

***Mycoplasma genitalium* Infections**

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] I have Dr. Lisa Manhart, a professor of Epidemiology and Global Health with the Center for AIDS and STD at the University of Washington, calling me from Washington today. We'll be talking about *Mycoplasma genitalium* infections. Welcome Dr. Manhart.

[Lisa Manhart] Hello, Sarah.

[Sarah Gregory] So, tell me, what is *Mycoplasma genitalium*?

[Lisa Manhart] *Mycoplasma genitalium* or *M. genitalium* is a sexually transmitted bacterium and it causes signs and symptoms that are very similar to those that occur with *Chlamydia trachomatis* infections, or Chlamydia. We've known about *M. genitalium* since 1980, when it was first identified. But unlike most other bacteria, it's actually very hard to grow in culture; it takes about six months and there are only three or four labs in the world that can actually culture it. So because of that, we couldn't really study the epidemiology of *M. genitalium* infections until PCR tests were developed and that didn't happen until the early 1990s. And PCR tests are tests that detect bacterial DNA, so that's important because it allows us to detect pathogens without having to grow them in culture. One of the most interesting things about *M. genitalium* is that it doesn't have a cell wall and most bacteria do have a cell wall. This is important because some antibiotics only work by disrupting the cell wall, for example, penicillin, which is a very common antibiotic and those medications actually won't work against *M. genitalium*.

[Sarah Gregory] So, how does it manifest, is it urethra, orally, rectally, vaginally? And who's most likely to get it?

[Lisa Manhart] So a little bit of all of that. There are a lot of studies that have shown that *M. genitalium* infections in men cause urethritis, which is discharge and inflammation of the urethra. A few studies have shown that it's been associated with urethritis in women also, but we actually don't study urethritis as much in women.

In women, we worry more about vaginal, cervical, and upper reproductive tract infections, like pelvic inflammatory disease. *M. genitalium* is not a vaginal infection like *Candida* or bacterial vaginosis, although sometimes women with *M. genitalium* will have vaginal discharge, the same way women with chlamydia or gonorrhea will have vaginal discharge. But *M. genitalium* primarily infects the cervix, and when that happens, it can cause cervicitis, or inflammation of the cervix. But what we really worry about is that it can then also move up the reproductive tract to infect the endometrium, which is the lining of the uterus, and eventually it can sometimes reach the fallopian tubes. Those are the upper reproductive tract infections that cause more serious consequences. Our team recently did a meta-analysis, which is where you combine all of the data across all of the studies that have been published, and we found that *M. genitalium* infections were associated with about a two-fold increase in the risk of cervicitis, pelvic inflammatory disease, preterm delivery, and spontaneous abortion. It was also associated with a two-fold increase in the risk of infertility, but the analysis of infertility had a result that wasn't statistically significant, which just means that there's a little less certainty about that relationship.

We also know that *M. genitalium* can infect the rectum. There aren't as many studies of this, so we know less about it than we do about other anatomic sites. But the prevalence of *M. genitalium*

in the rectum can be low, at about two percent all the way up to about 11 percent. Most of these studies have been in men who have sex with men, but two of them evaluated women and the prevalence was about the same, ranging from three to eight percent, so rectal infections aren't just limited to men who have sex with men. Despite the fact that it can infect the rectum, the few studies that we have don't really show that it causes proctitis, like some other STIs can. Most of the time, *M. genitalium* infections in the rectum are asymptomatic. So, our main concern with them is that they probably serve as a reservoir to maintain transmission within a population, but they are much less a clinical concern. They don't really cause rectal symptoms very often.

And then our last anatomic site, the throat, or the oropharynx, *M. genitalium* actually very rarely infects the oropharynx. There have been a number of studies that have looked and it's really only been detected in a handful of people. And this makes *M. genitalium* quite different from gonorrhea, which can infect the oropharynx quite a bit more easily.

And then your last question was, who is most likely to get *M. genitalium*? So *M. genitalium* is like most other STI's; the prevalence is higher in younger people, people who are more sexually active. It's also, like most STIs, higher in racial and ethnic minority populations, and really in people who have more sex partners than others.

[Sarah Gregory] I understand there's a lack of data on this infection, so tell me about that.

[Lisa Manhart] Yes. So part of the reason there's less data on this infection is that simply we've known about it for less time. We've known about gonorrhea and chlamydia for quite a bit longer. There are references to gonorrhea in the old testament, so that's been around forever, and chlamydia was identified in the early 1900s. So, there has just been a lot of time to accumulate knowledge about those STIs. *M. genitalium* actually wasn't identified until about 30 or 35 years ago, and we couldn't even begin doing studies on them until the 1990s. So in a sense, the pace of science is slow, and we are in some ways, finally getting into really studying this carefully.

The other reason there's a lack of data is that, when we're beginning to suspect that something might be a pathogen, we typically start with studies that are the easiest to do, and the ones that cost the least amount of money. Those are called cross-sectional studies and they just have people that they evaluate at one point in time. But, if you really want to show that a pathogen can cause a disease, you have to follow people over time and you have to see that first the person acquires the pathogen and then they get the disease in order to attribute cause to that pathogen. And there aren't very many studies like that, that have been done for *M. genitalium* yet. One really important piece of information that we still don't have is whether testing and treating an *M. genitalium* infection in asymptomatic women could actually prevent pelvic inflammatory disease and those other adverse consequences of the upper reproductive tract infections that we worry about so much, like infertility and ectopic pregnancy. We know this is true for chlamydia. That's why we have an annual screening recommendation for young women. Every year young women are supposed to get tested for chlamydia. To learn whether the same thing is true for *M. genitalium*, we'd have to do a randomized trial to test it. That's the kind of study that was done that is the foundation for the chlamydia screening recommendations. Those kinds of studies take a really long time to do, they're expensive, and they just haven't been done yet.

The final reason that we don't have as much data on *M. genitalium*, is that we don't have an FDA-approved diagnostic test for it, so your healthcare provider actually doesn't test for it regularly. Two companies that make diagnostic tests, are doing studies right now to get FDA-

approval. And if they're successful, which I'm very hopeful that they will be, I think that'll change in the next couple of years.

[Sarah Gregory] You mentioned before that antibiotics don't react the same because of the cell wall in this, so are there treatments for this kind of infection?

[Lisa Manhart] Yes and no. The CDC STD Treatment Guidelines recommend something called syndromic therapy for the syndromes of urethritis, cervicitis, and pelvic inflammatory disease when *M. genitalium* is suspected and this is primarily because we don't have that FDA-approved test for healthcare providers to use. With syndromic therapy, you treat the person based on the signs and symptoms that they have, and there are defined antibiotics that you use. This is problematic for *M. genitalium* because the antibiotics used in syndromic therapy are doxycycline and azithromycin and neither of those two antibiotics are very effective against *M. genitalium*. Doxycycline works about only 30 to 40 percent of the time, and azithromycin works on average about 60 percent of the time. We don't really know why doxycycline doesn't work well, but the reason that azithromycin doesn't work well is because of antibiotic resistance and this has really increased in recent years. In cases where treatment with azithromycin is not effective, there's another antibiotic called moxifloxacin that can be used. Moxifloxacin is generally still very effective, although resistance to moxifloxacin is also beginning to emerge, and it can have some undesirable side effects. Several other antibiotics have been used in Australia and Europe to treat antibiotic resistant infections, but those antibiotics actually aren't available in the United States. There are some new antibiotics in development though, that look like they would work well against *M. genitalium*. But, in general, treatment is one of the challenges of *M. genitalium* infections.

[Sarah Gregory] So, tell me about presumptive treatment?

[Lisa Manhart] Presumptive treatment is treating what you think might be there in the absence of a diagnostic test. And the CDC recommends presumptive partner treatment for people whose partners have gonorrhea or chlamydia, it's a routine recommendation. There is no recommendation for presumptive partner treatment for *M. genitalium*. Part of this is because we don't actually have an easily accessible diagnostic test, so that makes it difficult to diagnose and detect *M. genitalium* infections in the first place. But it's also because azithromycin would be the logical antibiotic to use for presumptive partner treatment, and we know that giving someone with an *M. genitalium* infection azithromycin will probably result in selection for antibiotic resistance about 12 to 18 percent of the time. So, there's some danger that we'll increase the antibiotic resistance problem if we give presumptive partner treatment. Until we have an FDA-approved diagnostic test, there probably won't be a recommendation to do presumptive partner treatment in the United States. My personal guess would be that once we do have the FDA-approved tests, the recommendation will probably be to test the partner before treating, but that's really just speculation at this point.

[Sarah Gregory] Would you tell us a little bit about how the study was conducted?

[Lisa Manhart] Yeah, this study from Australia is a great study. Australia has much more quickly made changes to clinical practice in response to increasing data on *M. genitalium* than many places. The Melbourne Sexual Health Clinic is one of the largest STI Clinics and they've been using an in-house test to detect *M. genitalium* in their patients for quite a while now. In about 2008 they decided to treat sexual contacts of patients who tested positive for *M. genitalium* in

their clinics, so essentially providing them presumptive partner treatment, like we just talked about. What they do is that they have the infected person refer his or her partner to the clinic for a test. And the study that they did used their electronic medical records data. So they just were able to go back to these electronic medical records and abstract information about all the contacts that came in for testing and determine how many of them also tested positive for *M. genitalium*. So this is a really important study because we don't have very good data on how often *M. genitalium* is transmitted from an infected person to an uninfected person. We only have a handful of studies with information like this, and all of them were fairly small studies. None of them involved men who have sex with men. So we base our recommendations to provide presumptive treatment to partners of people with chlamydia, in part, on the proportion of partners that are infected. So, we really need data like this for *M. genitalium* to see if we also need to be thinking about presumptive partner treatment.

[Sarah Gregory] So, what was found in this study?

[Lisa Manhart] So, this group of investigators from Australia looked at three different groups of people. They looked at heterosexual women whose male partner had *M. genitalium*; heterosexual men whose female partner had *M. genitalium*; and men who have sex with men whose male partner had *M. genitalium*. In the heterosexual men, about 31 percent of contacts were also infected with *M. genitalium*. In the heterosexual women, that proportion was even higher—it was nearly 50 percent. Somewhat surprisingly, in the men who have sex with men, the proportion of partners that also had an *M. genitalium* infection in the urethra, was quite a bit lower. It was only about eight percent. But in the rectum, 41 percent of men with an *M. genitalium* infected partner also had *M. genitalium*. What's key about this though, is that most of these people were asymptomatic and having symptoms, for the few who did, wasn't predictive of having *M. genitalium*. So, for perspective, the prevalence of *M. genitalium* in asymptomatic people, in general, in these populations is only about one to three percent. So the prevalence in partners of infected people is really much, much higher.

[Sarah Gregory] Are condoms effective in preventing this spread?

[Lisa Manhart] In general, I would say yes, although in this study, when they looked at the effect of condoms, they found that they were protective, but the result wasn't statistically significant. And measuring whether condoms are effective is actually very hard, in general. Some studies show that the risk of STIs is actually higher in people who report using condoms. And the same is true of studies on *M. genitalium*. Measuring condom use accurately is hard for several reasons. The first is that you have to use condoms correctly and consistently and not everyone who reports having used a condom actually used it correctly. Secondly, people are usually being asked if they used condoms by their health care provider, and health care providers are usually telling people they should be using condoms. So sometimes people report having used them when they actually haven't. This is something in epidemiology called social desirability bias. They're really just wanting to please the person who is asking the question of them. And then lastly, people usually use condoms with their riskiest partners. They know that condoms can protect them so condom users are sometimes the people at highest risk of getting an STI. All that said, my interpretation of the data is that condom use probably is protective against *M. genitalium*.

[Sarah Gregory] Does this study make any recommendations for prevention and treatment going forward?

[Lisa Manhart] Interestingly, they don't make a firm recommendation. They talk about the pros and cons of providing presumptive treatment to partners of persons infected with *M. genitalium* and really stop there. The advantages of providing presumptive treatment are that it reduces the risk of reinfection in the initial patient, and that should also reduce transmission in the population. And we do recommend presumptive partner treatment for high risk individuals who have the syndromes that are associated with *M. genitalium*—urethritis and cervicitis—and we already do it for people who have chlamydia and gonorrhea. In women, *M. genitalium* is often asymptomatic, like most STIs in women, so theoretically, if you could quickly treat an asymptomatic infection, you could prevent it from ascending to the upper tract where the complications and consequences can really be most serious. So that's an advantage of providing presumptive treatment, but the disadvantage is that we know it can increase the prevalence of resistant infections. And our options for treatment of azithromycin-resistant infections are actually pretty limited and they're becoming more so as resistance to additional antibiotics emerges. So, it's really hard to make a recommendation.

[Sarah Gregory] Okay Dr. Manhart. Finally, since you aren't an author on this article, how are you involved in this field of study?

[Lisa Manhart] I did my dissertation on *M. genitalium* about 15 years ago, when there were just a handful of studies done in women. And I've continued to study it ever since. I've done a number of studies, both in men and in women. I led the expert committee that reviewed the evidence and actually drafted the section on *M. genitalium* that's included in the most recent update to the CDC STD Treatment Guidelines, and in collaboration with several colleagues, I co-organized an NIH Technical Consultation on *M. genitalium*. So, I really have been immersed in the world of epidemiologic research on *M. genitalium* for most of my career.

[Sarah Gregory] Thank you so much for taking the time to speak with me, Dr. Manhart. Listeners can read the November 2017 article, *Mycoplasma genitalium* Infection in Adults Reporting Sexual Contact with Infected Partners, Australia, 2008–2016, at cdc.gov/eid.

I'm Sarah Gregory for *Emerging Infectious Diseases*.

[Announcer] For the most accurate health information, visit cdc.gov or call 1-800-CDC-INFO.