

2013 European Guideline on the Management of Lymphogranuloma Venereum

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WHAT IS NEW IN THIS UPDATED GUIDELINE?

Epidemiology:

- Based on clonal relatedness of prevalent LGV strains there is evidence that the LGV epidemic among MSM in the Western world prevailed already in the United States in the 1980s and was introduced into Europe by the end of the last century.

Aetiology and transmission

- A new LGV variant causing severe proctitis was unveiled and designated L2c.
- The L2b LGV variant causing the vast majority of infections among MSM is now also found among a few heterosexual women.

Management:

- Apart from HIV and STI screening, HCV testing should be offered to all LGV patients.
- To exclude reinfections, STI screening during a follow up visit 3 months after an LGV diagnosis should be offered.

LYMPHOGRANULOMA VENEREUM (LGV)

Epidemiology

LGV has re-emerged among European men who have sex with men (MSM) in the past decade [1] and is probably endemic in this population where it is a relatively common cause of proctitis and occasional genital ulcer-adenopathy disease. LGV among MSM in Europe is caused in the majority of cases by the *C. trachomatis* biovar L2b which shows a high degree of clonal relatedness as found by Multi Locus Sequence Typing (MLST) in a molecular epidemiological study. [2] This is in contrast to the strains circulating among MSM in the United States, which show more molecular diversity. Based on these findings it is now speculated that the LGV epidemic among MSM in Europe caused by the L2b variant may have been imported to Europe from the United States by the end of the previous century via the highly internationalized network of sexual contacts among MSM. Whilst 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. A new LGV variant originating from a recombination of L2 and D *C. trachomatis* lineages has been reported but the extent of transmission of this hybrid organism within the community needs further investigation. [3] 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 to 10% of GUD in areas such as India and Africa. In Western regions LGV is endemic among MSM, mainly those co-infected with HIV. [Heterosexual transmission of the LGV associated L2b strain has been described. [5, 6]
- 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 rectal infection and/or penile infection is the likely source of onward transmission.[7]

Clinical features

Depending on the site of inoculation LGV can cause inguinal disease (usually after inoculation of the genitalia), or the anorectal syndrome (usually after inoculation via the rectum). The disease course usually follows three separate stages.

- Incubation period - one to four weeks
- 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 characterised 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,

mucosal ulceration and tumorous masses. LGV proctitis is not usually accompanied by inguinofemoral lymphadenopathy; however radiological imaging may demonstrate pelvic node involvement.[8]

- In the present LGV epidemic among MSM, symptomatology has varied in different populations, with UK cohorts showing almost all LGV to be symptomatic[9], in contrast to Dutch studies where a significant proportion of asymptomatic infection has been detected.[10, 11]
- LGV proctitis mimics chronic inflammatory bowel diseases like Crohn's disease, both clinically and in the pathological substrate.
- Primary Lesion - small painless papule or pustule; may erode to form a small herpetiform ulcer. 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.
- Second stage: "inguinal stage" - begins 2 to 6 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 posterior 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.[14]
- The third stage of disease in LGV is often called the "anogenitoretal syndrome" and 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.[15]

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 inguinal LGV); historically LGV has been difficult to isolate from bubo aspirates in culture studies. (IV, C). Modern diagnostic approaches have been reviewed recently [11].
- Most modern laboratories follow a 2-step procedure:
 - First, a commercially available *C. trachomatis* NAAT test 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.[11, 16-18] (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” NAAT tests have been reported; firstly, a real-time PCR-based test that specifically detects all *C. trachomatis* LGV biovar strains[19] 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 control[20]. (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-MOMP antibodies) in a patient with a clinical syndrome suggestive of LGV supports the diagnosis.[21, 22] Nonetheless, a low titre does not exclude LGV, nor does a high titre in a patient without LGV symptomatology confirm LGV infection.[10,11] (III, B)The identification of rectal polymorphonuclear leucocytes (PMNLs) from rectal swabs is predictive of LGV proctitis, especially in HIV-positive MSM, with levels of >10 [11].

Management

- It is recommended to screen all MSM who report receptive anal sexual practices in the previous 6 months for anorectal *C. trachomatis* infection. Subsequently, MSM who are anorectal *C. trachomatis* positive are then screened for LGV proctitis according to local guidelines.[11] (IIa)
- The prevalence of HIV among LGV cases ranges from 67% to 100% in 13 descriptive studies. There is a significant association between HIV and LGV (odds ratio 8.19, 95% CI 4.68-14.33). (4). (I, A)

- Tests for STI, including HIV (if not already known HIV-pos), hepatitis B and hepatitis C should be offered before starting therapy. (III, C) [23]

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. (IV, C) Patient information leaflets focussed on the LGV epidemic among MSM are available from IUSTI (http://www.iusti.org/regions/europe/pdf/2010/PIL_LGV.pdf) and provided by several national organisations like the Terrence Higgins Fund (UK), and Schorer stichting (NL).
- Symptoms should resolve within 1-2 weeks of commencing antibiotic therapy. (III, B)
- Patients should abstain from any sexual contact until they have completed therapy. (IV, C)
- Screening for syphilis, *C. trachomatis*, *N. gonorrhoeae*, HIV, hepatitis B, and hepatitis C should be offered during a follow-up visit 3 months after an LGV diagnosis to exclude reinfections (IV, C) [23]

Therapy

Despite a paucity of robust evidence[24] regarding the efficacy of therapy for any rectal chlamydial infections (LGV or non-LGV), three weeks of oral doxycycline 100mg twice daily to treat LGV is recommended [25-27]. The vast majority of recent MSM case reports have observed complete responses to this therapy; shorter courses may not eradicate the organism[28].

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

*Azithromycin in single- or multiple-dose regimens has also been proposed[23,29,30] but evidence is lacking to recommend this drug currently. (IV, C) Doxycycline is contraindicated in pregnancy and breastfeeding.

Adjunctive therapy

- If fluctuant buboes appear they should be aspirated promptly through healthy adjacent skin. (IV, C)
- Surgical incision of buboes is not usually recommended due to potential complications such as chronic sinus formation. (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. (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 3 months should be offered testing for Chlamydia/LGV and empiric treatment with antibiotic therapy commenced until Chlamydia/LGV has been excluded in the partner. (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 (IV, C)
- to check that adequate partner notification has been completed (IV, C)
- to address any patient concerns (IV, C)
- to arrange suitable follow-up testing for syphilis and blood-borne viruses including hepatitis B, C and HIV (IV, C)*
- Although one case of doxycycline failure in LGV has been reported [31], a test of cure for LGV is not considered necessary if the recommended 21 day course of doxycycline is completed.[25] (III, B)

*In the recent MSM LGV epidemic incident cases of both HIV and hepatitis C [28] 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 post exposure 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 [32]. Although sharing of equipment was rare, it is prudent to advise against sharing any such equipment and to wash equipment thoroughly after use.

Auditable Outcome Measures (target 95% for all)

- All cases of suspected LGV should be subjected to laboratory investigations.
- All patients should be interviewed for the purpose of partner notification and this should be documented in the case notes. Sexual contacts within at least 3 months should be traced, tested and treated.
- HIV, syphilis, hepatitis B and hepatitis C serological testing as well as screening for concomitant other STIs, should be offered before starting therapy and after three months.
- Suspected or confirmed cases of LGV should be reported and relevant surveillance data collected according to local and national guidelines.

Proposed date of revision May 2015**European STI Guidelines Editorial Board**

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List of contributing organisations

This guideline has been produced on behalf of the following organisations: the European Branch of the International Union against Sexually Transmitted Infections (IUSTI Europe); the European Academy of Dermatology and Venereology (EADV); the European Dermatology Forum (EDF); the European Society of Clinical Microbiology and Infectious Diseases (ESCMID); the Union of

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APPENDICES

Search strategy:

MEDLINE and PubMed searches were performed from 2000 to December 2012 using Domain: HIV, MSM, homosexuals, men who have sex with men, Determinants: CT serovar L1-L3, CT infection* L1-L3, Chlamydia L1-L3, Chlamydia L1-L3, LGV, lymphogranuloma venereum, Chlamydia trachomatis genovar L1-L3, Chlamydia trachomatis biovar L1-L3, Chlamydia trachomatis serovar L1-L3 Outcome: Anal infection, LGV, lymphogranuloma venereum

Levels of Evidence

Ia Evidence obtained from meta-analysis of randomised controlled trials.

Ib Evidence obtained from at least one randomised controlled trial.

Ila Evidence obtained from at least one well designed study without randomisation.

Ilb 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 randomised control trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Evidence levels Ila, Ilb, III)

Requires availability of well conducted clinical studies but no randomised 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.

Declarations of Interest

Henry JC de Vries – none to declare

Alexander Kreuter – none to declare

Adele Zingoni - none to declare

John A White – none to declare

Harald Moi – none to declare