

2016 European guideline on *Mycoplasma genitalium* infections

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Running title:

M. genitalium guideline

Abstract

M. 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.

Clinical features and diagnostic tests

Asymptomatic infections are frequent. In women, symptoms are vaginal discharge and dysuria, in men, urethritis, dysuria and discharge. 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

Therapy for *M. genitalium* is indicated in case of identification of *M. genitalium* in clinical specimens or on an epidemiological basis.

Doxycycline has a poor efficacy (cure rates 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. A rapidly increasing prevalence of macrolide resistance, most likely due to widespread use of azithromycin as a 1 g single dose without test of cure, is drastically decreasing the overall cure rate. Moxifloxacin can be used as second line therapy but resistance is increasing.

Recommended treatment for uncomplicated *M. genitalium* infection:

Azithromycin 500 mg on day one, then 250 mg on days 2-5 (oral) or
Josamycin 500 mg 3 times daily for 10 days (oral).

Recommended second line treatment and treatment for uncomplicated macrolide resistant *M. genitalium* infection:

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

Recommended third line treatment for 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).

Recommended treatment for complicated *M. genitalium* infection (PID, epididymitis)

Moxifloxacin 400 mg od for 14 days.

Introduction

Mycoplasmas are the smallest free-living micro-organisms.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 NGU³ 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.⁴⁻⁶ In women, several studies have demonstrated the association between *M. genitalium* and urethritis, cervicitis, endometritis, and pelvic inflammatory disease (PID).⁷⁻¹¹ In a recent meta-analysis,¹² significant associations were found between *M. genitalium* and cervicitis (pooled odds ratio (OR) 1.66), and pelvic inflammatory disease (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,^{13,14} 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.¹²

Persistence of *M. genitalium* after treatment is associated with recurrent or persistent NGU, and up to 40% with this condition are *M. genitalium* positive.¹⁵ In a recent meta-analysis, persistent *M. genitalium* was associated with a pooled odds ratio 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. The role of *M. genitalium* in facilitating HIV transmission, in particular in Sub-Saharan Africa¹⁸⁻²⁰ is another reason for concern when eradication fails due to inappropriate treatment.

Transmission

Transmission is primarily by direct genital-genital mucosal contact. Genital-anorectal transmission has been shown²¹ and may play a role as *M. genitalium* is commonly

found in the anal mucosa^{22,23} and the organism can be cultured from this site (Jensen, unpublished). Oral-genital contact is less likely to contribute to any significant extent, as carriage of *M. genitalium* in the oro-pharynx is low. Mother-to-child transmission at birth has not been systematically studied, but *M. genitalium* has been detected in the respiratory tract of newborn children.²⁴ 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*,²⁵ it could be considered slightly less contagious than chlamydia.

There are no estimates of the global burden of disease. In 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.^{26,27}

Clinical features

Urogenital infections

Symptoms and signs in women:

- Among STD clinic attendees, 40 – 75% are asymptomatic.^{10,11}
- Symptoms are related to cervical and urethral infection and include increased or altered vaginal discharge (<50%), dysuria or urgency (30%) and, rarely, intermenstrual or post coital bleeding or menorrhagia.^{10,11,28}
- Cervicitis.
- Rectal and pharyngeal infections are usually asymptomatic.
- Lower abdominal pain (<20%) should raise suspicion of pelvic inflammatory disease (PID).

Complications in women:¹²

- PID (endometritis, salpingitis)
- Tubal factor infertility (probably)
- Sexually acquired reactive arthritis (SARA).²⁹

Symptoms and signs in men³

- 70% symptomatic.³⁰
- Urethritis (acute, persistent, and recurrent)
- Dysuria
- Urethral discharge
- Balanoposthitis has been associated with *M. genitalium* infection in one study.³¹

Complications in men:

- SARA.²⁹
- Epididymitis

Ocular infections

Ocular infections can result in conjunctivitis in adults³² but is not 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, more than 5 life-time partners and never tested)
- 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 breaks the cervical barrier.

- Regular testing of MSM, including anal sampling could be considered due to the risk of increased HIV transmission

Laboratory diagnostics [III; B]

Recommended diagnostic assays:

Nucleic acid amplification tests (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 FDA approval standard, and the CE marked tests on the market 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,^{27,33-37} and the main determinant for the selection of an assay is the practical aspects from a laboratory point of view, and the sensitivity measured as the proportion of screening positive tests capable of being 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%)³⁸ but it may be considered in the Asia-Pacific region where moxifloxacin resistance is more common³⁹⁻⁴¹ or in patients having acquired the infection in this region.

Specimens

Due to the various assay formats, it is difficult to make firm conclusions regarding the optimal sample type. First void urine (FVU) from men and women provide a good diagnostic specimen which may be self-obtained.²⁶ 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.⁴²⁻⁴⁴

No data is available regarding time after exposure to testing, but in analogy to *C. trachomatis*, a two-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,⁴⁵ but may also be relevant in women at risk.²³ 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[®] 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 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 test of cure 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 slight increase in the risk of spontaneous abortion and preterm birth.¹² In macrolide susceptible infections, a five-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. 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]

- Identification of *M. genitalium* specific nucleic acid in a clinical specimen.
- On epidemiological grounds if a recent sexual contact has confirmed *M. genitalium* infection (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 probably complications, including PID⁵ and tubal-factor infertility.¹²

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

Doxycycline has a poor efficacy⁴⁶⁻⁴⁹ 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.^{46,47} A rapidly increasing prevalence of macrolide resistance, most likely due to widespread use of azithromycin as a 1 g single dose without test of cure, however, is drastically decreasing the overall cure rate.

Azithromycin given as an extended regimen with 500 mg day one followed by 250 mg days 2-5 (1.5g 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 1g single dose regimen will not eradicate *M. genitalium*.

Macrolide resistance rates varies significantly geographically, but where azithromycin 1g single dose is used for treatment of NGU, it is usually found in 30-45% of samples.^{27,38,41,50}

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.^{16,51-53}

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.^{40,54-56}

Pristinamycin is the only antimicrobial with documented activity in patients failing both azithromycin, moxifloxacin, and in many cases also extended dosage doxycycline (100 mg twice daily for 14 days).⁵⁶ 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 1g 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.

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 3 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.⁵⁴

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 1g 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).⁵⁷

Partner notification

- Contact notification should be performed and documented by appropriately trained professionals at the time of diagnosis to improve outcome [IV;C]
- Sexual contacts should be contacted and offered testing together with counselling and treatment for *M. genitalium* infection (same antimicrobial as index patient) and testing for other STIs [IV; C]
- All sexual contacts within the preceding 6 months of onset of symptoms or diagnosis should ideally be evaluated, tested and treated [IV; C].
- If sexual contacts do not attend for evaluation and testing, epidemiological treatment should be offered to a current partner with the same regimen as given to the index patient [IV; C]

Follow-up and test of cure (TOC)

- A TOC should be routinely performed in all patients due to the high prevalence of macrolide resistance either present pre-treatment 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^{58,59} where TOC for asymptomatic cases is not recommended. However, it is a clinical experience that 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. Test of cure samples should be collected no earlier than three weeks after start of treatment [III, B]. In patients responding to treatment, *M. genitalium* will be undetectable within one week in most patients, but tests may become temporarily false negative in patients failing treatment.⁶⁰

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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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APPENDICES

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 1

Levels of evidence and Grading of recommendations

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

Appendix 2

Declarations of interest

Jørgen Skov Jensen: None

Marco Cusini: None

Mikhail Gomberg: None

Harald Moi: None