

MYCOPLASMA GENITALIUM

Mycoplasma genitalium: prevalence, clinical significance, and transmission

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Objectives: To study the prevalence, symptoms and signs of *Mycoplasma genitalium* and *Chlamydia trachomatis* infections in STD clinic attendees and in partners of *M genitalium* infected patients.

Methods: *M genitalium* and *C trachomatis* were detected by polymerase chain reaction from urethral and endocervical swab specimens in a cross sectional study among 445 female and 501 male STD clinic attendees. Partners of 26 female and 26 male *M genitalium* positive index patients were examined.

Results: The prevalence of *C trachomatis* and *M genitalium* was 4% and 6.3%, respectively, among the women and 5.4% and 6%, respectively, among the men. Dual infections were uncommon. *M genitalium* was strongly associated with urethritis in both men and women and with cervicitis in women. Among *M genitalium* infected men, symptomatic urethritis was more common than asymptomatic urethritis. *M genitalium* and *C trachomatis* were not associated with symptoms of urethritis or cervicitis in women. Of 26 male partners of *M genitalium* positive female index patients, 38% were positive, and 77% of the negative partners had symptoms of urethritis. The concordance rate for 22 female partners of male index patients was 45%. For both men and women the *M genitalium* prevalence was significantly higher in partners of *M genitalium* positive index patients than in *M genitalium* negative index patients with urethritis and/or cervicitis.

Conclusions: *M genitalium* is associated with urethritis in both men and women and with cervicitis in women. A high concordance rate was found among sexual partners of *M genitalium* infected patients, indicating that the infection is sexually transmitted.

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The organisms *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are generally accepted pathogens in urethritis and cervicitis. However, in many cases no pathogen can be identified. Possible causes are other bacterial species, non-bacterial infections such as those caused by viruses and probably non-infectious conditions. In recent years, *Mycoplasma genitalium* has been of increasing interest. This microbe is a very small prokaryote with the minimum of metabolism necessary for a free living cell. *M genitalium* was first isolated in 1980 from two of 13 men with urethritis.^{1,2} Owing to the slow cell replication and fastidious growth requirements, culture is impossible to use in clinical practice. Polymerase chain reaction (PCR)^{3,4} is currently the method of choice for detection.

Several studies have shown that *M genitalium* is strongly associated with non-gonococcal urethritis (NGU), and in particular with non-chlamydial NGU (NCNGU) (recently reviewed by Taylor-Robinson and Horner⁵ and Jensen⁶). An independent and significant association between *M genitalium* and mucopurulent cervicitis⁷ and an association to endometritis⁸ have also been established.

The aim of this study was to obtain information on *M genitalium* concerning prevalence, association to clinical manifestations, and mode of transmission.

METHODS

Study population Prevalence study

This study was performed among attendees at the STD clinic, Falun, Sweden. From September 1995 through October 1997, samples for *M genitalium*, *C trachomatis*, and *N gonorrhoeae* were collected from 946 consecutive patients attending because of symptoms of sexually transmitted infections or for a check up. A total of 445 women and 501 men were included. The median age of the women was 25 years (range

14–55). The median age of the men was 26 years (range 17–67).

Partner notification study

In order to obtain information about the transmission of *M genitalium*, sexual partners of *M genitalium* infected patients were traced whenever possible in the same way as partner notification for *C trachomatis* is performed in Sweden.^{9–11} According to this legislation, sexual partners within at least 6 months should be traced and examined as follows.

- (1) Patient referral: partners are informed by patient.
- (2) Provider referral: patient reports name and address or at least telephone number of partner to the contact tracer, a health worker.
- (3) Conditional approach: initial patient or provider referral is followed by a stronger provider referral after an agreed interval. If a named partner refuses to be examined the medical officer of health is informed.

However, since *M genitalium* is not included in the legislation, we tried to motivate index patients to ask their partners to be examined. As a minimum, partners in "ongoing relationships" were examined. No provider referral was practised and no letters were sent to partners. *M genitalium* positive patients identified from November 1997 through December 2001 were included as index patients. During this period, only selected patients were examined for *M genitalium*. Contact tracing during the prevalence study was not practicable because of a delay between examination and

Abbreviations: FVU, first void urine; hpf, high power field; NCNGU, non-chlamydial non-gonococcal urethritis; NGU, non-gonococcal urethritis; PCR, polymerase chain reaction; PMNLs, polymorphonuclear leucocytes

the availability of the test result. For comparison, partners of index patients treated for urethritis or cervicitis without known infection with *C trachomatis*, *Mycoplasma genitalium*, or *N gonorrhoeae* (non-specific infection) were examined. This was performed during 2003 as data concerning partner notification in non-specific infection were not available earlier.

Clinical assessment

Patients were regarded as having symptoms of urethritis if they complained of dysuria or urgency and for males if they had noticed a discharge. In females, discharge was regarded as a symptom of cervicitis.

Microscopic urethritis was diagnosed if >4 polymorphonuclear leucocytes (PMNLs) per high power field (hpf) (1000× magnification) were observed in >4 fields in a methylene blue stained smear of urethral secretion collected with a plastic loop from both men and women.

Microscopic cervicitis was diagnosed if ≥30 PMNLs per hpf were observed in >4 fields in a methylene blue stained smear of cervical secretion collected with a cotton tipped swab.

Clinical specimens for microbiological analysis

During the prevalence study, male urethral specimens were taken with a cotton tipped swab transported in a tube with 2 ml 2-SP medium. From women, endocervical and urethral swabs were transported in a tube with 2-SP medium.

During the partner notification study, specimens from men consisted of first void urines (FVU) and from females endocervical swabs were placed in the tube containing the woman's FVU specimen.

The specimens were refrigerated and transported to the laboratory within 1–18 hours. Specimens in 2-SP were frozen before testing, whereas urines were not.

Microbiological methods

PCR for *C trachomatis* was performed by the Roche Cobas Amplicor system (Roche Diagnostics Scandinavia AB, Bromma Sweden) following the guidelines from the manufacturer. PCR tests for *C trachomatis* and *M genitalium* were performed on the same specimen.

Sample preparation for the *M genitalium* PCR was performed by centrifuging 250 µl of the specimen in 2-SP medium at 30 000 × g for 15 minutes, resuspending the pellet in 50 µl lysis buffer (Roche *C trachomatis* sample preparation kit) with 200 µg proteinase K/ml, incubating at 55°C for 30 minutes, and at 94°C for 10 minutes. After heat treatment, 50 µl specimen diluent (Roche *C trachomatis* sample preparation kit) was added. Specimens were left for 30 minutes at room temperature before the PCR was performed. DNA extraction of urine was performed using the automated MagNA Pure LC (Roche Diagnostics) with DNA Isolation Kit I protocol. Before processing in the MagNA Pure, 2 ml of urine was centrifuged for 15 minutes at 30 000 × g. Most of the supernatant was discarded, leaving a final volume of 300 µl. Of this suspension 200 µl was processed and DNA was eluted in a volume of 100 µl. All samples were tested in a

PCR using primers for the 16SrRNA gene.¹² Positive results in the first PCR were confirmed in a new PCR using MgPa1 and MgPa3 primers.³ PCR products were visualised after gel electrophoresis in ethidiumbromide stained gels.

N gonorrhoeae was detected by culture.

Statistical analysis

Fisher's exact test was used for statistic analysis of categorical variables. The Mann-Whitney test was used to test for differences in continuous variables.

RESULTS

Prevalence study

Demographics

Among the 946 examined patients, *M genitalium* was detected in 58 (6.1%); 30 (6.0%) of the 501 men, and 28 (6.3%) of the 445 women. *C trachomatis* was detected in 45 patients (4.6%); 27 (5.4%) men and 18 (4%) women. Two men and one woman were co-infected with *M genitalium* and *C trachomatis*. One man and two women were infected with *N gonorrhoeae*. They were excluded from the study group, which thus consisted of patients with and without non-gonococcal urethritis and cervicitis.

The median age of the *M genitalium* infected men was 26 years (range 17–40 years). This was not different from the *C trachomatis* positive (median 24, range 18–43) or from the *C trachomatis* and *M genitalium* negative group (median 26, range 17–67). The *C trachomatis* positive men, however, were younger than the *C trachomatis* and *M genitalium* negative men ($p = 0.03$) (Mann-Whitney test). The median age of the *M genitalium* infected women was 25 years (range 19–54 years). This was not different from the *C trachomatis* positive (median 22, range 18–30) or *C trachomatis* and *M genitalium* negative groups (median 25, range 14–55) (Mann-Whitney test).

Associations between *M genitalium*, *C trachomatis*, and symptoms and microscopic signs of urethritis in males

M genitalium was detected in 17 (13.6%) of 125 men with symptomatic urethritis, and in two (1.2%) of 161 men without symptoms or microscopic signs of urethritis ($p < 0.0001$) (table 1). The presence of *M genitalium* was significantly associated both with symptoms and with microscopic signs. This association was also seen for *C trachomatis*. If patients co-infected with *M genitalium* and *C trachomatis* were excluded, 17 (61%) of the 28 *M genitalium* positive men had symptoms compared to 15 (60%) of the 25 men with *C trachomatis* infection (NS). Likewise, 26 (93%) of the *M genitalium* positive men had urethritis as defined by microscopy compared to 24 (96%) of the *C trachomatis* infected men (table 1) (NS). All *M genitalium* infected men with symptoms also had microscopic signs. Arthritis was reported by three of the men infected with *M genitalium* but not by any of those with *C trachomatis*. Two of the men with arthritis were referred with the question of sexually acquired arthritis.

Table 1 Symptoms (S) and microscopic signs (M) in men infected with *Mycoplasma genitalium* (Mg) and *Chlamydia trachomatis* (Ct), respectively

	M-S- (n = 161)	M+S+ (n = 125)	p Value	M+S- (n = 151)	p Value	M-S+ (n = 61)	p Value
Mg+ Ct- (n = 28)	2 (1.2%)	17 (13.6%)	<0.0001	9 (6%)	0.03	0 (0%)	NS (0.99)
Mg-Ct+ (n = 25)	0	15 (12.0%)	<0.0001	9 (6%)	0.001	1 (0.2%)	NS (0.27)

Total number of men in the study was 500. Two men co-infected with *M genitalium* and *C trachomatis* were excluded from the comparison. p Values given for comparison with the M-S- group.

Table 2 Symptoms (S) and microscopic signs (M) in women infected with *Mycoplasma genitalium* (Mg) and *Chlamydia trachomatis* (Ct), respectively

	M-S- (n=138)	M+S+ (n=129)	p Value	M+S- (n=85)	p Value	M-S+ (n=90)	p Value
Mg+ Ct- (n=27)	3 (2.2%)	15 (11.6%)	0.003	6 (7.0%)	NS (0.09)	3 (3.3%)	NS (0.68)
Mg-Ct+ (n=17)	6 (4.3%)	5 (3.9%)	NS (0.99)	5 (5.9%)	NS (0.75)	1 (1.1%)	NS (0.25)

Total number of women in the study was 443. One woman co-infected with *M genitalium* and *C trachomatis* was excluded from the comparison. p Values given for comparison with the M-S- group.

Associations between *M genitalium*, *C trachomatis*, and symptoms and microscopic signs of urethritis and cervicitis in females

Of the 443 examined women, 130 had symptoms as well as microscopic signs of urethritis and/or cervicitis. *M genitalium* was detected in 16 (12.3%) of those with and in three (2.2%) of the 138 women without urethritis or cervicitis ($p = 0.001$). One of the women with microscopic signs was co-infected with *M genitalium* and *C trachomatis* (table 2). Symptoms regardless of microscopic signs were not associated with *M genitalium* infection, whereas microscopic signs of urethritis and/or cervicitis were strongly associated with *M genitalium* infection (table 2). For the *C trachomatis* infected women, no association could be shown between symptoms and microscopic signs (table 2). Symptoms of urethritis or cervicitis were reported by 18 (67%) of the 27 *M genitalium* positive women compared to six (35%) of the 17 *C trachomatis* infected women (NS) (table 2).

Microscopic signs of cervicitis without concomitant urethritis were seen in 30 of the women. Of these, *M genitalium* was detected in four (13.3%) compared to six (2.6%) of the 227 women without microscopic signs ($p = 0.02$) (table 3A). Microscopic signs of urethritis without concomitant cervicitis were seen in 129 women. Of these, *M genitalium* was detected in 11 (8.5%) compared to six (2.6%) of women without microscopic signs ($p = 0.02$). *M genitalium* was significantly associated with cervicitis regardless of concomitant urethritis ($p = 0.006$) (table 3A) and with urethritis regardless of concomitant cervicitis ($p = 0.005$) (table 3B). *C trachomatis* was not associated with urethritis or cervicitis (table 3).

If dysuria and/or urgency were considered symptoms of urethritis and discharge was considered a symptom of cervicitis, no correlation between the presence of microscopic urethritis or cervicitis and their corresponding symptoms could be found. This held true for both *M genitalium* positive, *C trachomatis* positive and *M genitalium* and *C trachomatis* negative patients. Although the number of patients studied was small, not even a trend was observed towards the expected correlation (table 4).

Partner notification study

Partner notification was performed for 52 index patients, 26 women and 26 men, infected with *M genitalium*.

The 26 *M genitalium* infected women reported 38 male partners. Twenty six (68%) of the male partners were examined for *M genitalium* and 10 (38%) were positive.

Examination was performed on 22 (73%) of 30 female partners reported by 26 male index patients. Ten (45%) were infected.

Symptoms and microscopic signs in partners with negative PCR for *M genitalium* are presented in table 5. Surprisingly, six (50%) of the 13 *M genitalium* negative partners of *M genitalium* positive women, where this information was available, had microscopic urethritis and 10 (77%) had symptoms. Thus, it could be considered likely that at least some of these men were indeed infected with *M genitalium* but remained undetected for unknown reasons. Likewise, nine (82%) of the 11 *M genitalium* negative female partners of *M genitalium* positive men had symptoms and/or microscopic signs of cervicitis/urethritis. In the comparison group 61 female and 80 male partners of index patients with NSU were examined. *M genitalium* was found in one (1.6%) of the females and in four (5%) of the males. *C trachomatis* was found in one (1.6%) of the females. Thus, *M genitalium* was found significantly more often in partners of *M genitalium* positive patients than in partners of patients with non-symptomatic urethritis ($p < 0.0001$ for both male and female partners).

DISCUSSION

This is one of the very few true prevalence studies concerning *M genitalium*, in contrast with the many case-control studies published thus far. In this study, *M genitalium* was found more often than *C trachomatis* in both men and women. Furthermore, the prevalence of *C trachomatis* in male patients with NGU was only 9%. The reason for the low prevalence of *C trachomatis* is not clear. *C trachomatis* infection is notifiable and is included in the Swedish legislation on STIs; therefore, partner tracing can be performed more rigorously than in many other countries. In recent years, however, this has not

Table 3 Microscopic cervicitis (>30 PMNL/hpf) (A) and microscopic urethritis (>4 PMNL/hpf) (B) in 443 women according to *Mycoplasma genitalium* (Mg) and *Chlamydia trachomatis* (Ct) infection status. One woman co-infected with *M genitalium* and *C trachomatis* was excluded from the comparison.

	No cervicitis no urethritis (n=227)	Cervicitis no urethritis (n=30)	p Value	All cervicitis (n=84)	p Value	Cervicitis and urethritis (n=54)	p Value
(A) Microscopic cervicitis (>30 PMNL/hpf)							
Mg+ Ct- (n=27)	6 (2.6%)	4 (13.3%)	0.02	9 (10.6%)	0.006	5 (9.1%)	0.04
Mg-Ct+ (n=17)	7 (3.1%)	1 (3.3%)	NS (0.99)	5 (5.9%)	NS (0.31)	4 (7.3%)	NS (0.23)
(B) Microscopic urethritis (>4 PMNL/hpf)							
Mg+ Ct- (n=27)	6 (2.6%)	11 (8.5%)	0.02	17 (9.2%)	0.005	5 (9.1%)	0.04
Mg-Ct+ (n=17)	7 (3.1%)	5 (3.9%)	NS (0.76)	9 (4.9%)	NS (0.44)	4 (7.3%)	NS (0.23)

p Values given for comparison with the no urethritis and no cervicitis group.

Table 4 Distribution of symptoms in 443 women according to *Mycoplasma genitalium* (Mg) and *Chlamydia trachomatis* (Ct) infection status and their relation to microscopic cervicitis (>30 PMNL/hpf) and/or urethritis (>4 PMNL/hpf). One woman co-infected with *M genitalium* and *C trachomatis* was excluded from the comparison

	Discharge	Dysuria	Urgency	Any symptom
Mg+Ct- (n=27)*				
Cervicitis (n=4)	0	2 (50%)	0	2 (50%)
Urethritis (n=11)	6 (55%)	1 (9%)	1 (9%)	8 (73%)
Both (n=5)	3 (60%)	2 (40%)	1 (20%)	4 (80%)
None (n=6)	1 (17%)	2 (33%)	0	3 (50%)
Mg-Ct+ (n=17)				
Cervicitis (n=1)	0	0	0	0
Urethritis (n=5)	1 (20%)	0	1 (20%)	2 (40%)
Both (n=4)	2 (50%)	1 (25%)	1 (25%)	3 (75%)
None (n=7)	1 (14%)	0	0	1 (14%)
Mg-Ct- (n=398)*				
Cervicitis (n=25)	8 (32%)	8 (32%)	1 (4%)	16 (64%)
Urethritis (n=113)	42 (37%)	20 (18%)	12 (11%)	67 (59%)
Both (n=45)	18 (40%)	9 (20%)	0	26 (57%)
None (n=214)	47 (22%)	25 (12%)	24 (11%)	86 (40%)

*Cervix not examined in one *M genitalium* positive woman and in one *M genitalium* and *C trachomatis* negative woman.

been sufficient to ensure a decreasing prevalence of *C trachomatis* infection in Sweden in general. The age distribution of patients infected with the two pathogens was not significantly different, indicating that they may share a common behavioural and biological profile. The strong association between *M genitalium* and male urethritis independently of *C trachomatis* found in this study strongly indicates that it has an aetiological role in urethritis. Our findings confirm results from several other studies regarding the association between *M genitalium* and NGU in general and NCNGU in particular (see Jensen⁶ for review). We found that almost all *M genitalium* and *C trachomatis* positive male patients had urethritis (93% and 96%, respectively), whereas only less than two thirds had symptoms (61% and 64%, respectively). For both pathogens, the high proportion of asymptomatic carriers among the infected would facilitate the spread of the infection. Even though many *M genitalium* patients are asymptomatic, more patients had symptomatic than asymptomatic urethritis in this study. This is in accordance with earlier studies on smaller numbers of patients.^{13 14}

The remarkably few patients with gonorrhoea reflected the low prevalence of this infection in Sweden. Only 210 cases were reported in 1996 in a population of 8.5 million.

Table 5 Symptoms and signs among 12 Mg- and 10 Mg+ female partners of 26 male index patients and in 16 Mg- and 10 Mg+ male partners of 26 female index patients.

	M+S+	M+S-	M-S+	M-S-	Unknown
Female Mg- (n=12)	6*	2	1	2	1
Female Mg+ (n=10)	4	5	1	0	
Male Mg- (n=16)	6†	0	4	3	3
Male Mg+ (n=10)	3	5	0	1	1

*Two also had a history of irregular bleeding.

†One male partner was co-infected with *Chlamydia trachomatis*, and one male partner had arthritis.

M, microscopic urethritis and or cervicitis; S, subjective symptoms of urethritis and or cervicitis. One woman and four men did not have microscopic examination performed.

The few studies performed in women have indicated that *M genitalium* might be a pathogen in cervicitis.^{7 15 16} This is in agreement with our findings. We detected *M genitalium* five times more often in women with cervicitis than in those without (13.3% compared to 2.6%). Casin *et al*,¹⁷ however, did not show such an association. As a definition of cervicitis ≥ 10 PMNs/hpf was used compared with ≥ 30 in the present study. They also found a remarkably high prevalence of *M genitalium* (38%) in comparison with the prevalence of *C trachomatis* (8%) raising concern about the specificity of the PCR method used.

In the present study, *M genitalium* was detected three times more often in women with urethritis than in those without, (9.2% compared to 2.6%). This is to our knowledge the first study to show an association between *M genitalium* infection and female urethritis.

Discharge as reported by the women may be caused by urethritis as well as by cervicitis. Discharge from the urethra is probably a less important symptom in females than in males. Without microscopy, discharge from the vagina caused by bacterial vaginosis or candidiasis cannot be differentiated from discharge caused by cervicitis, and more than one condition may be present at the same time. Bacterial vaginosis may be a marker of STI as it is found more often in women with *C trachomatis* infection.¹⁶

The results of a few studies, apart from the present one, have indicated that *M genitalium* is a STI. Keane *et al*¹⁸ studied female partners of men with and without NGU and found *M genitalium* only in partners of men with NGU. Seven (58%) of the 12 partners of *M genitalium* positive male index were positive, and similarly, Falk *et al*¹⁹ found 67% positive female partners. These figures are slightly higher than the 45% positive female partners of *M genitalium* positive men found in this study, but not statistically significantly different. The surprising finding that 50% of 13 *M genitalium* negative male partners of *M genitalium* positive women had microscopic urethritis and that 77% had symptoms raises concern that the diagnostic methods may need improvement. The recent finding that 20% of urogenital swab specimens contain <1 genome copy/ μ l of the pretreated specimen indicates that sample preparation methods may need to be improved.²⁰ Furthermore, it would be interesting to examine first void morning urine specimens from such discrepant couples since this specimen type may provide a higher sensitivity.²¹

A study based on serological data²² found a significantly higher prevalence of antibodies against *M genitalium* in STD

Key messages

- *Mycoplasma genitalium* is strongly associated with microscopic urethritis in both men and women and with microscopic cervicitis in women
- Symptomatic urethritis is more common than asymptomatic urethritis in *M genitalium* positive men
- In women, symptoms of urethritis and cervicitis do not correlate with microscopic urethritis and cervicitis
- Partners of *M genitalium* infected men and women were significantly more often infected with *M genitalium* than partners of patients with non-specific infection. This supports the notion that *M genitalium* is sexually transmitted

clinic attendees than in healthy blood donors, indirectly supporting the notion that it is spread via sexual transmission.

In our prevalence study, three men infected with *M genitalium* had arthritis. In the partner notification study, one man infected with *M genitalium* and one male partner with negative PCR for *M genitalium*, but with symptoms and microscopic signs of urethritis also had arthritis. A possible causal association between *M genitalium* infection and arthritis has been implicated earlier by the detection of *M genitalium* from the knee joint of a patient with Reiter's syndrome²³ but this relation needs to be investigated further.

In conclusion, this study has further substantiated the role of *M genitalium* in lower genital tract infections and documented that *M genitalium* is sexually transmitted with a transmission rate comparable to that of *C trachomatis*. Further work is still needed, particularly in establishing the optimal treatment and in documenting upper genital tract disease.

CONTRIBUTORS

CA initiated the study, examined all patients, collected the data, and wrote the first draft of the manuscript; BL was responsible for the *N gonorrhoeae*, *M genitalium*, and *C trachomatis* tests, she provided major contributions to the design of the study, analysis of the data, and writing of the manuscript; JSJ provided advice on the *M genitalium* tests and the design of the study, he provided major contributions in the data analysis and in writing the manuscript.

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This study was approved by the ethics committee, Dalarna, Sweden, and all participants provided informed consent.

Parts of these data have previously been published in Swedish (Anagrius C, Lore B. *Läkartidningen* 2002;**99**:4854–5, 4858–9).

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