Lymphogranuloma Venereum

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Outline

• Epidemiology
• Clinical features
• MSM outbreak
• Diagnosis
• Management
LGV

- Lymphogranuloma venereum (LGV) is a sexually transmitted infection caused by *C. trachomatis* invasive serovars L1-L3
- L2b most common in current epidemic
Chlamydia trachomatis

• “Obligate intracellular parasite”
• Different *serovars*
• A, B, B\(_1\) & C = trachoma
• D to K = genital infection
• L\(_1\), L\(_2\) & L\(_3\) = *lymphogranuloma venereum* (LGV)
• Infect lymphocytes & macrophages
• Invasive pathogens

LGV Epidemiology

• Classical LGV endemic in parts of Africa, India, SE Asia, Caribbean & Central/South America
• Associated with urban areas, low SE group, use of CSWs, crack cocaine use
• Acute LGV more common in men (M:F = 5:1)
• Late complications more common in women
• Diagnosed rarely since 1980s in Europe & US – usually sporadic imported cases
• Before 2003 was considered a ‘tropical disease’
• Re-emerged in the last 10-15 yrs in MSM
A recent timeline of LGV infection in MSM

1980s

- Original descriptions of MSM with LGV proctitis in Seattle & San Francisco

1990s

- First of four cases of LGV in Hamburg MSM, 2003
- LGV not reported in Western MSM
- First Swedish & Canadian cases

2000 to 2003

- Appearance of LGV in Rotterdam, then Amsterdam, Antwerp and Paris
- Dutch LGV cases reach >100

2003

- First UK cases diagnosed
- Australian LGV L2 bubo case - no travel history

2004

- First US cases in San Francisco
- First of four cases of LGV in Hamburg MSM, 2003
- Appearance of LGV in Rotterdam, then Amsterdam, Antwerp and Paris
- Dutch LGV cases reach >100

Sustained LGV outbreaks within Europe, UK and USA 2005-2016

LGV MSM outbreak
(Rotterdam, Feb-Nov 2003)

- Initial cluster of 13 MSM LGV cases
- 11/13 HIV+ve
- 6 had other STIs, 1 recent Hep C
- Ulcerative proctitis found in all subjects
- 12 subjects = rectal CT PCR-positive
- Serovars L2 (n=8) and L1 (n=1)

Nieuwenhuis RF et al; CID 2004;39
LGV in the UK – current situation

Number of cases diagnosed with Lymphogranuloma venereum, per quarter, United Kingdom, 2003 to end March 2016 (n=4,663)

PHE Health Protection Report 2016

LGV in the UK

UK data consistent with Europe:

- 91.7% MSM; mostly white
- Median age 38
- HIV positive (78%); Hep C positive (17%)
- High levels of concurrent STIs
- Mostly anorectal disease (98%)
- 2% inguinogenital cases:
  - 1.4% Urine/Urethral, 0.6% Ulcer/lymph node
- Frequent misdiagnosis & delay before treatment, esp. in earlier cases
LGV in the UK

- LGV diagnoses have generally continued to increase in the UK; in 2016 919 LGV diagnoses were reported in the UK.

- In 2016, most cases of LGV were among white MSM aged 25-44 years (87%), living in London (73%) and diagnosed with HIV (68%).

- Most cases of LGV in 2015 were diagnosed with another STI or blood borne virus in the same year.

PHE Health Protection Report 2016
LGV Pathogenesis

• Organisms enter through abrasions
• Local primary inflammatory lesion
• Spread via lymphatic system
• Stellate abscesses form in LNs
• Rupture of LNs may form loculated abscesses, fistulae or sinus tracts
• Healing by fibrosis results in chronic lymphoedema, necrosis and ulceration

Clinical presentation:

“Classically” divided into 3 stages:

• Primary (incubation period 3-30 days)
  – Shallow ulcer/erosion, papule
  – Herpetiform
  – Often transient/not noticeable
  – Classically on the coronal sulcus also rectum, post vaginal wall, fourchette, vulva or cervix
Proctitis in MSM*

• Majority of current outbreak in MSM manifesting with proctitis

• Occurs following direct rectal inoculation of organism

• Acute haemorrhagic proctitis

• Rectal pain, bleeding, muco-purulent/bloody discharge, tenesmus, constipation

Secondary presentation – ‘classical LGV’ or ‘the inguinal syndrome’

• Incubation: 10 days – 6 months
  – Lymphadenopathy/lymphadenitis
    • usually tender, inguinal and unilateral (2/3)
  – Bubo formation
  – May rupture + cause chronic discharging sinuses/scars
  – When femoral and inguinal nodes enlarged + separated by the inguinal ligament – ‘groove sign’ pathognomic but rare!(15%)
  – Constitutional symptoms
Tertiary/Anorectal syndrome

• Majority of patients recover after the secondary stage

• Few patients: chronic inflammatory response and destruction of tissue in the involved areas

• Manifestations: proctitis, proctocolitis mimicking Crohn’s disease, fistulae, strictures and chronic granulomatous fibrosis and scarring of the vulva (lymphatic obstruction)

• More frequent in women due to involvement of retroperitoneal rather than inguinal lymphatics

• Within the current MSM outbreak, tertiary complications eg stricture are rare

Tertiary

*NB – classical tertiary LGV is a chronic inflammatory process not the same as MSM acute proctitis
LGV: The Genital Syndrome

- Referred to as *esthiomene* = Gk: “eating away”

- Hypertrophic ulceration & elephantiasis of the external genitalia

- Females are more commonly affected

- “Saxophone penis” and azoospermia

LGV: Other Late Complications

- perirectal abscesses
- ischiorectal fistulae
- rectovaginal fistulae
- anal fistulae
- rectal strictures
- rectal stenosis
LGV – Proctitis and Proctocolitis

LGV relatively common among MSM:
Grace (1943) & Greaves (1963)

Acute LGV proctitis
– Inflammation distal 10-15cm of large bowel
– Necrotic ulcers or hypertrophic granular mucosa
– Constitutional symptoms

TRACHOMA vs. LGV biovars in the rectum:
D-K usually asymptomatic with mild inflammation

Other manifestations

• Extra-genital
  – Systemic symptoms – fever and malaise
Can LGV be asymptomatic?

Asymptomatic Lymphogranuloma Venereum in Men who Have Sex with Men, United Kingdom
Cara Saxon, Gwenda Hughes, Catherine Ison, for the UK LGV Case-Finding Group

• Large, multi-centre case finding study (for PHE)
• 12 UK sites. Correlated with GUMCADv2 data

Results of Case Finding Study

• “We investigated prevalence of lymphogranuloma venereum (LGV) among men who have sex with men who were tested for chlamydia at 12 clinics in the United Kingdom during 10 weeks in 2012. Of 713 men positive for Chlamydia trachomatis, 66 (9%) had LGV serovars; 15 (27%) of 55 for whom data were available were asymptomatic. “
Risk factors for LGV acquisition

• HIV+ve
• Unprotected receptive (& insertive) anal sex
• Mucosally traumatic practices, including receptive & insertive fisting & use of sex toys, enemas
• Chemsex
• Group sex

LGV: Diagnostic Methods

Culture
Immunofluorescence
Enzyme Immunoassay
DNA Amplification Techniques
Serology
Diagnosis

- CT/GC NAAT
  - eg. GenProbe Aptima Combo 2 TMA Assay
  - Take a swab from ulcer, rectum, urethra/cervix, bubo pus
- Clinicians submit rectal, genital or urine specimens from patients diagnosed with chlamydia that have symptoms compatible with LGV for confirmation testing to the STBRU
- STBRU types CT+ samples using LGV-specific rtPCR
  - Subsequent typing of +ves; all L2 serovar

Diagnosis

- Real time PCR for LGV-specific DNA (now done ‘in-house’ at GSTT)
- Currently ALL MSM CT+ve specimens at GSTT are being tested for LGV DNA – this is under review
Diagnosis

• Buboes
  – Should be aspirated using a lateral approach
  – Pus transferred to a Chlamydia swab
  – Aspiration is an aspect of management as well as diagnosis (faster clinical resolution – as antibiotics may penetrate poorly into abscesses)

• Histology of lymph nodes if excised show follicular hyperplasia and abscesses

 Technique for aspiration

• 21G (green) needle
• Topical antiseptic
• Lateral approach through unaffected tissue
• Pus aspirated
• If non-fluctuant <0.5mls saline can be injected and aspirated

• Incision usually contra-indicated due to risk of sinus formation
Management

General advice:
• Curable STI with potential long term sequelae if untreated
• Patient info leaflet (BASHH)
• Screen for other STIs/BBV esp Hep C
• Risk reduction advice
  Cover anything which is moved from one rectum to another with a fresh condom or fresh latex glove for each new person it enters, or clean it with warm water and anti-bacterial soap. Enema equipment should not be shared
• PN – all partners last 3/12
• No sex until pt and partner(s) completed rx

Management

• Evidence base for LGV treatment including duration is very limited
• No published RCTs
• Rationale for prolonged treatment?
  – Invasive and systemic
  – Delayed microbial cure?
  – Based on observations of response of heterosexual disease
  – ‘mucosal’ proctitis likely a very different entity to anorectal syndrome of classical LGV + anecdotally appears to clear more rapidly
MANAGEMENT

FIRST LINE
• 3/52 Doxycycline 100mg bd

SECOND LINE
• Erythromycin 500mg qds for 21 days
• Azithromycin – appears to be effective (not a 1g stat dose). Consider 1g weekly x3 weeks, or 500mg od for 10-14 days
• Ofloxaxin, moxifloxacin and rifampicin may also be used

LGV at GSTT - treatment responses

MSM who took 7-14 days of doxycycline but were LGV+

Results (Dec 2012 –Nov 2016) :
• 60 MSM - 93% were HIV+, all rectal or 3-in-1 LGV+
• 27/60 (45%) had anorectal symptoms including pain, bleeding, tenesmus, discharge, constipation, ulceration.
• remainder = asymptomatic or had genital symptoms.
• 50/60 (83%) were treated with 7 days of doxycycline, 10 (17%) with 14 days doxycycline

LGV at GSTT - treatment responses

Results contd:

• 59 of 60 (97%) had a negative test of cure (TOC) for at a median of 31 days (7-200)

• Re-infection as opposed to treatment failure was considered likely in the patient testing positive.

• A second TOC at a median of 139 days later (37-638) was completed in 30 patients of whom 28/30 (93%) were negative for LGV

• These data suggest that 7 days of doxycycline is effective in achieving cure of rectal LGV in the majority of MSM

Follow-up

• Follow-up for review and ensure resolution

• No routine TOC necessary if treated with 3/52 doxycycline

• If already had a week of doxy for rectal CT and subsequently proven to be LGV..
  – Do a TOC AND give 2 further weeks of doxy
Genital ulcer aetiology in 587 patients in Durban 2000 - 2001

- HSV 48%
- *T. pallidum* 14%
- LGV 11%
- *H. ducreyi* 10%
- Donovanosis 1%
- No ulcer pathogen 27%

- HIV 75%

*Sex Transm Dis 2003;30:241-5*

Syndromic management

- The presence of inguinal buboes with genital ulcerations is often associated with chancroid or LGV

**WHO recommendations for treatment of inguinal buboes:**

- Ciprofloxacin 500mg twice daily for 3 days
  And
- Doxycycline 100mg twice daily - 14 days
  Or
- Erythromycin 500mg 4 times daily - 14 days
MSM & Hep C transmission

• HCV & LGV share similar risk factors in HIV+ MSM:
  – unprotected receptive & insertive anal sex
  – mucosally traumatic practices, including receptive & insertive fisting, & use of sex toys
  – group sex
  – sexual activity under the influence of 'club' drugs (including 'crystal meth', ketamine, GHB, poppers, LSD, and ecstasy)


Conclusion

• Sustained epidemic of LGV causing proctitis in MSM in the UK
• Increasing no. of cases of ‘classical LGV’ + other manifestations
• About a quarter of LGV infections are in asymptomatic patients - it is possible that an undiagnosed reservoir of infection is contributing to transmission
• More info needed on exact modes/risk of transmission
Conclusion

- New testing algorithms (2015 BASHH Chlamydia Guideline) reflect this:
  - LGV testing should be performed in individuals with proctitis (Level III, Grade B).
  - HIV-positive MSM with C. trachomatis at any site should be routinely tested for LGV regardless of symptoms (Level III, Grade B)
- Currently at GSTT : testing ALL MSM with +ve CT
- Rectal CT should always be treated with 1/52 Doxy (not azithromycin)
- Delayed or incorrect diagnoses remain frequent
- Need for an RCT to assess duration

References

- de Vries H et al, Delayed microbial cure of LGV CID, 2009; 48:e53–6
- Simons R et al. Observed Treatment Responses to Short-Course Doxycycline Therapy for Rectal Lymphogranuloma Venereum in Men Who Have Sex With Men, Sex Transm Dis. 2018 Jun;45(6):406-408