Azithromycin treatment failure in women diagnosed with genital chlamydia

Hocking JS,[1] Vodstrcil L, [1] Huston W, [2] Timms P, [3] Chen M,[4] Bradshaw C,[4] Worthington K,[4] Lawrence A,[2] McIver R,[5] Phillips S,[6] Tabrizi SN. [6-8]

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High repeat infection rates among women

- 18% to 57% in adolescents in the USA[1,2]
- 10% per year in general population sample in the Netherlands[3]
- 22.3% per year (Australia) to 29.9% per year (UK) in general practice[4,5]
  - Median time to repeat infection 4.6 months[4]

1. *J Adol Health 1996;18: 270–275;* ***2.*** *J Infect Dis 2010; 201: 42–51;* ***3.*** *STD 2005;32:599.* ***4.*** *Plos One 2012;7(5):e37778;* ***5.*** *Sex Trans Inf 2007;83: 282-303.*

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What does repeat infection mean?

- **Re-infection due to unprotected sexual contact with an infected partner**
- Treatment failure as a result of:
  - Non-compliance with treatment
  - Poor absorption of the drug
  - Reduced antimicrobial susceptibility or antimicrobial resistance
- Persistence due to host factors such as immune response

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Evidence to support azithromycin treatment failure?

- 2 studies of women in whom re-infection had been ruled out found azithromycin failure of ~8%. [1,2]
- RCT reported an azithromycin failure for chlamydia of 23% - significantly higher than 5.2% observed for doxycycline.[3]
- Failure for rectal chlamydia infection from 6% to 21%.[4-6]

1. *JID 2010;201:42-51;* ***2.*** *NEJM 2005;352:676-685;* ***3.*** *CID 2011;52:163-170;* ***4.*** *Int J STD&AIDS 2009;20:16-18;* ***5.*** *Int J STD&AIDS 2011; 22: 478-480 ;* ***6.*** *STI 2012;88:352-354.;* ***7.*** *Int J STD&AIDS 2010; 21:* 729–737.

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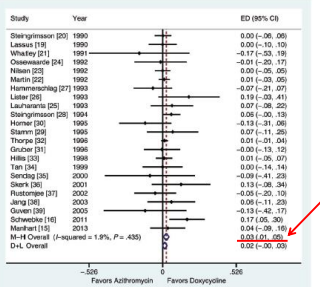
Meta-analysis comparing azithromycin with doxycycline for urogenital chlamydia



Doxycycline 3% greater efficacy than azithromycin

3% (95%CI: 1.0%, 5.0%)

Kong et al. CID 2014;59(2):193-205.

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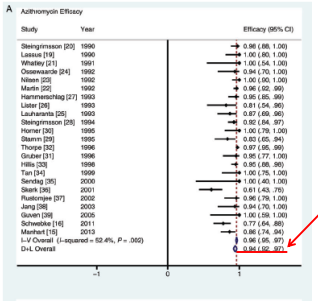

Azithromycin efficacy

94% (95%CI:92%, 97%)

Kong et al. CID 2014;59(2):193-205.

Aim

- To estimate the proportion of women infected with chlamydia who experience failure after treatment with 1 gram azithromycin.

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Methods – study design

- Cohort study of women diagnosed positive for urogenital chlamydia attending Melbourne Sexual Health Centre or Sydney Sexual Health Centre between Oct 2012 and Dec 2014.
- Participants – eligibility criteria
  - Age ≥16
  - NAAT positive for chlamydia
  - Adequate English for informed consent
  - Able to attend clinic in person at day 7
- Treated with 1 gram azithromycin
- Women followed up weekly through mail for 56 days OR until a repeat infection diagnosed

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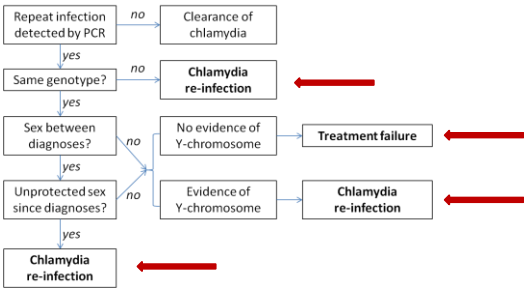
Outcome definition



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Study endpoint

- Test of cure conducted in real time on swabs collected at day 28, 42 or 56.
- If PCR+, then study endpoint reached, otherwise followed up until day 56.

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Methods – follow up and testing schedule

	Day 0	Day7	Day14	Day21	Day28	Day35	Day42	Day49	Day56	If PCR+ @ d28, 42 or 56
Culture +MIC	X									X
PCR	X	X	X	X	X	X	X	X	X	X
Organism load	X		X	X	X	X	X	X	X	X
mRNA[1]	X	X								X
Genovar	X		X	X	X	X	X	X	X	X
Sequencing	X									X
Y Chromosome[2]		X	X	X	X	X	X	X	X	X
Az absorption[3]		X								
Serology[4]	X									X
Rectal swab										X
Test of cure					X		X		X	
Venue	Clinic	Clinic	Home	Home	Home	Home	Home	Home	Home	Clinic

1. J Micro Methods 2005; 61: 361-367; 2 Sex Transm Dis 2007, 34:620–623; 3. Vodstrcil et al. ISHCI California 2014; 4. J Reprod Immunol 2010, 85:168–171

Methods - analysis

- Proportions and 95%CI calculated using exact binomial methods
- Kaplan Meier used to investigate time till repeat positivity
- Cox regression used to investigate factors associated with repeat infection.

Results (1)

- 305 women recruited – response rate = 66%
- 241 (79%) were retained till study endpoint
- 2,373 weeks of follow-up
- Median age 23 years (IQR=21-26yrs)
- A total of 36 repeat infections were detected
  - 14.9% (95%CI: 10.7%, 20.1%)
- Incidence of repeat infection
  - 1.5 per 100 weeks (95%CI: 1.1, 2.1)

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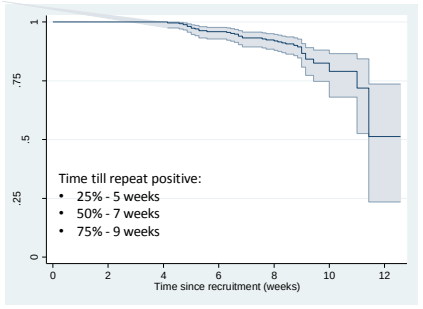
Time till repeat positivity



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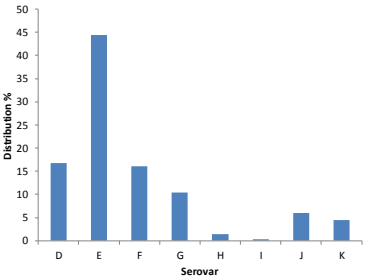
Genovar distribution at recruitment



Similar profile to that observed by Kirsty Smith among heterosexual men and women in Australia – See O15.3

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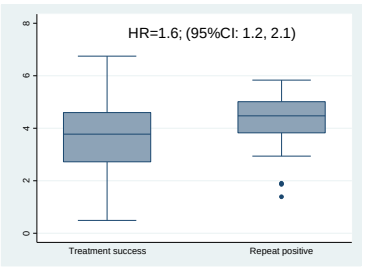
Organism load at recruitment by treatment outcome



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Results (2)

- Treatment failure[1] – based on sex behaviour and genovar
  - 12 cases
  - 5.0% (95%CI: 2.6%, 8.5%)

1. *Further laboratory analysis in process*

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MIC among repeat positives

Case	MIC at baseline	MIC for repeat positive
1	0.016	0.016
2	**0.032**	**0.125**
3	0.032	0.032
4	0.032	0.032
5	**0.032**	**0.064**
6	0.064	0.064
7	0.064	0.064

Further analysis

- Preliminary data only – further laboratory analysis needed to differentiate between treatment failure and new infection:
  - sequencing
  - Y chromosome
  - mRNA
  - azithromycin absorption
- Interval specimens will be used to investigate time till clearance of chlamydia.

See O05.6 – 3-3.15pm Monday 14th Willa Huston

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Discussion

- About 15% of women will present with a repeat positive chlamydia diagnosis within 12 weeks following treatment
  - Most repeat infections will occur within 9 weeks
- Repeat infection is associated with organism load
- At this stage, an estimated 1 in 20 women with chlamydia treated with 1 gram azithromycin will fail treatment – consistent with other studies.[1,2]
  - No evidence of MIC shift.
  - Likely to be less than that observed for rectal chlamydia infection.[3]

1. JID 2010;201:42-51; **2**. NEJM 2005;352:676-685 3. J Antimicrob Chemother. 2015 May;70(5):1290-7

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