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Mycoplasma genitalium: A Review of Current Issues and Challenges

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Case Report: Persistent Discharge and Pelvic Pain in a 19 YO Female

A 19-year-old female patient with PID presented with persistent discharge and pelvic pain despite multiple rounds of treatment with azithromycin, the treatment of choice per the most recent CDC STD treatment guidelines. Her partner was subsequently seen for persistent penile discharge and diagnosed with *non-gonococcal urethritis* (NGU) but tested negative for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* after treatment of an initial *C. trachomatis* infection. The couple reported to have continued intercourse due to the negative *C. trachomatis/N. gonorrhoeae* test results. The female patient was tested for *Mycoplasma genitalium* using a nucleic acid amplification test (NAAT) through a university research laboratory at her last visit. Further testing demonstrated the presence of a 23S rRNA gene mutation for macrolide resistance in the *M. genitalium* strain which explained the observed resistance to previous azithromycin treatment. Given these results, the couple was treated with moxifloxacin, a fourth-generation synthetic fluoroquinolone antibacterial agent, which eventually led to the resolution of reported symptoms.

While this case reports successful identification and treatment of *M. genitalium*, it reflects the current state of affairs in the management of sexually transmitted infections (STIs). In stark contrast to this case, an asymptomatic patient in a similar scenario or a symptomatic patient without access to advanced STI diagnostics would continue to harbor the azithromycin-resistant strain of *M. genitalium,* thereby remaining at risk for adverse reproductive outcomes and potentially transmitting the pathogen to other partners. *M. genitalium* has emerged as an important STI and warrants an accurate diagnosis and effective management strategies.

Mycoplasma genitalium: An Emerging STI that Demands Clinician Attention

Many clinicians haven't heard of *M. genitalium*, even though it is now included in the CDC STD treatment guidelines.[1] Although clearly sexually transmitted, with increasing evidence linking it to adverse reproductive outcomes for women, *M. genitalium* is still considered an emerging pathogen. Given potentially increasing prevalence and evidence of expanding antibiotic resistance, it is imperative to raise clinician awareness about this organism. *Mycoplasma genitalium* infects the male and female genital

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tracts and is associated with NGU among males as well as cervicitis, endometritis, pelvic inflammatory disease (PID), infertility and adverse birth outcomes among women. It has also been associated with an increase in risk for human immunodeficiency virus (HIV) infection. Detection of *M. genitalium* in clinical practice is challenging given the absence of an FDA-approved diagnostic assay; therefore, most infections are managed symptomatically. Furthermore, treatment of *M. genitalium* infection poses increasing challenges due to rising antibiotic resistance. This case report and literature review discussed herein underscore the need for improved awareness of *M. genitalium*.

Key Facts You Need to Know about *Mycoplasma genitalium*

M. genitalium is more common than many other sexually transmitted pathogens.

Data from several population-based studies of low-risk individuals estimate that the prevalence of *M. genitalium* among women ranges from 0.8%-4.1% and among men ranges from 1.1%-1.2%.[2-7] However, higher prevalence has been reported among patients attending STD clinics. For instance, among women attending an STD clinic in Seattle, WA, the prevalence of *M. genitalium* was 7.7%, but as high as 19% in both Baltimore, MD, and Durham, NC. [8-11] Among men attending US STD clinics, prevalence ranged from 12%-15% in a similar time period.[12-14] More recently, a multicenter clinical study from the US reported *M. genitalium* prevalence of 16.1% among women aged 14-70 years and 17.2% among men age 18-78 years, with the highest prevalence identified in adolescent and young adult men and women (> 24%) as well as among black men and women (27.9% and 23.2%), consistent with risk factors identified in population-based studies.[3,7,15] Similarly, a Midwestern commercial laboratory reported prevalence of 11.4% for females and 6.8% for males.[16,17] In all but a few cases, *M. genitalium* prevalence was higher than all other bacterial STI in these more recent studies.

M. genitalium is sexually transmitted.

Several studies provide evidence that *M. genitalium* is sexually transmitted. *M. genitalium* is more common among sexually experienced than sexually-naïve adolescents and occurs more frequently in individuals with more sexual partners. [2,8,18-20] Similar to other STIs, sexual partners of *M. genitalium*-positive individuals are more likely to have *M. genitalium* than partners of *M. genitalium*-negative individuals.[20-24] In addition, strain typing has demonstrated that most concordantly infected sex partners harbor genomically identical *M. genitalium* strains. [25,26]

M. genitalium can travel with other sexually transmitted organisms.

The extent to which individuals with *M. genitalium* are co-infected with other STIs varies by geographic setting and gender. In the Pacific Northwest co-infections are rare; however, co-infection has been observed more frequently in other areas.[8,12] In Baltimore STD clinic attendees, 37% of women but only 5.9% of men with *M. genitalium* were co-infected with another STI. [10,14] Co-infection with chlamydia and *M. genitalium* in US women ranged from 3.1% in a recent multi-site study to 37.5% among adolescent females in the Midwest, whereas among men it ranged from 9.7% in 7 US clinics to 35% of men in New Orleans.[13,15,18] Few instances of co-infection with *Trichomonas vaginalis* have been reported, with only 6.3% among women but none among men in 7 clinics.[15] In contrast, bacterial vaginosis (BV) has been associated with *M. genitalium* in some studies, and a recent study among Kenyan women reported that BV may increase susceptibility to *M. genitalium*.[27]

HIV is approximately twice as common in *M. genitalium*-infected as in *M. genitalium*-negative individuals and two studies have demonstrated that *M. genitalium* infection was associated with an increased risk for subsequent HIV acquisition.[28-30] *M. genitalium* may also increase the risk of HIV transmission to sex partners, given the elevated HIV viral shedding observed in dually infected individuals.[31,32]

Consider that *M. genitalium* may be a cause for symptoms.

Although most *M. genitalium* infections are asymptomatic, the organism has also been strongly associated with male and female reproductive tract syndromes. However, there are no distinguishing clinical features of an *M. genitalium* infection, making it infeasible to determine the presence or absence of *M. genitalium* based on clinical signs and symptoms alone. Symptoms, when present, are similar to those in individuals with C. trachomatis-associated urethritis, cervicitis and PID.[33]

M. genitalium is an acknowledged cause of male urethritis, and meta-analyses have demonstrated that men infected with *M. genitalium* are 5 and a half times more likely to have urethritis than men without *M. genitalium*.[34] Balanitis and posthitis have been reported among *M. genitalium*-positive men in one study, and rectal infections have been detected in 2%-12%, particularly among men who have sex with men.[35-38] Given the rising practice of anal intercourse among women, rectal infections are increasingly likely and have been reported in 2.7%- 8.1% of women.[39-41]

In meta-analyses of female reproductive tract disease syndromes, *M. genitalium* was associated with an approximately 2-fold increase in the risk of cervicitis, PID, preterm delivery, spontaneous abortion, and infertility. This increased risk was statistically significant for all syndromes but infertility and was stronger in studies that controlled for other STIs.[42] Although the meta-analysis strongly implicates *M. genitalium* in the etiology of female reproductive tract disease syndromes, additional definitive data are still lacking. Most studies of *M. genitalium* infection in women have been cross-sectional in nature and few have followed women over time to determine what proportion of infected women go on to experience severe sequelae. While an earlier randomized trial convincingly demonstrated the utility of screening and treating C. trachomatis infections in preventing PID, similar studies have not yet been carried out for *M. genitalium*.[43]

Although few studies of ectopic pregnancy have been conducted, in vitro infection of tubal tissue with *M. genitalium* has been shown to result in deformation

and destruction of cilia, similar to events after *C. trachomatis* infection.[44] This potential mechanism for ectopic pregnancy is consistent with a recent Saudi Arabian study, which tested tubal specimens by polymerase chain reaction (PCR). Women in whom *M. genitalium* was detected were 2-fold more likely to have an ectopic pregnancy suggesting that *M. genitalium* may be involved in the etiology of this syndrome as well.[45]

NAATs are the diagnostic method of choice for *M. genitalium.*

M. genitalium is a slow-growing organism that lacks a cell wall and therefore cannot be detected by Gram staining. It is very fastidious and culture is not a feasible option for diagnostic testing. When achieved, culture requires up to 6 months.[46,47] Current serological tests are insufficiently sensitive and specific and cannot differentiate between current and previous infection. Nucleic acid amplification tests (NAATs) are therefore the primary method of detection. Two types of NAATs have been developed and used to detect *M. genitalium*. PCR tests were initially developed by research laboratories for early research studies[48,49] and variations of these PCR tests have now been implemented by several large commercial laboratories. There is no FDA-approved diagnostic NAAT assay available in the US.[50]

All of the NAAT assays can be used with a variety of specimen types, including male and female urine, vaginal swabs (clinician- and self-collected), endocervical swabs; and male urethral, penile-meatal and rectal swabs. *M. genitalium* is rarely detected in the oropharynx, so oropharyngeal swabs are less often utilized.[34] Although most specimen types have good sensitivity and specificity, self-collected vaginal swabs have higher sensitivity than other female specimen types and self-collected penile-meatal swabs have recently been found to have slightly higher sensitivity than other male specimen types.[51-53]

M. genitalium is increasingly resistant to recommended antibiotic regimens.

Although the 2015 CDC STD treatment guidelines classify *M. genitalium* as an emerging sexually transmitted pathogen, in the absence of validated diagnostic tests, the treatment of most *M. genitalium* cases must rely on syndromic management.[1] The recommended first-line therapy for urethritis or cervicitis is either 100 mg doxycycline twice daily for 7 days or a single 1 g dose of azithromycin. Moxifloxacin (400 mg daily x 7, 10 or 14 days) is recommended in cases of persistent/recurrent urethritis or persistent/recurrent cervicitis where *M. genitalium* is suspected. For cases of PID in which *M. genitalium* is suspected or detected, a 14-day regimen of moxifloxacin 400 mg daily is recommended. However, the CDC guidelines do not currently suggest routine tests-of-cure or re-screening among asymptomatic patients after treatment for any of these syndromes.[1]

The 2016 European guidelines on *M. genitalium* make similar recommendations for treatment of urethritis, cervicitis and PID, but recommend a longer course of azithromycin instead of the 1g single dose (an initial 500-mg dose followed by 250 mg daily for 4 days).[54] Nevertheless, more recent data suggest that there is limited additional benefit to the extended duration regimen.[55] The European guidelines also suggest NAAT for initial detection of *M. genitalium*, followed by an assay to determine macrolide resistance to guide therapeutic decisions and tests-of-cure 3 weeks after the start of treatment.

The recommendation to employ a second assay to determine macrolide resistance is rooted in the rapid spread of macrolide resistance in *M. genitalium*. In most settings, azithromycin has been the treatment of choice for urethritis and cervicitis, in part due to its single-dose nature.[56] However, although azithromycin was initially highly effective against *M. genitalium*, cure rates after the 1 g dose have diminished to 69% in studies after 2009.[57] The emergence of resistance to azithromycin has been attributed to mutations in the 23S rRNA gene in *M. genitalium* that typically confer nearly complete resistance to macrolides.[58] These mutations can be detected by either PCR amplification and sequencing of the 23S rRNA gene in *M. genitalium* or by multiplex qPCR utilizing coupled PlexZyme primers.[59-60] In areas of the Asia-Pacific, where antibiotic resistance typically emerges first, these macrolide mediating resistance mutations (MRMM) have recently been detected in 63% of *M. genitalium*-positive patients in Melbourne, Australia, and 74% of Auckland, New Zealand patients.[38,61] Although macrolide resistance has been slower to emerge in the US, a recent study demonstrated that MRMM were found in 50.8% of female patients and 42% of male patients with *M. genitalium*, with a higher prevalence among younger than older individuals and among those of African American descent relative to other race/ethnicities.[15]

Moxifloxacin, the currently recommended second-line treatment, was initially highly successful in cases of azithromycin treatment failure, with cure rates of 100%.[62] However, the first reports of treatment failure after moxifloxacin began appearing in 2012,[63] and treatment failure in recent reports ranges from 12%-30%.[64,65] This emerging resistance is most strongly associated with mutations in the parC region of the quinolone resistance determining region (QRDR) in *M. genitalium*. Although little data exist on the prevalence of parC mutations in the US, frequencies of 5%-6% in Eastern Europe, and up to 14% in Australia, have been recently reported.[66,67] Of greater concern are increasing reports of markers of dual resistance to macrolides and quinolones and treatment failures after therapy with both antimicrobials.[64,66-69,70] In these cases, pristinamycin, a streptogrammin and spectinomycin, an aminoglycoside, have been effective.[64,70] But in many locations, including the US, these antibiotics are not available.

M. genitalium is a serious problem.

M. genitalium infection is clearly and strongly associated with urethritis in men and can be sexually transmitted to female partners. In an increasing number of settings, prevalence is as high as or higher than other bacterial STI pathogens, and accumulating evidence suggests that infection in women is associated with adverse reproductive outcomes such as PID, preterm delivery, and potentially infertility. This is coupled with the substantial and increasing treatment challenges for this pathogen. Standard antibiotics used in syndromic

therapy for reproductive tract infections are waning in terms of efficacy, macrolide resistance may already be widespread, quinolone resistance is emerging, and cases of dual resistance are occurring. In addition, management of *M. genitalium* infections is challenged by the current lack of an FDA-approved diagnostic test. Although laboratory-developed tests validated for clinical use by large commercial laboratories or analytic specific reagents (ASRs) developed for existing platforms are becoming increasingly available, the US lacks guidelines for the use of these tests. In the absence of this, most patients with *M. genitalium* will not be diagnosed nor will they receive a test-of-cure after therapy which has a high likelihood of being ineffective. To mitigate these threats to female reproductive health, future directions should include making an FDA-approved assay widely available, instituting widespread resistance testing and surveillance, and developing novel therapeutic regimens. Until this has been accomplished, clinicians will need to be aware of *M. genitalium* and consider it when engaged in syndromic management of reproductive tract infections. *(General guidelines to consider are summarized in Figure 1).*

Call to Action: Bringing Research into the Clinic

Given potentially rising prevalence of *M. genitalium* among young adults and its associated adverse effects on the female genital and reproductive tract, *M. genitalium* represents a serious problem. Improved access to testing among high-risk populations and research to aid the development of evidence-based screening guidelines for the general population will be essential to adequately manage infections with this pathogen and prevent disease complications at the population level.

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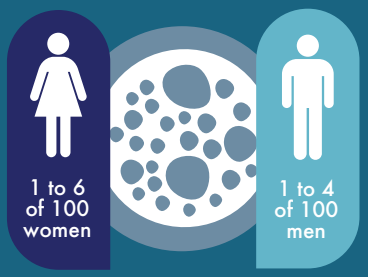
Mycoplasma genitalium Overview



- Global prevalence estimates vary[6,7,71]
- Associated with genital and reproductive tract disease
- More common than *Neisseria gonorrhoeae*

Most infections are asymptomatic, but symptoms may occur[1,7,37,71]

women

Clinical manifestations (if present)

- Mucopurulent cervical discharge, cervical friability and increased number of polymorphonuclear leukocytes
- Silent or asymptomatic pelvic inflammatory disease (PID)

Possible complications of untreated infections

- PID
- Preterm birth
- Spontaneous abortion
- Infertility

men

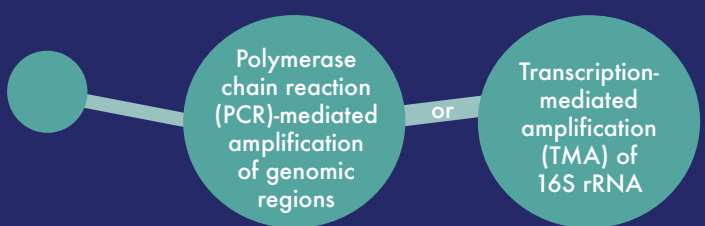
Typical urethritis symptoms (if present)

- Dysuria
- Urethral pruritus
- Urethral discharge

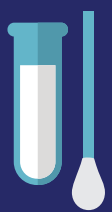
Other clinical manifestations

- Rectal symptoms
- Proctitis

The CDC recommends nucleic acid amplification testing (NAAT); there is no FDA-approved diagnostic test for *M. genitalium*[1]



M. genitalium testing in men and women can be performed using many sample types[52,72]



Types of samples used for women

- Vaginal swab*
- First-void urine
- Endocervical swab
- Rectal swab

Types of samples used for men

- First-void urine
- Penile meatal swab
- Urethral swab
- Rectal swab

*Clinician- or patient-collected; highest relative sensitivity for NAAT

Treatment with antibiotics that do not target cell-wall biosynthesis is recommended by the CDC since *M. genitalium* lacks a cell wall[1]