2013 UK National Guideline for the management of lymphogranuloma venereum: Clinical Effectiveness Group of the British Association for Sexual Health and HIV (CEG/BASHH) Guideline development group

John White, Nigel O'Farrell and David Daniels

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What is This?

2013 UK National Guideline for the management of lymphogranuloma venereum

Clinical Effectiveness Group of the British Association for Sexual Health and HIV (CEG/BASHH)
Guideline development group

John White[1], Nigel O'Farrell[2] and David Daniels[3]

Date of writing: April 2012
Date review due: 2017

New information in this guideline since 2006 publication:

- Aetiology and epidemiology:
  - LGV is now hyperendemic among MSM in the UK; higher levels than in 2005
  - no evidence of significant heterosexual spread within the UK
  - cases continue to be mostly MSM, most of whom were also known to be HIV positive and many co-infected with other STIs, including HCV
- Diagnosis:
  - Commercial molecular diagnostic techniques to detect *C. trachomatis* remain the primary test of choice, with referral of *C. trachomatis*-positive specimens for molecular tests to confirm the presence of LGV-associated DNA
- Management:
  - First-line treatment remains doxycycline 100 mg BD for 3 weeks. Evidence for the role of other antibiotics remains scarce, but azithromycin in multiple-dose regimens may be preferable to erythromycin.

The main purpose of this guideline is to offer recommendations on the diagnosis, treatment and health promotion principles for the effective management of lymphogranuloma venereum (LGV) infection. It is aimed primarily to assist in the management of people aged 16 years and older presenting to services offering level 3 care in sexually transmitted infection (STI) management within the UK. However, the principles of the recommendations could be adopted at all levels.

Editorial independence

This guideline was commissioned and edited by the Clinical Effectiveness Group (CEG) of the British Association for Sexual Health and HIV (BASHH). No external funding was sought or obtained.

Rigour of development

This guideline was produced according to specifications set out in the CEG's 2010 document "Framework for guideline development and assessment."[1] The previous guideline was based on the published CDC Guidelines for Treatment of Sexually Transmitted Diseases supplemented by a Medline search to 2005. The 2013 guideline has updated the previous guideline by searching Medline from 2005 to 2012 for published articles in any language using the search terms: "Lymphogranuloma venereum"; "LGV"; "Chlamydia trachomatis diagnosis"; "Chlamydia trachomatis treatment" and "rectal Chlamydia." There were no entries in the Cochrane Library of any randomized clinical trials on lymphogranuloma venereum. In addition, abstracts and proceedings from the most recent International Conferences on AIDS, Meetings of the International Society for STD Research (ISSTDR) and BASHH Spring Meeting were reviewed

The draft guideline was appraised with the AGREE instrument, posted on the BASHH website for a

[1]Department of Genitourinary medicine, Guy's & St Thomas' NHS Foundation Trust, London, UK
[2]Ealing Hospital NHS Trust, London, UK
[3]West Middlesex Hospital NHS Trust, London, UK

Corresponding author:
Nigel O'Farrell, Ealing Hospital NHS Trust, Uxbridge Rd, London, UB13HW UK.
Email: nigel.o'farrell@nhs.net

NICE accredited
www.nice.org.uk/accreditation

NICE has accredited the process used by BASHH to produce its UK National Guideline for the management of lymphogranuloma venereum. Accreditation is valid for 5 years from 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation

consultation period of 3 months and piloted in a sample of clinics. In response to the consultation, suitable amendments were made to the guideline and the final draft was submitted to the CEG.

Aetiology and epidemiology

Lymphogranuloma venereum (LGV) is a sexually transmitted infection (STI) caused by one of three invasive serovars (L1, L2 or L3) of *Chlamydia trachomatis*, though L2 is the most common strain involved. Molecular epidemiological studies have identified L2 as the main serovar causing the current outbreaks in Europe and North America. The L2b strain has been identified as a dominant strain,[2] although it appears through retrospective testing of archived samples that it was present as early as the 1980s in San Francisco.[3]

LGV has been a rare occurrence in industrialised countries since the mid-1960s. Since 2003, however, there have been a series of LGV outbreaks reported across Europe occurring mostly among HIV-positive men who have sex with men (MSM).[4] Since formal surveillance was launched in 2004, the UK has seen the highest number of confirmed MSM cases globally.[5] More than 2000 cases had been confirmed by April 2012, with an exponential increase noted from June 2005, followed by a lower but steady rate of approximately 50 cases per quarter from 2006 to 2009. A large increase in diagnosed cases occurred in late 2009, peaking at 150 cases per quarter in mid-2010; since then, UK rates have remained steady at around 80 cases per quarter until 2012 (unpublished data, Public Health England [PHE]). The majority of cases have been diagnosed in genito-urinary medicine (GUM) clinics throughout the UK, but most (77%) have been seen in London, Brighton and Manchester.[5]

A notable feature of the UK epidemiology is that almost all cases (99%) continue to occur among MSM, often involved in dense sexual networks associated with the sex party scene, and not obviously linked with known LGV-endemic countries. There is consistent evidence of a strong association between HIV and LGV found in recent reports in MSM,[6] with LGV cases 8.2 times more likely to be HIV-positive compared to those with non-LGV chlamydial infection; between 2004 and 2011, 78% of UK cases were in HIV-positive individuals (83% in 2010) and 4% of these were diagnosed with HIV within 3 months of their LGV diagnosis.[5] Many LGV-infected MSM have concomitant STIs and 14% of UK cases had infection with hepatitis C virus (HCV).[5,7] A small number of cases of L2 serovar LGV have been reported in heterosexuals in the UK and Europe (including 7 women in the UK since 2004), but these appear linked to bisexual male partners or sexual contact with those returning from endemic regions.[5,8] Prior to 2003, most cases in industrialised settings were imported via travellers, sailors or soldiers.

LGV remains endemic in several tropical areas, including Southern Africa,[9] West Africa,[10] Madagascar,[11] India,[12] South-East Asia[13] and the Caribbean.[14] The proportion of genital ulcer disease (GUD) that can be attributed to LGV in such settings varies between less than 1% to around 10%. However, studies from Durban based on molecular testing reported a rising prevalence of LGV from 2% to 10% over a 10-year period[15]; more recently LGV DNA was detected from 13.6% of Durban GUD cases in 2004.[9]

Clinical features

The clinical course of LGV is classically divided into three stages.

Primary lesion

The incubation period is extremely variable (range 3–30 days) from time of sexual contact with an infected individual; the primary lesion may be transient and imperceptible, in the form of a painless papule or pustule or shallow erosion or ulcer; it is often found on the coronal sulcus of men and on the posterior vaginal wall, fourchette or vulva, and occasionally on the cervix of women. Some ulcers in the recent MSM outbreak have been described as indurated and of variable tenderness; their duration has been as long as several weeks.[16] Extra-genital lesions have been reported such as ulcers and fissures in the perianal area in MSM,[17] the lip or oral cavity (tonsil) and extra-genital lymph nodes.

LGV proctitis in MSM. Haemorrhagic proctitis is the primary manifestation of infection seen in MSM following direct transmission to the rectal mucosa; a similar picture might present in the case of rectal exposure in women.[8] In the recent MSM outbreaks in Western Europe, approximately 96% of all cases presented with proctitis; symptoms included rectal pain, anorectal bleeding, mucoid and/or haemopurulent rectal discharge, tenesmus, constipation and other symptoms of lower gastro-intestinal inflammation. Some patients reported systemic symptoms such as fever and malaise. Genital ulcers and inguinal symptoms were less common; nonetheless "classical" LGV has been reported in MSM in the current outbreak and clinicians need to be alert for these presentations.[16]

Pharyngeal LGV infection. Several cases of pharyngeal LGV have been reported recently in MSM. While pharyngeal *C. trachomatis* infection is less common than

anogenital infection and usually involves non-LGV serovars, LGV can cause symptomatic ulceration and pharyngitis as well as asymptomatic carriage at this site.[18]

Asymptomatic LGV infection. Some studies from Europe found that up to 95% of rectal LGV cases were asymptomatic.[2,19] In contrast, the largest case finding study in MSM to date from the UK found LGV positivity to be 0.9% (95% symptomatic) in rectal samples and 0.04% from the urethra of MSM (one of two individuals was symptomatic).[20] However, one series from a large London centre found a higher proportion of asymptomatic rectal LGV (17.8%).[21] Asymptomatic rectal *C. trachomatis* infection in the UK is usually non-LGV Chlamydia and treatment with doxycycline 100 mg BD for 7 days has been shown to be efficacious in this setting without routine testing for LGV DNA.[22]

Secondary lesions, lymphadenitis or lymphadenopathy or bubo

- *C. trachomatis* serovars L1–L3 are lymphotropic, infecting lymphocytes and macrophages. The essential pathological process is thrombolymphangitis and perilymphangitis. Thus, regional dissemination will be characterised by inflammation and swelling of lymph nodes and surrounding tissue.
- Classically, the most common clinical manifestation of genital LGV amongst heterosexuals is tender inguinal and/or femoral lymphadenopathy that is typically unilateral (two-thirds of cases). The disease process may involve one lymph node or the entire chain, which can become matted with considerable periadenitis and bubo formation. Buboes may ulcerate and discharge pus from multiple points creating chronic fistulae.
- When both inguinal and femoral lymph nodes are involved, they may be separated by the so-called "groove sign," which consists of the separation of these two lymph node systems by the inguinal ligament. Though considered pathognomonic of LGV, the "groove sign" only occurs in 15–20% of cases.
- Lymphadenopathy commonly follows the primary lesion by a period of a few days to weeks (10–30 days, rarely months).
- The systemic spread of *C. trachomatis* may be associated with fever, arthritis, pneumonitis and more rarely abnormal hepatic enzymes and perihepatitis.[23]
- Reactive arthritis in MSM following LGV proctitis has been reported in several cases in recent years.[24]

Tertiary stage or the genito-anorectal syndrome

- The vast majority of patients recover after the secondary stage without sequelae, but in a few patients the persistence or progressive spread of *C. trachomatis* in anogenital tissues will incite a chronic inflammatory response and destruction of tissue in the involved areas, including: proctitis, proctocolitis mimicking Crohn's disease, fistulae, strictures and chronic granulomatous disfiguring fibrosis and scarring of the vulva with esthiomene (Greek word meaning "eating away").
- These conditions occur most frequently in women, reflecting the involvement of retroperitoneal lymphatics (rather than inguinal).
- Interestingly, within the current MSM outbreak, tertiary complications of anorectal LGV such as stricture and fistulae have been observed rarely.[25]

Long-term complications

- The destruction of lymph nodes may result in genital lymphoedema (elephantiasis) with persistent suppuration and pyoderma.
- An association with rectal cancer has been reported. The two conditions can be confused and histopathological confirmation may be necessary.[26]

Diagnosis

In the past, the diagnosis of LGV has often been one of exclusion after other causes of GUD or inguinal lymphadenopathy have been ruled out. In the case of anorectal syndrome, particularly in MSM, the diagnosis is based on clinical suspicion (e.g. combination of signs of proctocolitis, inguinal lymphadenopathy and history of genital ulcer would be highly suggestive) after the exclusion of other aetiologies of proctitis. Even when LGV is suspected, investigations for other potentially co-existing STIs must be undertaken, in particular for gonorrhoea, *Herpes simplex* virus and syphilis.

Positive diagnosis of LGV remains difficult in resource-poor settings, requiring a combination of good clinical acumen and supportive investigations. LGV can be suspected in the presence of positive chlamydial serology, isolation of *C. trachomatis* from the infected site or histological identification of *C. trachomatis* in infected tissue. Traditional methods for LGV diagnosis have been reviewed elsewhere,[27–29] but modern techniques now rely on nucleic acid amplification tests (NAATs).[30] The assays have high sensitivity and specificity and are able to detect LGV-associated DNA, not only from genital swabs but also rectal and

throat swabs, urine, bubo pus, lymph node aspirates and biopsy specimens.

The identification of rectal polymorphonuclear leucocytes (PMNLs) from rectal swabs is predictive of LGV proctitis, especially in HIV-positive MSM, with levels of >10[19] and >20[31] PMNLs per high-power field both shown to be significant.

Testing guidelines for referral of specimens for LGV DNA testing have been developed by the Sexually Transmitted Bacteria Reference Laboratory/Scottish Reference Laboratory (STBRL; PHE, UK).[32]

Collection of specimens

Chlamydiae are intracellular organisms so samples should aim to contain cellular material, which can be obtained from:

- the ulcer base exudate or from rectal mucosa;
- aspiration of enlarged or fluctuant lymph nodes or buboes; after topical disinfection, a 21-gauge needle should be inserted into the lymph node through healthy adjacent tissue and the pus aspirated into a syringe; a small volume (<0.5 mL) saline solution may be injected and re-aspirated for non-fluctuant nodes. If using culture, bubo pus is best homogenised in tissue culture medium before inoculation[29]; if using a *C. trachomatis* NAAT, express pus onto the swab and transport to the laboratory in the standard collection kit for that assay.
- rectal and pharyngeal swabs from MSM and women exposed at those sites; these should be collected as recommended in BASHH guidelines[33];
- a urethral swab or first-catch urine specimen; these can be used when urethritis and/or inguinal lymphadenopathy is present and LGV is suspected as the cause, as well as a swab from any suspected primary lesion.

Main diagnostic techniques

1. Detection of *C. trachomatis* nucleic acid (DNA/RNA) by NAATs such as polymerase chain reaction (PCR), strand displacement amplification (SDA) or transcription mediated amplification (TMA); these methods are now established for routine testing of urethral, cervical, urine, rectal and pharyngeal specimens and are highly sensitive and specific, including from the rectal site[34]; *C. trachomatis*-positive samples should be confirmed by real-time PCR for LGV-specific DNA[35] in cases of suspected LGV; only detection of LGV DNA confirms the diagnosis. The current guidelines from the STBRL/Scottish Reference Laboratory advise that LGV DNA testing should only be performed on specimens that have been confirmed as *C. trachomatis* positive at the local laboratory using a NAAT and have been sourced from either a symptomatic patient or a direct sexual contact. Either the residual processed NAAT specimen or a dry unprocessed specimen will be accepted.

or

2. Culture on cycloheximide-treated McCoy cells of material from suspected LGV lesions has a sensitivity of 75–85% at best, and less for bubo aspirates[27]; this method is labour-intensive, expensive and of increasingly restricted availability.

or

3. *Chlamydia* serology. Four types of techniques have been used: the complement fixation (CF) test, the single L-type immunofluorescence test, the micro-immunofluorescence test (micro-IF) and the anti-MOMP IgA assay. In general, a four-fold rise in antibody or single-point titres of $>1/64$[36] and >128 for the micro-IF test[37] has been considered positive, as only an invasive infection such as that caused by LGV could be responsible for such high titres. The test lacks sensitivity for the earlier manifestations of LGV such as ulcers,[38] and a high titre in the absence of symptoms cannot confirm LGV. It is only performed in a few specialised laboratories. Dutch investigators showed the anti-MOMP IgA to be the most useful assay for rectal LGV infection but sensitivity and specificity reached only ~75% in asymptomatic MSM with rectal *C. trachomatis*.[39] Serology cannot necessarily distinguish past from current LGV infection, which might prove restrictive given the high number of recurrent LGV infections now seen in MSM.

Other methods

Histology of the lymph nodes shows follicular hyperplasia and abscesses, but such findings are not specific; nonetheless, histopathologists need to be alert to these changes and include LGV in the differential diagnosis. In a recent study of 12 anorectal biopsies from MSM with LGV, cryptitis and crypt abscesses without distortion of crypt architecture were the most common findings.[40]

Distinguishing LGV from non-LGV serovars

Restriction fragment length polymorphism (RFLP) analysis of *C. trachomatis*-positive specimens is now

used to distinguish LGV-associated serovars from oculogenital *C. trachomatis*. Sequencing, which is increasingly widely available, is the method now recommended by the HPA for genotyping,[35] though various assays have been developed for this purpose.[41] These techniques have been applied with great success on anorectal specimens collected from patients with proctitis during the recent LGV outbreaks in Western Europe.

Management

General advice

1. Patients should be informed that LGV is an invasive bacterial STI that is curable with antibiotics. Left untreated it can have serious and permanent adverse sequelae.
2. Symptoms should resolve within 1 to 2 weeks of commencing antibiotic therapy.
3. Patients should be advised to avoid unprotected sexual intercourse until they and their partners(s) have completed treatment and follow-up.
4. Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partners(s). This should be reinforced by giving them clear and accurate written information.
5. High rates of incident HIV and HCV infections have been observed in LGV-infected MSM in the recent outbreaks and may reflect ongoing inflammatory proctitis. HIV risk reduction advice and interventions should be offered to HIV-negative MSM, focusing not only on risks of unprotected anal sex but also extended to risks associated with traumatic anoreceptive practices (including fisting, sex toy use), serosorting and recreational drug use in this population. Anal enema use has been associated with LGV infection in MSM[42] and they should be warned of possible transmission via shared equipment for rectal douching.

Further investigations

Screening for other possible causes of GUD should be arranged where relevant, i.e. diagnostic testing for *Haemophilus ducreyi*, *Treponema pallidum*, herpes simplex virus and *Klebsiella/Calymmatobacterium granulomatis* (see BASHH guidelines on chancroid, syphilis, genital herpes and donovanosis, respectively). *Neisseria gonorrhoeae*, syphilis and herpes can also cause proctitis and these infections should be tested for in addition to *C. trachomatis*. LGV in Europe is often associated with HIV and HCV infections and serological screening for these is therefore strongly recommended.

Lymph node aspiration and even biopsy of relevant lesions may be needed to distinguish LGV from atypical infections and neoplasia.

Treatment

No controlled, double-blind treatment trials of LGV have been published. The low incidence of the disease in industrialized nations, its complex presentation and its natural history, marked by spontaneous remissions and exacerbations, have precluded any rigorous evaluation of management. Only a single comparative trial published in 1957 demonstrated that the duration of buboes in patients receiving tetracycline, sulfadiazine or chloramphenicol was significantly shorter than in patients managed by non-specific supportive measures alone.[43] Subsequent observations have reported the successful use of tetracycline, minocycline and rifampicin.[36,44] Early treatment is important to prevent or reduce the chronic phase. Prolonged treatment (at least 3 weeks) is the norm and more than one course of therapy, alternating some of the above antibiotics, may be necessary for chronic cases.[45]

On the basis of the known response of *C. trachomatis* to antibiotics such as doxycycline, tetracycline and erythromycin in uncomplicated infections, the following recommendations have been made (summarized in Table 1).

Recommended regimens

1st choice: doxycycline 100 mg twice daily orally for 21 days (or tetracycline 2 g daily or minocycline 300 mg loading dose followed by 200 mg twice daily) (level of evidence IIb, III or IV, grading B).[27,45–47]

2nd choice: erythromycin 500 mg four times daily orally for 21 days (IV, B).[27,45,47] Azithromycin 1 g weekly for 3 weeks should also be considered.

The rationale for longer regimens relates to the systemic nature of LGV infection. In one recent study,[46] rectal swabs for *C. trachomatis* NAATs took up to 16 days to become negative in LGV proctitis, in contrast to non-LGV chlamydia, where DNA was undetectable after 7 days.

A single case of clinical failure with extended doxycycline therapy has been reported[51] in an HIV-negative MSM with LGV DNA-positive bilateral inguinal buboes and an anal ulcer. He subsequently responded to treatment with moxifloxacin 400 mg daily for 10 days; no isolate was available for resistance testing. No other treatment failures with doxycycline have been reported.

Table 1. Drugs shown to be effective in the treatment of lymphogranuloma venereum (LGV).

Drug	Dose	Route	Cost[a] of treatment	Grading of recommendation[b]	Level of evidence	Reference
Doxycycline[c]	100 mg twice daily × 21 days	Oral	£5.41	B	IV/IIb	Toomey and Barnes[45] de Vries et al.[46]
Erythromycin[c]	500 mg four times daily × 21 days	Oral	£10.14	C	IV	Bowie[47] Toomey and Barnes[45]
Minocycline	300 mg loading dose, followed by 200 mg twice daily × 21 days	Oral	£34.09	C	IV	Sowmini et al.[44] Stamm[27]
Tetracycline hydrochloride	500 mg four times daily × 21 days	Oral	£80.10	C/B	III	Greaves et al.[43]
Azithromycin	1.0 g stat	Oral	£3.01	C	IV	Nieuwenhuis et al.[48] Kamarashev et al.[49]
	1.0 g weekly × 3 weeks	Oral	£9.03	C	IV	CDC[36] Hill et al.[50]
Moxifloxacin	400 mg once daily × 21 days	Oral	£52.21	C	IV	Méchaï et al.[51]

[a]Costs from British National Formulary Number 63 (March 2012).
[b]There have been numerous randomized trials to prove the equivalent efficacies of doxycycline, erythromycin, tetracycline and minocycline for the management of uncomplicated *Chlamydia trachomatis* infections; however, these are lacking for LGV; a B grade is conferred for simplicity of use for doxycycline.
[c]Currently recommended by CDC/IUSTI.

Alternative regimens

Azithromycin

The activity of azithromycin against *C. trachomatis* suggests that it may be effective in multiple-dose regimens over 2–3 weeks, but clinical data on its use are lacking. Several case reports of rectal LGV in MSM have shown clearance with azithromycin regimens of 1 g stat[48,49] and 1 g weekly for 3 weeks[50] (level of evidence IV, grading C). If effective, many clinicians may prefer a multiple-dose regimen of azithromycin to erythromycin due to improved tolerability.

Fluoroquinolone-based therapy with active antichlamydial agents such as ofloxacin and moxifloxacin are expected to be effective in LGV infections but, apart from the above case,[51] no reports of their use in LGV are available. A course of at least 2 weeks would be advisable if clinical necessity warranted their use (level of evidence IV, grading C) and test of cure should be performed.

These recommended treatment regimens are similar to those of CDC (2010)[36] and European (2010) guidelines.[52] The vast majority of cases during the recent LGV outbreaks were successfully treated with standard 3-week courses of doxycycline.[5,7] Clearly, the current outbreaks afford the opportunity to conduct randomized comparative trials of newer/shorter drug regimens, as are used routinely in resource-poor settings[53] (e.g. doxycycline 100 mg twice daily orally for 14 days).

Accompanying measures

Fluctuant buboes should be aspirated through healthy adjacent skin and surgical incision is usually contraindicated due to risk of complications such as sinus formation. Adequate analgesia should be provided for painful LGV infections.

Allergy

Patients allergic to tetracyclines should be treated with either the erythromycin or the extended azithromycin regimen. Test of cure at the completion of treatment is advised.

Treatment for pregnant or breastfeeding women

Pregnant and breastfeeding women should be treated with the erythromycin regimen. Extended azithromycin therapy might be considered in this scenario due to improved tolerability, but no published data are available to guide safety, dosing and efficacy in pregnancy. Test of cure is advised in pregnancy if rectal or genital LGV are diagnosed.

HIV-positive individuals

LGV occurs commonly in HIV-infected individuals and they should receive the same regimens as those who are HIV negative. There are few significant drug–drug

interactions between commonly used antiretroviral agents and doxycycline.

Adverse reactions to treatment

The most common doxycycline side effects are upper gastrointestinal problems including dyspepsia and nausea; diarrhoea is less frequent. These might be mitigated by taking doses after meals. Photosensitivity can occur, especially in climates with abundant sunshine, and patients should be warned of this and advised not to expose themselves unduly. Oesophageal ulceration can occur from prolonged doxycycline mucosal contact, especially with the capsule formulations. It is recommended that doxycycline be taken with a large glass of water and that patients not lie down for at least 20 min after swallowing the medication.

The most common erythromycin side effects are also gastrointestinal problems including mild diarrhoea, stomach pain, nausea and vomiting.

Contact tracing and treatment

Persons who have had sexual contact with a patient who has LGV within the 4 weeks before onset of the patient's symptoms, or the last 3 months if asymptomatic LGV is detected, should be examined, tested for rectal, pharyngeal, urethral and/or cervical chlamydial infection (as applicable) and receive presumptive treatment with 21 days of doxycycline 100 mg twice daily or an alternative regimen for the same duration (level of evidence IV, grading C).

Follow-up

All patients should be followed clinically until signs and symptoms have resolved. This usually occurs within 1–2 weeks for early infection, including MSM proctitis, but may take up to 3–6 weeks for longstanding infections or sequelae. Some early LGV infections can be asymptomatic when first diagnosed and then might become symptomatic prior to or during the initial days of treatment[54]; these symptoms should settle promptly. Routine test of cure for LGV is no longer considered necessary if the recommended 21-day course of doxycycline has been completed.[46] If indicated, test of cure should be performed at 2 weeks after the completion of LGV treatment to avoid detection of non-viable *C. trachomatis* DNA/RNA (level of evidence IV, grading C).

Follow-up should also check that adequate partner notification has been completed, any patient concerns have been addressed and follow-up testing for syphilis and blood-borne viruses including hepatitis B, C and HIV done where necessary. In the recent MSM LGV epidemic, incident cases of both HIV and HCV have been observed and serological testing should be offered for both infections after appropriate window periods have elapsed according to relevant local guidelines. Abnormal liver enzymes should prompt further testing for HCV RNA as HCV antibody seroconversion in HIV-positive MSM might be delayed beyond 12 months.[55]

Patients with fibrotic lesions or fistulae are beyond the stage where antibiotic therapy is effective and surgical repair, including reconstructive genital surgery, often must be considered.

Auditable outcomes

- An agreed contact action (including no action) was documented for all sexual contacts since, and in the 4 weeks prior to, the onset of symptoms. Standard: 97% of index cases having this documented for all contacts.
- The presence of LGV serovar(s) was confirmed by the Sexually Transmitted Bacteria Reference Laboratory/Scottish Reference Laboratory for each case with a diagnosis of LGV. Standard: 97%.
- The Sexual Health & HIV Activity Property Type (SHHAPT) code "C2" was submitted to the Genito-Urinary Medicine Clinic Activity Dataset (GUMCAD) for each case with a diagnosis of LGV (England and Wales). Standard: 97%.
- A plan for HIV testing, that included repeat testing to detect early HIV infection, was documented. Standard: 97%.
- A plan for hepatitis C testing, that included repeat testing to account for early hepatitis C infection, was documented. Standard: 97%
- A plan for syphilis testing, that included repeat testing to account for early syphilis infection, was documented. Standard: 97%.

Applicability

Suggestions for diagnostic approaches made in this guideline should be tailored to local resources. *C. trachomatis* NAATs and the serological tests recommended may not be available in all laboratories. Additional testing may be available from the STBRL, PHE, Colindale, UK. In Scotland, the Scottish Bacterial Sexually Transmitted Infection Reference Laboratory (SBSTIRL), based at the Royal Infirmary of Edinburgh, offers an LGV confirmatory PCR service on swabs positive for *C. trachomatis* from: (i) symptomatic MSM; (ii) MSM with HIV infection and (iii) contacts of confirmed LGV cases.

Stakeholder involvement

Microbiologists and epidemiologists at PHE in Colindale, London, have been consulted.

Membership of the CEG

Clinical Effectiveness Group: Dr Keith Radcliffe (Chair), Dr Mark FitzGerald, Dr Deepa Grover, Dr Steve Higgins, Dr Margaret Kingston, Dr Neil Lazaro, Dr Louise Melvin and Dr Ann Sullivan.

Conflict of interest

All members of the guideline writing committee completed the BASHH conflict of interest declaration detailed below at the time the guideline's final draft was submitted to the CEG. The details of any actual or potential declarations of interest will be documented by the CEG at this point in the guideline.

References

1. Kingston M, Radcliffe K, Daniels D, et al. British Association for Sexual Health and HIV: framework for guideline development and assessment. *Int J STD AIDS* 2010; 21: 453–456.
2. Spaargaren J, Fennema HSA, Morre SA, et al. New lymphogranuloma venereum *Chlamydia trachomatis* variant, Amsterdam. *Emerg Infect Dis* 2005; 11: 1090–1092.
3. Spaargaren J, Schachter J, Moncada J, et al. Slow epidemic of lymphogranuloma venereum L2b strain. *Emerg Infect Dis* 2005; 11: 1787–1788.
4. Savage EJ, van de Laar MJ, Gallay A, et al. European Surveillance of Sexually Transmitted Infections (ESSTI) network. Lymphogranuloma venereum in Europe, 2003–2008. *Euro Surveill* 2009; 14: 19428.
5. Health Protection Agency. Epidemic of Lymphogranuloma venereum (LGV) in men who have sex with men in the UK intensifies. Health Protection Report 2010, **5**(22), 17 June 2011, www.hpa.org.uk/hpr/archives/2011/hpr2411.pdf (accessed 31 May 2012).
6. Rönn MM and Ward H. The association between lymphogranuloma venereum and HIV among men who have sex with men: systematic review and meta-analysis. *BMC Infect Dis* 2011; 11: 70.
7. Jebbari H, Alexander S, Ward H, et al. UK LGV Incident Group. Update on lymphogranuloma venereum in the United Kingdom. *Sex Transm Infect* 2007; 83: 324–326.
8. Peuchant O, Baldit C, Le Roy C, et al. First case of *Chlamydia trachomatis* L2b proctitis in a woman. *Clin Microbiol Infect* 2011; 17: E21–E23.
9. O'Farrell N, Morison L, Moodley P, et al. Genital ulcers and concomitant complaints in men attending a sexually transmitted infections clinic: implications for sexually transmitted infections management. *Sex Transm Dis* 2008; 35: 545–549.
10. Fayemiwo SA, Odaibo GN, Oni AA, et al. Genital ulcer diseases among HIV-infected female commercial sex workers in Ibadan, Nigeria. *Af J Med Med Sci* 2011; 40: 39–46.
11. Behets FM, Andriamiadana J, Randrianasolo D, et al. Chancroid, primary syphilis, genital herpes, and lymphogranuloma venereum in Antananarivo, Madagascar. *J Infect Dis* 1999; 180: 1382–1385.
12. Ray K, Latha R, Sachdeva KG, et al. Usefulness of immunoperoxidase for serodiagnosis of genital chlamydial infections. *Indian J Med Res* 1993; 97: 67–71.
13. Viravan C, Dance DA, Ariyarit C, et al. A prospective clinical and bacteriological study of inguinal buboes in Thai men. *Clin Infect Dis* 1996; 22: 233–239.
14. Fletcher H, Figueroa P, Brathwaite A, et al. Poverty, folate deficiency, human immunodeficiency virus and ulcerated vulval sexually transmitted diseases in Jamaica. *West Indian Med J* 2011; 60: 137–140.
15. Moodley P, Sturm PD, Vanmali T, et al. Association between HIV-1 infection, the etiology of genital ulcer disease, and response to syndromic management. *Sex Transm Dis* 2003; 30: 241–245.
16. Sethi G, Allason-Jones E, Richens J, et al. Lymphogranuloma venereum presenting as genital ulceration and inguinal syndrome in men who have sex with men in London, UK. *Sex Transm Infect* 2009; 85: 165–170.
17. Singhrao T, Higham E and French P. Lymphogranuloma venereum presenting as perianal ulceration: an emerging clinical presentation? *Sex Transm Infect* 2011; 87: 123–124.
18. Dosekun O, et al. Lymphogranuloma venereum detected from the pharynx in four London men who have sex with men. *Int J STD AIDS* 2013; 24: 495–496.
19. Van der Bij AK, Spaargaren J, Morré SA, et al. Diagnostic and clinical implications of anorectal lymphogranuloma venereum in men who have sex with men: a retrospective case-control study. *Clin Infect Dis* 2006; 42: 186–194.
20. Ward H, Alexander S, Carder C, et al. The prevalence of lymphogranuloma venereum infection in men who have sex with men: results of a multicentre case finding study. *Sex Transm Inf* 2009; 85: 173–175.
21. Annan NT, Sullivan AK, Nori A, et al. Rectal chlamydia - a reservoir of undiagnosed infection in men who have sex with men. *Sex Transm Infect* 2009; 85: 176–179.
22. Elgalib A, Alexander S, Tong CY, et al. Seven days of doxycycline is an effective treatment for asymptomatic rectal *Chlamydia trachomatis* infection. *Int J STD AIDS* 2011; 22: 474–477.
23. Kellock DJ, Barlow R, Suvarna SK, et al. Lymphogranuloma venereum: biopsy, serology, and molecular biology. *Genitourin Med* 1997; 73: 399–401.
24. Kober C, Richardson D, Bell C, et al. Acute seronegative polyarthritis associated with lymphogranuloma venereum

infection in a patient with prevalent HIV infection. *Int J STD AIDS* 2011; 22: 59–60.

25. Williams D and Churchill D. Ulcerative proctitis in men who have sex with men: an emerging outbreak. *BMJ* 2006; 332: 99–100.

26. Taylor G, Dasari BV, McKie L, et al. Lymphogranuloma venereum (LGV) proctitis mimicking rectal cancer. *Colorectal Dis* 2011; 13: e63–e64.

27. Stamm WE. Lymphogranuloma venereum. In: Holmes KK, Sparling PF, Stamm WE, et al (eds) *Sexually transmitted diseases*, 4th ed. New York: Mc-Graw Hill, 2008, pp.595–606.

28. Van Dyck E and Piot P. Laboratory techniques in the investigation of chancroid, lymphogranuloma venereum and donovanosis. *Genitourin Med* 1992; 68: 130–133.

29. Mabey D and Peeling RW. Lymphogranuloma venereum. *Sex Transm Infect* 2002; 78: 90–92.

30. Herring A and Richens J. Lymphogranuloma venereum. *Sex Transm Inf* 2006; 82: iv23–iv25.

31. Samarawickrama A, Nambiar K, Collins I, et al. Diagnostic utility of rectal microscopy in predicting lymphogranuloma venereum (LGV) in men who have sex with men (MSM): a case control study. *Sex Transm Inf* 2008; 84: 78.

32. Health Protection Agency. Enhanced surveillance for LGV, http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/LGV/EnhancedSurveillanceSystem/ (accessed 10 December 2012)

33. Chlamydia Trachomatis UK Testing Guidelines. 2010. Clinical Effectiveness Group, British association for Sexual Health and HIV, www.bashh.org/documents/3352 (accessed 31 May 2012).

34. Alexander S, Martin IM and Ison CA. Confirming the *Chlamydia trachomatis* status of referred rectal specimens. *Sex Transm Infect* 2007; 83: 327–329.

35. Alexander S, Martin IM and Ison C. A comparison of two methods for the diagnosis of lymphogranuloma venereum. *J Med Microbiol* 2008; 57: 962–965.

36. Centers for Disease Control and Prevention. 2010 Sexually Transmitted Diseases Treatment Guidelines. MMWR December 17, 2010, Vol. 59, No. RR–12.

37. 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: 255–258.

38. Sturm PD, Moodley P, Govender K, et al. Molecular diagnosis of lymphogranuloma venereum in patients with genital ulcer disease. *J Clin Microbiol* 2005; 43: 2973–2975.

39. de Vries HJ, Smelov V, Ouburg S, et al. Anal lymphogranuloma venereum infection screening with IgA anti-Chlamydia trachomatis-specific major outer membrane protein serology. *Sex Transm Dis* 2010; 37: 789–795.

40. Soni S, Srirajaskanthan R, Lucas SB, et al. Lymphogranuloma venereum proctitis masquerading as inflammatory bowel disease in 12 homosexual men. *Aliment Pharmacol Ther* 2010; 32: 59–65.

41. Quint KD, van Doorn LJ, Kleter B, et al. A highly sensitive, multiplex broad-spectrum PCR-DNA-enzyme immunoassay and reverse hybridization assay for rapid detection and identification of Chlamydia trachomatis serovars. *J Mol Diagn* 2007; 9: 631–638.

42. de Vries HJ, Van der Bij AK, Fennema JS, et al. Lymphogranuloma venereum proctitis in men who have sex with men is associated with anal enema use and high-risk behavior. *Sex Transm Dis* 2008; 35: 203–208.

43. Greaves AB, Hilleman MR, Taggart SR, et al. Chemotherapy in bubonic lymphogranuloma venereum: a clinical and serological evaluation. *Bull World Health Org* 1957; 16: 277–289.

44. Sowmini CN, Gopalan KN and Rao GC. Minocycline in the treatment of lymphogranuloma venereum. *J Am Vener Dis Assoc* 1976; 2: 19–22.

45. Toomey KE and Barnes RC. Treatment of *Chlamydia trachomatis* genital infection. *Rev Infect Dis* 1990; 12: S645–S655.

46. de Vries HJ, Smelov V, Middelburg JG, et al. Delayed microbial cure of lymphogranuloma venereum proctitis with doxycycline treatment. *Clin Infect Dis* 2009; 48: e53–e56.

47. Bowie WR. In vitro and in vivo efficacy of antimicrobials against. *Chlamydia trachomatis*. *Infection* 1982; 10: S46–S52.

48. Nieuwenhuis RF, Ossewaarde JM, van der Meijden WI, et al. Unusual presentation of early lymphogranuloma venereum in an HIV-1 infected patient: effective treatment with 1 g azithromycin. *Sex Transm Infect* 2003; 79: 453–455.

49. Kamarashev J, Riess CE, Mosimann J, et al. Lymphogranuloma venereum in Zurich, Switzerland: Chlamydia trachomatis serovar L2 proctitis among men who have sex with men. *Swiss Med Wkly* 2010; 140: 209–212.

50. Hill SC, Hodson L and Smith A. An audit on the management of lymphogranuloma venereum in a sexual health clinic in London, UK. *Int J STD AIDS* 2010; 21: 772–776.

51. Méchaï F, de Barbeyrac B, Aoun O, et al. Doxycycline failure in lymphogranuloma venereum. *Sex Transm Infect* 2010; 86: 278–279.

52. de Vries HJ, Morré SA, White JA, et al. European guideline for the management of lymphogranuloma venereum, 2010. *Int J STD AIDS* 2010; 21: 533–536.

53. World Health Organization. Guidelines for the management of sexually transmitted infections, www.who.int/entity/hiv/pub/sti/en/STIGuidelines2003.pdf (2003, accessed 31 May 2012).

54. White JA. Manifestations and management of lymphogranuloma venereum. *Curr Opin Infect Dis* 2009; 22: 57–66.

55. Thomson EC, Nastouli E, Main J, et al. Delayed anti-HCV antibody response in HIV-positive men acutely infected with HCV. *AIDS* 2009; 23: 89–93.