New paradigms in *Mycoplasma genitalium* testing and treatment

Dr Paddy Horner, Consultant Senior Lecturer, University of Bristol
Disclosures

• None
Outline

• Background
  – Epidemiology
  – Microbiology
  – Treatment and antimicrobial resistance
    • “superbug”
    – BASHH Mgen guidelines

• Pelvic inflammatory disease, NGU and Mgen testing
  – Treatment
  – Partner notification
    • Practical implications of Mgen testing for epidemiological treatment
    • Infection specific partner treatment
To consider

• Does epidemiological treatment of current Mgen -ve & CT -ve partners with doxycycline, of men with Mgen -ve & CT -ve NGU and women with PID (GC-neg) do more good than harm?
  – Yes vs No
Mycoplasma genitalium

• Sexually transmitted

• 1-2% 16-44 yrs olds
  – 7% (4-38%) Sexual Health Clinics

• Risk factors:
  – younger age,
  – non-white ethnicity,
  – higher number of sexual partners,
  – lack of barrier contraception
**M. genitalium – Microbiology and pathogenesis**

- Smallest free living micro-organism
- High mutation rate – single copy genome
  - Antimicrobial resistance – single gene mutations
    - Macrolides
    - Quinolones
- Immune evasion: duration infection: < 6mths - >2yrs
  - Antigenic shift
  - Replicates intracellularly and extracellularly
- Very slow growing: routine culture not possible
- Diagnosis and antimicrobial sensitivity testing
  - Nucleic amplification tests (NAATs)
Mycoplasma genitalium

- Ano-genital tract mucosa
  - Majority asymptomatic (>90%)
  - Women
    - Pelvic inflammatory disease (PID) (0.5-1.5% 16-44yrs)
      - <10% will develop PID if left untreated (personal communication – Lewis J, & White P)
    - Cervicitis – post coital bleeding (3% 16-44 yrs) (Bjartling 2012 and Sonnenberg 2015)
      - causal 10-20%
  - Men
    - Non-gonococcal urethritis (0.5% 16-44yrs)
      - 5-10% will develop urethritis (Horner 2017)
    - Proctitis
      - 10% carriage high risk MSM no association symptomatic proctitis (Read 2019)
Mycoplasma genitalium - treatment

- Treatment suboptimal without NAAT and antimicrobial resistance (AMR) testing
- Doxycycline 30-40% effective but very low risk of AMR
- Macrolides
  - 30->50% in some centres
  - Azithromycin 1 g (12% risk AMR)
  - Failure to detect infection and undertake test of cure
- Quinolone AMR increasing
  - 1->5% (50% Japan)
- Prior treatment doxycycline reduces “load” and risk AMR (2-3%)
  - Azithromycin 500mgs then 250mgs od 4 days
  - Azithromycin 1g then 500mgs od 3 days

Macrolide AMR Europe (J Jensen)
Selection pressure

- Antimicrobial
  - Exposure to sub minimum inhibitory concentrations (MIC) selects for resistance
- High load (symptomatic)
  - Random chance of containing macrolide resistance mutations
- Azithromycin
  - 1 g duration MIC levels too short
  - Prolonged presence sub MIC levels in tissues selects for resistance on re-infection
  - “The greater the dose the longer the duration”

Adapted by P Greenhouse

Horner P STI 2017;93:85; Foulds G JAC 1993 ; Kong F 2019; Horner STD 2019
Selection pressure - quinolones

- Single mutations also associated AMR
- High load (symptomatic)
  - Random chance of containing quinolone resistance mutations
  - Is this happening in vivo?
BASHH and Mgen AMR

• Developed new evidence based Mgen guidelines - 2018
  – Concern a “superbug” could become common within 10yrs
  – Mgen testing

• Stopped use of azithromycin 1g
  – Extended course
  – 2 weeks no sexual intercourse

• Unified new Mgen guideline with gonorrhoea, NGU & chlamydia
Recommendations for testing

• Who
  – No Asymptomatic screening
  – All women with PID
  – All men with NGU
  – Current partners of Mgen +ves

• Which test
  – Mgen NAAT
  – If +ve reflex NAAT AMR testing
    • Test of cure
    • Improves outcomes
    • Stops development AMR
Pelvic inflammatory disease (PID)

- 30-50000 women 16-44yrs
- Aetiology
  - Chlamydia 20% (35% <24 yrs)
  - *Mycoplasma genitalium* 10% (3-5000)
  - Gonorrhoea (GC) 1-3%
  - Bacterial vaginosis associated bacteria (anaerobes)
  - Respiratory tract and Enteric pathogens
- Complications
  - Tubal factor infertility 2.5% - 4%
  - Ectopic pregnancy risk increased 1-1.5% (normal 1%)
  - Chronic pelvic pain (10-20%)
- Early identification and treatment reduces risk of sequelae

PID treatment

• Ceftriaxone, doxycycline and metronidazole
  – Reduced efficacy Mgen-positive
    • Probable increased risk of sequelae ?doubled
  – Addition azithromycin 1g increase microbiological cure but not clinical cure (no ceftriaxone)
    • Extended azithromycin if macrolide sensitive more effective (+ceftriaxone)

• Moxifloxacin effective all causes PID
  – Second line because side effects
  – What do we do if quinolone resistant?

# PID costs and Mgen testing

<table>
<thead>
<tr>
<th>PID</th>
<th>Numbers</th>
<th>Mgen</th>
<th>Cost low</th>
<th>Cost Resist</th>
<th>Total cost (low)</th>
<th>New cost if 50% resistant</th>
<th>Difference in cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUM</td>
<td>12,000</td>
<td>1200</td>
<td>171</td>
<td>600</td>
<td>205,200</td>
<td>462,600</td>
<td>£257,400</td>
</tr>
<tr>
<td>Total</td>
<td>50,000</td>
<td>5000</td>
<td>171</td>
<td>600</td>
<td>855,000</td>
<td>1,927,500</td>
<td>£1,072,500</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PID</th>
<th>Numbers</th>
<th>Mgen</th>
<th>Cost sequelae (low)</th>
<th>Additional cost if 50% resistant*</th>
<th>Total increase in cost if 50% resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUM</td>
<td>12,000</td>
<td>1200</td>
<td>59,712</td>
<td>29,400</td>
<td>£287,256</td>
</tr>
<tr>
<td>Total</td>
<td>50,000</td>
<td>5000</td>
<td>248,800</td>
<td>1,244,000</td>
<td>£1,196,900</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PID</th>
<th>Numbers</th>
<th>Mgen</th>
<th>Cost Mgen testing (£10)</th>
<th>AMR testing</th>
<th>Cost testing plus Mgen +ve (£30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUM</td>
<td>12,000</td>
<td>1200</td>
<td>120,000</td>
<td></td>
<td>£156,000</td>
</tr>
<tr>
<td>Total</td>
<td>50,000</td>
<td>5000</td>
<td>500,000</td>
<td></td>
<td>£650,000</td>
</tr>
</tbody>
</table>

* Assumes risk sequelae doubles: TFI (3%), Ectopic pregnancy (1%), chronic pelvic pain syndrome (15%)

NB if assume high cost sequelae total increase in cost GUM : £701,316

PID - partners

- NAAT testing chlamydia, gonorrhoea current partner (1D)
  - Mgen if index case NAAT-positive
    - Will this miss some partners Mgen positive (46% concordance)
  - Screening partner(s) CT/GC in previous 6 months (2D)
    - Some cases CT PID may not be detectable at lower genital tract

- Epidemiological treatment partners as polymicrobial infection (2D)
  - Doxycycline 100mgs bd 7 days (broad spectrum)
  - Expert opinion weak evidence base

- Are women with CT/GC/Mgen neg partners at increased risk of recurrence if partners are not treated?
  - We do not rescreen for bacterial vaginosis
    - Metronidazole prophylaxis does not prevent PID
  - Treating male partner does prevent recurrence of BV

- What about antimicrobial stewardship?

Taylor B 2013, Price M 2016, Slifirski J 2017
Non-gonococcal urethritis (NGU)

- 40-80,000 cases annually
- Aetiology
  - Chlamydia 15-30%
  - Mgen 10-25% (20,000)
  - *Ureaplasma urealyticum* 5-10%
  - Unknown 30-40%
    - Bacterial vaginosis associated bacteria
    - Increased pelvic floor tone? Poster 133
- Treatment
  - Doxycycline 100mgs bd 1 week
- Complications
  - Chronic NGU 10-20%
    - 20-40% *M genitalium*
    - Significant morbidity
NGU - partners

- NAAT testing chlamydia current partner (1D)
  - Mgen if index case NAAT positive
  - Screening partner(s) CT/NG in previous 4 weeks (2D)
- Epidemiological treatment all partners previous 4 weeks (2D)
  - Doxycycline 100mgs bd 7 days
  - Expert opinion weak evidence base
- Are men with CT/Mgen -ve partners at increased risk of recurrence?
  - *U. urealyticum* risk of disease decreases with duration infection
  - No evidence treating CT and Mgen -ve partners of benefit
- Are CT/Mgen -ve female partners at increased risk PID
  - Weak evidence Ong J et al 2017 – biased: diagnosis of NGU more likely if contact of PID
- Antimicrobial stewardship?
PID & NGU partners – epidemiological Rx vs Mgen testing

• Time delay in identifying if index case Mgen-positive
  – Partners 40% risk Mgen-positive
  – 1) Epidemiological treatment all
    • Doxycycline 40% effective (NB 25% risk Mgen-positive post Rx)
    • Reduce sensitivity Mgen NAAT if index case Mgen-positive
    • Test of cure 5 weeks vs same treatment as index
      – Risk re-infection and need re-treatment
      – Vs Risk over treatment - quinolone
• Time delay in identifying if index case Mgen-positive
  – Partners 40% risk Mgen-positive
  – 2) Mgen test partner
    • Need result of index Mgen test to guide testing
    • Treat partner doxycycline
      – If Mgen-positive add azithromycin or Moxifloxacin
    • ?Save CT/GC specimen for Mgen testing if index Mgen-positive
      – Organisationally complex
PID & NGU partners – epidemiological Rx vs Mgen testing

• Time delay in identifying if index case Mgen-positive
  – Partners 40% risk Mgen-positive
  – 3) Test all partners for CT/GC and Mgen
    • Await results before partner treatment
      – Only treat if NAAT-positive unless
      – 2 week window period and index NAAT-positive
Conclusion

• Most persons with Mgen resolve infection without disease
• Treatment effective if sensitive to antimicrobial
  – Treatment of Mgen with macrolide or quinolone has risk of selecting for resistance.
  • Reduced by pre-treatment with doxycycline for azithromycin
  • Abstinence sexual intercourse 2 weeks post
  • Rationale for test of cure
• Mgen NAAT testing likely to be cost effective in PID and NGU
• Weak evidence that treating current partners of NGU of benefit if
  – CT and Mgen NAAT neg
• Weak evidence that treating current partners of PID of benefit if
  – CT, Mgen and GC NAAT neg
• Should we consider NAAT guided infection specific treatment for contacts?
  – Test all current partners for CT/GC and Mgen
  – RANDOMISED CONTROLLED TRIALS
Problems

• Lack of funding to support adoption of BASHH Mgen guidelines
  – Sexual Health clinics
  – Primary care
Acknowledgements

• NIHR Health Protection Research Unit Evaluation Interventions, University of Bristol
• PHE
  – Peter Muir
• Unity
  – Peter Greenhouse
• BASHH
  – Suneeta Soni
• Australia
  – Fabian Kong
• Sweden
  – Jorgen Jensen
Question

• Does epidemiological treatment of current Mgen -ve & CT -ve partners with doxycycline, of men with NGU and women with PID (GC-neg) do more good than harm?
  – Yes vs No
Questions

• Does epidemiological treatment of previous CT -ve partners with doxycycline of men with urethritis and women with PID (GC-neg) do more good than harm?
  – Yes vs No