**­­­­**GUIDELINES

**2021 European guideline on the management of *Mycoplasma genitalium* infections**

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**Conflicts of interest**

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2021 European *M. genitalium* guideline

**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.

**Clinical features and diagnostic tests**

Asymptomatic infections are frequent. In men, urethritis, dysuria and discharge predominate. In women, symptoms include vaginal discharge, dysuria, or symptoms of PID – abdominal pain and dyspareunia. Symptoms are the main indication for laboratory diagnostic testing. Diagnosis is achievable only through nucleic acid amplification testing and must include detection of macrolide resistance mutations.

**Therapy**

Therapy for *M. genitalium* is indicated if *M. genitalium* is detected.

Doxycycline has a low cure rate of 30-40%, but resistance is not increasing. Azithromycin has a cure rate of 85-95% in macrolide susceptible infections. An extended course of azithromycin appears to have a higher cure rate and pre-treatment with doxycycline may decrease organism load and the risk of macrolide resistance selection. Moxifloxacin can be used as second line therapy but resistance is increasing.

**Recommended treatment**

***Uncomplicated M. genitalium infection:***

Azithromycin 500 mg on day one, then 250 mg on days 2-5 (oral).

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

Moxifloxacin 400 mg od for 7 days (oral).

***Third line treatment for persistent M. genitalium infection after azithromycin and moxifloxacin:***

Doxycycline or minocycline 100 mg two times daily for 14 days (oral)may cure 40-70%.

Pristinamycin 1 g four times daily for 10 days (oral) has a cure-rate of around 75%.

***Complicated M. genitalium infection (PID, epididymitis):***

Moxifloxacin 400 mg od for 14 days.

**Main changes from the 2016 European *M. genitalium* guideline**

Due to increasing antimicrobial resistance and warnings against moxifloxacin use, indications for testing and treatment have been narrowed to primarily involve symptomatic patients. The importance of resistance-guided therapy is emphasised.

**Introduction**

Mycoplasmas are the smallest free-living micro-organisms. 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. [1]

*Mycoplasma genitalium* was first isolated in 1980.[2] *M. genitalium* infection is unequivocally associated with male non-gonococcal urethritis (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, Liset 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 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 important. *M. genitalium* has been shown to facilitate HIV transmission, in particular in studies from Sub-Saharan Africa.[18-20] If this applies also in regions with good access to HIV suppression is not clear.

The present 2021 European *M. genitalium* guideline is modified significantly compared to the previous version from 2016,[21] in particular in relation to indications for testing, which has been narrowed due to the emerging threat of untreatable *M. genitalium* infections and warning labels on quinolones, the main second-line antimicrobial, issued by the European Medicines Agency. With the lack of natural history studies estimating the risk of sequelae of asymptomatic infections, the authors estimated the benefits of treatment of asymptomatic infections to be outweighed by the risk of increased antimicrobial resistance and adverse events from widespread treatment.

**Transmission**

Transmission is primarily by direct genital-genital mucosal contact. *M. genitalium* has been detected in anorectal samples by culture and NAATs in both men and women,[22-24] and transmission through penile-anal sexual contact has been established.[25]. Oral-genital contact is less likely to contribute to any significant extent, as carriage of *M. genitalium* in the oro-pharynx is low.[26, 27] Mother-to-child transmission at birth has not been systematically studied, but *M. genitalium* has been detected in the respiratory tract of newborn children.[28] 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 *Chlamydia trachomatis*,[29, 30] it could be considered slightly less contagious than *C. trachomatis*.

There are no estimates of the global burden of infection. In STI patients, the prevalence usually ranges from 75% to 90% of that of *C. trachomatis*, but in some settings it is higher than chlamydia.[31] In the general population, the ratio is generally lower.[4, 6, 7] Compared to *C. trachomatis*, the prevalence of *M. genitalium* infected patients appears to peak approximately 5 years later for both men and women and to remain higher in the older age-groups.[7, 32, 33]

**Clinical features**

**Urogenital infections**

***Symptoms and signs in women:***

* Among sexually transmitted disease (STD) clinic attendees and in the general population, 40–75% of *M. genitalium* infected are asymptomatic.[7, 11, 12]
* Symptoms are related to cervical and urethral infection and include increased or altered vaginal discharge (<50%), dysuria or micturition urgency (30%) and, inter-menstrual or post coital bleeding or menorrhagia.[7, 11, 12, 34]
* Mucopurulent cervicitis and urethritis.[35]
* 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, further studies needed)
* Adverse pregnancy outcome (possibly, further studies needed)
* Sexually acquired reactive arthritis (SARA) may occur.[36]

***Symptoms and signs in men:***[3]

* 70% of *M. genitalium* infected are symptomatic in some STD clinic settings.[37]
* In the general population, less than 5% report symptoms.[6, 7]
* Urethritis (acute, persistent, and recurrent)
* Dysuria
* Urethral discharge
* Proctitis
* Balanoposthitis has been associated with *M. genitalium* infection in one study.[38]

***Complications in men:***

* SARA may occur.[36]
* Epididymitis may occur.[39, 40]

**Ocular infections**

Ocular infections can result in conjunctivitis in adults[41] but has not been systematically studied. Neonatal conjunctivitis has not been systematically studied.

**Indications for laboratory testing**

**Symptoms and signs (Grade 1B)**

* Symptoms or signs of urethritis in men
* Mucopurulent cervicitis
* Intermenstrual or post-coital bleeding
* Dysuria with no known other aetiology in women
* Acute pelvic pain and/or PID
* Acute epididymo-orchitis in a male aged <50 years
* Proctitis with no known other aetiology

**Risk factors**

* On-going sexual contacts of persons treated for *M. genitalium* infection (Grade 1B)
* Before termination of pregnancy, testing could be considered (Grade 2B)

# Laboratory diagnostics

**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. Some commercially available NAAT assays have been evaluated up to the US Food and Drug Administration (FDA) approval standard.[42] However, currently, none include detection of macrolide resistance mutations and some of the tests on the market which have been Conformitè Europëenne (CE) marked to document conformity according the European Union (EU) legislation suffer from limited validation. Consequently, it is extremely important that diagnostic laboratories use carefully validated and quality assured commercial or in-house assays, including participation in external quality assurance assessment (EQA) schemes such as the Quality Control for Molecular Diagnostics (QCMD; www.qcmd.org) EQA scheme and act upon the results.

With the widespread macrolide resistance in Europe, all *M. genitalium* positive tests must be followed up with an assay capable of detecting macrolide resistance mutations (Grade 1B). A variety of laboratory developed tests are available for this purpose,[33, 43-48] and CE-marked, commercially available methods have also become available.[49-51] The main determinants for the selection of a macrolide resistance assay are: 1) its practical implementation in the laboratory, 2) its sensitivity (proportion of *M. genitalium* screening positive tests that can be resistance typed), and 3) its specificity. The sensitivity varies significantly between assays.

Determination of quinolone resistance associated mutations (QRAMs) located in the *parC* gene can be carried out using molecular methods although the correlate between mutations in *parC* and treatment failure is less clear.[52, 53] Mutations in *gyrA* are not predictive of treatment failure alone, but may potentiate the effect of QRAMs in *parC*.[52] At present, detection of QRAMs is not indicated on a routine basis in Europe, i.e. due to the suboptimal correlates between QRAMs and treatment outcome and as the prevalence QRAM is low (<5-10%)[31, 54, 55] but *parC*-based resistance testing is useful in treatment failure after moxifloxacin treatment in order to reserve third-line antimicrobials for patients with documented moxifloxacin resistance (Grade 1D).

**Clinical specimens**

It is difficult to make accurate recommendations regarding the optimal sample type because of variations in nucleic acid extraction methods and assay performance. First void urine (FVU) from men provides a good diagnostic specimen which may be self-obtained (Grade 1B).[32, 56, 57]. No data regarding the importance of holding urine for a certain time are available, so procedures already in place for *C. trachomatis* and *N. gonorrhoeae* sampling can be followed. Vaginal swab (physician or self-collected) provide the best performance if only one sample is taken in women (Grade 1B).[56-60]

No data is available regarding time after exposure to testing, but in analogy with *C. trachomatis*, a two-week period is considered the minimal incubation time.

Anal samples may be useful in MSM where as many as 70% of the infections will be missed if this site is not sampled.[61, 62] However, due to the high risk of combined macrolide and quinolone resistance in MSM, testing from this location is only indicated in men with symptomatic proctitis where other aetiologies have been excluded (Grade 1D). Rectal infection in women at risk is not uncommon.[23, 24] The association between an anal infection and symptoms is uncertain, but it is possible to transmit the infection from the rectal site. As for men, anal samples are only indicated in symptomatic proctitis after exclusion of other aetiologies (Grade 1D).

In most settings it will be appropriate to use the same sampling procedure as for *C. trachomatis* and *N. gonorrhoeae* testing. For regulatory approved assays, the sampling procedure and transport medium recommended by the manufacturer should be used. For all in-house assays and assays where a validated collection and nucleic acid purification kit is not included, careful consideration should be given to the transport medium and nucleic acid extraction procedure (Grade 1C).

**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 (Grade 1D).
* 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 International Union against Sexually Transmitted Infections (IUSTI) website (https://iusti.org/treatment-guidelines/) (Grade 1D).
* Patients with *M. genitalium* infection should be screened for other STIs, including *C. trachomatis*, *N. gonorrhoeae*, syphilis, HIV, and *T. vaginalis* where appropriate (Grade 1D).

**Pregnancy**

* *M. genitalium* infections during pregnancy may be associated with a modest increase in the risk of spontaneous abortion and preterm birth.[13] However, most studies have not been controlled for other conditions associated with these outcomes. In macrolide susceptible *M. genitalium* infections, a five-day-course of azithromycin is generally acceptable. The choice of drugs for macrolide resistant infections is difficult, and the 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 postponed until after delivery. Pristinamycin is considered safe in pregnancy and may be considered in symptomatic women after specialist consultation. Although little is known about transmission during birth, the neonate should be observed for signs of infection, primarily conjunctivitis and respiratory tract infection (Grade 1D).

**Indications for therapy**

* Detection of *M. genitalium* specific nucleic acid in a clinical specimen (Grade 1B)
* Current partners of *M. genitalium* positive patients should be treated with the same antimicrobial as the index patient (Grade 1B)

**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[63-66] with microbiological cure rates between 30% and 40%. However, it may also decrease the load of *M. genitalium* in patients failing eradication.[67] Azithromycin given as a 1 g single oral dose has a cure rate of approximately 85% in macrolide susceptible infections but will select for macrolide resistance in more than 10% of the treated patients.[63, 64, 68] The rapidly increasing prevalence of macrolide resistance,[69] is drastically decreasing the overall cure rate. Most likely, this is caused by widespread use of azithromycin as a 1 g single dose for other STIs and for *M. genitalium* without a TOC and with the subsequent spread of macrolide 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 mutations will not eradicate *M. genitalium*.

Macrolide resistance rates vary significantly geographically and among patient groups, but where azithromycin 1 g single dose is used for treatment of NGU, it is usually found in at least 30-45% of samples.[33, 70-72]

Josamycin is widely used in Russia with 500 mg three times a day for 10 days, but will not eradicate macrolide resistant strains and macrolide resistance can be selected during treatment.[73]

Moxifloxacin is the most commonly used second line antimicrobial. It is bactericidal and has a cure rate approaching 100% in infections with susceptible strains.[74-77] 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 mutations leaving very few available treatment options.[78-82]

Pristinamycin has been the primary third-line antimicrobial in patients failing azithromycin and moxifloxacin, and some also extended dosage doxycycline (100 mg twice daily for 14 days).[81] In Europe, it is registered in France, but can be acquired after special permit in most European countries. It is generally used in the maximal recommended dose of 1 g four times a day for 10 days (oral), but combination therapy with doxycycline or doses as low as 2 g per day did not significantly change cure rate from around 75%.[83, 84]

Due to the observation that cure rates with azithromycin were lower for high-load infections [81, 85], the concept of resistance-guided sequential therapy (RGST) has developed [86]. In RGST, patients are treated with doxycycline for 7 days which lowers the *M. genitalium* bacterial load while waiting for results of macrolide resistance testing, and subsequently, the patient is treated with a 2.5 g dose of azithromycin (1 g day 1 followed by 500 mg days 2-4) or moxifloxacin for 7-10 days.[86, 87] RGST is now the recommended treatment in the Australian *M. genitalium* guidelines[88] and in a modified form also in the UK *M. genitalium* guideline.[89] Although RGST has shown higher cure-rates and lower selection of resistance in the observational studies,[67, 87] no controlled trials have confirmed this and giving two antimicrobials for up to 17 days depending on the dosing regimen may lead to selection of resistance in other STI as well as non-STI pathogens. There is no evidence that the high dose of azithromycin is better than the 1.5 g extended dosage scheme previously recommended or that moxifloxacin for 10 days is better than 7 days in uncomplicated infection although one observational study has suggested higher cure-rate after 10 days of treatment in cervicitis.[78] However, if treatment of symptomatic patients is indicated before the results of microbiological tests are available, RGST is recommended, but with the dosages suggested below. In compliant patients, it could be considered to avoid further treatment if symptoms have resolved during doxycycline treatment. TOC should then be offered 3 weeks later and condoms should be used until a negative TOC. If symptoms recur or if the TOC is *M. genitalium* positive, the patient should be treated according to resistance as described below without repeated treatment with doxycycline. Clinical trials, preferably randomised, evaluating this approach would be valuable.

**Recommended treatment for uncomplicated *M. genitalium* infection in the absence of macrolide resistance mutations**

* Azithromycin 500 mg on day one, then 250 mg od days 2-5 (oral) (Grade 1B)
* Josamycin 500 mg 3 times daily for 10 days (oral) (Grade 2C)

**Recommended treatment for uncomplicated *M. genitalium* infection in the presence of macrolide resistance mutations**

* Moxifloxacin 400 mg od for 7 days (oral) (Grade 1B)

**Recommended second line treatment for uncomplicated persistent *M. genitalium* infection after azithromycin treatment**

* Moxifloxacin 400 mg od for 7 days (oral) (Grade 1B)

**Recommended third line treatment for persistent *M. genitalium* infection after azithromycin and moxifloxacin treatment**

No optimal therapies can be suggested at present. Pristinamycin is the best evaluated third line treatment but has only approximately 75% cure-rate.[83, 84]

* Pristinamycin 1 g four times daily for 10 days (oral) (Grade 1B)
* Doxycycline 100 mg two times daily for 14 days (oral) may eradicate *M. genitalium* from approximately 30-40% 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 (Grade 2B).
* Minocycline 100 mg two times daily (oral) for 14 days is more active than doxycycline and was shown to have a microbiological cure rate of 71% among 35 evaluable patients [84] and this is supported by in vitro data (Jensen JS, unpublished). However, no systematic comparisons have been performed (Grade 2B).

Lefamulin has recently been registered in Europe for community acquired pneumonia. It is highly active in vitro against *M. genitalium* with combined macrolide and fluoroquinolone resistance,[90] however, only anecdotal experience with treatment of *M. genitalium* is available. The appropriate dosing is undetermined but 7 days of treatment is probably required (Grade 2D).

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

* Moxifloxacin 400 mg od for 14 days (oral) (Grade 1C).[91]

**Partner notification**

* Current partner(s) (i.e. one or more partners with whom the index patient recently had unprotected sex, and with whom the patient will continue to have sex) should always be tested and treated with the same antimicrobial as the index patient (Grade 2B).

**Follow-up and test of cure (TOC)**

* A TOC should be considered in all patients due to the high prevalence of resistance present either pre-treatment or developing during treatment (Grade 2C). However, in order to limit antimicrobial use in patients asymptomatic after treatment there is no firm evidence to suggest that TOC is beneficial in these asymptomatic cases. Many patients enter a stage of few or no symptoms after treatment, but with persistent carriage, the risk for spread of resistance in the community is considerable. TOC samples should be collected no earlier than three weeks after completion of treatment (Grade 1b). 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.[92]

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**Composition of the European STI Guideline Editorial Board**

Current composition can be found at: https://iusti.org/wp-content/uploads/2019/12/Editorial\_Board.pdf.

**List of contributing organizations**

Current list can be found at: https://iusti.org/treatment-guidelines/.

Proposed date of revision: 2025

**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**

**Search strategy**

A Medline search was conducted in December 2020 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 and Prevention (www.cdc.gov/std/), the British Association for Sexual Health and HIV (http://www.bashh.org), and the Australasian Sexual Health Alliance (ASHA) (https://www.sexualhealthalliance.org.au) were also reviewed.

**Levels of evidence**

Levels of evidence and grading of recommendations that were used in the present guideline can be found in the protocol for production and revision of European STI guidelines at: https://iusti.org/wp-content/uploads/2020/04/ProtocolForProduction2020.pdf

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