2012 National Guideline for the Management of Lymphogranuloma Venereum (LGV)

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

Date of writing: April 2012

Date review due: 2017

New information in this guideline since 2006 publication:

• **Aetiology and Epidemiology:**

- persistent LGV outbreaks in MSM in UK; higher levels than in 2005
- no evidence of significant heterosexual spread within UK
- cases continue to be mostly White 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
- asymptomatic LGV remains uncommon but further case finding indicated in view of ongoing spread

• **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.
- Enhanced clinical surveillance by the Health Protection Agency is no longer being conducted but will be replaced by enhanced venue surveillance from LGV cases. GUMCAD recording of LGV diagnoses is crucial to maintain epidemiological data

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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] outlined at http://bashh.org/guidelines. The previous guidelines (1998, 2000, 2006) were largely based on the published CDC Guidelines for Treatment of Sexually Transmitted Diseases of 1993, 1997, 2002, and on a Medline search spanning the years 1966-2005. The 2012 guideline has updated the previous guideline by searching Medline from 2005-2012 for published articles in any language using the search terms: "Lymphogranuloma venereum"; "LGV"; "Chlamydia trachomatis diagnosis"; "Chlamydia trachomatis treatment"; and "rectal Chlamydia". The most recent CDC guidelines (2010) and European IUSTI Guidelines (2010) have also been consulted. 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 consultation period of three months and piloted in a sample of clinics. In response to the consultation ….

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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 exponential increases 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, UK Health Protection Agency [HPA]). The majority of cases have been diagnosed in GUM clinics throughout the UK but most (77%) have been seen in London, Brighton and Manchester[5].

A notable feature of the UK outbreak is that most cases continue to occur among predominantly white MSM (88%) often involved in dense sexual networks associated with the sex party scene, and were 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; overall 78% of UK cases were HIV positive (83% in 2010) and 4% of these were diagnosed with HIV within three months of their LGV diagnosis. Many LGV-infected MSM have concomitant STIs and 14% of UK cases had infection with hepatitis C virus (HCV) [5,7]. Small

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numbers of cases of L2 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 on the 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

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outbreaks in Western Europe, approximately 96% of all cases presented with proctitis, and symptoms included severe 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. [ref Dosekun et al, in press]

ASYMPTOMATIC LGV INFECTION

Some studies from Europe found that up to 96% of rectal LGV cases were asymptomatic [2,18]. 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 symptomatic)[19]. Asymptomatic rectal *C. trachomatis* infection in the UK is usually non-LGV Chlamydia and treatment with doxycycline 100mg BD for 7 days has been shown to be efficacious in this setting without routine testing for LGV DNA[20].

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.

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- The most common clinical manifestation of LGV (mostly found in heterosexual men) 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 nodes 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 perihepatitis (Fitz-Hugh–Curtis syndrome)[21].
- Reactive arthritis in MSM following LGV proctitis has been reported in several cases in recent years[22].

TERTIARY STAGE OR THE GENITO-ANO-RECTAL 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[23].

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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[24].

Diagnosis

In the past the diagnosis of LGV is has often been one of exclusion after other causes of GUD or inguinal lymphadenopathy have been ruled out. In the case of anorectal syndrome, 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 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 [25,26,27), but modern techniques now rely on nucleic acid amplification tests (NAATs) [28]. 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.

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The identification of rectal polymorphonuclear leucocytes (PMNLs) from rectal swabs is predictive of LGV proctitis, especially in HIV-positive MSM, with levels of >10[18] and >20[29] 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 (STBRL; HPA, UK). For more details consult: http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/LGV/EnhancedSurveillanceSystem/

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 fluctuant lymph nodes or buboes; after topical disinfection, a 20-gauge needle should be inserted into the lymph node through healthy adjacent tissue and the pus aspirated into a syringe; a small volume (<0.5ml) saline solution may be injected and re-aspirated. If using culture, bubo pus is best homogenised in tissue culture medium before inoculation[27]; if using *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[30];
- 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

(i) Detection of *C. trachomatis* nucleic acid (DNA/RNA) by NAATs such as polymerase chain reaction (PCR), strand displacement amplification (SDA) or

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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[31]; *C. trachomatis*-positive samples should be confirmed by real-time PCR for LGV-specific DNA[32] in cases of suspected LGV; only detection of LGV DNA confirms the diagnosis. The current guidelines from the STBRL 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

(ii) Culture on cycloheximide-treated McCoy cells of material from suspected LGV lesions is considered the most specific method, but its sensitivity is 75-85% at best, and less for bubo aspirates[25]; this method is labour intensive, expensive and of increasingly restricted availability.

or

(iii) *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[33] and >128 for the micro-IF test[34] have 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[35], 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*[36]. 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

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The Frei test, direct immunofluorescence (DIF) test and enzyme immunoassay (EIA) sensitivities are lower than other methods and are no longer recommended.
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[37].

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[28], though various assays have been developed for this purpose[38]. 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 one to two 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

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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. HIV risk reduction advice should be offered, 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. Enema use has been associated with LGV infection and MSM 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 and *Klebsiella/Calymmatobacterium granulomatis* (see BASHH guidelines on chancroid, syphilis, genital herpes and donovanosis, respectively). *Neisseria gonorrhoeae*, syphilis and herpes can also cause MSM 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 encouraged.
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 symptomatically-treated patients[39]. Subsequent observations have reported the successful use of tetracycline, minocycline, and rifampicin [33,40]. Early treatment is important to prevent or reduce the chronic phase. Prolonged treatment (at least 3 weeks) is the norm and more

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than one course of therapy, alternating some of the above antibiotics, may be necessary for chronic cases [41].
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 100mg twice daily orally for 21 days (or tetracycline 2g daily or minocycline 300mg loading dose followed by 200mg twice daily) (level of evidence IIb, III or IV, grading B) [25,39,41-43].

2nd choice: erythromycin 500mg four times daily orally for 21 days (IV, B) [25,43]. Azithromycin 1gm weekly for three weeks should also be considered.

The rationale for longer regimens relates to the systemic nature of LGV infection. In one recent study[42], 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[44] in an HIV-negative MSM with LGV DNA-positive bilateral inguinal buboes and an anal ulcer. He subsequently responded to treatment with moxifloxacin 400mg daily for 10 days; no isolate was available for resistance testing. No other treatment failures with doxycycline have been reported.

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 1g stat[45,46] and 1g weekly for 3 weeks[47] (level of evidence IV, grading C). If effective, many clinicians may prefer a

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multiple-dose regimen of azithromycin to erythromycin due to improved tolerability.
Fluoroquinolone-based therapy with active anti-chlamydial agents such as ofloxacin and moxifloxacin are expected to be effective in LGV infections but, apart from the above case, 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 identical to those of CDC (2010) [33] and European (2010) guidelines [48]. 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[49] (e.g. doxycycline 100mg twice daily orally for 14 days).

Accompanying measures

Fluctuant buboes should be aspirated through healthy adjacent skin and surgical incision is usually contra-indicated 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.

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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 minutes 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 three months if asymptomatic LGV is detected, should be examined, tested for rectal, pharyngeal, urethral and/or cervical chlamydial infection (as applicable) and treated, or receive presumptive treatment with at least 14 days of doxycycline 100mg twice daily or 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. Routine test of cure for LGV is no longer considered necessary if

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the recommended 21-day course of doxycycline has been completed [42]. Follow-up should also check that adequate partner notification has been completed, address any patient concerns and for follow-up testing for syphilis and blood borne viruses including hepatitis B, C and HIV 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.

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 Outcome Measures

- All cases of suspected LGV should be subjected to laboratory investigations. Target 100%.
- Sexual partners should be traced, tested and treated. ?0.6 per index case
- HIV, syphilis, and HCV serological testing should be offered, as well as screening for concomitant STIs. Target 100% offer.
- GUMCAD data for all confirmed LGV cases should be completed and relevant HPA surveillance guidelines for the reporting of suspected or confirmed cases of LGV should be adhered to [4]. Target 100% GUMCAD, 90% surveillance.

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, HPA, Colindale, UK.

Stakeholder involvement

Microbiologists, clinicians and epidemiologists at the HPA in Colindale, London, the Regional Microbiology Laboratory, Plymouth, Devon, the HIV/STI

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Centre at University College London Medical School (UCLMS), and the London School of Hygiene & Tropical Medicine (LSHTM) have been consulted.

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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.

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

Drug	Dose	Route	Cost[2] of treatment	** Grading of recommendation	Level of evidence	Reference
Doxycycline*	100mg twice daily x 21 days	Oral	£ 5.41	B	IV/IIb	Toomey & Barnes, 1990 [41] de Vries, 2009 [42]
Erythromycin*	500mg four times daily x 21 days	Oral	£ 10.14	C	IV	Bowie, 1982 [43] Toomey & Barnes, 1990 [41]
Minocycline	300mg loading dose, followed by 200mg twice daily x 21 days	Oral	£ 34.09	C	IV	Sowmini et al, 1976 [40] Stamm, 2008 [25]
Tetracycline hydrochloride	500mg four times daily x 21 days	Oral	£80.10	C/B	III	Greaves, 1957 [39]
Azithromycin	1.0 g stat	Oral	£3.01	C	IV	Nieuwenhuis, 2003 [45] Kamarashev, 2010 [46]
	1.0g weekly x 3 weeks	Oral	£9.03	C	IV	CDC, 2010 [33] Hill, 2010 [47]
Moxifloxacin	400mg once daily x 21 days	Oral	£52.21	C	IV	Méchaï, 2010 [44]

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

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