CoLab Network

Technology Review

Evidence Review of Treatment Options for Uncomplicated Gonococcal Infection

Authors: Jasmeen Dourka, Carole Lunny, Menelaos Konstantinidis, Sarah C. McGill, Andrea C. Tricco

This Health Technology Review was conducted by the Knowledge Synthesis Team, Knowledge Translation Program, through the Post-Market Drug Evaluation Program.

August 2024

Key Messages

Gonorrhea is a sexually transmitted infection caused by the bacteria *Neisseria gonorrhea*. It is typically treated with antibiotics. However, increasing antibiotic resistance makes it challenging to adhere to current treatment recommendations.

We aimed to build upon a previous scoping search to address gaps in current treatment guidelines for uncomplicated *N. gonorrhea* infection.

This evidence review includes 19 treatment guidelines and 1 systematic review. Thirteen of the guidelines were identified in the previous scoping search, all published between 2013 and 2019. The remaining 6 guidelines and systematic review were all published between 2020 and 2022.

The included guidelines and systematic review lacked comparative efficacy data and had limited safety data.

The systematic review was rated as low quality because it did not report a list of excluded studies, did not perform a sensitivity analysis based on the risk of bias of the included randomized controlled trials, and did not account for biases in the primary studies when interpreting the results. It also evaluated treatment efficacy for throat infections, so the results may not be generalizable to other sites of infection.

Many guidelines lacked details on the methods used, making it difficult to judge the reliability of their recommendations based on the evidence they used.

Future research involving a systematic review with meta-analysis or a series of rapid reviews would help to inform the development of updated treatment guidelines by the Public Health Agency of Canada.

Table of Contents

List of Tables

List of Figures

Abbreviations

BASHH	British Association for Sexual Health and HIV
INESSS	Institut national d'excellence en santé et en services sociaux
IUSTI	International Union Against Sexually Transmitted Infections
KCE	Belgian Health Care Knowledge Centre
PHAC	Public Health Agency of Canada
RCT	randomized controlled trial
SR	systematic review
STI	sexually transmitted infection
US CDC	US Centers for Disease Control and Prevention
WHO	World Health Organization

Introduction and Rationale

Background and Policy Issue

Gonorrhea is a sexually transmitted infection (STI) caused by the bacteria *Neisseria gonorrhea*[1] that can be effectively controlled and managed through antibiotic treatment. However, increasing antimicrobial resistance and changing resistance profiles in *N. gonorrhea* pose significant challenges for implementing the current guidance on gonorrhea treatment.[2] Thus, CADTH commissioned this review of treatment options for uncomplicated *N. gonorrhea* infections to inform the development of updated recommendations by the Public Health Agency of Canada (PHAC).

The overall objective of this review was to identify evidence gaps related to the following 8 research questions:

Research Questions

1. What treatment options should be recommended for genital and nongenital infections caused by *N. gonorrhea*?
    a) What is the efficacy and safety of ceftriaxone monotherapy compared with ceftriaxone combined with azithromycin for the treatment of uncomplicated gonorrhea in adults and adolescents?
    b) What is the efficacy and safety of combination antibiotic therapy compared with monotherapy for the treatment of uncomplicated gonorrhea in adults and adolescents?
2. What is the efficacy and safety of high-dose (500 mg or 1 g) ceftriaxone monotherapy compared with the recommended dose of 250 mg for the treatment of uncomplicated gonorrhea in adults and adolescents?
3. What is the safety and efficacy of antibiotic therapy for the treatment of uncomplicated gonorrhea in adults and adolescents with a coinfection of *Chlamydia trachomatis* or *Mycoplasma genitalium*?
4. What is the safety and efficacy of antibiotic treatments after failure of a cephalosporin combined with azithromycin for the treatment of uncomplicated gonorrhea in adults and adolescents?
5. What is the efficacy and safety of ceftriaxone or cefixime administered as multiple doses per day or as multiple doses over several days, compared with ceftriaxone or cefixime administered in a single dose, for the treatment of uncomplicated gonorrhea in adults and adolescents?
6. What is the efficacy and safety of treatment based on a positive test result (need to wait for test result/do not provide immediate treatment) compared with treatment based on symptoms (empiric prescribing/immediate treatment) in adults and adolescents with uncomplicated gonorrhea and their sexual partners?
7. What is the feasibility, costs and resources, and acceptability of different treatment options for genital and nongenital infections caused by *N. gonorrhea*?

Main Take-Aways

Gonorrhea is an STI caused by the bacteria *N. gonorrhea*. It can be treated with antibiotics; however, the growing problem of antibiotic resistance makes it challenging to adhere to current treatment guidelines. The goal of this evidence review is to identify gaps in the research.

Methods

This evidence review provides an update to an unpublished PHAC scoping exercise.[6] The PHAC scoping exercise was used to develop the 8 research questions addressing gaps or outdated guidance in PHAC's current *N. gonorrhea* treatment recommendations. PHAC wants to determine if an existing systematic review (SR) can be updated or used to inform recommendations; if a new SR is necessary; or whether to adopt, adapt, or develop de novo recommendations.

As such, we conducted a literature search to identify new guidelines and SRs published after January 2020.

Literature Search Methods

An information specialist from CADTH developed and conducted the literature search, using a peer-reviewed search strategy according to CADTH's PRESS Peer Review of Electronic Search Strategies.[3] The following bibliographic databases were searched: MEDLINE via Ovid, Embase via Ovid, and the Cochrane Database of SRs via CochraneLibrary.com. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in EndNote. Search concepts were developed based on the elements of the population, intervention, comparator, and outcome(s) (PICO) framework and research questions, and comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was gonorrhea and synonyms. CADTH-developed search filters were applied to limit retrieval to health technology assessments, SRs, meta-analyses, indirect treatment comparisons, or guidelines. Retrieval was limited to documents in the English or French language and published between January 1, 2020, and April 27, 2023. Conference abstracts and protocols were excluded from the search results. The search was completed on April 27, 2023. The reference lists were not scanned for the included studies. The complete search strategy is presented in Appendix 1.

Grey literature was identified by searching sources listed in relevant sections of CADTH's Grey Matters: A Practical Tool for Searching Health-Related Grey Literature, which includes the websites of health technology assessment agencies, clinical guideline repositories, and SR repositories.[4] Google was used to search for additional internet-based materials.

Additional literature was identified through a previous scoping exercise completed by PHAC in September 2020 and revised in February 2022. Their literature search included studies published in the past 10 years

(January 2010 to February 2020) in English or French and that were conducted in a health care setting like Canada and in high-income countries.

Selection Criteria and Methods

One reviewer independently screened citations and selected studies using the Knowledge Translation Program's proprietary screening software (synthesi.SR).[5] 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. Due to time and resource constraints, pilot-testing of the screening process was not done for this review.

Table 1: Selection Criteria

Criteria	Description
Population	Q1a to Q2: Adults and adolescents with uncomplicated *N. gonorrhea* infections or clinical syndrome compatible with *N. gonorrhea* infection Q3: Adults and adolescents with uncomplicated *N. gonorrhea* (or clinical syndrome compatible with *N. gonorrhea* infection) and *C. trachomatis* or *M. genitalium* coinfections Q4: Adults and adolescents with uncomplicated *N. gonorrhea* infections (or clinical syndrome compatible with *N. gonorrhea* infection) who have failed combination therapy of azithromycin with a cephalosporin Q5: Adults and adolescents with uncomplicated *N. gonorrhea* infections or clinical syndrome compatible with *N. gonorrhea* infection Q6: Adults and adolescents with uncomplicated *N. gonorrhea* infections who are symptomatic and their sexual partners Q7: Adults and adolescents with uncomplicated *N. gonorrhea* infections or clinical syndrome compatible with *N. gonorrhea* infection
Intervention	Q1a: Ceftriaxone monotherapy (any dosage regimen) Q1b: Combination antibiotic therapies (any dosage regimens) (azithromycin with cefixime, azithromycin with ciprofloxacin, azithromycin with gentamicin, doxycycline with ceftriaxone, doxycycline with cefixime) Q2: Ceftriaxone 500 mg or 1 g Q3: Any dosing regimen of cefixime with azithromycin, ceftriaxone with azithromycin, cefixime with doxycycline, ceftriaxone with doxycycline, cefixime with azithromycin and doxycycline, or ceftriaxone with azithromycin and doxycycline Q4: Antimicrobial monotherapy of combination therapy after failure of a cephalosporin (cefixime or ceftriaxone) with azithromycin Q5: Ceftriaxone administered over several days or several doses; cefixime administered over several days or several doses Q6: Antibiotic treatment based on test result Q7: Oral treatment options; treatment provided as a single dose; treatment provided in the clinic (free medication provided by the clinic)
Comparator	Q1a: Ceftriaxone combined with azithromycin (any dosage regimen) Q1b: Monotherapy with ceftriaxone, cefixime, azithromycin, gentamicin, ciprofloxacin, ertapenem (any dosage regimens) Q2: Ceftriaxone 250 mg Q3: Monotherapy or combination antibiotic treatment (any dosing regimen)

Criteria	Description
	Q4: Azithromycin with cefixime; azithromycin with ceftriaxone Q5: Ceftriaxone administered in 1 single dose; cefixime administered in 1 single dose Q6: Antibiotic treatment based on symptoms Q7: Injectable treatment options, treatment provided as multiple doses, treatment that is prescribed (filled at a drugstore; medication paid out of pocket)
Outcomes	Q1a to Q7: Efficacy (clinical cure, microbiological cure, treatment failure); safety and toxicity (adverse drug events, serious adverse events, withdrawal due to adverse events (as applicable), allergic or anaphylactic reactions), adherence to treatment (completion of full treatment course), resistance, and loss to follow-up Q6: Inappropriate treatment, unnecessary treatment Q7: Feasibility of treatment use, costs and resources, acceptability, clinical practices
Settings	Q1a to Q7: All clinical settings in which gonorrhea treatment, and more broadly STBBI care, is provided, including but not limited to hospitals, clinics, STBBI clinics, private practice, and so forth; settings with a health care system comparable to Canada's context.
Study designs	Q1a to Q7: SRs, health technology assessments, meta-analyses, guidelines

SR = systematic review; STBBI = sexually transmitted and blood-borne infection.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published before August 1, 2020.

Data Abstraction and Critical Appraisal of Individual Studies

One reviewer independently abstracted data from all included studies from the new search and assessed the quality of the SR using the A MeaSurement Tool to Assess SRs version 2 (AMSTAR-2) tool.[7] Due to time and resource constraints, guidelines were not critically appraised.

Data Synthesis

The results were summarized descriptively and organized based on the related research question and the type of secondary source, namely a SR or clinical practice guideline/report. Additional data were organized into supplementary tables and included as appendices. The results of this review were merged with the PHAC scoping exercise. We have referenced the PHAC report where data from its scoping exercise were used.

Summary of Evidence

Quantity of Research Available

Main Take-Aways

From a total of 361 citations, 7 publications were included in this evidence review, consisting of 6 guidelines and 1 SR. Thirteen guidelines identified in the PHAC scoping exercise were also included.

There were 13 guidelines[16-28] on *N. gonorrhea* treatment published between 2013 and 2019 included in the PHAC scoping exercise. The PHAC search also identified 10 published SRs; however, none were related to our research questions and they were, therefore, excluded. Reasons for exclusion are outlined in Appendix 4.

A total of 325 citations were identified in the updated literature search. Following screening of titles and abstracts, 225 citations were excluded and 100 potentially relevant reports from the database search were retrieved for full-text review. A total of 36 potentially relevant publications were retrieved from the grey literature search. Of the potentially relevant articles, 129 were excluded for various reasons, as delineated in the Preferred Reporting Items for SRs and Meta-Analyses (PRISMA) flow diagram (Appendix 2).[8] A total of 7 publications met the inclusion criteria and were included in this report. These 7 publications comprised 6 guidelines[9-14] and 1 SR.[15] Refer to Appendix 3 for a list of the 7 publications as well as a list of publications included in the scoping exercise by PHAC.

Summary of Critical Appraisal

The identified SR[15] was assessed as being of low quality based on AMSTAR-2 (Appendix 6). It was deemed low quality due to 3 flaws: it did not include a list of excluded studies, did not include a sensitivity analysis based on risk of bias of the randomized controlled trials (RCTs), and did not account for the biases in the primary studies in the interpretation of the results.

Summary of Findings

Main Take-Aways

- The included SR found that using ceftriaxone alone is effective for treating gonorrhea in the throat, with similar cure rates across different doses.
- The SR also showed that both monotherapy and combination therapy were effective against gonorrhea in the throat but noted higher rates of nausea and diarrhea with combination therapy including azithromycin.
- Treatment recommendations varied across the included guidelines.
- No studies were found comparing the effectiveness and safety of administering ceftriaxone or cefixime in multiple doses per day or over several days versus a single dose for treating uncomplicated gonorrhea in adults and adolescents.

The findings of the 7 included publications are summarized by research question and by study type. The key recommendations from the 7 guidelines identified in this search, as well as the 13 guidelines identified by PHAC, are outlined in Table 2. A detailed summary of the main findings, recommendations, and type of evidence used are available in Appendix 5. Table 2 also differentiates the guidelines identified from this review from those identified in the scoping exercise by PHAC.[6]

Table 2: Summary of Recommendations From Included Guidelines

Guideline and year of publication (country or jurisdiction)	Author and organization	Preferred treatment for uncomplicated *N. gonorrhea* infection in adolescents and adults or clinical syndrome compatible with *N. gonorrhea* infection	Relevant research question(s)	Methods and types of evidence used	Search source
International guidelines					
Gonorrhea guide, 2022[13] (Canada)	PHAC	Ceftriaxone 250 mg IM plus azithromycin 1 g p.o. in a single dose.[a] Cefixime 800 mg orally plus azithromycin 1 g p.o. in a single dose is considered an alternative therapy for gbMSM.	Q1a and Q1b	No methods reported; all types of published and unpublished primary studies were included.	Identified in this review.
European Guideline on the management of proctitis, proctocolitis and enteritis caused by sexually transmissible pathogens, 2021[9] (Europe)	IUSTI — European regions	Ceftriaxone 1 g IM in 1 single dose with doxycycline 100 mg b.i.d. for 7 days. The guideline further recommends doxycycline to avoid azithromycin resistance in undiagnosed coinfection with *M. genitalium*.[b]	Q3 and Q4	No methods reported other than a search strategy and GRADE evidence tables. All types of published secondary and primary studies were included.	Identified in this review.
The JAID/JSC guidelines to Clinical Management of Infectious Disease 2017 concerning male urethritis and related disorders, 2021[10] (Japan)	JAID/JSC	Ceftriaxone 1 g IV in a single dose as the first-line treatment for male gonococcal urethritis.[b]	Q4	No methods reported other than recommendation levels of the evidence determined according to the *Outline for the Preparation of the Guidelines to Clinical Management of Infectious Disease* established by JAID/JSC. All types of published secondary and primary studies were included.	Identified in this review.

Guideline and year of publication (country or jurisdiction)	Author and organization	Preferred treatment for uncomplicated *N. gonorrhea* infection in adolescents and adults or clinical syndrome compatible with *N. gonorrhea* infection	Relevant research question(s)	Methods and types of evidence used	Search source
Southern African HIV Clinicians Society 2022 guideline for the management of sexually transmitted infections: Moving towards best practice[12] (southern Africa)	Southern African HIV Clinicians Society	Ceftriaxone 500 mg IM in a single dose for confirmed genital infection.[a] Ceftriaxone 1 g IM in a single dose for confirmed oropharyngeal infection.[a]	Q1a	No methods reported; all types of published secondary and primary studies were included.	Identified in this review.
Guidelines for the management of symptomatic sexually transmitted infections, 2021[14] (international)	WHO	For patients with symptoms of urethral discharge from the penis, a molecular test–based approach is recommended. For patients with symptoms of vaginal discharge, a molecular test–based approach is recommended. However, in settings where testing is not feasible or accessible, it is recommended that treatment be based on rapid point-of-care tests or on syndromic management.	Q6	SRs for each syndrome was conducted and modelling work on vaginal discharge was carried out. The GRADE approach was used. All types of published and unpublished primary studies were included.	Identified in this review.
WHO guidelines for the treatment of *Neisseria gonorrhoeae,* 2016[20] (international)	WHO	Ceftriaxone 250 mg IM as a single dose or cefixime 400 mg orally plus azithromycin 1 g orally as a single dose[a] or ceftriaxone 250 mg IM as a single dose (based on recent local resistance data).[a] In the event of treatment failure, WHO recommends re-treatment with 1 of the following regimens: • ceftriaxone 500 mg IM as a single dose plus azithromycin 2 g p.o. as a single dose • cefixime 800 mg orally as a single dose plus azithromycin 2 g p.o. as a single dose • gentamicin 240 mg IM as a single dose plus azithromycin 2 g p.o. as a single dose • spectinomycin 2 g IM as a single dose (if not an oropharyngeal infection) plus azithromycin 2 g p.o. as a single dose.	Q1a and Q4	SRs for each priority question were conducted and the GRADE approach was used. All SRs and primary studies were included.	Identified in PHAC scoping exercise.

Guideline and year of publication (country or jurisdiction)	Author and organization	Preferred treatment for uncomplicated *N. gonorrhea* infection in adolescents and adults or clinical syndrome compatible with *N. gonorrhea* infection	Relevant research question(s)	Methods and types of evidence used	Search source
Australian STI Management Guidelines, 2018[24] (Australia)	ASHM	Ceftriaxone 500 mg IM once plus azithromycin 1 g p.o.[a]	Q1a	No SR; based on a consensus-based approach drawing primarily from existing STI guidelines, gonococcal surveillance data, and studies conducted in Australia.	Identified in PHAC scoping exercise.
Diagnosis and treatment of gonorrhea, 2019[26] (Germany)	AWMF	Ceftriaxone 1 g to 2 g IM or IV per day over 3 days plus azithromycin 1.5 g orally as a single dose.[a] Ceftriaxone monotherapy 1 g to 2 g IM or IV under certain conditions.[a]	Q1a	No methods reported. All types of published secondary and primary studies were included.	Identified in PHAC scoping exercise.
2018 UK national guideline for the management of infection with *Neisseria gonorrhoeae*[18] (UK)	Fifer et al. (2020) from BASHH	Ceftriaxone 1 g in a single dose, if antimicrobial susceptibility is not known before treatment.[a]	Q1a and Q2	SR methods and GRADE approach used. SR states "priority was given to RCTs and SR evidence."(pg. 4). Local and global surveillance reports were used to make recommendations on the dosage increase from the previous guideline.	Identified in PHAC scoping exercise.
Sexually Transmitted Infections Treatment Guidelines, 2021[17] (USA)	US CDC	Ceftriaxone 500 mg IM in a single dose for persons weighing < 150 kg.[a] Ceftriaxone 1 g in a single dose for persons weighing ≥ 150 kg.[a] Note: If chlamydial infection has not been excluded, concurrent treatment with doxycycline 100 mg p.o. b.i.d. for 7 days is recommended.[a]	Q1a, Q2, and Q3	SR conducted for each question. All types of published primary studies were included. Meeting of CDC staff members and subject matter experts (with expertise in STI clinical management) from	Identified in PHAC scoping exercise.

Guideline and year of publication (country or jurisdiction)	Author and organization	Preferred treatment for uncomplicated *N. gonorrhea* infection in adolescents and adults or clinical syndrome compatible with *N. gonorrhea* infection	Relevant research question(s)	Methods and types of evidence used	Search source
				other federal agencies, nongovernmental academic and research institutions, and professional medical organizations to develop key questions to guide individual literature reviews. Expert opinions were used when data were insufficient.	
Diagnosis and management of gonorrhoea and syphilis, 2019 (Belgium)[22]	Jespers et al. (2020) from KCE	Ceftriaxone 500 mg in a single dose plus azithromycin 2 g p.o. in a single dose for anogenital and pharyngeal infections in nonpregnant persons, including young people.[a] Ceftriaxone 500 mg for anogenital and pharyngeal infections in pregnant persons.[a]	Q1a and Q2	SR conducted and the GRADE approach was used. All types of published secondary and primary studies were included.	Identified in PHAC scoping exercise.
2020 European guideline for the diagnosis and treatment of gonorrhoea in adults[19] (Europe)	Unemo et al. (2020) from the IUSTI – European regions	Ceftriaxone 1 g IM as a single dose plus azithromycin 2 g p.o. as a single dose.[a] Note: Monotherapy with ceftriaxone is recommended (only in well-controlled settings).	Q1a	No methods reported other than GRADE approach used. Guideline states "The Cochrane Library was searched and relevant STI guidelines produced by WHO, US CDC, and the British Association for Sexual Health and HIV were included." (pg. 8)	Identified in PHAC scoping exercise.

Guideline and year of publication (country or jurisdiction)	Author and organization	Preferred treatment for uncomplicated *N. gonorrhea* infection in adolescents and adults or clinical syndrome compatible with *N. gonorrhea* infection	Relevant research question(s)	Methods and types of evidence used	Search source
Recommandations diagnostiques et thérapeutiques pour les maladies sexuellement transmissibles, 2016 [27] (France)	SFD	Ceftriaxone 500 mg IM in a single dose.[a] Antichlamydial therapy with azithromycin is systematically combined with ceftriaxone.	Q1a, Q2, and Q3	No methods reported.	Identified in PHAC scoping exercise.
New Zealand Guideline for the Management of Gonorrhoea, 2017[28] (New Zealand)	NZSHS	Ceftriaxone 500 IM mg plus azithromycin 1 g p.o.[a] Dose frequency and duration of treatment was not reported.	Q1a	No methods reported. No references found.	Identified in PHAC scoping exercise.
Provincial guidelines					
Update of the optimal use guide on sexually transmitted and blood-borne infections — Syndromic approach, 2020[11] (Quebec)	INESSS	**For the treatment of cervicitis and urethritis:** First line: ceftriaxone 250 mg IM as a single dose with doxycycline 100 mg p.o. b.i.d. for 7 days. Second line: cefixime 800 mg p.o. as a single dose or ceftriaxone 250 mg IM as a single dose with azithromycin 2 g p.o. in a single dose. **For the treatment of PID:** First line: ceftriaxone 250 mg IM as a single dose with doxycycline 100 mg p.o. b.i.d. for 14 days and metronidazole 500 mg p.o. b.i.d. for 14 days. **For the treatment of rectitis:** First line: ceftriaxone 250 mg IM as a single dose and doxycycline p.o. 100 mg b.i.d. for 7 days. Second line: cefixime 800 mg p.o. as a single dose and doxycycline 100 mg p.o. b.i.d. for 7 days and azithromycin 2 g p.o. as a single dose.	Q4	SRs with narrative summaries were conducted for each PICO question and no GRADE framework used. All types of published and unpublished primary studies were included.	Identified in this review.
Alberta Treatment Guidelines for Sexually Transmitted Infections (STI) in Adolescents and Adults, 2018[23] (Alberta)	Alberta Health Services	Cefixime 800 mg p.o. in a single dose plus azithromycin 1 g p.o. in a single dose.[a] For gbMSM, ceftriaxone 250 mg IM as a single dose plus azithromycin 1 g p.o. as a single dose is	Q1b	Adaptation from the Canadian Guidelines on Sexually Transmitted Infections.	Identified in PHAC scoping exercise.

Guideline and year of publication (country or jurisdiction)	Author and organization	Preferred treatment for uncomplicated *N. gonorrhea* infection in adolescents and adults or clinical syndrome compatible with *N. gonorrhea* infection	Relevant research question(s)	Methods and types of evidence used	Search source
		recommended, and cefixime 800 mg p.o. as a single dose plus azithromycin 1 g p.o. as a single dose is considered an alternative therapy.			
British Columbia Treatment Guidelines for Sexually Transmitted Infections in Adolescents and Adults 2014[25] (British Columbia)	BCCDC	Cefixime 800 mg p.o. as a single dose or ceftriaxone 250 mg IM as a single dose plus azithromycin 1 g p.o. as a single dose or doxycycline 100 mg p.o. b.i.d. for 7 days.[a]	Q1b	Adaptation from the Canadian Guidelines on Sexually Transmitted Infections.	Identified in PHAC scoping exercise.
Ontario Gonorrhea Testing and Treatment Guide, 2018[21] (Ontario)	Public Health Ontario	Ceftriaxone 250 mg IM as a single dose plus azithromycin 1 g PO as a single dose.[a] In the event of treatment failure, a higher dose of both ceftriaxone and azithromycin should be given: ceftriaxone 1 g IM as a single dose plus azithromycin 2 g p.o. as a single dose.	Q1a and Q4	Literature review for each chapter (MEDLINE search). SRs and primary studies cited.	Identified in PHAC scoping exercise.
Guide d'usage optimal — Infection non compliquée à *Chlamydia trachomatis* ou à *Neisseria Gonorrhorae*, 2020[16] (Quebec)	INESSS	Ceftriaxone 250 mg IM as a single dose.[a] or Cefixime 800 mg p.o. in a single dose plus azithromycin 2 g p.o. in a single dose.[a] If ceftriaxone is used as monotherapy, a treatment for *C. trachomatis* should be prescribed when the presence of *C. trachomatis* cannot be excluded.	Q1a, Q1b, and Q3	SR for each chapter. Included SRs, RCTs and nonRCTs, and all observational studies.	Identified in PHAC scoping exercise.

ASHM = Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine; AWMF = Association of the Scientific Medical Societies in Germany; BASHH = British Association for Sexual Health and HIV; BCCDC = British Columbia Centre for Disease Control; b.i.d. = twice daily; gbMSM = gay, bisexual, and other men who have sex with men; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; IM = intramuscular; INESSS = Institut national d'excellence en santé et en services sociaux; IUSTI = International Union Against Sexually Transmitted Infections; JAID = Japanese Association for Infectious Disease; JSC = Japanese Society of Chemotherapy; KCE = Belgian Health Care Knowledge Centre; NZSHS = New Zealand Sexual Health Society; PHAC = Public Health Agency of Canada; PICO = population, intervention, comparator, outcome(s); PID = pelvic inflammatory disease; p.o. = orally; RCT = randomized controlled trial; SFD = Société Française de Dermatologie et de pathologies sexuellement transmissibles; SR = systematic review; STI = sexually transmitted infection; US CDC = US Centers for Disease Control and Prevention.

Some guidelines have recommendations that vary by site of infection, coinfections, or population. Refer to Appendix 5 for these variations.

Unless otherwise stated, the duration of treatment is once.

[a]Indicates that treatment recommendations are based on culture-testing results.

[b]Indicates that treatment recommendations are syndromic based.

What Treatment Options Should Be Recommended for Genital and Nongenital Infections Caused by *N. Gonorrhea*?

What Is the Efficacy and Safety of Ceftriaxone Monotherapy Compared With Ceftriaxone Combined With Azithromycin for the Treatment of Uncomplicated Gonorrhea in Adults and Adolescents?

Systematic Reviews

One SR[15] with meta-analysis that assessed treatment efficacy (defined as microbiological cure) at follow-up was identified based on the inclusion criteria for this research question. The microbiological cure was measured as a proportion, with the numerator being the number of patients treated and cured for pharyngeal *N. gonorrhea* infection and the denominator being the total number tested for pharyngeal *N. gonorrhea* at follow-up. The reported proportions cured from the single arms of 3 RCTs (n = 22) for ceftriaxone monotherapy (125 mg, 250 mg, and 500 mg) was the same for all 3 doses. Specifically, ceftriaxone 125 mg had a reported cured proportion of 100% (n = 5; 95% CI, 56.5% to100%), ceftriaxone 250 mg had a reported cured proportion of 100% (n = 13; 95% CI, 77.2% to 100%), and ceftriaxone 500 mg had a reported cured proportion of 100% (n = 4; 95% CI, 51.0% to 100%).

Combination therapy in subgroup analysis with ceftriaxone (500 mg) and azithromycin (1 g) had a pooled cured proportion of single arms of 2 RCTs of 97.1% (n = 132; 95% CI, 93.0% to 99.7%).[15] The authors identified only a single arm of 1 RCT of combination therapy with ceftriaxone (500 mg) and azithromycin (2 g) with an efficacy of 100% (n = 33; 95% CI, 89.6% to 100%).[15] The overall results of this SR suggest that ceftriaxone monotherapy is sufficiently efficacious as a treatment for pharyngeal infection, albeit the estimates are based on small sample sizes, single treatment arms from RCTs, and subgrouping.

The PHAC scoping exercise did not identify SRs that directly compared the safety and efficacy of ceftriaxone monotherapy with ceftriaxone and azithromycin combination therapy.

Treatment Guidelines

Two guidelines[12,13] that qualify under the inclusion criteria for this research question were identified. Thirteen guidelines[16-28] on uncomplicated *N. gonorrhea* treatment were also identified by the PHAC scoping exercise. The recommendations from each of these guidelines are summarized in Table 2.

To note, 2 guideline organizations[16,17] conducted literature reviews to inform their recommendations regarding ceftriaxone monotherapy or combination antibiotic therapy with ceftriaxone and azithromycin: the Institut national d'excellence en santé et en services sociaux (INESSS) and the US Centers for Disease Control and Prevention (CDC).

A SR was conducted by INESSS (2020) to assess the appropriateness of dual therapy in the treatment of confirmed *N. gonorrhea* infection by addressing the following question: *How efficacious is combined ceftriaxone/azithromycin antibiotic therapy compared to ceftriaxone alone in patients 14 years of age and older treated for an uncomplicated urethral, endocervical, rectal, or pharyngeal* Neisseria gonorrhoeae *infection?* Their SR identified 3 studies that evaluated the efficacy of combination antibiotic therapy comprised of ceftriaxone with azithromycin, compared to ceftriaxone monotherapy, in patients treated

for uncomplicated *N. gonorrhea* infection, with the results being reported narratively. They reported that the results of the studies by Singh et al.[39] and Wind et al.[40] indicate a treatment failure rate of 0% when ceftriaxone monotherapy is used to treat patients for urogenital, anorectal, and pharyngeal *N. gonorrhea* infections. For combination therapy comprised of ceftriaxone with azithromycin, the results of the Singh[39] and Wind[40] studies also reported a treatment failure rate of 0% for all sites of infection. INESSS reported that in a third study by Barbee et al.,[41] the proportion of repeat tests (between 7 days and 180 days after treatment) with a positive result for *N. gonorrhea* were similar for ceftriaxone monotherapy (9.1%) and ceftriaxone combined with azithromycin (11.7%). Although INESSS ultimately concluded that this level of scientific evidence is considered low, they updated their optimal use guide to recommend ceftriaxone monotherapy or cefixime plus azithromycin combination therapy based on these results.[16]

In addition to the US CDC guideline (2021), the US CDC also conducted a literature review (non-SR) on gonorrhea antimicrobial resistance, treatment failures, and clinical trials.[17] This review was supplemented with data on antimicrobial surveillance, pharmacokinetic and pharmacodynamic simulations and, when these data were insufficient, expert opinions. In these guidelines, combination therapy with ceftriaxone and azithromycin was updated from a previous version to ceftriaxone monotherapy for the treatment of uncomplicated *N. gonorrhea* infections at all sites of infection (i.e., pharyngeal, urogenital, and anorectal). The US CDC indicated that "concerns regarding the potential harm to the microbiome and the effect on other pathogens diminishes the benefits of maintaining dual therapy" (pg. 72).[17]

What Is the Efficacy and Safety of Combination Antibiotic Therapy Compared With Monotherapy for the Treatment of Uncomplicated Gonorrhea in Adults and Adolescents?

Systematic Reviews

The SR by Kong et al.[15] provided evidence on combination therapy (i.e., therapies comprising 2 antibiotics) regimens and monotherapy for the treatment of pharyngeal infections as a subgroup analysis. They found that monotherapy had a reported microbiological cure rate of 97.1% (95% CI, 90.8% to 100.0%;I^2 = 15.6%; P = 0.29) against pharyngeal *N. gonorrhea* infections, based on single arms of 5 trials (n = 128). For the treatment of pharyngeal *N. gonorrhea*, combination therapy had an efficacy of 98.0% (95% CI, 91.4% to 100%; I^2 = 79.1%; P < 0.01) from single arms of 3 trials (n = 324).[15] These subgroup analyses were stand-alone meta-analyses of proportions and were not statistically compared. They also found that nausea and diarrhea was high in patients taking combination antibiotic treatment regimens that included azithromycin (2 g).

However, included in this subgroup were treatment regimens comprised of antibiotics such as gatifloxacin and gemifloxacin, which are older treatments previously recommended but no longer used, and delafloxacin, which is a treatment that is not available in Canada.[15] Thus, a primary meta-analysis only of interventions relevant to this research question is necessary for future research.

The PHAC scoping exercise reported that there was a lack of SRs evaluating combination treatment regimens for uncomplicated *N. gonorrhea*, and thus did not identify any SRs related to this research question.

Treatment Guidelines

The Canadian gonorrhea guide[13] (authored by PHAC) was identified, which made recommendations based on this research question (without providing empirical evidence). Three additional guidelines were identified in the scoping exercise conducted by PHAC: the INESSS 2020 optimal use guide,[16] the US CDC 2021 guideline,[17] and the British Association for Sexual Health and HIV (BASHH) 2018 UK national guideline.[18] Overall, due to increasing concerns about antimicrobial resistance, the 3 guidelines identified by the PHAC scoping exercise recommend monotherapy with ceftriaxone (250 mg, 500 mg, or 1 g) for the treatment of uncomplicated *N. gonorrhea* infection for all sites of infection. These recommendations were made based on the results of the reviews conducted by INESSS and the US CDC, whereas BASHH applied the GRADE framework to develop the recommendations for their 2018 guideline. However, the current Canadian gonorrhea guide recommends combination therapy with ceftriaxone plus azithromycin as the preferred treatment for uncomplicated *N. gonorrhea* infection at urogenital, anorectal, and pharyngeal sites. For uncomplicated anorectal or urogenital *N. gonorrhea* infection only, the Canadian gonorrhea guide also lists combination therapy comprised of cefixime with azithromycin as a preferred treatment option. A summary of the key recommendations, with specific doses, from these guidelines is also presented in Table 2.

What Is the Efficacy and Safety of High-Dose (500 mg or 1 g) Ceftriaxone Monotherapy Compared With the Recommended Dose of 250 mg for the Treatment of Uncomplicated Gonorrhea in Adults and Adolescents?

Systematic Reviews

The SR by Kong et al.[15] was identified based on the inclusion criteria for this research question. While not a comparative analysis, the authors reported 100% pooled microbiological cure proportions based on single arms of trials for pharyngeal gonorrhea for both high doses of ceftriaxone monotherapy (500 mg), as reported in 1 single arm (n = 4; 95% CI, 51.0% to 100%), and low (250 mg) doses of ceftriaxone monotherapy, as reported in 1 single arm (n = 13; 95% CI, 77.2% to 100%).[15] Sample sizes in these 2 RCTs were very small and the results had wide confidence intervals.

Treatment Guidelines

Our search did not identify guidelines that made recommendations based on this research question. The US CDC 2021 guideline,[17] the BASHH 2018 UK national guideline,[18] and the Société Française de Dermatologie et de pathologies sexuellement transmissibles 2016 guideline[27] were identified in the scoping exercise conducted by PHAC that made recommendations based on this research question. Based on the findings of their SR, the US CDC 2021 guideline updated the previously recommended dose of ceftriaxone from a single 250 mg dose to a single 500 mg dose for individuals weighing less than 150 kg and a single 1 g dose for individuals weighing 150 kg or more for urogenital, anorectal, and pharyngeal *N. gonorrhea* infections.[17] Furthermore, the shift to ceftriaxone monotherapy represents a major change from the previous BASHH guideline. The dose of ceftriaxone was increased from 500 mg to 1 g based on local and global surveillance data identifying cases of ceftriaxone-resistant *N. gonorrhea* isolates.[18]

What Is the Safety and Efficacy of Antibiotic Therapy for the Treatment of Uncomplicated Gonorrhea in Adults and Adolescents With a Coinfection of *C. Trachomatis* or *M. Genitalium*?

Systematic Reviews

Both our search and the PHAC scoping exercise did not identify SRs on the treatment of *N. gonorrhea* coinfections with *C. trachomatis* or *M. genitalium*. The work by Creighton et al.,[33] which was included within the PHAC scoping exercise, also did not identify any SRs or RCTs on the treatment of *N. gonorrhea* coinfections with *C. trachomatis* or *M. genitalium*.

Treatment Guidelines

One guideline was identified that made a recommendation relevant for this research question (without providing empirical evidence): the 2021 European guideline on the management of proctitis, proctocolitis, and enteritis.[9] The scoping exercise conducted by PHAC[6] also identified 4 guidelines that provide recommendations pertaining to this research question: the INESSS 2020 optimal use guide,[16] US CDC 2021 guideline,[17] the 2020 European guideline,[19] and the Société Française de Dermatologie et de pathologies sexuellement transmissibles 2016 guideline.[27]

When using a syndromic approach to treatment and *N. gonorrhea* coinfection is suspected with *M. genitalium* or *C. trachomatis*, the 2021 European guideline states that doxycycline is preferred because of its superiority against (suspected) *C. trachomatis* infections and to avoid azithromycin resistance in undiagnosed coinfection with *M. genitalium*.[9] For confirmed uncomplicated *N. gonorrhea* infections, the 4 guidelines identified in the PHAC scoping exercise recommend that a treatment for *C. trachomatis* should be prescribed if concurrent *C. trachomatis* infection has not been excluded at the time of *N. gonorrhea* treatment, for all sites of infection.[9,16,17,] The key recommendations from these guidelines are also outlined in Table 2.

What Is the Safety and Efficacy of Antibiotic Treatments After Failure of a Cephalosporin Combined With Azithromycin for the Treatment of Uncomplicated Gonorrhea in Adults and Adolescents?

Systematic Reviews

In both searches, no SRs were found directly comparing the safety and efficacy of treatments after failure of cephalosporin and azithromycin combination therapy.

Treatment Guidelines

Three guidelines were identified that made recommendations relevant for this research question: the 2021 European guideline,[9] the Japanese guidelines,[10] and the INESSS syndromic approach guidelines.[11] Two guidelines with recommendations on antibiotic treatment after failure of cephalosporin combined with azithromycin were identified in the scoping exercise conducted by PHAC: the 2016 WHO guidelines[20] and the 2018 Ontario Gonorrhea Guide.[21] In brief, in the event of treatment failure, the WHO 2016 guidelines recommend the use of combination therapy (refer to Table 2 for WHO-recommended regimens), whereas the Ontario guidelines recommend the use of higher doses of ceftriaxone (1 g) plus azithromycin (2 g). The key recommendations for each of these guidelines is outlined in Table 2.

What Is the Efficacy and Safety of Ceftriaxone or Cefixime Administered as Multiple Doses Per Day or as Multiple Doses Over Several Days, Compared With Ceftriaxone or Cefixime Administered in a Single Dose for the Treatment of Uncomplicated Gonorrhea in Adults and Adolescents?

There were no reports identified based on the inclusion criteria for this research question.

What Is the Efficacy and Safety of Treating Based on a Positive Test Result (Need to Wait for Test Result/Do Not Provide Immediate Treatment) Compared With Treating Based on Symptoms (Empiric Prescribing/Immediate Treatment) in Adults and Adolescents With Uncomplicated Gonorrhea and Their Sexual Partners?

Systematic Reviews

This review and the PHAC scoping exercise did not identify any SRs directly comparing treatment based on test result with treatment based on symptoms.

Treatment Guidelines

One guideline that directly compared treating based on testing compared with treating based on symptoms was identified: the WHO 2021 guideline.[14]

For individuals with symptoms of urethral discharge from the penis, the WHO 2021 guideline recommends treatment based on a molecular test–based approach. In settings with limited or no molecular tests or laboratory capacity, a syndromic based approach is recommended.[14]

The WHO 2021 guideline also analyzed different scenarios related to the prevalence of *N. gonorrhea* and/or *C. trachomatis* infections among individuals with vaginal discharge. They considered 2 scenarios with low (5%) and high (20%) prevalence of *N. gonorrhea* and/or *C. trachomatis* infections, and considered different levels of antimicrobial resistance, and found that a low-cost, rapid point-of-care test was more effective compared to a syndromic approach (treating based on symptoms) or no treatment at all. Thus, for individuals with symptoms of vaginal discharge, this guideline recommends treatment based on the results of quality-assured molecular assays for *N. gonorrhea* and/or *C. trachomatis* and/or *Trichomonas vaginalis*. In settings where treatment based on molecular assay results are not feasible in the same visit or these tests are not accessible, WHO recommends treating based on rapid point-of-care tests or based on a syndromic approach.[14]

The PHAC scoping exercise did not identify any guidelines based on the inclusion criteria for this research question. The key recommendations from the WHO 2021 guideline are also summarized in Table 2, with detailed justifications provided in Appendix 5, Table 5.

What Is the Feasibility, Costs/Resources, and Acceptability of Different Treatment Options for Genital and Nongenital Infections Caused by *N. Gonorrhea*?

Systematic Reviews

This review and the PHAC scoping exercise did not identify any SRs involving relevant interventions (oral treatment options, treatment provided as a single dose, or treatment provided in the clinic) for this research question.

Treatment Guidelines

This review did not identify any guidelines based on the inclusion criteria for this research question. However, the PHAC scoping exercise identified 2 guidelines[20,22] that reported on patient acceptability of oral versus injectable treatment options for *N. gonorrhea* infection: WHO and the Belgium Health Care Knowledge Centre (KCE).

WHO found some evidence in the literature pertaining to patient acceptability of injections compared to oral treatment regimens, namely primary studies evaluating the acceptability of injections in patients with syphilis. WHO reported that 10% to 20% of patients refused injection.[20] Additionally, the KCE cited the WHO report, indicating the lack of available evidence in this area.[22] In addition to the additional labour costs and time associated with intramuscular administration, the KCE indicated that some health care providers may be averse to providing injections. The authors also noted that combination therapy appears to be acceptable among patients.[22]

Summary of the Types of Evidence Included

The Kong review[15] included RCTs but only extracted and analyzed data from single arms. Most of the included guidelines in this review and the PHAC scoping exercise included a combination of published secondary and primary sources. Many did not have a methods section, and a few did not include references. Online searches for additional files that could provide this information were not successful. The BASHH 2018 UK national guideline for the management of gonorrhea in adults reported that they included SRs and RCTs as "a priority," so it is unclear what other evidence might have been included.

Limitations

In addition to the lack of comparative efficacy data and the low quality of the SR, as identified by the critical appraisal (Appendix 6), several limitations exist. The identified SR and the majority of the guidelines from our search were published before 2022, with none being published in 2023. Older publications might not cover our research questions, since evidence pertaining to higher dose antibiotic therapies or combination treatment regimens might not have been explored at the time of publication. In addition, included evidence is out of date as there is a time lag between the dates of the included RCTs or nonRCTs and the published SRs. We, therefore, may have missed relevant and current primary studies. This is problematic for antibiotic effectiveness questions due to changing resistance profiles, such as the recent emergence of a novel *N. gonorrhea* strain demonstrating resistance to 5 drug classes in the US.[15] Additionally, the identified SR evaluated treatment efficacy for pharyngeal *N. gonorrhea* infection only, and thus may not be generalizable

to other sites of infection. Although we performed a comprehensive search strategy, our search may have missed relevant reports not categorized as SRs and guidelines.

Across our search and the PHAC scoping exercise, several guidelines provided little to no information on the methodology (or the methods were described elsewhere; that is, in previous versions of the guideline), posing challenges to evaluating the strengths and limitations of the methods used as well as the evidence their recommendations were based upon.

Discussion

We used the scoping review from PHAC to inform the findings of this evidence review and re-ran the literature search to find updated information. From this new search, we retrieved 361 citations of which we identified 7 publications published between January 1, 2020, and April 26, 2023, comprising 6 guidelines, 1 SR with meta-analysis of proportions, and comparison data on question 1b only. The PHAC scoping exercise[6] identified 13 guidelines related to 7 research questions (1a, 1b, 2, 3, 4, 6, and 7), and no SRs related to our 8 research questions.

Efficacy and Safety Data

Main Take-Aways

The included SR reported that ceftriaxone monotherapy, at various doses, showed 100% efficacy in small sample sizes of patients with gonorrhea infections in the throat. The SR also observed that combination therapy, particularly ceftriaxone with azithromycin, was effective, but higher doses of azithromycin led to higher rates of nausea and diarrhea.

The WHO 2021 guideline favours molecular testing over syndromic approaches for better treatment outcomes.

The identified SR and meta-analysis by Kong et al[15] estimated the efficacy of different antibiotic treatments for pharyngeal *N. gonorrhea* infection. Kong et al[15] assessed the efficacy of ceftriaxone monotherapy (125 mg, 250 mg, and 500 mg) as 100% (3 RCTs; n = 22). In subgroup analysis, ceftriaxone (500 mg) combined with azithromycin (1 g) had a pooled proportion for the microbiological cure rate of 97.1% (95% CI, 93.0% to 99.7%) in 2 arms (2 RCTs; n = 132) (Question 1a). Only 1 RCT was identified by Kong et al.[15] evaluating ceftriaxone (500 mg) combined with azithromycin (2 g) with an efficacy of 100% (n = 33). No comparison of safety data was conducted. The authors suggest that ceftriaxone monotherapy is sufficiently efficacious as a treatment for pharyngeal infection, although the estimates are based on small sample sizes and subgrouping.

For the treatment of pharyngeal *N. gonorrhea*, the Kong SR[15] also provided efficacy (defined as microbiological cure) data on monotherapy in single arms (5 RCTs; n = 128), which was efficacious. Combination therapy of ceftriaxone and azithromycin (3 RCTs; n = 324) was also found efficacious for the

treatment of pharyngeal *N. gonorrhea* (Question 1b).[15] In terms of safety, they found that the prevalence of nausea and diarrhea was higher in patients taking dual regimens that included azithromycin 2 g compared to 1 g of azithromycin. This analysis, however, was conducted among a subgroup of trial participants and all trials included in the Kong SR considered treating for pharyngeal *N. gonorrhea* as a secondary outcome. Thus, this analysis is underpowered to detect the true treatment effect. A primary meta-analysis would provide a more reliable evaluation of monotherapy versus combination therapy.

Across 3 trials of ceftriaxone monotherapy at doses of 125 mg, 250 mg, and 500 mg, the reported efficacy proportion for microbiological cure was 100% against pharyngeal *N. gonorrhea*, although no meta-analysis was conducted given the paucity of trials comparing the doses (Question 2). The Kong SR[15] identified 1 trial that showed improved efficacy with higher, multiple-dose regimens of cefixime for pharyngeal *N. gonorrhea* compared with single dose regimens in treating cephalosporin-resistant pharyngeal *N. gonorrhea* (Questions 2 and 4). Indeed, the Canadian 2022 guideline[13] recommends avoiding monotherapy due to potential antimicrobial resistance and administering cefixime (800 mg) orally plus azithromycin (1 g) orally in a single dose (Questions 2 and 4).

The WHO 2021 guideline[14] modelled 2 scenarios in which the prevalence of *N. gonorrhea* and/or *C. trachomatis* among people with vaginal discharge is low (5%) and high (20%) and applied different levels of antimicrobial resistance. They showed that a low-cost rapid point-of-care test was more efficacious compared with a syndromic approach or with no treatment (Question 6). The undesirable effects of a syndromic approach (such as missed cases) were greater than treating all or treating according to molecular testing; and the desirable effects (such as correct treatment) of a syndromic approach were outweighed by treating all or only cases identified by molecular testing. Therefore, the balance of benefits and harms favoured using molecular testing or treating all (Question 6). However, there were few details reported on this model and the results should be interpreted with caution.

Gaps in the Evidence

Given the results of the PHAC scoping exercise and our findings, the following gaps are identified:

While Question 1b data were available as a subgroup analysis, the analysis was secondary and underpowered, and only relevant to pharyngeal *N. gonorrhea* infections. Therefore, a primary meta-analysis (either pairwise or network) is recommended for the following treatment comparisons of interest: cefixime versus cefixime with azithromycin, cefixime with azithromycin versus ceftriaxone with azithromycin, and cefixime versus ceftriaxone.

Questions 1a, 2, 3, 4, and 5 did not provide any comparative efficacy data. The available evidence on the feasibility, costs, resources, and acceptability of the interventions of interest for Question 7 is also limited. Question 6 was partly answered by the WHO 2021 guideline, which considered both treating based on symptoms and laboratory testing. Furthermore, the guidelines 9 to 14, 16 to 28, and 1 review[15] included a

mixture of published secondary and primary sources of evidence. The review by Kong et al[15] included RCTs but did not conduct comparative analyses.

Conclusions

Main Take-Aways

This evidence review found that there is a lack of comparative efficacy and limited safety data, even though most guidelines suggest using combination therapy with ceftriaxone and azithromycin. Further research, involving an SR with meta-analysis or a series of targeted rapid reviews of primary studies would help address these gaps and keep guidelines current amid changing antibiotic resistance patterns.

This SR highlights the importance of a transparent and rigorous process that will inspire confidence in the updated guidance and promote its adherence. This review identified and analyzed 19 treatment guidelines[9-14,16-28] and 1 SR,[15] which provided a lack of comparative efficacy data and limited safety data for 7 research questions, highlighting a need for further primary and randomized study research into these questions.

Despite the lack of comparative data, the majority of gonococcal treatment guidelines recommend combination therapy with ceftriaxone and azithromycin. There were inconsistent data on the synergy or additive effect between these antimicrobials. A new modelling study on the feasibility, costs, resources, and acceptability of the interventions of interest for Question 7 is also recommended. There is evidence that exposure to azithromycin could induce resistance and, in fact, resistance to azithromycin has increased in Canada and many other countries.

As next steps, we would recommend a SR with meta-analysis approach or a series of rapid reviews, where an information specialist runs a targeted search for primary studies on the research questions that were the focus of this report. In an era of rapidly changing patterns of antimicrobial resistance, this strategy will enable PHAC to stay abreast of current research and provide up-to-date recommendations in a timely manner.

References

1. Edwards JL, Apicella MA. The molecular mechanisms used by Neisseria gonorrhoeae to initiate infection differ between men and women. *Clin Microbiol Rev.* 2004;17(4):965-981. PubMed
2. National Surveillance of Antimicrobial Susceptibilities of Neisseria gonorrhoeae: Annual Summary 2019. Ottawa (ON): Public Health Agency of Canada; 2019: https://www.publications.gc.ca/collections/collection_2022/aspc-phac/HP57-3-2019-eng.pdf. Accessed 2023 Apr 28.
3. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol*. 2016;75:40-46. PubMed
4. Grey matters: A tool for searching health-related grey literature. Ottawa (ON): CADTH; 2022: https://greymatters.cadth.ca. Accessed 2023 Apr 28.
5. Synthesi.SR [Computer Software]. Toronto (ON): Knowledge Translation Program, St. Michael's Hospital; 2022: https://knowledgetranslation.net/kt-tools/.
6. Public Health Agency of Canada. Monotherapy versus combination therapy in the treatment of uncomplicated gonococcal infections in adults and adolescents: A scoping exercise [unpublished internal report]. 2022.
7. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008. PubMed
8. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting SR systematic reviews. *BMJ*. 2021;372:n71. PubMed
9. de Vries HJC, Nori AV, Kiellberg Larsen H, et al. 2021 European Guideline on the management of proctitis, proctocolitis and enteritis caused by sexually transmissible pathogens. *J Eur Acad Dermatol Venereol*. 2021;35(7):1434-1443. PubMed
10. Hamasuna R, Yasuda M, Takahashi S, et al. The JAID/JSC guidelines to Clinical Management of Infectious Disease 2017 concerning male urethritis and related disorders. *J Infect Chemother*. 2021;27(4):546-554. PubMed
11. Institut national d'excellence en santé et en services sociaux (INESSS). Mise à jour du guide d'usage optimal sur les infections transmissibles sexuellement et par le sang – Approche syndromique. [Update of the optimal use guide on sexually transmitted and blood-borne infections – Syndromic approach]. Montreal (QC): INESSS; 2020: https://www.inesss.qc.ca/fileadmin/doc/INESSS/Outils/Guides_ITSS/INESSS_ITSS_App-Syndrome_Rapport.pdf. Accessed 2023 Apr 28.
12. Peters RPH, Garrett N, Chandiwana N, et al. Southern African HIV Clinicians Society 2022 guideline for the management of sexually transmitted infections: Moving towards best practice. *South Afr J HIV Med*. 2022;23(1):1450. PubMed
13. Public Health Agency of Canada. Gonorrhea guide: Key information and resources. 2023; https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/gonorrhea.html. Accessed 2023 Apr 28.
14. World Health Organization. Guidelines for the management of symptomatic sexually transmitted infections. 2021; https://www.who.int/publications/i/item/9789240024168. Accessed 2023 May 30.
15. Kong FYS, Hatzis CL, Lau A, et al. Treatment efficacy for pharyngeal Neisseria gonorrhoeae: A systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother*. 2020;75(11):3109-3119. PubMed
16. Institut national d'excellence en santé et en services sociaux (INESSS). Guide d'usage optimal - Infection non compliquée à Chlamydia trachomatis ou à Neisseria Gonorrhorae. Montreal (QC): INESSS; 2020: https://www.inesss.qc.ca/fileadmin/doc/INESSS/Outils/Guides_ITSS/Guide_ITSS-Chlamydia_gonorrhoeae.pdf. Accessed 2023 May 30.
17. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):1-187. PubMed
18. Fifer H, Saunders J, Soni S, Sadiq ST, FitzGerald M. 2018 UK national guideline for the management of infection with Neisseria gonorrhoeae. *Int J STD AIDS*. 2020;31(1):4-15. PubMed

19. Unemo M, Ross J, Serwin AB, Gomberg M, Cusini M, Jensen JS. 2020 European guideline for the diagnosis and treatment of gonorrhoea in adults. *Int J STD AIDS*. 2020:956462420949126. PubMed

20. World Health Organization. WHO guidelines for the treatment of Neisseria gonorrhoeae. 2026; https://www.who.int/publications/i/item/9789241549691. Accessed 2023 Jun 8.

21. Ontario Gonorrhea Testing and Treatment Guide, 2nd Edition. Toronto (ON): Public Health Ontario; 2018 https://www.publichealthontario.ca/-/media/documents/G/2018/guide-gonorrhea-testing-treatment.pdf. Accessed 2023 Jun 8.

22. Jespers V, Stordeur S, Desomer A, et al. Short report: Diagnosis and management of gonorrhea and syphilis (KCE report 310Cs). Brussels (BE): Belgian Health Care Knowledge Centre (KCE); 2019: https://kce.fgov.be/sites/default/files/2021-11/KCE_310C_Diagnosis_management_Gonorrhoea_and_Syphilis_Synthesis.pdf. Accessed 2023 Jun 8.

23. Alberta Health Services. Alberta treatment guidelines for sexually transmitted infections (STI) in adolescents and adults. 2018; https://open.alberta.ca/dataset/93a97f17-5210-487d-a9ae-a074c66ad678/resource/bc78159b-9cc4-454e-8dcd-cc85e0fcc435/download/sti-treatment-guidelines-alberta-2018.pdf. Accessed 2023 Jun 8.

24. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). Australian STI Management Guidelines for use in Primary Care (2019): Gonorrhoea. 2019; http://sti.guidelines.org.au/sexually-transmissible-infections/gonorrhoea. Accessed 2023 Jun 10.

25. British Columbia treatment guidelines: Sexually transmitted infections in adolescents and adults 2014. Vancouver (BC): BC Centre for Disease Control; 2014: http://www.bccdc.ca/resource-gallery/Documents/Communicable-Disease-Manual/Chapter%205%20-%20STI/CPS_BC_STI_Treatment_Guidelines_20112014.pdf. Accessed 2023 Jun 10.

26. Association of the Scientific Medical Societies in Germany (AWMF). Diagnostik und Therapie der Gonorrhoe [Diagnosis and treatment of gonorrhea]. 2019; https://www.verwaltung.awmf.org/en/clinical-practice-guidelines/detail/ll/059-004.html. Accessed 2023 Jun 8.

27. Section MST/SIDA de la Société Française de Dermatologie. Recommandations diagnostiques et thérapeutiques pour les maladies sexuellement transmissibles (Février 2016). Paris (FR): Société Française de Dermatologie; 2016: https://www.sfdermato.org/media/image/upload-editor/files/Guidelines%202016(1).pdf. Accessed 2023 Jun 8.

28. New Zealand Sexual Health Society (NZSHS). Gonorrhoea management guidelines. 2017; https://www.nzshs.org/docman/guidelines/management-of-sexual-health-conditions/gonorrhoea/165-gonorrhoea-guideline/file. Accessed 2023 Jun 10.

29. Bai ZG, Bao XJ, Cheng WD, Yang KH, Li YP. Efficacy and safety of ceftriaxone for uncomplicated gonorrhoea: A meta-analysis of randomized controlled trials. *Int J STD AIDS*. 2012;23(2):126-132. PubMed

30. Bignell C, Garley J. Azithromycin in the treatment of infection with Neisseria gonorrhoeae. *Sex Transm Infect*. 2010;86(6):422-426. PubMed

31. Chico RM, Hack BB, Newport MJ, Ngulube E, Chandramohan D. On the pathway to better birth outcomes? A systematic review of azithromycin and curable sexually transmitted infections. *Expert Rev Anti Infect Ther*. 2013;11(12):1303-1332. PubMed

32. Comunián-Carrasco G, Peña-Martí GE, Martí-Carvajal AJ. Antibiotics for treating gonorrhoea in pregnancy. *Cochrane Database Syst Rev*. 2018;2(2):Cd011167. PubMed

33. Creighton S. *Gonorrhoea.* BMJ Clin Evid. 2014;2014.

34. Dowell D, Kirkcaldy RD. Effectiveness of gentamicin for gonorrhoea treatment: Systematic review and meta-analysis. *Sex Transm Infect*. 2012;88(8):589-594. PubMed

35. Hathorn E, Dhasmana D, Duley L, Ross JD. The effectiveness of gentamicin in the treatment of Neisseria gonorrhoeae: A SR. *Syst Rev*. 2014;3:104. PubMed

36. Hayward RS, Harding J, Molloy R, et al. Adverse effects of a single dose of gentamicin in adults: A systematic review. *Br J Clin Pharmacol*. 2018;84(2):223-238. PubMed

37. Tanvir SB, Qasim SSB, Shariq A, Najeeb S, Shah AH. SR and meta-analysis on efficacy of cefixime for treating gonococcal infections. *Int J Health Sci (Qassim)*. 2018;12(5):90-100. PubMed

38. Yang J, Dhital S, Naderer T. Efficacy and safety of injectable and oral antibiotics in treating gonorrhea: A systematic review and network meta-analysis. *J Clin Med*. 2019;8(12):2182. PubMed

39. Singh AE, Gratrix J, Martin I, et al. Gonorrhea treatment failures with oral and injectable expanded spectrum cephalosporin monotherapy vs dual therapy at 4 Canadian sexually transmitted infection clinics, 2010-2013. *Sex Transm Dis*. 2015;42(6):331-336. PubMed

40. Wind CM, Schim van der Loeff MF, Unemo M, Schuurman R, van Dam AP, de Vries HJC. Test of cure for anogenital gonorrhoea using modern RNA-based and DNA-based nucleic acid amplification tests: A prospective cohort study. *Clin Infect Dis*. 2016;62(11):1348-1355. PubMed

41. Barbee LA, Kerani RP, Dombrowski JC, Soge OO, Golden MR. A retrospective comparative study of 2-drug oral and intramuscular cephalosporin treatment regimens for pharyngeal gonorrhea. *Clin Infect Dis*. 2013;56(11):1539-1545. PubMed

Authors and Contributors

Clinical Review

Jasmeen Dourka coordinated the study; screened articles, abstracted data, and carried out risk bias assessments; drafted the first version of the report; and contributed to report revision and interpretation of findings, key messages, and conclusions.

Carole Lunny screened articles; abstracted data; carried out risk of bias assessments; and contributed to report revision and interpretation of findings, key messages, and conclusions.

Menelaos Konstantinidis screened articles, abstracted data, and carried out risk of bias assessments; and contributed to report revision and interpretation of findings, key messages, and conclusions.

Andrea C. Tricco contributed to report revision and interpretation of findings, key messages, and conclusions; and provided oversight and leadership responsibility for all research activities.

Research Information Science

Sarah C. McGill developed and conducted the literature searches.

Acknowledgements

CADTH would like to acknowledge the following individuals:

Christine Perras and David Stock reviewed the drafts and final report. Emily Farrell provided knowledge mobilization support. Brandy Appleby provided project management support.

Conflicts of Interest

Andrea Tricco disclosed the following:

Presented to the Canadian Drug Expert Committee (CDEC) in November 2016 on anti-VEGF medications

No other conflicts of interest were declared.

Appendix 1: Search Strategy

Note that this appendix has not been copy-edited.

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946 – April 26, 2023)
- Embase (1974 – April 26, 2023)
- **Note:** Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: April 27, 2023.

Search filters applied: SRs; meta-analyses; network meta-analyses; health technology assessments; guidelines.

Limits:

- Published between January 1, 2020, and April 27, 2023.
- Language limit: English- and French-language.
- Conference abstracts: excluded.

Table 3: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word

Syntax	Description
.dq	Candidate term word (Embase)
.pt	Publication type
.mp	Mapped term
.jw	Journal title word (MEDLINE)
.jx	Journal title word (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Warning

To conduct a comprehensive search, we may have included antiquated, noninclusive, or potentially stigmatizing terms that may have appeared in past and present literature. We recognize and acknowledge the inappropriate and harmful nature of terms that may appear in search strategies and include this warning so the reader can determine how they would like to proceed.

The warning is modified from the University of Michigan Library's guidance, Addressing antiquated, nonstandard, exclusionary, and potentially offensive terms in evidence syntheses and systematic searches.

Multidatabase Strategy

1. Neisseria gonorrhoeae/ or Gonorrhea/
2. (gonorrhea* or gonorrhoea* or gonococc*).ti,ab,kf.
3. (gonorrhaea* or gonorrohea* or gonorrhorea*).ti,ab,kf.
4. 1 or 2 or 3
5. 4 use medall
6. exp gonorrhea/ or Neisseria gonorrhoeae/
7. (gonorrhea* or gonorrhoea* or gonococc*).ti,ab,kf,dq.
8. (gonorrhaea* or gonorrohea* or gonorrhorea*).ti,ab,kf,dq.
9. 6 or 7 or 8
10. 9 use oemezd
11. 10 not (conference abstract or conference review).pt.
12. 5 or 11
13. (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.

14. (guideline* or standards or consensus* or recommendat*).ti.
15. (practice parameter* or position statement* or policy statement* or CPG or CPGs or best practice*).ti.
16. (care adj2 (path or paths or pathway or pathways or map or maps or plan or plans or standard)).ti.
17. ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti.
18. (algorithm* and (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti.
19. (algorithm* and (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti.
20. (guideline* or standards or consensus* or recommendat*).au.
21. (guideline* or standards or consensus* or recommendat*).co.
22. systematic review.ti,pt,kf,sh. and (practice guideline* or treatment guideline* or clinical guideline* or guideline recommendation*).ti,ab,kf.
23. or/13-22
24. (systematic review or meta-analysis).pt.
25. meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or “meta analysis (topic)”/ or “systematic review (topic)”/ or exp technology assessment, biomedical/ or network meta-analysis/
26. ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.
27. ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.
28. ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.
29. (data synthes* or data extraction* or data abstraction*).ti,ab,kf.
30. (handsearch* or hand search*).ti,ab,kf.
31. (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.
32. (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.
33. (meta regression* or metaregression*).ti,ab,kf.
34. (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.

35. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
36. (cochrane or (health adj2 technology assessment) or evidence report).jw.
37. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf.
38. (outcomes research or relative effectiveness).ti,ab,kf.
39. ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.
40. (multi* adj3 treatment adj3 comparison*).ti,ab,kf.
41. (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.
42. umbrella review*.ti,ab,kf.
43. (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
44. (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.
45. (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
46. or/24-45
47. 23 or 46
48. 12 and 47
49. limit 48 to (english or french)
50. limit 49 to yr="2020 -Current"
51. remove duplicates from 50

Other Databases

Cochrane Database of Systematic Reviews (CDSR)

Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for CochraneLibrary.com platform. The search strategy is available on request.

Grey Literature

Search dates: February 23 – March 1, 2023.

Keywords: gonorrhea, gonorrhoea, gonorrhoea, gonococcal. Additionally for French websites: gonocoque, gonococciques.

Limits: no date limits.

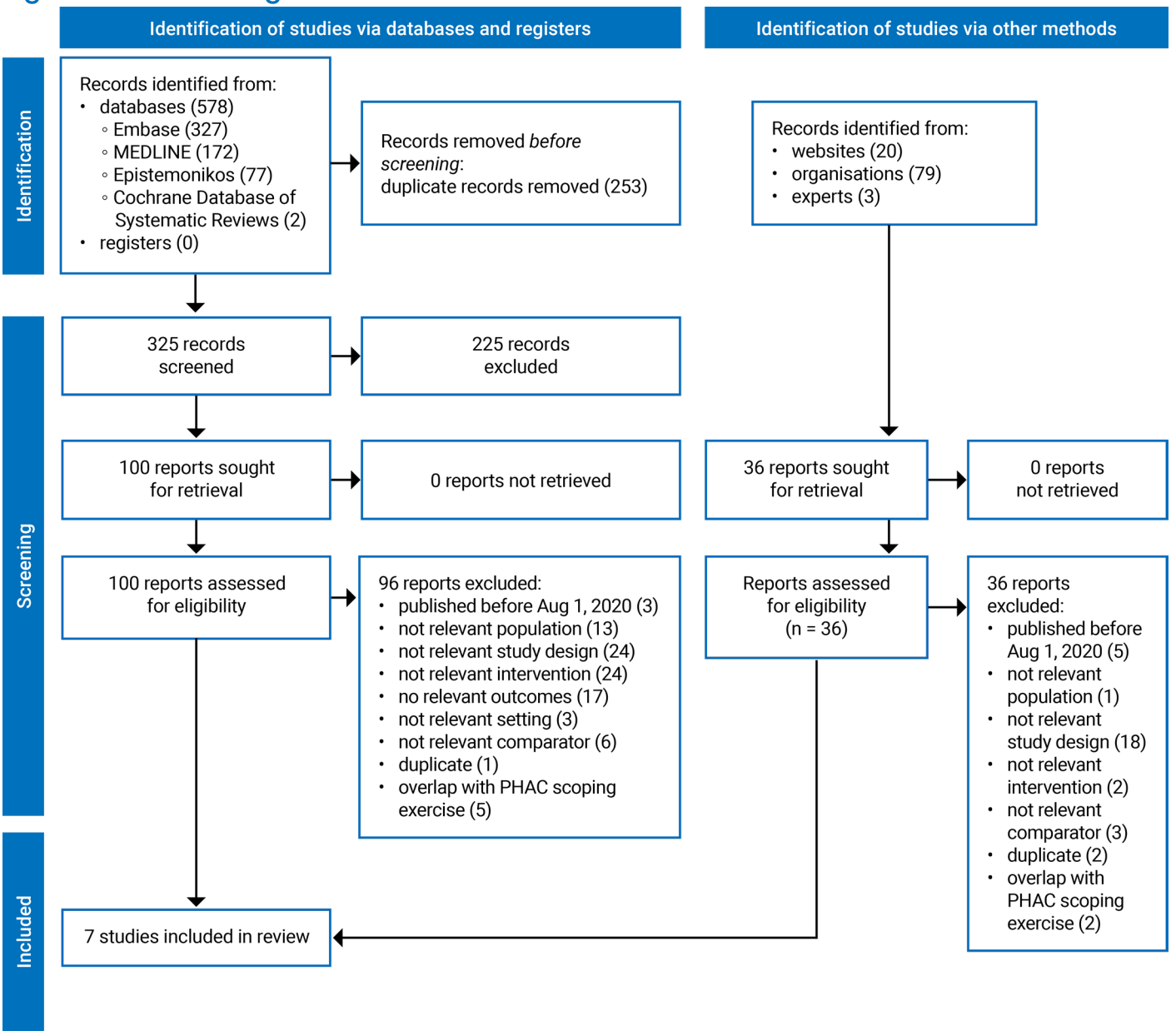
Updated: Search updated before the completion of stakeholder feedback period.

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Clinical Practice Guidelines
- Drug Class Reviews
- Databases (free)
- Internet Search

Appendix 2: PRISMA 2020 Flow Diagram of Selected Publications

Figure 1: PRISMA Diagram



PHAC = Public Health Agency of Canada.

Appendix 3: List of Included Studies

Note that this appendix has not been copy-edited.

Guidelines and SRs Included in This Review

de Vries HJC, Nori AV, Kiellberg Larsen H, et al. 2021 European Guideline on the management of proctitis, proctocolitis and enteritis caused by sexually transmissible pathogens. *J Eur Acad Dermatol Venereol.* 2021 Jul;35(7):1434-1443. PubMed

Hamasuna R, Yasuda M, Takahashi S, et al. The JAID/JSC guidelines to Clinical Management of Infectious Disease 2017 concerning male urethritis and related disorders. *Journal of Infection & Chemotherapy.* 2021 Apr;27(4):546-554. PubMed

INESSS. Mise à jour du guide d'usage optimal sur les infections transmissibles sexuellement et par le sang – Approche syndromique [Update of the optimal use guide on sexually transmitted and blood-borne infections – Syndromic approach]. 2020. https://www.inesss.qc.ca/fileadmin/doc/INESSS/Outils/Guides_ITSS/INESSS_ITSS_App-Syndrome_Rapport.pdf

Kong FYS, Hatzis CL, Lau A, et al. Treatment efficacy for pharyngeal Neisseria gonorrhea: a systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2020 11 01;75(11):3109-3119.

Peters RPH, Garrett N, Chandiwana N, et al. Southern African HIV Clinicians Society 2022 guideline for the management of sexually transmitted infections: Moving towards best practice. *South Afr J HIV Med.* 2022;23(1)

PHAC. *Gonorrhea guide.* 2022. https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/gonorrhea.html

WHO. *Guidelines for the management of symptomatic sexually transmitted infections.* 2021. https://www.who.int/publications/i/item/9789240024168

Guidelines and SRs Included in the PHAC Scoping Exercise

Bai ZG, Bao XJ, Cheng WD, Yang KH, Li YP. Efficacy and safety of ceftriaxone for uncomplicated gonorrhea: a meta-analysis of randomized controlled trials. *Int J STD AIDS*. 2012;23(2):126-132. doi:10.1258/ijsa.2009.009198 PubMed

Bignell C, Garley J. Azithromycin in the treatment of infection with Neisseria gonorrhoeae. *Sex Transm Infect* 2010 Nov; 86(6):422-426. PubMed

Chico RM, Hack BB, Newport MJ, Ngulube E, Chandramohan D. On the pathway to better birth outcomes? A systematic review of azithromycin and curable sexually transmitted infections. *Expert Rev Anti Infect Ther*. 2013;11(12):1303-1332. PubMed

Comunián-Carrasco G, Peña-Martí GE, Martí-Carvajal AJ. Antibiotics for treating gonorrhea in pregnancy. *Cochrane Database Syst Rev*. 2018;2(2):CD011167. Published 2018 Feb 21. doi:10.1002/14651858.CD011167.

Creighton S. Gonorrhoea. *BMJ Clin Evid*. 2014;2014:1604. *Published* 2014 Feb 21.

Dowell D, Kirkcaldy RD. Effectiveness of gentamicin for gonorrhea treatment: systematic review and meta-analysis. *Sex Transm Infect*. 2012;88(8):589-594. PubMed

Hathorn E, Dhasmana D, Duley L, Ross JD. The effectiveness of gentamicin in the treatment of Neisseria gonorrhoeae: a SR. *Syst Rev*. 2014;3:104. Published 2014 Sep 19. doi:10.1186/2046-4053-3-104

Hayward RS, Harding J, Molloy R, et al. Adverse effects of a single dose of gentamicin in adults: a systematic review. *Br J Clin Pharmacol*. 2018;84(2):223-238. doi:10.1111/bcp.13439 PubMed

Tanvir SB, Qasim SSB, Shariq A, Najeeb S, Shah AH. Systematic review and meta-analysis on efficacy of cefixime for treating gonococcal infections. *Int J Health Sci (Qassim)*. 2018;12(5):90-100. PubMed

Yang J, Dhital S, Naderer T. Efficacy and Safety of Injectable and Oral Antibiotics in Treating Gonorrhea: A Systematic Review and Network Meta-Analysis. *J Clin Med*. 2019;8(12):2182. Published 2019 Dec 11. doi:10.3390/jcm8122182

INESSS-2020 Uncomplicated Chlamydia Trachomatis or Neisseria Gonorrhoeae infection. https://www.inesss.qc.ca/fileadmin/doc/INESSS/Outils/Guides_ITSS/Guide_ITSS-Chlamydia_gonorrhoeae.pdf

Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, Reno H, Zenilman JM, Bolan GA. Sexually Transmitted Infections Treatment Guidelines, 2021. *MMWR Recomm Rep.* 2021 Jul 23;70(4):1-187. doi: 10.15585/mmwr.rr7004a1. PubMed

Fifer H, Saunders J, Soni S, Sadiq ST, FitzGerald M. 2018 UK national guideline for the management of infection with *Neisseria gonorrhoeae. Int J STD AIDS*. 2020;31(1):4-15. doi:10.1177/0956462419886775 PubMed

Unemo M, Ross J, Serwin AB, Gomberg M, Cusini M, Jensen JS. 2020 European guideline for the diagnosis and treatment of gonorrhoea in adults. *Int J STD AIDS.* 2020 Oct 29:956462420949126. doi: 10.1177/0956462420949126. PubMed

WHO Guidelines for the Treatment of *Neisseria gonorrhoeae*. Geneva: World Health Organization; 2016.

Public Health Ontario 2018. *Ontario Gonorrhea Testing and Treatment Guide*, 2nd Edition.

Jespers V, Stordeur S, Desomer A, Carville S, Jones C, Lewis S, Perry M, Cordyn S, Cornelissen T, Crucitti T, Danhier C, De Baetselier I, De Cannière A-S, Dhaeze W, Dufraimont E, Kenyon C, Libois A, Mokrane S, Padalko E, Van den Eynde S, Vanden Berghe W, Van der Schueren T, Dekker N. Diagnosis and management of gonorrhea and syphilis – Short report. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). 2019. KCE Reports 310C. D/2019/10.273/20

Alberta treatment guidelines for sexually transmitted infections (STI) in adolescents and adults, 2018. Available at: https://open.alberta.ca/dataset/93a97f17-5210-487d-a9ae-

Australian STI Management Guidelines for use in Primary Care (2019). Gonorrhoea. Available at: http://sti.guidelines.org.au/sexually-transmissible-infections/gonorrhoea

British Columbia Center for Disease Control. *British Columbia Treatment Guidelines Sexually Transmitted Infections in Adolescents and Adults.* 2014. http://www.bccdc.ca/resource-gallery/Documents/Communicable-Disease-Manual/Chapter%205%20-%20STI/CPS_BC_STI_Treatment_Guidelines_20112014.pdf

Association of the Scientific Medical Societies in Germany. *Diagnosis and Therapy of Gonorrhea.* 2019. https://www.verwaltung.awmf.org/en/clinical-practice-guidelines/detail/ll/059-004.html

New Zealand Sexual Health Society (NZSHS) Management of Gonorrhoea 2017. Available at: https://www.nzshs.org/docman/guidelines/management-of-sexual-health-conditions/gonorrhoea/165-gonorrhoea-guideline/file

Société Française de Dermatologie. Recommandations Diagnostiques et Thérapeutiques pour les Maladies Sexuellement Transmissibles. Section MST/Sida de la Société Française de Dermatologie. Février 2016. https://www.sfdermato.org/media/image/upload-editor/files/Guidelines%202016(1).pdf

Appendix 4: Reasons for Exclusion of Reviews Included in the PHAC Scoping Exercise

Note that this appendix has not been copy-edited.

Table 4: Reasons for Excluding From the Current Review

Reference (author, year)	Reason for exclusion
Bai et al., 2012[29]	No relevant comparator for monotherapy with ceftriaxone vs combination therapy with ceftriaxone and azithromycin (Q1a)
Bignell et al., 2010[30]	No relevant intervention or comparator for combination antibiotic treatment vs monotherapy (Q1b)
Chico et al., 2013[31]	No relevant intervention or comparator for combination antibiotic treatment vs monotherapy (Q1b)
Comunián-Carrasco et al., 2018[32]	No relevant comparator for monotherapy with ceftriaxone vs combination therapy with ceftriaxone and azithromycin (Q1a)
Creighton et al., 2014[33]	No relevant comparator for monotherapy with vs combination therapy with ceftriaxone and azithromycin (Q1a) or combination antibiotic treatment vs monotherapy (Q1b)
Dowell et al., 2013[34]	No relevant intervention or comparator for combination antibiotic treatment vs monotherapy (Q1b)
Hathorn et al., 2014[35]	No relevant intervention or comparator for combination antibiotic treatment vs monotherapy (Q1b)
Hayward et al., 2018[36]	No relevant intervention or comparator for combination antibiotic treatment vs monotherapy (Q1b)
Tanvir et al., 2018[37]	No relevant intervention or comparator for combination antibiotic treatment vs monotherapy (Q1b)
Yang et al., 2019[38]	No relevant comparator for monotherapy with vs combination therapy with ceftriaxone and azithromycin (Q1a) or combination antibiotic treatment vs monotherapy (Q1b)

Appendix 5: Summary of Available Evidence

Table 5: International Guidelines on Uncomplicated Gonococcal Infections in Adults and Adolescents

Author/group, country, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
Gonorrhea guide[13]								
PHAC, Canada, 2022	Adults and youth ≥ 9 years of age, including pregnant or lactating individuals	Not specified	Ceftriaxone and azithromycin combination therapy	Anogenital (ureteral, endocervical, vaginal, rectal)	The preferred therapy for uncomplicated infection is ceftriaxone 250 mg IM plus azithromycin 1 g p.o. in a single dose.	Q1a and Q1b	No methods reported; All types of published and unpublished primary studies were included.	Identified in this review
				Pharyngeal	The preferred therapy for uncomplicated infection is ceftriaxone 250 mg IM plus azithromycin 1 g p.o. in a single dose.			
2021 European Guideline on the management of proctitis, proctocolitis and enteritis caused by sexually transmissible pathogens[9]								
de Vries et al. from the IUSTI, European regions, 2021	Not reported	Not reported	Not reported	Anorectal	For the syndromic management of proctitis when *N. gonorrhea* is suspected, treat with ceftriaxone 1 g IM in a single dose with doxycycline 100 mg b.i.d. for 7 days. Note: Doxycycline is preferred when	Q3 and Q4	No methods reported other than a search strategy and GRADE evidence tables. All types of published secondary and primary studies were included.	Identified in this review

Author/group, country, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
					N. gonorrhea is suspected for its superiority against (suspected) C. trachomatis infections, and to avoid azithromycin resistance in undiagnosed coinfection with *M. genitalium*.			
JAID/JSC guidelines to Clinical Management of Infectious Disease 2017 concerning male urethritis and related disorders[10]								
Hamasuna et al. from JAID/JSC, Japan, 2021	Males	Not reported	Monotherapy	Urethra, Pharynx and Rectum	**For the treatment of male gonococcal urethritis** **First line:** Ceftriaxone 1 g IV in a single dose **Second line:** Spectinomycin 2 g IM in a single dose "As there have been a series of reports of *N. gonorrhea* strains highly resistant to azithromycin from foreign countries, azithromycin is not recommended as the first-line drug in the Japanese guidelines." (pg. 548)	Q4	No methods reported other than recommendation levels of the evidence determined according to the Outline for the Preparation of the Guidelines to Clinical Management of Infectious Disease established by JAID/JSC. All types of published secondary and primary studies were included.	Identified in this review

Author/group, country, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
Southern African HIV Clinicians Society 2022 guideline for the management of sexually transmitted infections: Moving towards best practice[12]								
Peters RPH, Garrett N, Chandiwana N, et al. from the Southern African HIV Clinicians Society, South Africa, 2022	People with confirmed *N. gonorrhea* infection	Primary care settings	Ceftriaxone monotherapy	Urogenital	Ceftriaxone 500 mg IM in a single dose without the addition of azithromycin for the treatment of confirmed genital *N. gonorrhea*.	Q1a	No methods reported other than a search strategy and GRADE evidence tables. All types of published secondary and primary studies were included.	Identified in this review
				Oropharyngeal	The ceftriaxone dose should be increased to 1 g IM (as a single dose) in the case of confirmed oropharyngeal infection.			
Guidelines for the management of symptomatic sexually transmitted infections[14]								
WHO, International, 2021	Men with urethral discharge	Outpatient	Syndromic management or test-based approach	Urogenital	"For people with symptoms of urethral discharge from the penis, management is recommended to be based on the results of quality-assured molecular assays. However, in settings with limited or no molecular tests or laboratory capacity,	Q6	SRs for each syndrome was conducted and modelling work on vaginal discharge was carried out. GRADE approach used. All types of published and unpublished	Identified in this review

Author/group, country, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
					we recommend syndromic treatment to ensure treatment on the same day of visit." (pg. 110) **Justifications:** "Studies show variability in the implementation of syndromic approaches based on symptoms or laboratory testing, and a simple management approach could lead to better implementation." (pg. 110) "Performing molecular assay tests for *N. gonorrhoeae*, *C. trachomatis* and *T. vaginalis* and/or *M. genitalium* and basing treatment on these results leads to the most people treated correctly." (pg. 110) "In a population with 60% prevalence of *N. gonorrhoeae* and *C.*		primary studies were included.	

Author/group, country, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
					trachomatis among those with urethral discharge, treating all for *N. gonorrhoeae* and *C. trachomatis* would mean that 40% of people would be unnecessarily treated. The Guideline Development Group agreed that this proportion is acceptable, as are higher proportions in lower-prevalence settings, because treating all would ensure that people with *N. gonorrhoeae* and *C. trachomatis* are treated, thereby reducing the chance of complications and further transmission." (pg. 110)			
	Women presenting to clinics with vaginal discharge symptoms Subgroups: Pregnant women and key populations	Outpatient; community	Syndromic management or test-based approach	Urogenital	"For people with symptoms of vaginal discharge, we recommend treatment for *N. gonorrhoeae* and/or *C. trachomatis* and/or *T. vaginalis* on	Q6	SRs for each syndrome was conducted and modelling work on vaginal discharge was carried out. GRADE approach	Identified in this review

Author/group, country, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
	including transgender persons, female sex workers, and people living with HIV (immuno-compromised)				the same visit. We suggest treatment based on the results of quality-assured molecular assays for *N. gonorrhoeae* and/or *C. trachomatis* and/or *T. vaginalis*." (pg. 128) "In settings in which treatment based on the results of molecular assay in the same visit is not feasible or that have limited or no molecular testing, we suggest treatment based on testing with quality-assured rapid point-of-care tests or on syndromic treatment." (pg. 128) "Performing molecular assay tests for *N. gonorrhoeae*, *C. trachomatis* or *T. vaginalis* and basing treatment on these results leads to the most people treated correctly when treatment is provided		used. All types of published and unpublished primary studies were included.	

Author/group, country, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
					on the same day." (pg. 129) "Using a low-cost rapid point-of-care test with 80% sensitivity and 90% specificity will lead to fewer missed and falsely treated people than other syndromic approaches and no treatment." (pg. 129)			
WHO guidelines for the treatment of *Neisseria gonorrhoeae*[20]								
WHO, International, 2016	Adults and adolescents (10 to 19 years of age), people living with HIV, and key populations, including sex workers, MSM, and transgender persons including pregnant women	Primary, secondary, and tertiary care	Combination antibiotic therapy or monotherapy	Urogenital-anorectal	Preferred treatment is combination therapy with ceftriaxone 250 mg IM as a single dose plus azithromycin 1 g p.o. as a single dose or cefixime 400 mg p.o. as a since dose plus azithromycin 1 g p.o. as a single dose Note: In the event of treatment failure, WHO recommends re-treatment with one of the following regimens: 1. Ceftriaxone 500 mg IM as a	Q1a and Q4	SRs for each priority question were conducted. GRADE approach was applied.	Identified in PHAC scoping exercise

Author/group, country, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
					single dose plus azithromycin 2 g p.o. as a single dose; 2. Cefixime 800 mg orally as a single dose plus azithromycin 2 g p.o. as a single dose; 3. Gentamicin 240 mg IM as a single dose plus azithromycin 2 g p.o. as a single dose; 4. Spectinomycin 2 g IM as a single dose (if not an oropharyngeal infection) plus azithromycin 2 g p.o. as a single dose.			
				Oropharyngeal	Preferred treatment is combination therapy with ceftriaxone 250 mg as a single dose plus azithromycin 1 g p.o. as a single dose or cefixime 400 mg p.o. as a single dose			

Author/group, country, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
					plus azithromycin 1 g p.o. as a single dose.			
Australian STI Management Guidelines[24]								
ASHA, Australia, 2018	Adults	Primary care	Combination antibiotic therapy or monotherapy	Urogenital-anorectal	Preferred treatment is combination therapy with ceftriaxone 500 mg IM as a single dose plus azithromycin 1 g p.o. Note: Alternative treatments are not recommended because of high levels of resistance, except for some remote Australian locations and severe allergic reactions.	Q1a	No SR; based on a consensus-based approach drawing primarily from existing STI guidelines, gonococcal surveillance data and studies conducted in Australia.	Identified in PHAC scoping exercise
				Pharyngeal	Preferred treatment is combination therapy with ceftriaxone 500 mg IM as a single dose plus azithromycin 2 g p.o. Note: Alternative treatments are not recommended because of high levels of resistance, except for some			

Author/group, country, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
					remote Australian locations and severe allergic reactions.			
Diagnosis and treatment of gonorrhea[26]								
AWMF, Germany, 2019	Adults	Not reported	Combination antibiotic therapy or monotherapy	Urogenital-anorectal, pharyngeal	Three options based on the following conditions: • Site of infection and availability of identification of the pathogen • Patient compliance in terms of treatment monitoring 1. Ceftriaxone 1 to 2 g IM or IV per day over 3 days plus azithromycin 1.5 g p.o. as a single dose, if pathogen identification not yet available and patient compliance unknown/not definitively ensured 2. Ceftriaxone 1 to 2 g IM or IV per day over 3 days if pathogen	Q1a	No methods reported. All types of published secondary and primary studies were included	Identified in PHAC scoping exercise

Author/group, country, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
					identification not yet available and patient compliance certain (additional diagnosis workup and follow-up in 4 weeks) 3. Ceftriaxone 1 to 2 g IM or IV per day over 3 days as a single dose if pathogen has been identified and patient compliance is certain and coinfection ruled-out For option 2 and 3 follow-up is required, 4 weeks after treatment for monitoring of treatment success using NAATs Note: Cefixime is insufficiently effective in case of pharyngeal infection. In such cases, treatment			

Author/group, country, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
					with ceftriaxone is required.			
2018 UK national guideline for the management of infection with *Neisseria* gonorrhoeae[18]								
Fifer et al. from BASHH, UK, 2019	Adults	Not reported	Combination antibiotic therapy or monotherapy	Urogenital-anorectal	Ceftriaxone 1 g in a single dose if antimicrobial susceptibility is not known before treatment When antimicrobial susceptibility is known: Ciprofloxacin 500 mg p.o.	Q1a and Q2	SR methods and GRADE approach used. SR states "priority was given to RCTs and SR evidence." (pg. 4). Local and global surveillance reports were used to make recommen-dations on the dosage increase from the previous guideline.	Identified in PHAC scoping exercise
Sexually Transmitted Infections Treatment Guidelines[17]								
US CDC, United States, 2021	Infants, children, adolescents, and adults	"Any patient care setting that serves persons at risk for STIs, including family planning clinics, HIV care clinics, correctional health care settings, private	Combination antibiotic therapy or monotherapy	Urogenital-anorectal, pharyngeal	Preferred treatment is ceftriaxone 500 mg IM in a single dose for persons weighing < 150 kg (ceftriaxone 1g IM as a single dose for persons weighing ≥ 150 kg) If ceftriaxone is not	Q1a, Q2, and Q3	SR conducted for each question. All types of published primary studies were included. Meeting of CDC staff members and subject	Identified in PHAC scoping exercise

Author/group, country, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
		physicians' offices, Federally Qualified Health Centers, clinics for adolescent care, and other primary care facilities." (pg.1)			an option, cefixime 400 mg IM as a single dose plus azithromycin 1 g p.o. as a single dose Note: If chlamydial infection has not been excluded, concurrent treatment with doxycycline 100 mg p.o. b.i.d. for 7 days is recommended.		matter experts (with expertise in STI clinical management) from other federal agencies, nongovern-mental academic and research institutions, and professional medical organizations to develop key questions to guide individual literature reviews. Expert opinions were used when data were insufficient.	
Diagnosis and management of gonorrhoea and syphilis[22]								
Jespers et al from the KCE, Belgium, 2019	Women and men including young people	Primary care	Combination antibiotic therapy	Urogenital-anorectal, pharyngeal	Combination therapy with ceftriaxone 500 mg IM in a single dose plus azithromycin 2 g p.o. in a single dose.	Q1a and Q2	SR conducted and the GRADE approach was used. All types of published secondary and primary studies were included.	Identified in PHAC scoping exercise

Author/group, country, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
	Pregnant women		Monotherapy	Urogenital-anorectal, pharyngeal	Ceftriaxone 500 mg IM in a single dose.			
2020 European guideline on the diagnosis and treatment of gonorrhoea in adults[19]								
Unemo et al. from IUSTI, European regions, 2020	Adults and adolescents	Not reported	Combination antibiotic therapy or monotherapy	Urogenital-anorectal, pharyngeal	Preferred treatment is combination therapy with ceftriaxone 1 g IM in a single dose plus azithromycin 2 g p.o. in a single dose Note: For uncomplicated *N. gonorrhea* infections of the urethra, cervix, and rectum in adults and adolescents when the antimicrobial sensitivity of the infection is unknown.	Q1a	No methods reported other than GRADE approach used. Guideline states "The Cochrane Library was searched and relevant STI guidelines produced by WHO, US CDC, and the British Association for Sexual Health and HIV were included." (pg. 8)	Identified in PHAC scoping exercise
Recommandations diagnostiques et thérapeutiques pour les maladies sexuellement transmissibles[27]								
SFD, France, 2016	Adults (men and women)	Not reported	Combination antibiotic therapy or monotherapy	Urogenital-anorectal, pharyngeal	Ceftriaxone 500 mg IM in a single dose Antichlamydial therapy with azithromycin is systematically combined with ceftriaxone.	Q1a, Q2, and Q3	No methods reported.	Identified in PHAC scoping exercise

Author/group, country, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
New Zealand Guideline for the Management of Gonorrhoea[28]								
NZSHS, New Zealand, 2017	Adults Note: Adults and children in 2014 guidelines	Primary care	Combination antibiotic therapy or monotherapy	Urogenital-anorectal, pharyngeal	Ceftriaxone 500 mg IM plus azithromycin 1 g p.o. Note: Dose frequency and duration was not reported If coinfection with rectal chlamydia treatment as above PLUS doxycycline 100mg p.o. b.i.d. for 7 days.	Q1a	Review of international gonorrhea management guidelines as well as studies conducted in New Zealand. Incorporated feedback from consensus. Recommen-dations were made by consensus.	Identified in PHAC scoping exercise

ASHA = Australasian Sexual Health Alliance; AWMF = Association of the Scientific Medical Societies in Germany; BASHH = British Association for Sexual Health and HIV; b.i.d. = twice daily; gbMSM = gay, bisexual, and other men who have sex with men; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; IM: intramuscular; IUSTI = International Union Against Sexually Transmitted Infections; JAID = Japanese Association for Infectious Disease; JSC = Japanese Society of Chemotherapy; KCE = Belgian Health Care Knowledge Centre; NAAT = nucleic acid amplification test; NZSHS = New Zealand Sexual Health Society; PHAC = Public Health Agency of Canada; p.o. = orally; SFD = Société Française de Dermatologie et de pathologies sexuellement transmissibles; SR = systematic review; STI = sexually transmitted infection; US CDC = US Centers for Disease Control and Prevention.

Unless otherwise stated, the duration of treatment is once, as one single dose.

Note that this table has not been copy-edited.

Table 6: Provincial and Territorial Guidelines on Uncomplicated Gonococcal Infections in Adults and Adolescents

Author/group, province/territory, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
Update of the optimal use guide on sexually transmitted and blood-borne infections — Syndromic approach[11]								
INESSS, Quebec, 2020	People aged 14 years and older	Primary care	Combination antibiotic therapy or monotherapy	Urogenital-anorectal	**For the treatment of cervicitis and urethritis** **First line:** Ceftriaxone 250 mg IM as a single dose with doxycycline 100 mg p.o. b.i.d. for 7 days **Second line:** Cefixime 800 mg p.o. as a single dose or ceftriaxone 250 mg IM as a single dose with azithromycin 2 g p.o. in a single dose **For the treatment of PID** **First line:** Ceftriaxone 250 mg IM as a single dose with doxycycline 100 mg p.o. b.i.d. for 14 days and metronidazole 500 mg p.o. b.i.d. for 14 days **For the treatment of rectitis** **First line:** Ceftriaxone 250 mg IM as a single dose and doxycycline p.o. 100 mg b.i.d. for 7 days **Second line:** Cefixime 800 mg p.o. as a single dose and doxycycline 100 mg p.o. b.i.d. for 7 days and azithromycin 2 g p.o. as a single dose	Q4	SRs with narrative summaries were conducted for each PICO question; and no GRADE framework used. All types of published and unpublished primary studies were included.	Identified in this review

Author/group, province/territory, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
Alberta Treatment Guidelines for Sexually Transmitted Infections (STI) in Adolescents and Adults 2018[23]								
Alberta Health Services, Alberta, 2018	Adults and adolescents	Primary care and provincial STI clinics	Combination antibiotic therapy or monotherapy	Urogenital-anorectal	Cefixime 800 mg p.o. in a single dose plus azithromycin 1 g p.o. as single dose Note: Ceftriaxone is recommended for gbMSM. Cefixime is considered an alternative therapy	Q1b	Adaptation from the Canadian Guidelines on Sexually Transmitted Infections.	Identified in PHAC scoping exercise
				Pharyngeal	Ceftriaxone 250 mg IM as a single dose plus azithromycin 1 g p.o. as a single dose			
British Columbia Treatment Guidelines for Sexually Transmitted Infections in Adolescents and Adults 2014[24]								
BCCDC, British Columbia, 2014	Adults and adolescents	Not reported	Combination antibiotic therapy or monotherapy	Urogenital-anorectal, pharyngeal	Cefixime 800 mg p.o. as a single dose or ceftriaxone 250 mg IM as a single dose plus azithromycin 1 g p.o. as a single dose or doxycycline 100 mg p.o. b.i.d. x 7 days	Q1b	Adaptation from the Canadian Guidelines on Sexually Transmitted Infections.	Identified in PHAC scoping exercise
Guide d'usage optimal — Infection non compliquée à *Chlamydia trachomatis* ou à *Neisseria Gonorrhorae*[16]								
INESSS, Quebec, 2020	Individuals 14 years and older	Primary care	Combination antibiotic therapy or monotherapy	Urogenital-anorectal	Ceftriaxone 250 mg IM as a single dose or cefixime 800 mg plus azithromycin 2 g p.o. as a single dose	Q1a and Q4	SR for each chapter. Included SRs, RCTs and nonRCTs, and all observational studies.	Identified in PHAC scoping exercise
				Pharyngeal	Ceftriaxone 250 mg as a single dose			

Author/group, province/territory, year	Population	Setting	Intervention	Site of infection	Recommendations	Relevant research question(s)	Methods and types of evidence used	Search source
Ontario Gonorrhea Testing and Treatment Guide[21]								
Public Health Ontario, Ontario, 2018	Adults	Primary care and provincial STI clinics	Combination antibiotic therapy or monotherapy	Urogenital-anorectal, pharyngeal	Ceftriaxone 250 mg as a single dose plus azithromycin 1 g p.o. as a single dose In the event of treatment failure, a higher dose of both ceftriaxone and azithromycin should be given: Ceftriaxone 1 g IM as a single dose plus azithromycin 2 g p.o. as a single dose	Q1a, Q1b, and Q3	Literature review for each chapter (MEDLINE search). SRs and primary studies cited.	Identified in PHAC scoping exercise

BCCDC = British Columbia Centre for Disease Control; b.i.d. = twice daily; gbMSM = gay, bisexual, and other men who have sex with men; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; IM = intramuscular; INESSS = Institut national d'excellence en santé et en services sociaux; PHAC = Public Health Agency of Canada; PICO = population, intervention, comparator, outcome(s); PID = pelvic inflammatory disease; p.o. = orally; RCT = randomized controlled trial; SR = systematic review; STBBI = sexually transmitted and blood-borne infection; STI = sexually transmitted infection.

Unless otherwise stated, the duration of treatment is once, as one single dose.

Note that this table has not been copy-edited.

Table 7: Published SRs

Reference (author/year)	Question asked	Population	Site of infection	Intervention/comparator	Results	Relevant research question(s)	Types of evidence used	AMSTAR-2 score
Treatment efficacy for pharyngeal *N. gonorrhea*: a systematic review and meta-analysis of randomized controlled trials								
Kong FYS, et al., 2020[15]	What is the treatment efficacy for pharyngeal gonorrhea?	Adults and youth ≥ 15 years of age	Pharyngeal	Ceftriaxone monotherapy (125 mg, 250 mg, 500 mg) Ceftriaxone (500 mg) plus azithromycin (1 g) Ceftriaxone (500 mg) plus azithromycin (2 g)	**Outcome:** Microbiological cure (defined as percent cured of pharyngeal *N. gonorrhea* at follow-up) **Ceftriaxone monotherapy** **125 mg**	Q1a	Single arm data extracted from RCTs	10/16 (Low quality)

Reference (author/year)	Question asked	Population	Site of infection	Intervention/comparator	Results	Relevant research question(s)	Types of evidence used	AMSTAR-2 score
					• Total diagnosed: 5 • Total cured at follow-up: 5 • Microbiological cure: 100% (n = 5; 95% CI, 56.5% to 100%) **250 mg** • Total diagnosed: 13 • Total cured at follow-up: 13 • Microbiological cure: 100% • (n = 13; 95% CI, 77.2% to 100%) **500 mg** • Total diagnosed: 4 • Total cured at follow-up: 4 • Microbiological cure: • 100% (n = 4; 95% CI, 51.0% to 100%) **Ceftriaxone plus azithromycin** *Ceftriaxone (500 mg) plus azithromycin (1 g):* • Total diagnosed: 132 • Total cured at follow-up: 127 • Random effect efficacy estimate:			

Reference (author/year)	Question asked	Population	Site of infection	Intervention/comparator	Results	Relevant research question(s)	Types of evidence used	AMSTAR-2 score
					97.1% (95% CI, 93.0% to 99.7%) *Ceftriaxone (500 mg) plus azithromycin (2 g):* • Total diagnosed: 33 • Total cured at follow-up: 33 • Microbiological cure: • 100% (95% CI, 89.6% to 100%)			
				Combination therapy vs monotherapy	**Outcome:** Microbiological cure (defined as percent cured of pharyngeal *N. gonorrhea* at follow-up) **Combination therapy** Number of studies: n = 3 • Total diagnosed: n = 324 • 98.1% (95% CI, 93.78% to 100%; I^2 = 79.1%; P < 0.01) **Monotherapy** • Number of studies: n = 5 • Total diagnosed: n = 124 • 97.1% (95% CI, 90.8% to 100%; I^2 = 15.6%; P = 0.29)	Q1b		

Reference (author/year)	Question asked	Population	Site of infection	Intervention/comparator	Results	Relevant research question(s)	Types of evidence used	AMSTAR-2 score
				High-dose (500 mg) ceftriaxone monotherapy Low dose (250 mg) ceftriaxone monotherapy	**Outcome:** Microbiological cure (defined as percent cured of pharyngeal *N. gonorrhea* at follow-up) **Low dose 250 mg** • Total diagnosed: 13 • Total cured at follow-up: 13 • Microbiological cure: 100% • (n = 13; 95% CI, 77.2% to 100%) **High dose 500 mg** • Total diagnosed: 4 • Total cured at follow-up: 4 • Microbiological cure: • 100% (n = 4; 95% CI, 51.0% to 100%)	Q2		

CI = confidence interval; RCT = randomized controlled trial

Note that this table has not been copy-edited.

Appendix 6: Quality of Appraisal of Included SR

Note that this appendix has not been copy-edited.

Table 8: Quality of Assessment of SR Using AMSTAR-II

AMSTAR-II questions	Kong et al., 2020 [15]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established before the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes
5. Did the review authors perform study selection in duplicate?	No
6. Did the review authors perform data extraction in duplicate?	Partial Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
Overall Rating	10/16 (Low quality)

For more information on CoLab and its work visit **colab.cadth.ca**

Canada's Drug and Health Technology Agency

CoLab Network

This Health Technology Review was conducted by the Knowledge Synthesis Team, Knowledge Translation Program, through the Post-Market Drug Evaluation Program. This work was supported by CADTH and its Post-Market Drug Evaluation Program, through funding provided by Health Canada.