Sexually Transmitted Infections

Editorial

The role of *Mycoplasma genitalium* in non-gonococcal urethritis

Mycoplasmas are the smallest prokaryotes capable of self replication. *Mycoplasma genitalium*, one of 14 mycoplasmas of human origin known so far, was isolated originally from the urethra of two of 13 men with non-gonococcal urethritis (NGU) attending the genitourinary medicine (GUM) clinic at St Mary's Hospital, Paddington, London, in 1980.[1 2] By electron microscopy, it was found to be flask shaped, the narrow terminal portion being instrumental in its attachment to eukaryotic cell surfaces.[1 2] Later, the genome of *M genitalium*, the smallest known for a self replicating micro-organism, 580 kb, was the first of any micro-organism to be fully sequenced.[3] The small genome size probably accounts, as least in part, for the fastidious growth requirements of *M genitalium*. Indeed, despite the original success of isolating this mycoplasma from the urogenital tract and the subsequent recovery of five strains from the respiratory tract,[4] further attempts to isolate it from the urogenital tract failed and it was not until the application of a molecular approach that progress was made. It was the advent of polymerase chain reaction (PCR) technology in the late 1980s that saw the development of sensitive and specific PCR assays for *M genitalium*, initially by two groups of workers and later by others, each group amplifying different fragments of the attachment protein designated MgPa.[5] This has enabled *M genitalium* to be detected reliably in urogenital specimens.

In the past 20 years there have been 19 studies,[1 6–23] undertaken largely in men attending GUM clinics, in 17 of which the relation of the mycoplasma to acute NGU has been examined by comparison with controls. As shown in table 1, in the majority of studies, *M genitalium* has been detected significantly more often in the urethra of men with acute NGU than in those without NGU; overall, in 19.8% of men with acute NGU and in 8.8% of those without NGU (p <0.00001; OR 2.84, 95% CI 2.24–3.62). It is not possible in all of the aforementioned studies to assess the relation of *M genitalium* to chlamydia negative NGU, but in 10 studies in which this is assessable (table 1), the mycoplasma has been found significantly more often in the urethra of men with chlamydia negative disease than in

Table 1 Occurrence of M genitalium in men with or without urethritis

	Number of men with urethritis who are M genitalium			*Number of men without urethritis who are M genitalium*			
Investigators (ref)	+	−	% +	+	−	% +	*Statistical values*
Studies of non-gonococcal disease							
Tully *et al* 1981 (1)	2	11	15.4				
Taylor-Robinson *et al* 1985 (6)	7	15	32.0	2	18	10.0	p=0.135; OR 4.2 (0.64–45.8)
Hooton *et al* 1988 (7)	7	54	11.5	10	74	11.9	p=0.94; OR 0.96 (0.29–3.00)
Taylor-Robinson *et al* 1993 (8)	9	9	50.0	1	6	14.3	p=0.18; OR 6.0 (0.51–306)
Jensen *et al* 1993 (9)	13	35	27.0	4	43	8.5	p=0.018; OR 3.99 (1.09–18.07)
Horner *et al* 1993 (10)	31	79	28.2	4	55	6.8	p=0.001; OR 5.4 (1.75–22.05)
de Barbeyrac *et al* 1993 (11)	8	40	16.7				
Deguchi *et al* 1995 (12)	17	97	14.9	0	28	0	p=0.025
Janier *et al* 1995 (13)	29	71	29.0	8	86	8.5	p=0.0003; OR 4.39 (1.8–11.75)
Lackey *et al* 1995 (14)	20	44	31.2	11	51	17.7	p=0.08; OR 2.1 (0.85–5.31)
Busolo *et al* 1997 (15)	6	46	11.5	0	44	0	p=0.03
Maeda *et al* 1998 (16)	10	66	13.1	0	21	0	p=0.11
Bjornelius *et al* 2000 (17)	13	37	26.0	5	46	9.8	p=0.03; OR 3.23 (0.96–12.52)
Gambini *et al* 2000 (18)	52	126	29.2	1	22	4.3	p=0.0011; OR 9.08 (1.38–382)
Johannisson *et al* 2000 (19)	17	98	14.8	1	117	0.8	p=0.00007; OR 20.3 (3.05–855)
Keane *et al* 2000 (20)	12	24	33.3	1	10	9.1	p=0.147; OR 5.0 (0.57–235)
Totten *et al* 2001 (21)	27	94	22.3	5	112	4.0	p=0.00005; OR 6.43 (2.3–22.1)
Pepin *et al* 2001 (22)	66	593	10.0	30	309	8.8	p=0.55; OR 1.15 (0.71–1.85)
Morency *et al* 2001 (23)	53	74	41.7	15	85	15.0	p=0.00001; OR 4.06 (2.02–8.23)
Total	399	1613	19.8	98	1127	8.8	p=<0.00001; OR 2.84 (2.24–3.62)
Studies of non-chlamydial non-gonococcal disease							
Hooton *et al* 1988 (7)	4	27	13.0	10	74	13.5	p=1.00; OR 1.1 (0.23–4.21)
Jensen *et al* 1993 (9)	12	22	54.5	4	39	10.2	p=0.005; OR 5.32 (1.36–24.85)
Horner *et al* 1993 (10)	16	42	27.6	3	40	7.5	p=0.008; OR 5.08 (1.29–28.8)
Deguchi *et al* 1995 (12)	14	62	18.4	0	27	0	p=0.018
Maeda *et al* 1998 (16)	9	25	26.5	0	21	0	p=0.009
Bjornelius *et al* 2000 (17)	13	23	36.1	5	46	10.9	p=0.007; OR 5.2 (1.48–20.57)
Gambini *et al* 2000 (18)	26	84	23.6	1	19	5.0	p=0.07; OR 5.88 (0.84–25.4)
Johannisson *et al* 2000 (19)	16	58	21.6	1	117	0.8	p=0.00001; OR 32.3 (4.72–136.5)
Keane *et al* 2000 (20)	10	12	45.5	1	10	9.1	p=0.054; OR 8.33 (0.85–397)
Totten *et al* 2001 (21)	24	61	28.2	5	108	4.4	p=0.00001; OR 8.5 (2.95–29.7)
Pepin *et al* 2001 (22)	37	172	17.7				
Total	181	588	23.5	30	501	5.6	p=<0.00001; OR 5.14 (3.38–7.87)

those without disease; overall, in 23.5% of men with acute chlamydia negative NGU and in 5.6% of those without disease (p <0.00001; OR 5.14, 95% CI 3.38–7.87). Thus, *M genitalium* behaves largely independently of *Chlamydia trachomatis* but seems to occur about as often as the latter. In one study[24] it was clear that *M genitalium* and *C trachomatis* were associated significantly with acute symptomatic NGU, but not with asymptomatic NGU. This is not a differentiation that has been made in most of the studies and may account for the failure of one group of investigators[7] to associate *M genitalium* with acute NGU. In one study,[6] an antibody response to *M genitalium* was seen in three of 10 men with acute NGU from whom a second serum sample was obtained 14 days after the first. Information on the association of *M genitalium* with chronic NGU is sparse. However, in two studies[7 24] there was a relation; in one[24] the continued presence of *M genitalium* was associated with chronic disease.

In summary, therefore, there is a very strong and significant association of *M genitalium* with acute NGU, sufficient to believe that the mycoplasma is a cause, and a strong suggestion that it is responsible for some cases of chronic disease. It could be argued, nevertheless, that the mycoplasma is merely an invader of damaged tissue caused by some other micro-organism. Causality, however, is supported by the fact that *M genitalium* behaves largely independently of *C trachomatis*, that it has many features in common with those of *M pneumoniae*, a known pathogenic mycoplasma, and by the changes following experimental inoculation of the urogenital tract of subhuman primates. These were demonstrated best by inoculation of the urethra of male chimpanzees[25 26] in which an acute inflammatory response dominated by polymorphonuclear leucocytes occurred at this site in most animals, accompanied by an antibody response.

So what of the future? Larger numbers of *M genitalium* organisms might be expected in symptomatic than in asymptomatic disease. This has not been investigated and would need the use of a quantitative PCR assay. It is noteworthy that similar information for *C trachomatis* is sparse. There are serological data[27] and the results of a small study[20] involving female partners of men with acute NGU which suggest, as might be expected, that *M genitalium* is sexually transmitted. However, ideally, this should be supported by a larger study of partners.

Information on the occurrence of the mycoplasma in men with urethritis in developing countries is beginning to accrue,[22 23 28] but more is needed; *Neisseria gonorrhoeae* often dominates and the aetiology of NGU seems to be different from that in many developed countries. In one study,[22] in west Africa, *M genitalium* was associated with NGU, particularly in *Trichomonas vaginalis* negative patients. These aspects, the influence of race on the association of *M genitalium* with NGU, the possibility of an association with oral sex and with NGU in homosexual men, need to be investigated further. So does the possibility of *M genitalium* causing urethritis and upper genital tract disease in women. Preliminary evidence for the involvement of the mycoplasma in cervicitis[29] and pelvic inflammatory disease[30] should foster such an effort.

The antibiotic susceptibility profile of *M genitalium* is similar to that of *M pneumoniae*,[31] the tetracyclines, erythromycin and azithromycin, and the fluoroquinolones being most active; in other words, in vitro *M genitalium* responds in a way akin to that of *C trachomatis*. However, antibiotics only suppress the growth of mycoplasmas, the help of a functioning immune system being required to kill them.[32] Complete antibiotic resistance could also occur but this is not easily assessable in a climate of molecular technology which does not lead to culturable isolates; thus, the ability to obtain isolates through the use of a cell culture system,[33] although difficult and not routine, is to be encouraged. These aspects of antibiotic susceptibility, added to the fact that *M genitalium* has the ability to invade epithelial cells[34] and, perhaps, become protected, might account for it sometimes continuing to be found in the urethra following what would seem to be adequate treatment of acute NGU. Suffice to say, the most appropriate treatment of *M genitalium* positive acute and chronic NGU needs attention in larger investigations. Apart from NGU itself, the possible role of *M genitalium* in some of the sequelae of acute NGU should be considered. The impetus to do this exists in sexually acquired reactive arthritis in which *M genitalium* has been detected already in the knee joint of such a patient[35]; its possible involvement in epididymo-orchitis and infertility is also wide open to investigation.

- *M genitalium* is strongly associated with acute NGU, largely independent of *C trachomatis*, and there is good evidence that it is a cause
- *M genitalium* may be associated causally with chronic NGU
- The involvement of *M genitalium* in genital tract disease of women needs further investigation
- Progress in studying *M genitalium* should be improved by commercial diagnostic input

There is a suggestion from limited serological data[36] that *M genitalium* infection might, as in the case of *C trachomatis*, enhance the transmission of the human immunodeficiency virus. This proposition and the foregoing evidence for *M genitalium* behaving as a pathogen in the male urogenital tract and the possibility of its involvement in genital tract disease in women should be sufficient to foster commercial diagnostic input. The availability of a commercial PCR or ligase chain reaction (LCR) assay would not only introduce greater comparability between studies but take studies of *M genitalium* outside the few centres that currently have the necessary technology.

DAVID TAYLOR-ROBINSON
Department of Medicine (Medicine A), Imperial College School of Medicine, St Mary's Hospital, Paddington, London W2 1NY, UK

PATRICK J HORNER
Department of Genitourinary Medicine, The Milne Centre for Sexual Health, Bristol Royal Infirmary, Bristol BS2 8HW, UK

Correspondence to: Professor D Taylor-Robinson

1 Tully JG, Taylor-Robinson D, Cole RM, *et al.* A newly discovered mycoplasma in the human urogenital tract. *Lancet* 1981;1:1288–91.
2 Taylor-Robinson D. The history and role of Mycoplasma genitalium in sexually transmitted diseases. *Genitourin Med* 1995;**71**:1–8.
3 Fraser CM, Gocayne JD, White O, *et al.* The minimal gene complement of Mycoplasma genitalium. *Science* 1995;**270**:397–403.
4 Baseman JB, Dallo SF, Tully JG, *et al.* Isolation and characterization of Mycoplasma genitalium strains from the human respiratory tract. *J Clin Microbiol* 1988;**26**:2266–9.
5 Taylor-Robinson D, Gilroy CB, Jensen JS. The biology of Mycoplasma genitalium. *Venereology* 2000;**13**:119–27.
6 Taylor-Robinson D, Furr PM, Hanna NF. Microbiological and serological study of non-gonococcal urethritis with special reference to Mycoplasma genitalium. *Genitourin Med* 1985;**61**:319–24.
7 Hooton TM, Roberts MC, Roberts PL, *et al.* Prevalence of Mycoplasma genitalium determined by DNA probe in men with urethritis. *Lancet* 1988; **1**:266–7.
8 Taylor-Robinson D, Gilroy CB, Hay PE, *et al.* Occurrence of Mycoplasma genitalium in different populations and its clinical significance. *Clin Infect Dis* 1993;**17**(Suppl 1):66–8.
9 Jensen JS, Orsum R, Dohn B, *et al.* Mycoplasma genitalium: a cause for male urethritis? *Genitourin Med* 1993;**69**:265–9.
10 Horner PJ, Gilroy CB, Thomas BJ, *et al.* Association of Mycoplasma genitalium with acute non-gonococcal urethritis. *Lancet* 1993;**342**:582–5.
11 de Barbeyrac B, Bernet-Poggi C, Febrer F, *et al.* Detection of Mycoplasma pneumoniae and Mycoplasma genitalium in clinical samples by polymerase chain reaction. *Clin Infect Dis* 1993;**17**(Suppl 1):83–9.

12 Deguchi T, Komeda H, Yasuda M, *et al.* Mycoplasma genitalium in non-gonococcal urethritis. *Int J STD AIDS* 1995;**6**:144–5.
13 Janier M, Lassau F, Casin I, *et al.* Male urethritis with and without discharge: a clinical and microbiological study. *Sex Transm Dis* 1995;**22**:244–52.
14 Lackey PC, Ennis DM, Cassell GH, *et al.* The etiology of nongonococcal urethritis (abstract 238). *Clin Infect Dis* 1995;**21**:759.
15 Busolo R, Camposampiero D, Bordignon G, *et al.* Detection of Mycoplasma genitalium and Chlamydia trachomatis DNAs in male patients with urethritis using the polymerase chain reaction. *Microbiologica* 1997;**20**:325–32.
16 Maeda S-I, Tamaki M, Nakano M, *et al.* Detection of Mycoplasma genitalium in patients with urethritis. *J Urol* 1998;**159**:405–7.
17 Bjornelius E, Lidbrink P, Jensen JS. Mycoplasma genitalium in non-gonococcal urethritis—a study in Swedish male STD patients. *Int J STD AIDS* 2000;**11**:292–6.
18 Gambini D, Decleva I, Lupica L, *et al.* Mycoplasma genitalium in males with nongonococcal urethritis. Prevalence and clinical efficacy of eradication. *Sex Transm Dis* 2000;**27**:226–9.
19 Johannisson G, Enstrom Y, Lowhagen G-B, *et al.* Occurrence and treatment of Mycoplasma genitalium in patients visiting STD clinics in Sweden. *Int J STD AIDS* 2000;**11**:324–6.
20 Keane FEA, Thomas BJ, Gilroy CB, *et al.* The association of Chlamydia trachomatis and Mycoplasma genitalium with non-gonococcal urethritis: observations on heterosexual men and their female partners. *Int J STD AIDS* 2000;**11**:435–9.
21 Totten PA, Schwartz MA, Sjostrom KE, *et al.* Association of Mycoplasma genitalium with nongonococcal urethritis in heterosexual men. *J Infect Dis* 2001;**183**:269–76.
22 Pepin J, Sobela F, Deslandes S, *et al.* Etiology of urethral discharge in West Africa: the role of Mycoplasma genitalium and Trichomonas vaginalis. *Bull Wld Hlth Organ* 2001;**79**:118–26.
23 Morency P, Dubois MJ, Gresenguet G, *et al.* Aetiology of urethral discharge in Bangui, Central African Republic. *Sex Transm Inf* 2001;**77**:125–9.
24 Horner P, Thomas B, Gilroy CB, *et al.* The role of Mycoplasma genitalium and Ureaplasma urealyticum in acute and chronic non-gonococcal urethritis. *Clin Infect Dis* 2001;**32**:995–1003.
25 Taylor-Robinson D, Tully JG, Barile MF. Urethral infection in male chimpanzees produced experimentally by Mycoplasma genitalium. *Br J Exp Pathol* 1985;**66**:95–101.
26 Tully JG, Taylor-Robinson D, Rose DL, *et al.* Urogenital challenge of primate species with Mycoplasma genitalium and characteristics of infection induced in chimpanzees. *J Infect Dis* 1986;**153**:1046–54.
27 Wang RYH, Grandinetti T, Shih JW-K, *et al.* Mycoplasma genitalium infection and host antibody immune response in patients infected by HIV, patients attending STD clinics and in healthy blood donors. *FEMS Immunol Med Microbiol* 1997;**19**:237–45.
28 Chandeying V, Skov S, Duramad P, *et al.* The prevalence of urethral infections amongst asymptomatic young men in Hat Yai, southern Thailand. *Int J STD AIDS* 2000;**11**:402–5.
29 Uno M, Deguchi T, Komeda H, *et al.* Mycoplasma genitalium in the cervices of Japanese women. *Sex Transm Dis* 1997;**24**:284–6.
30 Moller BR, Taylor-Robinson D, Furr PM. Serological evidence implicating Mycoplasma genitalium in pelvic inflammatory disease. *Lancet* 1984;i:1102–3.
31 Taylor-Robinson D, Bebear C. Antibiotic susceptibilities of mycoplasmas and treatment of mycoplasmal infections. *J Antimicrob Chemother* 1997;**40**:622–30.
32 Taylor-Robinson D, Furr PM. Observations on the antibiotic treatment of experimentally induced mycoplasmal infections in mice. *J Antimicrob Chemother* 2000;**45**:903–7.
33 Jensen JS, Hansen HT, Lind K. Isolation of Mycoplasma genitalium strains from the male urethra. *J Clin Microbiol* 1996;**34**:286–91.
34 Jensen JS, Blom J, Lind K. Intracellular location of Mycoplasma genitalium in cultured Vero cells as demonstrated by electron microscopy. *Int J Exp Pathol* 1994;**75**:91–8.
35 Taylor-Robinson D, Gilroy CB, Horowitz S, *et al.* Mycoplasma genitalium in the joints of two patients with arthritis.*Eur J Clin Microbiol Infect Dis* 1994;**13**:1066–9.
36 Perez G, Skurnick JH, Denny TN, *et al.* Herpes simplex type II and Mycoplasma genitalium as risk factors of heterosexual HIV transmission: report from the Heterosexual HIV Transmission Study. *Int J Infect Dis* 1998;**3**:5–11.