REVIEW ARTICLE

2016 European guideline on *Mycoplasma genitalium* infections

J.S. Jensen,[1,*] M. Cusini,[2] M. Gomberg,[3] H. Moi[4,†]

[1]Microbiology and Infection Control, Statens Serum Institut, Copenhagen, Denmark
[2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[3]Moscow Scientific and Practical Centre of Dermatovenereology and Cosmetology, Moscow, Russia
[4]Olafia Clinic, Oslo University Hospital, Institute of Medicine, University of Oslo, Oslo, Norway
*Correspondence: J.S. Jensen. E-mail: jsj@ssi.dk

[†]Guideline editor: Prof. Harald Moi, MD PhD, Section of STI, Department of infectious diseases, dermatology and rheumatology, Oslo University Hospital, and Faculty of Medicine, University of Oslo, Norway

Abstract

Mycoplasma genitalium infection contributes to 10–35% of non-chlamydial non-gonococcal urethritis in men. In women, *M. genitalium* is associated with cervicitis and pelvic inflammatory disease (PID). Transmission of *M. genitalium* occurs through direct mucosal contact. Asymptomatic infections are frequent. In women, symptoms include vaginal discharge, dysuria or symptoms of PID – abdominal pain and dyspareunia. In men, urethritis, dysuria and discharge predominates. Besides symptoms, indication for laboratory test is a high-risk sexual behaviour. Diagnosis is achievable only through nucleic acid amplification testing (NAAT). If available, NAAT diagnosis should be followed with an assay for macrolide resistance. Therapy for *M. genitalium* is indicated if *M. genitalium* is detected or on an epidemiological basis. Doxycycline has a low cure rate of 30–40%, but does not increase resistance. Azithromycin has a cure rate of 85–95% in macrolide susceptible infections. An extended course appears to have a higher cure rate. An increasing prevalence of macrolide resistance, most likely due to widespread use of azithromycin 1 g single dose without test of cure, is drastically decreasing the cure rate. Moxifloxacin can be used as second-line therapy, but resistance is increasing. Uncomplicated *M. genitalium* infection should be treated with azithromycin 500 mg on day one, then 250 mg on days 2–5 (oral), or josamycin 500 mg three times daily for 10 days (oral). Second line treatment and treatment for uncomplicated macrolide resistant *M. genitalium* infection is moxifloxacin 400 mg od for 7–10 days (oral). For third line treatment of persistent *M. genitalium* infection after azithromycin and moxifloxacin doxycycline 100 mg two times daily for 14 days can be tried and may cure 30%. Pristinamycin 1 g four times daily for 10 days (oral) has a cure rate of app. 90%. Complicated *M. genitalium* infection (PID, epididymitis) is treated with moxifloxacin 400 mg od for 14 days.

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Conflicts of interest

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Introduction

Mycoplasmas are the smallest free-living microorganisms.[1] In the urogenital tract, the relevant species are *M. genitalium, Ureaplasma urealyticum, U. parvum* and *M. hominis. M. hominis* and the ureaplasmas will not be dealt with in the present guideline.

Mycoplasma genitalium was first isolated in 1980.[2] *M. genitalium* infection is unequivocally associated with male NGU[3] and even stronger associated with non-chlamydial non-gonococcal urethritis (NCNGU). The prevalence of *M. genitalium* in men with NCNGU ranges from 10% to 35%,[3] thus contributing significantly to the overall burden of disease. In comparison, *M. genitalium* is detected in only 1% to 3.3% of men and women in the general population.[4–7] In women, several studies have demonstrated the association between *M. genitalium* and urethritis, cervicitis, endometritis, and pelvic inflammatory disease (PID).[8–12] In a recent meta-analysis,[13] significant associations were found between *M. genitalium* and cervicitis [pooled odds ratio (OR) 1.66], and PID (pooled OR 2.14). *M. genitalium* has been associated with preterm birth (pooled OR 1.89), and spontaneous abortion (pooled OR 1.82), but the prevalence of

M. genitalium in pregnant women in Europe is low,[14,15] and therefore, the relative importance of *M. genitalium* is probably small. Studies have also shown an association with increased risk of tubal factor infertility (pooled OR 2.43). In sub-analyses that accounted for co-infections, Lis *et al.* found these associations to be stronger.[13]

Persistence of *M. genitalium* after treatment is associated with recurrent or persistent NGU, and up to 40% with this condition are *M. genitalium* positive.[16] In a recent meta-analysis, persistent *M. genitalium* was associated with a pooled OR of 26 for persistent urethritis.[17] Thus, failure to eradicate *M. genitalium* leads to persistent or recurrent disease in the vast majority of men with persistent infection and diagnosis and optimal treatment is extremely important. *M. genitalium* has been shown to facilitate HIV transmission, in particular in studies from Sub-Saharan Africa.[18–20] If eradication fails due to inappropriate treatment, this may have particularly important implications for increased risk of HIV transmission.

Transmission

Transmission is primarily by direct genital-genital mucosal contact. *M. genitalium* has been detected in anorectal samples by culture and NAATs,[21,22] and transmission from penile-anal sexual contact has been established.[23] Oral-genital contact is less likely to contribute to any significant extent, as carriage of *M. genitalium* in the oro-pharynx is low.[24,25] Mother-to-child transmission at birth has not been systematically studied, but *M. genitalium* has been detected in the respiratory tract of newborn children.[26] The risk of contracting *M. genitalium* per sexual encounter has not been determined, but because *M. genitalium* is present in lower concentration in genital tract specimens than *C. trachomatis*,[27] it could be considered slightly less contagious than chlamydia.

There are no estimates of the global burden of disease. In sexually transmitted infection (STI) patients, the prevalence is usually from 60% to 85% of that of *C. trachomatis*, but in the general population, the ratio is generally significantly lower.[4,6]

Compared to *C. trachomatis*, the prevalence of *M. genitalium* infected patients appear to peak approximately 5 years later for both men and women and to remain higher in the older age groups.[28,29]

Clinical features

Urogenital infections

Symptoms and signs in women

- Among sexually transmitted diseases (STD) clinic attendees, 40–75% are asymptomatic.[11,12]
- Symptoms are related to cervical and urethral infection and include increased or altered vaginal discharge (<50%), dysuria or urgency (30%) and, occasionally, inter-menstrual or post coital bleeding or menorrhagia.[11,12,30]
- Cervicitis.
- Rectal and pharyngeal infections are usually asymptomatic.
- Lower abdominal pain (<20%) should raise suspicion of PID.

Complications in women[13]

- PID (endometritis, salpingitis).
- Tubal factor infertility (probably).
- Sexually acquired reactive arthritis (SARA) may occur.[31]

Symptoms and signs in men[3]

- 70% symptomatic in some STD clinic settings.[32]
- Urethritis (acute, persistent, and recurrent).
- Dysuria.
- Urethral discharge.
- Proctitis.
- Balanoposthitis has been associated with *M. genitalium* infection in one study.[33]

Complications in men

- SARA may occur.[31]
- Epididymitis may occur.

Ocular infections

Ocular infections can result in conjunctivitis in adults[34] but has not been systematically studied. Neonatal conjunctivitis has not been systematically studied.

Indications for laboratory testing [IV; C]

Symptoms

- Symptoms or signs of urethritis in men.
- Mucopurulent cervicitis.
- Cervical or vaginal discharge with risk factor for STI.
- Intermenstrual or post coital bleeding.
- Acute pelvic pain and/or PID.
- Acute epididymo-orchitis in a male aged <50 years.

Risk factors

- Any of the above symptoms in a regular sexual partner.
- Persons with high-risk sexual behaviour (age < 40 years and >3 new sexual contacts in the last year). However, the public health value of testing asymptomatic persons for *M. genitalium* has not been established and decisions on testing for *M. genitalium* should be informed by local epidemiology when available.
- Sexual contact of persons with an STI or PID, in particular, contacts of *M. genitalium* infected persons.
- Before termination of pregnancy or other procedures, that breaches the cervical barrier.

- Regular testing of men who have sex with men (MSM), including anal sampling could be considered due to the risk of increased HIV transmission.

Laboratory diagnostics [III; B]

Recommended diagnostic assays

NAATs identifying *M. genitalium* specific nucleic acid (DNA or RNA) in clinical specimens are the only useful methods for diagnosis [III; B]. However, no commercially available NAAT assays have been evaluated up to the US Food and Drug Administration (FDA) approval standard, and the tests on the market which have been CE marked to document conformity according to the European Union (EU) legislation suffer from limited validation. Consequently, it is extremely important that diagnostic laboratories carefully validate any commercial or in-house assays and participate in external quality assurance assessment (EQA) schemes such as the EQUALIS EQA scheme (http://www.equalis.se/sv/vaar-verksamhet/extern-kvalitetssaekring/kvalitetssaekringsprogram/m-r/mycoplasma-genitalium-nukleinsyra-288/). This EQA scheme has demonstrated substantial differences in the sensitivity of participating laboratories.

With the widespread macrolide resistance in Europe, it is strongly recommended that all positive tests be followed up with an assay capable of detecting macrolide resistance mediating mutations. A variety of methods are available for this purpose.[29,35–39] The main determinant for the selection of a resistance assay are: (i) its practical implementation in the laboratory, and (ii) its sensitivity (proportion of screening positive tests that can be resistance typed). The latter aspect varies significantly between assays.

Determination of moxifloxacin resistance can also be carried out using molecular methods although the correlate between mutations in parC and *in vitro* moxifloxacin resistance is less clear. At present, detection of moxifloxacin resistance mediating mutations is probably not indicated on a routine basis in Europe, as the level of resistance is low (<5%)[40] but it may be considered in the Asia-Pacific region where moxifloxacin resistance is more common[41–43] or in patients having acquired the infection in this region.

Specimens

It is difficult to make accurate recommendations regarding the optimal sample type. First void urine from men and women provide a good diagnostic specimen which may be self-obtained.[28] No data regarding the importance of holding urine for a certain time are available, so procedures already in place for *C. trachomatis* sampling can be followed. Vaginal swab (physician or self-collected) also provide an appropriate sensitivity.[44–46]

No data are available regarding time after exposure to testing, but in analogy to *C. trachomatis*, a 2-week period is considered the minimal incubation time. Anal samples are useful in MSM where as many as 70% of the infections will be missed if this site is not sampled,[47] but may also be relevant in women at risk.[22] The association between an anal infection and symptoms is uncertain, but the infection is likely to be transmitted if not detected and treated.

In most settings, it will be appropriate to use the same sampling procedure as for *C. trachomatis* testing. However, some transport media such as the Aptima® (Hologic, Inc., MA, USA) transport medium designed for *C. trachomatis* NAAT will lyse *M. genitalium*, and may provide a poor sensitivity in an in-house assay. This should be carefully evaluated for all in-house assays and even for assays where a validated collection and nucleic acid purification kit is not included [III B].

Management of patients

Information, explanation and advice for the patient

- Patients with *M. genitalium* infection should be advised to abstain from unprotected sexual contact until they and their partners have completed treatment, their symptoms have resolved, and their test of cure (TOC) is negative [IV; C].
- Patients with *M. genitalium* infection (and their sexual contacts) should be given information about the infection, including details about transmission, prevention and complications. It is recommended that both verbal and written information be provided. Patient information leaflets are available at the IUSTI website [IV; C].
- Patients with anal infection including MSM should be informed about the risk of transmission from this site and that the infection may be more difficult to eradicate. Consequently, a TOC is important.
- Patients with *M. genitalium* infection should be screened for other STIs, including *C. trachomatis*, *N. gonorrhoeae*, syphilis, HIV, and *T. vaginalis* where appropriate [IV; C].

Pregnancy

- *M. genitalium* infections during pregnancy may be associated with a modest increase in the risk of spontaneous abortion and preterm birth.[13] In macrolide susceptible infections, a 5-day-course of azithromycin is generally acceptable. The choice of drugs for macrolide-resistant infections is difficult, and risk associated with treatment with the available antibiotics may outweigh the risk of adverse pregnancy outcome. Thus, treatment, especially in women with infection with a macrolide-resistant *M. genitalium* strain, may be considered postponed until after delivery. Pristinamycin is considered safe in pregnancy and may be considered in symptomatic women after consultation with an experienced microbiologist. Although little is known about transmission during birth, the neonate should be observed for signs of infection, primarily conjunctivitis and respiratory tract infection [IV; C].

Indications for therapy [IV; C]

- Detection of *M. genitalium*-specific nucleic acid in a clinical specimen.
- Current partners of *M. genitalium*-positive patients should be treated with the same antimicrobial as the index patient.
- If current partner does not attend for evaluation and testing, epidemiological treatment should be offered with the same regimen as given to the index patient.
- On epidemiological grounds for recent sexual contacts (previous 3 months). Ideally, specimens for *M. genitalium* NAAT should be collected before treatment and treatment should await the result of testing.

Therapy

Treatment of individuals with *M. genitalium* urogenital infection prevents sexual transmission and is likely to reduce the risk of complications, including PID[5] and tubal factor infertility.[13]

Only few antimicrobial classes have activity against mycoplasmas including tetracyclines, macrolides and fluoroquinolones.

Doxycycline has a poor efficacy[48–51] with microbiological cure rates between 30% and 40%, whereas azithromycin given as a 1 g single dose has a cure rate of approximately 85% in macrolide-susceptible infections.[48,49] A rapidly increasing prevalence of macrolide resistance, however, is drastically decreasing the overall cure rate. Most likely, this is caused by widespread use of azithromycin as a 1 g single dose without TOC and subsequent spread of resistant strains.

Azithromycin given as an extended regimen with 500 mg day one followed by 250 mg days 2–5 (1.5 g total dose) is recommended as the primary choice for treatment of *M. genitalium* infections. Using extended azithromycin or other macrolide antibiotics after failure with the 1 g single-dose regimen or in the presence of pre-existing macrolide resistance mediating mutations will not eradicate *M. genitalium*.

Macrolide resistance rates vary significantly geographically, but where azithromycin 1 g single dose is used for treatment of NGU, it is usually found in 30–45% of samples.[29,40,43,52]

Josamycin is widely used in Russia with 500 mg three times a day for 10 days, but will not eradicate macrolide-resistant strains.

Moxifloxacin is the most commonly used second-line antimicrobial. It is bactericidal and has a cure rate approaching 100% in infections with susceptible strains.[53–56] However, resistance has developed with treatment failures in up to 30%, primarily in patients from the Asia-Pacific region. A significant proportion of the *M. genitalium* strains had concurrent macrolide resistance mediating mutations leaving very few available treatment options.[42,57–59]

Pristinamycin is the only antimicrobial with documented activity in patients failing both azithromycin and moxifloxacin. Many of these cases additionally failed eradication with extended dosage doxycycline (100 mg twice daily for 14 days).[59] In Europe, it is registered only in France, but can be acquired after special permit in most European countries. It should only be used in the maximal recommended dose of 1 g four times a day for 10 days (oral) as these patients are facing their last known active antimicrobial therapy and dose reduction may lead to failure. Treatment failure has been reported also for pristinamycin, but the influence of compliance in these cases is not fully understood.

Recommended treatment for uncomplicated *M. genitalium* infection in the absence of macrolide resistance mediating mutations [IIb; B]

- Azithromycin 500 mg on day one, then 250 mg od days 2–5 (oral).
- Josamycin 500 mg three times daily for 10 days [IV; C].

Recommended treatment for uncomplicated macrolide-resistant *M. genitalium* infection [IIb;B]

- Moxifloxacin 400 mg od for 7–10 days (oral). The optimal duration of treatment is uncertain and a few observational studies have found higher cure rate after longer treatment in cervicitis.[57]

Recommended second-line treatment for uncomplicated persistent *M. genitalium* infection [IIb; B]

- Moxifloxacin 400 mg od for 7–10 days (oral).

Recommended third-line treatment for persistent *M. genitalium* infection after azithromycin and moxifloxacin [III; B]

- Doxycycline 100 mg two times daily for 14 days can be tried and will eradicate *M. genitalium* from approximately 30% of the patients, but the patient must be informed about the poor eradication rate and accept to comply with advice regarding sexual abstinence or condom use.
- Pristinamycin 1 g four times daily for 10 days (oral). The patient should be informed about the need to comply strictly with the dosage scheme.

Recommended treatment for complicated *M. genitalium* infection (PID, epididymitis) [IV; C]

- Moxifloxacin 400 mg od for 14 days (oral).[60]

Partner notification

- Contact notification should be performed and documented by appropriately trained professionals at the time of diagnosis to improve outcome [IV; C].
- Current partner should always be tested and treated with the same antimicrobial as the index patient [IV; C].
- If current partner does not attend for evaluation and testing, epidemiological treatment should be offered with the same regimen as given to the index patient [IV; C].

- Recent sexual contacts (previous 3 months) should be contacted and offered testing for *M. genitalium* infection and testing for other STIs [IV; C].

Follow-up and TOC

- A TOC should be routinely performed in all patients due to the high prevalence of macrolide resistance either present pretreatment or developing during treatment with azithromycin and in the absence of routine testing for fluoroquinolone resistance [III; B]. This recommendation differs from the BASHH and CDC guidelines[61,62] where TOC for asymptomatic cases is not recommended. However, many patients enter a stage of few or no symptoms after treatment, but with persistent carriage and subsequent risk for spread of resistance in the community. TOC samples should be collected no earlier than 3 weeks after start of treatment [III, B]. In patients responding to treatment, *M. genitalium* will be undetectable within 1 week in most patients, but tests may become temporarily false negative in patients failing treatment.[63]

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Qualifying statement

Decisions to follow these recommendations must be based on professional clinical judgement, consideration of individual patient circumstances and available resources. All possible care has been undertaken to ensure publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing clinician to ensure the accuracy and appropriateness of the medication they prescribe.

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Appendix 1
Search strategy

A Medline search was conducted in May 2015 using PubMed. The search heading was kept broad (Mycoplasma genitalium) to include epidemiology, diagnosis, antimicrobial resistance, drug therapy, clinical trials and prevention and control. Only publications and abstracts in the English language were considered. The Cochrane library was searched for all entries related to mycoplasma. Sexually transmitted diseases guidelines produced by the US Centers for Disease Control (www.cdc.gov/std/) and the British Association for Sexual Health and HIV (www.bashh.org) were also reviewed.

Appendix 2
Levels of evidence and Grading of recommendations

http://iusti.org/regions/Europe/pdf/2013/Levels_of_Evidence.pdf