

# *Mycoplasma genitalium*

## The state of play

JOANNE PEEL MB BS, DTMH, MRCP

CATRIONA BRADSHAW MB BS(Hons), FChSHM, DipVen, PhD

***Mycoplasma genitalium* has emerged as the causative agent of sexually transmitted syndromes including urethritis in men, cervicitis and pelvic inflammatory disease in women; however, testing should be limited to specific clinical scenarios. Treatment challenges include widespread macrolide resistance and the emergence of multidrug-resistant strains. Treatment failure is not uncommon and resistance-guided therapy currently offers the highest probability of cure.**

**M***ycoplasma genitalium* infection is a bacterial sexually transmitted infection (STI). *M. genitalium* belongs to the bacterial class Mollicutes, distinguished by their tiny genome and absent cell wall (Figure). *M. genitalium* is an extremely slow-growing and fastidious organism to culture;<sup>1</sup> therefore, studies showing its association with genital syndromes really only began to accumulate after the development of the first diagnostic polymerase chain reaction (PCR) test in the early 1990s. Since the isolation of *M. genitalium* from the urethras of two men with nongonococcal urethritis in the early 1980s, evidence has shown its association with other clinical syndromes, including cervicitis, pelvic inflammatory disease and poor pregnancy outcomes in women.<sup>1,2</sup>

### Genital syndromes associated with *M. genitalium*

*M. genitalium* is a well-established cause of nongonococcal urethritis (pooled odds ratio [OR], 5.5 [95% confidence interval (CI), 4.3-7.0]) and chronic persistent nongonococcal urethritis in men.<sup>1,3,4</sup> With fewer studies performed in women and smaller sample sizes, the association of *M. genitalium* with female genital syndromes has been harder to establish. However, *M. genitalium*



has been shown to be significantly associated with cervicitis (OR, 1.66 [95% CI, 1.35-2.04]) and pelvic inflammatory disease (PID; OR, 2.14 [95% CI, 1.31-3.49]). This meta-analysis also suggested *M. genitalium* is associated with tubal factor infertility and poor pregnancy outcomes (preterm delivery and spontaneous abortion), although data supporting these associations were more limited, particularly in pregnant women.<sup>2</sup>

*M. genitalium* has been detected in the rectum in men who have sex with men (MSM), with significantly higher rates in those living with HIV infection.<sup>5</sup> Although there have been case series describing *M. genitalium*-associated proctitis, data are conflicting as to whether *M. genitalium* is significantly more common in men with proctitis compared with asymptomatic controls; therefore, its role as a causative agent in proctitis remains somewhat controversial and unclear.<sup>6-9</sup>

### Prevalence

Population-based studies in the US, UK and Europe have reported a prevalence of *M. genitalium* infection in the general population in both men and women of 1 to 3.3%.<sup>10</sup> *M. genitalium* infection is more common in higher-risk populations such as sexual health clinic attendees and MSM, in whom estimates of prevalence in the order of 7% and 9.5% were reported, respectively.<sup>8,11,12</sup>

### Antimicrobial resistance

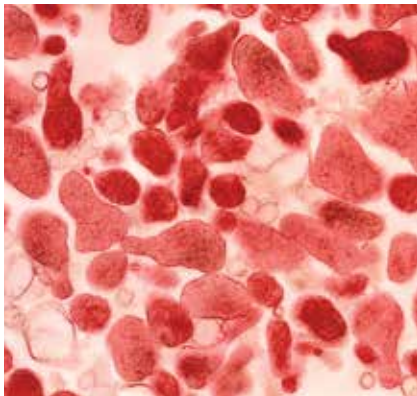
*M. genitalium* has no cell wall and, therefore, antibiotics such as penicillins or other beta-lactams, which target the cell wall, are ineffective. Antimicrobials that inhibit protein synthesis or DNA replication are required to treat this infection. The main currently available options with demonstrated efficacy include macrolides, streptogramins and later-generation fluoroquinolones.<sup>13</sup>

Although doxycycline appeared promising from early in-vitro studies, used alone it cures about 30% of infections.<sup>14,15</sup> However, a recent study in Melbourne showed the use of doxycycline for one week before subsequent treatment with a macrolide or fluoroquinolone significantly lowered bacterial load and improved overall likelihood of cure.<sup>13</sup>

Azithromycin was very potent in early susceptibility testing;<sup>14</sup> however, it now cures only 50% of infections globally, due to the

MedicineToday 2020; 21(3): 41-43

Dr Peel is a Physician and Sexual Health Registrar at Melbourne Sexual Health Centre, Alfred Health, Melbourne. Associate Professor Bradshaw is a Senior Sexual Health Consultant and Head of the Genital Microbiota and Mycoplasma Group at Melbourne Sexual Health Centre, Alfred Health, Melbourne; and an Associate Professor at the Central Clinical School, Monash University, Melbourne, Vic.



**Figure.** *Mycoplasma genitalium* bacteria, transmission electron micrograph.

rapid development of macrolide resistance. Australian studies have shown that macrolide resistance mutations are currently detected in 50% of *M. genitalium* strains from heterosexuals and in more than 80% of strains from MSM.<sup>8,15</sup> Macrolide resistance is caused by single nucleotide polymorphisms in the 23s rRNA gene, which also arise de novo in 10% of macrolide-susceptible infections after treatment with a 1g single dose of azithromycin.<sup>13,16</sup> The number of de-novo mutations is reduced to 3.8% when an extended azithromycin regimen is used.<sup>16,17</sup>

Moxifloxacin is under similar pressure from emerging resistance, with a meta-analysis reporting a decline in cure rates from 100% in studies before 2010 to 89% in studies after 2010.<sup>18</sup> Moxifloxacin resistance is caused by mutations affecting the quinolone resistance-determining regions, predominantly in the parC gene.<sup>19</sup> These mutations were detected in 20% of infections at Melbourne Sexual Health Centre in 2016-2018.<sup>19</sup>

### Testing for *M. genitalium* infection To screen or not to screen?

Although the prevalence of *M. genitalium* is similar to that of chlamydia, when it comes to screening, the situation for *M. genitalium* is significantly more complex and therefore screening is not currently recommended.<sup>20,21</sup> First, most infections remain asymptomatic and there are limited data regarding the

natural history of *M. genitalium* and long-term sequelae of asymptomatic infection.<sup>22</sup>

Furthermore, increasing antimicrobial resistance is resulting in the need to treat patients with costly antimicrobials that have uncommon but potentially serious adverse effects. These complexities generate considerable uncertainty regarding the potential cost benefit of screening, as the risk of adverse outcomes of treatment may exceed the risk from the infection itself. Until drug regimens that are more efficacious with fewer and less serious side effects become available, the benefit of testing and treating asymptomatic infection does not appear to outweigh risk on an individual or population level.

### When to test

Testing for *M. genitalium* is currently recommended and supported by evidence in the following groups or clinical scenarios:

- men with nongonococcal urethritis
- women with cervicitis or PID
- sexual contacts of people with *M. genitalium* infection
- test of cure (TOC) two to three weeks after completion of antimicrobial treatment for *M. genitalium* infection.

Routine testing is not currently recommended for MSM with proctitis, although it may be indicated in those with persistent symptoms who first test negative to other known pathogens. Although *M. genitalium* can co-exist with other STIs, the presence of another infection is not in itself an indication to screen for *M. genitalium*.

### How to test

Nucleic acid amplification testing (NAAT) and PCR testing are now available in laboratories throughout Australia and are TGA approved. Some assays provide simultaneous reporting of macrolide resistance markers, which enables selection of antibiotics based on evidence of macrolide resistance. Suitable specimens for testing in different patient groups are listed in the Table.

### Management of *M. genitalium* infection

To avoid selection of macrolide resistance, syndromic management of nongonococcal urethritis and cervicitis should be with doxycycline 100 mg twice daily for seven days rather than single-dose azithromycin. Similarly, the use of single-dose azithromycin for treatment of PID is no longer recommended. These changes are reflected in both the Australian STI management guidelines and Centers for Disease Control and Prevention STI guidelines.<sup>23,24</sup> Patients presenting with these clinical syndromes should be tested for *M. genitalium* (ideally with macrolide resistance testing) at baseline and recalled for resistance-guided therapy if positive (Box).

Moxifloxacin can be associated with significant side effects including diarrhoea, tendonitis, neurological complications and cardiac events. It is not recommended in pregnancy (Category B3). Patients should be counselled before use; and when contraindications exist, alternative options should be considered. Although moxifloxacin is not currently TGA approved for treatment of *M. genitalium*, it is the recommended first-line treatment in all macrolide-resistant infections.

### Considerations before treatment

Clinicians should maintain a high index of suspicion for treatment failure, particularly in settings where assays for detection of macrolide resistance are not available. Patients should be advised to abstain from sex or adhere to strict condom use until a TOC is negative. This should be performed two to three weeks after completion of antimicrobial therapy and is advised, given the high rates of resistance and persisting infection. When the above treatment fails (positive TOC), other antimicrobial options are available; however, these need to be accessed with input from a sexual health physician.

### Other antimicrobial options for treatment failures

Pristinamycin is a streptogramin antibiotic that is used primarily in the treatment of

**TABLE. SPECIMENS SUITABLE FOR MYCOPLASMA GENITALIUM TESTING**

Group	Most sensitive	Other options
Women	High vaginal swab	<ul style="list-style-type: none"> <li>• First-pass urine</li> <li>• Cervical swab</li> </ul>
Men	First-pass urine	<ul style="list-style-type: none"> <li>• Urethral swab</li> </ul>
MSM	Anorectal swab*	

Abbreviations: MSM = men who have sex with men.

\*Rectal swabs should only be performed in MSM with proctitis when tests for other causative organisms are negative, or in contacts of men with *M. genitalium* infection.

staphylococcal infections. It will cure 75% of macrolide-resistant *M. genitalium* infections.<sup>25</sup> Although not used as first-line treatment, it can be used in combination with doxycycline when fluoroquinolones have failed (or are contraindicated), or as monotherapy when doxycycline is contraindicated (such as during pregnancy and breastfeeding; pregnancy Category D).

Pristinamycin is available through hospital pharmacies (or via a specialist sexual health centre) using the Special Access Scheme of the TGA. Global shortages have been experienced at the end of 2019 into early 2020. When it is available, the recommended treatment is pristinamycin 1 g three times daily in combination with doxycycline 100 mg twice daily for 10 days. The recommended dose as monotherapy (with no combination doxycycline) is pristinamycin 1 g four times daily for 10 days.<sup>21</sup>

Four case reports exist in which *M. genitalium* infection that had failed treatment with both azithromycin and a quinolone was cured with an extended course of minocycline.<sup>26,27</sup> Minocycline is a tetracycline and is thought to be more effective than doxycycline, owing to lower mean inhibitory concentrations. However, data on minocycline are limited to published case reports as above, and treatment failures following its use have occurred in Melbourne (personal communication, C. Bradshaw).

A large Melbourne-based study achieved cure rates of 92.2% using sitafloxacin after seven days of doxycycline treatment of macrolide-resistant *M. genitalium* infection.<sup>13</sup> Sitafloxacin has lower mean

inhibitory concentrations than moxifloxacin and has been shown to cure strains harbouring quinolone resistance mutations.<sup>15</sup> However, sitafloxacin is difficult to access and is currently only available through specialist centres.

### How should we manage sexual partners?

Symptomatic or asymptomatic sexual contacts of people with *M. genitalium* infection, particularly those in a continuing relationship with a symptomatic person, should be offered testing, and treatment if the test result is positive. Studies in Melbourne showed that 48% of women, 42% of MSM and 31% of heterosexual males reporting sexual contact with an index case were also infected.<sup>28</sup>

Partners can be treated presumptively according to the resistance profile of the index case to expedite management. If antibiotic treatment has failed in the index case, it can be assumed the same treatment will fail in the partner. MSM who are contacts require urine and anorectal swabs. Throat swabs are unnecessary as pharyngeal infection is rare (1%).<sup>21</sup>

### Conclusion

*M. genitalium* has emerged over the past 30 years as the causative agent of important and common sexually transmitted syndromes, particularly urethritis in men, cervicitis and PID in women. Macrolide resistance is widespread and multidrug-resistant strains are emerging.

Testing in patients should be limited to specific clinical situations and, when

### RECOMMENDED THERAPY FOR PATIENTS TESTING POSITIVE FOR MYCOPLASMA GENITALIUM

#### For macrolide-susceptible *M. genitalium* infections, treat with:

- doxycycline 100 mg twice daily for seven days, followed immediately by
- azithromycin 1 g stat, then 500 mg daily for another three days (2.5 g total)

#### For macrolide-resistant *M. genitalium* infections, treat with:

- doxycycline 100 mg twice daily for seven days, followed immediately by
- moxifloxacin 400 mg daily for seven days

#### For pelvic inflammatory disease due to *M. genitalium*:

regular combination treatment with doxycycline and metronidazole is unlikely to be curative. Hence, it is recommended to cease these and use:

- moxifloxacin 400 mg daily for 14 days

possible, assays enabling detection of macrolide resistance mutations should be used. Resistance-guided treatment currently offers the highest probability of cure and reduces further development of antimicrobial resistance. A TOC should be performed two to three weeks after completion of antimicrobial therapy. Sexual partners should be tested and treated whenever possible. If infection persists despite treatment with first- or second-line antimicrobial regimens, guidance should be sought from a sexual health physician for further management.

More research is needed into the natural history of asymptomatic infection before screening can be recommended. There is an imperative to develop novel and inventive treatment strategies, including combinations of existing drugs, to target this ever-evolving pathogen. **MI**

### References

A list of references is included in the online version of this article ([www.medicinetoday.com.au](http://www.medicinetoday.com.au))

COMPETING INTERESTS: Melbourne Sexual Health Centre has received institutional funding from Speedx Pty Ltd for research on *M. Genitalium*.

# *Mycoplasma genitalium*

## The state of play

JOANNE PEEL MB BS, DTMH, MRCP; CATRIONA BRADSHAW MB BS(Hons), FChSHM, DipVen, PhD

### References

1. Taylor-Robinson D, Jensen JS. *Mycoplasma genitalium*: from chrysalis to multicolored butterfly. *Clin Microbiol Rev* 2011; 24: 498-514.
2. Lis R, Rowhani-Rahbar A, Manhart LE. *Mycoplasma genitalium* infection and female reproductive tract disease: a meta-analysis. *Clin Infect Dis* 2015; 61: 418-426.
3. Tully J, Cole R, Taylor-Robinson David, Rose D. A newly discovered mycoplasma in the human urogenital tract. *Lancet* 1981; 317: 1288-1291.
4. Wikström A, Jensen JS. *Mycoplasma genitalium*: a common cause of persistent urethritis among men treated with doxycycline. *Sex Transm Infect* 2006; 82: 276-279.
5. Bissessor M, Tabrizi SN, Bradshaw CS, et al. The contribution of *Mycoplasma genitalium* to the aetiology of sexually acquired infectious proctitis in men who have sex with men. *Clin Microbiol Infect* 2016; 22: 260-265.
6. Isabel Lázaro-Simó A, Esperalba-Esquerra, J, Vall-Mayans M. A case report of proctitis associated with *Mycoplasma genitalium* in a man who has sex with men. *Int J STD AIDS* 2019; 30: 623-625.
7. Finnerty F, Pinto-Sander N, Richardson D. Does *Mycoplasma genitalium* cause proctitis? A case report. [Abstract of oral case presentation]. *Sex Transm Infect* 2016; 92 (Suppl 1): A15. DOI: 10.1136/sextrans-2016-052718.41.
8. Read T, Murray GL, Danielewski JA, et al. Symptoms, sites, and significance of *Mycoplasma genitalium* in men who have sex with men. *Emerg Infect Dis* 2019; 25: 719-727.
9. Soni S, Alexander S, Verlander N, et al. The prevalence of urethral and rectal *Mycoplasma genitalium* and its associations in men who have sex with men attending a genitourinary medicine clinic. *Sex Transm Infect* 2010; 86: 21-24.
10. Skov Jensen J, Cusini M, Gomberg M, Moi H. 2016 European guideline on *Mycoplasma genitalium* infections. *J Eur Acad Dermatol Venereol* 2016; 30: 1650-1656.
11. McGowin CL, Anderson-Smits C. *Mycoplasma genitalium*: an emerging cause of sexually transmitted disease in women. *PLoS Pathog* 2011; 7: e1001324.
12. Unemo M, Salado-Rasmussen K, Hansen M, et al. Clinical and analytical evaluation of the new Aptima *Mycoplasma genitalium* assay, with data on *M. genitalium* prevalence and antimicrobial resistance in *M. genitalium* in Denmark, Norway and Sweden in 2016. *Clin Microbiol Infect* 2018; 24: 533-539.
13. Read TRH, Fairley CK, Murray GL, et al. Outcomes of resistance-guided sequential treatment of *Mycoplasma genitalium* infections: a prospective evaluation. *Clin Infect Dis* 2019; 68: 554-560.
14. Renaudin H, Tully JG, Bebear C. In vitro susceptibilities of *Mycoplasma genitalium* to antibiotics. *Antimicrob Agents Chemother* 1992; 36: 870-872.
15. Jensen JS, Bradshaw C. Management of *Mycoplasma genitalium* infections - can we hit a moving target? *BMC Infect Dis* 2015; 15: 343.
16. Horner P, Ingle SM, Garrett F, et al. Which azithromycin regimen should be used for treating *Mycoplasma genitalium*? A meta-analysis. *Sex Transm Infect* 2018; 94: 14-20.
17. Durukan C, Read T, Murray GL, et al. Resistance-guided antimicrobial therapy using doxycycline-moxifloxacin and doxycycline-2.5g azithromycin for the treatment of *Mycoplasma genitalium* infection: efficacy and tolerability. *J Clin Microbiol* 2019; Oct 20. pii: ciz1031. Epub ahead of print.
18. Li Y, Le W-J, Li S, Cao Y-P, Su X-H. Meta-analysis of the efficacy of moxifloxacin in treating *Mycoplasma genitalium* infection. *Int J STD AIDS* 2017; 28: 1106-1114.
19. Murray GL, Bodiya K, Danielewski J, et al. Moxifloxacin and sitafloxacin treatment failure in *Mycoplasma genitalium* infection: association with parC mutation G248T (S83I) and concurrent gyrA mutations. *J Infect Dis* 2019; Oct 22. pii: jiz550.
20. Bradshaw CS, Horner PJ, Jensen JS, White PJ. Syndromic management of sexually-transmitted infections and the threat of untreatable *Mycoplasma genitalium*. *Lancet Infect Dis* 2018; 18: 251-252.
21. Melbourne Sexual Health Centre. *Mycoplasma genitalium*. [Treatment guidelines]. Available online at: <https://mshc.org.au/HealthProfessional/MSHCTreatmentGuidelines/MycoplasmaGenitalium#.XW-Hk2QzZhA> (accessed March 2020).
22. Sonnenberg P, Ison CA, Clifton S, et al. Epidemiology of *Mycoplasma genitalium* in British men and women aged 16-44 years: evidence from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3). *Int J Epidemiol* 2015; 44: 1982-1994.
23. Australian STI management guidelines for use in primary care. Australasian Sexual Health Alliance. Available online at: <http://www.sti.guidelines.org.au> (accessed March 2020).
24. Sexually transmitted diseases treatment guidelines, 2015. Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, US Department of Health and Human Services Centers for Disease Control and Prevention. Available online at: <https://www.cdc.gov/std/tg2015/default.htm> (accessed March 2020).
25. Read T, Jensen JS, Fairley CK, et al. Use of pristinamycin for macrolide-resistant *Mycoplasma genitalium* infection. *Emerg Infect Dis* 2018; 24: 328-335.
26. Glaser AM, Geisler WM, Ratliff AE, Xiao L, Waites KB, Gaisa M. Two cases of multidrug-resistant genitourinary *Mycoplasma genitalium* infection successfully eradicated with minocycline. *Int J STD AIDS* 2019; 30: 512-514.
27. Deguchi T, Ito S, Yasuda M, et al. Emergence of *Mycoplasma genitalium* with clinically significant fluoroquinolone resistance conferred by amino acid changes both in GyrA and ParC in Japan. *J Infect Chemother* 2017; 23: 648-650.
28. Sliwinski JB, Vodstrcil LA, Fairley CK, et al. *Mycoplasma genitalium* infection in adults reporting sexual contact with infected partners, Australia, 2008-2016. *Emerg Infect Dis* 2017; 23: 1826-1833.