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

Jessica Krahn, Aaron Louette, Vera Caine, Shalane Ha, Tom Wong, Tim Y Lau, Ameeta E Singh

**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 anti-bacterial 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 accurately powered studies to evaluate rifalazil, delayed release doxycycline, levofloxacin and other agents for the treatment of uncomplicated CT infections.

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**BACKGROUND**

Urogenital *Chlamydia trachomatis* (CT), caused by serovars D-K, is the most commonly diagnosed and reported bacterial sexually transmitted infection (STI). 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. 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.

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. CT infections of the rectum are mainly asymptomatic but infection can also result in rectal discharge and discomfort. Pharyngeal infections are usually asymptomatic but patients may experience a mild sore throat.

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). 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. 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.

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. 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.

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.

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. |
| 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 1g orally single dose or doxycycline 100mg 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 and two examining the efficacy of rifaxilozil. 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 and the Newcastle-Ottawa Quality Assessment Scale 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. 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, while five were prospective single-arm, open-label studies, one was a retrospective cohort study and one a cohort study. Of these, the majority of the studies included males only. Two studies included female patients and three studies included both males and females. One retrospective study compared outcomes in pregnant patients. For diagnostic methods, six studies used the GenProbe Aptima Combo 2 assay for diagnosis of chlamydia, and four used other molecular diagnostic tests, and one older study used McCoy tissue culture.

Only 1 of the 11 studies specified whether patients were clinically symptomatic. HIV-positive patients were either excluded from the study or were not recruited in the study, or their HIV status was not reported. Patients with STI coinfection were excluded in two studies and coinfections were not reported in three studies. The remainder reported STI coinfections. Follow-up times for test of cure ranged from 21 to 42 days, with one study 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 and one study examined a 5-day azithromycin treatment regimen. 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. 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 2g 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. Topic et al compared azithromycin 1g orally single dose given weekly for three doses, with azithromycin 1g orally single dose and found no additional benefit (such as tolerability) to the higher total dose. Unemo et al examined the effects of a 5-day azithromycin treatment (500mg orally on day 1, followed by 250mg orally daily
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 in males.16 17 Takahashi et al reported a microbiological cure of 95.7% for CT17 while Ito et al reported a cure rate of 100%.16 One of the studies reported that 1.7% experienced mild diarrhea 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>
<thead>
<tr>
<th>First author, year and reference no</th>
<th>Study design</th>
<th>Diagnostic method</th>
<th>Sample size</th>
<th>Population characteristics</th>
<th>Follow-up time to test of cure</th>
<th>Attrition</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geisler, 2012</td>
<td>Randomised, double-blind, double-dummy, active-controlled, multicentre phase 3.</td>
<td>Gen-Probe APTIMA Combo 2 assay.</td>
<td>n=495 mITT n=378</td>
<td>38% 62%</td>
<td>Age: 19–45</td>
<td>Urogenital chlamydia diagnosis within preceding 14 days or a sexual partner with chlamydia. Exclusion: pregnant or breast feeding.</td>
<td>182 out of 378 (discharge observed and reported).</td>
</tr>
<tr>
<td>Takahashi, 2014</td>
<td>Prospective, open label, single-arm clinical study.</td>
<td>Gen-Probe APTIMA Combo 2 assay.</td>
<td>200 patients included: 55 with gonococcal urethritis (GU) 145 with non-GU (NGU).</td>
<td>100%</td>
<td>Age: &gt;20</td>
<td>heterosexual male patients with both GU and NGU.</td>
<td>Yes, but not n reported</td>
</tr>
<tr>
<td>Topic, 2006</td>
<td>Prospective, comparative, randomised.</td>
<td>McCoy culture</td>
<td>n=100</td>
<td>46% 54%</td>
<td>Age: &gt;18</td>
<td>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.</td>
<td>Not reported</td>
</tr>
<tr>
<td>Unemo, 2015</td>
<td>Cohort study</td>
<td>Nucleic acid amplification testing.</td>
<td>n=85</td>
<td>36% 64%</td>
<td>Age: 18–51</td>
<td>Initiation of treatment varied from 4 days to 5 weeks once a positive test result was obtained.</td>
<td>Not reported</td>
</tr>
<tr>
<td>Rahangdale, 2006</td>
<td>Retrospective cohort study.</td>
<td>DNA hybridisation probe.</td>
<td>n=611 meeting inclusion criteria: 277 enrolled (abortion=250; ectopic Pregnancy=3; unable to locate chart=81).</td>
<td>100%</td>
<td>Age: 14–39</td>
<td>Female patients with a positive chlamydia test within 280 days after a positive pregnancy test. Excluded women with abortions and ectopic pregnancies.</td>
<td>None reported</td>
</tr>
<tr>
<td>Nilsen, 2016</td>
<td>Prospective, single arm open label.</td>
<td>PCR</td>
<td>Intended n=50; study terminated after 20 participants due to treatment failures.</td>
<td>100%</td>
<td>Heterosexual men only asymptomatic.</td>
<td>None reported</td>
<td>None reported</td>
</tr>
<tr>
<td>Stamm, 2007</td>
<td>Randomised, double-blind trial, phase 2.</td>
<td>Gen-Probe APTIMA Combo 2 assay.</td>
<td>170 males.</td>
<td>100%</td>
<td>Age: 18–45</td>
<td>Symptoms of NGU of no more than 14 days; required to have history of urethral discharge or observable discharge at time of examination.</td>
<td>None reported</td>
</tr>
<tr>
<td>First author, year and reference no</td>
<td>Study design</td>
<td>Diagnostic method</td>
<td>Sample size</td>
<td>Population characteristics</td>
<td>Risk of Bias</td>
<td>Follow-up time to test of cure</td>
<td>Attrition</td>
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<tr>
<td>Geisler, 2014&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Randomised, double-blind, multicentre safety and efficacy phase 2.</td>
<td>Gen-Probe APTIMA Combo 2 assay.</td>
<td>n=82 84 screened (2 screen failures) mITT n=71.</td>
<td>100% Age: 19–35 Uncomplicated genital C. trachomatis.</td>
<td>++</td>
<td>Nilsen Days 22–26 post-treatment.</td>
<td>n=1 withdrew; no reason given.</td>
</tr>
<tr>
<td>Geisler, 2011&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Prospective, open-label, single-arm study.</td>
<td>Cobas Amplicor STD-1 and PCR.</td>
<td>91 patients with NGU, 4 excluded because diagnosed with GU 19 with symptomatic chlamydial urethritis and 5 with asymptomatic chlamydial urethritis.</td>
<td>100% Age: &gt;18 Symptomatic and asymptomatic NGU.</td>
<td>+++</td>
<td>1–3 weeks after the initial treatment.</td>
<td>n=29 29 had no second visit.</td>
</tr>
<tr>
<td>Ito, 2012&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Prospective, open label.</td>
<td>Gen-Probe APTIMA Combo 2 assay.</td>
<td>89 males.</td>
<td>100% Heterosexual men only included n=15 with persistent or recurrent NGU and n=1 with post-GU.</td>
<td>+++</td>
<td>Within 35 days post-treatment.</td>
<td>n=16 did not return to clinic for follow-up.</td>
</tr>
<tr>
<td>Takahashi, 2013&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Prospective, single-arm, open-label, clinical study.</td>
<td>Gen-Probe APTIMA Combo 2 assay.</td>
<td>208 eligible, data analysed for 118.</td>
<td>100% Age: &gt;20 Heterosexual male with NGU.</td>
<td>+++</td>
<td>2–4 weeks post-treatment (up to 6 weeks post-treatment).</td>
<td>n=72 36 failed to visit again; 34 visited to early; 1 patient data lost, 1 patient had sexual intercourse.</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>First author, year and reference no</th>
<th>Interventions</th>
<th>Comparison</th>
<th>Treatment outcomes (reported for <em>Chlamydia trachomatis</em>)</th>
<th>Adverse event(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Geisler, 2012</strong>&lt;sup&gt;23&lt;/sup&gt;</td>
<td>WC2031 (delayed-release doxycycline hyclate) 200 mg tablet orally once daily for 7 days n=246, mITT n=188.</td>
<td>Vibramycin (doxycycline hyclate capsule) 100 mg orally two times daily for 7 days n=248, mITT n=190.</td>
<td>Clinical cure: 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%).</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Takahashi, 2014</strong>&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Azithromycin Extended Release 2g orally single dose.</td>
<td>NA</td>
<td>Not reported</td>
<td>C. trachomatis: 91.5%. n=4 Diarrhoea in 35.2%, resolved within 1 day.</td>
</tr>
<tr>
<td><strong>Topic, 2006</strong>&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Azithromycin 1g orally.</td>
<td>Azithromycin 1.0g orally single dose given weekly for 3 weeks (total of 3 g).</td>
<td>Not reported</td>
<td>Efficacy: Females: Azithromycin 1g: 88.46%. Azithromycin 3g: 92.86% (p=0.6633). Males: Azithromycin 1g: 65%. Azithromycin 3g: 86.4% (p=0.1689).</td>
</tr>
<tr>
<td><strong>Unemo, 2015</strong>&lt;sup&gt;29&lt;/sup&gt;</td>
<td>5-day azithromycin (500mg on day 1 and 250mg on the following 4 days).</td>
<td>NA</td>
<td>Not reported</td>
<td>98.8% n=1 Not reported</td>
</tr>
<tr>
<td><strong>Rahangdale, 2006</strong>&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Azithromycin 1g orally single dose.</td>
<td>Erythromycin 500mg orally 4 times a day for 7 days or amoxicillin 500mg orally 3 times a day for 7 days.</td>
<td>Not reported</td>
<td>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&lt;0.0001).</td>
</tr>
<tr>
<td><strong>Nilsen, 2016</strong>&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Pivmecillinam hydrochloride 400mg orally three times a day for 7 days.</td>
<td>NA</td>
<td>Indirectly reported</td>
<td>Indirectly reported Only 2 of the 17 participants who delivered a test-of-cure sample were cured. Treatment was well tolerated.</td>
</tr>
<tr>
<td><strong>Stamm, 2007</strong>&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Rifalazil 2.5mg, 12.5mg or 25mg orally single dose.</td>
<td>Azithromycin 1g orally single dose.</td>
<td>Rates at 2 and 5 weeks were 85% and 83%, respectively, with rifalazil 25mg.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Geisler, 2014</strong>&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Rifalazil 25mg orally single dose. n=40, mITT n=33.</td>
<td>Azithromycin 1g orally single dose. n=42, mITT n=38.</td>
<td>Not reported</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Takahashi, 2011</strong>&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Levofloxacin 500mg orally once daily for 7 days.</td>
<td>NA</td>
<td>In chlamydial urethritis: 94%–100%.</td>
<td>C. trachomatis: 92% in the 24 asymptomatic and symptomatic patients. Not reported</td>
</tr>
<tr>
<td><strong>Ito, 2012</strong>&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Sitafloxacin (STFX) 100mg two times daily for 7 days.</td>
<td>NA</td>
<td>Symptoms were alleviated in 84.9% patients.</td>
<td>100% with C. trachomatis. n=2 Not reported</td>
</tr>
</tbody>
</table>

Continued
for uncomplicated CT infections, of which two evaluated the effects of modified release formulations of azithromycin\(^\text{17}\) and doxycycline.\(^\text{23}\) Extended release formulations offer the potential benefits of less frequent dosing and attenuation of adverse events since they reduce peaks in drug concentrations.\(^\text{29}\) 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.\(^\text{30}\) 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.\(^\text{31–34}\) 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.\(^\text{31}\) Some earlier work suggested that a prolonged course of azithromycin is likely to be bactericidal against CT.\(^\text{35}\) 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.\(^\text{31}\) Given the increasing concerns about TF, it is unfortunate that few studies consistently reported adherence to therapy and TFs.

Takahashi \textit{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 \textit{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 \textit{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 \textit{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.\(^\text{36}\) 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).\(^\text{23}\) 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.\(^\text{8}\)

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.\(^\text{37}\) 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. 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.8 9 15 16 but this agent is no longer available in Canada or the USA. Levo-floxacin is the optical S(-) isomer of ofloxacin.22 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 500mg 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.23 The two small Japanese studies examining sitafloxacin 100mg orally twice 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 twice 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.41 Our review identified a phase 2 study which enrolled men with NGU and reported the clinical benefit of a single oral dose of rifalazil 25mg 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 500mg orally for 7 days has reasonable cure rates for urogenital CT infections among pregnant women.33 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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REFERENCES


