

European guideline for the management of lymphogranuloma venereum, 2010

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Keywords: LGV, *Chlamydia trachomatis*, guideline, proctitis, antimicrobials, bowel disease

Lymphogranuloma venereum (LGV) has re-emerged among European men who have sex with men (MSM) in recent years¹ and is probably endemic in this population where it is a relatively common cause of proctitis and occasional genital ulcer-adenopathy disease. While occasional cases of heterosexual LGV are seen in Europe these have usually been imported from endemic countries.

AETIOLOGY AND TRANSMISSION

- Causative pathogen: *Chlamydia trachomatis* types L1, L2 and L3. Additional variants have been described such as L2b, the strain currently found in MSM. In contrast to serovars A-K which remain confined to the mucosa, serovar L strains are invasive organisms that disseminate via underlying connective tissue and spread to regional lymph nodes;
- Worldwide, LGV is thought to account for 2–10% of genitoulcerative disease in areas such as India and Africa. In Western regions LGV is endemic among MSM, mainly those co-infected with HIV.^{2,3} Heterosexual transmission has been described recently in Spain⁴ and Portugal;⁵
- Neither the degree of infectiousness nor the reservoir of disease has been accurately defined, but heterosexual transmission has been attributed largely to asymptomatic female carriers and in the MSM population, asymptomatic or unrecognized rectal infection is the likely source of onward transmission.³

CLINICAL FEATURES

The disease course usually follows three separate stages.

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(1) Primary stage

- Incubation period – one to four weeks;¹⁰
- In the current LGV epidemic among MSM, proctitis is the primary manifestation of infection, usually presenting within a few weeks of sexual contact. It is characterized by severe symptoms of anorectal pain, haemopurulent discharge and bleeding *per rectum*; tenesmus and constipation are also seen due to the mucosal and perirectal oedema. Proctoscopic examination may reveal a distal granular or haemorrhagic proctitis with purulent exudate and mucosal ulceration. LGV proctitis is not usually accompanied by inguinofemoral lymphadenopathy; however, radiological imaging may demonstrate pelvic node involvement;⁶
- In the present LGV epidemic among MSM, symptomatology has varied in different populations, with UK cohorts showing almost all LGV to be symptomatic,⁷ in contrast to Dutch studies where a significant proportion of asymptomatic infection has been detected;^{8,9}
- LGV proctitis mimics chronic inflammatory bowel diseases like Crohn's disease, both clinically and histopathologically;¹⁰
- A primary lesion may be evident – a small painless papule or pustule; this can erode to form a small herpetiform ulcer. It usually heals within one week and often remains unnoticed. Mucopurulent discharge may be present, affecting the urethra, the cervix or the rectum depending on the inoculation site;

(2) Second stage or 'inguinal stage' – begins two to six weeks after onset of primary lesion. Causes painful inflammation of the inguinal and/or femoral lymph nodes. Typically this produces unilateral enlargement, inflammation, suppuration and abscesses. These 'buboes' may become fluctuant and rupture in one-third of patients. Some patients develop the 'groove sign', which results from enlargement of the inguinal nodes above and the femoral nodes below Poupart's ligament;

- Inguino-femoral lymphadenopathy is mainly seen when the inoculation site is located on the external genitalia, which is the case in many male patients. In contrast,

women more often have primary involvement of the rectum, upper vagina, cervix or urethra; as these regions drain to the deep iliac or perirectal nodes, inguinofemoral lymphadenopathy is not seen. The resultant intra-abdominal or retroperitoneal lymphadenopathy may lead to symptoms of lower abdominal pain or low back pain;

- Constitutional symptoms, such as low-grade fever, chills, malaise, myalgias and arthralgias, may present during the second stage of disease. In addition, systemic spread of *C. trachomatis* occasionally results in arthritis, pneumonitis or (peri) hepatitis. Rare systemic complications include cardiac involvement, aseptic meningitis and ocular inflammatory disease;
 - A rare presentation is the pharyngeal syndrome affecting the mouth and throat. Cervical lymphadenopathy and buboes can occur;¹¹
- (3) Third stage, often called the 'anogenitoretal syndrome'. It is more often present in women. Patients initially develop proctocolitis followed by peri-rectal abscess, fistulas, strictures and stenosis of the rectum, possibly leading to 'lymphorrhoids' (haemorrhoid-like swellings of obstructed rectal lymphatic tissue). Without treatment, chronic progressive lymphangitis leads to chronic oedema and sclerosing fibrosis, resulting in strictures and fistulas of the involved region, which can ultimately lead to elephantiasis, esthiomene (the chronic ulcerative disease of the external female genitalia) and the frozen pelvis syndrome. If left untreated, LGV proctitis can lead to rectal stricture, with subsequent sequelae of soiling, pain, constipation and the possible development of mega colon.¹²

DIAGNOSIS

The diagnosis of LGV is confirmed by the detection of biovar-specific *C. trachomatis* DNA in: (1) ulcer material from primary anogenital lesions; (2) rectal specimens (in suspected cases of anorectal LGV) – anorectal swabs are preferably collected from the mucosal lining under proctoscopic vision, alternatively a blind anorectal swab can suffice; or (3) bubo aspirates (in suspected cases of inguinal LGV) – historically, LGV has been difficult to isolate from bubo aspirates in culture studies (see Appendix B: IV, C). Modern diagnostic approaches have been reviewed recently⁹ and most modern laboratories follow a two-step procedure:

- First, a commercially available *C. trachomatis* nucleic acid amplification test (NAAT) can be used to screen suspected samples. Although commercially available tests are not approved for extragenital sites, a large body of literature supports the use of these tests for the detection of rectal chlamydial infections^{9,13–15} (see Appendix B: III, B);
- If *C. trachomatis* is detected, LGV biovar-specific DNA then needs to be detected from the same specimen. For this purpose, two 'in house' NAATs have been reported; firstly, a real-time PCR-based test that specifically detects all *C. trachomatis* LGV biovar strains¹⁶ and, more recently, a real-time quadriplex PCR-based assay, which incorporates both LGV-specific and non-LGV-specific target sequences, a *C. trachomatis* plasmid target and the human RNase P gene as an internal control¹⁷ (see Appendix B: III, B).

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 titre (esp. IgA anti-major outer membrane protein [MOMP] antibodies) in a patient with a clinical syndrome suggestive of LGV supports the diagnosis.^{18,19} Nonetheless, a low titre does not exclude LGV, nor does a high titre in a patient without LGV symptomatology confirm LGV infection^{8,9} (see Appendix B: III, B).

MANAGEMENT

As the rectum is the most common site for the detection of *C. trachomatis* in MSM²⁰ and represents a potential reservoir of infection, it is recommended to screen all MSM who report receptive anal sexual practices in the previous six months for anorectal *C. trachomatis* infection (see Appendix B: III, B). Subsequently, MSM who are anorectal *C. trachomatis* positive are then tested for LGV infection according to local guidelines⁹ (see Appendix B: IIa)

INFORMATION, EXPLANATION AND ADVICE FOR THE PATIENT

Patients should be informed that LGV is an invasive bacterial infection that is sexually transmitted but curable with antibiotics. Left untreated it can have serious and permanent adverse sequelae. Most of these complications are preventable if treatment is initiated in the early stages (see Appendix B: IV, C). Patient information leaflets focused on the LGV epidemic among MSM are available and provided by several national organizations, such as the Terrence Higgins Trust (UK; www.tht.org.uk) and Schorer stichting (NL; www.schorer.nl);

- Symptoms should resolve within one to two weeks of commencing antibiotic therapy (see Appendix B: III, B);
- Patients should abstain from any sexual contact until they have completed the therapy (see Appendix B: IV, C);
- Screening for other sexually transmitted infections (STIs) including HIV and hepatitis C (see below under 'Follow up') should be offered prior to the commencement of therapy (see Appendix B: IV, C).

THERAPY

Despite a paucity of robust evidence²¹ regarding the efficacy of therapy for any rectal chlamydial infections (LGV or non-LGV), current guidelines recommend three weeks of oral doxycycline 100 mg twice daily to treat LGV^{22–24} and the vast majority of recent MSM case reports have observed complete responses to this therapy; shorter courses may not eradicate the organism.²⁵

- First line – doxycycline 100 mg twice a day orally for 21 days (see Appendix B: IIb, B);
- Second line – erythromycin 500 mg four times a day orally for 21 days (see Appendix B: III, B).

Azithromycin in single- or multiple-dose regimens has also been proposed,^{26,27} but evidence is lacking to recommend this drug currently (see Appendix B: IV, C).

ADJUNCTIVE THERAPY

- If fluctuant buboes appear they should be aspirated promptly through healthy adjacent skin (see Appendix B: IV, C);
- Surgical incision of buboes is not usually recommended due to potential complications such as chronic sinus formation (see Appendix B: IV, C);
- Patients with residual fibrotic lesions or fistulae do not benefit from further courses of antibiotics so surgical repair, including reconstructive genital surgery, should be considered (see Appendix B: IV, C).

PARTNER NOTIFICATION

As LGV is sexually transmitted, it is essential that partner notification is initiated when the diagnosis is made. Sexual contacts within the last four weeks from the onset of symptoms, or the last three months if asymptomatic LGV is detected, should be offered testing for chlamydia/LGV and empiric treatment with antibiotic therapy until chlamydia/LGV has been excluded in the partner (see Appendix B: IV, C).

FOLLOW UP

All patients diagnosed with LGV should be followed up at the end of treatment:

- To ensure resolution of symptoms and signs of infection (see Appendix B: IV, C);
- To check that adequate partner notification has been completed (see Appendix B: IV, C);
- To address any patient concerns (see Appendix B: IV, C);
- To arrange suitable follow-up testing for syphilis and blood-borne viruses including hepatitis B, C and HIV (see Appendix B: IV, C);
- A test of cure for LGV is not considered necessary if the recommended 21-day course of doxycycline has been completed²⁵ (see Appendix B: III, B).

In the recent MSM LGV epidemic incident cases of both HIV and hepatitis C²² have been observed and serological testing should be offered for both infections after appropriate window periods have elapsed according to relevant local guidelines.

PREVENTION/HEALTH PROMOTION

Patients diagnosed with LGV should be counselled regarding prevention of other STIs including HIV and hepatitis C:

- Offer regular sexual health screening including HIV testing;
- Condom use should be demonstrated and promoted;
- Offer hepatitis A and B vaccination for MSM;
- Patients at risk of HIV infection should be advised of the availability of postexposure prophylaxis for HIV;
- In particular, HIV-positive MSM should be made aware of recent trends in hepatitis C epidemiology and warned of the risks of unprotected anal sex, serosorting, recreational drug use and mucosally traumatic sexual practices such as fisting. Enema use may be implicated in LGV transmission.²

The association of enema use and LGV has not been elucidated yet, but it is prudent to warn the patient of any possible risks.

AUDITABLE OUTCOME MEASURES (TARGET 100% FOR ALL)

- All cases of suspected LGV should be subjected to laboratory investigations;
- Sexual contacts within three months should be traced, tested and treated;
- HIV, syphilis and hepatitis C serological testing should be offered, as well as screening for concomitant STIs;
- Suspected or confirmed cases of LGV should be reported and relevant surveillance data collected according to local and national guidelines.

ACKNOWLEDGEMENT

IUSTI/WHO European STD guidelines Editorial Board: Keith Radcliffe – Editor-in-Chief, Karen Babayan, Simon Barton, Michel Janier, Jorgen Skov Jensen, Lali Khotenashvili, Marita van de Laar, Willem van der Meijden, Harald Moi, Martino Neumann, Raj Patel, Angela Robinson, Jonathan Ross, Jackie Sherrard, Magnus Unemo. We thank Catherine Ison for an expert review of the manuscript.

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(Accepted 5 July 2010)

APPENDIX A

Search strategy

The previous European IUSTI guideline titled 'European Guideline for the Management of Tropical Genito-ulcerative

diseases' from October 2001 was used as a basis for the current guideline. MEDLINE and PubMed searches were performed from 2000 to December 2009 using MeSH headings 'lymphogranuloma venereum' including all documents and subheadings. Additional searches were conducted using MeSH headings 'LGV' and '*Chlamydia trachomatis*'.

APPENDIX B

Levels of evidence and grading of recommendations

Levels of evidence

- Ia Evidence obtained from meta-analysis of randomized controlled trials;
- Ib Evidence obtained from at least one randomized controlled trial;
- IIa Evidence obtained from at least one well-designed study without randomization;
- IIb Evidence obtained from at least one other type of well-designed quasi-experimental study;
- III Evidence obtained from well-designed non-experimental descriptive studies such as comparative studies, correlation studies and case-control studies;
- IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grading of recommendations

- A (Evidence levels Ia, Ib): Requires at least one randomized control trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
- B (Evidence levels IIa, IIb, III): Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation.
- C (Evidence IV): Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.