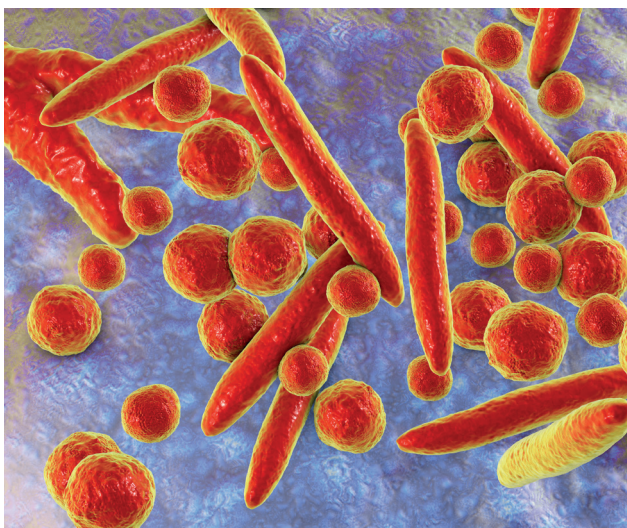


Mycoplasma genitalium-related infection: An STI not quite ready for prime time

By Melanie A. Deal, MS, WHNP-BC, FNP-BC

***Mycoplasma genitalium* has been designated by the CDC as an emerging concern among sexually transmitted pathogenic bacteria. Although *M. genitalium*-related infections are becoming more prevalent worldwide, and more is being learned about them, many questions about the pathogenesis and management of these infections remain unanswered. Until clear clinical guidelines are established, what should healthcare providers know about *M. genitalium*-related infections?**

Healthcare providers (HCPs) reading this article may be familiar with the bacterium's name, *Mycoplasma genitalium*, or perhaps they have heard some vague references to it in articles about sexually transmitted infections (STIs). However, if HCPs are not sure which symptoms are associated with *M. genitalium*-related infections, when to order a test or even if such a test exists, where to obtain a sample for testing, or how to treat a diagnosed infection, they are not alone. HCPs are likely to have many questions because STI experts



still have many questions. The picture of *M. genitalium* is slowly coming into view, but this bacterium and the clinical syndromes it causes are not quite ready for prime time.

What do HCPs need to know about this growing threat, and how do they integrate this knowledge into practice while waiting for clear clinical guidelines? HCPs can become familiar with the syndromes that *M. genitalium* causes, know when and how to test for the bacterium (or at least when to suspect it), and know which antibiotics are most effective in treating it. This article provides an overview of emerging knowledge of this bacterium, the diseases it causes, the challenges it poses, and developing clinical recommendations.

An emerging STI

Mycoplasma genitalium is a member of the class of bacteria called Mollicutes. Within the genus *Mycoplasma* are several species, many of which are not clinically relevant. The human genital tract is the main site of colonization for three known species of *Mycoplasma*: *M. hominis*, *M. genitalium*, and *M. penetrans*.¹ In 2015, the CDC first included *M. genitalium* informally in its Sexually Transmitted Disease Treatment Guidelines as an emerging STI.²

In the 1980s, *M. genitalium* was identified as a cause of male nongonococcal urethritis (NGU).³ Since then, the role of this pathogen in male NGU has been well established. The prevalence of *M. genitalium* infection in men with NGU is 10%-25%.⁴⁻⁷ Among men with persistent or recurrent NGU, however, *M. genitalium* positivity increases to 41%-50%.⁵⁻⁷ In most settings, *M. genitalium*-related NGU is more common than urethritis caused by *Neisseria gonorrhoeae* and almost as common as or more common than urethritis caused by *Chlamydia*.⁸ *M. genitalium*-related infections have been identified in the male foreskin, rectum, and epididymis as well. Less is known about the natural history of infections in these areas because they are mostly asymptomatic.

In addition, less is known about the pathogenesis of *M. genitalium*-related infections in women than in men. Fewer studies have been conducted in the former, and sample sizes have been small. *M. genitalium* has been found in the urethra, cervix, endometrium, and Fallopian tubes. Proving causation of genital tract syndromes such as cervicitis and pelvic inflammatory disease (PID) is more challenging. Many *M. genitalium*-related infections are asymptomatic. Furthermore, diagnoses for conditions such as cervicitis and PID are imprecise and subject to variability among HCPs. Proving any microbiologic diagnosis in PID is difficult, although evidence is building.

In vitro studies show microscopic damage of cilia in human Fallopian tubes by *M. genitalium*.⁹ Stronger

evidence of a causal role in female genital tract infections was provided by Lis et al¹⁰ in their recent meta-analysis. This meta-analysis, in which studies reported between 1980 and 2014 were reviewed, showed that *M. genitalium*-related infection was associated with an approximately two-fold increased risk of cervicitis, preterm birth, spontaneous abortion, PID, and infertility in women.

Challenges in diagnosis and treatment

The small size and simple structure of *M. genitalium* are at the root of the clinical challenges in addressing this bacterium. First, diagnosis is hampered by limited availability of testing. At present, no FDA-approved diagnostic tests are available. Culture takes weeks to months. Susceptibility testing is even more challenging and is available at only a few laboratories in the United States. Although nucleic acid amplification tests (NAATs) using polymerase chain reaction (PCR) and transcription-mediated assay (TMA) are not FDA approved, several large medical centers and large commercial laboratories have made them available by completing the required validation studies. Specimens from the cervix, urethra, vagina, and urine are all acceptable sites for NAATs.

Second, *M. genitalium* poses several treatment challenges. *Mycoplasma* bacteria lack a cell wall, a feature that makes them resistant to many common antibiotics (e.g., beta-lactams such as penicillins and cephalosporins). At present, only two antibiotics, azithromycin and moxifloxacin, have been shown to have acceptable efficacy in treating *M. genitalium*-related infections.¹¹ Treatment with a 7-day course of doxycycline is inadequate; the median cure rate is 31%.² Likewise, ciprofloxacin, ofloxacin, and levofloxacin have poor activity against *M. genitalium*.¹¹ Other agents such as gemifloxacin, sparfloxacin, grepafloxacin, trovafloxacin, and garenoxacin are under investigation.¹¹

Mycoplasma genitalium infections are rapidly developing resistance to azithromycin. Before 2009, the cure rate with azithromycin in these cases was about 85%; since 2009, it has dipped below 67%.¹² In some settings, approximately 50% of all *M. genitalium* infections are resistant to azithromycin.² Some studies have shown that retreatment with an extended-dose regimen of azithromycin may increase efficacy marginally, whereas other studies have shown no improvement.¹³ Although azithromycin is becoming less effective, the cure rate for moxifloxacin, between 85% and 100%, remains strong.^{2,13}

Screening for *Mycoplasma genitalium*

If *M. genitalium* infection is clearly established as a cause of genital tract syndromes in both men and women and

is known to be sexually transmitted, should HCPs start screening for it? Many criteria must be fulfilled before a large-scale public health screening program can be recommended. With respect to what is known about *M. genitalium*, some of these criteria are met, whereas others are not.¹⁴ It is known that this bacterium is common and communicable, two criteria that support screening efforts. By contrast, it is uncertain whether *M. genitalium* infection causes significant morbidity and how often it causes PID and other major sequelae.¹⁴ Is morbidity preventable? Treatment is not consistently effective. Is it associated with major costs? Few data exist on the potential healthcare-related costs and the population-level morbidity of infection.¹⁴

Routine *Chlamydia* screening of young women was recommended after clear evidence showed that such screening reduced the incidence of PID (and therefore ectopic pregnancy, chronic pelvic pain, and infertility).¹⁴ However, even the success of this intervention is in question. The prevalence of *Chlamydia* infections continues to rise despite 20 years of widespread screening.¹⁵

Current recommendations

For now, until more information becomes known about *M. genitalium*, Golden et al¹⁴ have suggested a few indications for testing: (1) persons failing treatment for urethritis, PID, or cervicitis; and (2) sex partners of persons diagnosed with *M. genitalium* infection. These authors go on to suggest that some HCPs may consider testing even first cases of urethritis, PID, and cervicitis if resources allow. If test results are negative for *Mycoplasma*, doxycycline may be preferred in an effort to decrease the drive toward azithromycin resistance.¹⁴

The CDC still recommends a single dose of azithromycin 1 g for treatment of *M. genitalium* infection. Study results suggest that longer regimens may be marginally superior, but only for persistent or recurrent infections. For patients with recurrent cases initially treated with azithromycin, the CDC recommends moxifloxacin 400 mg/day for 7, 10, or 14 days.² Routine tests-of-cure for asymptomatic persons are not recommended.

Although much remains unknown about this elusive bacterium, the body of evidence regarding *M. genitalium* is growing rapidly. The next CDC STD Treatment Guidelines will likely be released in 2020. HCPs can hope for much more robust guidance in this next issue of the guidelines.

Melanie A. Deal is a nurse practitioner at University Health Services at the University of California, (continued on page 50)

the most noteworthy inter-professional partnership I have fostered has been with our onsite pharmacists. Our work overlaps so notably in chemotherapy that this relationship has proved invaluable in managing patient care. Working together as an interdisciplinary team has demanded flexibility and creativity on all our parts. This collaboration has led to a more balanced workflow for the patients and the organization, and has provided me with a rich learning environment.

Now, a year later, this WHNP role is still evolving. We have added a similar NP position at our other treatment site, which includes chemo management, clinic coverage, and survivorship care. Both positions are still changing to fit the needs of a rapidly growing service line at The James, and I believe strongly in their potential to improve the lives of our patients. My WHNP education laid the groundwork for my future work in the field of women's health, and my fellowship training refined those skills to a more specific oncology patient population. It has been a privilege to cultivate this unique WHNP role and create a tailored approach to chemo management, clinic

visits, and inpatient care. This role elevates continuity of care for our patients and fosters the inter-professional relationships that augment that care. By moving outside the traditional WHNP role, we are finding ways to address and manage patient needs in a revolutionary way. ●

Sarah K. Szczepanik is a women's health nurse practitioner specialist at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital, Gynecologic Oncology, and Randee L. Masciola is an Assistant Professor at The Ohio State University, College of Nursing, and an actively practicing women's health nurse practitioner, both in Columbus, Ohio. The authors state that they do not have a financial interest in or other relationship with any commercial product named in this article.

Reference

1. Cook O, McIntyre M, Recoche K. Exploration of the role of specialist nurses in the care of women with gynaecological cancer: a systematic review. *J Clin Nurs*. 2015;24(5-6):683-695.
8. Manhart LE. *Mycoplasma genitalium*: an emergent sexually transmitted disease? *Infect Dis Clin North Am*. 2013;27(4):779-792.
9. Wiesenfeld HC, Manhart LE. *Mycoplasma genitalium* in women: current knowledge and research priorities for this recently emerged pathogen. *J Infect Dis*. 2017;216(suppl 2):S389-S395.
10. Lis R, Rowhani-Rahbar A, Manhart LE. *Mycoplasma genitalium* infection and female reproductive tract disease: a meta-analysis. *Clin Infect Dis*. 2015;61(3):418-426.
11. Couldwell DL, Lewis DA. *Mycoplasma genitalium* infection: current treatment options, therapeutic failure, and resistance-associated mutations. *Infect Drug Resist*. 2015;8:147-161.
12. Bradshaw CS, Jensen JS, Waites KB. New horizons in *Mycoplasma genitalium* treatment. *J Infect Dis*. 2017;216(suppl 2):S412-S419.
13. Manhart LE. *Mycoplasma genitalium* on the loose: time to sound the alarm. *Sex Transm Dis*. 2017;44(8):463-465.
14. Golden MR, Workowski KA, Bolan G. Developing a public health response to *Mycoplasma genitalium*. *J Infect Dis*. 2017;216(suppl 2):S420-S426.
15. Torrone E, Papp J, Weinstock H; CDC. Prevalence of *Chlamydia trachomatis* genital infection among persons aged 14-39 years—United States, 2007-2012. *MMWR Morbid Mortal Wkly Rep*. 2014;63(38

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References

1. Ljubin-Sternak S, Meštrovi T. Chlamydia trachomatis and genital *Mycoplasmas*: pathogens with an impact on human reproductive health. *J Pathog*. 2014;2014:183167.
2. CDC. Sexually Transmitted Diseases Treatment Guidelines, 2015. *MMWR Recomm Rep*. 2015;64(3):1-137. cdc.gov/std/tg2015/default.htm
3. Tully JG, Taylor-Robinson D, Cole RM, Rose DL. A newly discovered *Mycoplasma* in the human urogenital tract. *Lancet*. 1981;1(8233):1288-1291.
4. Taylor-Robinson D, Jensen JS. *Mycoplasma genitalium*: from Chrysalis to multicolored butterfly. *Clin Microbiol Rev*. 2011;24(3):498-514.
5. Wikström A, Jensen JS. *Mycoplasma genitalium*: a common cause of persistent urethritis among men treated with doxycycline. *Sex Transm Infect*. 2006;82(4):276-279.
6. Frølund M, Lidbrink P, Wikström A, et al. Urethritis-associated pathogens in urine from men with non-gonococcal urethritis: a case-control study. *Acta Derm Venereol*. 2016;96(5):689-694.
7. Sethi S, Zaman K, Jain N. *Mycoplasma genitalium* infections: current treatment options and resistance issues. *Infect Drug Resist*. 2017;10:283-292.