That Other Chlamydia: Lymphogranuloma Venereum (LGV)

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[video transcript]

All right. So, today I'm going to talk about the other Chlamydia known as Lymphogranuloma Venereum, which we often abbreviate LGV. Just the objectives, are to go over the clinical manifestations of LGV and review the current treatment recommendations. I have no financial disclosures, but I will talk about some non FDA approved diagnostic testing that is described in the literature. So, first just a little bit of background, I'm sure you're all familiar with *Chlamydia Trachomatis*, but LGV is caused really by a different different serovars of that typical chlamydia that you think of. Conveniently, the L1 through L3 serovars are the ones that cause LGV. As a side note I don't think I've ever taken any sort of board test were there, that was not asked on the exam. So, it seems to be a favorite question for any of you who might be in training. Historically, LGV was most common in tropical and subtropical climates, Africa, Southeast, Asia, the Caribbean, and it's been known about for quite some time; it was first described as a distinct clinical entity way back in 1913. Since 2003, this formerly, relatively unusual Western pathogen has been described with increasing frequency in both Europe and North America. And these reports have largely been coming out of men who have sex with men communities, who also had high rates of HIV co-infection.

The reports that were prominent, beginning in the early 2000s, would describe a syndrome that largely presented as proctitis or protocolitis, and it would be really very occasionally heterosexual cases were described. So, a little bit more background our typical chlamydia trachomatis that you think of as causing a sexually transmitted chlamydia infection, are serovars D through K. And these have the feature that they infect the columnar epithelium, really mucosal epithelium, and they are often asymptomatic. Most women who have a chlamydial or cervicitis don't have symptoms, and about 50 percent of men who might have a urethritis wouldn't have symptoms. Similarly, standard chlamydia causing proctitis, also has a high rate of asymptomatic infection. The organism though does cause mucosal inflammation, you know, at places where there are columnar epithelial cells. So, that would be arthritis, cervicitis, proctitis, conjunctivitis is a feature, and also is associated with neonatal infection, particularly pneumonia. In contrast, chlamydial infections, the organisms that cause LGV, these L serovars, infect monocytes and macrophages. There's only three serovars known, although there is a little bit of a subset in some of them, and the current outbreaks that have been described in the literature, that I'll go into in more detail later, have largely been due to serovar L2B. And we'll go into the clinical features of LGV, but you can think of it in somewhat of a similar way that you think of syphilis, that it really manifests as three stages. The first stage is really a local infection, then there's sort of a regional dissemination with lots of lymph node involvement, and then there may even be downstream or long term complications. So, the first local infection, that is actually called primary infection just like in syphilis, has a relatively short incubation period, generally less than a month sometimes as short as three days.

And that is manifest as a localized inflammation that generally is described as starting as a papule, that then gradually evolves into sort of a pustule that then ulcerates. This is generally quite short
lived usually two to three days and because it's so short lived and self limited oftentimes you as the clinical provider wouldn't actually see this part of the illness. It generally heals without a scar, and occasionally you can find case reports of other local inflammation also being seen as part of the initial primary infection such as your arthritis, cervicitis, or colitis. But, really classically we think of this it's put into the genital ulcer disease category as primary infection. And here's a CDC slide showing that very small, tiny, somewhat superficial ulcerative lesion there. Shortly thereafter, there is regional dissemination of the organism. So, it spreads, typically two to six weeks, but there are again, as with everything in medicine, rare reports of even having that dissemination happened greater than six months later. And the classic manifestation of this is very prominent regional lymph node involvement. And when you have a penile, or scrotal, or vaginal lesion, you will often get a very marked inguinal or femoral big time lymphadenopathy. You have primary rectal or anal involvement, that adenopathy would be more likely to be deep pelvic or a retroperitoneal, so not obvious on the clinical exam. These lymph nodes can be really so large that they become classified as buboes. And one out of three times, these will be large enough that they actually spontaneously drain and form sinus tracks. The drainage is described as being bright yellow pus.

[00:06:30] And that may persist for days to weeks. In this dissemination period, which I think of as being sort of akin to secondary syphilis, you can also have systemic symptoms similar to secondary syphilis actually with fevers, malaise, arthralgias, so you can kind of think of it as like a flu like illness with this very prominent local adenopathy. I should make a note that one feature, when you have the retroperitoneal nodes that are not, because the retroperitoneal you could only see them on a C.T. scan they're not obvious on exams, but they are sometimes associated with back pain you know back pain enough for someone to present for care. There have been rashes noted in this phase as well, both Erythema Nodosum, so sort of prominent nodular lesions and Erythema Multiforme, so sort of more erythematous lesions with a bull's eye, have both been reported. And chlamydia trachomatis has been isolated from blood and CSF in this stage. So, it really is kind of a dissemination in a manner similar to syphilis. And here is, again, a CDC slide showing some of that prominent inguinal and femoral adenopathy. I don't think you can see my laser pointer but if you look as you're looking at the screen, on your left, you can see an area where that adenopathy looks like it has a draining sinus tract. And sometimes this is described as as a groove sign where you'll have both prominent inguinal adenopathy .

[00:08:15] So, sort of forming a mountain, then a valley where the inguinal ligament is located, and then a second mountain with prominent femoral I adenopathy, and that's quite characteristic of LGV. Then finally, the long term downstream complications are fibrosis, or other sort of scarring related to chronic inflammation. This can lead to lymphedema even if you if you have significant scarring in the lymphoid tract or genital elephantiasis which has been described to be more common in women. This is a relatively rare complication and this sort of chronic inflammation with really significant chronic inflammation in these current outbreaks that I'll talk about in a minute has been more associated with clonic fibrosis and strictures, rather than lymphedema or elephantiasis. And here is, again, CDC slides showing that mark genital swelling related to chronic inflammation. So, how do you diagnose LGV if you
don't have these characteristic physical findings? So, historically it's been diagnosed with antibody testing. So, you would have a clinical syndrome, such as sort of a bubo, and with that a positive serology, so, a blood test, that would either be a micro immuno fluorescence or complement fixation. And you're looking for quite high titers, with the numbers shown there, greater than 1 to 256 with micro immuno fluorescence are greater than or equal to 64. They are both suggestive but not absolutely diagnostic of LGV. Rising titers are also a little bit more comfortable with a diagnosis by serology but, unfortunately, it turns out that these high titers may persist for years. So, that makes it difficult particularly if you're in a setting where the disease may be more common such as in a tropical country in Africa or Southeast Asia of how to interpret that antibody.

[00:10:38] We also know that as time has gone on and we've developed other more sensitive tests that there may be some cross reactivity with these chlamydia antibodies both with other chlamydia trachomatis species or even with other chlamydial infections such as chlamydia pneumoniae. So, really while this has historically been the way to make the diagnosis it's not the recommended way at this point. The other way, if you don't look for antibody or the immune response to the organism, is to look for the organism itself and it turns out that virtually all of the NAAT tests, NAAT is short for nucleic acid amplification test, that's the abbreviation we generally use in the sexually transmitted disease world when referring to PCR types of tests for STDs, and there are now a number of commercial companies that offer a NAAT test for chlamydia. There also are cultures that can be done for chlamydia and an immuno fluorescence tests that can be done for chlamydia. Unfortunately, NAAT tests are not FDA approved for use on rectal specimens. So, in the current outbreaks that makes it a little bit harder to get the proper testing. And the difficulty with using NAAT tests for diagnosing LGV is that while the LGV serovars are included in the in the antigens that the NAAT test is looking for, the read out just gives you a positive or a negative. So, if you have a positive chlamydia test you as the provider don't know if that positive refers to an LGV serovar or if it refers to a more routine D through K serovar. So, while you may get a positive, you can't distinguish kind of regular usual chlamydial infection from LGV chlamydial infection.

[00:12:44] There is no FDA approved test to get you down to that specific LGV NAAT kind of testing, but some labs have gone ahead and developed their own in-house molecular tests. CDC for instance, has a test and actually widespread lab in New York State, New York State Public Health Lab, does have a test that looks for L2 serovars. So, what the CDC recommends when you're in this situation where you think you may have a patient who has LGV, is to do some additional molecular procedures, so some PCR based genotyping, a NAAT test, that could be used to differentiate LGV from non LGV trachomatis, particularly in rectal specimens. And they give this comment that a positive serology might support the diagnosis of LGV in the appropriate clinical setting. I can tell you locally that Wadsworth state labs does offer this L2 PCR, performed on rectal or urethral specimens that are known positive for Chlamydia, for only a few labs in the state and they're doing that as sort of a surveillance project. So, it's not generally available for you just as a practicing clinician. So, if you have a clinical syndrome, or if you're lucky enough that you have a test that can prove that somebody has LGV, the standard treatment
recommendation is different than that for usual, typical chlamydial genital infection. It's the same drugs but for longer. So, the recommended regimen is doxycycline, 100 milligrams twice a day for three weeks or 21 days. Some people have used azithromycin one gram once a week for three weeks, although there have been case reports of failures with that. So, the cure rates do appear superior when using doxycycline. There have been very rare case reports of treatment failure with the doxycycline regimen and in that case report there was successful treatment with moxifloxacin, also for 21 days.

[00:15:00] So, I think the feature to remember is that if you think you have LGV you really need to be treating for three weeks and not just one week as with more typical chlamydial infection. So, then what's really interesting about LGV is what's been happening in the community, though as I mentioned earlier there have been outbreaks described really beginning way back in 2003, but increasing in frequency in both Europe and North America. These have largely been due to the L2 serovars and the feature in these outbreaks have been that the patients have presented with proctitis or proctocolitis rather than this inguinal manifestation. The clinical syndrome is sort of a typical Proctitis presentation, rectal pain, tenesmus, feeling like you have to have a bowel movement, and either a mucoid or a bloody discharge. And often people also have either abdominal or abdominal sort of deep pelvic pain or describe that as back pain, sometimes with fever. HIV co-infection has been quite common across the board. You can pretty much find an outbreak in almost every country in Europe and the rates of HIV co-infection have been very high, generally greater than 50 per cent. And in addition to this, proctitis syndrome, some of these reports have described sort of a prospective surveillance approach. And in those they've identified, in some cases as much as 40 percent of asymptomatic cases with LGV serovars, whereas in other series the rate of asymptomatic infection has been as low as 1 percent. So, some variability there about whether symptoms are always reported or not.

[00:16:53] So, one of the outbreaks I wanted to describe to you that I think is a good example comes from Amsterdam where they reviewed cases in their STI clinic going from 2005 out to 2012. And as standard practice in their clinic, in patients who were men who had sex with other men, they routinely screened for gonorrhea, chlamydia, Hep B, HIV, and syphilis. They have a medical record system where they record symptoms and a physical exam. And if the patient's self reports receptive anal intercourse they also perform anoscopy. Their standard testing was urethral, anal/rectal, and, you know, genital ulcers as well as any aspirates of buboes were tested for chlamydia trachomatis. So, that's a little bit different. I can't say that I personally have ever done a test on a genital ulcer looking for chlamydia. And in their setting if chlamydia was positive on there, they were using NAAT test, they had an in-house PCR to break down L serovars. In addition, if the patient had anal symptoms or any inflammation visible on anoscopy, they also did a gram stain so that they could look for white cells and organisms that look like gonorrhea, that's gram negative intracellular diplococci, that's that abbreviation. And if the person had any sort of anogenital ulcer, in addition to the test for chlamydia, they did a dark field my microscope exam looking for syphilis. A a T pallidum type of PCR and an HSV PCR; so, they looked for syphilis and herpes. So, here's their numbers, they're kind of big numbers, so, they had almost 49000 men with sex with men over this timeframe.
This was 2005 to 2012. And then they break this down by how the chlamydia tests were done. So, if somebody reported receptive anal intercourse in the prior six months, they had approximately 37000 who had anal swabs for chlamydia done, and of those they had about a 10 percent positivity. If they then took those that were positive for chlamydia and did their in-house PCR looking for the LGV serotype, it was one percent of all of those people who had receptive anal intercourse, but actually 11 percent of those that were positive for chlamydia. So, it was eleven point three percent of the anal chlamydial specimens. If you go to the middle column, these are those with genital ulcers. There were about 1650 of those. That was three point four percent of their total. Of those, 65 were positive for chlamydia which surprised me. That was about 4 percent of their genital ulcer specimens and of those that was less than 1 percent being the LGV serotype of the total population, but 15 percent of the chlamydia positive specimens. And then the last column are those who had incentive anal intercourse, which was the whole population, 48000, they had a four point seven percent chlamydia positivity rate and they didn't look for LGV in that group. So, sort of the take home points here where there was roughly twice as much chlamydia isolated in rectal specimens than urethral specimens. There was even some chlamydia almost equal to urethral in ulcers specimens and it was 11 to 15 percent of the ulcers and rectal specimens that were actually LGV serovars. This is their positivity of the LGV serovars, the anal rectal specimens are the dark lines and the clear hatch marks are those with inguinal LGV. So, you can see it sort of varies over time from 2005.

But, these are by quarter so it's a little bit deceptive. So, if you went by year, they clearly increased over time frames and they had many more cases in 2012, four quarters, than they did in 2005, four quarters. of the 411 rectal cases, they occurred in 365 men. So, there were some who had repeated infection and there were 10 inguinal cases in ten men. They looked for symptoms and they had 84 of the 411 also had G.C.. So, they didn't include those for symptom evaluation because they couldn't distinguish if the symptoms were from gonococcal proctitis or LGV proctitis. So, the remaining are shown in this table below. So, almost 60 percent report one or more symptoms. And 51 percent had some sort of sign on physical exam and 27 percent had neither symptoms nor signs. So, only 27 percent were completely without findings. And of those who had a gram stain, they had 85 percent that had a greater than 10 Poly's on that gram stain. So, that was the most helpful finding, that you did have an inflammatory gram stain with lots of weight cells. They looked at how many had HIV co-infection and that was roughly 82 percent. They also had roughly 70 percent who are TPAA positive. For those of you who aren't familiar, this is a specific antibody for syphilis. So, that means that these patients had syphilis at some point in their life or currently.

You can't distinguish it's a antibody that persists for life. 25 percent were positive for G.C. at the time that they had LGV, and they had no changes in any trends about their background STI's over this whole time frame except for the overall rise in the sheer number of LGV cases. So, basically they report an increase in LGV cases over time. They're largely rectal, at the same time frame they're similar rising cases seen in the UK. In the Netherlands, in this study, they had 40 percent who were without
symptoms, but only 27 percent without symptoms or physical findings. And the UK had somewhere between 1 and 25 percent without symptoms depending on the study you look at. Here's another just quicker look at some information from the UK from 2003 to 2015. This is a laboratory based evaluation and they do LGV typing at their national public health labs that are in London and Edinburgh. They had rectal, genital, and urine samples from patients and from partners with LGV symptoms who also had a positive chlamydia test. And starting in 2007, they started testing all HIV positive MSM who had a chlamydia test positive looking for LGV. And what they find here, you can see just basically rising cases, fairly dramatically, over time between 2003 and 2015. These, again, are by quarter. So, by the end, they're seeing about 250 cases per quarter sent to their public health lab. They do look at some of the clinical characteristics they can get out through their surveillance system. They have almost eleven thousand five hundred chlamydia cases diagnosed among MSM in this, in the year of 2014.

[00:25:17] They can identify 633 LGV cases through their sexual health clinic electronic record. And through their laboratory database they can do some matching and they get this kind of information out that they're sort of a median age that's older than most medians reported for sexually transmitted infections; the quartile was 31 to 44. Most gonorrhoea and chlamydia peaks in men at the 25 year, around 25 years of age. So, this was a little bit older. They were slightly more likely to be Caucasian, to have a city residence in London. They had a, again, a high rate of HIV co-infection of 74 percent and a very high rate of G.C. co-infection of 50 percent. Syphilis was a bit lower at 18 percent and Hep C at 13 percent. So, they conclude that there has been a significant marked increase in LGV diagnosis in the U.K. over recent years. They had a rise in other STI's in that same timeframe both G.C. and syphilis.

[00:26:26] They felt that this was likely an underestimate in the number of cases because for the first half of this period they required symptoms in order to send the specimen for Serovar testing, and this group proposed adding presumptive treatment for LGV into their national guidelines for MSM with rectal symptoms which actually hasn't happened to date. And then when I was preparing this talk, actually, I just searched to see if there were any more recent data. And I went to the same Euro statistic dataset and I could see right after this they had a decrease in cases in 2016. This is basically a snapshot off of this public health report. There is no text associated with it so I'm not sure exactly what happened there. If they lost their funding to do testing or if there is an actual change because of some public health intervention.

[00:27:24] But that sort of steady rise has stopped. And then I just want to give you a couple of cases in the U.S. They had, this is out of Michigan about a year and a half ago maybe two years ago, no reported LGV in Michigan since 2005. In August of 2015, they had a patient with marked inguinal adenopathy who also had a small penile ulcer and well controlled HIV. They tested that ulcer for chlamydia and ultimately identified that it was LGV with help from the CDC. One month later, they had three more cases compatible with LGV and the CDC started an outbreak investigation. So, they had a sort of standard outbreak approach where they had a suspected case, a probable case, and a confirmed case, with again
sort of standard definitions that confirm you had to have a positive LGV serovar. A probable, you met that you had a clinical syndrome and you had a positive test for chlamydia. And a suspected, you had a clinical syndrome and you were a sexual partner who was chlamydia. So, they end up with 38 cases, all are MSM with HIV. 21 were confirmed by lab testing the remainder were probable or suspected. They were largely rectal as you can see 19 of the 21. Ages were a little bit lower than described in England, 29, median CD4 count, 483. HIV RNA was undetectable in 12 of the 21, but six of those 21 were newly detected. So, it was really 12 of, what's six from twenty-one, 15 that were known HIV.

They had some HIV co-infection, some syphilis co-infection, as you can see, and quite a lot of gonorrhea co-infection as was described in both the Netherlands and England. 19 of the 38 had symptoms of proctitis. And then, perhaps a little bit closer to home, this is out of New York City, where along with Wadsworth, the city health department has had a protocol to screen chlamydia isolates from male recta specimens for the LGV L2 serovar. And in the years between 2008 and 2011, about 8 percent screened positive, and by 2012 to 2016 it was up to almost 17 percent were positive. The correlates in the most recent years were black race, age greater than 30, HIV co-infection, partner to HIV, or a history of syphilis. They had no correlation with being LGV or screen positive with G.C., chlamydia, condom use, or a number of partners. Of the LGV cases, 86 percent had rectal symptoms, and of their rectal chlamydia that wasn't LGV it was 60 percent with symptoms. Having no anal discharge did have a negative predictive value of 88 percent. So, kind of like that Netherlands study where they had a lot of white cells on the anal smear. So, in there they presented this at the CDC, STD prevention conference and suggested that you could use a history of syphilis, HIV status, and the presence of anal discharge maybe to target presumptive therapy for LGV. So, I just want to give you two other North American cases as an example and then we'll finish up. This is a case described out of Canada. A 34 year old man with a two week history of a painful red swollen inguinal bump, no other symptoms. He had both insertive and receptive oral and anal intercourse with male partners. He was treated for a presumptive kind of staph infection with cloxacillin with no improvement.

He had an erythematous inguinal bubo. No groove sign. And ultimately, all of his tests were negative except for a newly diagnosed HIV. And they ended up using antibody testing which was high 1 to 512, and diagnosed him with probable LGV. They treated him with doxycycline and his symptoms resolved. Another case of a proctitis, sort of a classic case, this was out of North Carolina I believe. And this was a 60 year old who had a past medical history of well controlled HIV with a normalcy four count who developed hematochezia, rectal bleeding for one month. Two to three stools per day and G.I. symptoms, no history of inflammatory bowel disease. He was found to have a rectal mass with numerous fragments and two polyps. Ultimately, it looked all inflammatory and not like cancer and lots of tests were done and ultimately, the rectal swab was positive for Chlamydia. He also was treated empirically and his symptoms resolved. The partner also had proctitis symptoms similar finding on the colonoscopy and he also was treated empirically. And there is multiple reports with sort of a similar presentation to that last one where there's a misdiagnosis as lymphoma, inflammatory bowel disease,
or even cancer. So, that's something to think about. And I think that the G.I. community has now become more aware of this. As I mentioned earlier, there is one case report of a treatment failure with Moxy to doxy that was successfully treated with Moxifloxacin. There's a couple case reports of reactive arthritis that used to be called reiter's syndrome, associated with LGV.

[00:33:28] And one very recent case report of a wild type HIV acquisition in a patient on PrEP who presented with fever, also had a UTI due to E.coli, and was found to have asymptomatic rectal LGV infection at the time of his HIV diagnosis. So, in conclusion, there has been a shift in epidemiology over the last 10 years or so and there is now two syndromes really with the rectal syndrome being more common particularly in the western world. In U.S. and Western Europe, the cases are highest in MSM with high rates of co-infection of other STI's and particularly HIV. Definitive diagnosis is really hard if you don't have access to that LGV serovar. So, you can consider empiric treatment in those with LGV consistent syndromes when you don't have diagnostic tests. So, if you have a man who has sex with other man with proctitis, you don't have the ability to do a chlamydia test. You could consider treating as LGV particularly if there was HIV co-infection. If you can do a chlamydia test that's positive, and you don't have the ability to do the LGV specific test, you could consider treating his LGV. Again, maybe with a little bit more impetus if someone has co-infection with HIV. And if you have both test done, obviously you would treat based on the result. I think the data for asymptomatic infection are not quite as strong. So, there you might really only consider empiric treatment based on low prevalence, and again maybe with a little bit more concern if there's co-infection with HIV. This is a selected bibliography. Just a plug for our STD ECHO the fourth Wednesday of every month.

[00:35:23] And the CEI line where you could call with STI questions. And I'll stop there.

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