

**CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL**

Management and Treatment of Cervicitis: A Review of Clinical Effectiveness and Guidelines

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Authors: Calvin Young, Charlene Argáez

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Context and Policy Issues

Cervicitis is a clinical syndrome characterized by the presence of a purulent or mucopurulent discharge that is visible in the endocervical canal or that can be detected with an endocervical smear.¹⁻³ Additionally, other clinical signs of inflammation, such as persistent endocervical bleeding (intermenstrual or post-coital vaginal bleeding) which can be induced by the gentle passing of a cotton swab through the endocervix, can indicate cervicitis.¹⁻³ One study reported that up to 40% of women assessed at a sexually transmitted disease clinic showed signs and symptoms of cervicitis, demonstrating the importance of improving treatment strategies for these women.⁴

Currently, it is common clinical practice to prescribe presumptive antibiotics for *Chlamydia trachomatis* and *Neisseria gonorrhoea* to patients with signs of cervicitis.¹⁻³ However, fewer than one third of cervicitis cases are determined to be a result of *Chlamydia trachomatis* or *Neisseria gonorrhoea* infection following laboratory analysis.^{2,4,5} Other potential causes of cervicitis include *Chlamydia trachomatis*, *Bacterial vaginosis*, *Mycoplasma genitalium*, genital herpes, abnormality of vaginal flora, frequent douching, chemical irritants, or contraceptive methods.^{1,3-5} In addition to presumptive antibiotics being ineffective for treating some of these etiologies, there is growing concern that the overprescription of azithromycin, cephalosporins, and other antimicrobials may be leading to decreased susceptibility and increased resistance in bacterial strains found in Canada and the rest of the world.^{6,7}

The purpose of this report is to summarize and critically appraise the evidence available regarding the treatment and management of cervicitis in non-pregnant women. This will include evidence on the comparative clinical effectiveness of doxycycline versus azithromycin for cervicitis caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Mycoplasma genitalium* and evidence on the clinical effectiveness of using a test-and-wait approach for the management of cervicitis of unknown etiology. As well, this report aims to review evidence-based guidelines regarding the the management and treatment of cervicitis in non-pregnant women.

Research Questions

1. What is the comparative clinical effectiveness of doxycycline versus azithromycin for the treatment of non-pregnant women with cervicitis caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Mycoplasma genitalium*?
2. What is the clinical effectiveness of using a test-and-wait approach for the management of non-pregnant women with diagnosed cervicitis?
3. What are the evidence-based guidelines regarding the management and treatment of cervicitis in non-pregnant women?

Key Findings

Evidence regarding the comparative clinical effectiveness of doxycycline versus azithromycin for the treatment of non-pregnant women with cervicitis caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Mycoplasma genitalium* suggested that azithromycin was more effective at achieving both microbiological and clinical cure.⁷ It is important to note that this evidence was limited to one non-randomized study.⁷

Regarding cervicitis treatment management strategies, evidence from one randomized controlled trial⁵ favoured using a test-and-wait approach over presumptive treatment in non-pregnant women with cervicitis of unknown etiology.

The evidence-based guidelines recommended azithromycin or doxycycline (alone or in combination with cephalosporins) for cervicitis of unknown etiology.^{1,3} One guideline¹ stated that presumptive treatment for *Chlamydia trachomatis* and *Neisseria gonorrhoea* should be provided to women at high risk for these sexually transmitted infections. Alternatively, deferring treatment until results of diagnostic tests are available is an option for women at lower risk of sexually transmitted diseases.¹

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit the retrieval to health technology assessments, systematic reviews, and meta analyses, randomized controlled trials, non-randomized studies, and guidelines. Where possible, retrieval was limited to the human population. The search was limited to English language documents published between January 1, 2012 and August 29, 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1: Non-pregnant females (adolescents and adults) with cervicitis known to be caused by <i>Neisseria gonorrhoeae</i> , <i>Chlamydia trachomatis</i> , or <i>Mycoplasma genitalium</i>
	Q2, Q3: Non-pregnant females (adolescents and adults) with cervicitis (regardless of etiology)
Intervention	Q1: Treatment using doxycycline (alone or in combination with cephalosporins)
	Q2: Testing for <i>Neisseria gonorrhoeae</i> , <i>Chlamydia trachomatis</i> , or <i>Mycoplasma genitalium</i> followed by treatment only as necessary
	Q3: Testing and treatment strategies for cervicitis

Comparator	<p>Q1: Treatment using azithromycin (alone or in combination with cephalosporins)</p> <p>Q2: Presumptive or empirical treatment for <i>Neisseria gonorrhoeae</i>, <i>Chlamydia trachomatis</i>, or <i>Mycoplasma genitalium</i></p> <p>Q3: No comparator required</p>
Outcomes	<p>Q1: Clinical benefits and harms, including:</p> <ul style="list-style-type: none"> - Cure rate (test of cure) - Failure rate (positive for <i>Neisseria gonorrhoeae</i>, <i>Chlamydia trachomatis</i>, or <i>Mycoplasma genitalium</i> at test of cure) - Development of resistance mutations (i.e., % or n resistant at test of cure) - Adverse effects <p>Q2: Clinical benefits and harms, including:</p> <ul style="list-style-type: none"> - Number or proportion of patients given antibiotics - Cure rate - Number or proportion of patients with unresolved cervicitis after treatment - Provision of incorrect treatment (positive for <i>M. genitalium</i> after presumptive treatment for <i>Neisseria gonorrhoeae</i> or <i>Chlamydia trachomatis</i>, antimicrobial resistance) - Positive predictive value/negative predictive value (i.e., proportion of presumptive diagnoses that were correct [based on test results or successful treatment], proportion of presumed negative cases that were in fact negative) - Loss to follow-up <p>Q3: Recommendations for treatment regimens or choice of antibiotics, and recommended management strategies (i.e., test-and-wait approach versus presumptive or empirical treatment)</p>
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2012. Studies on the treatment and management of sexually transmitted infections (e.g., *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Mycoplasma genitalium*) without specific mention of cervicitis were excluded.

Critical Appraisal of Individual Studies

The included randomized controlled trial (RCT) and non-randomized study (NRS) were critically appraised using the Downs and Black checklist,⁸ and guidelines were assessed with the AGREE II instrument.⁹ Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 421 citations were identified in the literature search. Following screening of titles and abstracts, 395 citations were excluded and 26 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications

were retrieved from the grey literature search. Of these potentially relevant articles, 24 publications were excluded for various reasons, while four publications met the inclusion criteria and were included in this report. These four publications comprised one RCT,¹⁰ one NRS,⁷ and two evidence-based guidelines.^{1,11} Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

One RCT,¹⁰ one NRS,⁷ and two evidence-based guidelines^{1,11} were eligible for inclusion in this review.

The included RCT⁵ appears to have been unblinded, and the NRS was a retrospective case-study.⁷

Year of Publication and Country of Origin

The RCT⁵ was published in 2016, and the NRS⁷ was published in 2013. The guidelines were published in 2017³ and 2015.¹

The RCT and the NRS were conducted in India and Sweden, respectively.^{5,7} The two guidelines were published in Canada³ and United States.¹

Patient Population

The identified RCT⁵ included 200 women who presented with abnormal vaginal discharge caused by vaginitis or cervicitis. The patient age ranged between 18 years and 45 years.⁵

The NRS by Anagrus et al.⁷ included 407 patients (195 women) who tested positive for *Mycoplasma genitalium* infection detected with polymerase chain reaction. Cervicitis or urethritis was microbiologically confirmed in 98% of women treated with doxycycline, 91% of women treated with azithromycin 1 g, and 100% of the of women treated with azithromycin 1.5 g.⁷

The Centers for Disease Control and Prevention (CDC) guidelines¹ and the National Institute for Excellence in Health and Social Services (INESSS) guidelines³ were published to inform the treatment of patients diagnosed with or who are at risk for sexually transmitted infections or diseases. These guidelines both included recommendations for patients with cervicitis of various etiologies.

Interventions and Comparators

The interventions of interest in the SR¹² were antimicrobial therapies targeting *Mycoplasma genitalium*. These included doxycycline, azithromycin, tetracycline, erythromycin, metronidazole, levofloxacin, lymecycline, minocycline, spectinomycin, moxifloxacin, ofloxacin, rifalazil, cefoxitin, gatifloxacin, sitafloxacin, clarithromycin, pristinamycin, josamycin, and solithromycin.¹² Primary studies compared these antimicrobials to each other or to the same drug at an alternative dosing strategy.¹²

In the RCT by Meena and Bansal,⁵ the intervention was laboratory identification of the causative organism (e.g., *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Mycoplasma genitalium*) followed by treatment only as necessary in women presenting with vaginitis or cervicitis. The comparator group was given syndromic management on the same day of examination based on symptoms and risk factors; patients with endocervical discharge or high risk factors were given azithromycin (2 g single dose) plus tinidazole (2 g single dose) plus fluconazole (150 mg single dose). Patients with only vaginal discharge were given tinidazole (2 g single dose) and fluconazole (150 mg).⁵

The NRS⁷ evaluated three treatment strategies for patients infected with *Mycoplasma genitalium*. These strategies utilized doxycycline (1 g) or azithromycin (at 1 g or 1.5 g). Patients who required a second-line treatment were given azithromycin 1.5 g (if doxycycline had failed) or moxifloxacin (if azithromycin had failed).⁷

The CDC guidelines¹ included both pharmacological and nonpharmacological interventions for the prevention and treatment of sexually transmitted diseases. These included antimicrobial therapies, prevention counselling, vaccination, and contraceptive methods.

The INESSS guidelines³ contained pharmacological interventions for the management of clinical symptoms associated with sexually transmissible and blood-borne infections.

Outcomes

The RCT⁵ used the rate of complete cure of abnormal vaginal discharge at follow-up (two weeks after treatment initiation) as the primary outcome. The NRS⁶ assessed microbiological cure of *Mycoplasma genitalium* (confirmed with polymerase chain reaction) and clinical cure (absence of urethritis and/or cervicitis) at test of cure follow-up (four to 52 weeks after treatment initiation).

The outcomes of interest in the guidelines published by the CDC¹ were microbiologic eradication, alleviation of signs and symptoms, cost-effectiveness, and prevention sequelae and transmission. The outcomes used in the INESSS guidelines³ were the successful management of symptoms and elimination of infection determined by test of cure.

Summary of Critical Appraisal

A summary of the critical appraisal of the included clinical studies, and evidence based guidelines are briefly described below. Details are available in Appendix 3, Tables A3 and A4.

Clinical Studies

The RCT⁵ was generally well-conducted but had some limitations, based on the assessment made using the Downs and Black checklist⁸. The authors used an appropriate method of randomization, described patient characteristics in sufficient detail, defined the objectives of the study, and all patients had the same time of follow-up and outcome assessment. Important limitations of this publication include a lack of blinding of patients and outcome assessors, the analysis did not address potential confounders, there was no mention of patients lost to follow-up, and there was an absence of explicit inclusion and exclusion criteria.

The included NRS⁷ was of moderate-to-low quality. The authors described the objective, intervention, main outcomes, and the inclusion and exclusion criteria. Because the study was based on a retrospective chart review, the trial design was likely representative of the

patient population and care setting of interest. The nature of this study made it so that the randomization of patients and the blinding of patients and outcome assessors were not done. There was reference to a potential assignment of patients to various treatment groups based on risk factors present at initial assessment. This could have led to biased results that were not corrected for. A final major flaw in this study was the large variety in time of follow-up. This ranged between four weeks and 52 weeks and there does not appear to be any corrections in the data analysis to account for this variation.

Evidence-Based Guidelines

Both the CDC¹ and INESSS³ guidelines were explicit in terms of scope and purpose, clarity of presentation, and consulted relevant clinical experts. Both guidelines conducted a systematic review to gather evidence to help formulate recommendations; however, the CDC guideline¹ appears to have used only one electronic database (MEDLINE). The strength of the evidence appears to have been considered when drafting the recommendations. Conflicts of interest were declared in both guidelines. Prior to publication, both guidelines were externally reviewed by experts. Neither guideline appeared to include patient views and preference during their development nor made mention to a policy or plans for updating the guideline in future years as additional evidence becomes available. Overall, the identified guidelines were of fairly high quality.

Summary of Findings

The overall findings of the included literature are summarized below. A detailed summary of the main findings and recommendations are available in Appendix 4: Table A5 and Table A6.

1. *What is the comparative clinical effectiveness of doxycycline versus azithromycin for the treatment of non-pregnant women with cervicitis caused by Neisseria gonorrhoeae, Chlamydia trachomatis, and Mycoplasma genitalium?*

Microbiologic Cure

One NRS⁷ assessed the outcome and microbiologic cure in non-pregnant women treated with either doxycycline or azithromycin for cervicitis. Included patients were diagnosed with cervicitis known to be a result of *Mycoplasma genitalium* infection. Microbiological cure rates of 47.5% (38/80), 96.2% (50/52), and 100% (12/12) were reported for women receiving 1.0 g doxycycline, 1.0 g azithromycin, and 1.5 g azithromycin, respectively.⁷ Based on the results of this study, it appears as if azithromycin was more effective than doxycycline for the eradication of *Mycoplasma genitalium* in this population.

Adverse Events

The NRS⁷ made no specific mention of adverse events related to the treatment of cervicitis with doxycycline or azithromycin. Therefore, no further comments can be made regarding the potential adverse effects of these treatment regimens.

2. *What is the clinical effectiveness of using a test-and-wait approach for the management of non-pregnant women with diagnosed cervicitis?*

Cure of Cervicitis and Vaginitis Symptoms

One RCT⁵ evaluated the cure of symptoms (cervicitis and vaginitis) outcome in non-pregnant women with cervicitis alone or cervicitis and vaginitis treated with either targeted

management (i.e., diagnostic testing followed by treatment only as necessary) or syndromic management (i.e., empirical treatment). The study reported that targeted management was more effective in achieving symptom cure in both women with cervicitis and women with cervicitis and vaginitis.⁵ Although the data from this study would suggest that targeted management is superior for the treatment of women with cervicitis of unknown etiology, the results must be taken with caution due to the sample size (N=48).

Adverse Events

The identified RCT⁵ made no specific mention of adverse events related to treatment of cervicitis with targeted management or syndromic management. Therefore, no further comments can be made regarding the potential adverse effects of these treatment strategies.

3. *What are the evidence-based guidelines regarding the management and treatment of cervicitis in non-pregnant women*

Two evidence-based guidelines that qualify under the inclusion criteria for this research question were identified. The CDC guidelines¹ included recommendations regarding the management and treatment of a large variety of STDs. The following recommendation was made specifically regarding cervicitis:

“Several factors should affect the decision to provide presumptive therapy for cervicitis. Presumptive treatment with antimicrobials for C. trachomatis and N. gonorrhoeae should be provided for women at increased risk (e.g., those aged <25 years and those with a new sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually transmitted infection), especially if follow-up cannot be ensured or if testing with NAAT is not possible. Trichomoniasis and BV should also be treated if detected (see Bacterial Vaginosis and Trichomoniasis). For women at lower risk of STDs, deferring treatment until results of diagnostic tests are available is an option. If treatment is deferred and NAATs for C. trachomatis and N. gonorrhoeae are negative, a follow-up visit to see if the cervicitis has resolved can be considered.”(p.54)

The guidelines published by INESSS³ included recommendations regarding the syndromic approach to treating various STBIs. These guidelines recommended the following treatment regimens for patients (aged 14 or older) presenting with cervicitis:

- 1st choice: azithromycin 1 g p.o. in a single dose and either cefixime 800 mg p.o. in a single dose or ceftriaxone 250 mg IM in a single dose
- 2nd choice: doxycycline 100 mg p.o. b.i.d. for 7 days and either cefixime 800 mg p.o. in a single dose or ceftriaxone 250 mg IM in a single dose
- For patients with a history of allergic reaction to cephalosporins or history of severe or very severe delayed or immediate reaction to penicillins: Azithromycin 2 g p.o. in a single dose

Limitations

A number of limitations were identified in the critical appraisals (Appendix 3), however, additional limitations exist. Overall, there was a limited amount of evidence which provided answers to our research questions. In addition, the studies which were identified were often of moderate quality and utilized sample sizes that ranged from 200 to 407 patients.

Of the primary studies included in the SR,¹² one was relevant to this report. It, however, was difficult to examine as the authors' analysis did not focus on non-pregnant women with cervicitis, receiving either doxycycline or azithromycin.

Adverse events were not reported in the SR¹², the RCT⁵, or the NRS.⁷ It is unclear if this is a result of a low occurrence of adverse events or if it is due to a lack of reporting.

Neither the SR nor any of the included clinical studies were conducted in Canada, hence may not be generalizable for the Canadian setting. This is especially problematic for antibiotic effectiveness questions due to the potential for regional differences in the prevalence of antimicrobial resistance.⁶

Conclusions and Implications for Decision or Policy Making

A total of five relevant publications, including one SR,¹² one RCT,⁵ one NRS,⁷ and two evidence-based guidelines^{1,3} were identified.

Azithromycin was generally favoured over doxycycline as a treatment for non-pregnant women with cervicitis caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Mycoplasma genitalium*. An exception to this was the CDC guidelines,¹ where both azithromycin and doxycycline were presented as treatment options, with no preference given to one over the other. Policy-makers should be aware that neither of the primary studies cited supporting this statement were conducted in Canada,^{7,12} and regional differences in resistance to antimicrobial agents may vary.⁶

The use of a test-and-wait (followed by treatment as necessary) approach for the management of non-pregnant women with cervicitis of unknown etiology was favoured in the identified RCT.⁵ Patients with cervicitis who received targeted management had higher rates of both clinical and microbiological cure.⁵ This conclusion was echoed in the CDC guidelines,¹ where a test-and-wait approach is suggested as an option for women at lower risk of STDs. The INESSS guidelines³ made no mention of using a test-and-wait approach, but recommended that appropriate laboratory analyses must be completed for patients with cervicitis, and that the choice of treatment can be reassessed when the results are available.

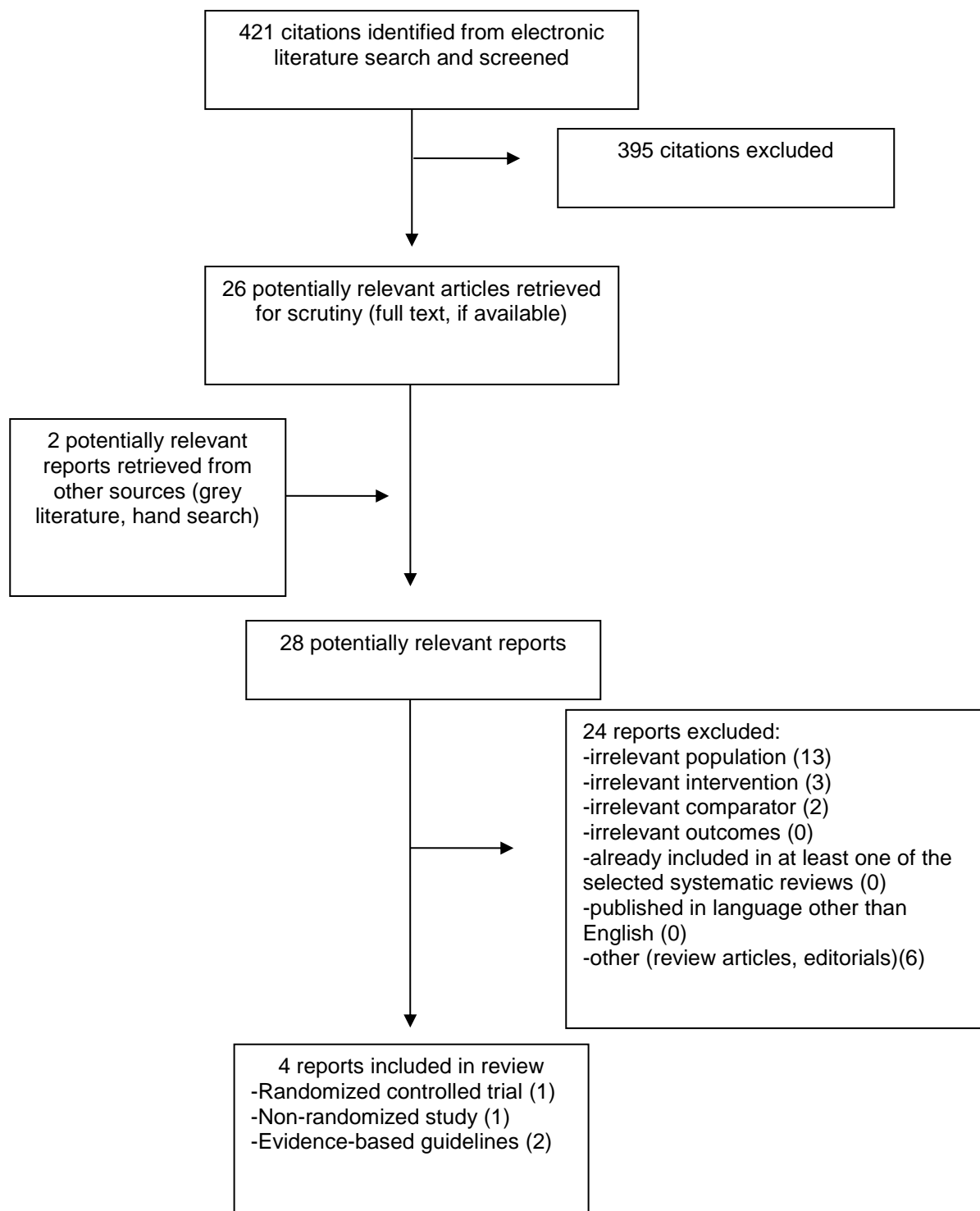
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Abbreviations

b.i.d.	twice daily (from the Latin “bis in die”)
CDC	Centers for Disease Control and Prevention
DNA	deoxyribonucleic acid
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IM	intramuscular
INESSS	Institut national d'excellence en santé et en services
NAAT	Nucleic Acid Amplification Test
NR	not reported
NRS	non-randomized study
PCR	polymerase chain reaction
p.o	orally, by mouth (from the Latin “per os”)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
RNA	ribonucleic acid
STBBI	sexually transmitted and blood-borne infection
STD	sexually transmitted disease

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
Meena and Bansal, 2016⁵ India	RCT	Women (between 18 years and 45 years) who presented with abnormal vaginal discharge (vaginitis or mucopurulent cervicitis). N = 200	Laboratory identification of the causative organism followed by treatment only as necessary. Tinidazole (2 g single dose) was given for bacterial vaginosis and trichomoniasis, fluconazole (150 mg single dose) was given for candidiasis, and azithromycin (2 g single dose) was given for gonorrhoea and chlamydia.	Syndromic management on the same day of examination based on symptoms and risk factors. Patients with endocervical discharge or high risk factors were given azithromycin (2 g single dose) plus tinidazole (2 g single dose) plus fluconazole (150 mg single dose). Patients with only vaginal discharge were given tinidazole (2 g single dose) and fluconazole (150 mg).	Complete cure of abnormal vaginal discharge at follow-up (2 weeks).
Anagrius et al., 2013⁷ Sweden	Retrospective case-study	Men and women with a diagnosis of <i>M. genitalium</i> infection confirmed by PCR N = 407 patients (195 women)	Doxycycline (1 g)	Azithromycin (1 g or 1.5 g)	Microbiological and clinical cure at test of cure follow-up (4 to 52 weeks after treatment initiation).

PCR = polymerase chain reaction; RCT = randomized controlled trial

Table A2: Characteristics of Included Guidelines

Target Population, Intended Users	Objectives		Evidence Collection, Selection and Synthesis	Methodology	
	Intervention and Practice Consideration	Major Outcomes Considered		Evidence Quality Assessment	Recommendations Development and Evaluation
CDC 2015¹					
<p>Target population: Patients who have or who are at risk for sexually transmitted infections or diseases</p> <p>Intended users: Physicians and other health-care providers</p>	Pharmacological and non-pharmacological interventions for the prevention and treatment sexually transmitted diseases	<p><i>“These reviews also focused on four principal outcomes of STD therapy for each individual disease or infection: 1) treatment of infection based on microbiologic eradication; 2) alleviation of signs and symptoms; 3) prevention of sequelae; 4) prevention of transmission, including advantages such as cost-effectiveness and other advantages (e.g., single-dose formulations and directly observed therapy) and disadvantages (e.g., side effects) of specific regimens.”¹</i></p>	<p><i>“...a systematic literature review using an extensive MEDLINE database evidence-based approach (e.g., using published abstracts and peer-reviewed journal articles).”¹</i></p>	Quality of retrieved articles was assessed; however, the methods used were not stated.	<p><i>“The workgroup evaluated the quality of evidence, provided answers to the key questions, and rated the recommendations based on the United Services Preventive Services Task Forces (USPSTF) modified rating system.”¹</i></p>
INESSS 2017³					
<p>Target population: Individuals aged 14 and over with signs or symptoms of STIBBIs</p> <p>Intended users: Physicians and other health-care providers</p>	Pharmacological interventions for the management of clinical symptoms potentially associated with STBBIs	Management of symptoms and elimination of infection (determined by test of cure).	Evidence was collected from a systematic search in the MEDLINE and Embase databases, a grey literature search, and official antibiotic monographs (approved by Health Canada).	SRs were evaluated using the R-AMSTAR tool. CPGs were evaluated using the AGREE II assessment tool	Expert consensus based on evidence from systematic reviews Stakeholders and public consultation; unclear if stakeholders were internal or external

AGREE= Appraisal of Guidelines for Research and Evaluation; CDC = Centers for Disease Control and Prevention; CPG = clinical practice guideline; INESSS = Institut national d'excellence en santé et en services sociaux; R-AMSTAR = Revised Measurement Tool to Assess Systematic Reviews; SR = systematic review; STD = sexually transmitted disease; STIBBI = sexually transmitted and blood-borne infection; STI = sexually transmitted infection

Appendix 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Clinical Studies using Downs and Black Checklist

Strengths	Limitations
Meena and Bansal 2016 ⁵	
<ul style="list-style-type: none"> • The objective of the study was stated and explained in detail • Patients were allocated to treatment groups through computer-generated randomization • Interventions of interest were clearly described • Patient characteristics were described • <i>P</i>-values were reported • The authors mentioned that there were no conflicts of interest • Study participants and care setting appear to be representative of the population and care setting of interest • Time of follow-up was the same for all patients 	<ul style="list-style-type: none"> • The outcomes of interest were not stated until they were presented as results • Inclusion and exclusion criteria were not explicitly stated • Open-label, unblinded trial • Confounders were not mentioned or adjusted for • Unclear if sample size calculations were undertaken • Unclear if there were any withdrawals or patients lost to follow-up • Unclear if there were any adverse events resulting from the intervention
Anagrus et al. 2013 ⁷	
<ul style="list-style-type: none"> • The objectives and outcomes of the study were stated and explained in detail • Inclusion and exclusion criteria were described in the methods section • Interventions were defined and specific dosages were provided • Due to the nature of the study (retrospective case-study), the patient population, staff, and care setting are likely relevant to those of interest • The findings of the study are described • The outcome measures appear to be valid and reliable 	<ul style="list-style-type: none"> • Time of follow-up (and test of cure assessment) was not standardized and varied between patients (ranged from 4 weeks to 52 weeks). Additionally, there was no mention of adjustment to correct for this variation • Confounders were not mentioned or adjusted for • Unclear if there were any adverse events resulting from the intervention • The characteristics of patients lost to follow-up were not mentioned • Because this is a retrospective case-study, there was no attempt at blinding patients or healthcare staff to the treatment given • There was no randomization to intervention groups • Patients were likely recruited into intervention groups during alternate time periods (doxycycline from 1998 to 2003 and azithromycin from 2003 to 2005) • Patient recruitment into different intervention groups appears to have been risk factor based

Table A4: Strengths and Limitations of Guidelines using AGREE II

Strengths	Limitations
Centers for Disease Control and Prevention 2015 ¹	
<ul style="list-style-type: none"> • Scope, purpose, and target population were stated • Developed by CDC staff and an independent workgroup selected on the basis of their expertise in the clinical management of STDs • All workgroup members disclosed potential conflicts of interest • A systematic review was conducted using MEDLINE • Recommendations were rated based on the United Services Preventive Services Task Forces modified rating system • Strengths and limitations of the cited evidence were considered when drafting the recommendations • The guideline was externally reviewed by a second independent panel of public health and clinical experts • Recommendations were specific and easily identifiable 	<ul style="list-style-type: none"> • Unclear if patient views and preferences were considered • Unclear if there is a policy for updating of the recommendations
National Institute for Excellence in Health and Social Services (INESSS) 2017 ³	
<ul style="list-style-type: none"> • Scope, purpose, and target population were stated • A systematic search was conducted using multiple databases (MEDLINE and Embase) as well as a grey literature search • The experiential knowledge of Quebec experts and clinicians who collaborated in the project was consulted when writing recommendations • The target users of the guideline were stated • The methodology for selecting evidence, including inclusion and exclusion criteria, is well-defined • Strengths and limitations of the cited evidence were considered when drafting the recommendations • Recommendations were specific and easily identifiable • The guideline was externally reviewed by experts prior to its publication • Potential conflicts of interest of the authors were declared 	<ul style="list-style-type: none"> • Unclear if patient views and preferences were considered • Unclear if there is a policy for updating of the recommendations

Appendix 4: Main Study Findings and Author’s Conclusions

Table A5: Summary of Findings of Included Primary Studies

Main Study Findings	Author’s Conclusion
Meena and Bansal 2016 ⁵	
<p>This randomized controlled trial included a total of 200 women with vaginitis (n=145), cervicitis (n=37), or both (n=18). However, only the results relevant under the inclusion criteria of this report will be presented (women with cervicitis).</p> <p>Comparison of targeted management (diagnostic testing followed by treatment only as necessary) vs. syndromic management (empirical treatment) for women with cervicitis</p> <ul style="list-style-type: none"> • 55 women with cervicitis or cervicitis and vaginitis were treated with either targeted management or syndromic management • Of those that received targeted management (and had their cervicitis and vaginitis laboratory confirmed), 5/7(71.4%) of those with cervicitis and 10/14 (71.4%) of those with cervicitis and vaginitis were cured of their symptoms (<i>p</i> value <0.001) • Of those that received syndromic management, 14/26 (54%) of those with cervicitis and 0/1 (0%) of those with cervicitis and vaginitis were cured of their symptoms (<i>p</i> value <0.001) 	<p><i>“Response to treatment for vaginitis was 76.3 % in targeted management group, whereas it was 41 % in syndromic management group. With cervicitis, 71.4 % women responded to treatment in targeted group as compared to 54 % in syndromic management group. This difference was statistically significant. Low response to treatment in syndromic management group is due to low sensitivity of clinical examination in diagnosing the nature of vaginal discharge. Thus, in clinics where laboratory facilities are available, they should be used to confirm the diagnosis for targeted management.”</i>(p539)</p>
Anagnius et al. 2013 ⁷	
<p>This retrospective case-study included both men (n=212) and women (n=195) with a diagnosis of <i>M. genitalium</i> infection confirmed by PCR. However, only the results relevant under the inclusion criteria of this report will be presented (women with cervicitis).</p> <p>Comparison of doxycycline vs. azithromycin in women with cervicitis</p> <ul style="list-style-type: none"> • 180 women with a diagnosis of <i>M. genitalium</i> infection were treated with 1.0 g doxycycline (n=102), 1.0 g azithromycin (n=62), or 1.5 g azithromycin (n=16). Microscopic signs of urethritis and/or cervicitis were observed in 98%, 91%, and 100% of these women at inclusion, respectively. These rates of urethritis and/or cervicitis decreased to 53%, 50%, and 30% for those microbiologically cured at follow-up • Of those that received 1.0 g doxycycline, 38/80 (47.5%) had microbiologic cure at follow-up (22 patients were excluded) • Of those that received 1.0 g azithromycin, 50/52 (96.2%) had microbiologic cure at follow-up (10 patients were excluded) • Of those that received 1.5 g azithromycin, 12/12 (100%) had microbiologic cure at follow-up (4 patients were excluded) 	<p><i>“Azithromycin 1 g single dose and 1.5 g extended dosage had a significantly higher microbiological cure-rates then doxycycline when all patients were compared (p,0.0001 for both). For men and women separately, all comparisons between doxycycline and azithromycin were also significantly in favour of azithromycin (p,0.0005). No statistically significant difference in the cure rates between the two azithromycin dosages when given as primary treatment could be found, to some extent due to the small number of patients given 1.5 g as the primary treatment.”</i>(pe61481)</p> <p><i>“These findings confirm the results from other studies showing that doxycycline is inefficient in eradicating M. genitalium. Although azithromycin 1 g was not significantly less efficient than extended dosage, it was associated with selection of macrolide resistant M. genitalium strains and should not be used as first line therapy for M. genitalium. Monitoring of M. genitalium macrolide resistance should be encouraged.”</i>(pe61481)</p>

PCR = polymerase chain reaction

Table A6: Summary Included Evidence-Based Guidelines

Guideline	Selected Recommendations
<p>CDC 2015¹ - Sexually Transmitted Diseases Treatment Guidelines</p>	<p><i>“Several factors should affect the decision to provide presumptive therapy for cervicitis. Presumptive treatment with antimicrobials for C. trachomatis and N. gonorrhoeae should be provided for women at increased risk (e.g., those aged <25 years and those with a new sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually transmitted infection), especially if follow-up cannot be ensured or if testing with NAAT is not possible. Trichomoniasis and BV should also be treated if detected (see Bacterial Vaginosis and Trichomoniasis). For women at lower risk of STDs, deferring treatment until results of diagnostic tests are available is an option. If treatment is deferred and NAATs for C. trachomatis and N. gonorrhoeae are negative, a follow-up visit to see if the cervicitis has resolved can be considered.”(p54)</i></p>
<p>INESSS 2017³ - STBBI - Syndromic Approach</p>	<p>These guidelines recommend the following treatment regimens for patients (aged 14 or older) presenting with cervicitis:</p> <ul style="list-style-type: none"> • 1st choice: azithromycin 1 g p.o. in a single dose and either cefixime 800 mg p.o. in a single dose or ceftriaxone 250 mg IM in a single dose • 2nd choice: doxycycline 100 mg p.o. b.i.d. for 7 days and either cefixime 800 mg p.o. in a single dose or ceftriaxone 250 mg IM in a single dose • For patients with a history of allergic reaction to cephalosporins or history of severe or very severe delayed or immediate reaction to penicillins: Azithromycin 2 g p.o. in a single dose

b.i.d = twice daily (from the Latin “bis in die”); CDC = Centers for Disease Control and Prevention; CPG = clinical practice guideline; IM = intramuscular; INESSS = Institut national d'excellence en santé et en services sociaux; NAAT = Nucleic Acid Amplification Test; p.o. = orally, by mouth (from the Latin “per os”); STD = sexually transmitted disease

Appendix 5: Additional References of Potential Interest

Systematic Reviews and Meta-Analyses

Alternative Population

Horner P, Ingle SM, Garrett F, Blee K, Kong F, Muir P, et al. Which azithromycin regimen should be used for treating *Mycoplasma genitalium*? A meta-analysis. *Sex Transm Infect.* 2017 Jul 17. [PubMed: PM28717050](#)

Manhart LE, Jensen JS, Bradshaw CS, Golden MR, Martin DH. Efficacy of antimicrobial therapy for *Mycoplasma genitalium* infections. *Clin Infect Dis.* 2015 Dec 15;61 Suppl 8:S802-S817. [PubMed: PM26602619](#)

Lau A, Bradshaw CS, Lewis D, Fairley CK, Chen MY, Kong FY, et al. The Efficacy of azithromycin for the treatment of genital *Mycoplasma genitalium*: a systematic review and meta-analysis. *Clin Infect Dis.* 2015 Nov 1;61(9):1389-99. [PubMed: PM26240201](#)

Kong FY, et al. Azithromycin versus doxycycline for the treatment of genital chlamydia infection: a meta-analysis of randomised controlled trials. *Clin Infect Dis;* 2014 Jul 15;59(2):193-205. [PubMed: PM24729507](#)

Randomized Controlled Trials

Alternative Comparator

McCormick DF, Rahman M, Zadrozny S, Alam A, Ashraf L, Neilsen GA, et al. Prevention and control of sexually transmissible infections among hotel-based female sex workers in Dhaka, Bangladesh. *Sex Health.* 2013 Dec;10(6):478-86. [PubMed: PM24262217](#)

Alternative Population

Wind CM, Schim van der Loeff MF, Unemo M, Schuurman R, van Dam AP, de Vries HJ. Time to clearance of *Chlamydia trachomatis* RNA and DNA after treatment in patients coinfecting with *Neisseria gonorrhoeae* - a prospective cohort study. *BMC Infect Dis.* 2016 Oct 11;16(1):554. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5057251> [PubMed: PM27724878](#)

Geisler WM, Uniyal A, Lee JY, Lensing SY, Johnson S, Perry RC, et al. Azithromycin versus doxycycline for urogenital chlamydia trachomatis infection. *N Engl J Med.* 2015 Dec 24;373(26):2512-21. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4708266>

Falk L, Enger M, Jensen JS. Time to eradication of *Mycoplasma genitalium* after antibiotic treatment in men and women. *J Antimicrob Chemother.* 2015 Nov;70(11):3134-40. [PubMed: PM26283670](#)

Non-Randomized Studies

Alternative Comparator

Terada M, Izumi K, Ohki E, Yamagishi Y, Mikamo H. Antimicrobial efficacies of several antibiotics against uterine cervicitis caused by *Mycoplasma genitalium*. *J Infect Chemother.* 2012 Jun;18(3):313-7. [PubMed: PM22020630](#)

Alternative Population

Craig AP, Kong FY, Yeruva L, Hocking JS, Rank RG, Wilson DP, et al. Is it time to switch to doxycycline from azithromycin for treating genital chlamydial infections in women? Modelling the impact of autoinoculation from the gastrointestinal tract to the genital tract. *BMC Infect Dis.* 2015 Apr 30;15:200. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4419407>

Schumacher CM, Ghanem KG. Retreatment rates for uncomplicated gonorrhoea infection: comparing ceftriaxone and azithromycin versus ceftriaxone and doxycycline. *Sex Transm Dis.* 2013 Jul;40(7):539-

45. [PubMed: PM23965767](#)

Anagrus C, Lore B, Jensen JS. Treatment of Mycoplasma genitalium. observations from a Swedish STD clinic. PLoS ONE. 2013;8(4):e61481. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3620223>

No Comparator

Lusk MJ, Garden FL, Cumming RG, Rawlinson WD, Naing ZW, Konecny P. Cervicitis: a prospective observational study of empiric azithromycin treatment in women with cervicitis and non-specific cervicitis. Int J STD AIDS. 2017 Feb;28(2):120-6. [PubMed: PM 26792283](#)

Review Articles

Wagenlehner FM, Brockmeyer NH, Discher T, Friese K, Wichelhaus TA. The presentation, diagnosis, and treatment of sexually transmitted infections. Dtsch Arztebl Int. 2016 Jan 11;113(1-02):11-22. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4746407>

Jensen JS, Cusini M, Gomberg M, Moi H. Background review for the 2016 European guideline on Mycoplasma genitalium infections. J Eur Acad Dermatol Venereol. 2016 Oct;30(10):1686-93. [PubMed: PM 27605499](#)

Manhart LE, Jensen JS, Bradshaw CS, Golden MR, Martin DH. Efficacy of antimicrobial therapy for Mycoplasma genitalium infections. Clin Infect Dis. 2015 Dec 15;61 Suppl 8:S802-S817. [PubMed: PM 26602619](#)