Mycoplasma genitalium: the new chlamydia

Catriona Bradshaw

Mycoplasma genitalium

- First isolated in 1980
- Fastidious with slow growth (>50 days)
- Difficult to culture
- Few isolates available for antimicrobial susceptibility testing
Mg prevalence of 1-3% in community studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Age Range</th>
<th>Gender</th>
<th>Mg Prevalence</th>
<th>Ct Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manhart 2007</td>
<td>18-27 yo</td>
<td>North America</td>
<td>Men 1.1% (0.5-2.4%)</td>
<td>Women 0.8% (0.4-1.6%)</td>
</tr>
<tr>
<td></td>
<td>NHANES N=2932</td>
<td></td>
<td></td>
<td>4.5% (1.4-13.5%)</td>
</tr>
<tr>
<td>Andersen 2006</td>
<td>21-23 yo</td>
<td>Denmark</td>
<td>Men 1.1% (0.3-1.9%)</td>
<td>Women 2.3% (1.3-3.2%)</td>
</tr>
<tr>
<td></td>
<td>Pop Ct screening N=1652</td>
<td></td>
<td></td>
<td>8.4% (6.6-10.2%)</td>
</tr>
<tr>
<td>Walker 2009</td>
<td>16-25 yo</td>
<td>Australia</td>
<td>Men 1.6% (0.7-2.6%)</td>
<td>Women 1.6% (0.7-2.6%)</td>
</tr>
<tr>
<td></td>
<td>Ct screening in GP/SHC n=1116</td>
<td></td>
<td></td>
<td>4.9% (2.9-7.0%)</td>
</tr>
<tr>
<td>Oakshott 2009</td>
<td>15-27 yo</td>
<td>United Kingdom</td>
<td>Men 1.1% (0.3-1.9%)</td>
<td>Women 3.3% (2.6-4.1%)</td>
</tr>
<tr>
<td></td>
<td>Female uni students n=2246</td>
<td></td>
<td></td>
<td>8.4% (6.6-10.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.6% (3.9-7.3%)</td>
</tr>
<tr>
<td>Sonnenberg 2015</td>
<td>16-44 yo</td>
<td>United Kingdom</td>
<td>Men 1.2% (0.7-1.8%)</td>
<td>Women 1.3% (0.9-1.9%)</td>
</tr>
<tr>
<td></td>
<td>Ntsal-3 Population n=4507</td>
<td></td>
<td></td>
<td>1.5% (1.1-2.0%)</td>
</tr>
</tbody>
</table>

M. genitalium and Non-gonococcal Urethritis

- Established cause of NGU
- Higher prevalence in acute NGU than controls
- Responsible for 10-30% of cases of NGU
- Combined OR = 5 (4-7)
- Co-infection with chlamydia uncommon
- Similar clinical features to chlamydia

*Bradshaw 2008, Iser 2005, Taylor Robinson 2002*

Odds ratio

5.32 (4.15-6.81)
M. genitalium and Cervicitis

Lis et al CID 2015

Pooled effect estimate of 1.66 (1.35-2.04)

M. genitalium and PID

Lis et al CID 2015

Pooled effect estimate 2.14 (1.31-3.49)
**M. genitalium and Pre-term Birth**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>OR (95% CI)</th>
<th>%</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labbe</td>
<td>2002</td>
<td>1.37 (1.24, 2.53)</td>
<td>45.00</td>
<td></td>
</tr>
<tr>
<td>Delaware</td>
<td>2004</td>
<td>2.39 (1.12, 5.04)</td>
<td>1.91</td>
<td></td>
</tr>
<tr>
<td>Edwards</td>
<td>2006</td>
<td>2.62 (1.09, 6.33)</td>
<td>21.05</td>
<td></td>
</tr>
<tr>
<td>Kazicka</td>
<td>2006</td>
<td>2.63 (1.05, 6.57)</td>
<td>2.00</td>
<td></td>
</tr>
<tr>
<td>Hida*</td>
<td>2010</td>
<td>2.40 (1.10, 5.06)</td>
<td>27.46</td>
<td></td>
</tr>
<tr>
<td>Averback*</td>
<td>2013</td>
<td>1.34 (0.62, 2.69)</td>
<td>1.45</td>
<td></td>
</tr>
<tr>
<td>Overall (P&lt; 0.01, P = 0.009)</td>
<td></td>
<td>1.89 (1.25, 2.85)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random-effects analysis.

Pooled effect estimate of 1.89 (1.25-2.85)

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**M. genitalium and Spontaneous Abortion**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>OR (95% CI)</th>
<th>%</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marhart</td>
<td>2009</td>
<td>1.79 (1.64, 3.84)</td>
<td>44.00</td>
<td></td>
</tr>
<tr>
<td>Burt*</td>
<td>2019</td>
<td>0.60 (0.30, 0.96)</td>
<td>11.90</td>
<td></td>
</tr>
<tr>
<td>Vandeputte*</td>
<td>2012</td>
<td>2.25 (1.84, 4.18)</td>
<td>63.38</td>
<td></td>
</tr>
<tr>
<td>Overall (P&lt; 0.01, P = 0.007)</td>
<td></td>
<td>1.92 (1.10, 3.20)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random-effects analysis.

Pooled effect estimate =1.82 (1.10-3.03)
M. genitalium and Tubal Factor Infertility

- Serostudies examined association between M. genitalium and TFI
- Antibodies to M. genitalium more common in women with TFI compared to fertile women or women with non-TFI
- Consensus in the field that assays are generally poorly performing

Pooled effect estimate = 2.43 (0.93-6.34)  
Lis et al CID 2015

M. genitalium and Rectal Infection

Limited data on M. genitalium in rectal infections
Predominantly asymptomatic

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Rectal Mg prevalence (%)</th>
<th>95% CIs</th>
<th>Association with symptoms/signs and HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Francis 2008</td>
<td>500 consecutive rectal samples MSM at STI clinic - USA</td>
<td>27/500 (5.4%; 3.6-7.7%)</td>
<td>Not significantly associated with symptoms/signs or HIV</td>
<td></td>
</tr>
<tr>
<td>Bradshaw 2009</td>
<td>521 asymptomatic MSM attending SOPV - AUS</td>
<td>8/497 (1.6%; 0.8-3.0%)</td>
<td>Asymptomatic. No HIV data</td>
<td></td>
</tr>
<tr>
<td>Soni 2009</td>
<td>438 MSM attending STI clinic - UK</td>
<td>19/412 (4.6%; 2.6-6.8%)</td>
<td>Not significantly associated with symptoms/signs. Associated with HIV</td>
<td></td>
</tr>
<tr>
<td>Zheng 2014</td>
<td>409 consecutive MSM attending VCT Clinic - China</td>
<td>22/405 (5.4%; 3.5-7.7%)</td>
<td>No association with symptoms. Associated with HIV (OR 4.5; 1.2-17.1%)</td>
<td></td>
</tr>
<tr>
<td>Philbert 2014</td>
<td>116 asymptomatic MSM attending STI clinic - France</td>
<td>1/115 (1%; 0-2.8%)</td>
<td>Asymptomatic. No HIV association.</td>
<td></td>
</tr>
</tbody>
</table>
How do you test for *M. genitalium*?

- Diagnosis by NAATs
- Testing limited to specialized services using *in house* PCR assays
  - targeting MgPa gene or 16S rRNA gene\(^1\)\(^-\)\(^5\)
- Commercial assays undergoing regulatory approval
  - SpeeDx PlexPCR assay –diagnostic-resistance assay – 2017
  - Hologic Aptima TMA (RNA)
- Low loads of *M. genitalium* not uncommon, sensitivity is an issue with assays
- FVU more sensitive than urethral swab in men\(^6\)
- Women - HVS or Cx swab more sensitive than urine\(^5\)\(^,\)\(^7\)

\(^1\)Hardick 2006, \(^2\)Yoshida 2002, \(^3\)Jensen 2004, \(^4\)Wroblewski 2006 \(^5\)Edberg 2009 \(^6\)Jensen 2004 \(^7\)Jurstrand 2005
How do you treat *M. genitalium*?

- β-lactams and antibiotics that target the cell wall are not active as *M. genitalium* lacks a peptidoglycan containing cell wall
- Few classes of available antimicrobials\(^1\)\(^-\)\(^4\) have activity against *M. genitalium*
  - Macrolides, Fluoroquinolones, and Tetracyclines
- Although most strains appear to have MICs within susceptible range to doxycycline\(^1\)
- Clinical trials show low overall efficacy with cure rates of 22-45% - not recommended\(^2\)\(^-\)\(^5\)
- Reduced susceptibility to 2nd and 3rd generation quinolones
- Greater susceptibility to 4th generation quinolones
  - moxifloxacin, sitafloxacin, sparflavoxcin, and gatifloxacin\(^2\)\(^-\)\(^4\)

1g AZI versus DOXY

- Observational studies & trials of NGU predominantly show
  - 1g AZI is more effective than 7d of DOXY for *M. genitalium*
    - 67-87% versus 30-45%, \(p=0.002\) \(^1\)\(^-\)\(^3\)
  - 1g AZI recommended as 1st line therapy for *M. genitalium* by majority of STI guidelines\(^4\)\(^,\)\(^5\)
  - Recent meta analysis\(^6\) of 21 studies (1490 participants)
    - pooled microbial cure rate for AZI of 77.2% (71.1-83.4%), \(p<0.01\)
  - Notable decline over the past decade

\(^1\) Hamasuna AAC 2005, \(^2\) Hamasuna AAC 2009, \(^3\) Hannan J Med Microbiol 1998, \(^4\) Jensen & Bradshaw BMC ID 2015

\(^1\) Hamasuna AAC 2005, \(^2\) Schwebke CID 2011, \(^3\) Manhart CID 2013, \(^4\) STI treatment guidelines, ASHM 2014
\(^5\) 2015 CDC STI Treatment Guidelines, \(^6\) Lau CID 2015
Cure following 1 g of AZI for urogenital *M. genitalium*

**Table:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year</th>
<th>Conducted Year</th>
<th>Monochloride cure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gennari et al. 2008</td>
<td>2008</td>
<td>2008</td>
<td>62.35 (56.07, 68.60)</td>
</tr>
<tr>
<td>Tahvanainen et al. 2008</td>
<td>2008</td>
<td>2008</td>
<td>100.00 (100.00, 100.00)</td>
</tr>
<tr>
<td>Marion et al. 2008</td>
<td>2008</td>
<td>2008</td>
<td>100.00 (100.00, 100.00)</td>
</tr>
<tr>
<td>Benn et al. 2007</td>
<td>2007</td>
<td>2007</td>
<td>62.71 (52.13, 73.64)</td>
</tr>
<tr>
<td>Burt et al. 2006</td>
<td>2006</td>
<td>2006</td>
<td>88.71 (73.78, 95.62)</td>
</tr>
<tr>
<td>Mine et al. 2008</td>
<td>2008</td>
<td>2008</td>
<td>88.89 (74.58, 95.88)</td>
</tr>
<tr>
<td>Bradley et al. 2013</td>
<td>2013</td>
<td>2013</td>
<td>71.00 (53.25, 88.25)</td>
</tr>
<tr>
<td>Anguprasert et al. 2013</td>
<td>2013</td>
<td>2013</td>
<td>61.65 (49.48, 73.82)</td>
</tr>
<tr>
<td>Jermak et al. 2015</td>
<td>2015</td>
<td>2015</td>
<td>75.92 (72.04, 94.36)</td>
</tr>
<tr>
<td>Hageman et al. 2011</td>
<td>2011</td>
<td>2011</td>
<td>83.33 (55.26, 94.36)</td>
</tr>
<tr>
<td>Boccalini et al. 2008</td>
<td>2008</td>
<td>2008</td>
<td>64.17 (38.38, 90.19)</td>
</tr>
<tr>
<td>Refen et al. 2013</td>
<td>2013</td>
<td>2013</td>
<td>59.69 (14.68, 96.62)</td>
</tr>
</tbody>
</table>


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**Figure:**

Loss of Azithromycin

- At MSHC experienced a similar decline in cure rates
  - 85% (77-90%) in 2005-7 to 61% (53-69%) in 2012-13 \(^1\) \(p<0.001\)
- Accompanied by increase in macrolide resistance mutations (MRM) in 23S rRNA gene
- In 2016 at MSHC
  - MRM detected in >50% of infected patients \(^3\)
  - preliminary data indicates 80-90% in MSM
  - shown that extended regimens of azithromycin are not more effective than 1g and still select for MRM\(^3\)
- MRM prevalence now exceeds 30% in Asia-Pacific\(^4,5\), North America and Northern Europe/UK\(^6,7\)

\(^1\)Bradshaw EID 2006, \(^2\)Bissessor CID 2015, \(^3\)Read CID 2016, \(^4\)Tagg JCM 2013, \(^5\)Kikuchi JAAC 2014, \(^6\)Pond CID 2014, \(^7\)Gesink Int J Circum Health 2012
Moxifloxacin for *M. genitalium*

- Moxifloxacin most commonly used 2nd line antimicrobial since 2006
  - 400mg daily for 7-10 days
- Bactericidal, and generally well tolerated, and in early studies had a cure rate approaching 100%1-4
- Recent warnings -hepatotoxicity, tendonitis, arrhythmias by FDA and restricted to second line indications in Europe5.
- Last decade reports of MOXI failure emerged particularly in the Asia-Pacific region accompanied by mutations (Par C)6-9
  - treatment failures now reported in 12% of patients at MSHC6
  - 9% of strains had dual macrolide/quinolone resistance leaving very limited treatment options (G. Murray, unpublished data)

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**Need for New Antimicrobials**

- Urgent need for new antimicrobials
- Pristinamycin - streptogramin comprising two structurally unrelated synergistic components
- Binds to bacterial ribosome arrests protein synthesis
- Wide range of *in vitro* activity –GPC, Clostridium, Haemophilus, Neisseria, Ureaplasma and Mycoplasma spp2-3
- Not routinely available in Australia
- Imported via SAS from France (tertiary services)
- Favourable MICs for *M. genitalium*
- Evaluated in 114 patients with macrolide or dual class resistance
  - 1g qid or 1g tds with doxycycline 100mg bd for 10d
  - Cure rates of 75% (66-82%)4
- Well tolerated

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5Kaye Pharmaco 2014, 6Bissessor CID 2015, 7Gundleva Int J STD AIDS 2015,

---

1Guschin BMC ID 2015, 2Reid AA Chemo 2010, 3Cooper J Achemo 2014, 4Read TRH unpublished data
### Treatment recommendations for Mg?

- Treatment guidelines for *M. genitalium* lag well behind those for chlamydia
- Considerable resistance to *M. genitalium* specific guidelines in many countries
  - Lack of commercial assays, delays in establishing disease in women……..
- Specific treatment guidelines have not been available in the majority of countries until 2014+ - Aus, CDC, Europe.
- Focus exclusively on urogenital *M. genitalium* infections - little or no mention of rectal infection
- Now we finally have *M. genitalium* guidelines their recommendations do not reflect the current status of antimicrobial resistance

### Australian and US MG guidelines

<table>
<thead>
<tr>
<th>Australian MG Guidelines</th>
<th>Principal Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Situation</strong></td>
<td><strong>Recommended</strong></td>
</tr>
<tr>
<td><em>Uncomplicated genital infection</em></td>
<td>Azithromycin 1g PO, stat</td>
</tr>
</tbody>
</table>

### CDC 2015 MG guidelines

*Urethritis and cervicitis* - 1-g dose of azithromycin.
A longer course of azithromycin (500-mg dose followed by 250 mg daily for 4 days) might be marginally superior to the single dose but not if 1g has failed.
If azithromycin has failed use moxifloxacin (400 mg daily x 7, 10 or 14 days)

Neither guideline has indications for rectal MG
2016 European *M. genitalium* guidelines

Treatment for uncomplicated *M. genitalium*:
- Azithromycin 500 mg stat, then 250 mg on days 2-5

2nd line treatment and for uncomplicated macrolide resistant *M. genitalium*:
- Moxifloxacin 400 mg od for 7-10 days.

3rd line treatment for persistent *M. genitalium* infection after azithromycin and moxifloxacin
- Pristinamycin 1 g four times daily for 10 days

Recommended treatment for complicated *M. genitalium* infection (PID, epididymitis)
- Moxifloxacin 400 mg daily for 14 days

Patients with anal infection should be informed about the risk of transmission from this site and that the infection may be more difficult to eradicate. Test of cure is important.

UK does not have MG guidelines – only mentioned within NGU

Summary

- *M. genitalium* is very similar to chlamydia in its clinical manifestations and sequelae
- Commercial assays are about to emerge onto the market
- Who should you test?
  - no evidence for screening asymptomatic individuals
  - evidence supports testing in NGU, cervicitis, PID, proctitis, and sexual contacts
- What sample should you collect?
  - Men – FVU
  - Women – HVS or Cx swab
  - If anal sex – anal swab
- What test should you use?
  - if available one that provides macrolide resistance status to direct choice of antimicrobial therapy
Conclusion

• Overall *M. genitalium* is becoming challenging to treat
• Guidelines lag behind resistance data and still recommend 1g AZI
  • May be associated with ≥50% treatment failure
• Test of cure 3-4 weeks following treatment and partner treatment is essential
• No readily available antimicrobial in the community to treat AZI failures
• Moxifloxacin 400mg daily for 7-10 days is recommended for failure following AZI or for macrolide resistant infections
• PID should be treated at 400mg daily for 14 days

Call a specialist sexual health physician if
  • cannot access moxifloxacin or moxifloxacin failure occurs
• Only current option for moxifloxacin failures is pristinamycin
  • 1g qid for 10 days - limited availability
• Emergence of commercial assays will result in an escalation in community diagnosis of *M. genitalium* and infections that are challenging to cure in primary care
• Need funding for evaluation of registered and new antimicrobials, combinations of antimicrobials and treatment trials
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