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Non-standard treatment for uncomplicated *Chlamydia trachomatis* urogenital infections: a systematic review

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ABSTRACT

Objectives To review the literature for non-standard treatment options for uncomplicated *Chlamydia trachomatis* (CT) infections in adolescents and adults.

Design Systematic review.

Data sources Ovid MEDLINE/PubMed, Ovid EMBASE, Cochrane Trials & Systematic Review Databases, CINAHL Plus with Full Text, Web of Science Core Collection, Scopus, ProQuest Dissertations & Theses Global, ClinicalTrials.gov and Health Canada Trials Database were searched for studies in English or French from 1 January 2006 to 6 August 2017. Keywords included CT, anti-infective or antibacterial agents, therapy/pharmacotherapy/management.

Review methods Included were primary research studies. Outcome measures included clinical or microbiological cure, treatment failure and adverse events. We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Studies were assessed for risk of bias using the Revised Cochrane Risk of Bias V.2.0 tool for randomised and the Newcastle-Ottawa Quality Assessment Scale for non-randomised studies.

Funding source Public Health Agency of Canada.

Results Of the 6899 records identified through the database search, 11 studies were included. One randomised controlled trial reported that delayed release doxycycline was non-inferior to azithromycin. Two studies examined higher doses of azithromycin but reported no additional benefit. One study looked at a 5-day azithromycin treatment regimen and reported a high cure rate. Two studies reported efficacy of sitafloxacin, and a single study supports the use of levofloxacin. Two phase 2 studies reported efficacy of single-dose rifalazil in both men and women. Only one retrospective study was identified that examined treatment in pregnant women and reported that efficacy with single-dose azithromycin exceeded that of amoxicillin and erythromycin. A single study examining the efficacy of a beta-lactam antibiotic was stopped early due to high treatment failures.

Conclusions The paucity of existing data highlights the need for further adequately powered studies to evaluate rifalazil, delayed release doxycycline, levofloxacin and other agents for the treatment of uncomplicated CT infections.

PROSPERO registration number CRD42017073096.

Strengths and limitations of this study

- ► This review assesses non-standard treatment for *Chlamydia trachomatis* urogenital infections, a significant cause of global morbidity.
- ► A broad search strategy was used, including studies in English and French and not restricting the geographical location of the studies.
- ► Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Cochrane quality assessment tools were used to conduct the review.
- ► Studies published after August 2017 were not included in the original study design.
- ► The small number of included studies together with the variation in study methodologies precluded meta-analysis.

BACKGROUND

Urogenital *Chlamydia trachomatis* (CT), caused by serovars D-K, is the most commonly diagnosed and reported bacterial sexually transmitted infection (STI).[1] In 2012, WHO estimated that 131 million new cases of chlamydia occurred with a global incidence rate of 38 per 1000 females and 33 per 1000 males; in many countries, the incidence is highest among adolescents aged 15–19 years.[1] In Canada, the reported incidence has steadily increased since 1998; between 2005 and 2014, reported cases of chlamydia increased 49% from 206 to 307 per 100 000, with the highest relative rate increase among males.[2] Urogenital infections are often asymptomatic in both genders, but if untreated can lead to complications of pelvic inflammatory disease, ectopic pregnancy, infertility and epididymo-orchitis.[3 4] CT infections of the rectum are mainly asymptomatic but infection can also result in rectal discharge and discomfort.[5] Pharyngeal infections are usually asymptomatic but patients may experience a mild sore throat.[6]

For many years, the standard treatment for CT infections in Canadian and other global guidelines has included azithromycin (1 g orally single dose) or doxycycline (100 mg orally two times daily for 7 days).[1 7–11] A meta-analysis of 23 randomised controlled

trials comparing these regimens reported efficacies of 96.2% (95% CI 94.9% to 97.5%) for azithromycin and 97.4% (95% CI 96.2% to 98.7%) for doxycycline, a small increase in efficacy for doxycycline.[12] The overall 3% increased efficacy for doxycycline compared with azithromycin increased to 7% increased efficacy for the treatment of symptomatic urethral infection in men. Another meta-analysis including eight observational studies comparing azithromycin with doxycycline for rectal chlamydia infections reported a pooled efficacy difference of 19.9% (95% CI 11.4% to 28.3%) in favour of doxycycline.[13]

Although azithromycin and doxycycline are the standard treatments, there is concern that cure rates might be declining for both these drugs due to antimicrobial resistance (although of note, no antimicrobial resistance to CT has been reported to date), increasing the need for alternative regimens.[14] Alternate treatment options are also required in individuals who have allergies or intolerances to tetracycline (doxycycline or tetracycline) or macrolide (azithromycin or erythromycin) antibiotics, or where drug interactions may occur. In addition, due to rising antimicrobial resistance in gonorrhoea to both azithromycin and doxycycline, alternate agents for patients coinfected with both gonorrhoea and chlamydia are desirable. Other antibiotics listed in the guidelines include quinolones (ofloxacin, levofloxacin, sitafloxacin) and amoxicillin, all requiring multiday courses of treatment thus raising concerns about adherence.[1 7–11]

Given the limited treatment options for CT, we conducted a systematic review to determine alternate options to the standard regimens for CT infections in adolescent (13–19 years of age) and adults (older than 19 years of age).

METHODS

This study was performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[15]

Search strategy

The search was conducted with the assistance of two librarians, who conducted the search independently of each other. Ovid MEDLINE/PubMed, Ovid EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CINAHL Plus with Full Text, Web of Science Core Collection, Scopus, ProQuest Dissertations & Theses Global, ClinicalTrials.gov and Health Canada Trials Database were searched from 1 January 2006 to 6 August 2017. Only English and French language studies were included. For more details, see table 1.

Table 1 Systematic literature search strategy protocol

Criteria for studies	Inclusion	Language: English and French literature. Search period: 1 January 2006 to 6 August 2017. Population: adolescents (13–19 years) and adults (>19 years) with non-LGV *Chlamydia trachomatis* infections (urethral, endocervical, rectal, conjunctival). Intervention: any antibiotic used for treatment other than azithromycin and doxycycline. Comparison: preferred therapy (azithromycin or doxycycline), other antibiotics, no therapy, placebo. Outcomes: effectiveness outcomes: clinical cure (complete/partial), microbiological cure (nucleic acid amplification test and/or culture and/or immunofluorescence and or enzyme immunoassay negative), symptom resolution, clinical and microbiological cure rate, pain, infertility, treatment failure. Unintended effects: adverse events during treatment, development of antimicrobial resistance. Study design: inclusion: primary research studies, including: Interventional studies (randomised controlled trials, controlled clinical trials), observational studies (cohort, case–control, cross-sectional) and modelling studies. Exclusion: case reports, case series, modelling studies, letters, comments, opinion pieces, narrative reviews.
	Exclusion	If multiple publications report the same data, the most relevant publication will be used.
Databases		Ovid MEDLINE/PubMed Ovid EMBASE Cochrane Central Register of Controlled Trials Cochrane Database of Systematic Reviews CINAHL Plus with Full Text Web of Science Core Collection Scopus ProQuest Dissertations & Theses Global ClinicalTrials.gov Health Canada Trials Database
Keywords (only primary ones listed)*		*C. trachomatis* (exp. or abbreviated); anti-infective agents/or antibacterial agents (includes general search terms and specific drugs); therapy/pharmacotherapy/management.

*See online supplementary file for MeSH headings.
LGV, lymphogranuloma venereum; MeSH, Medical Subject Heading.

Inclusion and exclusion criteria

All primary research studies including interventional studies (randomised controlled trials, controlled clinical trials) and observational studies (cohort, case–control, cross-sectional) were included in the review. Excluded studies were case reports, case series, modelling studies, letters, comments, opinion pieces, narrative reviews and studies using non-standardised genital testing. The study population were adolescents (13–19 years) and adults (>19 years) with non-lymphogranuloma venereum (LGV) CT infections (urethral, endocervical, rectal, conjunctival).

Data extraction process

The following data were extracted from the included studies: author, year of publication, study design, diagnostic method, sample size, population characteristics, symptomatic status, HIV status, STI coinfection and timing for test of cure and attrition. We also extracted information on treatment outcomes.

Outcomes

Treatment efficacy for the standard antibiotic (azithromycin 1 g orally single dose or doxycycline 100 mg orally two times a day for 7 days) versus the comparator antibiotic for randomised trials, or antibiotics used in prospective open label or retrospective studies were noted. Outcomes of included studies were clinical cure (complete/partial), microbiological cure (nucleic acid amplification test and/or culture and/or immunofluorescence and or enzyme immunoassay negative), symptom resolution, clinical and microbiological cure rate, treatment failure (TF) and adverse events during treatment.

Analysis

The analysis of this systematic review was descriptive. We considered meta-analysis to synthesise the data from several studies into a single estimate or effect size, however, this was not warranted. Treatment (both for standard and comparators) varied between individual studies except for two studies examining the efficacy of sitafloxacin[16 17] and two examining the efficacy of rifalazil.[18 19] For meta-analysis, it is advisable to have at least three studies with similar outcomes for data to be pooled in meaningful ways. Population characteristics also differed between studies, increasing the heterogeneity of studies and making data pooling less desirable. The dosage of treatments also varied between studies making it difficult to pool data.

Assessment of bias and quality

Two independent reviewers (JK and AL) assessed the risk of bias of included randomised controlled trials using the Revised Cochrane Risk of Bias V.2.0 tool for randomised[20] and the Newcastle-Ottawa Quality Assessment Scale[21] for non-randomised studies.

Patient and public involvement

No patient or public involvement was sought prior to conducting this systematic review.

RESULTS

Study selection

Of the 6899 records identified through the database search, 5706 records were reviewed. Fifty-seven articles were assessed for eligibility and 11 studies were included.[16–19 22–28] Figure 1 summarises the review process.

Characteristics of included studies

The attributes of the 11 cited studies are summarised in table 2.

Of note, although the search criteria included all non LGV CT infections involving urethral, endocervical, rectal and conjunctival sites, only studies from urogenital sites met criteria for inclusion in this systematic review.

Four studies were randomised trials,[18 19 22 23] while five were prospective single-arm, open-label studies,[16 17 24 26 27] one was a retrospective cohort study[25] and one a cohort study.[28] Of these, the majority of the studies included males only.[16–18 24 26 27] Two studies included female patients[19 25] and three studies included both males and females.[22 23 28] One retrospective study compared outcomes in pregnant patients.[25] For diagnostic methods, six studies used the GenProbe Aptima Combo 2 assay for diagnosis of chlamydia,[16–19 23 27] four used other molecular diagnostic tests[24–26 28] and one older study used McCoy tissue culture.[22]

Only 1 of the 11 studies specified whether patients were clinically symptomatic.[23] HIV-positive patients were either excluded from the study[23] or were not recruited in the study,[18] or their HIV status was not reported.[16 17 19 22 24–28] Patients with STI coinfection were excluded in two studies[17 23] and coinfections were not reported in three studies.[18 22 24] The remainder reported STI coinfections.[16 19 25–28] Follow-up times for test of cure ranged from 21 to 42 days, with one study[28] up to 43 weeks.

Table 3 summarises the interventions and outcomes of the studies.

Two studies examined the effect of delayed release (DR) formulations of doxycycline or azithromycin[23 27] and one study examined a 5-day azithromycin treatment regimen.[28] The DR formulation of doxycycline was non-inferior to the standard formulation of doxycycline with regard to efficacy, and was associated with fewer adverse events, such as nausea and vomiting.[23] Additionally, the DR formulation had the benefit of being dosed once daily versus the two times daily dosing regimen of standard doses of doxycycline. Takahashi *et al* conducted a single-arm prospective study of extended release azithromycin 2 g orally single dose and reported a rate of microbiological cure of CT of 91.5%, but 35% of patients experienced diarrhoea which resolved (on its own) within 1 day.[27] Topic *et al* compared azithromycin 1 g orally single dose given weekly for three doses, with azithromycin 1 g orally single dose and found no additional benefit (such as tolerability) to the higher total dose.[22] Unemo *et al* examined the effects of a 5-day azithromycin treatment (500 mg orally on day 1, followed by 250 mg orally daily

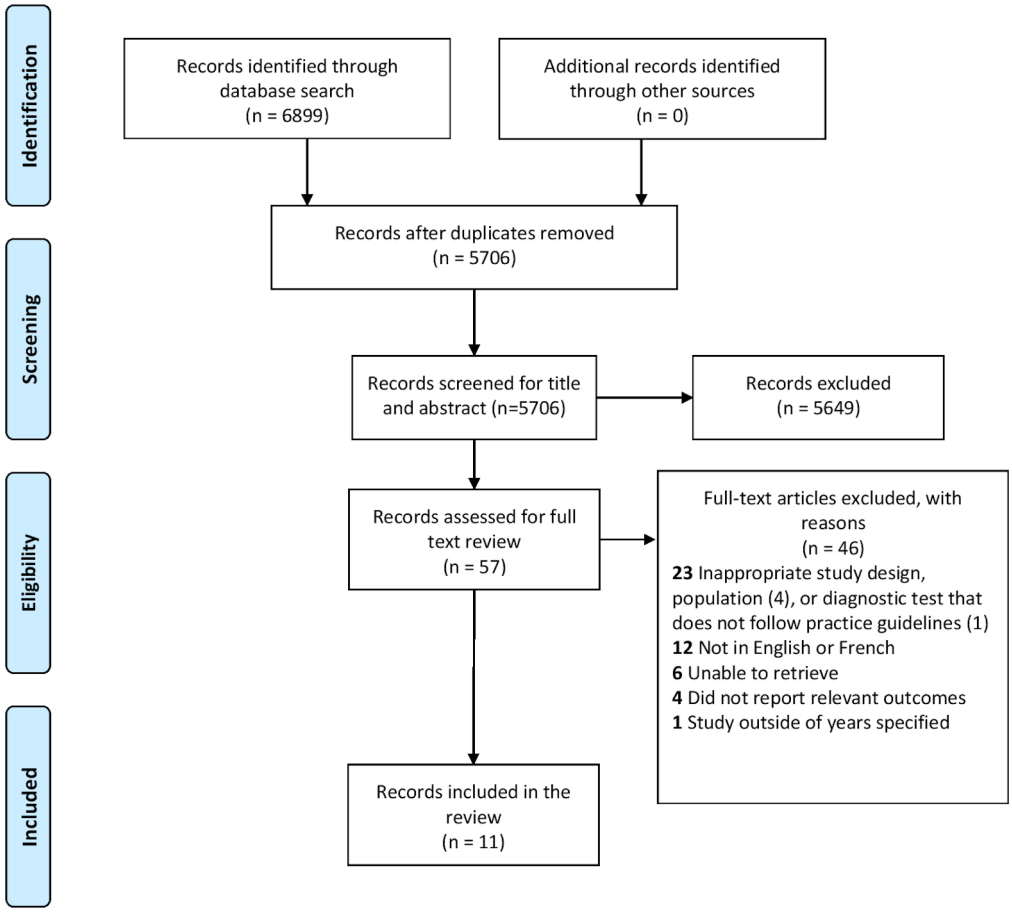

Figure 1 PRISMA flow diagram of study selection. From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7):e1000097. doi: 10.1371/journal.pmed1000097.

for 4 days) and found it 98.8% effective; however, no CIs were reported.[28]

One retrospective study of pregnant women reported the highest efficacy with azithromycin 1 g single oral dose when compared with erythromycin 500 mg orally four times daily for 7 days or amoxicillin 500 mg orally three times daily for 7 days; reported treatment efficacies were 97% (95% CI 92.9% to 99.2%), 64% (95% CI 44.1% to 81.4%) and 95% (95% CI 76.2% to 99.9%), respectively.[25] No differences in complications were reported for women or infants exposed to azithromycin as compared with those treated with erythromycin or amoxicillin.[25]

Nilsen *et al* examined the effect of pivmecillinam hydrochloride but the study was terminated early due to a high failure rate in patients receiving this drug.[24]

Two studies compared the effect of rifalazil with azithromycin 1 g orally single dose for treatment of CT.[18 19] Stamm *et al* determined that rifalazil 25 mg orally single dose had similar cure rates to azithromycin at 2 and 5 weeks, but a higher rate of microbiological cure at 5 weeks. Rifalazil patients were more likely to experience headaches, while azithromycin treated patients were more likely to experience gastrointestinal side effects. The study by Geisler *et al* confirmed similar microbiological cure and overall rates of adverse events with rifalazil 25 mg orally single dose and azithromycin 1 g orally single dose.

A single-arm prospective study reported a microbiological cure rate for CT of 92% and clinical cure rate of 94%–100% with levofloxacin 500 mg orally daily for 7 days.[26] Five per cent of subjects reported adverse events, all of which were mild and improved without treatment.

Two prospective single arm studies examined the effect of sitafloxacin 100 mg two times daily for 7 days in males.[16 17] Takahashi *et al* reported a microbiological cure of 95.7% for CT[17] while Ito *et al* reported a cure rate of 100%.[16] One of the studies reported that 1.7% experienced mild diarrhoea with the sitafloxacin.[17]

Risk of bias assessment

All included studies were assessed for risk of bias (see table 2 for details). While no studies were excluded based on the risk of bias assessment, most studies had moderate or higher risk of bias, which was often due to the study design selected and a lack of data included in publications.

DISCUSSION

The results of our systematic review identified 11 studies examining alternatives to the standard treatment regimens

Table 2 Characteristics of included studies

First author, year and reference no	Study design	Diagnostic method	Sample size	Population characteristics			Symptomatic*†	HIV positive	STI coinfection†‡	Follow-up time to test of cure	Attrition	Risk of Bias+low ++medium +++high
				Male	Female	Other						
Geisler, 2012[23]	Randomised, double-blind, double-dummy, active-controlled, multicentre phase 3.	Gen-Probe APTIMA Combo 2 assay.	n=495 mITT n=378	38%	62%	Age: 19–45 Urogenital chlamydia diagnosis within preceding 14 days or a sexual partner with chlamydia. Exclusion: pregnant or breast feeding.	182 out of 378 (discharge observed and reported).	Excluded	Excluded	Day 21–42 post-treatment.	n=4 withdrew due to adverse events.	++
Takahashi, 2014[27]	Prospective, open label, single-arm clinical study.	Gen-Probe APTIMA Combo 2 assay.	200 patients included: 55 with gonococcal urethritis (GU) 145 with non-GU (NGU).	100%		Age: >20 heterosexual male patients with both GU and NGU.	Yes, but no n reported	Not reported	n=48 (n=2 *Mycoplasma genitalium*; n=3 *Ureaplasma urealyticum*; n=43 *Neisseria gonorrhoeae*).	Day 7–27 post-treatment.	n=80 n=61 had no second visit; n=3 lack of data; n=16 violation of protocol.	+++
Topic, 2006[22]	Prospective, comparative, randomised.	McCoy culture	n=100	46%	54%	Age: >18 Men who were sexual partners of female patients with chlamydial mucopurulent cervicitis. Females who were sexual partners of patients with chronic prostatitis caused by *Chlamydia trachomatis*.	Not reported	Not reported	Not reported	4 weeks after completion of treatment.	Not reported	+++
Unemo, 2015[28]	Cohort study	Nucleic acid amplification testing.	n=85	36%	64%	Age: 18–51 Initiation of treatment varied from 4 days to 5 weeks once a positive test result was obtained.	Not reported	Not reported	100% positive or *M. genitalium.*	4–43 weeks, with a median time of 6 weeks.	Not reported	+++
Rahangdale, 2006[25]	Retrospective cohort study.	DNA hybridisation probe.	611 meeting inclusion criteria; 277 enrolled (abortions=250; ectopic Pregnancy=3; unable to locate chart=81).		100%	Age: 14–39 Female patients with a positive chlamydia test within 280 days after a positive pregnancy test. Excluded women with abortions and ectopic pregnancies.	None reported	None reported	n=58 (n=9 cases gonorrhoea, n=7 cases trichomonas, no syphilis; n=37 cases of bacterial vaginosis, n=5 herpes simplex virus)	3–4 weeks post-treatment start.	n=87 52 did not have a test-of-cure (TOC) 7 days or more after treatment; 35 patients had received non-standardised drugs or a change in treatment.	++
Nilsen, 2016[24]	Prospective, single arm open label.	PCR	Intended n=50; study terminated after 20 participants due to treatment failures.	100%		Heterosexual men only asymptomatic.	None reported	None reported	None reported	The primary endpoint was a negative. TOC sample 3–6 weeks after treatment.	None reported	+++
Stamm, 2007[18]	Randomised, double-blind trial, phase 2.	Gen-Probe APTIMA Combo 2 assay.	170 males.	100%		Age: 18–45 Symptoms of NGU of no more than 14 days; required to have history of urethral discharge or observable discharge at time of examination.	None reported	None	None	2 and 5 weeks post-treatment start.	n=89 13 lost to follow-up; 76 protocol violation.	++

Continued

Table 2 Continued

First author, year and reference no	Study design	Diagnostic method	Sample size	Population characteristics			Symptomatic*†	HIV positive	STI coinfection†‡	Follow-up time to test of cure	Attrition	Risk of Bias+low ++medium +++high
				Male	Female	Other						
Geisler, 2014[19]	Randomised, double-blind, multicentre safety and efficacy phase 2.	Gen-Probe APTIMA Combo 2 assay.	n=82 84 screened (2 screen failures) mITT n=71.		100%	Age: 19–35 Uncomplicated genital *C. trachomatis.*	None reported	None reported	n=3 tested positive for *N. gonorrhoeae*	Nilsen Days 22–26 post-treatment.	n=1 withdrew; no reason given.	++
Takahashi, 2011[26]	Prospective, open-label, single-arm study.	Cobas Amplicor STD-1 and PCR.	91 patients with NGU, 4 excluded because diagnosed with GU 19 with symptomatic chlamydial urethritis and 5 with asymptomatic chlamydial urethritis.	100%		Age: >18 Symptomatic and asymptomatic NGU.	Not reported	Not reported	n=13 (n=4 *M. genitalium*; n=3 *U. urealyticum*; n=5 *U. parvum*; n=1 *Mycoplasma hominis*)	1–3 weeks after the initial treatment.	n=29 29 had no second visit.	+++
Ito, 2012[16]	Prospective, single arm open label.	Gen-Probe APTIMA Combo 2 assay.	89 males.	100%		Heterosexual men only Included n=15 with persistent or recurrent NGU and n=1 with post-GU.	None reported	None reported	n=63 positive for one or more microbes	Within 35 days post-treatment.	n=16 did not return to clinic for follow-up.	+++
Takahashi, 2013[17]	Prospective, single-arm, open-label, clinical study.	Gen-Probe APTIMA Combo 2 assay.	208 eligible, data analysed for 118.	100%		Age: >20 Heterosexual male with NGU.	Not reported	Not reported	Excluded	2–4 weeks post-treatment (up to 6 weeks post-treatment).	n=72 36 failed to visit again; 34 visited to early; 1 patient data lost, 1 patient had sexual intercourse.	+++

*Symptoms among those included in final analysis.
†Numerator and denominator provided if data available.
‡Coinfections at any site reported if coinfections at the rectal site was not available.
mITT, modified intention to treat.

Table 3 Summary of interventions and outcomes

First author, year and reference no	Interventions		Treatment outcomes (reported for *Chlamydia trachomatis*)			
	Standard	Comparison	Clinical cure	Microbiological cure	Treatment failure	Adverse event(s)
Geisler, 2012[23]	WC2031 (delayed-release doxycycline hyclate) 200 mg tablet orally once daily for 7 days n=246 mITT n=188.	Vibramycin (doxycycline hyclate capsule) 100 mg orally two times daily for 7 days. n=248. mITT n=190.	Clinical cure: WC2031 95.584.8% (95% CI 74.4% to 95.2%). Vibramycin 76% (95% CI 64.2% to 87.8%).	WC2031 95.5% (95% CI 92.3 to 98.8). Vibramycin 95.2% (95% CI 92.0 to 98.4) mITT results: Microbiological cure WC2031 86.7% (95% CI 81.8% to 91.6%). Vibramycin 90% (95% CI 85.7% to 94.3%).	Not reported	WC2031: 40.2%, nausea 13.2%, vomiting 8.1%. Vibramycin: 53.2%, nausea 20.6%, vomiting 12.1%.
Takahashi, 2014[27]	Azithromycin Extended Release 2 g orally single dose.	NA	Not reported	*C. trachomatis*: 91.5%.	n=4	Diarrhoea in 35.2%, resolved within 1 day.
Topic, 2006[22]	Azithromycin 1 g orally.	Azithromycin 1.0 g orally single dose given weekly for 3 weeks (total of 3 g).	Not reported	Efficacy: Females: Azithromycin 1 g: 88.46%. Azithromycin 3 g: 92.86% (p=0.6633). Males: Azithromycin 1 g: 65%. Azithromycin 3 g: 84.6% (p=0.1689).	Not reported	No adverse events
Unemo, 2015[28]	5-day azithromycin (500 mg on day 1 and 250 mg on the following 4 days).	NA	Unemo Not reported	98.8%	n=1	Not reported
Rahangdale, 2006[25]	Azithromycin 1 g orally single.	Erythromycin 500 mg orally 4 times a day for 7 days or amoxicillin 500 mg orally 3 times a day for 7 days.	Not reported	Azithromycin: 97% (95% CI 92.9% to 99.2%). Amoxicillin: 95% (95% CI 76.2% to 99.9%). Erythromycin: 64% (95% CI 44.1% to 81.4%) (p<0.0001).	Not reported	No difference between groups.
Nilsen, 2016[24]	Pivmecillinam hydrochloride 400 mg orally three times a day for 7 days.	NA	Indirectly reported	Indirectly reported	Only 2 of the 17 participants who delivered a test-of-cure sample were cured.	Treatment was well tolerated.
Stamm, 2007[18]	Rifalazil 2.5 mg, 12.5 mg or 25 mg orally single dose.	Azithromycin 1 g orally single dose.	Rates at 2 and 5 weeks were 85% and 83%, respectively, with rifalazil 25 mg.	At 2 weeks, 85% rifalazil-treated patients demonstrated microbiological cure versus 83% azithromycin-treated patients. At 5 weeks, 83% rifalazil-treated patients and 64% azithromycin-treated patients demonstrated microbiological cure.	Therapeutic failure for *C. trachomatis* was reported in n=15 in the rifalazil group and n=5 in the azithromycin group.	Rifalazil: 15% overall; 8% headaches vs 5% with azithromycin. Azithromycin: 19% overall; GI side effects in 12% vs 5% with rifalazil.
Geisler, 2014[19]	Rifalazil 25 mg orally single dose. n=40. mITT n=33.	Azithromycin 1 g orally single dose. n=42. mITT n=38.	Not reported	Rifalazil 84.8% (95% CI 92.4% to 97.3%), azithromycin 92.1% (95% CI 83.4% to 100%).	n=7	Overall rates were comparable between groups.
Takahashi, 2011[26]	Levofloxacin 500 mg orally once daily for 7 days.	NA	In chlamydial urethritis: 94%–100%.	*C. trachomatis*: 92% in the 24 asymptomatic and symptomatic patients.	Not reported	5% (mild and improved without treatment).
Ito, 2012[16]	Sitafloxacin (STFX) 100 mg two times daily for 7 days.	NA	Symptoms were alleviated in 84.9% patients.	100% with *C. trachomatis*.	n=2	Not reported

Continued

Table 3 Continued

First author, year and reference no	Interventions		Treatment outcomes (reported for *Chlamydia trachomatis*)			
	Standard	Comparison	Clinical cure	Microbiological cure	Treatment failure	Adverse event(s)
Takahashi, 2013[17]	STFX 100 mg tablet two times daily orally for 7 days.	NA	Total clinical cure: 91.3%.	95.7% for *C. trachomatis*.	The two patients with treatment failure for *C. trachomatis*-positive non-gonococcal urethritis obtained a clinical cure.	1.7% (n=2) had mild diarrhoea.

mITT, modified intention to treat; NA, not applicable.

for uncomplicated CT infections, of which two evaluated the effects of modified release formulations of azithromycin[17] and doxycycline.[23] Extended release formulations offer the potential benefits of less frequent dosing and attenuation of adverse events since they reduce peaks in drug concentrations.[29] In recent years, concern has been raised over clinical failures in CT-infected patients, with some of the TFs attributed to reinfection, poor adherence or tolerance of treatment, or detection of non-viable nucleic acid from CT due to test of cure performed too early.[30] Fortunately, although induced resistance to CT has been demonstrated in vitro, there is still no evidence of genotypic or phenotypic resistance to any antimicrobial used to treat clinical CT strains.[31–34] The reasons for the remaining TFs remain unclear but a suboptimal duration of exposure to azithromycin after the 1 g single dose and a low-level absorption of azithromycin in some patients may be contributing factors.[31] Some earlier work suggested that a prolonged course of azithromycin is likely to be bactericidal against CT.[35] Based on the half-life (68 hours) of azithromycin, it has been suggested that increasing the dose of azithromycin to 3 g may maintain tissue levels for over 12 days.[31] Given the increasing concerns about TF, it is unfortunate that few studies consistently reported adherence to therapy and TFs.

Takahashi *et al* examined the use of extended release azithromycin 2 g orally single dose and reported microbiological cure of 91.5% for CT. Two other studies evaluated the effect of modifying the interval and dose of azithromycin. Topic *et al* compared azithromycin 1 g orally single dose given weekly for three doses with azithromycin 1 g orally single dose and reported no additional benefit with the higher total dose. Unemo *et al* reported using an azithromycin 3 g total dose but with a different dosing schedule (administered as 500 mg orally for 1 day then 250 mg daily for 4 days) resulted in an eradication rate for CT of 98.8% in patients coinfected with *Mycoplasma genitalium*.

In regimens requiring multiple doses, compliance is always a concern. For example, suboptimal adherence to multiday dosing of doxycycline was associated with microbiological failure in men with non-gonococcal urethritis (NGU) who had CT infections.[36] In a double-blinded randomised control trial, a doxycycline DR 200 mg tablet administered daily for 7 days was as efficacious as generic doxycycline 100 mg two times daily for 7 days for treatment of urogenital CT infection in men and women and had a lower frequency of gastrointestinal side effects; nausea and vomiting occurred less frequently in subjects treated with the DR doxycycline as compared with doxycycline (nausea in 13% vs 21% and vomiting in 8% vs 12%, respectively).[23] While the less frequent dosing and fewer side effects may help with adherence, the DR formulation is more costly than those that involve multiple daily doses and may therefore preclude its routine use.[8]

In a previous meta-analysis of randomised controlled trials comparing azithromycin with alternative regimens for the treatment of CT in pregnancy, no difference regarding treatment success was noted between azithromycin and erythromycin or amoxicillin.[37] Azithromycin was also associated

with fewer adverse events than erythromycin or amoxicillin. In contrast, however, a retrospective study included in our review reported higher efficacy with azithromycin than for erythromycin or amoxicillin.[25] There were no differences in complications for women or infants exposed to azithromycin compared with those treated with erythromycin or amoxicillin. In pregnancy, azithromycin may therefore be preferable to erythromycin or amoxicillin because of its greater effectiveness and it may also be more acceptable due to its single-dosage regimen.

Very few studies have been conducted on other antibiotics for the treatment of uncomplicated CT infections. Several studies have reported on the efficacy of ofloxacin, a fluoroquinolone antibiotic, for the treatment of CT,[38–41] but this agent is no longer available in Canada or the USA. Levofloxacin is the optical S-(-) isomer of ofloxacin.[42] Few studies have been conducted examining the efficacy of this drug for CT. In our review, Takahashi *et al* reported microbiological cure of 92% for CT with levofloxacin 500 mg orally daily for 7 days in 24 patients. Sitafloxacin, a newer fluoroquinolone antibiotic, is approved for use in Japan and exhibits in vitro activity against multiple organisms including CT.[43] The two small Japanese studies examining sitafloxacin 100 mg orally two times daily for 7 days reported microbiological eradication rates for uncomplicated CT of 95.7%–100%[16 17] but the use of this drug appears to offer no advantages over levofloxacin which is listed in the CDC and European guidelines as an alternate once daily regimen for CT.[8 9] Since sitafloxacin is dosed two times daily, it also offers no advantages over doxycycline.

Rifalazil, a new semisynthetic rifamycin with a long half-life of approximately 60 hours, shows promise as it has excellent in vitro activity against CT.[44] Our review identified a phase 2 study which enrolled men with NGU and reported the clinical benefit of a single oral dose of rifalazil 25 mg in treating CT.[18] A second phase 2 study confirmed these findings in females with uncomplicated CT infections.[19] In both studies, rifalazil was non-inferior to azithromycin, and overall rates of adverse events were similar with both drugs. These results suggest that rifalazil is a promising single dose alternate to azithromycin for the treatment of uncomplicated CT in males and females, but adequately powered studies are still necessary to demonstrate the non-inferiority of rifalazil to azithromycin.

Beta-lactam antibiotics have been identified as a potential alternative treatment for CT, given that amoxicillin 500 mg orally for 7 days has reasonable cure rates for urogenital CT infections among pregnant women.[37] Nilsen *et al* conducted a proof of concept study for the treatment of CT in heterosexual males using pivmecillinam hydrochloride, a beta-lactam antibiotic available in Scandinavian countries for the treatment of urinary tract infections.[24] The study was terminated after the enrolment of only 20 participants due to a high failure rate of the treatment. The authors concluded that mecillinam was, in their opinion, an unattractive candidate for further clinical trials as treatment against CT.

One of the strengths of our systematic review was the broad search strategy, the ability to include studies published in English and French, and not restricting the geographical location of studies. The limitations of this systematic review are the small number of published studies and the moderate to high risk of bias in most of the included studies. In addition, since the search for published studies commenced in September 2017, any publications after August 2017 were not included in this review. In addition, while our search strategy included CT infections involving the urethra, endocervix, rectum and conjunctiva, no studies of alternate treatments were identified for CT infections of the rectum and conjunctiva. Also of concern was that no clear international agenda has been set for research in this area and study designs were so variable that a meta-analysis could not be conducted, thus restricting our ability to make broad clinically relevant recommendations.

In summary, our systematic review of studies evaluating alternate treatments for uncomplicated chlamydia genital infections identified only 11 eligible studies in the last 11 years. One high-quality study supports the use of DR doxycycline as it is equally efficacious, may enhance compliance due to once daily dosing when compared with two times daily dosing of doxycycline for 7 days and is associated with fewer adverse effects; the higher cost, however, may preclude its routine use. Sitafloxacin is equally efficacious compared with standard regimens but offers no additional advantages over doxycycline, since it is also dosed two times daily for 7 days. In addition to previously published data on ofloxacin, a single study supports the use of levofloxacin. There are promising phase 2 data on the efficacy of rifalazil in both men and women. The paucity of existing data highlights the need for further adequately powered studies to evaluate rifalazil and other newer agents for the treatment for uncomplicated urogenital CT infections.

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