Treatment of Lymphogranuloma Venereum

Catherine A. McLean,[1,2] Bradley P. Stoner,[3] and Kimberly A. Workowski[1,2]

[1]Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention (proposed), Centers for Disease Control and Prevention, and [2]Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia; and [3]Division of Infectious Diseases and Department of Anthropology, Washington University School of Medicine, St. Louis, Missouri

Background. Lymphogranuloma venereum (LGV) classically presents with 1 or more genital ulcers or papules, as well as inguinal lymphadenopathy (buboes). Recently reported cases of LGV proctitis in men who have sex with men, many of whom are coinfected with human immunodeficiency virus (HIV), have highlighted the importance of optimal clinical treatment of LGV.

Methods. A review was conducted of the literature on LGV published between 1998 and 2004, as part of the development of the 2006 sexually transmitted disease treatment guidelines of the Centers for Disease Control and Prevention (CDC).

Results. Doxycycline (100 mg orally twice daily for 21 days) remains the treatment of choice for LGV. No controlled trials support the use of azithromycin or the use of alternative treatment regimens for persons with HIV infection.

Conclusions. On the basis of the present literature review, the CDC's treatment recommendations for LGV remain unchanged. LGV clinical care, surveillance, and research are severely hindered by the lack of widely available, rapid, standardized tests for the diagnosis of LGV; therefore, patients with symptoms suggestive of LGV, including LGV proctitis, should be presumptively treated with antibacterial therapy for 3 weeks.

BACKGROUND

Lymphogranuloma venereum (LGV), a sexually transmitted disease (STD) caused by *Chlamydia trachomatis* serovar L1, L2, or L3, typically presents with 1 or more genital ulcers or papules, followed by the development of unilateral or bilateral, fluctuant, inguinal lymphadenopathy (buboes) [1]. LGV is endemic in Southeast Asia, the Caribbean, Latin America, and regions of Africa; historically, rates of LGV have been low in industrialized countries [1, 2]. Clinical experience suggests that LGV is highly responsive to antibacterial therapy; however, if LGV is not treated, extensive tissue damage may occur, leading to deep-tissue abscesses, chronic fissures, strictures, and severe abdominal pain [2].

LGV proctitis, a less common form of LGV that occurs in both men and women, may present with rectal ulcerations, purulent or sanguineous anal discharge, tenesmus, and lower abdominal cramping or pain. Prolonged infection may result in perirectal abscesses, anal fissures, fistula formation, and such constitutional symptoms as fever, malaise, generalized fatigue, and weight loss [1, 3]. Beginning in 2003, clusters of cases of LGV proctitis have been identified in Europe, Canada, and the United States. Reported cases of LGV proctitis have occurred primarily among men who have sex with men, many of whom are coinfected with HIV; concern has been raised about the recognition and manifestations of LGV proctitis [3–12]. Similar to other ulcerative STDs, LGV proctitis may increase the risk of acquiring and transmitting HIV infection [13].

The Centers for Disease Control and Prevention (CDC) routinely examines the evidence for treatment recommendations for STDs, including evidence for treatment recommendations for LGV [14]. The present article summarizes a review of the literature published between 1998 and 2004 that was used in the development of the section on LGV in the CDC's 2006 STD treatment guidelines [14]. Although information about LGV diagnostic testing is presented, this article does not include a comprehensive review of LGV diagnostic testing.

Reprints or correspondence: Dr. Catherine A. McLean, HIV Prevention Branch, Global AIDS Program, Centers for Disease Control and Prevention, Mailstop E-04, 1600 Clifton Rd., Atlanta, GA 30333 (CMcLean@cdc.gov).

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METHODS

Questions were formulated that addressed important aspects of LGV management and treatment. A computerized search for articles on LGV treatment published from 1998 through 2004 was conducted using the Medline databases (as of 2005) of the US National Library of Medicine and the National Institutes of Health. The terms "lymphogranuloma venereum" and "LGV" (as subjects) and "treatment" were used as key words in searches of article titles and abstracts. Abstracts relevant to LGV treatment that were presented at meetings of the Infectious Diseases Society of America, the Interscience Conference on Antimicrobial Agents and Chemotherapy, the International Congress of Sexually Transmitted Diseases/International Society for Sexually Transmitted Disease Research, or the National Sexually Transmitted Disease Prevention Conference were reviewed. When necessary, reference was also made to medical literature that predated the period covered in the search.

Evidence from the scientific literature was used to answer key questions regarding LGV management and treatment. The evidence was coded as level I if the findings were from a meta-analysis of randomized controlled trials or from ⩾1 randomized controlled trial; as level II if the evidence was obtained from ⩾1 well-designed controlled study without randomization or from ⩾1 other type of well-designed quasi-experimental study; and as level III if the evidence was obtained from well-designed, nonexperimental descriptive studies (such as comparative studies, correlation studies, and case-control studies), expert committee reports/opinions, and/or clinical experience of respected authorities. Grading of the evidence was as follows: grade A denoted good evidence; B, moderate evidence; and C, insufficient evidence. This article presents the key questions that were addressed and the scientific literature that supports the recommendations in the 2006 STD treatment guidelines developed by the CDC [14].

RESULTS

What is the best laboratory method for the diagnosis of LGV? There are limited comparative data regarding laboratory methods for the diagnosis of LGV. Recommendations for laboratory testing for LGV heavily rely on assumptions made about diagnostic testing for genitourinary chlamydia in general, and, to our knowledge, there have been no published studies of the performance of these tests in the diagnosis of LGV proctitis [15, 16].

Diagnosis of LGV is based on clinical suspicion, epidemiologic information, and the exclusion of other etiologies (of proctocolitis, inguinal lymphadenopathy, or genital or rectal ulcers), along with the results of *C. trachomatis* testing, if available. Genital and lymph node specimens (i.e., lesion swab specimens or bubo aspirates) may be tested for *C. trachomatis* by culture, direct immunofluorescence, or nucleic acid detection. However, nucleic acid amplification tests for *C. trachomatis* have not been cleared by the US Food and Drug Administration for the testing of rectal specimens. Even if testing identifies *C. trachomatis,* additional procedures (e.g., genotyping) are required but are not widely available for differentiating LGV from non-LGV chlamydial infections. *C. trachomatis* culture is difficult to perform and is available only in specialized laboratories.

Serologic testing for *Chlamydia* organisms (with complement fixation titers >1:64 denoting a positive result) can support the diagnosis in the appropriate clinical context. Comparative data between types of serologic tests are lacking, and the diagnostic utility of serologic methods other than complement fixation and microimmunofluorescence procedures has not been established. Interpretation of the results of serologic tests for LGV is not standardized, tests have not been validated for clinical presentations of proctitis, and *C. trachomatis* serovar-specific serologic tests are not widely available. In the absence of specific diagnostic testing for LGV, patients with a clinical syndrome consistent with LGV, including proctocolitis or genital ulcer disease with lymphadenopathy, should be treated for LGV as described in this article.

What data support the use of doxycycline, and what is the role of macrolides in the treatment of LGV? Treatment cures LGV and prevents ongoing tissue damage, although tissue reaction to the infection can result in scarring. On the basis of a treatment trial published in 1957 and long-standing clinical experience with the effectiveness of the drug, doxycycline is recommended as first-line treatment for LGV (table 1) [14, 19]. In what is, to our knowledge, the only comparative treatment trial for LGV published to date, Greaves et al. [19] studied 43 patients who had LGV diagnosed on the basis of clinical examination and serologic tests. Overall, patients treated with an antibacterial (chloramphenicol, chlortetracycline, oxytetracycline, or sulfadiazine) had a reduction in bubo duration, compared with patients treated only on a symptomatic basis. Several tetracycline formulations, doxycycline, and minocycline were studied and appeared to be effective in small (sample size, <30 participants), uncontrolled clinical studies [17, 18, 20, 21]. Because its pharmacokinetics are similar to those of the tetracyclines, and because of its convenient dosing (100 mg orally twice daily for 21 days) and minimal toxicity, doxycycline was selected as and remains the recommended treatment for LGV [14]. Most experts recommend a treatment period of 3 weeks, because of the deep-seated nature of the infection.

Because azithromycin has proved to be highly effective against genital and systemic non-LGV chlamydial infections, some STD specialists believe that azithromycin (1.0 g orally once weekly for 3 weeks) is likely to be effective against LGV chlamydial infections [24–26, 28, 36]. The high tissue concen-

Table 1. Lymphogranuloma venereum (LGV): summary of data on treatment and the level of evidence for treatment recommendations.

Treatment	First author of study, year of publication [reference]	Results/comments	Level of evidence for recommendation[a]	Grading of recommendation[b]
Tetracyclines	Wright, 1948 [17]; Wright, 1951 [18]; Greaves, 1957 [19]; Neves, 1968 [20]; Sowmini, 1976 [21]	To our knowledge, Greaves [19] remains the only comparative treatment trial to date and showed that chemotherapy had a minimal effect on bubo duration; long-standing clinical effectiveness has been demonstrated for 50 years; a variety of preparations have been effective in clinical studies (Tet, Dox, and Mino); 20 cases were successfully treated with Otet,[c] and 25 cases were successfully treated with Ctet;[d] Dox has similar pharmacodynamics, convenient dosing (100 mg orally twice daily), and minimal toxicity as Tet	III	B
Erythromycin	Banov, 1953–1954 [22]; Banov, 1954 [23]	Clinically effective and safe during pregnancy; not well tolerated because of GI effects	III	C
Azithromycin	Martin, 1992 [24]; Nilsen, 1992 [25]; Hammerschlag, 1993 [26]; Ballard, 1996 [27]; Thorpe, 1996 [28]	To our knowledge, no published studies have been conducted for LGV treatment; highly effective for other genital and systemic chlamydial infections; minimal clinical data are available: 2 patients suspected of having chancroid (and later shown to have LGV) were cured by single-dose azithromycin	III	C
Ofloxacin	Hooten, 1992 [29]; Martens, 1993 [30]	No clinical data for LGV treatment; highly effective for treatment of other genital chlamydial infections; theoretically, should be effective if given as 300 mg twice daily for 3 weeks, although this would be costly	III	C
Sulfonamides	Jones, 1945 [31]; Tucker, 1945 [32]; Rake, 1948 [33]	Widely used in the 1940s and 1950s; clinically, sulfonamides reduce the size of buboes and heal fistulae, but they do not sterilize lesions	III	C
Chloramphenicol	Greenblatt, 1952 [34]	Effective but more toxic than available alternative agents	III	C
Rifampin	Menke, 1979 [35]	Study was reported as a letter to the editor	III	C

NOTE. Ctet, chlortetracycline; Dox, doxycycline; GI, gastrointestinal; Mino, minocycline; Otet, oxytetracycline; Tet, tetracycline.

[a] Level I evidence was obtained from meta-analysis of randomized controlled trials or from ⩾1 randomized controlled trial; level II evidence was obtained from ⩾1 well-designed controlled study without randomization or from ⩾1 other type of well-designed quasi-experimental study; and level III evidence was obtained from well-designed, nonexperimental descriptive studies (such as comparative studies, correlation studies, and case-control studies), expert committee reports/opinions, and/or clinical experience of respective authorities.

[b] Grade A denotes good (level I) evidence; grade B, moderate (level II) evidence; and grade C, insufficient (level III) evidence.

[c] Terramycin (Pfizer).

[d] Aureomycin (Wyeth).

tration and long half-life of azithromycin are attractive properties when considering treatment for an infection that achieves deep-tissue penetration, such as that which occurs in association with chlamydial LGV serovars. However, minimal clinical data are available on the effectiveness of azithromycin in the treatment of LGV. For example, one published report found single-dose azithromycin to be effective treatment for 2 cases of LGV that were initially thought to be chancroid [27]. Comparative treatment studies of the use of azithromycin for LGV (including proctitis) are needed to determine efficacy at varying drug doses and treatment durations. In addition, monitoring for the emergence of azithromycin resistance should be a component of azithromycin treatment trials, because macrolide resistance has been demonstrated in association with *C. trachomatis* non-LGV serovars [37].

In addition to the use of antibacterials to eradicate LGV infection and prevent ongoing tissue damage, either aspiration or incision and drainage (through intact skin) may be performed on fluctuant buboes, to prevent the formation of inguinal/femoral ulcerations. However, the effectiveness of this intervention has not been well demonstrated.

Do fluoroquinolones have a role in the treatment of LGV? The antichlamydial activity of fluoroquinolones has been well demonstrated; therefore, fluoroquinolones are probably effective treatment for LGV (table 1) [29, 30]. Oral fluoroquinolones are recommended for the treatment of uncomplicated chlamydial infections of the lower genital tract and are included in the treatment regimens for pelvic inflammatory disease (treatment duration, 14 days) [14]. However, there have been no published trials on the use of fluoroquinolones for the treatment of LGV. As with other antibacterial agents, extended treatment may be required.

Do sulfonamides have a role in the treatment of LGV? Sulfonamides were widely used for the treatment of LGV in the 1940s and 1950s, and clinical cures were reported with reductions in buboe and fistulae size (table 1) [19]. However, sulfonamide treatment may not sterilize LGV lesions, and treatment failures have occurred [31]. For these reasons, most experts believe that other agents, such as tetracyclines or macrolide antibacterials, are better alternatives for the treatment of LGV.

What is the best LGV treatment regimen for HIV-infected patients? Little is known about the natural history of LGV, including that in immunosuppressed persons. Theoretically, LGV may be more severe among immunosuppressed persons, or latent infection may reactivate with immunosuppression. To our knowledge, no comparative treatment trials examining outcomes for HIV-infected and -uninfected patients have been published. On the basis of clinical experience, standard treatment with doxycycline or erythromycin is recommended for HIV-infected patients. Delay in the resolution of symptoms may occur in immunosuppressed persons, and prolonged therapy may be required; therefore, HIV-infected persons should be closely monitored for relapse or treatment failure.

What are the LGV treatment options during pregnancy? Tetracyclines and fluoroquinolones are contraindicated in pregnant and lactating women. Erythromycin is clinically effective and safe for pregnant women, and, despite being less well tolerated because of gastrointestinal side effects, it remains the drug of choice for the treatment of LGV during pregnancy (erythromycin base, 500 mg orally 4 times daily for 21 days) [22]. Clinical experience and studies suggest that azithromycin is safe and effective for use during pregnancy. With its effectiveness against genitourinary and ocular *Chlamydia* organisms, azithromycin may prove to be a safe alternative to erythromycin during pregnancy. Multiple doses of azithromycin (1.0 g orally once weekly for 3 weeks) would likely be required for effective treatment.

What is the optimal duration of therapy? The natural history of LGV is marked by spontaneous remissions and exacerbations, and relapses have occurred with short-course therapy. Although, to our knowledge, there have been no comparative studies of the treatment duration for LGV, the recommended treatment, on the basis of clinical experience, is ⩾3 weeks' duration.

What is the best interval for partner-notification activities? The optimum contact interval for risk notification of recent sex partners and the value of empirical antibacterial treatment in the absence of clinical symptoms are unknown. The incubation period for the primary lesions (e.g., ulcerations) is thought to be 3–30 days. A 30-day contact interval may miss persons exposed to earlier, subclinical lesions, because primary lesions are often imperceptible, and because most patients have LGV diagnosed during later stages of infection. As a result, some experts argue for the use of a longer contact interval (i.e., 60 days). Although data are lacking, the current recommendation is that persons who have had sexual contact with a patient with LGV within the 60 days before onset of the patient's symptoms should be examined, tested for urethral or cervical chlamydial infection (determined by exposure), and treated with a standard *Chlamydia* treatment regimen (azithromycin, 1 g orally once, or doxycycline, 100 mg orally twice daily for 7 days) [14]. Some specialists use longer contact intervals.

CONCLUSION

On the basis of a review of recent literature, the treatment of choice for LGV—doxycycline (100 mg orally twice daily for 21 days)—remains unchanged from prior recommendations [14]. Although azithromycin is effective against other chlamydial strains and may prove to be effective against infection with LGV serovars, there are no controlled treatment trials sup-

porting the use of azithromycin treatment for LGV. Until further information becomes available, immunocompromised persons, such as those with HIV infection, should receive the same treatment as immunocompetent persons; however, given the lack of data, patients with HIV infection and other immunocompromising conditions should be followed closely to assess resolution of symptoms, and extended treatment may be needed.

LGV clinical care, surveillance, and research are severely hindered by the lack of widely available, rapid, standardized diagnostic tests for LGV. As a result, patients with symptoms that are highly suggestive of LGV should be presumptively treated with antibacterial therapy for ⩾3 weeks, as indicated in the STD treatment guidelines developed by the CDC in 2006 [14, 38]. It is important to be aware of the clinical manifestations of LGV proctitis, which are particularly relevant in the evaluation of proctitis in men who have sex with men or in women. Expert consultation for the laboratory diagnosis of LGV is available through state health departments and the CDC.

Comparative treatment trials for LGV, including evaluations of azithromycin, appropriate durations of antibacterial therapy, and the response to treatment in immunocompromised patients, need to be conducted. Furthermore, little is known about the natural history of LGV (particularly in HIV-infected persons); the sensitivity and specificity of available diagnostic tests, especially those for rectal LGV; and, where diagnostic testing is available, the utility of screening for LGV proctitis. This information will be particularly important if the recently reported increases in the number of cases of LGV proctitis in men who have sex with men continue.

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