Correlates of repeat anorectal infections among men who have sex with men

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Current treatment

• Recommended treatment for chlamydia1
  – Single 1g azithromycin or 7 days (100mg twice daily) doxycycline
  – Varies internationally and nationally
• Sexual health guidelines: Doxycycline preferred for rectal infection in EU and Australia2-3
• Meta-analysis rectal chlamydia treatments
  – Azithromycin 82.9% vs doxycycline 99.6%4
• Organism load may be associated with treatment failure5-7

Methods

• Setting and participants: MSM attending a large urban sexual health centre (MSHC) who tested positive for rectal chlamydia
• MSHC guidelines: rectal chlamydia treatment is 1g azithromycin
• Chlamydia positive samples are stored for further research
• Eligible: MSM tested positive for rectal chlamydia between July 2008 and Oct 2013 & retested within 100 days of treatment
• MSM with clinical proctitis/symptomatic LGV excluded
• Laboratory testing: Chlamydia bacterial load and genovar/MLST
  – Load estimates: quantitative PCR targeting the omp1 gene (aPCR)
  – Genovar: (1) 3 distinct phylogenetic clades based on the omp1 gene; B group (B/Ra, D, E, L1, L2), C group (A, C, H, L1, K, L3), Intermediate group (F and G)
  – Multilocus sequence typing (MLST): Differentiate between identical genovars from the same individual; analysis over 5 regions of the chlamydia genome hctA, CT682-pdpB, CT144, CT172, CT058

Aim

To investigate repeat rectal chlamydia infection among MSM and:

1. Estimate the risk of repeat rectal chlamydia among MSM following treatment
2. Describe genovar and organism load profile of rectal chlamydia among MSM
3. Differentiate between re-infection and treatment failure
4. Investigate association of organism load with re-infection and treatment failure
5. Estimate azithromycin treatment efficacy

Background

• Most common bacterial STI among MSM
  – Prevalence twice that of urethral infections
  • Rectal CT prevalence 5.6-11.3%1,8
• Increasing reports of treatment failure with repeat infection rates from 13-22%9-12
• Lymphogranuloma venereum (LGV) mainly considered symptomatic, but up to 27% can be symptom free and without genotyping could be missed13

1. CDC MMWR 2010; 59(45): 1100
2. Royal Women’s Hospital, Melbourne, Australia.
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Electronic patient data

– Age, treatment received on initial diagnosis, co-infections with other STIs (including HIV), past STIs, sexual practices, condom use, rectal symptoms, diagnosis of proctitis, time between test results

Statistical analysis:

– The proportion re-testing positive was calculated with 95%CI using binomial methods
– Organism load was log 10 transformed
– Load was calculated as copies per swab
– Factors associated with treatment success vs treatment failure or reinfection were investigated using logistic regression. Load for index cases was included in the model and variables selected for inclusion on the basis of literature and likelihood ratio test.

Ethical approval from Alfred Hospital Ethics Committee

1.1/10/2015
Outcome definition

<table>
<thead>
<tr>
<th>Genovar</th>
<th>Index vs follow-up result</th>
<th>Had sex in past 3 months</th>
<th>Any condom use, as receptive partner, in past 3 months</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different</td>
<td>Same</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Same</td>
<td>Same</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Same</td>
<td>Same</td>
<td>No</td>
<td>N/A</td>
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</tr>
<tr>
<td>Same</td>
<td>N/A</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A¹ = genovar data not available; N/A² = sexual practice data not available

Results - profile of participants

227 index cases included in this analysis

| AGE | Median 29 years (range: 18-78 years) |
| # partners / condom use (last 3 months) | 26% (>6 partners) and 21% condom all the time |
| TIME TO RETEST | Median 62 days (50% retested: 6-11 weeks) |

Results – repeat positive among index cases (n=227)

<table>
<thead>
<tr>
<th>Repeat positive</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>64</td>
<td>28%</td>
<td>22%-35%</td>
</tr>
<tr>
<td>Probable/probable reinfections</td>
<td>35</td>
<td>15%</td>
<td>11%-21%</td>
</tr>
<tr>
<td>Definite reinfections</td>
<td>11</td>
<td>5%</td>
<td>2%-9%</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>29</td>
<td>13%</td>
<td>9%-18%</td>
</tr>
</tbody>
</table>

Genovar distribution

- 64 repeat positives
  - 2 (3%) different genovar
  - 46 (71%) same genovar

- 45 positive pairs (same genovar) tested with MLST
  - 9 (20%) different

Factors associated with treatment failure and reinfection

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95%CI)</th>
<th>Adjusted OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment success vs treatment failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success vs probable/probable reinfection</td>
<td>1.97 (1.44-2.71)</td>
<td>1.93 (1.40-2.65)</td>
</tr>
<tr>
<td>Treatment success vs definitive reinfection</td>
<td>1.64 (1.26-2.19)</td>
<td>1.59 (1.20-2.12)</td>
</tr>
<tr>
<td>Treatment success vs definitive reinfection</td>
<td>1.51 (0.98-2.31)</td>
<td>1.55 (0.99-2.40)</td>
</tr>
</tbody>
</table>

²adjusted for age, HIV status, number of sex partners last 3 months and time between index and repeat test.

Compared to treatment success, load was associated with:
- 93% increase in odds of treatment failure
- 55%-59% increase in odds of definitive/probable reinfection
Azithromycin efficacy

- Treatment records for 97% (220/227) – Azithromycin 1g only in 203 cases (n=2 doxy)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>1g Azithro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment success</td>
<td>72% (152/211)</td>
<td>70% (143/203)</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>13% (29/227)</td>
<td>14% (29/203)</td>
</tr>
<tr>
<td>Reinfection</td>
<td>15% (35/227)</td>
<td>16% (32/203)</td>
</tr>
</tbody>
</table>

*1g Azithromycin efficacy of 86% (95% CI: 81-91%)

Discussion

- Repeat positivity rate is common; 28% consistent with previous results
- Genovar distribution was similar among MSM globally
- Azithromycin efficacy 86% similar to meta-analysis (83%)

- Association between high load and treatment failure is consistent with past findings and raises possibility of:
  - Heterotypic resistance
- Association between high load and reinfection:
  - Impaired rectal immune response to infection?

Strengths and Limitations

- Analysed all positive rectal samples in past 5 years with 95% providing a genovar & load estimate
- Small sample size for analysis of outcome
- MLST cannot definitively discriminate between treatment failure and reinfection
- No MLST data available for 33% of repeat positive samples
- Possible degradation of organism load over time in stored swabs

Implications for practice?

- Better methods for detecting organism load?
  - mRNA (viable organism) vs DNA/rRNA (dead organism)
  - What is the threshold for defining ‘high’ load?
- Strong recall and test for reinfection to break transmission
- Give everyone 7 day doxycycline? (99% vs 83% efficacy)
  - Issues of compliance?
- Increasing the dose of azithromycin?
  - Total dose over 2-3 days? Need pharmacokinetic studies
  - See poster on dosing in extended doses of Azithromycin (#100)
  - Forthcoming RCT comparing azithromycin vs doxycycline for treating rectal infections (ANZCTR: 12614001125617)

Disclosure of interest and thanks

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- World STI & HIV Congress Scholarship
Results

227 index cases with second test result

- 64 with second positive
  - genovar + load=56 (87.5%)
  - genovar + load=160 (98.2%)
- 163 tested negative

Organism load (n=227)

- 218 (96.0%) load data
  - 87.5% (56/64) repeat positive
  - 99.4% (162/163) no repeat positive

Organism load – repeat positive

Organism load (log10) among index cases (n=227)

- Crude: 4.8 vs 3.7* & Adjusted: 1.7 vs 0.8* (*p<0.01)

Organism load by outcome

Organism load (log10) among index cases (n=227)

- Treatment success: 3.7 ± 1.3
- Treatment failure: 6.0 ± 1.9
- Relapse: 4.6 ± 1.4

Repeat infection vs Tx success (p<0.01)

Organism load - 1st vs 2nd positive

Organism load (log10) among repeat positive

- Prevalent (baseline) vs incident (follow up) infection
  - Crude: 4.8 vs 4.4 (p=0.14) & Adjusted: 1.7 vs 1.4 (p=0.21)
Persistent infection

• Persistence of chlamydia in-vitro
  – Exposure to β-lactam antibiotics, interferon-γ or deprived of iron supplements or amino acids can exhibit persistence 1-6
• Penicillin can induce azithromycin treatment resistance in-vitro (eg. treatment for syphilis) 7,8
• Co-infection with herpes simplex can contribute to persistence 9-12 although not with HIV13
• Re-infections 4x higher with persisted infections at enrolment14