Symptomatic urethritis is more prevalent in men infected with *Mycoplasma genitalium* than with *Chlamydia trachomatis*

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**ORIGINAL ARTICLE**

**METHODS**

**Patients**

During a 6 month study period from 1 February 2000 to 31 July 2000, all male attendees at the Örebro University Hospital STD clinic were included. Data were collected on a standard questionnaire regarding the reasons for attendance, age, symptoms of urethritis (dysuria and discharge), number of sexual partners within the past 6 months, condom use, sexual intercourse with men, history of STIs, probable STIs among the partners, recent or current antibiotic treatment, and other diseases.

**Sampling**

A total of 519 men between 16 and 67 years of age (median 27 years) were included. Smears were taken with a blunt curette from the distal urethra and stained with methylene blue. The amount of exudate recovered was estimated, using profuse as a definition of discharge (>1 cm² of a single cell layer smear on the slide), moderate and poor as a graduation in the normal amount of secretion. During the study period, the patients were seen by seven clinicians, but four of those examined 95% of all patients. All smears were examined microscopically (1000×) with a Nikon Labophot microscope. The definition of urethritis is generally >4 polymorphonuclear leukocytes (PMNL) per high power field (HPF) in more than four high power fields, but in the current study, smears with 5–10 PMNL per HPF were defined as “grey zone urethritis” and >10 PMNL per HPF as urethritis. After urethral smear was sampled the first void urine (FVU) was collected for *C trachomatis* and *M genitalium* tests and distributed in two screw capped 13 ml polypropylene tubes (Sarstedt, Nürnbrecht, Germany). Partners, women and men, attending the STD clinic during the study were all examined for *C trachomatis* and *M genitalium*.

**Microbiological analysis**

One of the tubes containing 5–10 ml of urine was sent the same day to the department of clinical microbiology, Örebro University Hospital, and stored at 2–8°C. The urine samples were all examined for *C genitalium* and *C trachomatis* infections in men attending a Swedish STD clinic and to study the criteria for urethritis.

**Results**

The prevalence of *M genitalium* and *C trachomatis* was 7% (34/512) and 12% (61/512), respectively. Dual infection was diagnosed in four men. In both infections 90% of the patients had signs of microscopic urethritis. *M genitalium* positive men had symptomatic urethritis significantly more often than those infected with *C trachomatis* (73% vs 40%, RR 1.8; 95% CI 1.2 to 2.7). 63% of female partners of men infected with *M genitalium* were infected with *M genitalium* compared with chlamydial infection in 67% of female partners of men infected with *C trachomatis*. Non-chlamydial non-gonococcal urethritis without evidence of *M genitalium* infection was diagnosed in 180 men (35%). Symptoms and/or visible discharge were reported in 49% in this group.

**Conclusions**

*M genitalium* is a common infection associated with symptomatic urethritis and with a high prevalence of infected sexual partners supporting its role as a sexually transmitted infection.
The other tube containing 5–10 ml FVU was sent the same day by express mail to Statens Serum Institut, Copenhagen, Denmark for M genitalium PCR test. M genitalium was detected by an inhibitor controlled PCR using primers detecting the M genitalium 16S rRNA gene.24 All positive results were confirmed by a PCR detecting the MgPa adhesin gene.22 Samples for Neisseria gonorrhoeae (culture) were taken from 88 men. Samples were taken selectively on certain indications—that is, unprotected sexual contacts abroad, purulent discharge, unprotected sexual contacts between men, and partner notification because of gonorrhea, and not as a screening test because of the current low incidence in Sweden (0.7/100 000 inhabitants—that is, 588 cases in 2000).22

**Follow up**

All patients infected with C trachomatis and/or M genitalium were asked to re-attend for a follow up visit 4–5 weeks after commencing antibiotic treatment. All recent partners of C trachomatis and M genitalium infected patients were notified and asked to attend the STD clinic for C trachomatis and M genitalium testing and genital examination. Recent partners were defined as all partners during the past 6 months before attendance or at least the two latest partners. As a part of this study the treatment efficacy in M genitalium infected patients was evaluated in an open pilot study.23 The results from that study suggest that tetracyclines are not sufficient to eradicate M genitalium, but that azithromycin might be effective.

**Statistical analysis**

The χ² test and Fisher's exact test were used to test for differences in proportions and Mann-Whitney U test and Kruskal-Wallis test for non-parametric comparison of groups. Stata statistical software version 8.0 was used for calculating confidence intervals.

**RESULTS**

Neisseria gonorrhoeae was isolated from two men. No patient was smear positive and culture negative for N gonorrhoeae. Non-gonococcal urethritis (NGU) was detected in 271 men, comprising 61 patients between 16 and 56 years of age (median 23 years) with C trachomatis infection and 34 patients between 20 and 55 years of age (median 28 years) with M genitalium infection. Four patients with chlamydia had a concurrent M genitalium infection and were excluded in the comparison of signs and symptoms between M genitalium and C trachomatis. Initially, 41 men had positive PCR tests for M genitalium, but seven, of which three had a microscopic urethritis and four not, had tests that were not confirmed and hence they were excluded from the study. Among these seven patients one had symptoms—that is, symptoms of epididymitis, but the remaining six were asymptomatic. The remaining 180 men with M genitalium negative NCNGU were between 16 and 54 years old (median 25.5 years). These patients were considered as having non-specific urethritis (NSU). Among the 180 men 42 had a microscopic urethritis, where the physician diagnosed 11 as prostatitis, 22 as genital papillomavirus infection, and nine with genital herpes simplex infection; these diseases themselves might be the cause of urethritis. The overall prevalence of M genitalium was 7% (34/512), and that of C trachomatis 12% (61/512) and of NSU 35% (180/512). M genitalium infected men had symptoms of urethritis significantly more often than those with chlamydial infection—that is, 73% (22/30) versus 40% (23/57) and with a relative risk (RR) of 1.8 (95% CI 1.2 to 2.7). The M genitalium and C trachomatis groups were also compared with the NSU group where the C trachomatis group was indexed as 1 (table 1). The rate of microscopic signs of urethritis was high in both infections reaching about 90% and no significant difference was found (RR 0.8; 95% CI 0.3 to 2.0). The number of patients in the M genitalium positive NGU, C trachomatis positive NGU, and NSU groups was significantly different (p = 0.03). The patients with C trachomatis NGU reported significantly more partners in the previous 6 months. There were no significant differences regarding history of previous STI (urethritis) between the different groups (table 1).

The mean duration of symptoms was 4.2 weeks (median 3, range 1–25) for the 21/23 (data missing from two) men with symptomatic C trachomatis NGU, 5.7 weeks (median 2, range 1–60) for the 22 men with symptomatic M genitalium positive NGU (p = 0.42), and 6.5 weeks (median 2.5, range 1–12) for the three men with symptoms and verified infection with both bacteria. Only 27% (49/180) of the men with NSU had symptoms correlated to urethritis compared to 23% (40%) of 57 with chlamydial infection (p = 0.068) and 22% (73%) of 30 with M genitalium infection (p=0.0001). Of the men with NSU 49% (75/152) had neither symptoms nor visible discharge compared to 20% (10/51) (p<0.001) and 7% (2/27) (p<0.001), respectively, among C trachomatis and M genitalium positive men (table 2). Men with C trachomatis positive or M genitalium positive NGU were more likely to have discharge (as a sign) than were those with NSU (p<0.001).

**Table 1**  Symptoms (self reported dysuria and/or discharge), signs (observed discharge—that is, ≥1 cm² smear on the slide and urethritis (>4 PMNL/HPF)), number of partners, and STI history among all male attendees (n = 512)

<table>
<thead>
<tr>
<th>Symptom status</th>
<th>Urethral smears (PMNL/HPF)</th>
<th>Symptoms of urethritis</th>
<th>Number of partners</th>
<th>STI history (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count (%)</td>
<td>RR (CI 95%)</td>
<td>Mean (range)</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>≤5</td>
<td>23 (40)</td>
<td>1 (reference)</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>5–10</td>
<td>0</td>
<td>1 (2–27)</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>2</td>
<td>1 (2–6)</td>
<td>1.1</td>
</tr>
<tr>
<td>C trachomatis</td>
<td>4</td>
<td>0</td>
<td>ND</td>
<td>6 (3)</td>
</tr>
<tr>
<td>(n = 57)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>12 (5)</td>
</tr>
<tr>
<td>M genitalium</td>
<td>3</td>
<td>0</td>
<td>22 (73)</td>
<td>2.1</td>
</tr>
<tr>
<td>(n = 30)</td>
<td></td>
<td>0</td>
<td>1.8 (1.2 to 2.7)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Mg and Ct pos</td>
<td>0</td>
<td>0</td>
<td>3 (75)</td>
<td>9 (30)</td>
</tr>
<tr>
<td>(n = 4)</td>
<td></td>
<td>0</td>
<td>7.5</td>
<td>7 (125)</td>
</tr>
<tr>
<td>Urethritis,</td>
<td>0</td>
<td>0</td>
<td>4 (2–20)</td>
<td>4 (125)</td>
</tr>
<tr>
<td>negative tests</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>12 (5)</td>
</tr>
<tr>
<td>(n = 180)</td>
<td></td>
<td>3 (75)</td>
<td>4.7 (4.4 to 5.0)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>The rest of</td>
<td>235</td>
<td>1 (1)</td>
<td>36 (15)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>attendees (n</td>
<td></td>
<td></td>
<td>0.4 (0.2 to 0.6)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>= 241)</td>
<td></td>
<td></td>
<td>1.8</td>
<td>12 (5)</td>
</tr>
</tbody>
</table>

*One (homosexual) man had a gonococcal urethritis;†Data were missing from one patient.
ND = microscopic examination not done; Mg = Neisseria gonorrhoeae; Ct = Chlamydia trachomatis; Mg = Mycoplasma genitalium; NCNGU = non-chlamydial non-gonococcal urethritis.

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Altogether, among all 512 attendees in the current study, eight men reported having sex with men, of which four had had only passive anal sex, three both active and passive anal sex, and one only reciprocal oro-genital sex (fellatio). The 34 M genitalium infected men were all heterosexual, except one who also had a concurrent C trachomatis infection and had had fellatio with a man a year before attendance, but who subsequently had only had sexual intercourse with women (>20 partners). Among the other C trachomatis positive men, there were two homosexual men, of which one was notified because of his partner’s chlamydial infection (tested at another clinic) and the other had had partners who could not be identified. Also, among the 180 men with a NSU there was one homosexual man, but his partners did not attend the clinic for testing.

Nineteen female partners of 18 men infected with M genitalium were examined; 12 (63%) of them were M genitalium positive. Four (21%) were C trachomatis positive; two of these patients had partners who were infected with both C trachomatis and M genitalium. One woman had negative tests but a mucopurulent cervicitis. Correspondingly, 39 partners of 28 C trachomatis positive men were examined; three men each had three partners and six men each had two partners. Twenty six (67%) of those partners were C trachomatis positive and two (5%) were M genitalium positive. The M genitalium positive women were partners of dual infected men. Eight (17%) of the 47 examined partners of men with NSU were C trachomatis positive, and three (6%) were M genitalium positive. Both C trachomatis and M genitalium were found significantly more often in partners of men with the corresponding infection, than in partners of men with NSU (p<0.0001 for both). The diagnosis and number of partners of each group are shown in table 3.

**DISCUSSION**

In this cross sectional study, the prevalence of C trachomatis infection was higher than that of M genitalium infection among male STD clinic attendees (12% versus 7%, respectively). Only four patients were infected with both bacteria. Only a few true cross sectional studies of STD clinic populations have been published.1–4 Most investigations have been case-control studies. The inclusion criterion in the case group has been either symptoms or microscopic signs of urethritis; in the control group, asymptomatic men or men without microscopic signs of urethritis have been included.3,4,13,14 In a recent Swedish report,14 all attendees were tested for both M genitalium and C trachomatis and a similar prevalence for M genitalium (6%) was found; however, the prevalence of C trachomatis was surprisingly low (5%). In patients examined in another Swedish study,3 3 years earlier than those in the present study, a C trachomatis prevalence of 19% and an M genitalium prevalence of 7% were found. The

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**Table 2** Correlation between symptoms (self reported dysuria and/or discharge) and signs (observed discharge—that is, >1 cm² smear on the slide and urethritis (>4 PMNL/HPF)) among male attendees infected with C trachomatis (Ct), M genitalium (Mg), or neither organism (NSU)

<table>
<thead>
<tr>
<th></th>
<th>Cs (n = 57)</th>
<th>Mg (n = 30)</th>
<th>Mg and Cs (n = 4)</th>
<th>NSU (n = 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge and symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Discharge but no symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms but no discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms, discharge not noted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No symptoms, discharge not noted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No discharge or symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data lacking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total count (%)</td>
<td>57 (100)</td>
<td>30 (100)</td>
<td>4 (100)</td>
<td>180 (100)</td>
</tr>
</tbody>
</table>

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**Table 3** Clinical findings in female sexual partners of 24 men infected with C trachomatis (Ct), 14 infected with M genitalium (Mg), and 44 with non-specific urethritis (NSU)—that is, NGU without positive tests for C trachomatis and/or M genitalium

<table>
<thead>
<tr>
<th>Male patients’ diagnosis</th>
<th>Ct (n = 24/57)</th>
<th>Mg (n = 14/30)</th>
<th>Mg and Ct (n = 4)</th>
<th>NSU (n = 44/180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female partners’ diagnosis*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C trachomatis</td>
<td>24 (69)</td>
<td>21 (13)</td>
<td>21 (50)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>M genitalium</td>
<td>0 (0)</td>
<td>10* (67)</td>
<td>21 (50)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Non-specific infection</td>
<td>7 (20)</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>17 (36)</td>
</tr>
<tr>
<td>Other diagnoses</td>
<td>4 (11)</td>
<td>3 (20)</td>
<td>1 (25)</td>
<td>19 (41)</td>
</tr>
<tr>
<td>Total number of partners</td>
<td>35 (100)</td>
<td>15† (100)</td>
<td>41 (100)</td>
<td>47 (100)</td>
</tr>
</tbody>
</table>

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*Among the Ct infected patients, 3 had 3 partners, 6 had 2 partners, and 14 had 1 partner examined. Of the 14 Mg infected patients, 1 had 2 partners, and the rest had 1 partner examined at the clinic. Of the 44 patients with NSU, 3 had 2 partners and the rest had 1 partner examined at the clinic.
†One female partner in each group was both C trachomatis and M genitalium positive.

Non-specific infection indicates urethritis and/or cervicitis with negative test results for C trachomatis and M genitalium. Percentages given in parentheses.
reason for the differences in the C trachomatis prevalence in three Swedish STD clinics within a relatively limited time frame is not clear, but may reflect differences in the populations studied. It is surprising though that such differences were not found in the prevalence of M genitalium.

In a recent French study, M genitalium was found significantly more frequently among a group of men with urethritis and symptoms than in a group of men with symptoms but no urethritis, which was also the case for C trachomatis but not for Ureaplasma urealyticum, where the same prevalence (26% vs 22%) was found in both groups. The criteria for urethral symptoms were wider than in the present study. Also the criterion for urethritis was different, based on examination of EVU and not urethral smears.

In the above mentioned case-control studies the proportion of M genitalium and C trachomatis in the NGU groups was similar to the results in the current study, although the number of patients with NGU in our study was higher than in some reports and equal to others.

M genitalium infected men had symptoms of urethritis significantly more often than those infected with C trachomatis. This was not reflected in the microscopic signs of urethritis and the reason for this finding is not clear. It could be speculated that the production of hydrogen peroxide by M genitalium may contribute to the symptoms. Whether the symptoms reflect also a potential for deeper invasion such as is seen in a chimpanzee model, where two of the 10 inoculated animals had M genitalium isolated from the blood stream is not clear. The number of patients in the present study was limited and therefore our findings have to be verified in future studies. There is evidence that M genitalium may cause endometritis, PID, and sexually acquired reactive arthritis. M genitalium may contribute to the symptoms. Whether the symptoms reflect also a potential for deeper invasion such as is seen in a chimpanzee model, where two of the 10 inoculated animals had M genitalium isolated from the blood stream.

Most published studies have focused on asymptomatic patients comparing signs and symptoms of infected people with the two organisms. In this study there was no difference in microscopic signs between the bacteria. The high proportion of urethritis in men infected with M genitalium and the low rate of mixed infections support the conclusion made by others that M genitalium is a pathogen. The present study also showed that M genitalium infection seems to have a high prevalence in the society and therefore might be considered for screening purposes at STD clinics.

In this study, 12 of 19 (63%) female partners of men infected with M genitalium tested at the STD clinic also had a M genitalium infection compared with 26 of 39 (67%) chlamydial infected female partners of men with C trachomatis infection. These data emphasise the role of M genitalium as a sexually transmitted pathogen, since only three of 47 partners of men with NGU were M genitalium positive. C trachomatis is a notifiable infection including mandatory partner notification, but partners can attend any clinic, which therefore not have been treated if both symptoms and microscopic signs were set as criteria for treatment. The sensitivity of C trachomatis PCR tests is high but less than 95% and possibly even lower for M genitalium PCR tests, so patients with false negative test results may benefit from treatment.

The most widely accepted and used criterion for urethritis is >4 PMNL/HPF which was established in the late 1970s. The result of this study calls for a reconsideration of this criterion, since none of the patients with C trachomatis or M genitalium infection had fewer than 10 PMNL/HPF. Only among the men with NGU was “grey zone urethritis” found—in 29 patients. Obviously, the interpretation of the smear depends on several variables: the instrument for sampling, the standard of the microscope and how it is used.

Unfortunately, we do not have data on the number of lifetime partners, which may have provided an explanation for this difference; however, no difference in the duration of symptoms was seen. Only eight men reported sexual contact with other men, although three had a C trachomatis infection, and one of those was also infected with M genitalium. It is not possible from this study to draw any conclusions as to whether M genitalium is more or less prevalent among men who have sex with men than among heterosexual men.

In the large NSU group comprising 180 men with urethritis without recognised cause (66% of NGU), significantly more patients were asymptomatic compared with both the M genitalium and C trachomatis groups, 27% versus 73% and 40% respectively. This presents a serious dilemma in daily clinical work. Is the inflammation caused by a bacterial infection, and are these patients in need of treatment? Most C trachomatis infected men are asymptomatic and they should therefore not have been treated if both symptoms and microscopic signs were set as criteria for treatment. The present study was limited and therefore our findings have to be verified in future studies. There is evidence that M genitalium may cause endometritis, PID, and sexually acquired reactive arthritis. The most widely accepted and used criterion for urethritis is >4 PMNL/HPF which was established in the late 1970s. The result of this study calls for a reconsideration of this criterion, since none of the patients with C trachomatis or M genitalium infection had fewer than 10 PMNL/HPF. Only among the men with NGU was “grey zone urethritis” found—in 29 patients. Obviously, the interpretation of the smear depends on several variables: the instrument for sampling, the standard of the microscope and how it is used.

Key messages

- Mycoplasma genitalium is an important and frequent cause of male urethritis and this cross sectional study indicates that M genitalium even more often than C trachomatis gives symptoms of urethritis among male STD attendees.
- There are no significant differences in microscopic signs between both bacteria.
- Partners of men infected with M genitalium were most often infected with M genitalium and to the same extent partners of men infected with C trachomatis were infected with C trachomatis (67%) supporting the role of the bacteria as pathogens and sexually transmitted infections.
- More studies are needed to examine the diagnostic tools for determining the clinically relevant definition of urethritis.

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Mycoplasma genitalium infection in men as well as in women. Studies are needed to determine the potential sequelae of large proportion (two thirds) of their sexual partners. More and C Medical Centre Research Foundation. The research ethic committee of

REFERENCES

N gonorrhoeae collected all data, and wrote the first draft of the manuscript; HF was responsible for the M genitalium responsible for the to the design of the study and analysis of the data; JSJ was tests and provided major contribu-

CONTRIBUTORS

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the experience of the clinician, and the interpretation of discharge and smears. This subjective procedure can never be strictly scientifically standardised. We believe that more studies are required to examine the diagnostic tools for determining the clinically relevant definition of urethritis.

In summary, M genitalium was strongly associated with symptomatic urethritis and men infected with both C trachomatis and M genitalium transmitted the infections to a large proportion (two thirds) of their sexual partners. More studies are needed to determine the potential sequelae of M genitalium infection in men as well as in women.

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