LymphogranulomaVenereum

EPIDEMIOLOGY

- Lymphogranuloma venereum (LGV) is a sexually transmitted disease due to specific Chlamydia variants that is rare in developed countries.
- It is endemic in East and West Africa, India, Southeast Asia, South and Central America, and some Caribbean Islands; and accounts for 7%–19% of genital ulcer diseases in areas of Africa and India.
- The peak incidence occurs in persons 15–40 years of age, in urban areas, and in individuals of lower socioeconomic status.
- Men are six times more likely than women to manifest clinical infection.
- Since 2003, outbreaks of LGV have appeared in Europe, Australia, and North America, particularly in the form of proctitis, among human immunodeficiency virus (HIV) positive men who have sex with men (MSM).
- LGV is contracted by direct contact with infectious secretions, usually through any type of unprotected intercourse, whether oral, vaginal, or anal.
- Due to underdiagnosis and underreporting, the epidemiology of LGV remains poorly understood.
- Common diagnostic laboratory methods are nonspecific and not readily available in endemic areas. Even in industrialized countries, only a few laboratories offer specific assays to LGV serovars. Without such assays, many LGV cases are misdiagnosed as common chlamydial urogenital infection.
- Underdiagnosis of LGV is also largely due to the presence of an asymptomatic carrier state. Women, in particular, may harbor asymptomatic persistent infection in the cervical epithelium, thus serving as reservoirs of the infection as they do for other urogenital chlamydial infections and gonorrhea.

ETIOLOGY AND PATHOGENESIS

- LGV (tropical or climatic bubo, lymphopathia venerea,Nicolas–Favre disease) is caused by Chlamydia trachomatis serovars (serologic variants) L1, L2, and L3.
- Chlamydiae are obligate intracellular bacteria characterized by two distinct morphologic forms: (1) the small metabolically inactive and infectious elementary body, and (2) the larger metabolically active and noninfectious reticulate body.
- C. trachomatishas been subdivided into several serovars that differ in their major outer membrane proteins, and which are associated with several diseases.

- ❖ Serovars A, B, and C are the causes of trachoma ocular infections, whereas
- ❖ serovars D-K are responsible for ocular, genital and respiratory infections

- After being inoculated onto the mucosal surface, the organisms replicate within macrophages, and find their way to the draining lymph nodes (LNs), and cause lymphadenitis.

CLINICAL FINDINGS

CUTANEOUS LESIONS AND RELATED PHYSICAL FINDINGS

Three clinical stages characterize LGV. Nonspecific cutaneous lesions such as erythema nodosum, erythema multiforme, urticaria, and scarlatiniform exanthema may occur with any of these stages.

PRIMARY STAGE

- Three to 30 days after infection,5- to 8-mm painless erythematous papule(s) or small herpetiform ulcers appear at the site of inoculation.
- Painful ulcerations and nonspecific urethritis are less common.
- In males, the lesion is usually found on the coronal sulcus, prepuce, or glans penis; and in females on the posterior wall of the vagina, vulva, or, occasionally, the cervix. Inoculation may also be rectal or pharyngeal.
- The primary lesion is transient, often heals within a few days, and may go unnoticed

SECONDARY STAGE

- A few weeks after the primary lesion appears, marked LN involvement and hematogenous dissemination occur, manifested by variable signs and symptoms, including fever, myalgia, decreased appetite, and vomiting.
- Photosensitivity may develop in up to 35% of the cases, often1–2 months after bubo formation
- The lymphadenitis episodes often resolve spontaneously in 8–12weeks.
- Depending on the mode of transmission, two major syndromes are distinguished.
  - ❖ The acute genital syndrome (GS) or inguinal syndrome
    - o is characterized by inguinal and/or femoral LN involvement and is the major presentation in men.
    - o Initially, the skin overlying the affected LN is erythematous and indurated
    - o Over the subsequent 1–2 weeks, the LN enlarge and coalesce to form a firm and tender immovable mass (bubo),which may rupture

and drain through the skin, forming sinus tracts. Bilateral involvement occurs in one third of the cases.
    - Nodal enlargement on either side of the inguinal ligament, the "groove sign," is pathognomonic of LGV, but only presents in 10%–20% of cases and is rarely bilateral
    - In women, inguinal lymphadenitis is unusual because the lymphatic drainage of the vagina and cervix is to the deep pelvic/retroperitoneal LN. When these nodes are involved, low abdominal/back pain that exacerbates upon lying supine and pelvic adhesions may ensue.
- ❖ The acute anorectal syndrome (ArS)
    - is characterized by perirectal nodal involvement, acute hemorrhagic proctitis, and pronounced systemic symptoms.
    - It is the most common presentation in women and in homosexual men who practice anal sex.
    - The major source of rectal spread in women is the internal lymphatic drainage of the lower two-thirds of the vagina
    - Patients may complain of anal pruritus, bloody rectal discharge, tenesmus, diarrhea, constipation, and lower abdominal pain

TERTIARY STAGE

- This stage is more seen in women with untreated ArS, and includes rectal strictures (most common) and abscesses, perineal sinuses, rectovaginal fistulae (leading to "watering can perineum"), and "lymphorrhoids" (perianal outgrowths of lymphatic tissue).
- Esthiomene (Greek, "eating away") is a rare primary infection of the external genitalia (mostly in women), leading to progressive lymphangitis and genital destruction.
- Infertility and "frozen pelvis" are potential sequelae of ruptured deep pelvic nodes in women.
- Late sequelae of the GS are less common and include urethral strictures and genital elephantiasis with ulcers and fistulas (in 4%of cases). Penile deformities such as the saxophone penis may also occur.

OTHER UNUSUAL MANIFESTATIONS.

- Extragenito-anal inoculation of LGV is rare.
- Oropharyngeal infection may manifest initially as pinhead sizedvesicles on the lip, and later on as cervical ymphadenopathy with constitutional symptoms, closely mimicking lymphoma.

- Tonsillitis, supraclavicular and mediastinal lymphadenopathy, and pericarditis rarely occur.
- Ocular autoinoculation of infected discharges may lead to conjunctivitis with marginal corneal perforation, often with preauricular lymphadenopathy.
- Inhalation of LGV serovars L1and L2 may accidentally occur in laboratory workers and lead to pneumonitis with mediastinal and supraclavicular lymphadenopathy.

LABORATORY TESTS

- Diagnosis of LGV may be difficult, but LGV should be suspected in any patient with infected sexual contacts, genital ulcer, perianal fistula, or bubo.
- laboratory tests are important to establish the diagnosis and are usually divided into two broad categories: (1) nonspecific tests that do not distinguish between LGV and (2) specific LGV tests.
- In practice, a positive test on LN aspirate is considered diagnostic of LGV, in contrast to a positive test on primary genital lesion where further specific testing is required to rule out common chlamydial urogenital infections

SPECIFIC TESTS FOR LYMPHOGRANULOMA VENEREUM

- Nucleic acid amplification using polymerase chain reaction (PCR) may be performed on all specimens, and has been the diagnostic method of choice in the recent outbreak.
- Several generations of PCR analysis have been developed over the past decade; however, most of them lacked the ability to differentiate between LGV and non-LGV strains
- In 2008, a new diagnostic technique with a quadriplex reverse transcriptase PCR assay was developed. This unique technology can detect individual LGV and non-LGV infection, as well as mixed infections in rectal specimens. However its main disadvantage is that it is available only in the Centers for Disease Control and Prevention and in a few US laboratories.
- Other newly introduced biomolecular techniques exploring immune-mediated lysis, heparin sulfate lysis, use of pooled antibody, and structural genetic differences seem to be promising.

NONSPECIFIC CHLAMYDIAL TESTS

- The complement fixation test is the most commonly used test. Titers greater than 1:256 are highly suggestive of LGV and titers below 1:32 exclude the diagnosis unless the disease is in its early stages.
- The microimmunofluorescence test for the L-type serovaris more sensitive & specific but less readily available.

- In addition, culture studies may be performed; however, they do not distinguish between LGV and non-LGV serovars, are tedious, and require special growth media. Nevertheless, a positive culture without centrifugation is highly suggestive of LGV.
- In addition, direct fluorescence microscopy using conjugated monoclonal antibody against C. trachomatis on smears from bubo material or genital swab can be done.
- Serology assays are sensitive but nonspecific due to cross reactivity with other chlamydial infections.
- Frei test, the earliest diagnostic modality to identify LGV, consists of an intradermal skin test assessing delayed hypersensitivity to chlamydial antigens. It is no longer used because of it slow sensitivity and limited specificity due to cross-reaction with C. trachomatis D-K.
- Finally, other non-specific laboratory findings include mild leukocytosis, false-positive VDRL, cryoprecipitates, rheumatoid factor, and high serum levels of immunoglobulin A and immunoglobulin G.

DIAGNOSTIC PROCEDURES

- Bubo aspiration to obtain material for culture and direct microscopy should be performed through a lateral approach, and may require injection of 2–5 mL of sterile saline before the aspiration due to the paucity of milky fluid.
- Proctoscopic examination reveals, in the setting of the ArS, multiple discrete and irregular superficial ulcerations and friable granulation tissue, usually confined to the distal 10 cm of the anorectal canal.

DIFFERENTIAL DIAGNOSIS

- In contrast to LGV primary stage, chancroid ulcers are usually larger and more painful, and granuloma inguinale ulcers have abundant friable granulation tissue without associated lymphadenitis.
- Acute GS may be hard to differentiate from chancroid.
- Buboes containing little or no pus are, however, more likely to be caused by LGV.
- Suspecting LGV proctitis in HIV positive MSM who present with signs and symptoms of Crohn's disease is important, even in the absence of LGV pathognomonic findings. Both conditions have similar proctoscopic findings; however, Crohn's disease is more proximally localized.
- Primary stage:
    - ❖ Ulcerogenital diseases (herpes simplex virus, chancre, chancroid, granuloma inguinale)
    - ❖ Neisseria gonorrhoeae and/or common chlamydial urogenital infection

- ❖ Noninfectious causes: trauma, Zoon balanitis, fixed drug eruption

- Secondary stage:
  - ❖ Acute genital syndrome
    - o Ulcerogenital diseases with lymphadenopathy (syphilis, chancroid, herpes simplex virus)
    - o Incarcerated inguinal hernia
    - o Reactive inguinal lymphadenitis to a lower extremity focus of infection
    - o Bubonic plague (in endemic areas)
    - o Acquired immunodeficiency syndrome
    - o Kaposi sarcoma
    - o Tularemia
    - o Mycobacterial infections
  - ❖ Acute anorectal syndrome: Inflammatory bowel disease
  - ❖ Oropharyngeal lymphogranuloma venereum
    - o Lymphoma
    - o Infectious mononucleosis
    - o Cat-scratch disease
- Tertiary stage
  - ❖ Malignancy
  - ❖ Filariasis and other parasitic infections
  - ❖ Pseudoelephantiasis (no lymphadenitis) of tuberculosis and granuloma inguinale
  - ❖ Deep fungal infection
  - ❖ Hidradenitis suppurativa
  - ❖ Trauma

COMPLICATIONS

- In addition to the complications seen in the tertiary stage, the ulcerative nature of LGV may facilitate the acquisition and transmission of blood-borne pathogens such as HIV and hepatitis C.
- LGV may also lead to immune disturbances ranging from mild gammaglobulinemia to rare but fatal immunoblastic lymphoma.
- Recently several case reports have described an association between LGV and sexually acquired reactive arthritis(SARA) in HLA-B27 positive individuals.

TREATMENT

- Oral doxycycline, 100 mg twice daily for 3 weeks, is the treatment of choice. When contraindicated, oral erythromycin base, at a dose of 500 mg four times a day for3 weeks, may be given. Treatment with azithromycin (1 g once weekly for 3 weeks or in a single dose) is likely curative but still lacks data regarding its efficacy and safety in pregnancy.
- It should be noted that the duration of treatment needed to eradicate C. trachomatis is longer for the LGV serovars compared with the other less invasive serovars of C. trachomatis. Therefore, when in doubt about the Chlamydia serovar, a 3-week course of antibiotics is advised.
- Therapy maybe prolonged in HIV-positive patients and, in general, should not be stopped until the complete resolution of all signs and symptoms.
- Surgery is often required in late stages and includes lateral aspiration of buboes through intact skin (direct incision has a high risk of fistula formation), rectal stricture dilatation, abscess drainage, rectovaginal fistula repair, genital reconstruction, and colostomy.
- Avoidance of sexual activity until complete resolution of signs and symptoms is important

First line	Oral doxycycline	100 mg bid	3 weeks
Second line	Oral erythromycin	500 mg qid	3 weeks
Third line	Oral azithromycin	1 g once weekly	3 weeks

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