

Resurgence of Lymphogranuloma Venereum in Western Europe: An Outbreak of *Chlamydia trachomatis* Serovar L₂ Proctitis in The Netherlands among Men Who Have Sex with Men

Rutger F. Nieuwenhuis,^{1,a} Jacobus M. Ossewaarde,² Hannelore M. Götz,⁶ Jan Dees,³ H. Bing Thio,¹ Maarten G. J. Thomeer,⁴ Jan C. den Hollander,⁵ Martino H. A. Neumann,¹ and Willem I. van der Meijden¹

Departments of ¹Dermatology and Venereology, ²Medical Microbiology and Infectious Diseases, ³Gastroenterology and Hepatology, ⁴Radiology, and ⁵Clinical Pathology, Erasmus Medical Center, and ⁶Department of Infectious Diseases, Municipal Health Service, Rotterdam, The Netherlands

Background. Lymphogranuloma venereum (LGV) is a sexually transmitted disease (STD) and is rare in the Western world. Recently, 3 men who have sex with men presented with LGV proctitis at the Erasmus Medical Center, Rotterdam, The Netherlands. We investigated a possible outbreak in a sexual network of men who have sex with men (MSM).

Methods. After active case finding, a total of 15 men presented and were investigated. Serum antibody titers to *Chlamydia trachomatis* were determined. Urine and rectum specimens were analyzed by polymerase chain reaction (PCR) for the presence of *C. trachomatis*. *C. trachomatis*-positive specimens were genotyped to detect the specific *C. trachomatis* serovars. All subjects underwent routine STD screening. Sociodemographic, clinical, and endoscopic characteristics were evaluated.

Results. Thirteen subjects had high immunoglobulin (Ig) G and IgA titers to *C. trachomatis*, suggesting an invasive infection. Rectal specimens of 12 subjects were PCR-positive for *C. trachomatis*. All urine specimens were negative. Genotyping revealed serovars L₂ ($n = 8$) and L₁ ($n = 1$). An ulcerative proctitis was found in all subjects obtaining sigmoidoscopy ($n = 9$). Eleven of 13 subjects with an LGV diagnosis were seropositive for human immunodeficiency virus (HIV), 6 had another concomitant STD, and 1 had recently acquired a hepatitis C virus infection. Further sexual contacts were reported from The Netherlands, Germany, Belgium, the United Kingdom, and France.

Conclusions. We revealed an outbreak of LGV proctitis among MSM in The Netherlands. The ulcerous character favors transmission of HIV, other STDs, and blood-borne diseases. From a public health perspective, it seems important to increase the awareness of possible LGV in MSM with symptomatic proctitis.

Men who have sex with men (MSM) regularly consult physicians about proctitis. One of the most common causes in this patient population is infection with *Chlamydia trachomatis*. The etiology of clinical proctitis in MSM was recently discussed in this journal [1]. Proctitis due to lymphogranuloma venereum (LGV) is caused by

C. trachomatis serovars L₁, L₂, and L₃, but is infrequently referred to. Unlike other anogenital *C. trachomatis* infections, LGV is invasive and preferably affects the lymphatic system. Depending on the site of inoculation, patients usually seek medical attention for enlarged and tender inguinal lymph nodes with bubo formation or for acute proctitis [2]. Untreated, the infection may lead to a chronic inflammatory process with the formation of fistulae and strictures. Chronic inflammation of the lymphatic vessels, progressive lymph edema, and sclerosing fibrosis may cause severe disfiguring conditions, such as genital elephantiasis and esthiomene [3, 4]. Genotyping *C. trachomatis* by nested PCR and restriction fragment-length polymorphism (RFLP) allows a reliable diagnosis [5–7].

In the preantibiotic era, LGV was endemic in Europe

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^a Present affiliation: Department of Medical Microbiology, University Hospital Maastricht, The Netherlands.

Reprints or correspondence: Dr. Willem I. van der Meijden, Dept. of Dermatology and Venereology, Erasmus MC, PO Box 2040, 3015 GD Rotterdam, The Netherlands (w.i.vandermeijden@erasmusmc.nl).

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and the United States [8, 9]. The incidence of LGV in these parts of the world has decreased since antibiotic drugs have become available. Today, incidental cases in the Western world are considered to be imported from areas where LGV is still endemic, such as West and East Africa, India, Southeast Asia, South and Central America, and some Caribbean islands [2]. However, the possibility of LGV outbreaks in the West should not be neglected because of the ever-increasing commercial travel to and from regions of endemicity.

In February 2003, a white bisexual man with a recently acquired HIV infection presented with early-phase LGV (serovar L₂) at the sexually transmitted disease (STD) clinic of the Erasmus Medical Center in Rotterdam, The Netherlands [5]. Two months later, 2 other white HIV-infected MSM with men presented with acute proctitis. Laboratory examination showed again *C. trachomatis* serovar L₂ in both patients. On the basis of these 3 cases, a possible outbreak of LGV (serovar L₂) among MSM was suspected. An investigation was started to determine its nature and extent.

PATIENTS AND METHODS

Patient population. During the period of February through May 2003, 3 HIV-infected MSM with men presented with LGV (serovar L₂) at the STD clinic of the Erasmus Medical Center. These men were considered to be the index patients of a possible LGV outbreak in a sexual network of MSM; 2 of them were casual partners. Specialized nursing personnel performed counseling, including the importance of partner notification. Contact tracing was performed for the first ring of sexual contacts. The index patients were asked to list as many sexual partners in the previous 6 months as possible and to notify them about the possibility of infection. Partners were advised to visit the Rotterdam STD clinic.

During the period of May through October 2003, 14 MSM, all part of the same sexual network (including 2 of the 3 index patients and 12 sexual partners), were included in an observational study. One of the 3 index patients only had a single anonymous sexual contact in the previous 6 months and was therefore excluded from the study population. The patients within the study population were from different parts of The Netherlands, the majority being from the Amsterdam and Rotterdam regions. One patient was of Belgian origin but was currently living in Rotterdam. In addition, 1 man in this sexual network had been treated for symptomatic *C. trachomatis* proctitis in our STD clinic in May 2002, and he was therefore investigated by a retrospective chart analysis. The stored rectum and serum specimens of the latter patient were used for LGV testing. Informed consent was obtained by sending a letter with information about the study and its intended purposes.

Case definitions. Case definitions were developed to facilitate the outbreak management. All patients should have had

a history of high-risk sexual contact (i.e., a sexual partner with suspected or known LGV), proctitis, and/or inguinal bubo formation. The case definitions were based on laboratory results, as follows. A confirmed case of LGV was defined as PCR result positive for *C. trachomatis* with a rectum and/or urine specimen and detection of serovar L₂ through genotyping. A probable case of LGV was defined as a PCR result positive for *C. trachomatis* with a rectum and/or urine specimen, with no genotyping data (genotyping not performed), but with high levels of *C. trachomatis* IgG and IgA serum antibodies. A possible case of LGV was defined as a PCR result negative for *C. trachomatis* in both rectum and urine specimens (e.g., false-negative results or a sample error), but high levels of *C. trachomatis* IgG and IgA serum antibodies.

Observational study. A standardized questionnaire was used to interview the patients about urogenital and gastrointestinal complaints, sociodemographic characteristics, and sexual behavior. The information collected included age, ethnic background, travel habits, STD history, HIV infection status, receipt of antibiotic treatment in the previous 6 months, sexual preference, sexual techniques, and condom use, as well as whether the patient had already been seen by other specialists. The external genitalia were physically examined, and a routine STD screening was performed in accordance with the STD guideline of the Dutch Institute for Healthcare Improvement [10]. The distal part of the rectum was inspected by proctoscopy. If a patient had symptomatic rectal disease and/or the proctoscopy revealed abnormalities, an elective sigmoidoscopy was performed at the Department of Gastroenterology and Hepatology of the Erasmus Medical Center. Biopsies were performed, and samples were obtained for both histopathologic examination and PCR testing. To better understand the anatomy of rectal LGV, we performed MRI of the pelvic region in 2 patients with a state-of-the-art 1.5-T scanner (Sonata; Siemens). Patients with suspected LGV were treated with doxycycline (100 mg b.i.d. for 21 days) [11, 12].

Laboratory methods. To detect *C. trachomatis* DNA in clinical specimens, the automated *C. trachomatis* Cobas Amplicor PCR system (Roche Diagnostics) was used throughout the study, in accordance with the instructions of the manufacturer. Urine and rectal swabs, which were collected in 2SP medium, were used for PCR testing. Genotyping of the gene encoding the major outer membrane protein (MOMP) was performed by nested PCR and RFLP analysis [6]. Serum specimens were collected and analyzed for the presence of specific IgA and IgG antibodies to *C. trachomatis* by peptide EIA (SeroCT; Savyon Diagnostics). Results were reported as the ratio of the optical density of the serum specimen to the optical density of the cutoff control specimen.

RESULTS

LGV cluster. Contact tracing resulted in the identification of 54 men who were part of a sexual network of MSM. Of these men, 15 subjects were investigated. Table 1 summarizes the laboratory results for these 15 subjects. The results of PCR tests for *C. trachomatis* were positive for 12 subjects. Of note, this was only shown in rectum specimens; all urine specimens had negative results. Figure 1 shows the PCR-based RFLP of the *MOMP* gene, which demonstrates the presence of LGV serovars in the rectal specimens. Genotyping of the *C. trachomatis*-positive specimens was successful in 9 subjects: serovar L₂ was revealed in 8 subjects, and serovar L₁ was revealed in 1 subject. Genotyping was not possible for 2 subjects, but high *C. trachomatis* antibody titers were present, suggesting invasive infection. One subject showed high *C. trachomatis* antibody titers, but the subject had already been treated for *C. trachomatis* proctitis. A PCR-positive specimen was not available for this subject. Another subject had high *C. trachomatis* antibody titers without positive PCR results. In 2 subjects, the results of both PCR tests and serologic tests were negative. These findings yielded 9 confirmed LGV cases, 3 probable LGV cases, 1 possible LGV case, and 2 LGV-negative subjects.

HIV infection and routine STD screening. Eleven (84.6%) of 13 patients in the LGV cluster were HIV seropositive. Four (36.4%) of them were receiving HAART. One (7.7%) of 13

patients was HIV seronegative, and 1 patient (7.7%) refused an HIV test. Another concomitant STD was present in almost one-half of the 13 cases (6 cases [46.2%]), including rectal gonorrhea (4 cases [30.8%]), genital herpes simplex virus (HSV) infection (2 cases [15.4%]), syphilis (1 case [7.7%]), and chronic hepatitis B virus infection (1 case [7.7%]) (table 1).

Sociodemographic data. The 54 individuals, identified by contact tracing, were part of an international network. The majority were Dutch (36 subjects [66.7%]). The other reported contacts were from Germany (11 subjects [20.4%]), Belgium (4 subjects [7.4%]), the United Kingdom (2 subjects [3.7%]), and France (1 case [1.9%]).

All 13 patients in the LGV cluster were white, and all were Dutch residents. The median age was 39 years (range, 29–47 years). None of the patients had traveled overseas in the previous 6 months. Two patients had had male sexual partners of African and Latin American ethnic background in the previous 6 months, but these sexual encounters were anonymous. The majority of our patients (8 patients [61.5%]) had >10 sexual partners in the previous 6 months. Five patients (38.5%) had 5–10 sexual partners. All patients reported having anal intercourse, both receptive and insertive. Ten (76.9%) also reported regular “fisting” contacts. The use of condoms was limited: 6 patients (46.2%) never used condoms, and 7 (53.8%) used them sometimes. Most men in this network met several times a year

Table 1. Results of laboratory tests for *Chlamydia trachomatis*, HIV, and other causes of sexually transmitted diseases (STDs) in 15 patients in the lymphogranuloma venereum (LGV) outbreak study.

Patient	Diagnosis of LGV	Peptide EIA ^a		PCR		Genotype	HIV infection (receipt of HAART)	Other STD findings
		IgG	IgA	Urine	Rectum			
1	Confirmed	>6.2	3.4	Negative	Positive	Serovar L ₂	Yes (No)	Gonorrhea
2	Confirmed	>8.6	3.5	Negative	Positive	Serovar L ₂	Yes (No)	Chronic hepatitis B
3	Confirmed	>6.9	5.2	Negative	Positive	Serovar L ₂	Yes (No)	Hepatitis C ^b
4	Confirmed	>8.6	2.7	Negative	Positive	Serovar L ₂	Yes (Yes)	Primary syphilis, anogenital herpes
5	Confirmed	>6.5	2.6	Negative	Positive	Serovar L ₂	No	No
6	Confirmed	>6.5	10.4	Negative	Positive	Serovar L ₂	Yes (No)	No
7 ^c	Probable	>4.2	>3.9	Negative	Positive	...	Yes (Yes)	Gonorrhea, anogenital herpes
8	Confirmed	6.2	11.4	Negative	Positive	Serovar L ₂	Yes (Yes)	No
9	Probable	6.2	12.9	Negative	Positive	Not available ^d	Yes (Yes)	No
10	Probable	>7.0	6.0	Negative	Positive	...	Unknown ^e	Gonorrhea
11	Confirmed	3.0	3.5	Negative	Positive	Serovar L ₁	Yes (No)	Gonorrhea
12	Confirmed	>3.8	>4.1	Negative	Positive	Serovar L ₂	Yes (No)	No
13	No LGV	0.4	0.5	Negative	Negative	...	Yes (Yes)	No
14	Possible	6.2	8.4	Negative	Negative	...	Yes (No)	No
15	No LGV	0.9	0.4	Negative	Negative	...	No	No

^a IgG and IgA antibodies to *C. trachomatis* are measured as the ratio to the cutoff value.

^b Hepatitis C was reported to the Municipal Health Service in Rotterdam by an infectious disease specialist.

^c Retrospectively studied patient; stored specimens were used for laboratory analysis.

^d This patient was tested and treated elsewhere. His specimens were not available for genotyping.

^e The patient refused to undergo an HIV test.

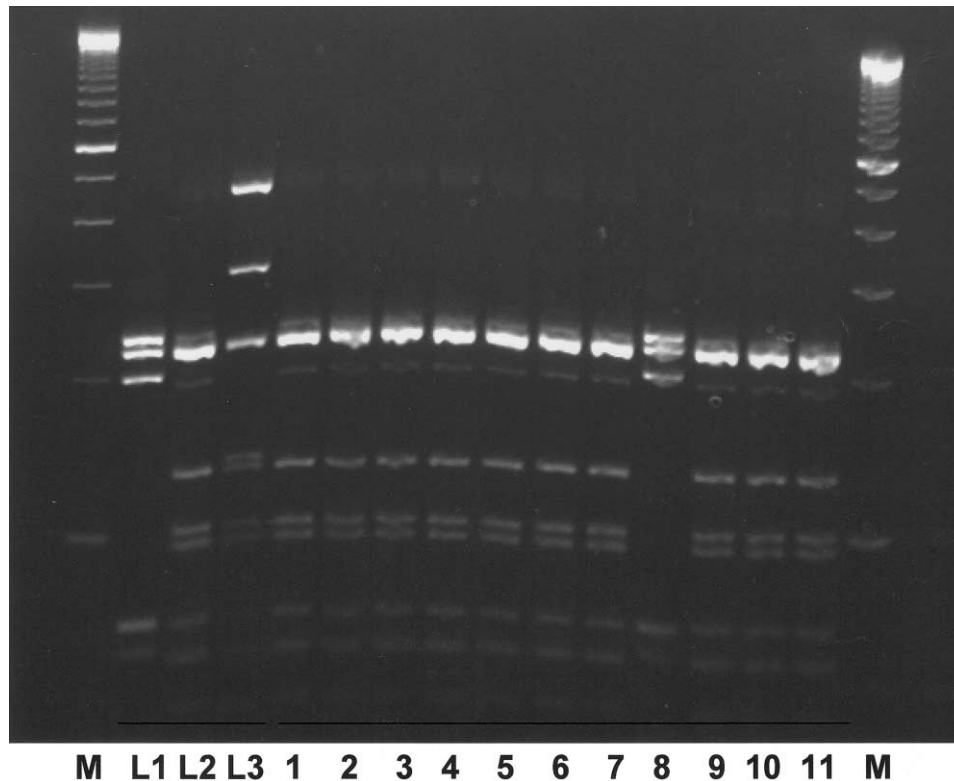


Figure 1. Agarose gel of restriction fragment–length polymorphism analysis of 11 rectal specimens and controls. All specimens were analyzed by *AluI* restriction enzyme. Lane M, 100-bp marker; lanes L1, L2, and L3, respective lymphogranuloma venereum prototypes; lanes 1–11, clinical specimens.

at gay parties and clubs in Amsterdam; Antwerp, Belgium; Berlin, Germany; and Cologne, Germany. Three patients mentioned the Canary Islands, Spain, as a yearly meeting place.

STD history, symptoms, and physical examination. All patients in the LGV cluster had a positive history of STDs. These included hepatitis B virus infection (10 patients [76.9%]), syphilis (9 patients [69.2%]), gonorrhea (8 patients [61.5%]), chlamydia (8 patients [61.5%]), genital HSV infection (1 patient [7.7%]), and genital warts (1 patient [7.7%]). Table 2 summarizes symptoms and signs, proctoscopic findings, and sigmoidoscopic findings in patients with confirmed, probable, or possible LGV ($n = 13$). At presentation, 12 patients (92.3%) had intestinal symptoms, with a median duration of 3 months (range, 1–13 months). The most common symptoms included mucopurulent discharge, constipation, and blood loss. Less frequently reported symptoms were tenesmus and weight loss. One patient reported that he had had a rectum abscess in the previous year, which drained spontaneously. No patient reported a history of enlarged inguinal lymph nodes or urogenital symptoms. Physical examination revealed perianal erosions in 2 patients, both of whom were positive for HSV. None of the patients showed urethral discharge. Tender inguinal lymphadenopathy was not found.

Endoscopic and histopathologic findings. Proctoscopy was

performed in 12 patients (table 2). Abnormalities noted were mucopurulent exudate (9 patients [75%]), ulcers (3 patients [35%]), and erythema (2 patients [16.7%]). In 1 patient, a tumorous mass (categorized as extrinsic impression in table 2) was found in the distal part of the rectum (figure 2, left), which could no longer be demonstrated by sigmoidoscopy 2 weeks after antibiotic treatment. Analysis of the results of a punch biopsy of this tumor revealed ulcerative granulation and severe inflammation. *C. trachomatis* was detected by both immunofluorescence (figure 3) and PCR testing.

Sigmoidoscopy was performed in 9 patients, revealing ulcers in 100% (table 2). Other abnormalities found were exudate (3 patients [33.3%]), extrinsic impressions (3 patients [33.3%]), friable mucosa with easy bleeding (3 patients [33.3%]), and erythema (1 patient [11.1%]). In general, nodular and ulcerative mucosa characterized the endoscopic picture of the rectum ampoule. The ulcers, with normal interjacent mucosa, had a diameter of ~0.5–2 cm, were sharply demarcated, and were covered with fibrin or a purulent exudate. Occasionally, a circular ulcer was seen in the rectum ampoule (figure 2, right).

Histopathologically, there was a dense mixed inflammatory infiltrate in the lamina propria adjacent to the ulcers, consisting of neutrophils, lymphocytes, plasma cells, histiocytes, and occasional eosinophils. Other features were architectural distur-

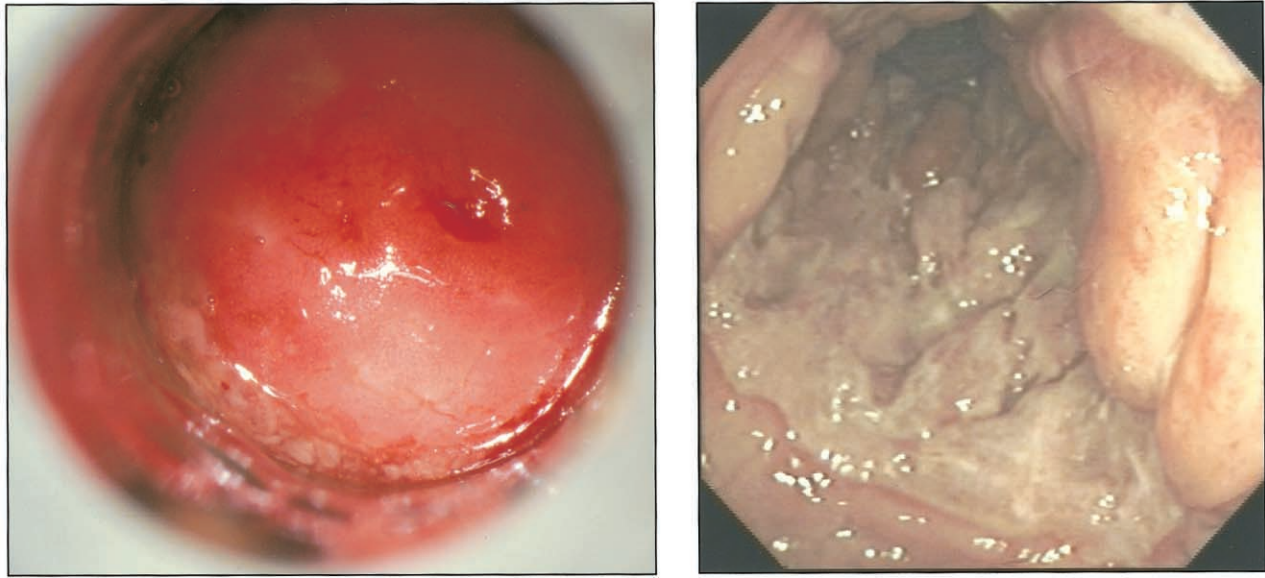


Figure 2. Endoscopic view of the rectum in 2 patients with acute proctitis due to lymphogranuloma venereum. *Left*, Proctoscopy showing a large tumor with some purulent exudate in the distal part of the rectum. The center of the tumor shows a defect after punch biopsy. *Right*, Sigmoidoscopy showing almost circular rectal ulceration with sharp demarcation and normal interjacent mucosa.

tion of the remaining crypts and occasional crypt abscess formation. Additional periodic acid-Schiff, Grocott, and Giemsa staining showed no specific features. The results of PCR assays for *C. trachomatis* were positive for all biopsy samples.

MRI findings. Diffuse mucosal wall thickening with sub-mucosal edema (figure 4, *left*) was identified on MRIs of the rectum of 2 patients with confirmed LGV. The intramural edema was visible as a hyperintense signal on T2-weighted

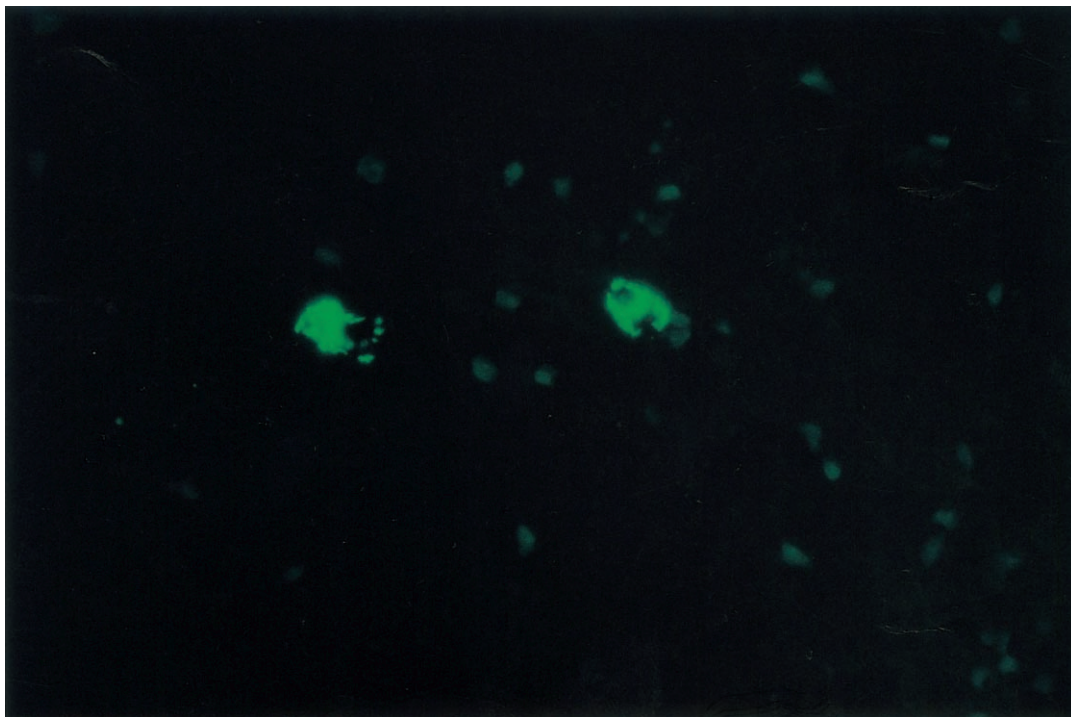


Figure 3. Direct immunofluorescence of *Chlamydia trachomatis* in a biopsy specimen of a rectum tumor. *C. trachomatis* inclusions show as bright apple-green fluorescence in 2 host cells (monoclonal antibodies; original magnification, $\times 400$).

Table 2. Symptoms, proctoscopy findings, and sigmoidoscopy findings in 13 patients with confirmed, probable, and possible rectal lymphogranuloma venereum (LGV) and in 2 subjects without LGV.

Characteristic	Patients with confirmed LGV (n = 9)	Patients with probable LGV (n = 3)	Patients with possible LGV (n = 1)	Patients without LGV (n = 2)
Symptom^a				
All	9	3	0	1
Mucopurulent rectal discharge	8 (88.9)	2	...	1
Rectal blood loss	6 (66.7)	2
Constipation	8 (88.9)	2
Tenesmus	2 (22.2)
Weight loss	2 (22.2)
Anogenital ulcer/erosion	2 (22.2)	1
Inguinal bubo formation
Proctoscopy^b				
All	8	1	1	2
Exudate	7 (87.5)	1	1	...
Ulcers/erosions	3 (37.5)
Erythema	1 (12.5)	...	1	...
Extrinsic impressions ^c	1 (12.5)
Sigmoidoscopy^d				
All	8	1	NP	NP
Exudate	3 (37.5)
Ulcers/erosions/fissures	8 (100)	1
Erythema	1 (12.5)
Extrinsic impressions	3 (37.5)
Friable mucosa/easy bleeding	3 (37.5)

NOTE. Data are no. (%) of subjects. NP, not performed.

^a Data are for 13 patients.

^b Data are for 12 patients.

^c Extrinsic impressions are bowel wall impressions from outside, with intact mucosa being the most important endoscopic feature.

^d Data are for 9 patients.

images and a more hypointense signal on T1-weighted images with preservation of the different wall layers. Both patients also presented with a rather remarkable perirectal halo of infiltration and adenopathies (figure 4, right). Some slightly enlarged iliacal and inguinal lymph nodes were also visible. No signs of ascites were found.

DISCUSSION

We report an outbreak of LGV in The Netherlands among MSM in a sexual network. *C. trachomatis* serovar L₂ was identified in 8 men. In addition, 1 patient had a *C. trachomatis* serovar L₁ infection. Outbreaks of LGV are not often reported in the Western world. In the past 2 decades, only 2 clusters of LGV were described (by Scieux et al. [13] in Paris and Bauwens et al. [14] in Seattle, Washington). However, these cases were studied retrospectively. To our knowledge, this is the first extensive description of a series of clinically observed LGV cases in the Western world.

The best recognized presentation of LGV in the early phase

is the inguinal syndrome, which is characterized by acute inguinal lymphadenitis with bubo formation, sometimes preceded by a solitary primary lesion (e.g., herpetic ulcer, papule, or pustule) [4, 8]. The other clinical presentation of LGV, the anogenitoretal syndrome, causes moderate to severe ulcerative proctocolitis, which can clinically and histopathologically resemble Crohn disease [15, 16]. In contrast, non-LGV strains of *C. trachomatis* (serovar D-K) may produce mild inflammation of the rectal mucosa accompanied by small erosions, but these infections are usually asymptomatic [15, 17].

Clinical proctitis is a common problem in MSM, and *C. trachomatis* is one of the most frequent infectious agents in this population [1]. Our observations show patients presenting with moderate-to-severe symptomatic proctitis. However, preliminary data from our patients and some reference gastroenterologists showed that the underlying cause often remained unclear, even after several endoscopic examinations. Crohn disease, extraordinary forms of ulcerous proctitis, syphilis, and herpetic proctitis may be considered in the differential diagnosis. This underscores



Figure 4. MRI of confirmed lymphogranuloma venereum. *Left*, Fat-suppressed early gadolinium enhanced T1-weighted axial image showing a remarkable perirectal halo (arrows) of contrast-enhancing fat infiltration with local adenopathies. *Right*, Late enhanced midsagittal T1-weighted image revealing an increased contrast-enhancement in a thickened rectal mucosa (arrowhead). Diffuse thickening of the bowel submucosa with preservation of the different wall layers, indicating submucosal edema (arrows), is evident. Prominent rectal wall edema without signs of mucosal or submucosal mass lesion suggests benign inflammatory pathology (proctitis) instead of tumor. The asterisks denote the intestinal lumen.

the unfamiliarity with LGV by Western health care professionals, emphasizing the need for adequate reporting and education. Moreover, some patients did not seek medical attention until their partners informed them about this study, suggesting that contact tracing is of major importance in these patients.

Our investigation showed only cases of rectal LGV. Despite the fact that all patients had experienced both receptive and insertive anal intercourse, urethral infection with LGV strains of *C. trachomatis* was not demonstrated. Thus far, the reasons for this are unclear. The transmission of rectal LGV may be related to other sexual activities, such as “fisting,” because this was a common activity in the reported network. The data from our study population support the previously reported rates of promiscuity and high-risk sexual behaviors among MSM [18, 19].

Sigmoidoscopy showed ulcerative proctitis in all patients with rectal LGV. The ulcerous nature of rectal LGV, like all genital ulcer diseases (GUDs), may enhance both the transmission and acquisition of HIV infection and other STDs, as well as blood-borne diseases [20–22]. First, the majority of our patients had concomitant HIV infection. Almost one-half of the HIV-infected patients were receiving HAART. It was previously suggested that GUDs may appear atypically and more extensive in cases of concomitant HIV infection [23]. Therefore, HIV infection might have contributed to facilitated transmission of LGV pathogens because of increased exposure as a result of ulcers, which may serve as a portal of entry and egress. The interrelation between HIV infection, GUD, and high-risk sexual behavior was previously discussed by Bauwens et al. [21].

Our study shows a clear parallel with their findings. The exact effect of HIV infection on transmission and the clinical presentation has yet to be investigated. Second, routine STD screening showed the existence of concomitant infectious agents, such as *Neisseria gonorrhoeae*, HSV, and *Treponema pallidum*, demonstrating coprevalence of other STDs in the presence of rectal LGV. Whether this should be attributed to increased susceptibility as a result of loss of the mucosal barrier, is merely based on behavioral factors, or is a combination of both remains to be seen. Third, one of our patients was reported in December 2003 to the Municipal Health Service in Rotterdam with a recent hepatitis C virus infection. Risk factor evaluation suggested sexual transmission, a finding in line with recent reports [22, 24]. Contact tracing and further investigation to support the evidence of sexual hepatitis C virus transmission is ongoing at the Municipal Health Service in Rotterdam. These findings underscore the public health importance of the LGV outbreak.

Individual contact tracing was often hampered as a result of many anonymous sexual contacts, which may indicate that the numbers reported here are just a small part of a large outbreak. Moreover, the reported LGV cluster we report here shows an international sexual network of MSM, with participation from The Netherlands, Belgium, Germany, the United Kingdom, and France. Although no cases were reported elsewhere at the time that this article was being prepared, we suspected that transmission and spread of LGV had already affected a major part of Western Europe. In January 2004, an international alert was sent to the members of the European network of STD surveillance

and to professionals in infectious diseases control and curative care through the early warning system of the European Union. Preliminary data were reported in *Eurosurveillance Weekly* [25].

In conclusion, this report describes an outbreak of LGV among MSM in The Netherlands with implications for other countries in Western Europe. Because of high-risk sexual behaviors in the homosexual scene and the ulcerous character of rectal LGV, both the acquisition and transmission of HIV and other STDs are facilitated. Even sexual transmission of blood-borne diseases may be favored in these patients. Health care professionals who treat patients with acute proctitis should consider LGV, especially when it concerns MSM. Recognition of this clinical entity is important to ensure the appropriate therapy. We advise proctoscopy and PCR testing for *C. trachomatis* in these patients. Patients with acute ulcerative proctitis in combination with positive chlamydial testing should be treated with doxycycline (100 mg b.i.d. for 21 days) [10, 11] and should be followed up until the results of chlamydial tests are negative and the patient has clinically recovered.

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Conflict of interest. All authors: No conflict.

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