SUPPLEMENT ARTICLE

Lymphogranuloma Venereum 2015: Clinical Presentation, Diagnosis, and Treatment

Bradley P. Stoner[1] and Stephanie E. Cohen[2,3]

[1]Department of Anthropology and Division of Infectious Diseases, Washington University, St Louis, Missouri; [2]San Francisco Department of Public Health, and [3]Division of Infectious Diseases, University of California, San Francisco

Lymphogranuloma venereum (LGV) has emerged as an important cause of proctitis and proctocolitis in men who have sex with men; classical inguinal presentation is now increasingly uncommon. We report summary findings of an extensive literature review on LGV clinical presentation, diagnosis, and treatment that form the evidence base for the 2015 Centers for Disease Control and Prevention treatment guidelines for sexually transmitted diseases. Proctitis and proctocolitis are now the most commonly reported clinical manifestations of LGV, with symptoms resembling those of inflammatory bowel disease. Newer molecular tests to confirm LGV infection are sensitive and specific, but are generally restricted to research laboratory or public health settings. Doxycycline (100 mg twice daily for 21 days) remains the treatment of choice for LGV. Patients with rectal chlamydial infection and signs or symptoms of proctitis should be tested for LGV, or if confirmatory testing is not available, should be treated empirically with a recommended regimen to cover LGV infection.

Keywords. LGV; proctitis; proctocolitis; diagnosis; treatment.

Lymphogranuloma venereum (LGV) is a condition caused by invasive serovars of *Chlamydia trachomatis* (L1, L2, or L3). Classically, LGV is characterized by the development of transient genital ulcer(s) or papule(s), followed by the appearance of tender inguinal and/or femoral lymphadenopathy (most commonly unilateral) with a characteristic "groove sign" formed by swollen, matted lymph nodes developing along the course of the inguinal ligament. Untreated, the infection may lead to long-term complications such as deep tissue abscess formation, strictures, fissures, and chronic pain [1, 2].

In recent years, developed countries have experienced a shift in LGV epidemiological patterns and clinical presentation. Over the past decade, LGV has emerged in Europe and North America as a leading cause of proctitis and proctocolitis in men who have sex with men (MSM). Rectal ulcerations, bleeding, tenesmus, and lower abdominal cramping and pain are the primary clinical features, and prolonged infection can lead to the development of perirectal abscesses, fissures, and systemic symptoms such as fever, malaise, weight loss, and fatigue. Today in developed countries, LGV is predominantly associated with rectal infection, and the classical findings of inguinal lymphadenopathy are increasingly uncommon.

Diagnosis and treatment of LGV infections are paramount for preventing long-term consequences of infection, as well as preventing secondary spread to sex partners. Moreover, to the extent that LGV proctitis is increasingly identified in human immunodeficiency virus (HIV)–infected persons, there is concern for potential LGV enhancement of HIV acquisition or transmission. In this article, we report on our review of the literature on LGV and proctitis in support of updating and revising the evidence-based guidelines for treatment of sexually transmitted diseases (STDs) prepared by the US Centers for Disease Control and Prevention (CDC) [3].

METHODS

In preparation for the expert guidelines panel convened by the CDC, we reviewed articles published from 1 January 2008 through 1 February 2013 and formulated key

Correspondence: Bradley P. Stoner, MD, PhD, Department of Anthropology, Washington University, 1 Brookings Dr, Campus Box 1114, St Louis, MO 63130 (bstoner@wustl.edu).

Clinical Infectious Diseases® 2015;61(S8):S865–73

© The Author 2015. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/civ756

Downloaded from http://cid.oxfordjournals.org/ at University of California, San Francisco on January 14, 2016

questions to address issues related to LGV management and treatment. Using the Medline database of the US National Library of Medicine, we searched for all articles containing "lymphogranuloma venereum" or "LGV" (all documents) in the title, abstract, substance word, subject heading word, keyword, protocol supplementary concept, rare disease supplementary concept, or unique identifier. In addition, abstracts relevant to LGV treatment from professional conference proceedings were reviewed, including the International Society for Sexually Transmitted Diseases Research, National Sexually Transmitted Disease Prevention Conference, Infectious Disease Week, Interscience Conference on Antimicrobial Agents and Chemotherapy, and Conference on Retroviruses and Opportunistic Infections. Additionally, international treatment guidelines, workshop papers, and gray literature addressing LGV treatment were examined. Articles and abstracts were systematically reviewed for content related to new developments in LGV clinical presentation, diagnosis, and treatment since the previous STD treatment guidelines update process in 2009. A total of 45 references were included in our final review, and key findings were summarized in the tables of evidence for the expert panel (Table 1).

LGV CLINICAL MANIFESTATIONS

Most case series and case reports describe clinical manifestations of LGV among MSM, and most of these individuals have been HIV infected [4–32]. Proctitis and proctocolitis are the most commonly reported clinical manifestations of LGV in several case series [4–6, 16, 21], with findings that resemble, and may be confused with, inflammatory bowel disease. Symptoms include rectal bleeding, pain, tenesmus, mucoid discharge, constipation, or hematochezia [10]. Gram stain of the anorectal discharge smear commonly shows elevated white blood cell counts (>10 per high-power field) [5, 28, 32]. Colonoscopic examination commonly reveals rectal ulcers with erythema and friability, with mucosal biopsies demonstrating lymphohistiocytic infiltrates, crypt abscesses, or granulomatous changes [4, 6, 8, 10, 13, 21]. Genital tract infection with lymphadenopathy and bubo formation is relatively uncommon [5, 7, 24]. Reactive polyarthropathy, with or without conjunctivitis, has been noted in several case reports; the most commonly affected joints included the wrist, knee, ankle, or elbow [9, 18, 26, 29]. Zoonotic transmission has also been described [33]. Although most rectal LGV among MSM appears to be symptomatic, some investigators have noted that asymptomatic infections can occur [5, 30, 31].

LGV DIAGNOSIS

Historically, LGV diagnosis has been based on clinical presentation coupled with appropriate serologic findings (microimmunofluorescence titers >1:256 or complement fixation titers >1:64) [3]. However, criteria for serologic test interpretation have not been standardized, nor has test performance been validated for rectal infections. Numerous research teams have developed novel molecular methods to confirm LGV infection from clinical material (particularly anorectal swabs in MSM) [34–39]. These methods focus on confirming LGV-associated serovars through sequencing of the outer membrane protein A (*ompA*) gene, or through the use of real-time polymerase chain reaction to identify an L2b-specific deletion in the polymorphic membrane protein H (*pmpH*) gene, or by combining *C. trachomatis* detection and genotyping with reverse hybridization assay. Unfortunately, amplified sequencing tests are not commercially available or cleared by the US Food and Drug Administration for use in the United States, and access is restricted to research centers and public health laboratories that have developed such assays. Additional LGV-specific serologic tests are also in development (eg, immunoglobulin A anti-MOMP) [40]. The lack of standardized and validated laboratory assays for use in clinical settings means that, in most circumstances, the diagnosis of LGV is typically based on epidemiological and clinical findings, confirmation of *C. trachomatis* infection by routinely available nucleic acid amplification tests (which are positive in both LGV and non-LGV chlamydial infections), and the exclusion of other potential etiologies of proctocolitis, lymphadenopathy, or genital ulcers. In clinic-based cohorts in Australia, the Netherlands, and the United Kingdom, significant numbers of patients (7%–23%) with rectal chlamydial infection and either signs or symptoms of proctitis were found to have an LGV strain of chlamydia [5, 20, 41]. The prevalence of LGV among patients with symptomatic rectal chlamydial infection in the United States is unknown, given the absence of systematic surveillance or commercially available assays.

LGV TREATMENT

More than half a century of clinical experience supports the use of doxycycline, 100 mg twice daily for 21 days, as the treatment of choice for LGV [2, 3, 42]. This recommendation is based on reported treatment efficacy in numerous case series, coupled with a favorable pharmacokinetic profile, minimal toxicity, and convenient dosing. A 3-week duration of therapy is required because LGV infections are more invasive and more difficult to eradicate than uncomplicated genital tract infections, which typically respond to 1 week of treatment. Erythromycin base, 500 mg 4 times daily for 21 days, is a reliable alternative treatment with many years of demonstrated use efficacy, although gastrointestinal intolerance and inconvenient dosing may limit its utility. In addition to antimicrobial therapy, local management of buboes (by aspiration through intact skin, or incision and drainage) may also be considered to prevent the development of ulcerations or fistulous tracts.

Downloaded from http://cid.oxfordjournals.org/ at University of California, San Francisco on January 14, 2016

Table 1. Lymphogranuloma Venereum Tables of Evidence

Reference	Study Design	Study Population	Exposure/Intervention	Outcome Measures	Reported Findings	Design Analysis Quality/Biases
LGV clinical manifestations						
Arnold et al [4]	Case series	7 syphilis pts, 2 LGV pts, 1 syphilis/LGV pt (US)	Clinically confirmed LGV or syphilis	Histologic core features of anocolonic biopsies	Biopsies showed intense lymphohistiocytic infiltrate w/ prominent plasma cells & lymphoid aggregates, mild-to-moderate inflammation, rare granulomas	None of the initial impressions included LGV. Clinical correlates of 10 pts were: HIV^+ (10), MSM (9), bleeding (9), ulcerations (7), pain (6), tenesmus (4).
de Vrieze et al [5]	Cross-sectional prevalence study	48 570 MSM attending STI clinic (Netherlands)	LGV infection (confirmed by PCR of *pmpH*)	Clinical correlates of LGV and non-LGV chlamydial infection	27.2% of pts with rectal LGV had no signs or symptoms; 85.3% of symptomatic pts had anorectal Gram stain smear with >10 PMNLs/high-power field	Inguinal LGV cases were rare, and were less likely to be HIV coinfected.
Gallegos et al [6]	Case series	3 pts with rectal LGV (US)	LGV proctosigmoiditis	Clinical and endoscopic correlates of LGV	Cases characterized by incomplete/undisclosed history, and endoscopic/histologic findings suggesting IBD	Consider LGV after failure to respond to IBD therapy, further history is elicited (travel, MSM), positive chlamydia test, or inadequate response to antibiotics.
Verweij et al [7]	Case report	1 pt with inguinal bubo (Netherlands)	CT infection	Confirmation of L2b serovariant	rt-PCR confirmation of CT, serovariant L2b	First case report of female with bubonic LGV caused by L2b serovariant (probably from bisexual male partners).
Cunningham et al [8]	Case report	1 pt with rectal LGV (US)	LGV proctitis	Clinical and endoscopic correlates of LGV	Pt had 6 mo of hematochezia, rectal pain. Colonoscopy showed multiple rectal ulcers with thick white exudate, erythema.	HIV^+, CD4 count = 429 cells/μL. CDC confirmed L2 serotype. Responded to 3 wk of doxycycline.
Kennedy & Higgins [9]	Case report	1 pt with LGV (UK)	LGV proctitis with reactive arthropathy	Clinical correlates of LGV infection	LGV proctitis was followed by reactive arthropathy that mimicked DVT (acute swelling of lower limb)	HIV^+ MSM. Early treatment of LGV may have prevented reactive arthropathy.
Geisler et al [10]	Case report	1 pt with LGV (US)	LGV proctocolitis (L2b variant confirmed by *ompA* sequencing)	Clinical correlates of LGV infection	Pt had chronic rectal bleeding ×3 mo, with mucoid discharge, tenesmus. Colonoscopy revealed erythema, friability, shallow and deep ulcers, with active focal colitis in cecum, sigmoid, and rectum.	HIV^+ MSM. 21-d course of doxycycline improved symptoms; repeat treatment led to clinical cure.
Vanousova et al [11]	Case series	4 pts with LGV (Czech Republic)	LGV proctitis (LGV genotype confirmed by PCR amplification of *pmpH*)	Clinical correlates of LGV infection	Symptoms included intense rectal pain, blood in stool, mucus discharge, tenesmus, constipation. Endoscopy showed congested, irritated mucus membranes.	All were HIV^+ MSM. Lymph node abscess occurred in 1 pt. Treatment with oral doxycycline was curative.
Vargas-Leguas et al [12]	Case series	146 pts with LGV (Spain)	CT infection with L serovar confirmed by rt-PCR	Epidemiological and clinical characteristics of LGV	Most cases were HIV^+ MSM with proctitis. Median 35 d from symptom onset to diagnosis.	70 cases were reported in 2011 (compared with 69 reported from 2007 to 2010); control measures ramped up.

Downloaded from http://cid.oxfordjournals.org/ at University of California, San Francisco on January 14, 2016

Table 1 continued.

Reference	Study Design	Study Population	Exposure/Intervention	Outcome Measures	Reported Findings	Design Analysis Quality/Biases
Peuchant et al [13]	Case report	1 pt with LGV (France)	LGV proctitis (L2b variant, confirmed by *ompA* genotype and sequencing)	Clinical correlates of LGV infection	Symptoms included anorectal pain, mucopurulent discharge, rectal bleeding, tenesmus. Colonoscopy showed ulcerative proctitis.	HIV^- with multiple sex partners. Responded to 3 wk of doxycycline.
Ronn & Ward [14]	Meta-analysis	Published studies of LGV among MSM (17 studies, 1145 pts)	LGV infection	HIV infection among MSM with LGV	OR 8.19 for HIV^+ among LGV patients (95% CI, 4.68–14.33)	Raw pooled HIV prevalence estimate of 77.9% among MSM with LGV.
Quint et al [15]	Case series	201 CT-positive rectal swabs from MSM (99 LGV, 102 non-LGV)	Rectal CT infection	Detection of concomitant CT genotypes in CT-positive specimens	Concomitant non-LGV genotype was detected in 6.1% of LGV samples. No concomitant LGV infections were identified in the non-LGV samples.	Concomitant non-LGV genotypes do not lead to missed LGV diagnoses.
Hoie et al [16]	Case series	4 pts with LGV (Denmark, Norway)	LGV proctitis	Clinical correlates of LGV infection	Gastrointestinal symptoms raised suspicion of IBD.	All cases were MSM. Three-quarters were HIV^+. All responded to doxycycline.
Heras et al [17]	Case series	15 pts with LGV (Spain)	LGV proctocolitis (L2 serovar confirmed with reverse hybridization)	Clinical correlates of LGV infection	80% had clinical proctitis	All pts responded to 21 d of doxycycline, with negative follow-up test results.
Kober et al [18]	Case report	1 pt with LGV (UK)	LGV rectal infection	Clinical correlates of LGV infection	Asymmetrical polyarthropathy ×3 mo, which resolved after successful treatment of LGV	HIV^+ MSM.
Singhrao et al [19]	Case report	2 pts with LGV (UK)	LGV rectal infection (confirmed LGV-associated serovar on rectal swab)	Clinical correlates of LGV infection	Both pts presented with isolated perianal ulcers.	Both pts responded to 3 wk of doxycycline. High index of suspicion required for nonproctitis presentations.
Bissessor [20]	Case series	25 pts with LGV (Australia)	LGV infection (confirmed by *omp1* genotyping)	Clinical correlates of LGV infection	LGV found in 7.2% of pts with chlamydial infection and symptomatic proctitis	72% of cases coinfected with HIV.
Soni et al [21]	Case series	15 pts with LGV (UK)	LGV proctitis (confirmed with LGV-specific DNA)	Clinical and endoscopic correlates of LGV infection	Retrospective analysis. Pts had mucosal ulcers, cryptitis, crypt abscesses, and granulomas.	LGV proctitis closely resembles IBD.
Castro et al [22]	Case series	9 pts with chronic proctitis (Portugal)	LGV proctitis (confirmed by rt-PCR/*omp1* gene amplification)	Clinical correlates of LGV infection	Two patients confirmed infected with L2b serovar, with ≥10 000 antibody titers.	First 2 cases of LGV in Portugal.
Kamarashev et al [23]	Case series	12 pts with proctitis (Switzerland)	LGV proctitis (confirmed serovar L2 by PCR)	Clinical correlates of LGV infection	12 confirmed cases since 2003: anorectal pain, discharge, tenesmus, change in stool frequency.	All pts were MSM, most were HIV^+. 4 pts successfully treated with 1 g azithromycin, 7 cases successfully treated with doxycycline 100 mg twice daily for 10–20 d.

Downloaded from http://cid.oxfordjournals.org/ at University of California, San Francisco on January 14, 2016

Table 1 continued.

Reference	Study Design	Study Population	Exposure/Intervention	Outcome Measures	Reported Findings	Design Analysis Quality/Biases
Flexor et al [24]	Case report	1 pt with LGV (France)	Genital LGV infection (PCR-confirmed serovar L2)	Clinical correlates of LGV infection	Penile ulceration ×3 wk with large swollen granulomatous lesion and inguinal lymph node, but no proctitis.	Genital bubo due to LGV. Responded to doxycycline 200 mg daily.
Savage et al [25]	Case series	1693 cases of LGV (8 European countries)	LGV infection	Clinical correlates of LGV infection	Cases were predominantly MSM, most were HIV$^+$. Anorectal symptoms were most common.	Little evidence of spread to the wider population.
Vall-Mayans & Caballero [26]	Case series	7 pts with proctitis (Spain)	LGV infection (confirmed serovar L)	Clinical correlates of LGV infection	Mean duration of proctitis symptoms 28 d	All cases were MSM, HIV$^+$.
Vall-Mayans et al [27]	Case report	1 pt with proctitis and arthropathy (Spain)	LGV infection (confirmed by rt-PCR)	Clinical correlates of LGV infection	Proctitis, conjunctivitis, and arthritis affecting knees and right elbow.	LGV and SARA – responded to doxycycline ×21 d.
Heras et al [28]	Case report	1 pt with proctitis (Spain)	LGV infection (serotype L2a confirmed by PCR)	Clinical and endoscopic correlates of LGV infection	Rectal pain, tenesmus, mucopurulent discharge. Endoscopy revealed ulcerations, friability.	MSM, HIV$^+$. Pt was initially misdiagnosed with lymphoma. Symptoms resolved completely with doxycycline.
El Karoui et al [29]	Case report	1 pt with proctitis and reactive arthritis (France)	LGV infection (confirmed L2b serovar by PCR of *omp1*)	Clinical correlates of LGV infection	Pt had fever, weight loss, purulent rectal discharge, tenesmus, followed by conjunctivitis and oligoarthritis (wrist, knee, ankles).	HIV$^+$ MSM with SARA, responded to doxycycline ×30 d.
Ward et al [30]	Multicenter cross-sectional survey	4825 urethral and 6778 rectal samples from MSM attending genitourinary clinics (UK)	Presence of LGV and non-LGV serovars	Clinical correlates of LGV and non-LGV chlamydial infection	Prevalence of non-LGV: 6.06% rectal, 3.21% urethral. Prevalence of LGV: 0.90% rectal, 0.04% urethral. 95% of rectal LGV was symptomatic.	Did not identify a large reservoir of asymptomatic LGV in rectum or urethra. Serovar typing not indicated in the absence of symptoms.
Annan et al [31]	Cross-sectional prevalence study	3076 MSM attending genitourinary clinics (UK)	Presence of LGV and non-LGV serovars	Clinical correlates of LGV and non-LGV chlamydial infection	CT prevalence (LGV and non-LGV) 8.2% in rectum, 5.4% in urethra. 69.2% of rectal infections were asymptomatic.	Most rectal infections would have been missed if routine screening had not been performed. 36 cases of LGV identified.
Cusini et al [32]	Case series	13 pts with LGV (Italy)	LGV infection (confirmed by PCR or clinical/ epidemiologic criteria)	Clinical correlates of LGV infection	Symptoms included anal discharge, rectal erosion, nodular erosive lesions, and inguinal abscess.	All pts MSM, most HIV$^+$.
Khorvash et al [33]	Case report	1 pt with inguinal and femoral mass (Iran)	LGV infection (confirmed by histopathology and IgG titer)	Clinical correlates of LGV infection	History of sexual contact with mare 14 d before illness onset	Zoonotic transmission.
LGV laboratory diagnosis						
Almeida et al [34]	Laboratory analysis	51 Chlamydia strains (LGV, ocular, urogenital) (Portugal)	Analyses of polymorphisms and phylogeny of 48 Inc proteins	Amino acid differences between LGV and ocular/urogenital isolates	LGV strains showed significant AA differences; 10 Inc genes likely under positive selective pressure. Subtle nonsilent mutations contribute to tropism/ invasiveness of LGV strains.	Inhibition of phagolysosomal fusion is hypothesized to account for LGV invasiveness.

Downloaded from http://cid.oxfordjournals.org/ at University of California, San Francisco on January 14, 2016

Table 1 continued.

Reference	Study Design	Study Population	Exposure/Intervention	Outcome Measures	Reported Findings	Design Analysis Quality/Biases
Korhonen et al [35]	Cross-sectional study	140 CT NAAT-positive rectal and pharyngeal swabs	Genotyping by *pmpH* and *ompA* rt-PCR	Detection of LGV and non-LGV CT types	114/140 (81%) were successfully typed by pmpH PCR (104 non-LGV, 9 LGV, 1 both). Of the L-types, 6 were L2b, and 2 were L2 by *ompA* PCR and sequencing. L types were mostly rectal.	Genotyping by pmpH PCR is feasible in diagnostic labs that already perform NAATs to detect chlamydia.
Mobius et al [36]	Laboratory assay development	CT L serovar primers	Development of rt-PCR protocol	Detection of LGV-associated L serovars	Step-by-step description of a protocol for using TaqMan multiplex rt-PCR to detect LGV-associated serovars	Allows subtyping of L1, L2, and L3 variants.
Verweij et al [37]	Laboratory assay development	CT L2b serovars	Development of rapid L2b-specific PCR	Detection of L2b-specific serovar	Description of an L2b-specific primer/probe set for rapid identification of L2b variant using rt-PCR	Based on unique insertion in *pmpH* gene; avoids laborious ompA sequencing.
Quint et al [38]	Laboratory assay development	50 CT-positive specimens (Aptima Combo 2)	Detection of CT by *omp1* sequencing, CT-DT assay, and *pmpH* rt-PCR	Differentiation of LGV and non-LGV infections	CT-DT assay was best for distinguishing LGV from non-LGV infections.	*pmpH* rt-PCR assay performed well for LGV, but missed substantial numbers of non-LGV infections.
Cai et al [39]	Laboratory assay development	15 rectal specimens from patients with COBAS Amplicor PCR-confirmed CT infection	Comparison of HRMA and MAS-PCR	Detection of L2 serovars	Both methods identified 2/15 samples as serovar L2.	Both HRMA and MAS-PCR are inexpensive, rapid, and easy tools to identify LGV in clinical and research settings.
de Vries et al [40]	Laboratory assay development	61 pts with anal CT infection (42 CT^+/LGV^+ vs 19 CT^+/LGV^-)	Serologic assays for chlamydia: IgA anti-MOMP, IgG anti-MOMP, IgA anti-LPS, IgG anti-LPS	Differential LGV from non-LGV anal infections	IgA anti-MOMP performed best, even in asymptomatic pts: sensitivity 85.7%, specificity 84.2%.	Subsequent validation showed the test was most accurate when cutoff point was set to 2.0 (sensitivity and specificity both ~75%), could be useful screening tool.
LGV treatment						
Hill et al [41]	Retrospective case series	63 episodes of LGV in 60 pts (UK)	Treatment with doxycycline, erythromycin, or azithromycin	Treatment failure/TOC within 3 mo	Clinical and microbiological cure in 18/19 (95%) doxycycline vs 1/1 (100%) erythromycin vs 4/4 (100%) azithromycin pts	All 7 pts treated with azithromycin (1 g weekly ×3 wk) had complete resolution of symptoms (but only 4 received TOC).
de Vries et al [42]	Guideline	Meta-analysis	Review of literature on clinical management of LGV	Appropriate clinical management of LGV	First-line therapy: doxycycline 100 mg twice daily ×21 d. Second-line therapy: erythromycin 500 mg 4 times daily ×21 d	Azithromycin has been proposed, but evidence lacking to support this medication.

Downloaded from http://cid.oxfordjournals.org/ at University of California, San Francisco on January 14, 2016

Table 1 continued.

Reference	Study Design	Study Population	Exposure/Intervention	Outcome Measures	Reported Findings	Design Analysis Quality/Biases
Mechai et al [43]	Case report	1 pt with LGV (France)	Treatment with doxycycline	Resolution of proctitis and lymphadenopathy	Anal pain, anal ulceration, and inguinal lymphadenopathy, not improving despite >3 wk of doxycycline. Recovered after treatment with moxifloxacin 400 mg daily ×10 d.	HIV^- male. LGV diagnosis presumed from clinical presentation (but not confirmed L2 serovar).
Asymptomatic rectal chlamydia treatment						
Khosropour et al [44]	Retrospective cases series	70 pts with rectal CT (US)	Treatment with azithromycin vs doxycycline	Persistent/recurrent infection after 6 mo	CT-positive at follow-up among 8/49 (16%) azithromycin-treated pts, vs 2/21 (10%) doxycycline-treated pts.	Did not examine treatment failure vs reinfection.
Steedman & McMillan [45]	Retrospective case series	101 pts with rectal CT (UK)	Treatment with azithromycin	Treatment failure/TOC after 21 d	9/68 (87%) were CT-positive at test of cure (but 8/9 had sexual contact since treatment).	Unable to discern repeat infection vs treatment failure.
Drummond et al [46]	Retrospective case series	116 pts with rectal CT (Australia)	Treatment with azithromycin	Treatment failure/TOC after 6 wk	11/85 (13%) were CT-positive at test of cure; 5 were suspected treatment failure)	"Possible treatment failure" = did not report anal sex, or used condoms consistently.
Hathorn et al [47]	Prospective observational cohort study	265 pts with rectal CT (UK)	Treatment with azithromycin vs doxycycline	Treatment failure/ TOC after 21 d	11/42 (26%) azithromycin pts CT-positive at TOC vs 2/40 (5%) doxycycline pts CT-positive at TOC	Low rates of TOC follow-up.
Elgalib et al [48]	Prospective single-arm cohort	487 pts with rectal CT (UK)	Treatment with doxycycline	Treatment failure/TOC after 28 d	163/165 (99%) were CT^- at TOC	No comparison group.

Abbreviations: AA, amino acid; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CT, *Chlamydia trachomatis*; DT, Detection genoTyping; DVT, deep vein thrombosis; HIV, human immunodeficiency virus; HRMA, high-resolution melting analysis; IBD, inflammatory bowel disease; IgA, immunoglobulin A; IgG, immunoglobulin G; LGV, lymphogranuloma venereum; LPS, lipopolysaccharide; MAS, multiplex allele-specific; MOMP, major outer membrane protein; MSM, men who have sex with men; NAAT, nucleic acid amplification test; OR, odds ratio; PCR, polymerase chain reaction; PMNL, polymorphonuclear leukocyte; pt(s), patient(s); rt-PCR, real-time polymerase chain reaction; SARA, sexually acquired reactive arthritis; STI, sexually transmitted infection; TOC, test of cure.

Downloaded from http://cid.oxfordjournals.org/ at University of California, San Francisco on January 14, 2016

Azithromycin may also be effective for treating LGV, given its efficacy against other genital tract and systemic non-LGV chlamydial infections. However, clinical evidence is lacking to support the routine use of azithromycin, and multiple doses may be required to provide a similar level of sustained antimicrobial activity (eg, 1.0 g weekly for 3 weeks) [41]. Fluoroquinolone antibiotics with demonstrated antichlamydial activity (such as ofloxacin or levofloxacin) may also be effective for treating LGV, but no comparative treatment trials have been published, and extended treatment durations are likely required. Moxifloxacin (400 mg daily for 10 days) has been reported as effective treatment for doxycycline treatment failure [43].

Many patients with LGV are HIV infected, particularly MSM with proctocolitis. These patients respond well to recommended treatment regimens, although some patients may have a delayed resolution of symptoms and may benefit from prolonged courses of treatment. In the absence of a diagnostic assay for LGV, MSM with acute proctitis and a positive rectal chlamydia test should be offered presumptive treatment with a recommended regimen for LGV.

Treatment of asymptomatic rectal chlamydial infections is controversial. Some investigators have raised concerns about the efficacy of single-dose azithromycin in this context. Retrospective analyses of asymptomatic rectal chlamydia treated with 1 g of azithromycin found that >10% of patients who returned for test of cure were persistently positive [45, 46]. Moreover, prospective observational studies have documented persistent positivity rates of 16%–20% among persons who were treated with azithromycin, compared with only 1%–10% among persons who were treated with doxycycline [44, 47, 48]. Clearly, additional research is required to clarify the optimal treatment regimen for patients with asymptomatic rectal chlamydial infection.

CONCLUSIONS

LGV continues to be an important cause of morbidity among MSM, and clinicians should have a high index of suspicion for LGV when assessing patients with proctitis or symptoms suggestive of inflammatory bowel disease. Diagnosing LGV remains a challenge, although newer molecular tests show great promise and are likely to become more widely available in the coming years. Serologic assays are limited by lack of sensitivity and specificity, but can be helpful in providing a presumptive diagnosis of LGV in the proper clinical context.

Our review of the literature supports the current treatment recommendation of doxycycline 100 mg twice daily for 21 days. Alternative agents such as azithromycin are promising due to their antichlamydial activity, but extended treatment regimens are likely required. HIV-infected persons should be treated with standard LGV regimens, but extended treatment courses may be required if symptom resolution is delayed. Additional research is required to clarify optimal treatment approaches for asymptomatic rectal chlamydial infections.

Notes

Financial support. The Centers for Disease Control and Prevention (CDC) provided travel support for both authors to attend the Sexually Transmitted Disease Treatment Guidelines expert panel in Atlanta, Georgia, April 2013.

Supplement sponsorship. This article appears as part of the supplement "Evidence Papers for the CDC Sexually Transmitted Diseases Treatment Guidelines," sponsored by the Centers for Disease Control and Prevention.

Potential conflict of interest. Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Stamm WE. Lymphogranuloma venereum. In: Holmes KK, Sparling PF, Stamm WE, et al., eds. Sexually transmitted diseases. 4th ed. New York: McGraw-Hill Professional, **2007**:595–606.
2. McLean CA, Stoner BP, Workowski KA. Treatment of lymphogranuloma venereum. Clin Infect Dis **2007**; 44(suppl 3):S147–52.
3. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep **2015**; 64(RR-3):1–137.
4. Arnold CA, Limketkai BN, Illei PB, Montgomery E, Voltaggio L. Syphilitic and lymphogranuloma venereum (LGV) proctocolitis: clues to a frequently missed diagnosis. Am J Surg Pathol **2013**; 37:38–46.
5. de Vrieze NHN, van Rooijen M, Schim van der Loeff M, de Vries HJC. Anorectal and inguinal lymphogranuloma venereum among men who have sex with men in Amsterdam, the Netherlands: trends over time, symptomatology and concurrent infections. Sex Transm Infect **2013**; 89:548–52.
6. Gallegos M, Bradly D, Jakate S, Keshavarzian A. Lymphogranuloma venereum proctosigmoiditis is a mimicker of inflammatory bowel disease. World J Gastroenterol **2012**; 18:3317–21.
7. Verweij SP, Ouburg S, de Vries H, et al. The first case record of a female patient with bubonic lymphogranuloma venereum (LGV), serovariant L2b. Sex Transm Infect **2012**; 88:346–7.
8. Cunningham SE, Johnson MD, Laczek JT. Lymphogranuloma venereum proctitis. Gastrointest Endosc **2012**; 75:1269–70.
9. Kennedy JE, Higgins SP. Complicated lymphogranuloma venereum infection mimicking deep vein thrombosis in an HIV-positive man. Intl J STD AIDS **2012**; 23:219–20.
10. Geisler WM, Kapil R, Waites KB, Smith PD. Chronic rectal bleeding due to lymphogranuloma venereum proctocolitis. Am J Gastroenterol **2012**; 107:488–9.
11. Vanousova D, Zakoucka H, Jilich D, et al. First detection of *Chlamydia trachomatis* LGV biovar in the Czech Republic, 2010–2011. Euro Surveill **2012**; 17:pii:20055.
12. Vargas-Leguas H, Garcia de Olalla P, Arando M, et al. Lymphogranuloma venereum: a hidden emerging problem, Barcelona 2011. Euro Surveill **2012**; 17:pii:20057.
13. Peuchant O, Baldit C, Le Roy C, et al. First case of *Chlamydia trachomatis* L2b proctitis in a woman. Clin Microbiol Infect **2011**; 17: E21–3.
14. Ronn MM, 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.
15. Quint KD, Bom RJ, Quint WG, et al. Anal infections with concomitant *Chlamydia trachomatis* genotypes among men who have sex with men in Amsterdam, the Netherlands. BMC Infect Dis **2011**; 11:63.

Downloaded from http://cid.oxfordjournals.org/ at University of California, San Francisco on January 14, 2016

16. Hoie S, Knudsen LS, Gerstoft J. Lymphogranuloma venereum proctitis: a differential diagnosis to inflammatory bowel disease. Scand J Gastroenterol **2011**; 46:503–10.
17. Heras E, Llibre JM, Martro E, Casabona J, Martin-Iguacel R, Sirera G. Lymphogranuloma venereum proctocolitis in men with HIV-1 infection. Enferm Infecc Microbiol Clin **2011**; 29:124–6.
18. Kober C, Richardson D, Bell C, Walker-Bone K. Acute seronegative polyarthritis associated with lymphogranuloma venereum infection in a patient with prevalent HIV infection. Intl J STD AIDS **2011**; 22:59–60.
19. Singhrao T, Higham E, French P. Lymphogranuolma venereum presenting as perianal ulceration: an emerging clinical presentation? Sex Transm Infect **2011**; 87:123–4.
20. Bissesor M. Characteristics of lymphogranuloma venereum (LGV) infection among homosexual men in Melbourne. Abstracts of the 19th Biennial Conference of the International Society for Sexually Transmitted Diseases Research, Quebec City, Canada, 2011. Sex Transm Infect **2011**; 87(suppl 1):A139.
21. Soni S, Srirajaskanthan R, Lucas SB, Alexander S, Wong T, White JA. Lymphogranuloma venereum proctitis masquerading as inflammatory bowel disease in 12 homosexual men. Aliment Pharmacol Ther **2010**; 32:59–65.
22. Castro R, Baptista T, Vale A, et al. Lymphogranuloma venereum serovar L2b in Portugal. Int J STD AIDS **2010**; 21:265–6.
23. Kamarashev J, Riess CE, Mosimann J, Lauchli S. Lymphogranuloma venereum in Zurich, Switzerland: *Chlamydia trachomatis* serovar L2 proctitis among men who have sex with men. Swiss Med Wkly **2010**; 140:209–12.
24. Flexor G, Clarissou J, Gaillet M, de Barbeyrac B, Perronne C, de Truchis P. Genital lymphogranuloma venereum in an HIV-1 infected patient. Ann Dermatol Venereol **2010**; 137:117–20.
25. Savage EJ, van de Laar MJ, Gallay A, et al. Lymphogranuloma venereum in Europe 2003–2008. Euro Surveill **2009**; 14:pii:19428.
26. Vall-Mayans M, Caballero E. Lymphogranuloma venereum: an emerging cause of proctitis in homosexual men in Barcelona. Rev Clin Esp **2009**; 209:78–81.
27. Vall-Mayans M, Caballero E, Sanz B. The emergence of lymphogranuloma venereum in Europe. Lancet **2009**; 374:356.
28. Heras E, Llibre JM, Sirera G, et al. Lymphogranuloma venereum proctitis in the setting of HIV: a case report and differential diagnosis. AIDS Patient Care STDS **2009**; 23:493–4.
29. El Karoui K, Mechai F, Ribadeau-Dumas F, et al. Reactive arthritis associated with L2b lymphogranuloma venereum proctitis. Sex Transm Infect **2009**; 85:180–1.
30. 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 Infect **2009**; 85:173–5.
31. Annan NT, Sullivan AK, Nori A, et al. Rectal chlamydia—a reservoir of undiagnosed infection in MSM. Sex Transm Infect **2009**; 85:176–9.
32. Cusini M, Boneschi V, Arancio L, et al. Lymphogranuloma venereum: the Italian experience. Sex Transm Infect **2009**; 85:171–2.
33. Khorvash F, Keshteli AH, Salehi H, Szeredi L, Morre SA. Unusual transmission route of lymphogranuloma venereum following sexual contact with a female donkey. Intl J STD AIDS **2008**; 19:563–4.
34. Almeida F, Borges V, Ferreira R, Borrego MJ, Gomes JP, Mota LJ. Polymorphisms in inc proteins and differential expression of inc genes among *Chlamydia trachomatis* strains. J Bacteriol **2012**; 194:6574–85.
35. Korhonen S, Hiltunen-Back E, Puolakkainen M. Genotyping of *Chlamydia trachomatis* in rectal and pharyngeal specimens: identification of LGV genotypes in Finland. Sex Transm Infect **2012**; 88:465–9.
36. Mobius N, Brenneisen W, Schaeffer A, Henrich B. Protocol for the rapid detection of the urogenital tract mollicutes and chlamydia with concomitant LGV-(sub)typing. Methods Molec Biol **2012**; 903:235–53.
37. Verweij SP, Catsburg A, Ouburg S, et al. Lymphogranuloma venereum variant L2b-specific polymerase chain reaction: insertion used to close an epidemiological gap. Clin Microbiol Infect **2011**; 17:1727–30.
38. Quint KD, Bom RJ, Bruisten SM, et al. Comparison of three genotyping methods to identify *Chlamydia trachomatis* genotypes in positive men and women. Mol Cell Probes **2010**; 24:266–70.
39. Cai L, Kong F, Toi C, van Hal S, Gilbert GL. Differentiation of *Chlamydia trachomatis* lymphogranuloma venereum-related serovars from other serovars using multiplex allele-specific polymerase chain reaction and high-resolution melting analysis. Int J STD AIDS **2010**; 21:101–4.
40. 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**; 37:789–95.
41. Hill SC, Hodson L, Smith A. An audit on the management of lymphogranuloma venereum in a sexual health clinic in London, UK. Intl J STD AIDS **2010**; 21:772–6.
42. de Vries HJC, Morre SA, White JA, Moi H. European guideline for the management of lymphogranuloma venereum, 2010. Int J STD AIDS **2010**; 21:533–6.
43. Mechai F, de Barbeyrac B, Aoun O, Merens A, Imbert P, Rapp C. Doxycycline failure in lymphogranuloma venereum. Sex Transm Infect **2010**; 86:278–9.
44. Khosropour CM, Duan R, Metsch LR, Feaster DJ, Golden MR. Persistent/recurrent chlamydial infection among STD clinic patients treated with CDC-recommended therapies. Abstracts of the STI and AIDS World Congress, Vienna, Austria, 2013. Sex Transm Infect **2013**; 89(suppl 1):A29.
45. Steedman NM, McMillan A. Treatment of asymptomatic rectal *Chlamydia trachomatis*: is single-dose azithromycin effective? Int J STD AIDS **2009**; 20:16–8.
46. Drummond F, Ryder N, Wand H, et al. Is azithromycin adequate treatment for asymptomatic rectal chlamydia? Int J STD AIDS **2011**; 22: 478–80.
47. Hathorn E, Opie C, Goold P. What is the appropriate treatment for the management of rectal *Chlamydia trachomatis* in men and women? Sex Transm Infect **2012**; 88:352–4.
48. Elgalib A, Alexander S, Tong CY, White JA. Seven days of doxycycline is an effective treatment for asymptomatic rectal *Chlamydia trachomatis* infection. Int J STD AIDS **2011**; 22:474–7.

Downloaded from http://cid.oxfordjournals.org/ at University of California, San Francisco on January 14, 2016