Azithromycin resistance and subtyping of *Treponema pallidum*

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**Introduction**

A Randomized, Comparative Pilot Study of Azithromycin Versus Benzathine Penicillin G for Treatment of Early Syphilis


STD 2002  29:486-90

Int J STD AIDS 2008 19: 217-21

**Use of azithromycin**

- San Francisco
  - 1g for contacts
  - 2g for cases
- British Columbia- Vancouver
  - Mass treatment of >4000 people in 2000
  - Control, then increased
- Appeared as alternative therapy in many guidelines

**Reports of resistance**

- Street 14 strain of *T.pallidum* has known macrolide resistance mutation A2058G

<table>
<thead>
<tr>
<th>Geographic Site</th>
<th>Azithromycin (%)</th>
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**Worldwide reports of macrolide resistance**

- Seattle 95% by 2005
- San Francisco 68%
- London 66%
- Mainland China 60%
- Taiwan 0%
- Madagascar 0%
- Dublin 93%
- San Francisco 68%

**Reason for increasing resistance?**

Selection pressure for de novo mutations?
Selection of existing resistant strains?

RR for resistance 2.2 in Seattle², and 19.65 in China³ if receipt of macrolide in prior year

Grimes et al STD 2012 39:954-8
Marra et al STD 2006 34:771-3
Chen et al Clin Microbiol Infect 2013
Alternative mutation A2059G

- First reported in Czech republic 2009
  - Treatment failure with spiramycin
  - 14% of samples from Czech republic
- Also:
  - UK 5.6%
  - USA 10-13.2%
  - (Taiwan/South Africa 0%)
- NO samples contained A2058G and A2059G

Azithromycin resistance- Sydney

- Stored samples from 2004-2011 tested for A2058G

Risk factors for azithromycin resistance

<table>
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<tr>
<th>Factor</th>
<th>Univariate OR (95% CI)</th>
<th>P value</th>
<th>Multivariate OR (95% CI)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age of samples (years)</td>
<td>1 (0.98-1.01)</td>
<td>0.23</td>
<td>1 (0.97-1.02)</td>
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T.pallidum subtyping

- Published in 1998
- 1.14Mb 1040 genes- we known what 55% do
- Fully capable of DNA RNA and protein synthesis
- No phosphate uptake, no fatty acid synthesis
- Minimal DNA repair, no nucleotide/amino synthesis
- No electron transport
- Only 22 lipoproteins (vs 132 for B. burgdorferi)
- Tpr gene repeats
- In summary: highly adapted obligate parasite

Syphilis subtypes

- First subtyping system developed in 1998 by CDC
  - Number of 60bp repeats in Acidic Base Protein (apr gene)
  - RFLP analysis of T. pallidum repeat (tpr) sub-family-II genes

Subtypes in Melbourne

- Muller et al STI 2012
-Cole et al STI 2009

Azato et al J Clin Micro 2012
Enhanced subtyping

• Addition of tp0548 gene sequence analysis

Caveat: one study shows possible variability in same patient- arp and tpr genes

Alternative typing systems—pure sequence based on 23s rRNA, TP0136 and TP0548

Mikalová et al. BMC Microbiology 2013

Association of subtype with drug resistance?

• No association found in UK\(^1\) or San Francisco\(^2\)
• Some association in Seattle\(^3\)

Association of subtype with neurosyphilis

• South Africa: Strain 14a associated with 7/13 cases of NS - 14d more common at time\(^1\)

• Seattle: \(^2\)
  – 21/42 (50%) of patients with 14d/f had NS
  – 10/41 (24%) of patients with another strain had NS (p=0.02)
    • (15/42 vs 5/41 had positive CSF VDRL; p=0.01)

• Rabbits: subtypes can give different phenotypes, 14d/f causes neuroinvasion\(^3\)

\(^1\)Molepo et al STI 2007, \(^2\)Marra et al JID 2010, \(^3\)Tantalo JID 2005

Conclusion

• Azithromycin resistance is common in resource-rich settings, including Australia
• Subtyping has utility in tracking epidemics, identifying clusters
• Association with neurosyphilis and clinical utility of subtype regarding remains to be determined

Acknowledgements

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