PART 2G

Lymphogranuloma venereum

A Herring, J Richens

Sex Transm Infect 2006;**82**(Suppl IV):iv23–iv25. doi: 10.1136/sti.2006.023143

Lymphogranuloma venereum (LGV) is caused by the invasive L1, L2, and L3 serovars of *Chlamydia trachomatis*. In contrast with serovars A-C that cause ocular infections and the more common D-K serovars of *C trachomatis* associated with genital infections, the L1-3 strains cause considerable disturbance in the local lymph nodes creating the characteristic clinical picture of painful swelling in the inguinal lymph glands. Recent whole genome sequence comparisons of oculo-genital and LGV strains have thus far failed to identify novel virulence factors that would account for the pathology of LGV.

Classic LGV

Historically patients were unlikely to acquire the disease in the United Kingdom and most cases were diagnosed in those who had travelled to Asia, Africa, South America, or the Caribbean. Clinical LGV infection has three stages. The first stage arises at the site of inoculation and is usually a small ulcer somewhere on the external genitalia. This stage is transient and frequently passes unnoticed. If rectal transmission occurs, the first manifestation may be an acute proctitis, and this has been the most common presenting symptom of recent cases in the United Kingdom. Classically most patients present at the second stage, when the regional lymph nodes involved become firm, swollen, and painful, although this has been uncommon in UK acquired infections. Fever and malaise commonly accompany local symptoms. The primary ulcerative lesions often resolve before or during this stage but proctitis is likely to persist. Late stage disease results from lymphatic damage during the second stage and is characterised by lymphoedema and sometimes secondary ulceration. Scarring, strictures and fistulae involving the inguinal glands, genitalia, anus, and rectum may develop. Diseases most readily confused with LGV are chancroid, donovanosis, tuberculosis, cat scratch disease, plague, lymphoma, irritable bowel syndrome, and Crohn's disease.

Recent LGV in the United Kingdom

Most recent UK cases differ significantly from the classic presentation above:

- Following initial outbreaks in western Europe,[1–6] LGV infections that have been acquired in the United Kingdom have now been identified[7–9] and acquisition from abroad is unusual.
- Acute proctitis is the key presenting complaint, with constipation, tenesmus, and rectal discharge.
- Lymphadenopathy is rare.

Widespread screening is currently not recommended; the need to test for LGV will arise in the following patients:

- Patients presenting with an acute proctitis who have been at high risk
- Patients presenting with inguinal buboes (inflammatory lymph node swellings in the inguinal-femoral lymph gland group) and a suggestive travel history
- Patients with manifestations of late stage disease
- Sexual contacts of confirmed cases of LGV infection.

RECOMMENDED TESTS

The laboratory diagnosis is dependent on the detection of *C trachomatis* specific DNA followed by genotyping to identify serovars L1, L2, or L3.

- The method of choice for the laboratory diagnosis of LGV is the detection of *C trachomatis* specific DNA belonging to an LGV serovar, L1, L2, or L3.
- The first step is the detection of *C trachomatis* using a nucleic acid amplification test (NAAT). Routinely available NAATs for *C trachomatis* will detect all serovars including LGV serovars and are licensed for genital specimens. However, rectal specimens need to be tested in most patients recently identified. There are no licensed NAATs for the detection of *C trachomatis* in rectal specimens but data are available supporting the validity of these tests for use with rectal specimens (evidence level III, recommendation grade B).
- Confirmation of the presence of LGV specific DNA can then be obtained by direct detection of LGV specific DNA using real time polymerase chain reaction (PCR).[10] Alternatively genotyping can be performed by amplifying the *omp*1 gene followed by restriction endonuclease digestion to identify specific serovars.[11] An additional restriction fragment length polymorphism (RFLP) method is based on the digest of the CrP gene, which differentiates between L1-3.[12] (evidence level III, recommendation grade B).
- The Health Protection Agency has published an algorithm for the detection of LGV, which recommends that any NAAT positive for *C trachomatis* from men who have sex with men presenting with proctitis should be sent to the sexually transmitted bacteria reference laboratory (STBRL) for confirmation. At STBRL, the *C trachomatis* status of the specimen will be confirmed using an ''in-house'' real time PCR with independent primers specific to all known *C trachomatis* strains. Specimens positive for *C trachomatis* will be screened using RT-PCR to detect LGV serovars directly including L1, L2, and L3.[10] Any LGV positive samples will be genotyped to determine the LGV serovar[11] (evidence level III, recommendation grade B).
- Typing for epidemiological purposes using DNA sequencing of the *omp1* gene should only be performed at a reference laboratory.
- Culture is the most specific test but very few laboratories have culture facilities and sensitivity can be prejudiced by

Abbreviations: CF, complement fixation; LGV, lymphogranuloma venereum; MIF, microimmunofluorescence; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; STBRL, sexually transmitted bacteria reference laboratory

the toxic nature of bubo aspirates[13] (evidence level IV, recommendation grade C).

- Serology may be useful if direct detection has been unsuccessful. A high titre in a patient with symptoms is highly suggestive of LGV. However, a low titre cannot exclude LGV and a high titre in the absence of symptoms cannot confirm LGV. The two methods most used have been complement fixation (CF) and microimmunofluorescence-IgG (MIF); single point titres more than or equal to 1/64[14] (evidence level IV, recommendation grade C) and 1/256,[15] respectively, are considered positive. The whole inclusion fluorescence test[16] has also been used.[17] Where MIF is used, it is important that a L serovar is included as an antigen.
- There are now many commercial immunoassays on the market for *C trachomatis* serology but their use for LGV diagnosis has not been reported. Many of these kits use undisclosed peptide antigens that may not include LGV serovar sequences and thus are not recommended.

RECOMMENDED SITES FOR TESTING

- Ulcer material (if ulcer is present)
- Lymph node aspirate (may require injection and re-aspiration of saline)
- Lymph node biopsy (if investigation by other means is unsuccessful)
- Rectal swabs (if proctitis is present)
- Urine
- Urethral swab
- Rectal biopsy tissue
- Clotted blood (for serology).

FACTORS THAT ALTER TESTS RECOMMENDED OR SITES TESTED

Sites for testing will be determined by the clinical presentation. Clinicians should consult with their microbiology laboratory colleagues to alert them regarding unusual specimens and to inform them that specialist tests will be required.

Sexual history

- Travel to, and sexual exposure in, an LGV endemic country by the index patient or his/her partner (no alteration to standard recommendation).

Risk groups

- MSM with high risk behaviour, in particular attendance at sex parties, anonymous sex, fisting, and use of enemas (no alteration to standard recommendation).
- Patients who are known contacts of the infection (no alteration to standard recommendation)

RECOMMENDATION FOR FREQUENCY OF REPEAT TESTING IN AN ASYMPTOMATIC PATIENT

DNA amplification tests

Repeat testing 4 weeks after exposure only in individuals with known or strongly suspected exposure to LGV if the initial test has been done within 3 weeks of exposure and epidemiological treatment has been declined.

Serology

Repeat testing is only required if symptoms suggestive of LGV develop following the initial test.

RECOMMENDATION FOR TEST OF CURE AND FOLLOW UP

Test of cure is necessary and should be provided 3–5 weeks after treatment. For those very few patients who may have extensive lesions or fistulas as a result of late treatment, surgical intervention may be required.

STAKEHOLDER INVOLVEMENT

The rare nature of this disease precluded patient consultation.

RIGOUR OF DEVELOPMENT

The main evidence for the development of this guideline was obtained by searching Medline using the term ''lymphogranuloma venereum''. The Cochrane Library was also searched (no records). In addition, standard textbooks were consulted as was the 2002 CDC STI treatment guidelines.

APPLICABILITY

This guideline recommends the use of DNA amplification tests that may not be available in all microbiology laboratories.

The identification of LGV strain infection by *omp-1* sequence analysis will incur additional costs for primers and sequencing reactions. It will also need to be performed by a clinical/biomedical scientist skilled in PCR and Amplicon purification.

The serological tests recommended are available only in a limited number of laboratories.

AUDITABLE OUTCOME MEASURES

All cases of LGV should be subjected to clinicopathological review and reported to the Health Protection Agency. Target 100%, subject to annual audit.

Authors' affiliations

A Herring, formerly head of the PHLS Genitourinary Infections Reference Laboratory, Bristol, UK
J Richens, Centre for Sexual Health and HIV Research, The Mortimer Market Centre, Mortimer Market, off Capper Street, London, UK

Conflict of interest: none.

The authors wish to thank Professor David Mabey of the London School of Tropical Medicine and Hygiene for his comments on this guideline.

Correspondence to: J Richens, Centre for Sexual Health and HIV Research, The Mortimer Market Centre, London WC1E 6AU, UK; jrichens@gum.ucl.ac.uk

Accepted for publication 31 August 2006

REFERENCES

1 **Van de Laar MJ**, Gotz H, de Zwart O, *et al*. Lymphogranuloma venereum among men who have sex with men—Netherlands, 2003–2004. *MMWR Morb Mortal Wkly Rep* 2004;**53**:985–8 (www.cdc.gov/mmwr/preview/mmwrhtml/mm5342a2.htm).
2 **Vandenbruaene M**. Uitbraak van lymphogranuloma venereum in Antwerpen en Rotterdam. *Epidemiologisch Bulletin van de Vlaamse Gemeenschap* 2004;**47**:4–6 (www.wvc.vlaanderen.be/epibul/47/lymphogranuloma.htm).
3 **Herida M**, Sednaoui P, Couturier E, *et al*. Rectal lymphogranuloma venereum, France [letter]. *Emerg Infect Dis* [serial on the internet]. February 2005 (www.cdc.gov/ncidod/EID/vol11no03/04-0621.htm).
4 **Berglund T**, Herrmann B. Utbrott av Lymfogranuloma venereum (LGV) i Europa. *EPI-aktuellt* 2004;**3**:17/06/2004. http://www.smittskyddsinstitutet.se/SMItemplates/BigArticle____3942.aspx#LGV.
5 **Robert Koch-Institut**. Zum gehäuften Auftreten von Lymphogranuloma venereum in Hamburg im Jahr 2003. *Epidemiologisches Bulletin* 2004;**25**:18/06/2004 (www.rki.de/INFEKT/EPIBULL/2004/25_04.PDF).
6 **Mayans MV**, Colomo BS, Ossewaarde J M. First case of LGV confirmed in Barcelona. *Eurosurveillance Weekly* 2005;**10**(5):03/02/2005.
7 **Simms I**, Macdonald N, Ison C, *et al*. Enhanced surveillance of LGV starts in England. *Eurosurveillance Weekly* 2004;**8**:07/10/2004 (www.eurosurveillance.org/ew/2004/041007.asp).

8 **Macdonald N**, Ison C, Martin I, *et al*. Initial results of enhanced surveillance for lymphogranuloma venereum in England. *Eurosurveillance Weekly* 2005;**10**:27/01/2005 (www.eurosurveillance.org/ew/2005/050127.asp#5).
9 **McMillan A**. Lymphogranuloma venereum proctitis in Edinburgh. *HPS Weekly Report* 2005;**39**:16/02/2005 (www.show.scot.nhs.uk/scieh/PDF/pdf2005/0506.pdf).
10 **Morre S**, Spaargaren J, Fennema JS, *et al*. Molecular diagnosis of lymphogranuloma venereum: PCR-based restriction fragment length polymorphism and real-time PCR. *J Clin Microbiol* 2005;**43**:5412–3.
11 **Lan J**, Walboomers JM, Roosendaal R, *et al*. Direct detection and genotyping of Chlamydia trachomatis in cervical scrapes by using polymerase chain reaction and restriction fragment length polymorphism analysis. *J Clin Microbiol* 1993;**31**:1060–5.
12 **Sturm PD**, Moodley P, Govender K, *et al*. Molecular diagnosis of lymphogranuloma venereum in patients with genital ulcer disease. *J Clin Microbiol* 2005;**43**:2973–5.
13 **Van Dyck E**, Piot P. Laboratory techniques in the investigation of chancroid, lymphogranuloma venereum and donovanosis. *Genitourin Med* 1992;**68**:130–3.
14 **Workowski KA**, Levine WC. Sexually transmitted diseases treatment guidelines—2002. *MMWR* 2002;**51**:1–80.
15 **Bauwens JE**, Orlander H, Gomez MP, *et al*. Epidemic lymphogranuloma venereum during epidemics of crack cocaine use and HIV infection in the Bahamas. *Sex Transm Dis* 2002;**29**:253–9.
16 **Richmond SJ**, Caul EO. Fluorescent antibody studies in chlamydial infections. *J Clin Microbiol* 1975;**1**:345–52.
17 **Kellock DJ**, Barlow R, Suvarna SK, *et al*. Lymphogranuloma venereum: biopsy, serology, and molecular biology. *Genitourin Med* 1997;**73**:399–401.