

# Lymphogranuloma venereum in Zurich, Switzerland: *Chlamydia trachomatis* serovar L2 proctitis among men who have sex with men

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## Summary

**Background:** Whereas until 2003 Lymphogranuloma venereum (LGV) was rare in industrialised countries, there have been increasing reports of cases of LGV proctitis in men having sex with men (MSM) over the last six years in Europe, America and Australia.

**Patients and methods:** After the alarming message from the Netherlands in 2003, physicians in a dermatological and STI private clinic in Zurich started examining rectal swabs from patients with proctitis for LGV serovars of *C. trachomatis* on a regular basis. A test system based on PCR with sequencing and databank comparison was used. Clinical files of all patients with proctitis observed in this time period were examined.

**Results:** Since 2003 twelve cases of proctitis, all in MSM, caused by the LGV serovar L2 *C. trachomatis* were observed. Of the overall 11 patients the majority were HIV positive and only 2 were HIV negative. Only one patient reported previous sex-

ual contacts outside Europe (Thailand) as the likely place of infection. The clinical presentation was characterised by anorectal pain, discharge, tenesmus and change in stool frequency. Four patients were successfully treated with a single dose of 1 g azithromycin. In all seven cases treated with doxycycline 2x100 mg for 10–20 days clinical cure and a negative PCR result after treatment were observed, except for one patient lost to follow-up.

**Conclusions:** Zurich has not been spared by the recent outbreaks of LGV proctitis in MSM. Anorectal LGV infections may progress to severe destructive changes, with formation of granulomas, strictures, and perirectal abscesses. Increased awareness of this problem and establishment of reliable diagnostic tools are required.

**Key words:** Lymphogranuloma venereum, *Chlamydia trachomatis*, proctitis, epidemiology

## Introduction

*Chlamydia trachomatis* is an obligate intracellular parasite that is subdivided into numerous serovars or serotypes [1]. Serotypes A–C cause trachoma, while serotypes D–K are responsible for a wide spectrum of diseases including cervicitis, urethritis and endometritis. Lymphogranuloma venereum (LGV), or Nicolas-Favre disease, is a sexually transmitted infection (STI) caused by *C. trachomatis* serovar L1, L2, or L3 [2]. Unlike other chlamydial urogenital infections that are generally restricted to epithelial surfaces, L serovars are invasive, can cause severe inflammation, often with systemic symptoms, and have a preference for lymphatic tissue. LGV typically occurs in both sexes and presents with one or more genital ulcers or papules, followed by the development of unilateral or bilateral, fluctuant, inguinal lymphadeno-

pathy (buboes) in the second stage and by lymphoedema, abscesses, granulomas and strictures in the third stage [3]. Before 2003 LGV was considered to be a “tropical” disease, endemic in parts of Africa, Latin America, and Asia, but rare in Western industrialised countries. In 2003 an outbreak of LGV in 13 MSM was reported in Rotterdam, Netherlands [4]. Since then further reports of outbreaks of LGV in MSM from The Netherlands, Belgium [5], France [6], Germany [7, 8], Sweden [9], the United Kingdom [10], North America [11] and Australia [12] have followed. One confirmed case of LGV was reported in Geneva in 2005 [13]. To date, most LGV outbreaks have been caused by the strain L2, have occurred in MSM and have manifested as proctitis.

## Patients and methods

This study is based on information obtained from the clinical files of patients diagnosed with LGV in a gay-friendly dermatological and STI private clinic in Zurich in the time period 2003–2007. After the alarming message from the Netherlands in 2003 the physicians in this clinic started regularly examining rectal swabs from patients with proctitis for LGV serovars of *C. trachomatis*. Clinical

files, including detailed clinical history, epidemiologically relevant information, symptoms, manifestation, treatment regimens and outcome were reviewed for all patients observed with proctitis in this time period. *C. trachomatis* was detected in rectal swabs by a test system based on PCR with sequencing and databank comparison [14].

## Results

The charts of 262 patients who presented with the chief complaint of anal pain and/or discharge and were examined by rectal swab for *C. trachomatis* PCR between 2003 and 2007 were reviewed. Of these swabs, 49 were positive for *C. trachomatis*. Various serotypes were found: 13 samples (11 patients) with serotype L2, 11 samples (10 patients) with serotype D, 15 samples with serotype G and 10 samples with serotype J. Of the 11 patients with proctitis due to *C. trachomatis* serotype L2, nine were HIV positive and two HIV negative (table N 1). Two patients had *Neisseria gonorrhoeae* co-infection and one patient was diagnosed with concomitant syphilis. All of the patients with serotype L2 were MSM. Most of the patients reported the likely place of infection to be in Western European cities: London, Amsterdam, Brussels, Berlin, Frankfurt and Zurich. Only one patient reported previous sexual contacts outside Europe (Thailand) as the most likely place of infection. The clinical presentation was characterised by anorectal pain, discharge, tenesmus and change in stool

frequency. In seven cases the discharge was purulent, in two cases it was purulent and haemorrhagic, in a further two cases it was serous and in one haemorrhagic. One patient with purulent proctitis developed a perirectal abscess. Lymphadenopathy was not a feature in any of the cases. At the time when treatment was prescribed no information on the causative microorganism was yet available. Four cases were treated with a single dose of 1 g azithromycin, achieving clinical cure and negative PCR control one month later. Two patients were initially treated with 500 mg azithromycin daily over three days. One failed to respond. In the second the symptoms improved, but one month later he presented with recurrent anorectal pain and *C. trachomatis* serotype L2 was again detected. Seven cases (including the two that did not respond to azithromycin) were treated with doxycycline 2 x 100 mg for 10–20 days. Clinical cure was observed and confirmed by control PCR examination after treatment in all six cases available for follow-up.

**Table 1**

Overview of patient characteristics, treatment and outcome. Total number of positive samples is 13, obtained from 11 patients (patient 2 and patient 4 had two symptomatic episodes and 2 positive samples each).

Patient	Diagnosis	Clinical presentation	Presumed place of infection	Treatment	Comorbidities	Follow-up
1	03/2003	Purulent proctitis	unknown	Azithromycin 1g	HIV neg.	PCR neg 4/03
2	04/2003	Purulent and hemorrhagic proctitis	London	Azithromycin 1g	HIV pos.	PCR neg 4/03
	10/2003	Purulent proctitis	London	Azithromycin 1g		PCR neg 9/05
3	05/2003	Hemorrhagic proctitis	Thailand	Azithromycin 500 mg/d for 3 days, Doxycyclin 100 mg bid for 10 days	HIV pos.	PCR neg 07/03
4	11/2003	Purulent proctitis	Amsterdam	Azithromycin 500 mg/d for 3 days	HIV neg., Syphilis	
	12/2003	Purulent proctitis		Doxycyclin 100 mg bid for 10 days		PCR neg 7/05
5	11/2003	Purulent proctitis	Brussels	Ofloxacin 300 mg bid for 7 days	HIV pos., N. gonorrhoe pos.	PCR neg 3/04
6	04/2005	Proctitis, non-purulent (serous)	Berlin	Azithromycin 1g	HIV pos.	PCR neg 07/05
7	07/2005	Purulent proctitis	Zürich	Doxycyclin 100 mg bid for 12 days	HIV pos.	lost for follow-up
8	06/2006	Proctitis, non-purulent (serous)	Berlin	Doxycyclin 100 mg bid for 10 days	HIV pos.	PCR neg. 08/06
9	03/2007	Purulent proctitis	Zürich	Doxycyclin 100 mg bid for 20 days	HIV pos., N. gonorrhoe pos.	PCR neg. 04/2007
10	04/2007	Purulent proctitis, perirectal abscess	Frankfurt	Doxycyclin 100 mg bid for 20 days	HIV pos	PCR neg 05 2007
11	08/2007	Purulent and hemorrhagic proctitis	Frankfurt	Doxycyclin 100 mg bid for 20 days	HIV pos.	PCR neg 10/07

## Discussion

Rectal infections with LGV immunotypes of *C. trachomatis* have been recognised since 1936 [15] but were rarely diagnosed until 2003. Early sporadic reports of LGV in MSM are found in the literature. Although LGV has been known to affect the rectum in the late stages of classical disease, proctitis became recognised as the major manifestation of LGV in MSM following case series such as those identified in Seattle [16, 17] and San Francisco [18, 19] in the late 1970s and early 1980s. In 2003 an outbreak of LGV in 13 MSM was reported in Rotterdam, Netherlands. Since then further reports of outbreaks of LGV in MSM from many other European countries, North America and Australia have followed. To date, most LGV cases have been caused by the L2 strain. Another feature of these new outbreaks is the fact that most cases have occurred in MSM and that most patients have presented with the symptoms of anal discharge and proctitis. The mode of transmission of LGV in MSM is only partly understood. Almost all reported cases of LGV in MSM present as proctitis, and even though a series of 13 MSM presenting with inguinal LGV lesions has recently been published [20], inguinal disease in this population remains very rare and suggests rectum-to-rectum transmission. Case finding studies [21, 22] suggest that involvement of an asymptomatic reservoir of LGV is very unlikely. HIV infection has been reported to be present in over 70% of patients with LGV proctitis and represents the most important risk factor [10], a finding corroborated by our study. On the other hand, there is no evidence that LGV should be regarded as an opportunistic infection. In our series the HIV infection preceded the LGV proctitis in all cases. All HIV positive patients were receiving HAART and had stable T-cell counts without clinical signs of immunosuppression (data not shown). The high degree of coinfection with HIV and *C. trachomatis*, serovar L2 is not fully clear, but risk sexual behaviour seems to play an important role. Large numbers of sexual partners, unprotected anal sex and practices such as fisting, rectal drug use and the use of sex toys and enemas are further risk factors which have been associated with LGV proctitis [10].

This new epidemic has necessitated the development of trustworthy laboratory techniques for diagnostic and screening purposes. Although nucleic acid amplification tests are well established in the diagnosis of urogenital CT infections in both males and females, culture is still regarded as standard for testing at extragenital sites. Concerns

have been raised about the specificity of nucleic acid amplification tests in low-prevalence settings, but studies in recent years have shown that these tests are much more sensitive than culture and should be the method of choice for the detection of CT at extragenital sites in MSM [23–25].

Zurich has not been spared by the recent outbreaks, although up to now most cases seem to be associated with outbreaks in other European countries and no epidemiological connection between the observed cases has been established.

Some of the patients were treated with a single dose of azithromycin or short courses (10 days) of doxycycline for chlamydial infection before typing was available, and the attending physician learned about the serotype only afterwards. The fact that no chlamydia could be detected in these patients at follow-up may indicate that these treatment regimens are sufficient for some cases, but this hypothesis has not been formally tested. It must be clearly stated that the current guidelines for treatment of rectal LGV infection recommend doxycycline 100 mg bid for 21 days.

Anorectal LGV infections may progress to severe destructive changes with formation of granulomas, strictures, and perirectal abscesses. LGV may be contributing to the epidemic of human immunodeficiency virus infection by facilitating transmission [26]. Recently sexually acquired reactive arthritis (SARA) and conjunctivitis have been reported as complications in a patient with LGV proctitis [27]. LGV proctitis can be confused clinically with other rectal STDs as well as non-infectious enteropathies. A recent study identified LGV as the third most frequent sexually transmitted infection causative of proctitis in MSM, after gonorrhoea and HSV infection [26]. The diagnosis of LGV proctitis is usually delayed and requires a high index of clinical suspicion. Increased awareness of this recently recognised problem in European communities of MSM, new forms of surveillance and establishment of reliable diagnostic tools are required to prevent avoidable complications and diminish the chances of its spreading.

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## References

- 1 Cabral T, Jolly AM, Wylie JL. Chlamydia trachomatis omp1 genotypic diversity and concordance with sexual network data. *J Infect Dis.* 2003;187:279–86.
- 2 Geisler WM, Suchland RJ, Whittington WL, Stamm WE. The relationship of serovar to clinical manifestations of urogenital Chlamydia trachomatis infection. *Sex Transm Dis.* 2003;30:160–5.
- 3 Mabey D, Peeling RW. Lymphogranuloma venereum. *Sex Transm Infect.* 2002;78:90–2.
- 4 Nieuwenhuis RF, Ossewaarde JM, Gotz HM, Dees J, Thio HB, Thomeer MG, et al. Resurgence of lymphogranuloma venereum in Western Europe: an outbreak of Chlamydia trachomatis serovar I2 proctitis in The Netherlands among men who have sex with men. *Clin Infect Dis.* 2004;39:996–1003.
- 5 Vandenbruaene M, Ostyn B, Crucitti T, De Schrijver K, Sasse A, Sergeant M, et al. Lymphogranuloma venereum outbreak in men who have sex with men (MSM) in Belgium, January 2004 to July 2005. *Euro Surveill.* 2005;10; E050929 050923.
- 6 Herida M, Sednaoui P, Couturier E, Neau D, Clerc M, Scieux C, et al. Rectal lymphogranuloma venereum, France. *Emerg Infect Dis.* 2005;11:505–6.
- 7 Spornraft-Ragaller P, Luck C, Straube E, Meurer M. Lymphogranuloma venereum. Two cases from Dresden. *Hautarzt.* 2006;57:1095–100.
- 8 Meyer T, Arndt R, von Krosigk A, Plettenberg A. Repeated detection of lymphogranuloma venereum caused by Chlamydia trachomatis L2 in homosexual men in Hamburg. *Sex Transm Infect.* 2005;81:91–2.
- 9 Berglund T, Bratt G, Herrmann B, Karlsson A, Lofdahl M, Payne L. Two cases of lymphogranuloma venereum (LGV) in homosexual men in Stockholm. *Euro Surveill.* 2005;10; E050303 050303.
- 10 Ward H, Martin I, Macdonald N, Alexander S, Simms I, Fenton K, et al. Lymphogranuloma venereum in the United Kingdom. *Clin Infect Dis.* 2007;44:26–32.
- 11 Ahdoot A, Kotler DP, Suh JS, Kutler C, Flamholz R. Lymphogranuloma venereum in human immunodeficiency virus-infected individuals in New York City. *J Clin Gastroenterol.* 2006;40:385–90.
- 12 van Hal SJ, Hillman R, Stark DJ, Harkness JL, Marriott D. Lymphogranuloma venereum: an emerging anorectal disease in Australia. *Med J Aust.* 2007;187:309–10.
- 13 Liassine N, Caulfield A, Ory G, Restellini A, de Barbeyrac B, Sitavanc R, et al. First confirmed case of lymphogranuloma venereum (LGV) in Switzerland. *Euro Surveill.* 2005;10; E050714 050714.
- 14 Lysen M, Osterlund A, Rubin CJ, Persson T, Persson I, Herrmann B. Characterization of ompA genotypes by sequence analysis of DNA from all detected cases of Chlamydia trachomatis infections during 1 year of contact tracing in a Swedish County. *J Clin Microbiol.* 2004;42:1641–7.
- 15 Bensaude R, Lambling A. Discussion on the aetiology and treatment of fibrous stricture of the rectum (including lymphogranuloma inguinale). *Proc R Soc Med.* 1936;29:1441–60.
- 16 Quinn TC, Goodell SE, Mkrtychian E, Schuffler MD, Wang SP, Stamm WE, et al. Chlamydia trachomatis proctitis. *N Engl J Med.* 1981;305:195–200.
- 17 Bauwens JE, Lampe MF, Suchland RJ, Wong K, Stamm WE. Infection with Chlamydia trachomatis lymphogranuloma venereum serovar L1 in homosexual men with proctitis: molecular analysis of an unusual case cluster. *Clin Infect Dis.* 1995;20:576–81.
- 18 Bolan RK, Sands M, Schachter J, Miner RC, Drew WL. Lymphogranuloma venereum and acute ulcerative proctitis. *Am J Med.* 1982;72:703–6.
- 19 Schachter J, Osoba AO. Lymphogranuloma venereum. *Br Med Bull.* 1983;39:151–4.
- 20 Sethi G, Allason-Jones E, Richens J, Annan NT, Hawkins D, Ekbote A, et al. Lymphogranuloma venereum presenting as genital ulceration and inguinal syndrome in men who have sex with men in London, UK. *Sex Transm Infect.* 2009;85:165–70.
- 21 Ward H, Alexander S, Carder C, Dean G, French P, Ivens D, 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.
- 22 Annan NT, Sullivan AK, Nori A, Naydenova P, Alexander S, McKenna A, et al. Rectal chlamydia – a reservoir of undiagnosed infection in men who have sex with men. *Sex Transm Infect.* 2009;85:176–9.
- 23 Alexander S, Martin I, Ison C. Confirming the Chlamydia trachomatis status of referred rectal specimens. *Sex Transm Infect.* 2007;83:327–9.
- 24 Ota KV, Tamari IE, Smieja M, Jamieson F, Jones KE, Towns L, et al. Detection of Neisseria gonorrhoeae and Chlamydia trachomatis in pharyngeal and rectal specimens using the BD Probetec ET system, the Gen-Probe Aptima Combo 2 assay and culture. *Sex Transm Infect.* 2009;85:182–6.
- 25 Schachter J, Moncada J, Liska S, Shayevich C, Klausner JD. Nucleic acid amplification tests in the diagnosis of chlamydial and gonococcal infections of the oropharynx and rectum in men who have sex with men. *Sex Transm Dis.* 2008;35:637–42.
- 26 Davis TW, Goldstone SE. Sexually transmitted infections as a cause of proctitis in men who have sex with men. *Dis Colon Rectum.* 2009;52:507–12.
- 27 Vall-Mayans M, Caballero E, Sanz B. The emergence of lymphogranuloma venereum in Europe. *Lancet.* 2009;374:356.