The Clinical Role of *Mycoplasma genitalium*

Reflections on an Emerging STI

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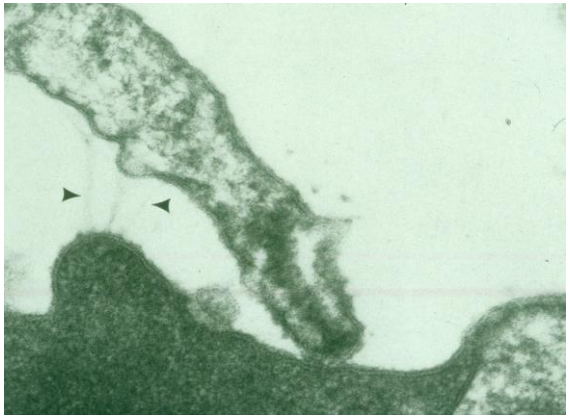
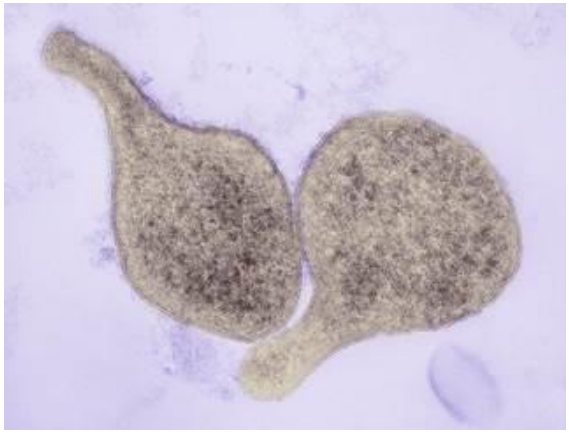
Disclosures

- **GSK**: External Advisory Support for Gepotidacin development for treatment of gonorrhoea (current)
- **GARDP-Entasis**: External Advisory Support for Zoliflodacin development treatment of gonorrhoea (2017-2019)
- **SpeedX**: ResistancePlus™ MG assay research samples, video production

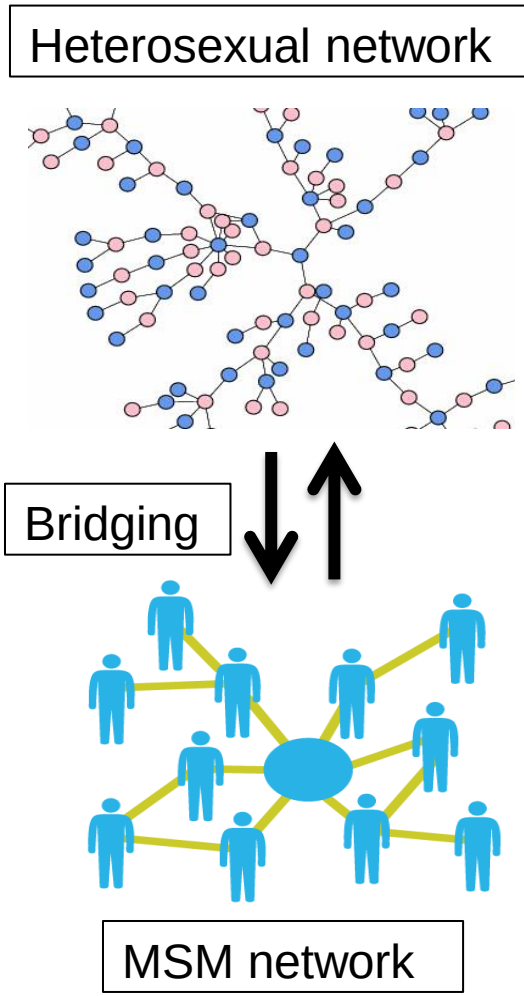
Mycoplasma genitalium





- Small 580 kb genome = fastidious bacterium
- 140 kDa Mg surface adhesin (Mg Pa)
- Can grow intracellularly and extracellularly
- Difficult to culture *in vitro* – impeded research
- Important role of molecular diagnostics:
  - enhanced our understanding of this pathogen's role
  - can now simultaneously detect the bacterium and its susceptibility to antibiotics

Evidence to Support Sexual Transmission



- High concordance rate of *M. genitalium* infection among sexual partners
- Concordant *M. genitalium* multi-locus genotypes reported among 87% of co-infected sexual partners
- Increased prevalence in high risk groups for STIs
- Association with number of sex partners
- Estimates for chlamydial transmission from men to women per episode of vaginal coitus based on observational studies and range from 10% to 39.5%
- Transmission for *M. genitalium* likely to be lower based on lower bacterial loads

McGowin & Anderson-Smits, PLoS Pathogens 2011;7:e10013224; Ma *et al.,* BMC Microbiol. 2008;8:130; Horner & Martin, J. Infect. Dis. 2017;216(S2):S396–405

Population-based Survey Studies

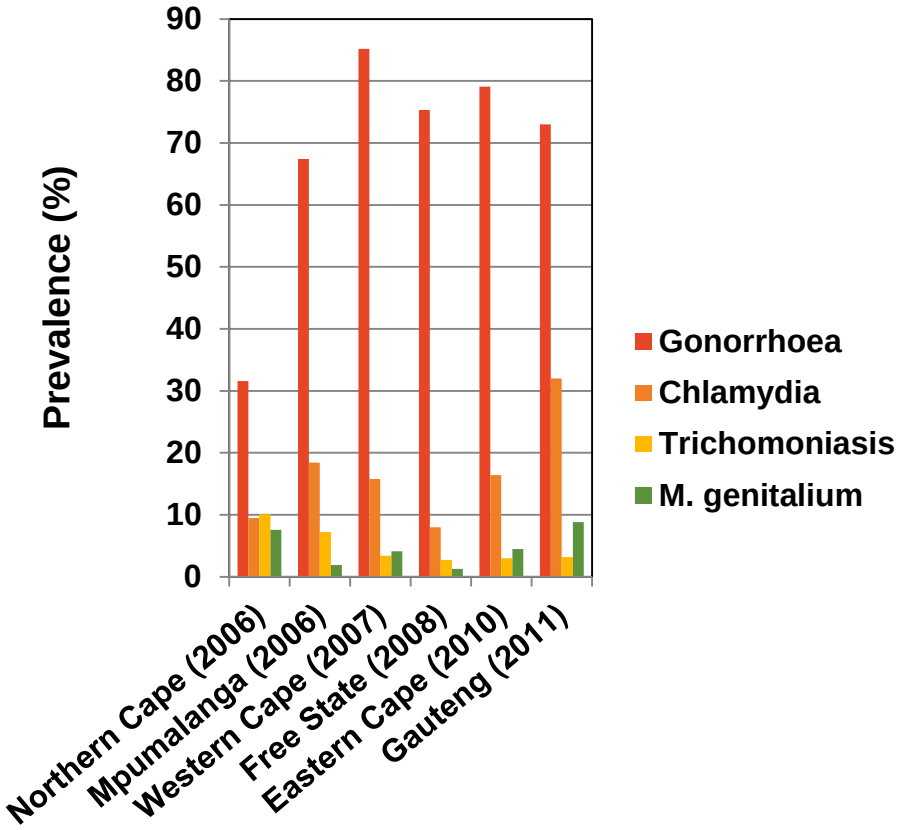
- Wave III, National Longitudinal Study of Adolescent Health, USA
  - Young men (n=1,218) and women (n=1,714) aged 18-27 yrs enrolled in 2001-2002
  - *M. genitalium* prevalence: 1.1% in men, 0.8% in women
  - Strongly associated with increasing numbers of sexual partners and black race
- Third National Survey of Sexual Attitudes and Lifestyles (NATSAL-3), UK
  - Probability sample survey (2010-2012)
  - Sexually experienced men and women between aged 16-44 (n=4,507, no gender split)
  - *M. genitalium* prevalence: 1.2% in men, 1.3% in women
  - Risk factors: black race, numbers of total & new sex partners, unsafe sexual practices
- Population-based survey, Aarhus County, Denmark
  - Survey undertaken in 1997-1998
  - Population: young adults (731 males, 921 females) aged 21-24 yrs
  - *M. genitalium* prevalence: 1.1% in men, 2.3% in women
  - Detection associated with increasing number of sexual partners

Manhart *et al*., Am. J. Public Health 2007;97:1118–1125;
Sonnenberg P *et al*., Int. J. Epidemiol. 2015;44:1982–1994;
Andersen B *et al*., Sex. Transm. Infect. 2007;83:237–241

Mycoplasma genitalium in Men

Relative Importance of *M. genitalium* as a Cause of Urethritis

- Prevalence of *M. genitalium* cases varies geographically and by socio-economic status
- *Neisseria gonorrhoeae* - most common cause of urethritis in most developing regions of the world
- *Chlamydia trachomatis* - most common pathogen associated with NGU
- *Mycoplasma genitalium* - main organism associated with persistent NGU following first-line treatment



Lewis *et al.*, Unpublished surveillance data from six aetiological surveys among men attending primary health care clinics with urethral discharge

Survey Studies in MSM

- MSM have higher rates of *M. genitalium, N. gonorrhoeae* and *C. trachomatis* infections than are observed in population-based surveys
  - Prevalence highest at ano-rectal sites for all three bacteria
  - Oro-pharyngeal *M. genitalium* uncommon

	MSM attending six SOPVs, Melbourne, 2001-2002 (N = 521, 24% response rate)				MSM attending Western Sydney Sexual Health Centre, 2017 (N = 508, consecutive)			
Site of Infection	**Overall**	Anal	Urethral	Throat	**Overall**	Anal	Urethral	Throat
M. genitalium	**2.1%**	1.6%	0.6%	0.0%	**13.4%**	4.7%	8.9%	0.0%
C. trachomatis	**8.1%**	6.2%	1.8%	0.6%	**12.8%**	9.1%	4.1%	2.0%
N. gonorrhoeae	**4.8%**	2.2%	0.2%	2.5%	**12.2%**	6.5%	1.6%	8.5%

NGU than in heterosexual men – more NGU cases in MSM are idiopathic

- *M. genitalium* is reportedly more prevalent in men with HIV infection

Bradshaw *et al*., Sex. Transm. Infect. 2009;85:432–435; Couldwell *et al*., Sex. Transm. Infect. 2018;94:406-410
Soni S *et al*., Sex. Transm. Infect. 2010; 86:21–4

M. genitalium and Non-Gonococcal Urethritis

TABLE 2. Fulfillment of criteria required to determine whether *M. genitalium* or *C. trachomatis* causes NGU[a]

Criterion	Fulfillment of criterion for:	
	M. genitalium	*C. trachomatis*
Detection significantly more often than in controls for:		
Acute NGU	++++	++++
Chronic NGU	+++	+
Homosexual NGU	+++	+++
Larger no. of organisms than in controls	+++	++
Antibody titers and responses more often than in controls	+	++
Effective microbiological and clinical response to therapy	++++	++++
Reproduction of disease in inoculated subhuman primates	++++	+++
Reproduction of disease in inoculated human volunteers	ND	ND
Wide geographic involvement	++++	++++
Disease prevented by natural or exptl immunity	ND	+

[a] ++++, excellent; +++, good; ++, moderate; +, poor; ND, not determined. The second to eighth criteria relate mainly to acute NGU.

- *M. genitalium* was first isolated from urethral samples of two men with NGU
- Strong + consistent associations with NGU
- Higher bacterial load in symptomatics
- Pro-inflammatory cytokines released during infection – biologically plausible
- Taylor-Robinson & Jensen reviewed literature and reported:
  - *M. genitalium* detected in 15%–25% of men with symptomatic NGU
  - *M. genitalium* detected in 5%–10% of those without disease
  - Association with NGU: OR 5.5; 95%CI, 4.3–7.0

Taylor-Robinson & Jensen, Clin. Microbiol. Rev 2011;24:498–514

M. genitalium and other Conditions in Men - I

1. PROCTITIS

- Bissessor *et al*. reported 12% *M. genitalium* prevalence among 154 MSM with proctitis (c.f. *N. gonorrhoeae*, 25%; chlamydia, 19%; HSV, 18%)
- Rectal *M. genitalium* bacterial load was significantly higher in men with proctitis vs. asymptomatic men.
- We lack treatment effectiveness studies for *M. genitalium* proctitis

2. EPIDIDYMO-ORCHITIS

- *M. genitalium* may be a cause of acute epididymitis in some patients – however, still not proven and requires further study
- Ito *et al*. reported *M. genitalium* was detected in 8% of 56 cases of epididymitis in men <40 years old (c.f. *C. trachomatis* in 50%)

Bissessor *et al*., Clin. Microbiol. Infect. 2016;22:260–265;
Ito *et al*., Int. J. Urol. 2012;19:234–238

M. genitalium and other Conditions in Men - II

3. PROSTATITIS

- Sparse evidence that *M. genitalium* is associated with chronic prostatitis
  - *M. genitalium* not detected by PCR in prostatic biopsy specimens from 50 patients with chronic abacterial prostatitis
  - *M. genitalium* detected by PCR in prostatic biopsy specimens from 5/135 (4%) men
  - *M. genitalium* detected in semen from 2/18 men with chronic abacterial inflammatory prostatitis, compared to 0/20 controls (non-significant)
  - Mo *et al.* evaluated 235 Chinese men with prostatitis and 152 asymptomatic STI clinic controls who underwent specimen collection procedures including prostate massage – the *M. genitalium* PCR assay was positive in 10% men with clinical prostatitis and 3% of controls (p=0.005)

4. BALANOPOSTHITIS

- *M. genitalium* associated with balanoposthitis in 114 men with acute NGU
- Further studies required

Doble *et al*., Br. J. Urol. 1989;64:297–301; Krieger *et al*., J. Clin. Microbiol. 1996;34:3120–3128; Mandar *et al*., Scand. J. Urol. Nephrol. 2005;39:479–482; Mo *et al*., Sex. Health 2016;13:474-479; Horner & Taylor-Robinson, Sex. Transm. Infect. 2011; 87:38–40

Mycoplasma genitalium in Women

Vaginal Discharge

- *M. genitalium* is not thought to cause vaginal discharge
  - positive vaginal swab NAATs likely reflect endocervical infections
  - no association with other organisms causing vaginitis (*T. vaginalis, Candida* spp.)
  - relationship with bacterial vaginosis (BV) inconsistent between studies

Female Urethritis

- Most studies have been conducted in Scandinavia – data lacking elsewhere
- Moi *et al*. reported a significant association between *M. genitalium* and microscopic urethritis in one large Scandinavian study BUT three other Scandinavian studies failed to show any significant associations
- Need to exclude patients with concomitant cervicitis as inflammation at other sites may cause urethral contamination and false positive diagnosis of urethritis

McGowin & Anderson-Smits, PLoS Pathogens 2011;7:e10013224;
Wiesenfeld & Manhart, J. Infect. Dis. 2017;216(S2):S389-395

Mucopurulent Cervicitis

- Characterised by clinical signs (mucopulent discharge, friability at the cervical os) or by elevated PMNLs in endocervical smears
- Research hampered by the lack of a generally-accepted case definition
- *M. genitalium* has been positively associated with microscopically-proven cervicitis but, only in some studies, with cervical discharge
- Controlling for concomitant chlamydial infection in several studies found significant associations between *M. genitalium* and cervicitis
- Lack of studies controlling for the effect of concomitant gonorrhoea
- The magnitude of the increased risk of cervicitis is comparable to that due to *C. trachomatis* and *N. gonorrhoeae*

McGowin & Anderson-Smits, PLoS Pathogens 2011;7:e10013224;
Manhart *et al.,* J. Infect. Dis. 2008;197:733-736

Pelvic Inflammatory Disease

- *M. genitalium* serologically linked to PID in 1984 and later detected by NAATs in both endometrial/fallopian tube samples from women with acute PID
- Several NAAT-based studies have found a +ve association between *M. genitalium* and clinically diagnosed PID in geographically diverse populations
- *M. genitalium* has been significantly associated with endometritis in a small number of studies where the endometrium was sampled
- Studies are hampered by the sub-optimal specificity of some of the clinical signs used to diagnose PID and the recognized lack of correlation with laparoscopic findings
- No clear trend observed when comparing studies that excluded co-infections with *C. trachomatis* or controlled for co-infections in multivariate analyses

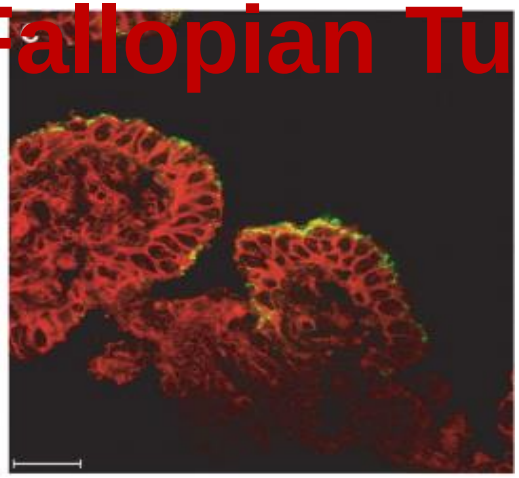
McGowin & Anderson-Smits, PLoS Pathogens 2011;7:e10013224; Moller *et al*., Lancet 1984;1:1102-1103; Cohen *et al.,* Sex. Transm. Infect. 2005;81:463-466; Manhart *et al.,* J. Infect. Dis. 2008;197:733-736

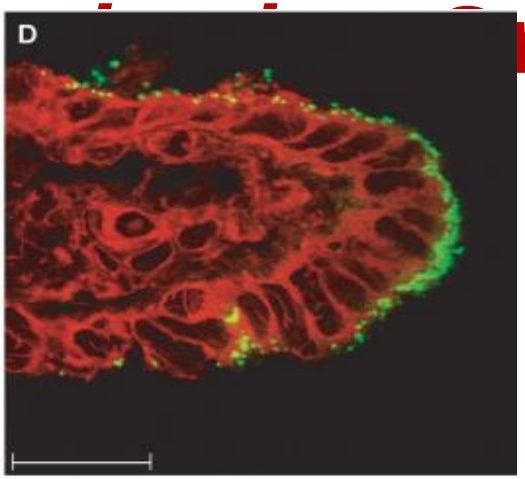
Pregnancy Complications and Infertility

- *M. genitalium* independently associated with pre-term birth in some studies and a recent meta-analysis
- Consistent strong correlations reported between serological evidence of *M. genitalium* infection and laparoscopically-confirmed tubal infertility
  - Association is maintained after excluding women with prior chlamydia
- Grzesko *et al.* reported NAAT detection of *M. genitalium* in endocervical samples was more frequent in infertile women vs. healthy fertile women
- Other studies has indicated that endocervical testing is not useful in predicting upper genital tract infection
- Experimental models (monkeys, mice, fallopian tube organ cultures) indicate *M. genitalium* can colonize upper genital tract leading to salpingitis and/or endometritis

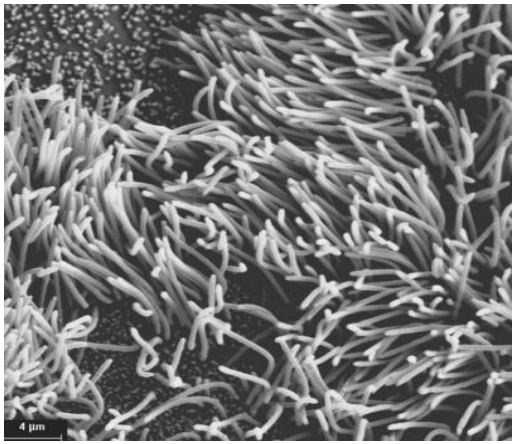
McGowin & Anderson-Smits, PLoS Pathogens 2011;7:e10013224; Grzesko *et al*., Fertil. Steril. 2009;91:2376-2380; McGowin *et al.,* Infect. Immun. 2010;78:;726-736; Moller *et al*., Br. J. Exp. Pathol. 1985;66:417-426

Mycoplasma genitalium Binds to & Damages Fallopian Tube Organ Cultures

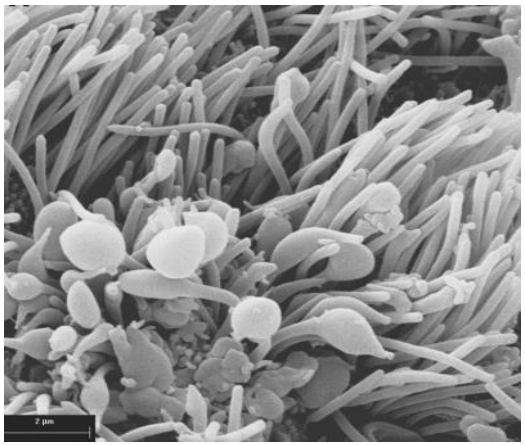




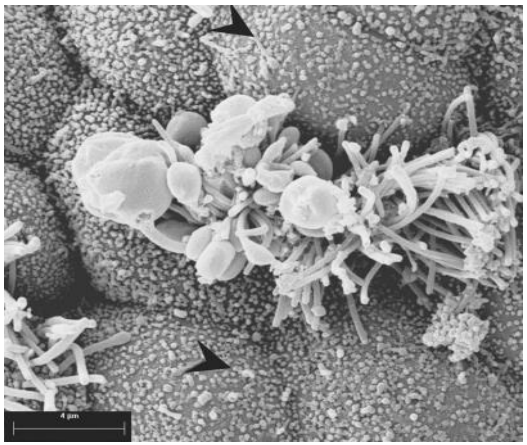
Immunofluorescence demonstrates *Mycoplasma genitalium* binding



Uninfected control FTC



FTC showing cilia swellings due to *M. genitalium*



Damaged cilia with *M. genitalium* attached to secretory cells (arrow)

Baczynska *et al.,* Human Reprod. 2007;22:;968-979

Systematic Review and Meta-Analysis
M. genitalium and female reproductive tract disease

- Examined associations of *M. genitalium* and 5 reproductive tract syndromes
  - cervicitis
  - Pelvic inflammatory disease
  - preterm birth
  - spontaneous abortion
  - infertility
- Well-designed study
  - 2 independent reviewers screened/examined 1080 relevant studies
  - examined Forest plots and conducted random-effects meta-analysis to estimate prevalence
  - between study heterogeneity examined with the I^2 statistic and meta-regression
  - publication bias assessed via funnel plots and Begg & Egger tests; rated methodology quality
- ~2-fold increased risks were demonstrated for all 5 conditions examined
- All pooled estimates were significant except for infertility

Lis *et al.,* Sex. Transm. Infect. 2018;94:255-262

Conclusions

- *M. genitalium* is an STI that presents many clinical challenges
- Causative role in NGU now clearly established
- Significant associations recognized with cervicitis, endometritis, pelvic inflammatory disease (PID), spontaneous abortion and pre-term labour
- Evidence of non-significant association with female infertility through a recent meta-analysis
- Role in proctitis, prostatitis, epididymo-orchitis balanoposthitis remains unclear
- Further clinical research is required to move the field forward …. !!!