

Mycoplasma genitalium. Where are we now?

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Mycoplasma genitalium is an established and important sexually transmitted infection. Women present with symptoms of urethritis/cervicitis and men with urethritis. In both genders infection can be asymptomatic. In women *M. genitalium* is strongly associated with pelvic inflammatory disease (PID), endometritis and post-abortion infection and, serologically, with infertility. *M. genitalium* affects the motility of sperm, sporadic cases have been reported with epididymitis; and there is sparse evidence of prostatitis. Although sporadically detected in joints, its role in arthritis has not been confirmed. Recommended treatment is an extended regimen of azithromycin; a single 1 g dose may select for resistance. Resistant strains can be treated with moxifloxacin, but strains resistant to both antibiotics have been reported.

In the 1970s, during studies of acute non-gonococcal urethritis (NGU), spiroplasma-like motile helical organisms were observed in smears from men with urethritis, as well as response to tetracyclines. In the early 1980s *M. genitalium* was isolated from 2 men with NGU (1). Now its role in non-gonococcal, non-chlamydial urethritis (NGNCU) and non-gonococcal, non-chlamydial cervicitis (NGNCC) is also well documented (2). Convincing data provide evidence for its role in ascending genital infection in women.

Microbiology and pathogenesis

M. genitalium, with the smallest genome known for a self-replicating organism, is forced to live as a parasite. Fastidious growth requirements, together with very slow growth, make isolation of *M. genitalium* in primary culture impossible. A terminal structure is needed for movement, adherence and entrance to cells. It has affinity to epithelial cells, erythrocytes, Vero monkey kidney cells and Hep-2 cells *in vitro*, and Fallopian tube epithelial cells, and it is immunodominant, with antigenic variation eluding the host's immune system and perhaps also the diagnostic test (3, 4).

Detection

Because *M. genitalium* is very difficult to culture, nucleic acid amplification technology is the only reliable means of detection. In the late 1980s Jensen et al. (5), described a polymerase chain reaction (PCR) amplification method targeting the MgPa adhesin gene. This, and other diagnostic approaches, made it possible to study the relationship between *M. genitalium* and various clinical conditions. There is, however, still no "gold standard" or current evidence-based consensus test. Many specimens carry a low load of DNA, and the choice of assay

and processing is extremely important for optimal sensitivity. In one study first-void urine from men and, for women, urine supplemented with a cervical specimen, yielded the highest sensitivity (6). In a later study vaginal specimens were found to be superior (7). However, there is insufficient information to be able to make general recommendations about the best specimen for detection.

Transmission

The fact that *M. genitalium* is detected in urogenital specimens raised the question as to whether it is sexually transmitted. This hypothesis was confirmed by seroepidemiological studies (8) as well as studies of sexual partners (9, 10), and the detection of a high rate of concordance of *M. genitalium* genotypes in infected couples (11). Different routes of invasion from primary sites are by direct spread, haematogenous spread, e.g. to joints, and by sperm.

Epidemiology

A total of 48 published reports have documented more than 27,000 women screened for *M. genitalium* infection worldwide, with an estimated prevalence of 7.3% (high-risk individuals) and 2.0% (low-risk individuals), respectively (12).

Complications

M. genitalium and upper genital infection in women

Like most genital tract diseases, inflammation ascending beyond the cervix, PID including endometritis and salpingitis, does not have a single cause.

- A majority of studies support an association with cervicitis, independent of chlamydia and gonorrhoea, odds ratio 2.2 (2).
- Cervicitis is a risk factor for progression to PID, which may lead to major reproductive morbidity, including infertility.
- Non-human primate studies show that *M. genitalium* induces salpingitis (13).
- *M. genitalium* has been detected in the Fallopian tube in a female with salpingitis.
- *M. genitalium* adheres to (14) and causes morphological changes in ciliated Fallopian tube cells (15).
- In more than half of women infected with *M. genitalium* and with clinical signs of upper genital tract infection *M. genitalium* was detected in endometrial biopsies (16).

Endometritis. In the PID Evaluation and Clinical Health Study (PEACH), *M. genitalium* was detected in 88/856 (15%) women

with clinically suspected PID. Endometrial *M. genitalium* (8%) was associated with baseline endometritis (OR 3.0) and with a high degree of infertility (22%), recurrent PID (31%) and chronic pelvic pain (42%) (17). *M. genitalium* was found in 9/58 (16%) of women with histologically diagnosed endometritis, compared with 1/57 (2%) without endometritis (18).

Salpingitis. In a study with laparoscopically verified salpingitis, *M. genitalium* was detected in the cervix/endometrium in 9/123 women (7%) (19). *M. genitalium* has been significantly associated with PID occurring after termination of pregnancy (20).

Tubal factor infertility. Two sero-epidemiological studies have shown that *M. genitalium* is a risk factor for tubal factor infertility in women (21, 22).

In conclusion, *M. genitalium* is one of several causes of PID.

Complications in men

Studies concerning possible complications due to *M. genitalium* infection in men are sparse. In one study chronic prostatitis was diagnosed in 2 of 18 infected men compared with none out of 20 without the infection (23). In a serological study *M. genitalium* has been shown to have a positive correlation with epididymitis (24).

Complications in women and men

Clinical experience indicates that reactive arthritis occurs in patients with *M. genitalium* infection, but studies on the effect of *M. genitalium* on joints are lacking.

Influence on HIV transmission

Until recently little was known about the influence of *M. genitalium* infection on HIV infection, although it has been reported that 50% of men with AIDS and with no urethritis are infected with *M. genitalium*, compared with 10% of HIV-infected without AIDS (25). *M. genitalium* was more frequent in the urethra and rectal sites in HIV-positive men who have sex with men (MSM) than in HIV-negative MSM (26). *M. genitalium*-induced cervicitis (27) and *M. genitalium* in endometrial biopsies are more frequent in HIV-positive than in HIV-negative women (28). Furthermore, the positive association between *M. genitalium* and HIV infection is strongly supported by a meta-analysis of 19 studies (29).

Treatment and resistance

A few controlled studies concerning the efficacy of antibiotic therapy for *M. genitalium* have been performed (30–32, 34), only one of which was randomized (34). The antibiotics studied were tetracycline; azithromycin as a single 1 g dose immediately, followed by an extended dosage of 500 mg on day 1 and 250 mg/day for 4 days thereafter; older quinolones (e.g. ciprofloxacin); and newer quinolones (e.g. moxifloxacin).

Efficacy of treatments

Tetracycline: 20–40%

Azithromycin 1 g immediately: 65–90%

Azithromycin extended dosage: 70–100%

Ciprofloxacin: 30–55%

Moxifloxacin: >99%

There is now strong evidence that some strains of *M. genitalium* have developed resistance to azithromycin through mutations in region V of the 23S rRNA gene (34). Single-dose azithromycin is not sufficiently effective and may select for macrolide resistance. If azithromycin treatment is not effective, moxifloxacin should be considered. Different prevalence of macrolide resistance in different regions, e.g. 30% in Denmark (7) and 100% in Greenland, may reflect different treatment traditions. Strains with resistance to both azithromycin and moxifloxacin have been detected. Exploration of new therapies is essential.

In Falun, 306/407 sexually transmitted disease (STD) patients detected with *M. genitalium* in the years 1998–2005 were followed up after treatment. The eradication rate for doxycycline was 43%, for azithromycin 1 g 91%, and for extended azithromycin 99%. PCR for macrolide resistance was performed at baseline from 2006 until 2010, as well as before and after non-effective treatment with azithromycin. The results have been submitted for publication.

Current situation

We know that *M. genitalium* is a common sexually transmitted disease and that it is one of several factors causing infection of the upper tract in women.

Future research

For reliable estimation of the importance of the infection, further information concerning the type and frequency of complications is urgently needed. The mechanism(s) for development of resistance must be further evaluated in order to be able to prevent resistance.

Important recommendations awaiting further studies

Avoid the use of single-dose azithromycin 1 g as treatment for *C. trachomatis* and *M. genitalium*, as well as for non-gonococcal, non-chlamydial urethritis and cervicitis, in order to prevent an increase in macrolide resistance.

Prevent a further increase in the infection by using diagnostics with sufficiently good sensitivity and specificity, together with well-defined reasonable indications for testing (35) until we have determined whether screening high-risk populations has sufficient cost-benefit. Directed screening of sexual partners

for *M. genitalium* infection is the most efficient means of finding infected persons and preventing re-infection and further spread, but this may be controversial when the disease is not included in the *Act for Communicable Diseases*.

References

1. Tully JG, Taylor-Robinson D, Cole RM, Rose DL. A newly discovered mycoplasma in the human urogenital tract. *Lancet* 1981; 317: 1288–1291.
2. Taylor-Robinson D, Jensen JS. *Mycoplasma genitalium*: from chrysalis to multi-coloured butter butterfly. *Clin Microbiol Rev* 2011; 24: 498–514.
3. Svenstrup HF, Nielsen PK, et al. Adhesion and inhibition assay of *Mycoplasma genitalium* and *Mycoplasma pneumoniae* by immunofluorescence microscopy. *J Med Microbiol* 2002; 51: 361–373.
4. Svenstrup HF, Jensen JS, Drasbek M, Birkelund S, Christiansen G. Identification and characterization of immunogenic proteins of *Mycoplasma genitalium*. *Clin Vaccine Immunol* 2006; 13: 913–922.
5. Jensen JS, Uldum SA, Söndergard-Andersen J, Vuust J, Lind K. Polymerase chain reaction for detection of *Mycoplasma genitalium* in clinical samples. *J Clin Microbiol* 29: 46–50.
6. Wroblewski JK, Manhart LE, Dickey KA, Hudspeth MK, Totten PA. Comparison of transcription-mediated amplification and PCR assay results from various genital specimen types for detection of *Mycoplasma genitalium*. *J Clin Microbiol* 2006; 44: 3306–3312.
7. Jensen JS, Björnelius E, Dohn B, Lidbrink P. Comparison of first void urine and urogenital swab specimens for detection of *Mycoplasma genitalium* and *Chlamydia trachomatis* by polymerase chain reaction in patients attending a sexually transmitted disease clinic. *Sex Transm Dis* 2004; 31: 499–507.
8. Wang RY, Grandinetti T, Shih JW, Weiss SH, Haley CL, Hayes MM, et al. *Mycoplasma genitalium* infection and host antibody immune response in patients infected by HIV, patients attending STD-clinics and in healthy blood donors. *FEMS Immunol. Med. Microbiol.* 1997; 19: 237–245.
9. Anagrius C, Loré B, Jensen JS. *Mycoplasma genitalium*: prevalence, clinical significance, and transmission. *Sex Transm Infect* 2005; 83: 237–241.
10. Keane F, Thomas BJ, Gilroy CB, Renton A, Taylor-Robinson D. The association of *Chlamydia trachomatis* and *Mycoplasma genitalium* with non-gonococcal urethritis: observations on heterosexual men and their female partners. *Int. J. STD AIDS* 2000; 11: 435–360.
11. Hjort SV, Björnelius E, Lidbrink P, Falk L, Dohn B, Berthelsen L, et al. Sequence-based typing of *Mycoplasma genitalium* reveals sexual transmission. *J Clin Microbiol* 2006; 44: 2078–2083.
12. McGovin CL, Anderson-Smits C. *Mycoplasma genitalium*: an emerging cause of sexually transmitted disease in women. *PLoS Pathog* 2011; 7 (5), e1001324.
13. Moller BR, Taylor Robinson D, Furr PM. Serological evidence implicating *Mycoplasma genitalium* in pelvic inflammatory disease. *Lancet* 1984; 1: 1102–1103.
14. Collier AM, J. Carson JL, Hu PC, Hu SS, Huang CH, Barile MF. Attachment of *Mycoplasma genitalium* to the ciliated epithelium of human fallopian tubes. In: Stanek GHCG, Tully JG, Whitcomb RF, editors. *Recent advances in mycoplasmaology*. Stuttgart: Gustav Fischer Verlag; 1990, p. 730–732.
15. Baczynska A, Funch P, Fedder J, Knudsen HJ, Birkelund S, Christiansen G. Morphology of human Fallopian tubes after infection with *Mycoplasma genitalium* and *Mycoplasma hominis* – in vitro organ culture study. *Hum Reprod* 2007; 22: 968–979.
16. Haggerty CL. Evidence for a role of *Mycoplasma genitalium* in pelvic inflammatory disease. *Curr Opin Infect Dis* 2008; 21: 65–69.
17. Haggerty CL, Totten PA, Astete SG, Lee S, Hoferka SL, Kelsey SF, Ness RB. Failure of cefoxitin and doxycycline to eradicate endometrial *Mycoplasma genitalium* and the consequence for clinical cure of pelvic inflammatory disease. *Sex Transm Infect* 2008; 84: 338–342.
18. Cohen CR, Manhart LE, Bukusi EA, Astete S, Brunham RC, Holmes KK, et al. Association between *Mycoplasma genitalium* and acute endometritis. *Lancet* 2002; 359: 765–766.
19. Cohen CR, Mugo NR, Astete SG, Odonodo R, Manhart LE, Kiehlbauch JA, et al. Detection of *Mycoplasma genitalium* in women with laparoscopically diagnosed acute salpingitis. *Sex Transm Infect* 2005; 81: 463–466.
20. Bjartling C, Osler S, Persson K. The association between *Mycoplasma genitalium* and pelvic inflammatory disease after termination of pregnancy. *BJOG* 2010; 117: 361–364.
21. Clausen HF, Fedder J, Drasbek M, Nielsen PK, Toft B, Ingerslev HJ, et al. Serological investigation of *Mycoplasma genitalium* in infertile women. *Hum Reprod* 2001; 16: 1866–1874.
22. Svenstrup HF, Fedder J, Kristoffersen SE, Trolle B, Birkelund S, Christiansen G. *Mycoplasma genitalium*, *Chlamydia trachomatis* and tubal factor infertility – a prospective study. *Fertil Steril* 2008; 90: 513–520.
23. Mandar R, Raukas E, Türk S, Korrovits P, Punab M. *Mycoplasmas* in semen of chronic prostatitis patients. *Scand J Urol Nephrol* 2005; 39: 479–482.
24. Eickhof JH, Frimodt-Møller N, Walter S, Frimodt-Møller C. A double-blind, randomized, controlled multicentre study to compare the efficacy of ciprofloxacin with pivampicillin as oral therapy for epididymitis in men over 40 years of age. *BJU Int* 1999; 84: 827–834.
25. Taylor-Robinson D. *Mycoplasma genitalium* – an update. *Int J STD AIDS* 2002; 13: 145–151.
26. Soni S, Alexander S, Verlander N, Saunders P, Richardson D, Fisher M, Ison C. The prevalence of urethral and rectal *Mycoplasma genitalium* and its association in men who have sex with men attending a genitourinary medicine clinic. *Sex Transm Infect* 2010; 86: 21–24.
27. Lusk M, Konecny P, Naing ZW, Garden FL, Cumming RG, Rawlinson WD. *Mycoplasma genitalium* is associated with cervicitis and HIV-infection in an urban Australian STI clinic population. *Sex Transm Infect* 2011; 87: 107–109.
28. Irwin KL, Moorman AC, O'Sullivan MJ, Sperling R, Koestler ME, Soto I, et al. Influence of human immunodeficiency virus infection on pelvic inflammatory disease. *Obstet Gynecol* 2000; 95: 525–534.
29. Napierala Mavedzenge S, Weiss HA. Association of *Mycoplasma genitalium* and HIV infection: a systematic review and meta-analysis. *AIDS* 2009; 23: 611–620.
30. Björnelius E, Anagrius C, Bojs G, Carlberg H, Johannisson G, Johansson E, et al. Antibiotic treatment of symptomatic *Mycoplasma genitalium* infection in Scandinavia: a controlled clinical trial. *Sex Transm Infect* 2008; 84: 72–76.
31. Mena LA, Mroczkowski TF, Nsuami M, Martin DH. A randomized comparison of azithromycin and doxycycline for the treatment of *Mycoplasma genitalium*-positive urethritis in men. *Clin Infect Dis* 2009; 48: 1649–1654.
32. Jernberg E, Moghaddam A, Moi H. Azithromycin and moxifloxacin for microbiological cure of *Mycoplasma genitalium* infection: an open study. *Int J STD AIDS* 2008; 19: 676–679.
33. Schwebke JR, Rompalo A, Taylor S, Peña AC, Martin DH, Lopez LM, et al. Re-evaluating the treatment of nongonococcal urethritis: emphasizing emerging pathogens – randomized clinical trial. *Clin Infect Dis* 2011; 52: 163–170.
34. Jensen JS, Bradshaw CS, Tabrizi SN, Fairley CK, Hamasuna R. Azithromycin treatment failure in *M. genitalium*-positive patients with nongonococcal urethritis is associated with induced macrolide resistance. *Clin Infect Dis* 2008; 47: 1546–1553.
35. Guidelines for treatment of STI in Swedish STI-clinics. Available from: <http://www.medicaljournals.se/forum/?page=guidelines> and from <http://www.pdf.nu>.