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Treating *Neisseria gonorrhoeae* and *Mycoplasma genitalium* in the era of azithromycin-resistance

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MONASH University

Gonorrhoea notifications in Victoria

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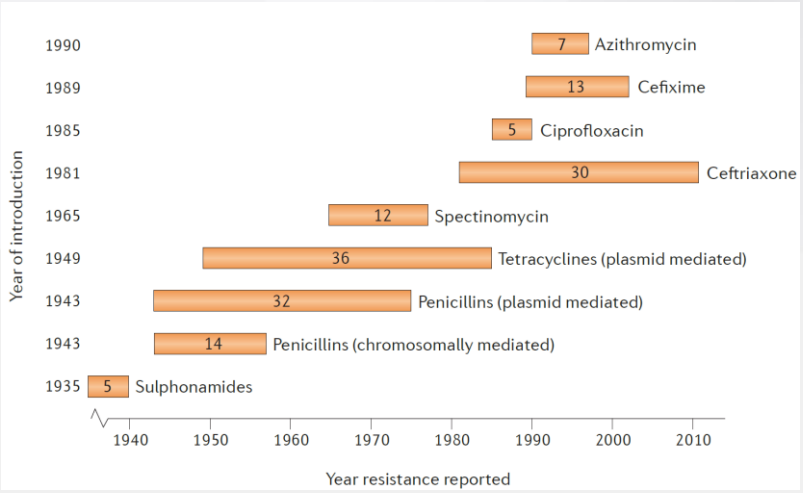
The lifespan of a wonder-drug.
- Goire *Nat Rev Microbiol* 2014



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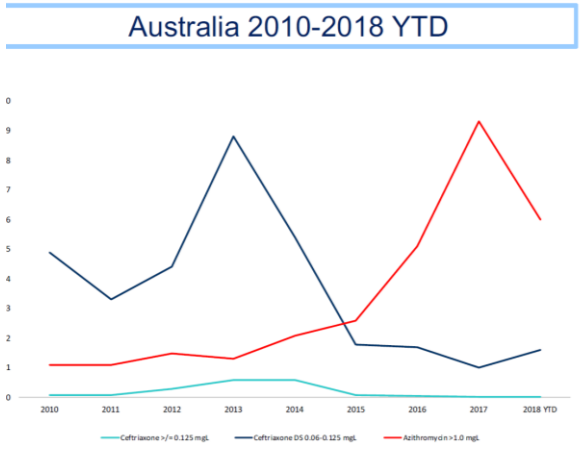
Treatment for uncomplicated *N. gonorrhoeae**

- **1995 - 2004**
  - ciprofloxacin 500mg
- **2004 – 2009**
  - ceftriaxone 250mg IM
- **2009 – 2012**
  - ceftriaxone 500mg IM
- **2012 – present**
  - ceftriaxone 500mg IM with azithromycin 1g

*Dates vary by state



AlfredHealth

http://www.health.gov.au/internet/main/publishing.nsf/content/cda-pubs-annlrpt-gonoanrep.htm
2018 data Lahra MM CDI In press with permission

Ceftriaxone treatment failures – almost all pharyngeal

Oral cefixime treatment failures were being reported by 2010
Ceftriaxone resistant, azithro less-susceptible, strain identified in Japan 2009
Ohnishi *Emerg Inf Dis* 2011

Pharyngeal gonococcal treatment failures with ceftriaxone alone

- Sydney n=2 Tapsall *J Med Microbiol* 2009
- Slovenia n=1 Unemo *Euro Surveill* 2012
- Sweden n=1 Unemo *Euro Surveill* 2011
- Melbourne n=1 Chen *J Antimicrob Chemother* 2013
- Sydney n=2 Read P *Sex Health* 2013
- Sweden n=3 Golparian *Euro Surveill* 2014

Case of failure of ceftriaxone 500mg IM and azithromycin 1g oral
Pharyngeal gonorrhoea acquired in Japan Dec 2014, treated in UK
Fifer *NEJM* 2016

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Adding azithromycin

UK outbreak

- 118 cases of high-level azithromycin resistant gonorrhoea in UK from Nov 2014 to May 2018.
- MIC >256 Mg/L
- Heterosexual then MSM, spread from Leeds to London

Smolarchuk et al *Euro Surveill* 2018

Hawaii

- 7 cases with MIC >16 mg/L and 5 less susceptible to ceftriaxone MIC = 0.125 mg/L

Katz *CID* 2017

South Australian outbreak

- 50 cases in first half of 2016
- MIC 1.0 – 8.0 mg/L
- All susceptible to ceftriaxone – one allergic patient Rx gentamicin 240mg IM

Lahra et al *Lancet ID* 2017

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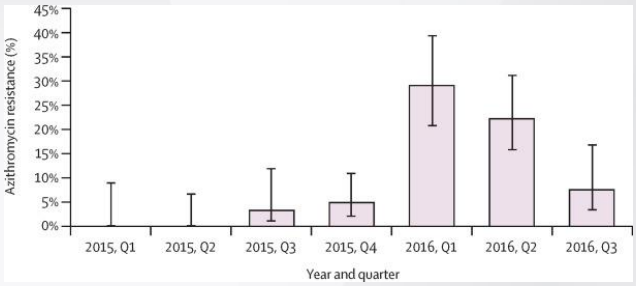

Figure. Azithromycin resistance levels among Neisseria gonorrhoeae isolates in the Australian state of South Australia (2015–16)Error bars denote 95% CI.

Monica M Lahra, Alison Ward, Ella Trembizki, Jamie Hermanson, Emma Clements, Andrew Lawrence, David Whiley

Treatment guidelines after an outbreak of azithromycin-resistant Neisseria gonorrhoeae in South Australia

Lancet Infectious Diseases, Volume 17, Issue 2, 2017, 133–134

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How much does azithromycin add to ceftriaxone?

Gentamicin 240 mg IM + 1g azithromycin *vs* ceftriaxone 500mg IM + azithromycin 1g, RCT n = 720

Ross J, International Society for STD Research conference, Rio de Janiero 2017

	Ceftriaxone + azithro 1g cleared	Gentamicin + azithro 1g cleared
Overall	98%	91%
Pharyngeal	96%	80%
Risk difference	- 15.3% (-24%, -6.5%)	
Rectal	98%	90%
Risk difference	-7.8% (-13.6%, -2%)	
Genital	98%	94%
Risk difference	-4.4% (-8.7%, 0%)	

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What options remain?

Ceftriaxone

- Cure requires 20 – 24 hours above MIC
- Most isolates MIC <0.06 mg/l
- In 2017 0.04% MIC ≥0.125 mg/l, two cases MIC 0.5 mg/l (2017)

MIC	500mg fT>MIC	1000mg fT>MIC
0.125 mg/l	33 hours	41 hours
0.5 mg/l	16 hours	23 hours (95%CI 11 – 50)

Lahra et al Emerg Inf Dis 2018
Chisolm *J Antimicrob Chem* 2010, Unemo *BMC Inf Dis* 2015

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Options

Azithromycin

- MICs in most resistant cases in UK are >256 mg/l
  - (n=4 in Australia, 2017)
- MICs in Australia mostly 1-2 mg/l “low level resistance” for which 2g dose likely to be effective

In development

- Topoisomerase inhibitors: zoliflodacin and gepotidacin

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Likely guideline response

Anogenital gonorrhoea
- ceftriaxone 500mg IM with azithromycin 1g oral

Oro-pharyngeal gonorrhoea
- ceftriaxone 500mg IM with azithromycin 2g oral

Practical considerations

For 2g azithromycin dose
- Use tablets not capsules
- With food

- Don't re-treat with 2g azithromycin if treated with ceftriaxone (+/- 1g azithromycin) for urethritis or PID etc
- Not essential for patients at increased risk of vomiting, QT prolongation

Alternative strategies
- Ceftriaxone 1g IM
- Test of cure at 3 weeks (NAAT) or 1 week (culture)

XDR *N. gonorrhoeae*

XDR gono

Three cases of extensively drug resistant *N. gonorrhoeae* isolated in Feb and March 2018. Two from Australia, one in UK.

Two were acquired in SE Asia.

Resistance profile

Resistant to: ceftriaxone (MIC 0.5 mg/l) and azithromycin (MIC>256 mg/l)

Also: penicillin and ciprofloxacin.

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Treating *N. gonorrhoeae*

Main points

- Obtain culture whenever treating gonococcal infection
- Pharyngeal infections at greatest risk of treatment failure
- Test of cure
- Ceftriaxone remains highly effective in almost all cases
- Azithromycin MAY prolong usefulness of ceftriaxone

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Mycoplasma genitalium

Trivia
- First genome to be sequenced
- Nobody (almost) can culture it except Jorgen Jensen's lab in Copenhagen
- Smallest free living organism

Seriously
- Causes 10 – 15% of non-gonococcal urethritis
- High prevalence in sexual contacts
  - MSM 42%, women 48%, hetero men 31% Slifirski *Emerg Inf Dis* 2017
- Consistent association with pelvic inflammatory disease, cervicitis, premature labor Lis et al *CID* 2015

Diagnosis
- NAAT - vaginal swab, first catch urine
- Don't confuse it with *M. hominis, U. urealyticum*

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M. genitalium – macrolide resistance

Azithromycin resistance
- Some assays report 23SRNA macrolide resistance mutation
- Macrolide resistance, once uncommon, now in 2/3 cases in Melbourne:
- 81% of MSM, 52% of heterosexuals (n=1100)
- Approx 10% of infections treated with azithromycin stat fail, selecting resistance

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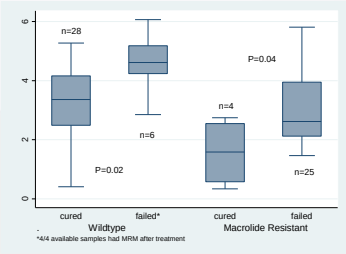
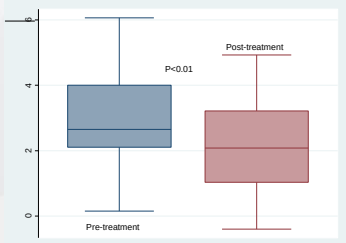
Bacterial load

Melbourne Sexual Health Centre (MSHC) audited outcomes of extended azithromycin 1.5g (500mg then 250mg daily x4) for NGU
58% of *M. genitalium* cured (95%CI: 49%, 68%)
12% (95%CI: 3%, 27%) of azithromycin-susceptible infections failed with selection of resistance
Read *Clin Infect Dis* 2017





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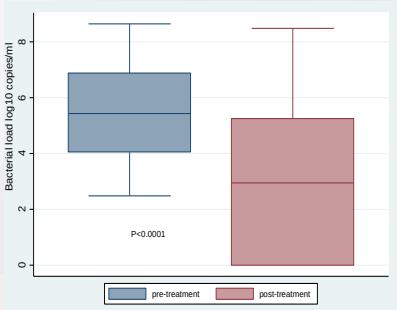
Bacterial load

56 men treated with doxycycline for NGU provided a second urine sample after 1 week when collecting second antibiotic
Results
Median 13 doses doxycycline (IQR 11-14)
6/56 (11%) load increased
28/56 (50%) load decreased
22/56 (39%, 95%CI: 26.5%, 53.2%) *M.genitalium* not detected
Overall mean 2.60 log_{10} (400-fold) decrease, P<0.0001



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M. genitalium – when to test, and when to wish you hadn't.

Urethritis
- Test for *N. gonorrhoeae, C. trachomatis* and *M. genitalium* (if available)

Pelvic inflammatory disease, cervicitis
- Test for *N. gonorrhoeae, C. trachomatis* and *M. genitalium* (if available)

Contacts
- Partners of the above in a continuing relationship – no need to trace past contacts

The expense and potential toxicity of treatment do not justify screening/testing:
- asymptomatic people,
- past contacts,
- syndromes not strongly associated with *M. genitalium* (epididymitis, proctitis)

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M. genitalium – how to treat.

Treat initial syndrome
- Non-gonococcal urethritis: doxycycline 100mg bd, 7 days

- Pelvic inflammatory disease (mild/moderate):
  doxycycline 100mg bd + metronidazole 400mg bd (both 14 days) + ceftriaxone 500mg stat

Doxycycline approx. 25% efficacy
- But lowers bacterial load, increasing likelihood of cure with macrolide

If *M. genitalium* detected
- PID switch to moxifloxacin immediately 400mg daily, 14 days

Macrolide resistance (known or suspected*)
- Complete doxycycline 7 days
- Moxifloxacin 400mg daily 7 days

Macrolide susceptible (known or optimistically suspected)
- Complete doxycycline 7 days
- Azithromycin 1g stat, then 500mg daily for 3 days (2.5g total)

*Macrolide resistance likely in MSM, previous azithromycin treatment

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Treating *M genitalium*.

Main points

- Consider cost, availability and toxicity of treatment before testing
- Test NGU and PID
- Do not screen asymptomatics
- Asymptomatic, macrolide resistant infection is common in MSM attending sexual health centres

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