

## ***Mycoplasma Genitalium* Infection: An Emerging Sexually Transmitted Infection**

### ***Introduction***

Although the first reported association of *Mycoplasma genitalium* (*M. genitalium*) with inflammatory urogenital disease was over 35 years ago,<sup>1</sup> we have just begun to appreciate the clinical significance of this pathogen as a sexually transmitted infection (STI) in the last 15 years. Recently, *M. genitalium* has been labeled as an “emerging” STI.<sup>2</sup> *M. genitalium* was originally isolated from men with urethritis<sup>1</sup> and since then has been strongly linked to non-gonococcal urethritis (NGU).<sup>3,4</sup> In women, *M. genitalium* infection has now been strongly linked to cervicitis, and there is also evidence that it may lead to reproductive complications, including pelvic inflammatory disease (PID) and tubal factor infertility; evidence supporting that the infection causes perinatal complications is more limited.<sup>3-5</sup> *M. genitalium* infection may also be asymptomatic in men and women, and the natural history and clinical consequences of untreated asymptomatic infection remains to be elucidated.

One of the driving forces behind the emergence of this infection has been the development of nucleic acid amplification tests (NAATs), such as PCR, that have provided the means to detect *M. genitalium* in specimens collected from general- and clinic-based populations. Because of the challenges of growing *M. genitalium* in culture, there was no *M. genitalium* test readily available for clinical or research applications prior to the availability of NAATs. Before 2019, the *M. genitalium* NAATs available in the U.S. were research-based. However, to date in 2019, there are now two commercially available FDA-cleared NAATs for *M. genitalium* detection. Their availability should contribute to advancement of our knowledge on the natural history of the infection and its morbidity. Such knowledge is essential in the consideration of screening guidelines for *M. genitalium*, especially since there are no current screening recommendations for *M. genitalium* in the U.S. The 2015 CDC STD Treatment Guidelines recommends to consider *M. genitalium* as a possible etiology for recurrent or persistent urethritis, cervicitis, and PID in your approach to managing these cases.<sup>2</sup> Golden and colleagues discussed European *M. genitalium* testing guidelines along with proposed Public Health Guidelines from Washington State as evidence of the urgent need to identify and quickly manage *M. genitalium* infection in the U.S.<sup>6</sup> Contributing to this urgency is the rapid development of macrolide resistance among *M. genitalium* strains.<sup>3,7-13</sup> Of greater concern is the emergence of *M. genitalium* strains with fluoroquinolone resistance,<sup>9,10,14-16</sup> which may be associated with *M. genitalium* infection treatment failure in patients treated with moxifloxacin,<sup>15,16</sup> and the lack of consistently effective treatments in the U.S for *M. genitalium* infections failing macrolide and fluoroquinolone treatments. All of these challenges make it that much more important for healthcare professionals to be aware of this emerging STI and of optimal screening and treatment strategies.

### ***Epidemiology and Burden of Disease with M. genitalium Infection***

In 1981, Tully and colleagues reported cell culture isolation of a new mycoplasma from the urogenital tract of 2 of 13 men with NGU.<sup>1</sup> In 1983, this new mycoplasma was named a new species, *M. genitalium*.<sup>17</sup> *M. genitalium* is highly fastidious in culture and can take anywhere from weeks to months to grow. For this reason, there had been sparse clinical data on *M. genitalium* infection until the last 15

years. With the development of research-based (“in-house”) *M. genitalium* NAATs, studies began to emerge on the prevalence of the infection, risk factors, clinical manifestations, natural history, and treatment outcomes.

### **General Population Studies**

Limited studies on the prevalence of *M. genitalium* infections in general populations suggest the infection is more prevalent than gonorrhea but less or similar to chlamydia.<sup>18-21</sup> Manhart and colleagues evaluated the U.S. prevalence of *M. genitalium* infection in 18 to 27 year old individuals by testing stored urine specimens using PCR; they found a prevalence of 1.1% in men and 0.8% in women, higher than the 0.4% prevalence of gonorrhea in the cohorts but lower than the prevalence of chlamydia (3.7% in men and 4.7% in women).<sup>18,19</sup> Prevalence of *M. genitalium* infection was higher in African Americans and those who reported living with a sexual partner.<sup>18</sup> Only 2.2% of participants reported painful urination and none reported urethral or vaginal discharge.<sup>18</sup> A population-based study of *M. genitalium* prevalence in individuals 16 to 44 years of age in Britain that also tested urine by PCR found a prevalence of 1.2% in men and 1.3% in women, which was higher than the prevalence of gonorrhea found in the cohort (<0.1% for both genders) but similar to chlamydia prevalence (1.1% in men and 1.5% in women).<sup>20,21</sup> Prevalence was higher in African American men and both genders who reported select sexual risk behaviors.<sup>20</sup> Most men (94%) and the majority of women (56%) did not report any symptoms consistent with an STI.<sup>20</sup> Studies in clinic-based populations have revealed a much higher *M. genitalium* prevalence than what is seen in the general population and still higher than gonorrhea with similar or higher prevalence than chlamydia.<sup>8</sup> In one of the largest clinic-based population studies, Getman and colleagues tested urine and genital swab specimens from 431 men (ages 18 to 78 years) and 515 women (ages 14 to 70 years) who were seen at 7 geographically dispersed clinics in the U.S. using a research-based *M. genitalium* NAAT. They reported an *M. genitalium* prevalence of 17.2% in men (similar to chlamydia [17.8%] but higher than gonorrhea [4.2%]) and 16.3% in women (higher than chlamydia [9.3%] and gonorrhea [1.9%]).<sup>8</sup> Predictors of higher *M. genitalium* infection prevalence were African American race and women having symptoms.<sup>8</sup> In 3 recent studies in U.S. clinic-based populations, *M. genitalium* prevalence ranged from 11% to 24%.<sup>10,22,23</sup>

While *M. genitalium* infections are often asymptomatic, some can present with clinical syndromes that are also seen with chlamydia and gonorrhea. Therefore, specific testing for *M. genitalium* is required to confirm the bacteria as an etiology for the syndrome. Testing for other STIs is also necessary since co-infection of *M. genitalium* with other pathogens can occur (albeit infrequent)<sup>8</sup>, and different etiologies may require different treatments.

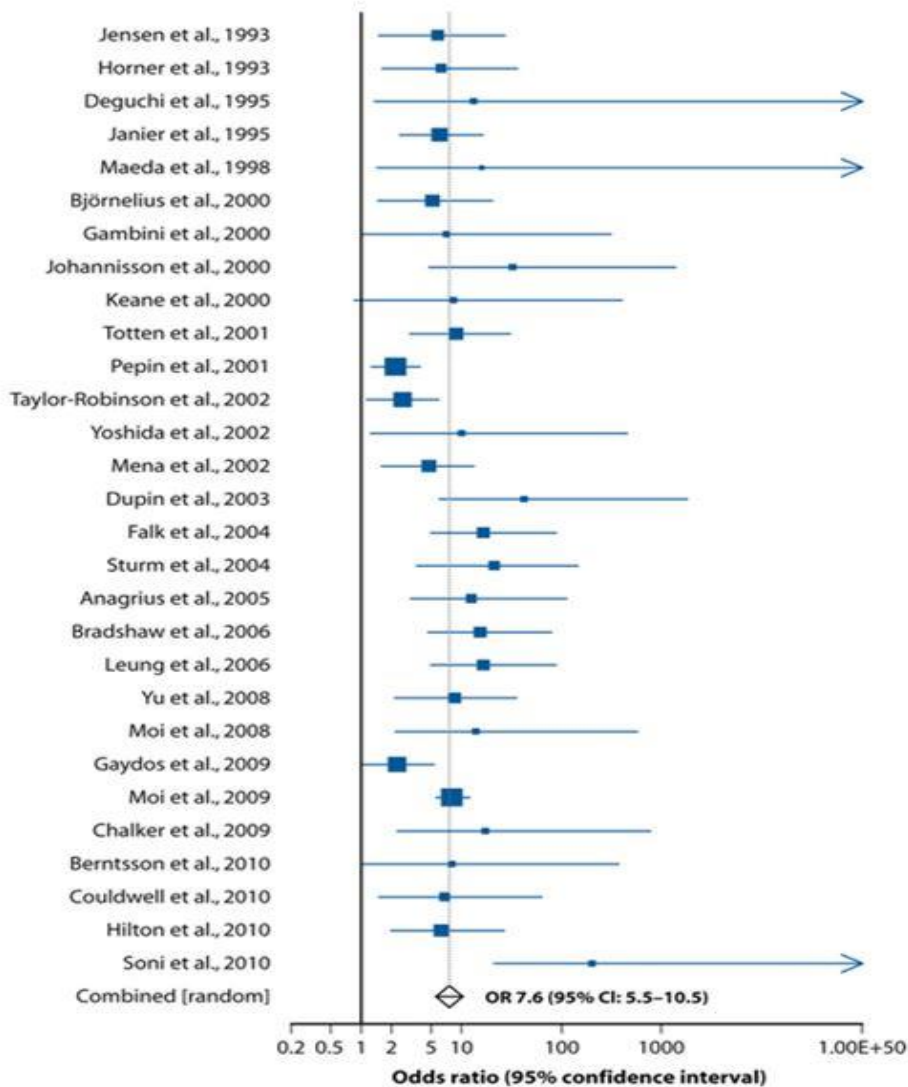
### ***M. genitalium* Infection in Men**

In men, numerous studies have demonstrated a strong association of *M. genitalium* with symptomatic acute NGU, particularly nonchlamydial NGU (**Figure 1**).<sup>4</sup> *M. genitalium* has been detected by PCR in 15% to 25% of symptomatic NGU cases and about 30% of cases of persistent or recurrent urethritis.<sup>2,4</sup> There are sparse data that *M. genitalium* urethritis in men is complicated by epididymitis.<sup>2,4</sup> *M. genitalium* has

also been detected in anorectal samples, usually in individuals without rectal symptoms.<sup>2,4</sup> However, the bacteria has been reported as a cause of proctitis in men who have sex with men (MSM).<sup>24</sup>

**Figure 1**

**Association between *Mycoplasma genitalium* and acute nonchlamydial nongonococcal urethritis**  
(Odds ratios and 95% confidence intervals were calculated from published studies of PCR positivity).

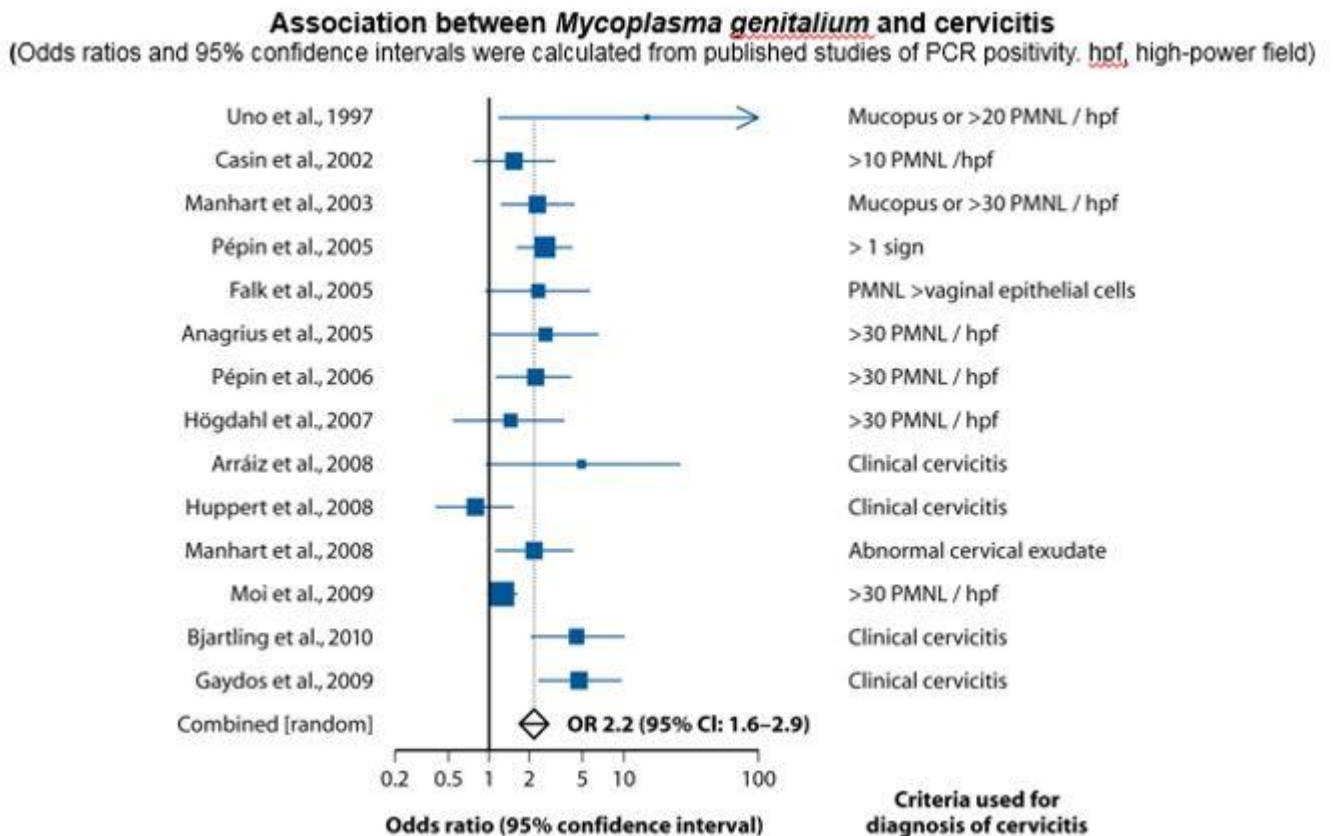


**M. genitalium Infection in Women**

Numerous studies have shown an etiologic association between infection with *M. genitalium* and cervicitis (Figure 2).<sup>4</sup> The bacteria has been detected in 15% to 30% of women presenting with clinical cervicitis as well as in women with persistent or recurrent cervicitis.<sup>2</sup> There is evidence that *M. genitalium* infection can ascend to the upper genital tract in women resulting in PID. A study by Baczynska and colleagues demonstrated that human fallopian tube cells can be infected with *M.*

*genitalium*, leading to inflammation and damaged cilia.<sup>25</sup> Animal studies revealed that *M. genitalium* can also infect and cause inflammation of the upper genital tract.<sup>26,27</sup> Cohen and colleagues presented data that *M. genitalium* was detected in endometrium and/or fallopian tube tissue from women with salpingitis.<sup>28</sup> Several other human studies strongly supported *M. genitalium* infection in the development of PID.<sup>5</sup> *M. genitalium* has also been associated with an approximate 2-fold increased risk for spontaneous abortion, preterm birth, and infertility.<sup>5</sup> Although these associations are based on weaker evidence and with some studies having contradictory findings, awareness of the risks associated with *M. genitalium* infection continue to grow and have become more clinically concerning.<sup>5</sup> In addition to the above clinical syndromes, *M. genitalium* has been associated with over a 2-fold increased risk for HIV infection.<sup>29</sup>

**Figure 2**



**Natural History of *M. genitalium* Infection**

There are very limited data on the natural history of *M. genitalium* infection. Findings from a few studies suggest that the majority of *M. genitalium* infections in women naturally resolve (presumably through immune-mediated clearance) within 6 months of initial detection. One study of female sex workers in Kenya reported 83% of *M. genitalium* infections resolved after 3 months, with 91% of infections resolving by 6 months from the time of initial testing.<sup>30</sup> Similarly, a study of female sex workers in

Uganda reported that 55% of *M. genitalium* infections resolved by 3 months after initial testing and 83% by 6 months; the time to resolution was longer in HIV-infected women with CD4 counts <350/mL.<sup>31</sup> A study of adolescent females in the U.S., mostly African American, reported that 69% resolved *M. genitalium* infection by 8 weeks and 78% by 12 weeks after initial detection.<sup>32</sup>

The natural history of asymptomatic *M. genitalium* infection in men is poorly understood. Sparse data from 2 studies on the concordance of *M. genitalium* infection in couples have demonstrated low concordance rates from the perspective of the infected female patient. About 25% to 35% of male partners of infected female patients report becoming infected.<sup>32,33</sup> While the low concordance rates of *M. genitalium* infection could reflect possible inefficient sexual transmission of bacteria from infected females to their male partners, it also could reflect the short duration of the infection.

### **Diagnosis**

Notwithstanding the limited data on the natural history of *M. genitalium* infection, the clinical risks associated with infection and the inherent propensity of *M. genitalium* to develop antibiotic resistance reflect that accurate diagnosis is necessary for rapid and appropriate treatment. *M. genitalium* culture and serological testing are not useful for the diagnosis of active *M. genitalium* infection; the former is not useful because of the slow growth of the organism and challenges of culture, and the latter is not useful due to serological testing not distinguishing past from current infection and the lack of accurate *M. genitalium* serological assays.

Prior to 2019, there were no FDA-cleared *M. genitalium* assays available in the U. S.; there were, however, highly sensitive and specific research-based *M. genitalium* NAATs being used primarily for research purposes rather than clinical management.<sup>8-10,33,34-39</sup> At this time two *M. genitalium* NAATs have become FDA-cleared for testing on female and male urogenital specimens in 2019: the Hologic Aptima<sup>®</sup> *Mycoplasma genitalium* assay, which is an assay based on transcription-mediated amplification of *M. genitalium*-specific 16S rRNA, and the Roche cobas<sup>®</sup> TV/MG assay, which is a multiplex assay that detects *M. genitalium* mgbB “A” and “EF” regions (and can also be used to test for *Trichomonas vaginalis* if indicated). Neither of these assays test for the macrolide resistance-associated mutations in the 23S rRNA gene. There are other *M. genitalium* NAATs currently being investigated in the U.S.

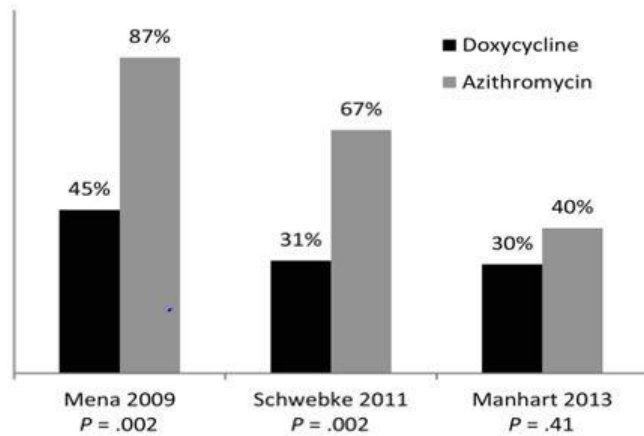
Screening for *M. genitalium* infections is not recommended in the 2015 CDC STD Treatment Guidelines, which only recommends considering *M. genitalium* in cases of recurrent or persistent urethritis, cervicitis, or PID, and testing could be performed in such instances if a validated test was available to help guide treatment decisions.<sup>2</sup> However, the 2020 CDC STD Treatment Guidelines preparations are underway, and with the availability of new evidence and FDA-cleared *M. genitalium* tests, it is possible that *M. genitalium* testing recommendations could change from those in the 2015 Guidelines. Testing for *M. genitalium* at the time of initial evaluation of urethritis, cervicitis, and PID may not only help guide therapy, but could also improve clinical outcomes and limit the development of antibiotic-resistant *M. genitalium* strains.

### **Treatment**

The three classes of antibiotics traditionally used to treat mycoplasmas are tetracyclines (e.g., doxycycline), macrolides (e.g., azithromycin), and quinolones (e.g., moxifloxacin). Doxycycline has been ineffective against *M. genitalium* NGU and cervicitis with median microbial cure rates under 50%.<sup>3</sup> Limited doxycycline efficacy does not appear to be due to resistance.<sup>40</sup> Azithromycin 1 g has been the first-line antibiotic treatment regimen for *M. genitalium* infections in the U.S. (often empirically used for urethritis and cervicitis treatment), but the microbial cure rates of azithromycin 1 g for urogenital *M. genitalium* infections have been declining since 2009. This has been demonstrated over the course of three randomized controlled NGU treatment trials (**Figure 3**)<sup>40</sup> and in a meta-analysis of *M. genitalium* treatment consisting of mostly observational data (**Figure 4**).<sup>41</sup>

**Figure 3**

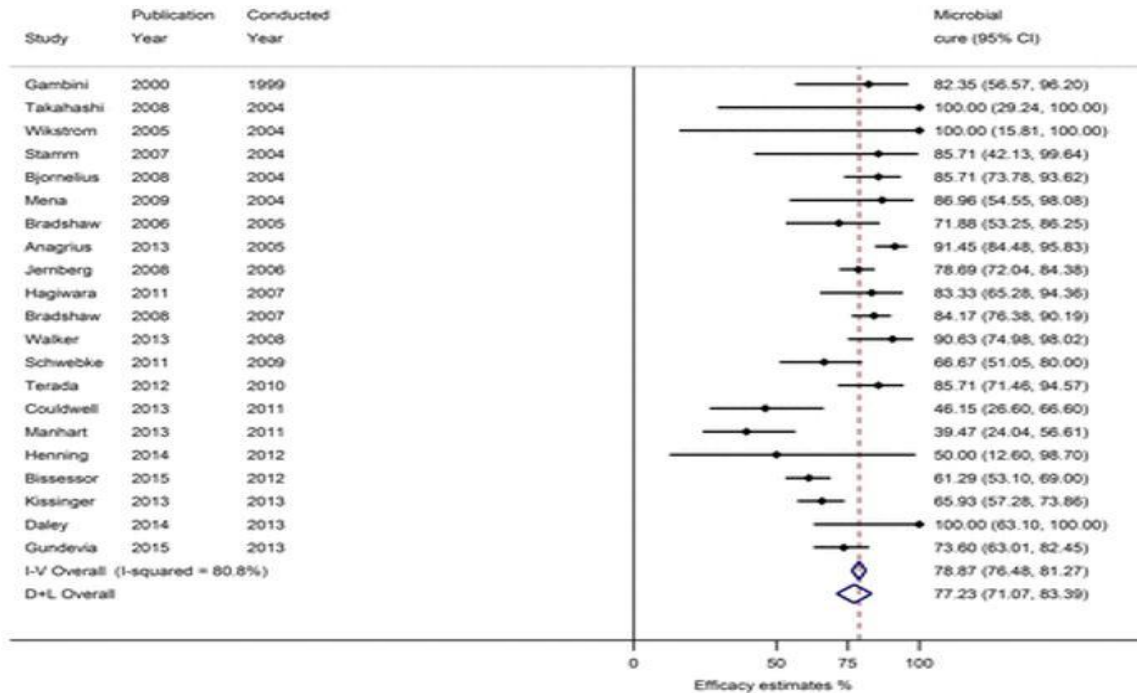
Randomized controlled trials comparing the efficacy of doxycycline (100 mg bid x 7 days) vs. azithromycin (1 g single dose) for the treatment of *Mycoplasma genitalium* urogenital infections in men



**Figure 4**

**Microbial cure following treatment with azithromycin 1g (single dose)  
for urogenital *Mycoplasma genitalium* infection.**

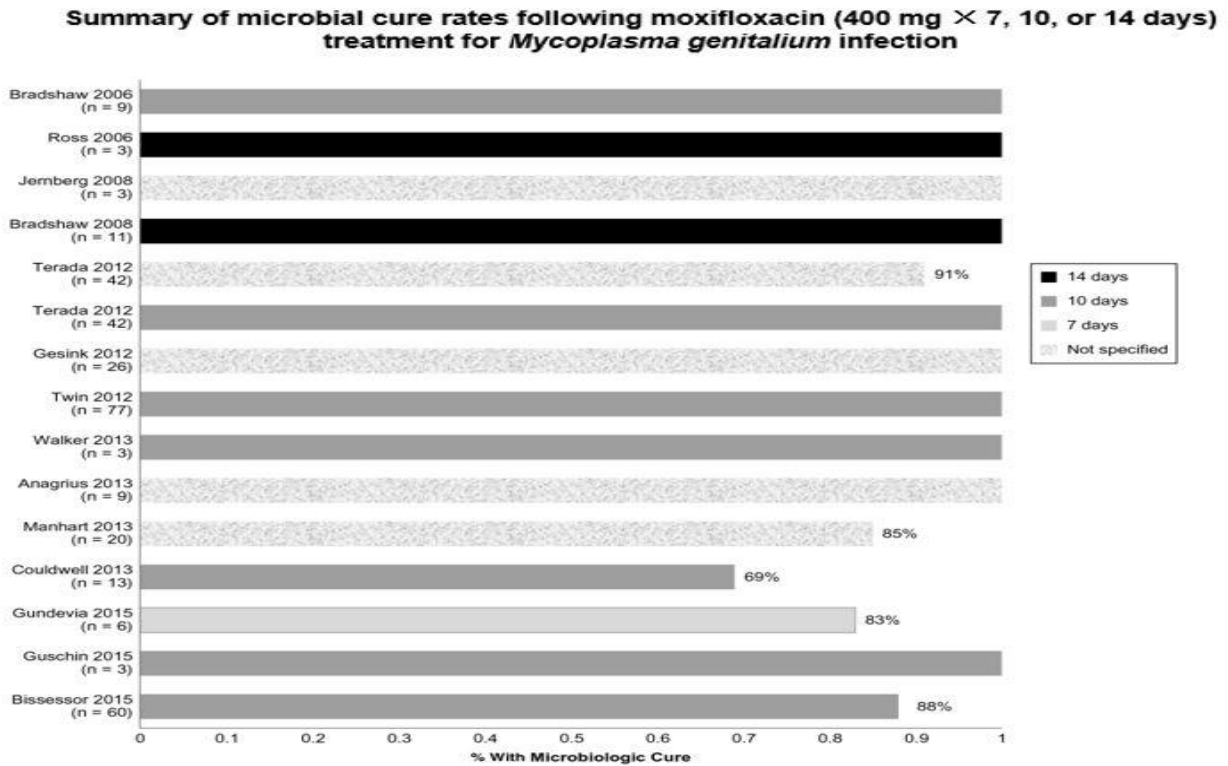
(Abbreviations: CI, confidence interval; D+L, DerSimonian and Laird method; I-V, inverse-variance method)



*M. genitalium* treatment failure with azithromycin 1 g is strongly associated with the presence of macrolide resistance-associated mutations in the 23S rRNA gene, and the development of these resistance mutations is often induced by treatment with azithromycin 1 g.<sup>3,7,16,42</sup> A recent study showed that a longer course of azithromycin (1.5 g over 5 days) for *M. genitalium* urethritis did not cure more infections or lower the likelihood of azithromycin resistance development after treatment compared to single doses of azithromycin 1 g.<sup>43</sup> Based on several U.S. studies, azithromycin-resistant *M. genitalium* strains occur in up to 42% to 94% of infections;<sup>8-13</sup> high resistance rates are also being reported outside the U.S.<sup>14,15</sup>

The quinolone moxifloxacin, given at 400 mg daily for 7-14 days, has been successful in curing most urogenital *M. genitalium* infections that failed azithromycin and/or doxycycline.<sup>40</sup> However, quinolone-resistant *M. genitalium* strains have emerged, and cure rates with moxifloxacin have been declining based on studies published since 2013 (**Figure 5**).<sup>7,16,40</sup> The *M. genitalium* quinolone resistance-associated mutation that is most strongly associated with quinolone treatment failure is the S83I mutation in the *parC* gene.<sup>44</sup> The 2015 CDC STD Treatment Guidelines recommend moxifloxacin for the treatment of suspected or documented *M. genitalium* infections in the setting of persisting urethritis, cervicitis, or PID (after azithromycin treatment).<sup>2</sup> Three recently published U.S. studies have reported detection of the *parC* S83I mutation in 7% to 30% of *M. genitalium* infections.<sup>9-11</sup>

Figure 5



There is no guidance at this time on how to best manage *M. genitalium* infections in individuals in the U.S. who have failed azithromycin and moxifloxacin due to resistance. There have been two publications that have described a total of 4 cases of men with *M. genitalium* urethritis who failed moxifloxacin with strains that were quinolone- and macrolide-resistant and who were then cured with minocycline 100 mg given twice a day for 14 days.<sup>45,46</sup> While minocycline is available in the U.S., there is insufficient data on its efficacy for *M. genitalium* infections at this time to consider it a first-line recommended treatment. There is a newer tetracycline drug, omadacycline, now available in the U.S.; however, its *in vitro* activity and clinical effectiveness for *M. genitalium* is unknown. There is also a new pleuromutilin class antibiotic, lefamulin, that has been demonstrated to have good *in vitro* activity against *M. genitalium*<sup>47</sup> and was just FDA approved for the treatment of community-acquired bacterial pneumonia. However, lefamulin's efficacy for the treatment of *M. genitalium* infections has not been studied.

With the propensity of *M. genitalium* for developing resistance, a novel resistance testing-based sequential treatment approach has become recommended in Australian and United Kingdom treatment guidelines in which uncomplicated *M. genitalium* infection (e.g. urethritis or cervicitis) is initially treated with doxycycline (100 mg twice daily for 7 days) to lower the bacterial load. That is followed by treatment with either azithromycin (regimens differ by guidelines, but include 1g first day, then 500mg daily for 2 or 3 days) or moxifloxacin (400mg daily dose with differing duration by guidelines, either for 7 or 10 days) depending on the results of testing for macrolide resistance-associated mutations.<sup>48,49</sup> In the absence of availability of macrolide resistance testing, the choice of azithromycin vs. moxifloxacin would



be based on local resistance rates and other patient clinical considerations. The success of this resistance testing-guided sequential treatment strategy, in terms of high *M. genitalium* cure rates and lower resistance development on treatment, has been reported in a study of men and women with *M. genitalium* infections who were treated at the Melbourne Sexual Health Centre.<sup>50</sup> It remains to be determined whether this novel *M. genitalium* treatment strategy will be adopted into the upcoming CDC STD Treatment Guidelines.

### **Summary**

*M. genitalium* infection is an emerging STI that is asymptomatic in many infected individuals. The infection can cause clinical syndromes such as urethritis and cervicitis, but there is limited evidence for an association with reproductive morbidity and perinatal complications. NAATs are preferred for diagnosing *M. genitalium* infection, and there are now two commercially available *M. genitalium* NAATs in the U.S. that are cleared by the FDA. Even though screening for *M. genitalium* is not recommended at this time, *M. genitalium* testing should be considered in individuals with urethritis, cervicitis, or PID, as results may guide the management of this infection. Azithromycin has previously been considered the first-line treatment for *M. genitalium* infections in the U.S. However, several recent studies suggest up to half or more of *M. genitalium* infections are due to strains with macrolide resistance-associated mutations, and most of these infections fail treatment with azithromycin. Moxifloxacin is the recommended antibiotic for treating individuals with suspected or proven *M. genitalium* infection resistant to treatment with azithromycin. With the emergence of *M. genitalium* strains resistant to both macrolides and quinolones in the U.S., there are limited other *M. genitalium* treatment options available. That is why a resistance testing-guided sequential treatment strategy may be ideal for optimizing treatment outcomes and limiting further antibiotic resistance development until new drugs become available in the U.S. for treating *M. genitalium* infection.

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