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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) worldwide[1] 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 asymptomatic[9,14] 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 reported[12,20–22] and, in response, both European[23] and Australian[24] 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 secondary 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 reference 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 venereum (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 genotyping 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 detected[27] 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 minimize misclassification bias, cases of reinfection identified in the studies using sexual risk behaviour data were excluded from the analysis. Two publications by Elgalib *et al.*[28,29] reported results from the same study and we used data from the 2010 publication[28] as this provided efficacy for both drugs. For studies reporting both azithromycin and doxycycline efficacy, we calculated a pooled efficacy difference. We used the I^2 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 $I^2 > 25\%$ and fixed-effects model results if $I^2 \leq 25\%$. 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.[33] Assessment of within-study bias for observational studies was undertaken using the evaluation criteria adopted by Sanderson *et al.*[34] 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 summarized 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 studies[12,32] using prospectively collected data and the remaining six studies using retrospective case note reviews. One paper[35] provided secondary data from an RCT of an HIV behavioural intervention.[36] In total, 529 and 422 cases of rectal chlamydia were evaluated for azithromycin 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 cure[12,20–22,28,32] with one study providing results using culture pre-2010 and PCR from 2010.[22] Two studies[12,20] included both sexes, one study included women only[32] 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.[31,35] All studies reported follow-up times of >3 weeks except for one study

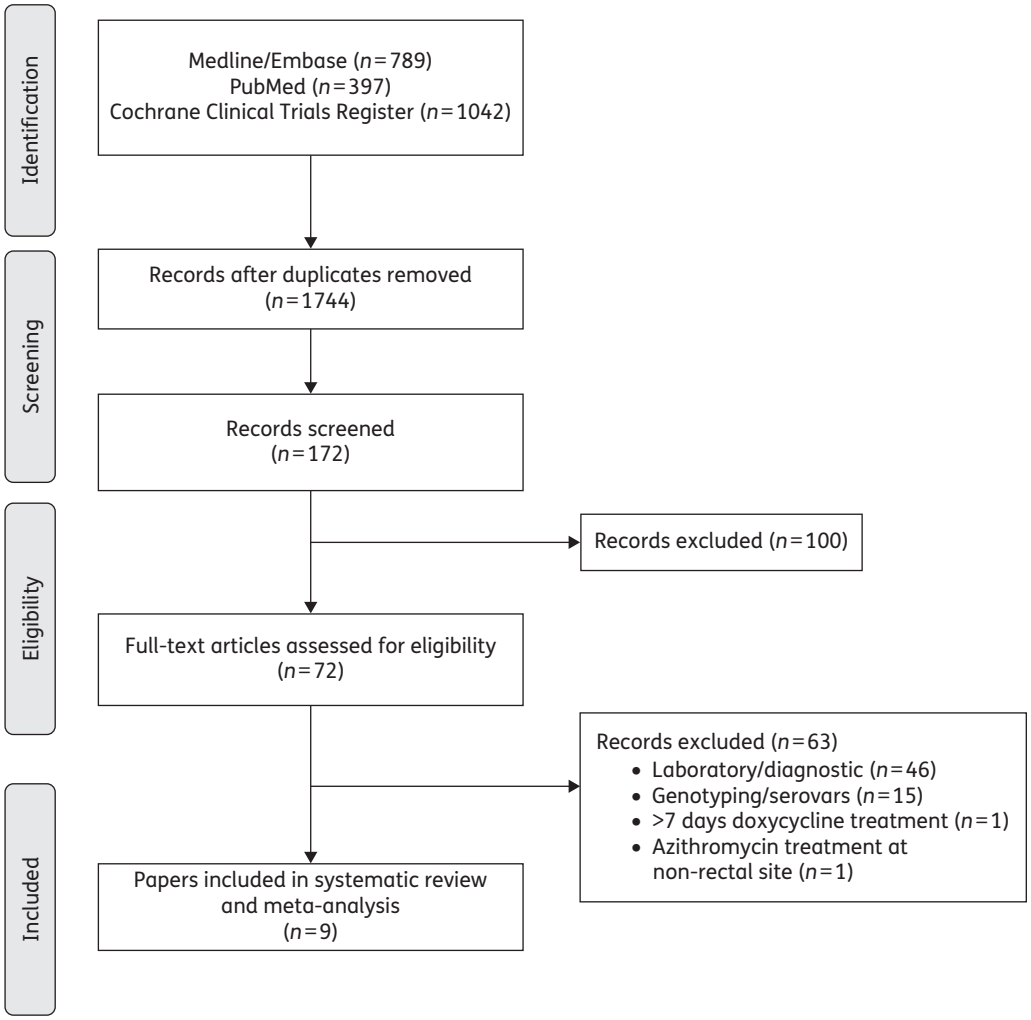

Figure 1. Identification of eligible studies in a systematic review of 1 g of azithromycin as a single dose and 100 mg of doxycycline twice daily for 7 days for the treatment of rectal chlamydia infections.

reporting multiple follow-up times;[22] two studies measured cure in some patients at timepoints after 3 months.[21,35] Seven studies reported attrition[12,20–22,28,32,35] with three reporting attrition of ≥25%.[12,21,22] Six studies had a total sample size >100.[12,21,22,28,31,35]

Treatment efficacy

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%; $I^2=71.0\%$; $P<0.01$) (Figure 2) and for doxycycline (based on five studies) the fixed-effects estimate was 99.6% (95% CI 98.6%–100%; $I^2=0\%$; $P=0.571$) (Figure 3). The random-effects pooled efficacy difference (based on five studies) was 19.9% (95% CI 11.4%–28.3%; $I^2=48.5\%$; $P=0.101$) in favour of doxycycline (Figure 4).

Among six studies that measured cure between 3 and 12 weeks after treatment,[12,20,21,28,31,32] the random-effects pooled efficacy for azithromycin and efficacy difference were 83.8% (95% CI 75.1%–92.5%; $I^2=65.3$ %; $P=0.013$) and 25.8% (95% CI 12.4%–39.2%; $I^2=50.9$; $P=0.13$), respectively (data not shown).

Study bias

Within-study bias

All but one study[31] reported the sampling frame (Table 2 and Table S1, available as Supplementary data at *JAC* Online). Six studies[12,20–22,28,32] addressed study biases, including four confirming LGV serovar using genotyping,[12,20,29,31] two excluding LGV by symptoms[20,21] and one using genotyping and/or symptoms to exclude LGV.[20] The study by Elgalib *et al.*[29] used genotyping mainly among symptomatic patients; Hathorn *et al.*[12] used genotyping only among men to confirm LGV. Studies that investigated factors that could have contributed to treatment failure including poor drug absorption,[20] use of non-protocol antibiotics,[12,22,29] treatment non-compliance[12] and reinfections[12,20–22,28,32] were also reported. Possible reinfection was reported using sexual behaviour data in all but two studies[29,31]

Table 1. Attributes of studies reporting azithromycin or doxycycline efficacy

Study, year	Study type	Diagnostic method	Serovar	Males	Females	Symptomatic—rectal[a,b]	HIV positive[b]	STI coinfections[b,c]	Follow-up time when test of cure undertaken	Attrition	Azithromycin efficacy[d]	Doxycycline efficacy[d]
White, 2009[31]	observational	not specified	non-LGV	137	0	0%	not specified	not specified	5 weeks	not specified	10/18 (55.6%)	119/119 (100%)
Steedman, 2009[20]	observational	PCR	non-LGV[e]	78	6	0%	17/97 (17.6%)	38/97 (39.2%) at any site	>3 weeks	10/78 (12.8%)	61/68 (89.7%)[f]	NA
Elgalib, 2010[28]	observational	PCR	non-LGV	252	0	0%	19%	12% (rectal GC)	6 weeks	0/252 (0%)	21/26 (80.8%)	185/186 (99.5%)
Drummond, 2011[21]	observational	PCR	non-LGV[e]	116	0	0%	14/85 (16.5%)	26/85 (30.6%) at any site	median: 11 weeks	31/116 (26.7%)	80/85 (94.1%)[g]	NA
Hathorn, 2012[12]	observational	PCR	non-LGV[h]	94	73	females: 0% males: 5/167 (3.0%)	6/167 (3.6%)	34/167 (20.4%) at any site	6 weeks	85/167 (50.9%)	33/42 (78.6%)	40/40 (100%)
Ding, 2013[32]	observational	PCR	not specified	0	75	1/75 (1.3%)[i]	not specified	1/97 (1.0%) rectal GC	6 weeks	0/75 (0%)	9/11 (81.8%)[j]	NA[k]
Khosropour, 2013[35]	observational[l]	not specified	not specified	338 men and women[m]		not specified	not specified	not specified	6 months	37/338 (10.9%)	41/49 (83.7%)	19/21 (90.5%)
Khosropour, 2014[22]	observational	culture/PCR	not specified	1480	0	92/502 (18.3%)	110/502 (21.9%)	60/502 (12.0%) urethral CT and 91/502 (18.1%) rectal GC	2–13 weeks	978/1480 (66.1%)	180/230 (78.3%)	54/56 (96.4%)

NA, not available; GC, gonorrhoea.
[a]Symptoms among those included in final analysis.
[b]Numerator and denominator provided if data available.
[c]Coinfections at any site reported if coinfections at the rectal site was not available.
[d]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.
[e]Used anorectal symptoms partially or wholly to identify LGV patients.
[f]Excludes three possible false positives.
[g]Excludes six probable reinfections.
[h]Only male (not female) positive rectal samples were sent for LGV genotyping.
[i]Patient had concurrent perianal herpes simplex infection.
[j]Excludes two patients at risk of reinfection.
[k]No efficacy data reported for the 60 patients treated with doxycycline.
[l]Rectal chlamydia data were from a secondary analysis from an RCT of an HIV behavioural intervention.
[m]Study included both men and women but rectal infections were only among men.

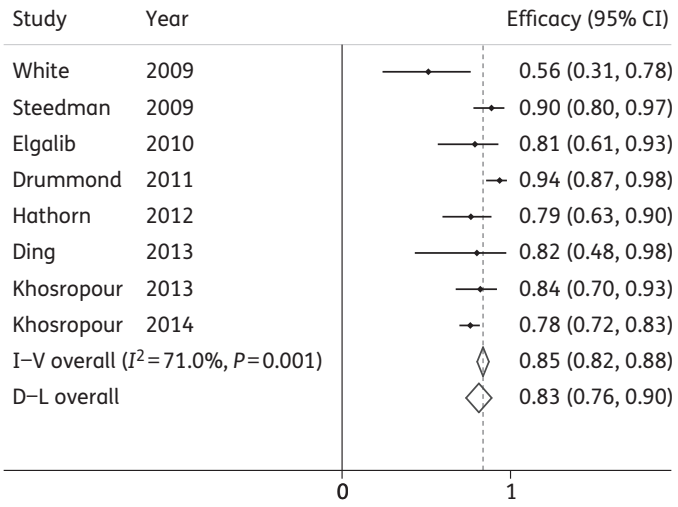

Figure 2. Efficacy of 1 g of azithromycin as a single dose for the treatment of rectal chlamydia infections. I–V, inverse-variance (fixed) method; D–L, DerSimonian and Laird (random-effects) method; I^2, test for heterogeneity.

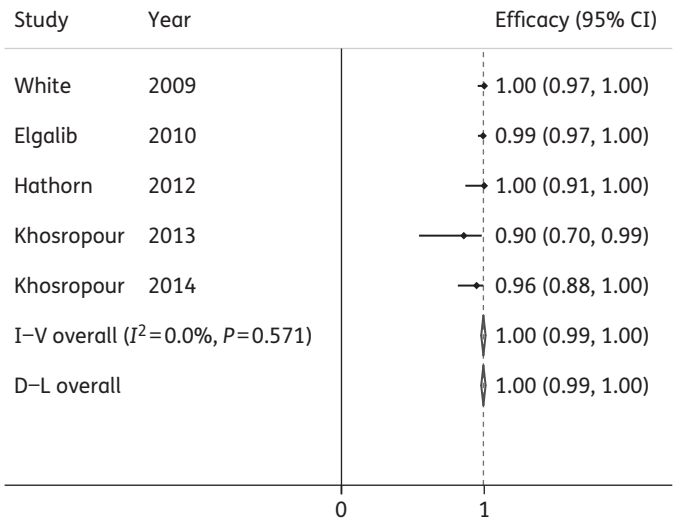

Figure 3. Efficacy of doxycycline (100 mg twice daily) for 7 days for the treatment of rectal chlamydia infections.

with no studies using genotyping to assist discrimination between reinfection and treatment failure. Two studies adjusted for confounders using statistical methods[22,35] with one study[22] reporting azithromycin treatment as the only factor associated with repeat positivity in the adjusted analysis.

Two studies considered false positive results[20,22] and four studies reported the authors' conflicts of interest and funding source.[12,22,29,32] 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

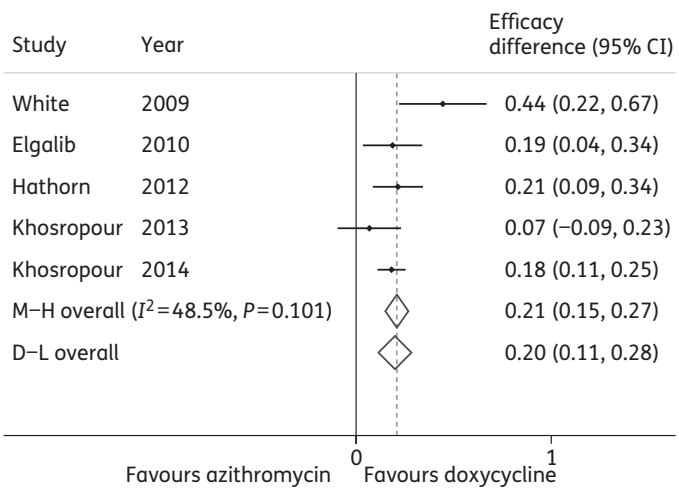

Figure 4. Efficacy difference between 7 days of doxycycline versus single-dose azithromycin for the treatment of rectal chlamydia infections. M–H, Mantel–Haenszel (fixed) methods.

follow-up bias. In the study by Khosropour *et al.*[22] 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. We investigated this further by analysing only studies that measured cure at 3–12 weeks post-treatment and this still showed doxycycline was considerably more efficacious. Secondly, it is possible that taking a daily dose of doxycycline may deter patients from resuming sex, thereby reducing their risk of reinfection during the first week of treatment, although this is not possible to assess without comprehensive sexual behaviour data. Thirdly, in the absence of genotyping, it is possible that cases of undiagnosed LGV were included in our analysis given five of eight studies were from the UK[12,20,28,31,32] and there have been reports of up to 17%

Table 2. Summary of risk of bias for included studies[a]

	Methods for selection of participants	Methods for measuring exposure and outcome variables	Methods to control confounding	Statistical methods	Conflict of interest
White, 2009	NR	+	NR	++	NR
Steedman, 2009	+	++	++	++	NR
Elgalib, 2011	++	++	++	++	+
Drummond, 2011	++	++	++	++	NR
Hathorn, 2012	++	++	++	++	+
Ding, 2013	++	+++	++	++	+
Khosropour, 2013	++	NR	++	++	NR
Khosropour, 2014	++	+++	++	++	+

Key: +, low risk of bias; ++, moderate risk of bias; +++, high risk of bias; NR, no information provided.
[a]See Table S1 for included studies.

of LGV cases in the UK being asymptomatic.[7] Additionally, some men in the study by Elgalib *et al.*[29] later developed proctitis despite initially being asymptomatic, confirming that signs/symptoms alone are poor predictors of rectal LGV.[37,38] 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.[39] 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 leucocytes (PMN)] released during the immune response following chlamydial infections.[40,41] Animal studies investigating chlamydia in the large intestine have shown a lack of a local immune response and an absence of PMN.[42] A recent study examining the inflammatory response to rectal chlamydia infections reported suppressed inflammatory cytokines in chlamydia-infected HIV-negative patients.[43] Therefore, it may be biologically plausible that the lack of a local immune response in the rectum may attenuate azithromycin efficacy.[44]

It is possible that an extended course of azithromycin may be more effective;[45,46] 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[47,48] 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,[49,50] anal sex is increasing among heterosexuals[51,52] and cervical autoinoculation of chlamydia from the rectal site is possible.[11–13] 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,[53,54] 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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Transparency declarations

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.

Supplementary data

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

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