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

L Falk, H Fredlund, J S Jensen

Methods: A cross sectional study among STD clinic attendees in Örebro, Sweden. Attendees were examined for microscopic urethritis and first void urine (FVU) was tested for *M genitalium* and *C trachomatis*.

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. All positive results were confirmed by a PCR detecting the MgPa adhesin gene. 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 gonorrhoea, 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. 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 NGU 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 partners 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>Symptomatic (%)</th>
<th>Non-symptomatic (%)</th>
<th>Relative risk (RR)</th>
<th>Confidence interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethral smear</td>
<td>Symptoms of urethritis</td>
<td>Number of partners</td>
<td>STI history (%)</td>
</tr>
<tr>
<td>≥5</td>
<td>5–10</td>
<td>&gt;10</td>
<td>ND</td>
</tr>
<tr>
<td>C trachomatis</td>
<td>5–10</td>
<td>&gt;10</td>
<td>ND</td>
</tr>
<tr>
<td>M genitalium</td>
<td>5–10</td>
<td>&gt;10</td>
<td>ND</td>
</tr>
<tr>
<td>Mg and Ct</td>
<td>5–10</td>
<td>&gt;10</td>
<td>ND</td>
</tr>
<tr>
<td>Urethritis, negative</td>
<td>5–10</td>
<td>&gt;10</td>
<td>ND</td>
</tr>
</tbody>
</table>

*One (homosexual) man had a gonococcal urethritis.†Data were missing from one patient.

ND = microscopic examination not done; Ng = Neisseria gonorrhoeae; Ct = Chlamydia trachomatis; Mg = Mycoplasma genitalium; NCNGU = non-chlamydial non-gonococcal urethritis.
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 of the 47 examined partners of C trachomatis positive men were examined; 26 (67%) of those partners were C trachomatis positive and two (5%) were M genitalium positive.

## DISCUSSION

In this cross section 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. 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. In a recent Swedish report, 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 years earlier than those in the present study, a C trachomatis prevalence of 19% and an M genitalium prevalence of 7% were found.

<table>
<thead>
<tr>
<th>Discharge and symptoms</th>
<th>Ct (n = 57) No (%)</th>
<th>Mg (n = 30) No (%)</th>
<th>Mg and Ct (n = 4) No (%)</th>
<th>NSU (n = 180) No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethritis</td>
<td>+16 (29)</td>
<td>15 (50)</td>
<td>3 (75)</td>
<td>24 (13)</td>
</tr>
<tr>
<td></td>
<td>–0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Discharge but no symptoms</td>
<td>+21 (37)</td>
<td>4 (13)</td>
<td>1 (25)</td>
<td>40 (22)</td>
</tr>
<tr>
<td></td>
<td>–1 (2)</td>
<td>2 (7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Symptoms but no discharge</td>
<td>+3 (5)</td>
<td>3 (10)</td>
<td>0</td>
<td>13 (7)</td>
</tr>
<tr>
<td></td>
<td>–0</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Symptoms, discharge not noted</td>
<td>+2 (3)</td>
<td>3 (10)</td>
<td>0</td>
<td>12 (7)</td>
</tr>
<tr>
<td></td>
<td>–1 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No symptoms, discharge not noted</td>
<td>+2 (3)</td>
<td>0</td>
<td>0</td>
<td>16 (9)</td>
</tr>
<tr>
<td></td>
<td>–0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No discharge or symptoms</td>
<td>+8 (14)</td>
<td>2 (7)</td>
<td>0</td>
<td>75 (42)</td>
</tr>
<tr>
<td></td>
<td>–2 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Data lacking</td>
<td>+1 (2)</td>
<td>0</td>
<td>0</td>
<td>0</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>

**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).
Infection, but had negative test results. This might explain because of one of their female partners had C. trachomatis clinic. This might explain the rather low attendance rate does not exist, often only current partners attended the STD clinic. Since legislation regarding C. trachomatis might explain the rather low number of partners per man partner notification, but partners can attend any clinic, which is a notifiable infection including mandatory examination of FVU 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 NSU 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. Most published studies have focused on symptomatic 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 NSU were M. genitalium positive. C. trachomatis is a notifiable infection including mandatory partner notification, but partners can attend any clinic, which might explain the rather low number of partners per man infected with C. trachomatis (39/61) who were examined at our STD clinic. Since legislation regarding M. genitalium infection does not exist, often only current partners attended the STD clinic. This might explain the rather low attendance rate among partners. For NSU cases some patients attended because of one of their female partners had C. trachomatis infection, but had negative test results. This might explain the high prevalence of C. trachomatis among the partners of men with NSU. The men with chlamydial infection reported a higher number of recent partners than the other groups, including the M. genitalium positive group. Such a difference has not been demonstrated in other studies. M. genitalium positive men were older than those with C. trachomatis infection. Whether the M. genitalium positive men have carried the infection for a longer period of time is not known. 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 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. Horner and co-workers have suggested that treatment guidelines should be revised, and propose that asymptomatic men without discharge should not receive antibiotic treatment. In the current study we attempted to set more objective criteria for the measurement of discharge, and experienced clinicians examined most patients (approximately >85%). The high rate of patients without discharge in combination with lack of symptoms in the NSU group (49%) and the corresponding high rate of discharge and symptoms in C. trachomatis and M. genitalium infected men support the proposal by Horner et al., although some patients would have been missed at the examination. In these patients, treatment would have been delayed with the risk for further transmission of the infections and possible risk for sequelae.

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 NSU 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.
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.

ACKNOWLEDGEMENTS

We thank the staff at the Örebro STD clinic and, especially, Maritha Holmquist. Birthe Dohn at Statens Serum Institut provided excellent technical assistance. We also thank Anders Magnuson for statistical computations.

CONTRIBUTORS

LP initiated the study, examined and sampled most of the patients, collected all data, and wrote the first draft of the manuscript; HF was responsible for the N. gonorrhoeae and C. trachomatis tests, contributed to the design of the study and analysis of the data; JSJ was responsible for the M. genitalium tests and provided major contributions to the design of the study and analysis of the data.

Authors’ affiliations

1. Falk, Department of Dermatology and Venereology, Örebro University Hospital, Sweden
2. Fredlund, Department of Clinical Microbiology and Immunology, Örebro University Hospital, Sweden
3. S. Jensen, Mycoplasma Laboratory, Statens Serum Institut, Copenhagen, Denmark

Funded by the Research Committee of Örebro County Council, Örebro Medical Centre Research Foundation. The research ethic committee of Örebro County Council approved the study 1 November 1999.

Conflict of interest: None declared.

REFERENCES