The efficacy of azithromycin and doxycycline for the treatment of rectal chlamydia infection: a systematic review and meta-analysis

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Background: There are increasing concerns about treatment failure following treatment for rectal chlamydia with 1 g of azithromycin. A systematic review and meta-analysis was conducted to investigate the efficacy of 1 g of azithromycin as a single dose or 100 mg of doxycycline twice daily for 7 days for the treatment of rectal chlamydia.

Methods: Medline, Embase, PubMed, Cochrane Controlled Trials Register, Australia New Zealand Clinical Trial Register and ClinicalTrials.gov were searched to the end of April 2014. Studies using 1 g of azithromycin or 7 days of doxycycline for the treatment of rectal chlamydia were eligible. Gender, diagnostic test, serovar, symptomatic status, other sexually transmitted infections, follow-up time, attrition and microbial cure were extracted. Meta-analysis was used to calculate pooled (i) azithromycin and doxycycline efficacy and (ii) efficacy difference.

Results: All eight included studies were observational. The random-effects pooled efficacy for azithromycin (based on eight studies) was 82.9% (95% CI 76.0%–89.8%; $I^2 = 71.0\%$; P < 0.01) and for doxycycline (based on five studies) was 99.6% (95% CI 98.6%–100%; $I^2 = 0\%$; P = 0.571), resulting in a random-effects pooled efficacy difference (based on five studies) of 19.9% (95% CI 11.4%–28.3%; $I^2 = 48.5\%; P = 0.101$) in favour of doxycycline.

Conclusions: The efficacy of single-dose azithromycin may be considerably lower than 1 week of doxycycline for treating rectal chlamydia. However, the available evidence is very poor. Robust randomized controlled trials are urgently required.

Keywords: rectal chlamydia, meta-analysis, treatment efficacy, azithromycin, doxycycline

Introduction

Chlamydia trachomatis is the most common bacterial sexually transmitted infection (STI) worldwide1 with ~40% of diagnoses being among men.2–5 Although these data do not differentiate between rectal and non-rectal sites, data suggest that among MSM, the prevalence of rectal chlamydia is higher than urethral infection.6–10 There are also discussions about rectal infection among women and the potential for cervical autoinoculation of chlamydia from the rectal site.11–13 Rectal chlamydia infections are usually asymptomatic9,14 and regular screening of MSM is considered important,15 particularly because of the increased risk of HIV transmission and acquisition.16–18

Current guidelines for MSM in the USA recommend rectal chlamydia be treated with a single 1 g dose of azithromycin or 7 days (100 mg twice daily) of doxycycline.19 However, treatment failure rates from 13% to 21% have been reported12,20–22 and, in response, both European23 and Australian24 guidelines now recommend treating rectal chlamydia with 7 days of doxycycline, which can be associated with poor compliance.25

We conducted a systematic review and meta-analysis of all studies reporting microbial cure among those aged ≥15 years using 1 g of azithromycin as a single dose or 100 mg of doxycycline twice daily for 7 days for the treatment of rectal chlamydia.

Our primary aim was to measure pooled estimates of the efficacy of 1 g of azithromycin as a single dose or 100 mg of doxycycline
twice daily for 7 days for rectal chlamydia infection and our sec-
ondary aim was to measure the difference in efficacy between the
two treatments.

Methods
This systematic review and meta-analysis is reported according to the
PRISMA Statement.26

Protocol and registration
The study protocol was registered with Prospective Registration of
Systematic Reviews (registration number: CRD42013005645; http://
www.crd.york.ac.uk/PROSPERO/).

Search strategy
The electronic bibliographic databases of Medline (from 1946), Embase
(from 1974), PubMed (from 1946), ClinicalTrials.gov, Cochrane Controlled
Trials Register and the Australia New Zealand Clinical Trial Register were
searched to the end of April 2014. In addition, we hand-searched the refer-
cence lists of identified papers.
The search terms used were (‘chlamydia’ or ‘chlamydia trachomatis’)
AND (‘rect*’ or ‘anal’). Medical subject headings were used where possible.
The search strategy was not restricted to doxycycline or azithromycin in
order to capture all relevant articles.

Inclusion and exclusion criteria
We searched for any published studies providing microbial cure estimates
for either 1 g of azithromycin as a single dose or 100 mg of doxycycline
twice daily for 7 days for the treatment of rectal chlamydia in men and
women. Eligible studies were English language, included participants
aged ≥15 years and measured microbial cure (defined as a negative
test result at the last follow-up) following treatment. Observational and
experimental studies, including randomized controlled trials (RCTs), were
eligible. Studies of prostatitis treatment in men, lymphogranuloma vener-
um (LGV) specifically, different dosing regimens and review or discussion
papers were excluded. Conference abstracts cited in papers identified in
the electronic sources were also included if they fulfilled the inclusion
criteria.

Data extraction process
Data extracted from each study included: study design, treatment received,
sample size, gender, rectal signs/symptoms at diagnosis, diagnostic
method for assessing microbial cure, follow-up times, attrition, microbial
cure (at point of last follow-up) and concurrent STIs. In studies using geno-
typing to differentiate between LGV and non-LGV serovars, only confirmed
non-LGV cases were included in the analysis. One author (F. Y. S. K.) selected
the included studies and extracted the data and a second author (J. S. H.)
checked the selected studies and extracted data. Disagreements were
resolved by discussion and consultation with a further author (C. K. F.)
until a consensus was reached.

Outcomes
Primary outcome
Absolute treatment efficacy for azithromycin or doxycycline at the last
follow-up confirmed by microbial cure was calculated as follows: the
numerator is the number of treated patients with a microbial cure and the
denominator is the number of patients who were treated and tested.

Secondary outcome
Efficacy difference: doxycycline efficacy minus azithromycin efficacy at the
last follow-up.

Analysis
We reviewed the included studies for the efficacy of each drug at the last
follow-up. If studies reported efficacy at multiple timepoints, we reported
the estimate closest to 3 months because efficacy estimates prior to
8 weeks could include false positive diagnoses as a result of non-viable
chlamydia detected27 and estimates beyond 3 months are more likely
to include cases of reinfection.19 Meta-analysis was used to calculate
the pooled estimates of azithromycin and doxycycline efficacy. To minim-
ize misclassification bias, cases of reinfection identified in the studies using
sexual risk behaviour data were excluded from the analysis. Two publica-
tions by Elgalib et al.28,29 reported results from the same study and we
used data from the 2010 publication28 as this provided efficacy for both
drugs. For studies reporting both azithromycin and doxycycline efficacy,
we calculated a pooled efficacy difference. We used the I2 test to estimate
the approximate proportion of variability in point estimates attributed to
heterogeneity other than due to chance.30 Random-effects model results
were presented if I2 > 25% and fixed-effects model results if I2 ≤ 25%.
Pooled treatment efficacies were also calculated for studies with follow-up
between 3 and 12 weeks.12,20,21,28,31,32 No other subgroup analyses were
undertaken because of the small numbers of study participants.

Assessment of bias and quality
Publication bias was not assessed using a funnel plot because <10 studies
fulfilled the inclusion criteria.34 Assessment of within-study bias for obser-
vational studies was undertaken using the evaluation criteria adopted by
Sanderson et al.35 in their systematic review of tools used to assess bias in
observational studies. Meta-analysis was conducted using STATA (version
13; StataCorp, College Station, TX, USA).

Results
Study selection
Figure 1 outlines the review process and eligible papers are sum-
marized in Table 1. Of the 1744 references identified, 72 papers
were reviewed with 9 papers (8 studies) meeting the inclusion
criteria.

Study characteristics
All eight studies were observational with two studies12,32 using
prospectively collected data and the remaining six studies using
retrospective case note reviews. One paper35 provided secondary
data from an RCT of an HIV behavioural intervention.56 In total,
529 and 422 cases of rectal chlamydia were evaluated for azith-
romycin and doxycycline efficacy, respectively. Three studies
reported azithromycin efficacy only,20,21,32 with the remaining five reporting efficacy for both drugs. Six studies reported using
PCR tests to assess microbial cure15,20,22,28,32 with one study pro-
viding results using culture pre-2010 and PCR from 2010.32 Two
studies12,20 included both sexes, one study included women only32
and the remaining studies included only men.

Six studies included mainly (>97%) patients without rectal
signs/symptoms in their final analysis.12,20,21,28,31,32 Coinfection
with other STIs was reported in all but two studies.31,32 All studies
reported follow-up times of >3 weeks except for one study

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reporting multiple follow-up times; two studies measured cure in some patients at timepoints after 3 months. Seven studies reported attrition with three reporting attrition of ≥25%. Six studies had a total sample size.

Reported treatment efficacy for rectal chlamydia infections ranged from 55.6% to 94.1% and from 90.5% to 100% for azithromycin and doxycycline, respectively. The random-effects pooled efficacy for azithromycin (based on eight studies) was 82.9% (95% CI 76.0%–89.8%; I² = 71.0%; P = 0.013) and 25.8% (95% CI 12.4%–39.2%; I² = 50.9; P = 0.13), respectively (data not shown).

Study bias

Within-study bias

All but one study reported the sampling frame (Table 2 and Table S1, available as Supplementary data at JAC Online). Six studies addressed study biases, including four confirming LGV serovar using genotyping, two excluding LGV by symptoms and one using genotyping and/or symptoms to exclude LGV. The study by Elgalib et al. used genotyping mainly among symptomatic patients; Hathorn et al. used genotyping only among men to confirm LGV. Studies that investigated factors that could have contributed to treatment failure including poor drug absorption, use of non-protocol antibiotics, treatment non-compliance and reinfections were also reported. Possible reinfection was reported using sexual behaviour data in all but two studies.
Table 1. Attributes of studies reporting azithromycin or doxycycline efficacy

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Study type</th>
<th>Diagnostic method</th>
<th>Serovar</th>
<th>Males</th>
<th>Females</th>
<th>Symptomatic—rectal&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>HIV positive&lt;sup&gt;b&lt;/sup&gt;</th>
<th>STI coinfections&lt;sup&gt;b,c&lt;/sup&gt;</th>
<th>Follow-up time when test of cure undertaken</th>
<th>Attrition</th>
<th>Azithromycin efficacy&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Doxycycline efficacy&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>White, 2009&lt;sup&gt;11&lt;/sup&gt;</td>
<td>observational</td>
<td>not specified</td>
<td>non-LGV</td>
<td>137</td>
<td>0</td>
<td>0%</td>
<td>not specified</td>
<td>not specified</td>
<td>5 weeks</td>
<td>not specified</td>
<td>10/18 (55.6%)</td>
<td>119/119 (100%)</td>
</tr>
<tr>
<td>Steedman, 2009&lt;sup&gt;10&lt;/sup&gt;</td>
<td>observational</td>
<td>PCR</td>
<td>non-LGV&lt;sup&gt;e&lt;/sup&gt;</td>
<td>78</td>
<td>6</td>
<td>0%</td>
<td>17/97 (17.6%)</td>
<td>38/97 (39.2%) at any site</td>
<td>&gt;3 weeks</td>
<td>10/78 (12.8%)</td>
<td>61/68 (89.7%)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>NA</td>
</tr>
<tr>
<td>Elgalib, 2010&lt;sup&gt;18&lt;/sup&gt;</td>
<td>observational</td>
<td>PCR</td>
<td>non-LGV</td>
<td>252</td>
<td>0</td>
<td>0%</td>
<td>19%</td>
<td>6 weeks</td>
<td>0/252 (0%)</td>
<td>21/26 (80.8%)</td>
<td>68/158 (99.5%)</td>
<td>NA</td>
</tr>
<tr>
<td>Drummond, 2011&lt;sup&gt;21&lt;/sup&gt;</td>
<td>observational</td>
<td>PCR</td>
<td>non-LGV&lt;sup&gt;e&lt;/sup&gt;</td>
<td>116</td>
<td>0</td>
<td>0%</td>
<td>14/85 (16.5%)</td>
<td>26/85 (30.6%) at any site</td>
<td>median: 11 weeks</td>
<td>31/116 (26.7%)</td>
<td>80/85 (94.1%)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>NA</td>
</tr>
<tr>
<td>Hathorn, 2012&lt;sup&gt;12&lt;/sup&gt;</td>
<td>observational</td>
<td>PCR</td>
<td>non-LGV&lt;sup&gt;h&lt;/sup&gt;</td>
<td>94</td>
<td>73</td>
<td>females: 0% males: 5/167 (3.0%)</td>
<td>6/167 (3.6%)</td>
<td>34/167 (20.4%) at any site</td>
<td>6 weeks</td>
<td>85/167 (50.9%)</td>
<td>40/40 (100%)</td>
<td></td>
</tr>
<tr>
<td>Ding, 2013&lt;sup&gt;22&lt;/sup&gt;</td>
<td>observational</td>
<td>PCR</td>
<td>not specified</td>
<td>0</td>
<td>75</td>
<td>1/75 (1.3%)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>not specified</td>
<td>not specified</td>
<td>6 weeks</td>
<td>0/75 (0%)</td>
<td>NA&lt;sup&gt;k&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Khosropour, 2013&lt;sup&gt;35&lt;/sup&gt;</td>
<td>observational&lt;sup&gt;l&lt;/sup&gt;</td>
<td>not specified</td>
<td>not specified</td>
<td>338 men and women&lt;sup&gt;m&lt;/sup&gt;</td>
<td>not specified</td>
<td>not specified</td>
<td>6 months</td>
<td>37/338 (10.9%)</td>
<td>41/49 (83.7%)</td>
<td>19/21 (90.5%)</td>
<td>54/56 (96.4%)</td>
<td></td>
</tr>
<tr>
<td>Khosropour, 2014&lt;sup&gt;22&lt;/sup&gt;</td>
<td>observational</td>
<td>culture/PCR</td>
<td>not specified</td>
<td>1480</td>
<td>0</td>
<td>0%</td>
<td>92/502 (18.3%)</td>
<td>110/502 (21.9%)</td>
<td>2–13 weeks</td>
<td>978/1480 (66.1%)</td>
<td>180/230 (78.3%)</td>
<td>54/56 (96.4%)</td>
</tr>
</tbody>
</table>

NA, not available; GC, gonorrhoea.
<sup>a</sup>Symptoms among those included in final analysis.
<sup>b</sup>Numerator and denominator provided if data available.
<sup>c</sup>Coinfections at any site reported if coinfections at the rectal site was not available.
<sup>d</sup>Efficacy measured as microbial cure: numerator is number of treated subjects with a microbial cure and the denominator is the number of subjects assigned to the treatment and tested.
<sup>e</sup>Used anorectal symptoms partially or wholly to identify LGV patients.
<sup>f</sup>Excludes three possible false positives.
<sup>g</sup>Excludes six probable reinfections.
<sup>h</sup>Only male (not female) positive rectal samples were sent for LGV genotyping.
<sup>i</sup>Patient had concurrent perianal herpes simplex infection.
<sup>j</sup>Excludes two patients at risk of reinfection.
<sup>k</sup>No efficacy data reported for the 60 patients treated with doxycycline.
<sup>l</sup>Rectal chlamydia data were from a secondary analysis from an RCT of an HIV behavioural intervention.
<sup>m</sup>Study included both men and women but rectal infections were only among men.
with no studies using genotyping to assist discrimination between reinfection and treatment failure. Two studies adjusted for confounders using statistical methods, with one study reporting azithromycin treatment as the only factor associated with repeat positivity in the adjusted analysis.

Two studies considered false positive results and four studies reported the authors’ conflicts of interest and funding source. Sample size calculations were not reported in any study.

None of the studies reporting both doxycycline and azithromycin efficacy indicated when the test of cure was undertaken in each treatment group, raising the possibility of differential follow-up bias. In the study by Khosropour et al. there was a statistically significant higher proportion of patients treated with doxycycline rather than azithromycin who had anorectal symptoms or proctitis.

As no RCTs were identified, treatment was not randomly allocated and physician’s prescribing preferences were unknown, confounding by indication cannot be ruled out.

Discussion

Our meta-analysis reports an efficacy of 83% for single-dose azithromycin, >99% for 1 week of doxycycline and an efficacy difference of 20% in favour of doxycycline. While this suggests that doxycycline may be a more effective treatment, it must be emphasized that the quality of the evidence was poor. We found no RCT directly comparing azithromycin with doxycycline, so any observed differences could have arisen due to uncontrolled confounding.

There are several possible explanations for the observed differences in treatment efficacy. Firstly, it is unclear whether there were differences in the timing of microbial cure between the two treatments. If the follow-up test was measured at an earlier stage among doxycycline-treated patients, a lower efficacy among azithromycin-treated patients may be due to an increased opportunity for reinfection. We attempted to minimize this by excluding cases of suspected reinfection from our analysis.

However, in the absence of genotyping and sexual behaviour data, cases of reinfections could have been included in our analysis. In the study by Khosropour et al. there was a statistically significant higher proportion of patients treated with doxycycline rather than azithromycin who had anorectal symptoms or proctitis.

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of LGV cases in the UK being asymptomatic. Additionally, some men in the study by Elgalib et al. later developed proctitis despite initially being asymptomatic, confirming that signs/symptoms alone are poor predictors of rectal LGV. If those treated with azithromycin had a greater proportion of LGV cases than the doxycycline group, this could contribute to a lower azithromycin efficacy. Nevertheless, an apparent treatment efficacy of ~83% for azithromycin is concerning and is lower than the 94% reported in a recent meta-analysis evaluating treatment efficacy for urogenital infections. If azithromycin efficacy is lower, one possible factor contributing to this is the bioavailability of azithromycin in rectal tissue. With no pharmacokinetic data available, it remains unknown whether bioavailability in rectal mucosa is similar to that in urethral and cervical mucosa. Azithromycin has unique pharmacokinetic properties, being delivered to the site of infection by phagocytic cells (e.g., polymorphonuclear leukocytes (PMN)) released during the immune response following chlamydial infections. Animal studies investigating chlamydia in the large intestine have shown a lack of a local immune response and an absence of PMN. A recent study examining the inflammatory response to rectal chlamydia infections reported suppressed inflammatory cytokines in chlamydia-infected HIV-negative patients. Therefore, it may be biologically plausible that the lack of a local immune response in the rectum may attenuate azithromycin efficacy.

It is possible that an extended course of azithromycin may be more effective; however, in the absence of rectal pharmacokinetic data, the optimum dosing regimen is unknown. Further, extended courses may lead to reduced patient compliance and increased adverse events and may not provide any clear benefit over 1 week of doxycycline.

Women remain an understudied population with evidence suggesting rectal chlamydia may be common among women, and anal sex is increasing among heterosexuals and cervical autoinoculation of chlamydia from the rectal site is possible. Given the potential complications of cervical infection, this provides further evidence of the need for effective rectal treatments among women.

There are a number of limitations to our meta-analysis. Firstly, the analysis was based on poor-quality data: no RCTs were included, no sample size calculations were conducted and little control of confounding was undertaken. Further, there was considerable heterogeneity between studies with 71% heterogeneity found for studies reporting azithromycin efficacy and 49% heterogeneity for studies comparing doxycycline and azithromycin efficacy. All studies included in our review were observational and there was considerable variation in sample size and timing of when microbial cure was measured, which will have contributed to this heterogeneity. This makes interpretation of the results difficult. Our review was limited to published, English language studies, potentially reducing the generalizability of our findings. The use of conference abstracts that only present preliminary results and do not provide sufficient detail about study design is also a limitation. Lastly, undiagnosed cases of LGV or reinfection may have been included, leading to an underestimation of efficacy. To minimize this, we excluded any confirmed LGV cases or known cases of reinfection from analysis. Finally, we cannot rule out the impact of publication bias on our results and given that there is increasing discussion in the medical literature, it is possible that papers that report lower efficacy for azithromycin are being preferentially submitted for publication. The strengths of our systematic review are that we examined the potential for bias within studies using a validated tool.

**Conclusions**

Our meta-analysis showed that the efficacy of 1 g of azithromycin as a single dose for the treatment of rectal chlamydia infection may be considerably lower than that of 7 days of doxycycline. However, the available evidence is very poor and there are no pharmacokinetic data available for azithromycin in rectal mucosa. Given that HIV and STI rates continue to increase among MSM and anal sex is increasing in women, treatment for rectal chlamydia infection must be efficacious. Well-designed RCTs are urgently needed, but until results from these trials are available, clinicians should consider treating rectal chlamydia infection with 7 days of doxycycline.

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None to declare.

**Author contributions**

J. S. H. conceived the research question, wrote the protocol, checked extracted data, supervised the analysis and contributed to the manuscript. F. Y. S. K. extracted the data, conducted the analysis and wrote the manuscript. S. N. T., C. K. F., L. A. V., W. M. H., M. C. and C. B. contributed to the interpretation of the results and drafting of the manuscript. C. K. F. advised on the data extraction and contributed to drafting of the manuscript.

Table S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

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