indicate presence of strictures, deep pelvic lymph nodes**
MRI of abdomen and pelvis • Imaging of the abdomen and pelvis is ordered when deep pelvic and rectosigmoid involvement is suspected.	**may indicate presence of strictures, deep pelvic lymph nodes**
fluid or swab for culture • Isolation with tissue culture from fluid aspiration, genital, or rectal ulcers is the most specific study. Culture of *C trachomatis* has a yield of about 30%.[22] Techniques vary by laboratory, are not widely available as they are more demanding and less sensitive than other molecular techniques.	**positive for *C trachomatis* including LGV genovars**

Emerging tests

Test	Result
fluid or swab for genovar typing • For use with reference testing for epidemiologic purposes. If this test is not available locally, the state health department can forward samples to the CDC.	**DNA sequencing of the major outer-membrane protein gene**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Syphilis (Treponema pallidum)	• Syphilis is in the differential with the presentation of a genital ulcer; however, the primary chancre caused by syphilis differs by its indurated margins, and the associated inguinal lymphadenopathy is usually bilateral and nontender.	• A rapid plasma reagin or Venereal Disease Research Laboratory test with a confirmatory fluorescent treponemal antibody absorbed test should always be sent as part of a diagnostic work-up for LGV. Dark field microscopy from the swab of a primary syphilitic chancre may also reveal treponemes.[35]
Gonococcal proctitis	• Particularly in women and men who have sex with men who report a history of receptive anal intercourse, gonococcus is frequently cotransmitted, and though frequently asymptomatic, the acute presentation is very similar to LGV in early stages of proctitis, but LGV progresses to late stages marked by granulomatous inflammation, strictures, and chronic ulcerations.[36]	• Diagnosis can be made with swab sent for culture, Gram stain, nucleic acid amplification test, or DNA probe for *Neisseria gonorrhoeae* .
Genital herpes (HSV)	• HSV usually presents as painful vesicles that ulcerate; whereas LGV primary ulcers are painless. Genital herpes is also usually associated with bilateral inguinal lymphadenopathy, as opposed to LGV, which tends to be unilateral.	• Clinical diagnosis can be confirmed by swabbing lesions for HSV culture or HSV polymerase chain reaction (PCR).[30]
Mpox	• Patients typically present with a characteristic vesiculopustular rash that progresses in sequential stages that may involve the palms and soles. Prodromal symptoms may include fever, lymphadenopathy, backache, and myalgia. In the 2022-2023 clade II mpox outbreak, rash lesions were atypical, often localized to the genital, perineal/perianal,	• Polymerase chain reaction of skin lesion material: positive for mpox or *Orthopoxvirus* DNA.

Condition	Differentiating signs / symptoms	Differentiating tests
	or perioral areas and not spreading further.	
Chancroid	• Chancroid differs from LGV by the predominance of multiple painful papules that rapidly become pustular and exudative.	• Gram stain (with Gram-negative rods in a pattern referred to as "school of fish") and culture for *Haemophilus ducreyi* are often helpful but the specificity and yield are poor. Polymerase chain reaction assays are available.[30]
Granuloma inguinale/ donovanosis (Klebsiella granulomatis)	• Similar to LGV, ulcerative lesions are painless, but granuloma inguinale spreads subcutaneously and usually progress without true lymphadenitis. Genital lesions are highly vascular, tend to be very friable and coalesce.	• Definitive diagnosis requires visualization of dark-staining, Donovan bodies on tissue preparation or biopsy. Routine isolation by culture is difficult.[30]
Filariasis	• Lymphatic filariasis is in the differential for inguinal lymphadenopathy presenting in endemic regions; however, pruritus and cutaneous manifestations in the extremities suggest parasitic infection rather than LGV.	• Microfilariae that cause lymphatic filariasis can be detected in blood. Nocturnally periodic microfilariae can be provoked into the blood circulation during the daytime with a dose of diethylcarbamazine if blood testing at night is unfeasible.
Cat-scratch disease (Bartonella henselae)	• Though regional lymphadenopathy is the most characteristic manifestation of cat-scratch disease, most patients will report a history of recent contact with a kitten.	• Diagnosis may be confirmed by polymerase chain reaction from a lymph node, but in combination with clinical findings, serologic testing is the initial test of choice.[37]
Tularemia (Francisella tularensis)	• Tularemia is usually transmitted by tick or animal exposure. Depending on the portal of entry, tularemia may present as an ulceroglandular syndrome, but the primary skin lesion is a papule that necroses and leaves behind a painful ulcer. Regional lymphadenopathy may precede, coincide or follow this. In LGV, lymphadenopathy appears	• *F tularensis* can occasionally be isolated from blood, lymph nodes or wounds, but because of the danger to laboratory personnel and its potential use as an agent of bioterrorism, laboratory personnel should be cautioned if suspected. Rapid diagnostic tests are available by serologic and

Condition	Differentiating signs / symptoms	Differentiating tests
	after the primary ulcer, which is painless and recedes.	polymerase chain reaction assays.[38]
Bubonic plague (Yersinia pestis)	• Patients with an inguinal bubo due to plague will usually be acutely ill. Buboes tend to develop rapidly with exquisite tenderness.	• *Y pestis* may be isolated by culture from blood or swabs of skin lesions. Because of the danger to laboratory personnel and its potential use as an agent of bioterrorism, laboratory personnel should be cautioned if suspected. Serologic tests are available in patients suspected, but who have negative cultures.[39]
TB (Mycobacterium tuberculosis or disseminated Mycobacterium avium complex)	• LGV and tuberculosis (TB) share the propensity for the formation of chronic sinuses, especially in HIV-positive patients, when extrapulmonary TB may present with genitourinary, gastrointestinal involvement or as lymphadenitis (scrofula). Usually systemic mycobacterial infections are associated with hematogenous spread and constitutional symptoms.	• A tuberculin test, or purified protein derivative, is usually positive. Biopsy with acid-fast stains of surgical specimens and/or culture is required for definitive diagnosis.
Amebiasis (Entamoeba histolytica)	• In men who have sex with men presenting with proctocolitis in endemic regions, *E histolytica* infection may resemble LGV.[40] Prominent signs and symptoms of invasive disease include diarrhea, dysentery, and heme-positive stool.	• Diagnosis of amebic proctocolitis is made by recovery of parasites in the stool.
Lymphoma	• Lymphoma will usually be associated with constitutional symptoms and generalized lymphadenopathy.	• Diagnosis of lymphoma is made by histopathology from a lymph node biopsy.
Incarcerated inguinal hernia	• Differential for an inguinal mass. Hernia most often can be identified by physical exam and maneuvers to reduce the hernia.	• CT scan may be helpful to assess the pelvic anatomy.
Inflammatory bowel disease	• Differential for proctocolitis. LGV is generally confined	• Distinction should be made by performing polymerase

Condition	Differentiating signs / symptoms	Differentiating tests
	to the distal sigmoid colon and rectum, whereas Crohn disease may present anywhere in the gastrointestinal tract.[24]	chain reaction for *Chlamydia trachomatis* on rectal swab specimen or biopsy.
Cytomegalovirus (CMV) colitis	• Differential for proctocolitis in patients with HIV/AIDS. LGV is generally confined to the distal sigmoid and rectum.[41]	• Histopathology obtained with proctosigmoidoscopy may help distinguish CMV. Polymerase chain reaction from the serum should also detect a high level viremia.

Criteria

Centers for Disease Control and Prevention[30]

The diagnosis of LGV is based on the clinical findings in combination with a supportive confirmatory test, such as the identification of *Chlamydia trachomatis* by nucleic acid amplification test, polymerase chain reaction-based genotyping, or *Chlamydia* serology (complement fixation titers). The diagnosis is also supported by epidemiologic information and exclusion of other causes of genital ulcers, regional lymphadenopathy, or proctocolitis. Serologic testing alone is not sufficient, but in combination with the appropriate clinical context, a complement fixation titer of greater than 1:64 may also support the diagnosis of LGV.

International Union against Sexually Transmitted Infections[1]

The diagnosis of LGV is confirmed by the detection of genovar-specific *Chlamydia trachomatis* DNA in specimens obtained from the site of infection (e.g., ulcer material from primary anogenital lesions, anorectal swabs from proctoscopic examination, or bubo aspirates). If modern laboratories are available, testing follows a two-step procedure: nucleic acid amplification test (NAAT) screening for *C trachomatis* then, if positive, NAAT is used to detect LGV genovar-specific DNA. If molecular diagnostic test facilities are not available, then a presumptive LGV diagnosis can be made using *Chlamydia* genus-specific serological assays. A high antibody titer (especially IgA anti-major outer membrane protein antibodies) in a patient with a clinical syndrome suggestive of LGV supports the diagnosis.[42] A low titer, however, does not exclude LGV infection, nor does a high titer in a patient without LGV symptomatology confirm LGV.

DIAGNOSIS

Screening

Sexually active women

The US Preventive Services Task Force (USPSTF) recommends that all sexually active women 24 years or younger, including pregnant women, and women 25 years or older who are at increased risk for infection (e.g., new or multiple sex partners), should be screened for *Chlamydia trachomatis* , but there are no recommendations to specifically screen for LGV genovar-specific *C trachomatis* .[43]

Men who have sex with men (MSM)

MSM with anorectal chlamydia can be screened by rectal swab with subsequent analysis by real-time polymerase chain reaction. Targeted empiric treatment for MSM with proctitis and early treatment for those

diagnosed can prevent transmission, late complications, and morbidity. Recommendations for screening and empiric treatment in MSM are based on the sporadic outbreaks in Europe and North America.[21] [44]

Approach

Early stages of disease can be treated effectively with antibiotics. Advanced disease may require surgical evaluation; however, incision, and drainage or surgical excision should be avoided when possible as these procedures may impair lymphatic drainage, lead to formation of sinus tracts, and complicate healing. If confirmatory laboratory tests are not rapidly or readily available, then a patient at risk with a clinical syndrome suspicious LGV warrants empiric treatment.[21]

Patients with primary LGV

Doxycycline is the recommended first-line treatment for early stage of disease. Prolonged antibiotic treatment should not be required for primary LGV. Although one retrospective review in men who have sex with men suggests that 7 to 14 days of doxycycline may be sufficient for rectal LGV, there is not enough evidence to support a duration of treatment shorter than 21 days.[46]

When tetracyclines are contraindicated (e.g., patients with allergies to tetracyclines or pregnant or lactating women), erythromycin is the treatment of choice.

Azithromycin is also an alternative treatment. Although it has not been confirmed to be effective in clinical trials, the use of azithromycin is generally accepted if a patient is pregnant or lactating, if a patient has an adverse drug reaction to doxycycline or erythromycin, or if poor adherence with medication is a legitimate concern.[1] [30] [44] In one trial of 125 patients with LGV proctitis, clinical and microbiologic cure rates suggest azithromycin taken once weekly for 3 weeks may be as effective as standard doxycycline.[47]

If disease is still present after 3 weeks of therapy, alternative diagnoses should be ruled out. Prolonging or broadening the spectrum of antibiotics, therefore, may be necessary for other infections or bacterial superinfection.

Patients with secondary LGV

Antibiotics are used to eradicate infection as in the early stages of disease.

Pus is aspirated from bubonuli using a lateral approach through normal skin to prevent rupture and formation of sinus tracts.[1] [48]

Incision and drainage or surgical excision of inguinal buboes is avoided where possible as these procedures may impair lymphatic drainage, lead to formation of sinus tracts, and complicate healing.[1] [22] [48]

Patients with tertiary LGV

Antibiotics are used to eradicate infection as in the early stages of disease.

Disfiguration of the genitalia associated with esthiomene or elephantiasis may not resolve with antibiotic treatment alone. Plastic surgical reconstruction is considered several months after antibiotic treatment is completed and there is evidence that there has been resolution of active disease.[1] [22] [48]

Advanced anorectal disease may require surgical evaluation by specialized and experienced teams. Though inflammation greatly improves, rectal strictures do not resolve with antibiotic treatment alone. Indications for surgical intervention include stricture formation, bowel obstruction, rectovaginal fistula, and gross destruction of the anal canal, anal sphincter, and perineum.[1] [48]

Patients with asymptomatic LGV

A regimen of doxycycline for 7 days has been typically used for asymptomatic rectal infections caused by non-LGV C trachomatis; however, European guidelines do not recommend courses shorter than 21 days.[1]

Although there is lack of evidence to support either single- or multi-dose regimens of azithromycin, up to 20% of patients with asymptomatic rectal chlamydial infections remained persistently positive when returning for test of cure after a single dose of azithromycin, compared with 1% to 10% of patients treated with doxycycline.[44]

Patients exposed to LGV

Anyone who may have been exposed by contact, either from unprotected sexual intercourse within 60 days to 3 months of the partner's presentation of symptoms, or by direct contact with an LGV lesion or discharge from a lymph node or the rectum, should be contacted for assessment, counseling, and postexposure prophylaxis or antibiotic treatment.[1] [30]

Early presumptive treatment is indicated in this situation because primary lesions are seldom discovered.

Coinfection with HIV

Patients with HIV and LGV should receive the same treatment regimens as those who are HIV-negative; however, close follow-up is required to ensure resolution is achieved.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial (summary)		
asymptomatic adolescent and adult patients who have been exposed to lymphogranuloma venereum (LGV)		
	1st	**antibiotics**

Acute (summary)		
all stages of lymphogranuloma venereum (LGV)		
	1st	**antibiotics**
patients with secondary lymphogranuloma venereum (LGV)	**adjunct**	**aspiration of pus**
patients with tertiary lymphogranuloma venereum (LGV)	**adjunct**	**surgical reconstruction**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial

asymptomatic adolescent and adult patients who have been exposed to lymphogranuloma venereum (LGV)

1st **antibiotics**

Primary options

» doxycycline: 100 mg orally twice daily for 7-21 days

» For asymptomatic persons who have had sexual contact with a patient with LGV.

» Treatment guidelines for sexual contacts differ by region. Anyone who may have been exposed by contact, either from unprotected sexual intercourse within 60 days to 3 months of the partner's presentation of symptoms, or by direct contact with an LGV lesion or discharge from a lymph node or the rectum, should be contacted for assessment, counseling, and postexposure prophylaxis or antibiotic treatment.[1] [30]

» The CDC recommends a 7-day course of doxycycline.[30] European guidelines do not recommend a course shorter than 3 weeks.[1]

Acute

all stages of lymphogranuloma venereum (LGV)

all stages of lymphogranuloma venereum (LGV) — **1st** — **antibiotics**

Primary options

» doxycycline: 100 mg orally twice daily for 21 days

Secondary options

» azithromycin: 1 g orally once weekly for 3 weeks

OR

» erythromycin base: 500 mg orally four times daily for 21 days

» Doxycycline is the recommended first-line treatment.

» Doxycycline is contraindicated in patients with allergies to tetracyclines and women who are pregnant or lactating. Macrolides are an acceptable alternative in these patients. Expert opinion suggests that macrolides, given their effectiveness against other chlamydial genovars/serovars, are effective treatments for LGV.[44]

» If disease is still present after 3 weeks of therapy, alternative diagnoses should be ruled out. Prolonging or broadening the spectrum of antibiotics, therefore, may be necessary for other infections or bacterial superinfection.

patients with secondary lymphogranuloma venereum (LGV) — **adjunct** — **aspiration of pus**

Treatment recommended for SOME patients in selected patient group

» Advanced disease may require surgical evaluation.

» Pus should be aspirated from bubonuli using a lateral approach through normal skin as a measure to prevent rupture and formation of sinus tracts.

» Incision and drainage or surgical excision is avoided where possible as these procedures may impair lymphatic drainage, lead to formation of sinus tracts, and complicate healing.[1] [22] [48]

patients with tertiary lymphogranuloma venereum (LGV) — **adjunct** — **surgical reconstruction**

Treatment recommended for SOME patients in selected patient group

Acute

» Disfiguration of the genitalia associated with esthiomene or elephantiasis may not resolve with standard antibiotic treatment for LGV alone. Plastic surgical reconstruction is considered several months after antibiotic treatment is completed and there is evidence that there has been resolution of active disease.[1] [22] [48]

» Advanced anorectal disease may require surgical evaluation as rectal strictures do not resolve with standard antibiotic treatment for LGV alone. Indications for surgical intervention include stricture formation, bowel obstruction, rectovaginal fistula, and gross destruction of the anal canal, anal sphincter, and perineum.[1] [48]

Emerging

Vaccines

Strategies for chlamydial vaccines have been proposed that would boost an immune response, specifically the T-helper type 1 (Th1) response, to *Chlamydia trachomatis* . Select chlamydial proteins, including structural, membrane, and secretory proteins such as the major outer-membrane protein, have been proposed as subunit vaccine candidates.[49] [50] An effective vector or adjuvant, however, has yet to be demonstrated. Likewise, effectiveness of such a vaccine for LGV genovars/serovars, as well as other manifestations of *C trachomatis* infection, remains to be investigated.[51]

Primary prevention

Primary prevention is abstinence from sexual contact with someone known to have LGV; condoms may not be completely effective in preventing transmission of *Chlamydia trachomatis* from more extensive ulcerative lesions, especially if lesions involve the perineum and groin. Consistent use of barrier methods during oral, vaginal, and anal sex may reduce the risk of acquiring LGV. Sex toys should not be shared unless washed between partners and protected with a condom.

Secondary prevention

Anyone who may have been exposed by contact, either from unprotected sexual intercourse within 60 days of the partner's presentation of symptoms, or by direct contact with an LGV lesion or discharge from a lymph node or the rectum, should be contacted for assessment, counseling and postexposure prophylaxis or antibiotic treatment.[30]

Patient discussions

Patients are advised to abstain from sexual contact completely until symptoms have resolved and the full course of antibiotics has been completed. Condoms may break or may not effectively prevent transmission to their partner from more extensive ulcerative lesions, especially if they are involving the perineum and groin.

Once treated, patients should be aware that previous infection with LGV does not provide immunity against future infection; therefore, safe sex practices should be reinforced.

Monitoring

Monitoring

Patients should follow-up with their primary care physician to confirm the results of diagnostic tests and to ensure the condition has clinically resolved. Some authorities recommend a test of cure (negative nucleic acid amplification test) 3 to 4 weeks after finishing treatment.[52] European guidelines suggest that a test of cure is not necessary if the recommended 21-day course of doxycycline is completed; but, if alternative treatment regimens are used, a test-of-cure is recommended 4 to 6 weeks after treatment completion.[58]

Patients with LGV should also be evaluated for other STDs, including infections that are endemic to areas shared by LGV such as gonorrhea, chancroid, syphilis, granuloma inguinale, genital herpes, human papillomavirus, HIV, and viral hepatitis.

Complications

Complications	Timeframe	Likelihood
increased susceptibility to HIV and other STIs	**short term**	**high**
Primary LGV ulcers tend to resolve without consequence, regardless of therapy. The ulcerative nature of LGV may augment transmissibility and susceptibility to HIV and other STIs.[53]		
reactive arthritis	**short term**	**low**
The association of reactive arthritis with urogenital *Chlamydia trachomatis* infections (serovars D-K) has been well documented, but cases have also been reported with L serovars.[54] [55] [56] [57]		
chronic lymphedema	**long term**	**low**
In tertiary LGV, chronic lymphedema can produce disfiguring anatomical changes in the genitalia that may require plastic reconstructive surgery.		
stricture formation	**long term**	**low**
When LGV manifests as an anorectal syndrome in tertiary LGV, chronic proctocolitis may lead to stricture formation and fistula formation. Though rare, if these strictures are not surgically corrected, bowel perforation from obstruction could result in sepsis and death.		
fistulae or sinus tracts	**variable**	**high**
In secondary LGV, bubonuli may rupture to create fistulae or sinus tracts. This can complicate healing and ultimately lead to deforming scars and fibrosis.		

FOLLOW UP

Prognosis

Full recovery can be expected, especially when treatment is started early; however, reinfection or relapse may occur. When antibiotics are not started early, LGV can progress to late stages. Chronic genital edema can result in scarring, fibrosis, and permanent disfiguration, which may require surgical reconstruction. In the late stages of anogenital LGV, proctectomy, perineal excision, and permanent colostomy may also be required for stricture or fistula formation. Healing in these cases can be prolonged and morbid.[1]

Diagnostic guidelines

International

Sexually transmitted infections treatment guidelines, 2021 (https://www.cdc.gov/std/treatment) [30]

Published by: Centers for Disease Control and Prevention **Last published:** 2021

2019 European guideline on the management of lymphogranuloma venereum (https://iusti.org/treatment-guidelines) [1]

Published by: International Union against Sexually Transmitted Infections **Last published:** 2019

BASHH summary guidance on testing for sexually transmitted infections, 2023 (https://www.bashh.org/resources/guidelines) [45]

Published by: British Association of Sexual Health and HIV; Clinical Effectiveness Group **Last published:** 2023

Treatment guidelines

International

Sexually transmitted infections treatment guidelines, 2021 (https://www.cdc.gov/std/treatment) [30]

Published by: Centers for Disease Control and Prevention **Last published:** 2021

Lymphogranuloma venereum (LGV) in Canada: recommendations for diagnosis and treatment and protocol for national enhanced surveillance (https://www.canada.ca/en/public-health/services/reports-publications/disease-prevention-control-guidelines.html#stds) [52]

Published by: Public Health Agency of Canada **Last published:** 2005

2019 European guideline on the management of lymphogranuloma venereum (https://iusti.org/treatment-guidelines) [1]

Published by: International Union against Sexually Transmitted Infections **Last published:** 2019

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Images

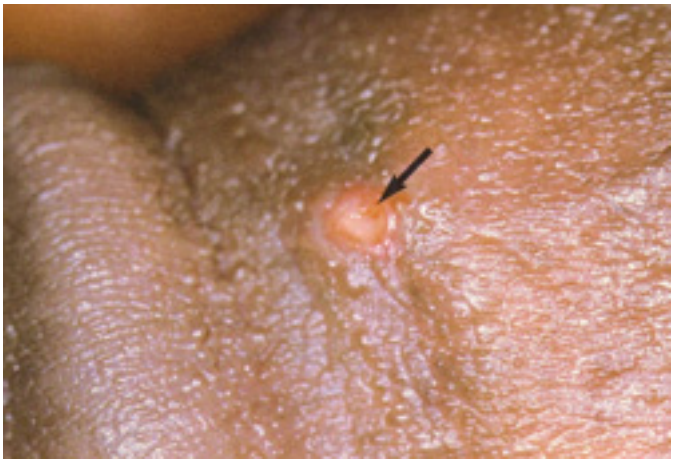

Figure 1: Penile ulceration, a primary manifestation of lymphogranuloma venereum

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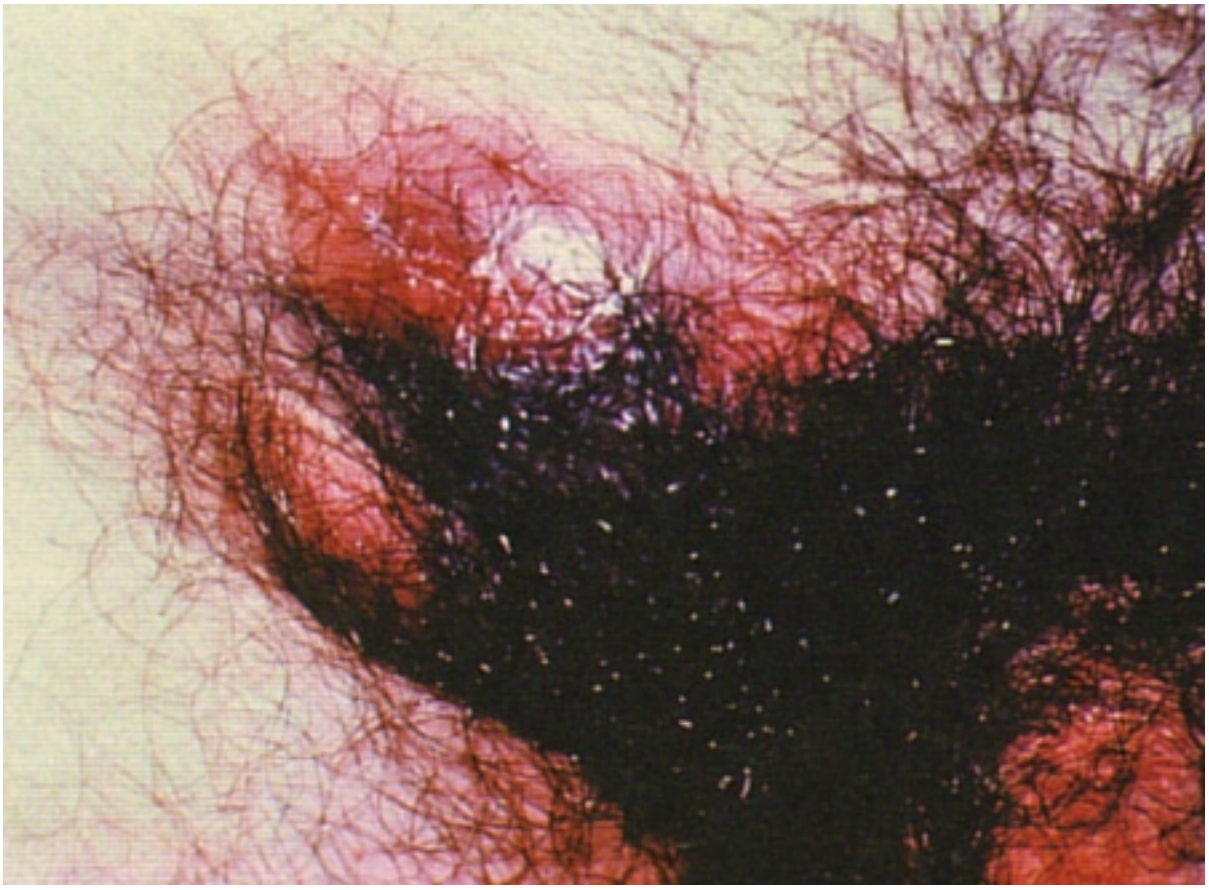

Figure 2: Inguinal and femoral lymphadenopathy, a secondary manifestation of lymphogranuloma venereum

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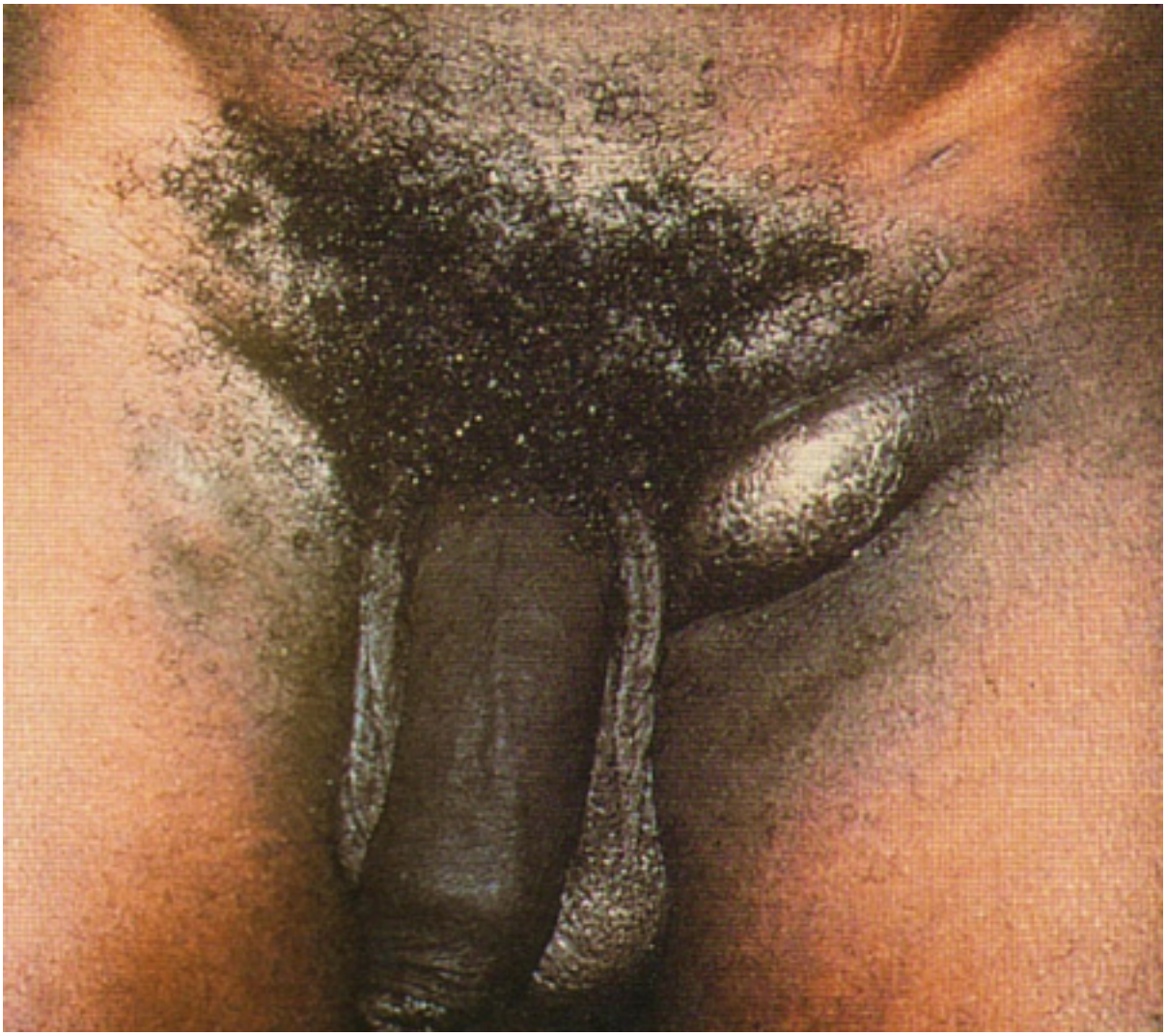

Figure 3: Chronic inflammation from inguinal buboes leading to scarring and fibrosis, a tertiary manifestation of lymphogranuloma venereum

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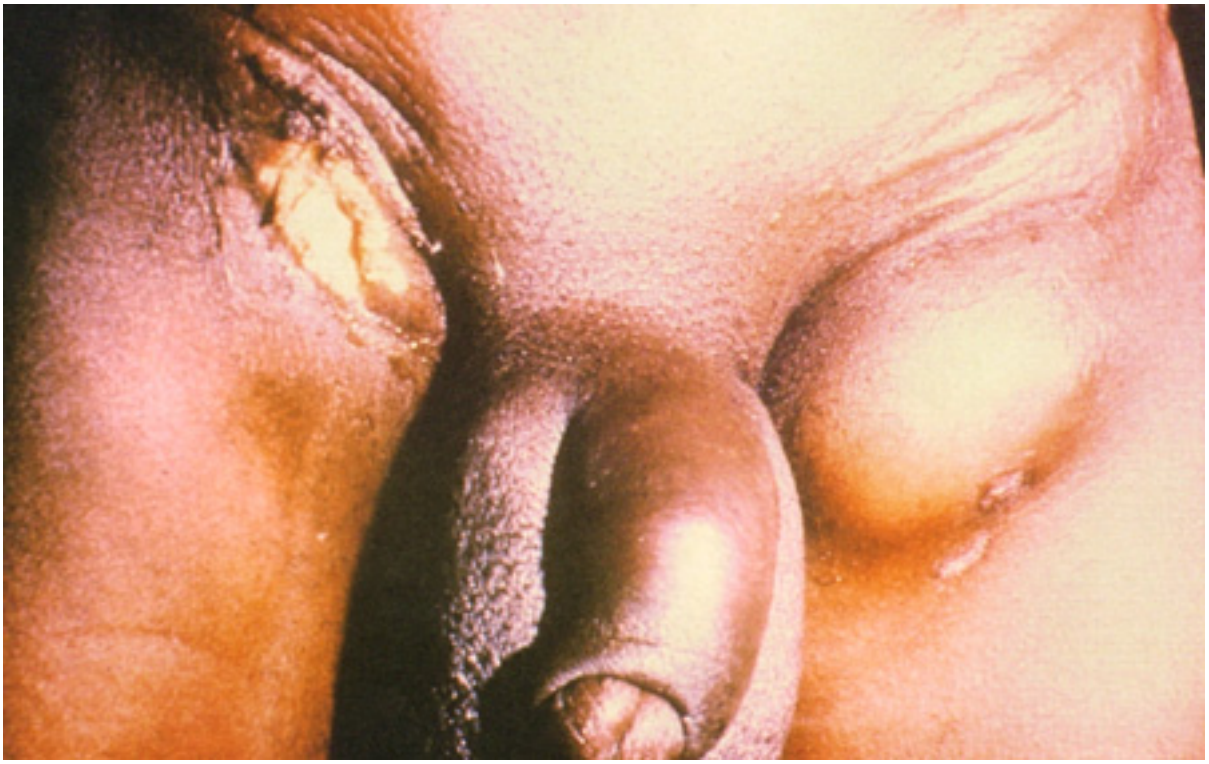

Figure 4: Lymphedema of the genitals with abscess and fistula formation

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

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Contributors:

// Authors:

Benjamin D. Lorenz, MD

Assistant Professor
Division of Hospital Medicine, MedStar Georgetown University Hospital, Washington, DC
DISCLOSURES: BDL declares that he has no competing interests.

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// Peer Reviewers:

Cees van Nieuwkoop, MD

Department of General Internal Medicine
Leiden University Medical Centre, Leiden, The Netherlands
DISCLOSURES: CvN declares that he has no competing interests.

David Chelmow, MD

Chair
Department of Obstetrics and Gynecology, Virginia Commonwealth University, Richmond, VA
DISCLOSURES: DC declares that he has no competing interests.