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.

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