# Canadian Guidelines on Sexually Transmitted Infections

## *Mycoplasma genitalium* Infections

July 2018

Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

**Canadian Guidelines on Sexually Transmitted Infections**

**TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.**

—Public Health Agency of Canada

Également disponible en français sous le titre :

*Lignes directrices canadiennes sur les infections transmissibles sexuellement – Infections à Mycoplasma genitalium*

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This publication can be made available in alternative formats upon request.



Publication date: July 2018



Cat.: HP40-1/2018E-3-PDF
ISBN: 978-0-660-42309-8
Pub.: 210709

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The Public Health Agency of Canada wishes to thank Dr. Lisa Manhart and Dr. J.S. Jensen for critical review and comments on this chapter.

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Contributions for writing, editorial and research support were provided by the Centre for Communicable Diseases and Infection Control of the Public Health Agency of Canada.

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# MYCOPLASMA GENITALIUM INFECTIONS

*Mycoplasma genitalium* **(***M. genitalium*) is an emerging sexually transmitted pathogen. Given the lack of routine diagnostic testing for *M. genitalium* in Canada, the management of most *M. genitalium* infections will occur in the context of syndromic management of urethritis, cervicitis and pelvic inflammatory disease (PID).

- Refer to the Antimicrobial resistance considerations section of this chapter for information on how this may impact initial management of these syndromes.

## Etiology

- Mycoplasmas are small facultative anaerobic bacteria (0.2-0.3 µm) without a cell wall.[1,2] They are pleiomorphic and cannot be Gram stained or identified by light microscopy.
- Genital mycoplasmas belong to the Mollicutes class in the family Mycoplasmataceae, which includes two genera: Mycoplasma and Ureaplasma.[1,2]
  - There are currently seven Mycoplasma species identified in the genital tract, of which *M. genitalium* is emerging as an important cause of genital tract disease. *M. hominis* is among a number of bacteria found in women with bacterial vaginosis and pelvic inflammatory disease, but it is not known whether it can cause these two conditions.[1]
  - Ureaplasmas are ubiquitous micro-organisms which can be isolated from the genital tract of 30-40% of healthy sexually active young men. The exact role of ureaplasmas in non-gonococcal urethritis (NGU) is controversial, due to the conflicting observations in clinical studies.

Due to limited data on the role of ureaplasma and *M. hominis* in genital tract infections, the focus of this chapter is *M. genitalium* exclusively.

## Epidemiology

- Internationally, the prevalence of *M. genitalium* (using molecular diagnostic tests) is estimated to range from 1-4% among men and 1-6% among women; in those at elevated risk for sexually transmitted infections (STI), the prevalence is as high as 38%.[3]
  - The National Longitudinal Study of Adolescent Health from the U.S., which included adults between the ages of 18-27, reported that the prevalence of *M. genitalium* was 1%.[4]
  - The *National Survey of Sexual Attitudes and Lifestyles* (NATSAL) survey, a UK study of sexually experienced men and women, found that 1.2% of men and 1.3% of women between the ages of 16-44 years were positive for *M. genitalium*; of these the majority were asymptomatic (94% and 56% for men and women respectively).[5]
- In addition to associations between *M. genitalium* infection and non-chlamydial/non-gonococcal urethritis, associations have been reported between *M. genitalium* infection and *C. trachomatis/N. gonorrhoeae* in some settings but not all.[6-12]
- A large systematic review and meta-analysis found that individuals with *M. genitalium* infection were twice as likely to be HIV-infected; however, the reasons for this are not clear.[13]
- In a multi-site Canadian study that used remnant samples collected in women for detection of *C. trachomatis* and *N. gonorrhoeae*, *M. genitalium* was detected in 53/396

(13.4%) women infected with *C. trachomatis* and in 22/406 (5.4%) women not infected with *C. trachomatis*.[14]

- In addition, a Toronto study, which screened 1193 attendees at a sexual health clinic, reported that 4.5% of males and 3.2% of females tested positive for *M. genitalium;* 50% of males and 40% of females were symptomatic.[15]
- An Alberta study of attendees at two STI clinics reported a *M. genitalium* prevalence of 5.3% in males and 7.2% in females. Correlates of female infection included younger age, Indigenous/other ethnicity and *C. trachomatis* and *N. gonorrhoeae* co-infection.[16]

## Risk factors

Reported risk factors for *M. genitalium* include:

- Multiple sexual partners[2,10]
- Young age[6,10,17]
- Young age at sexual debut[2]
- Non-Caucasian race[17]
- Sexual partner with a history of recent STI[2]

## Transmission

- *M. genitalium* is sexually transmissible.
  - Studies demonstrate concordant infection between partners.[18-20]
  - Some evidence shows indistinguishable strain types between partners.[21]
  - *M. genitalium* is rarely detected in sexually inexperienced individuals.[4]
- Consistent condom use may reduce an individual's risk of *M. genitalium* infection.[20]

## Symptoms, signs and sequelae

- Incubation period is unclear.[22]

### Females

- Often asymptomatic. Symptoms may include vaginal discharge, dysuria, inter-menstrual or post-coital bleeding.[9]
- Available data suggest an association between *M. genitalium* and cervicitis and a causal association with endometritis/PID.[3,6,23-28]
- Some evidence suggests that PID cases associated with *M. genitalium* may be similar to chlamydia in terms of severity of symptoms and signs.[29]
- A 2015 meta-analysis suggests a significant association between *M. genitalium* and preterm birth, spontaneous abortion and female infertility.[23]
- Insufficient evidence exists to determine whether there is an association with ectopic pregnancy.[3,30]

### Males

- *M. genitalium* has been widely implicated as an etiologic agent of acute and persistent or recurrent urethritis.[3,23,31-33]
  - A Swedish sexually transmitted diseases (STD) clinic study found that 73% of *M. genitalium*-positive males had symptomatic urethritis (e.g., urethral discharge, dysuria) in comparison to 40% of men infected with *C. trachomatis*.[34]
  - This is consistent with findings from another STD clinic study.[28]
- Insufficient evidence exists to determine whether *M. genitalium* causes epididymitis or proctitis.[35]
- Available evidence does not support *M. genitalium* infection as a cause of male infertility.[36]

## Diagnostic testing

- Laboratory testing capacity with nucleic acid amplification test (NAAT) may vary across the country.
  - Consult with your laboratory regarding local availability of *M. genitalium* testing, specimen collection and transportation requirements.
- Cervical, vaginal, and urethral or meatal swabs, urine, and endometrial biopsies are acceptable specimens.[37,38]
- *M. genitalium* positive specimens can be forwarded to the National Microbiology Laboratory (NML) for molecular detection of mutations associated with macrolide and moxifloxacin resistance.[39,40]
  - Refer to the NML *Guide to Services* for specific information on specimen collection and transportation requirements.

### Indications for testing

- Routine screening for *M. genitalium* is not recommended.
- Testing for *M. genitalium* is recommended **only**:
  - in the presence of persistent or recurrent urethritis, cervicitis, or PID despite empiric treatment when initial tests for gonorrhea and chlamydia are negative.
- No data are available to guide recommendations for testing in pregnant women and neonates.

## Considerations for other STIs: screening and immunization

If clinically indicated, consider:

- obtaining a blood sample for serologic testing for *syphilis*;
- HIV counselling and testing as per the recommendations in the *HIV Screening and Testing Guide*;
- immunization for
  - *hepatitis B* for all individuals being evaluated or treated for an STI, if not already immune;

  - hepatitis A for high-risk individuals (e.g., MSM, injection drug users) if not already immune. For a complete list of individuals at increased risk of hepatitis A, refer to the *Canadian Immunization Guide, Part 4, Active Vaccines, Hepatitis A Vaccine*;
- discussing human papillomavirus (HPV) vaccine with male and female patients as per the recommendations outlined in the National Advisory Committee on Immunization (NACI) *Update on Human Papillomavirus (HPV) Vaccines*, and the *Canadian Immunization Guide, Part 4, Active Vaccines, Human Papillomavirus Vaccine*.

## Management and treatment

The following treatment recommendations have been developed based on limited Canadian data on the prevalence of *M. genitalium* and on the limited knowledge of *resistance to macrolides* or other antibiotics at the local level.[14,15]

Antimicrobial resistance (AMR) must be considered when choosing a course of treatment for *M. genitalium*.

The Expert Working Group for the *Canadian Guidelines on Sexually Transmitted Infections* reviewed the rapidly evolving scientific literature available to date on *M. genitalium* treatment efficacy, safety and escalating AMR issues. Their review resulted in the *recommendations* presented below.

### Antimicrobial resistance considerations

Due to limited access to *M. genitalium* testing in Canada at this time, currently known and emerging AMR patterns should be taken into consideration when initially treating patients who present with acute NGU or cervicitis.

- In a multi-site Canadian study, resistance mutations to macrolides and fluoroquinolones were found in 47.3% and 1.9% of specimens, respectively.[14]
- 58% of *M. genitalium* infections in a Toronto study carried macrolide resistance-mediating mutations, however no treatment failures were observed in cases treated with a multi-day course of azithromycin.[15] In the same study, 20% of patients harboured strains with mutations previously reported to mediate moxifloxacin resistance; treatment failures were suspected in 16% of patients.[15]
- In an Alberta study, over half of specimens for which sequencing data was available had mutations associated with macrolide resistance, and 12.2% of specimens from men and 2.6% of specimens from women had a *parC* mutation signifying possible moxifloxacin resistance.[16]
- Decreased susceptibility to tetracyclines has been reported in studies conducted in the US and Japan.[41-44]

### General treatment considerations

- Azithromycin has been shown to be more effective than doxycycline in treating *M. genitalium* in most settings,[41,42,45,46] but not all.[43]
- Although azithromycin is recommended as the preferred agent over moxifloxacin (as it is more widely used, less costly, has a narrower spectrum, a shorter duration of therapy and fewer side effects), rising resistance to macrolides may rapidly preclude the use of this medication as the initial choice of therapy.

- Given that azithromycin (1 g) may select for macrolide resistance, patients failing this regimen for the treatment of cervicitis or urethritis would not benefit from retreatment with the multi-day regimen.[45]
- In patients presenting with uncomplicated NGU and cervicitis, documented cure rates of *M.genitalium* are:
  - 40-91% with azithromycin 1 g PO single dose.[41-43,45-48]
  - 84% with azithromycin 1 g PO single dose in one Australian study from 2005-2007, whereas another study found a cure rate of 69% in 2007-2009, suggesting a decline in cure rate over time.[49,50]
  - 78-100% with azithromycin 500 mg PO single dose on day 1 followed by 250 mg PO single dose on days 2–5.[45-47]
- *In vitro* comparisons of the activity of fluoroquinolones against *M. genitalium* showed that moxifloxacin had the highest bactericidal activity.[51]
- Moxifloxacin has been shown to be an effective treatment option for those with *M. genitalium* infection if treatment failure occurs with azithromycin.[47,49,52,53]
  - Although cure rates as high as 100% have been reported with moxifloxacin, treatment failures have also been reported and may be related to fluoroquinolone resistance.[54,55]
- Patients who fail both macrolide and moxifloxacin treatment have been successfully treated with pristinamycin;[56] this drug is not currently available in Canada.

### Recommended treatment for suspected *M. genitalium* infection (i.e., persistent cervicitis or urethritis) not previously treated with azithromycin

- *Test for M. genitalium*, if not yet done and test is available.
- **Azithromycin** 500 mg PO on day 1, followed by 250 mg PO on days 2-5 *[B-II]*[45-47]

Rationale:

- Treatment failures have been reported with azithromycin 1 g PO single dose, and this has been implicated in the selection of antimicrobial-resistant strains in some studies.[41,45,46,49,52,57-62]
- Multi-day azithromycin treatment may be less likely to select for macrolide resistance than single dose azithromycin; however, it may be associated with higher rates of side effects and is unlikely to be effective in azithromycin-resistant infections.[3,45,48,63]

### Suspected treatment failure (i.e., persistent or recurrent urethritis or cervicitis); or confirmed macrolide-resistant *M. genitalium*

- **Moxifloxacin** 400 mg PO once daily for 7 days *[B-II]*[43,45,47,49,52,53,55,61]

Note:

- Seven days appears to be as effective as 10 days.[52]

### PID with probable or confirmed *M. genitalium* infection

- Moxifloxacin 400 mg PO once daily for 14 days *[B-I]*[64,65]

  - Moxifloxacin should be used in addition to standard treatment regimens for PID. Refer to the *Pelvic Inflammatory Disease* chapter for recommended parenteral and outpatient treatment regimens.

Note:

- An American study demonstrated that a cefoxitin and doxycycline regimen is not effective for *M. genitalium*-associated PID.[66]

## Reporting and partner notification

- *M. genitalium* is not a reportable infection in Canada.
- Although insufficient evidence exists to provide recommendations for routine partner notification, treatment of current partners should be considered (regardless of symptoms) to prevent reinfection of the index case.
  - It is not necessary to screen partners for *M. genitalium*.
  - Treat sexual partners with the same therapy as the index case.

## Follow-up

- Insufficient data are available to guide recommendations for test of cure. It should be done in cases that remain persistently symptomatic after the completion of appropriate treatment for *M. genitalium* and in regions with documented high prevalence[a] of antibiotic resistance.
- The appropriate timing of a test of cure is uncertain. Some experts recommend waiting at least 3 weeks after the completion of treatment, as earlier testing can lead to the detection of residual *M. genitalium* nucleic acid (i.e., a false positive result) despite cure.[48]
- In the event of persistent *M. genitalium* infection after treatment with azithromycin and/or moxifloxacin antimicrobial resistance testing should ideally be done.[48]
  - The *National Microbiology Laboratory (NML)* can test for macrolide and quinolone resistance-mediating mutations.

[a] 2014 data suggest high prevalence of azithromycin-resistant mycoplasma from the Toronto, Ontario region.[15]

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