Sexually Transmitted Infection (STI)

Frequently Asked Questions

Note: These guidelines were produced by SH-UHN ASP in collaboration with ID physicians, clinical pharmacists and public health experts, including previous team members of Public Health Ontario.

Gonorrhea

1. Why was the ceftriaxone dosage increased to 500 mg?

The rationale for increasing the ceftriaxone dose for the treatment of gonorrhea is three-fold:

1) *Increasing population prevalence of non-susceptible clones despite combination therapy*

Although cephalosporin MICs are generally low in Canada, the proportion of isolates with decreased susceptibility is trending up. In Ontario, 1.12% of isolates had decreased susceptibility to ceftriaxone (defined as MIC ≥ 0.125 mg/L) in 2020, compared to 0.23% in 2016[1].

2) *Optimizing dosing based on a murine model*

In a murine model, the lowest dose of ceftriaxone needed to cure urogenital gonorrhea was estimated to be 5 mg/kg – this was 100% successful at eradicating susceptible *Neisseria gonorrhoeae* (NG) isolates (MIC 0.008 mg/L), corresponding to an fT > MIC[2]. With the modal MIC for ceftriaxone[3], the current dosing of 250 mg may be more ideally suited to individuals weighing 50 kg or less.

3) *Optimizing treatment of pharyngeal infection*

The minimal dose for eradicating pharyngeal gonorrhea is currently unknown. Pharyngeal NG infection is often asymptomatic but may contribute to gonorrhea transmission. It is also more difficult to achieve microbiological cure at the pharyngeal site, even with susceptible strains[4]. Some proposed theories explaining the higher failure rate include suboptimal concentrations in oropharyngeal tissues and horizontal transfer of genetic material with commensal Neisseria species, thereby promoting resistance[5]. It has been suggested that a higher fT > MIC may be needed to eradicate NG in the oropharynx, but this has not yet been demonstrated in a pharmacokinetic study (animal or human).

2. Why has azithromycin been removed from first-line therapy?

The rationale for combination therapy with azithromycin was based on theoretical benefits in preventing the emergence of resistant strains.

However, the ecological impact of azithromycin on other microorganisms such as *Streptococcus pneumoniae* and *Mycoplasma genitalium* has been recognized[6,7].

In addition, there is ongoing NG resistance to azithromycin. In Ontario, the proportion of NG isolates considered non-susceptible to azithromycin (generally defined as MIC ≥ 2 mg/L) fluctuated between 3.6% and 15% in the years 2016-2020[1]. These numbers are not far from the > 5% resistance threshold traditionally set by the WHO for recommending against the empiric use of an antibiotic.

3. What is the rationale for cefixime 800 mg PO once as one of the alternative treatment options?

For the treatment of uncomplicated gonococcal infections, the original recommended dose is 400 mg in a single oral dose[8]. Due to the global rise in the proportion of isolates with decreased susceptibility in the late 2000s and early 2010s, some jurisdictions have removed cefixime altogether from their guidelines; others have recommended an increased dosage to 800 mg if used as an alternative agent.

In a pharmacokinetic study of 25 healthy volunteers, Cmax and AUC plateaued at single doses of 800 mg but concentrations were almost undetectable in pharyngeal fluid[9]. Increasing the dosage to 800 mg would thus theoretically increase the probability of target attainment, however isolates with MICs as low as 0.12 mg/L were associated with treatment failures, irrespective of dose or anatomic site[10].

Cefixime should only be reserved for patients unable to receive intramuscular injections, and if pharyngeal gonorrhea is excluded. A test of cure is strongly recommended.

Chlamydia

4. Do we uniformly favour doxycycline over azithromycin? Can we still give azithromycin in select patient populations?

We favour universal doxycycline use due to data from RCTs and observational studies substantiating the superiority of doxycycline for the treatment of rectal chlamydia in both men and women[11-13]. Rectal chlamydia is often asymptomatic and can act as a reservoir for ongoing community transmission. In women, there is also a possibility of transmission between anatomic sites via autoinoculation.

Azithromycin continues to be the preferred choice in pregnancy due to the teratogenic risk associated with tetracyclines. Azithromycin can also be considered in patients unlikely or unable to adhere to a 7-day treatment course. Although some evidence implies that imperfect adherence has little impact on treatment success[14,15], the data is conflicting[16].

Pelvic Inflammatory Disease (PID)

5. What is the role of metronidazole in the treatment of PID?

We recommend adding metronidazole routinely as part of the standard regimen, in agreement with CDC[17] and European guidelines[18]. This is based on results of an RCT of 233 women with acute PID treated in the outpatient setting[19]. The addition of metronidazole resulted in reduced pelvic tenderness at 30 days and lower likelihood of isolating anaerobes and *Mycoplasma genitalium*.

Syphilis

6. Can you use penicillin G sodium (or aqueous penicillin G) instead of penicillin G benzathine?

NO. Due to the organism's slow rate of replication (30-33 hours), prolonged treponemicidal concentrations are required[20]. Penicillin G benzathine (PGB) is specially formulated to be "long-acting"; the drug is slowly absorbed into the bloodstream and hydrolyzed to become penicillin G. PGB and penicillin G sodium are thus NOT interchangeable.

One dose of 2.4 million units of PGB yields treponemicidal concentrations lasting as long as 3-4 weeks[20].

7. For neurosyphilis, do you need to give three IM injections of penicillin G benzathine in addition to 10-14 days of intravenous penicillin therapy?

Intravenous penicillin x 10-14 days is recommended for the treatment of neurosyphilis due to penicillin G benzathine's (PGB) inability to achieve treponemicidal levels in the CSF. Since the treatment duration is comparatively shorter than for non-neurologic late syphilis, three additional doses of PGB to ensure prolonged serum penicillin concentrations can be given as per CDC guidelines, but this is not required[17].

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8. Can pregnant patients receive antibiotics other than penicillin?

Penicillin is the drug of choice for the treatment of syphilis in pregnant patients because it is the only antibiotic with evidence supporting its effectiveness in treating fetal infection and preventing congenital syphilis, two important therapeutic goals[20]. Alternatives such as doxycycline and azithromycin are not recommended due to the teratogenicity of tetracyclines and the emergence of macrolide-resistant strains of *T. pallidum*.

9. Can you give cephalosporins to patients who are truly allergic to penicillin?

There is emerging data that ceftriaxone is an acceptable alternative to penicillin, especially for neurosyphilis (excluding late-stage neurosyphilis)[20]. However, there are currently no comparative randomized, controlled trials. We recommend consulting with Infectious Diseases if an alternative treatment to penicillin is required.

Table 1. Comparison between Canadian, American, European and British STI guidelines[a]

Guideline recommendations	CDC 2021[17]	PHAC 2021[21]	TPH 2018[22]	European	BASHH
Gonorrhea			PHO 2018[23]	2020[24]	2020[25]
1st line	*Anogenital or pharyngeal:* **Ceftriaxone** 500 mg IM once[b]	*Anogenital or pharyngeal:* **Ceftriaxone** 250 mg IM once **AND** **Azithromycin** 1 g PO once	*Anogenital or pharyngeal:* **Ceftriaxone** 250 mg IM once **AND** **Azithromycin** 1 g PO once	*Anogenital or pharyngeal:* **Ceftriaxone** 1 g IM once **AND** **Azithromycin** 2 g PO once[c]	*Anogenital or pharyngeal:* **Ceftriaxone** 1 g IM once
Select alternative(s)	*Anogenital:* **Cefixime** 800 mg PO once -- **Gentamicin** 240 mg IM once **AND** **Azithromycin** 2 g PO once *No reliable alternatives for pharyngeal gonorrhea*	*Anogenital or pharyngeal:* **Cefixime** 800 mg PO once **AND** **Azithromycin** 1 g PO once -- **Gentamicin** 240 mg IM/IV once **AND** **Azithromycin** 2 g PO once	*Anogenital or pharyngeal:* **Cefixime** 400 mg PO once **AND** **Azithromycin** 1 g PO once -- **Gentamicin** 240 mg IM/IV once **AND** **Azithromycin** 2 g PO once -- **Azithromycin** 2 g PO once (least preferred)	*Anogenital:* **Ceftriaxone** 1 g IM once -- **Cefixime** 400 mg PO once **AND** **Azithromycin** 2 g PO once[c] -- **Gentamicin** 240 mg IM once **AND** **Azithromycin** 2 g PO once[c] *Pharyngeal:* **Ceftriaxone** 1 g IM once	*Anogenital or pharyngeal:* **Cefixime** 400 mg PO once **AND** **Azithromycin** 2 g PO once -- **Gentamicin** 240 mg IM once **AND** **Azithromycin** 2 g PO once -- **Azithromycin** 2 g PO once
Chlamydia (non-LGV)				2015 (under review)[26]	Updated 2018[27]
1st line	**Doxycycline** 100 mg PO bid for 7 days	**Doxycycline** 100 mg PO bid for 7 days	**Doxycycline** 100 mg PO bid for 7 days	*Urogenital:*	**Doxycycline** 100 mg PO bid for 7 days

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		-- **Azithromycin** 1 g PO once	-- **Azithromycin** 1 g PO once	**Doxycycline** 100 mg PO bid for 7 days -- **Azithromycin** 1 g PO once *Rectal and pharyngeal:* **Doxycycline** 100 mg PO bid for 7 days	
Alternative(s)	**Azithromycin** 1 g PO once -- **Levofloxacin** 500 mg PO daily for 7 days	**Levofloxacin** 500 mg PO daily for 7 days		*Urogenital:* **Erythromycin**[d] 500 mg PO bid for 7 days -- **Levofloxacin** 500 mg PO daily for 7 days *Rectal and pharyngeal:* **Azithromycin** 1 g PO once	**Erythromycin**[d] 500 mg PO bid for 10-14 days
In pregnancy	**Azithromycin** 1 g PO once *Alternative:* **Amoxicillin** 500 mg PO tid for 7 days)	**Azithromycin** 1 g PO once -- **Amoxicillin** 500 mg PO tid for 7 days) -- **Erythromycin**[d] 2 g/day PO in divided doses for 7 days -- **Erythromycin**[d] 1 g/day PO in divided doses for 14 days	**Azithromycin** 1 g PO once -- **Amoxicillin** 500 mg PO tid for 7 days) -- **Erythromycin**[d] 2 g/day PO in divided doses for 7 days	**Azithromycin** 1 g PO once *Alternatives*: **Amoxicillin** 500 mg PO tid for 7 days -- **Erythromycin**[d] 500 mg PO qid for 7 days)	**Azithromycin** 1 g PO once, followed by 500 mg PO daily for 2 days -- **Amoxicillin** 500 mg PO tid for 7 days) -- **Erythromycin**[d] 500 mg PO qid for 7 days -- **Erythromycin**[d] 500 mg PO bid for 14 days
PID Select 1st line (outpatient)	**Ceftriaxone** 500 mg IM **AND** **Doxycycline** 100 mg PO bid for 14 days	**Ceftriaxone** 250 mg IM once **AND**	**Ceftriaxone** 250 mg IM once **AND**	2017[18] **Ceftriaxone** 500 mg IM once **AND**	2019[28] **Ceftriaxone** 1 g IM **AND** **Doxycycline** 100 mg PO bid for 14 days

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	AND **Metronidazole** 500 mg PO bid for 14 days	**Doxycycline** 100 mg PO bid for 14 days *May add:* **Metronidazole** 500 mg PO bid for 14 days	**Doxycycline** 100 mg PO bid for 14 days *May add:* **Metronidazole** 500 mg PO bid for 14 days	**Doxycycline** 100 mg PO bid for 14 days *AND* **Metronidazole** 500 mg PO bid for 14 days -- **Levofloxacin** 500 mg PO daily for 14 days *AND* **Metronidazole** 500 mg PO bid for 14 days -- **Moxifloxacin** 400 mg daily for 14 days	*AND* **Metronidazole** 500 mg PO bid for 14 days -- **Moxifloxacin** 400 mg daily for 14 days
Select 1st line (inpatient)	**Ceftriaxone** 1 g IV q24h *AND* **Doxycycline** 100 mg IV/PO bid *AND* **Metronidazole** 500 mg IV/PO bid (transition to oral doxycycline and metronidazole to complete 14 days of therapy)	None provided	None provided	**Ceftriaxone** 1 g IV q24h *AND* **Doxycycline** 100 mg IV/PO bid *AND* **Metronidazole** 500 mg IV/PO bid (transition to oral doxycycline and metronidazole to complete 14 days of therapy) -- **Clindamycin** 900 mg IV q8h *AND* **Gentamicin** 3-6 mg/kg IV q24h (transition to oral clindamycin 450 mg PO qid to complete 14 days)	**Ceftriaxone** 2 g IV q24h *AND* **Doxycycline** 100 mg IV/PO bid *AND* **Metronidazole** 500 mg IV/PO bid (transition to oral doxycycline and metronidazole to complete 14 days of therapy) -- **Clindamycin** 900 mg IV q8h *AND* **Gentamicin** 2 mg/kg IV once, followed by 1.5 mg/kg IV q8h (transition to oral clindamycin 450 mg PO qid to complete 14 days)

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Select alternative(s) (outpatient)	**Levofloxacin** 500 mg PO daily for 14 days **AND** **Metronidazole** 500 mg PO bid for 14 days -- **Moxifloxacin** 400 mg daily for 14 days	**Levofloxacin** 500 mg PO daily for 14 days *May add:* **Metronidazole** 500 mg PO bid for 14 days	**Levofloxacin** 500 mg PO daily for 14 days *May add:* **Metronidazole** 500 mg PO bid for 14 days	**Ceftriaxone** 500 mg IM once **AND** **Azithromycin** 1 g PO weekly x 2 doses	**Ceftriaxone** 1 g IM **AND** **Azithromycin** 1 g PO weekly x 2 doses
Select alternative(s) (inpatient)	**Clindamycin** 900 mg IV q8h **AND** **Gentamicin** 2 mg/kg IV once, followed by 1.5 mg/kg IV q8h; 3-5 mg/kg IV q24h can be substituted	None provided	None provided	None commercially available in Canada	None commercially available in Canada

[a]Only products commercially available in Canada are displayed
[b]If weight ≥ 150 kg, increase dosage to 1 g
[c]Can be given in 2 doses 6-12 h apart to limit gastrointestinal side effects
[d]Dosage refers to erythromycin base; of note, the only dosage form available in Canada is 333 mg

REFERENCES

1. Canada PHAC. GC-AMR Laboratory Program 2022-05-09 [PowerPoint presentation].
2. Connolly KL, Eakin AE, Gomez C, Osborn BL, Unemo M, Jerse AE. Pharmacokinetic Data Are Predictive of In Vivo Efficacy for Cefixime and Ceftriaxone against Susceptible and Resistant Neisseria gonorrhoeae Strains in the Gonorrhea Mouse Model. Antimicrobial agents and chemotherapy. 2019;63(3).
3. Canada PHAC. National Surveillance of Antimicrobial Susceptibilities of Neisseria gonorrhoeae Annual Summary 2019. Ottawa; 2019.
4. Barbee LA, St. Cyr SB. Management of Neisseria gonorrhoeae in the United States: Summary of Evidence From the Development of the 2020 Gonorrhea Treatment Recommendations and the 2021 Centers for Disease Control and Prevention Sexually Transmitted Infection Treatment Guidelines. Clinical Infectious Diseases. 2022;74(Supplement_2):S95-S111.
5. Unemo M. Current and future antimicrobial treatment of gonorrhoea - the rapidly evolving Neisseria gonorrhoeae continues to challenge. BMC infectious diseases. 2015;15:364.
6. Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. Lancet. 2007;369(9560):482-90.
7. Seña AC, Bachmann L, Johnston C, Wi T, Workowski K, Hook EW, 3rd, et al. Optimising treatments for sexually transmitted infections: surveillance, pharmacokinetics and pharmacodynamics, therapeutic strategies, and molecular resistance prediction. The Lancet Infectious diseases. 2020;20(8):e181-e91.
8. Suprax (cefixime) [product monograph]. Pointe-Claire, Quebec, Canada: Odan Laboratories Ltd; July 2017.
9. Barbee LA, Nayak SU, Blumer JL, O'Riordan MA, Gray W, Zenilman JM, et al. A Phase 1 Pharmacokinetic and Safety Study of Extended-Duration, High-dose Cefixime for Cephalosporin-resistant Neisseria gonorrhoeae in the Pharynx. Sex Transm Dis. 2018;45(10):677-83.
10. Allen VG, Mitterni L, Seah C, Rebbapragada A, Martin IE, Lee C, et al. Neisseria gonorrhoeae Treatment Failure and Susceptibility to Cefixime in Toronto, Canada. Jama. 2013;309(2):163-70.
11. Páez-Canro C, Alzate JP, González LM, Rubio-Romero JA, Lethaby A, Gaitán HG. Antibiotics for treating urogenital Chlamydia trachomatis infection in men and non-pregnant women. The Cochrane database of systematic reviews. 2019;1(1):Cd010871.
12. Dukers-Muijrers NHTM, Wolffs PFG, De Vries H, Götz HM, Heijman T, Bruisten S, et al. Treatment Effectiveness of Azithromycin and Doxycycline in Uncomplicated Rectal and Vaginal Chlamydia trachomatis Infections in Women: A Multicenter Observational Study (FemCure). Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2019;69(11):1946-54.
13. Chen L-F, Wang T-C, Chen F-L, Hsu S-C, Hsu C-W, Bai C-H, et al. Efficacy of doxycycline versus azithromycin for the treatment of rectal chlamydia: a systematic review and meta-analysis. Journal of Antimicrobial Chemotherapy. 2021;76(12):3103-10.
14. Reedy MB, Sulak PJ, Miller SL, Ortiz M, Kasberg-Preece C, Kuehl TJ. Evaluation of 3-Day Course of Doxycycline for the Treatment of Uncomplicated Chlamydia trachomatis Cervicitis. Infect Dis Obstet Gynecol. 1997;5(1):18-22.

15. Bachmann LH, Stephens J, Richey CM, Hook EW, 3rd. Measured versus self-reported compliance with doxycycline therapy for chlamydia-associated syndromes: high therapeutic success rates despite poor compliance. Sex Transm Dis. 1999;26(5):272-8.
16. Khosropour CM, Manhart LE, Colombara DV, Gillespie CW, Lowens MS, Totten PA, et al. Suboptimal adherence to doxycycline and treatment outcomes among men with non-gonococcal urethritis: a prospective cohort study. Sex Transm Infect. 2014;90(1):3-7.
17. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187.
18. Ross J, Guaschino S, Cusini M, Jensen J. 2017 European guideline for the management of pelvic inflammatory disease. Int J STD AIDS. 2018;29(2):108-14.
19. Wiesenfeld HC, Meyn LA, Darville T, Macio IS, Hillier SL. A Randomized Controlled Trial of Ceftriaxone and Doxycycline, With or Without Metronidazole, for the Treatment of Acute Pelvic Inflammatory Disease. Clinical Infectious Diseases. 2020;72(7):1181-9.
20. Radolf JD, Tramont EC, Salazar JC. Syphilis (Treponema pallidum). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Philadelphia, PA: Elsevier; 2020. p. 2865-92.
21. Government of Canada. Canadian Guidelines on Sexually Transmitted Infections. 2010, updated 2016. Available from: https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines.html.
22. Toronto Public Health. STI Treatment Reference Guide 2018. Available from: https://www.toronto.ca/wp-content/uploads/2018/05/97a3-tph-sti-treatment-guide-2018.pdf.
23. Ontario Agency for Health Protection and Promotion (Public Health Ontario). Ontario Gonorrhea Testing and Treatment Guide. 2nd ed. Toronto, ON: Queen's Printer for Ontario; 2018.
24. 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.
25. Fifer H, Saunders J, Soni S, Sadiq ST, FitzGerald M. 2018 UK national guideline for the management of infection with Neisseria gonorrhoeae. International Journal of STD & AIDS. 2020;31(1):4-15.
26. Lanjouw E, Ouburg S, de Vries HJ, Stary A, Radcliffe K, Unemo M. 2015 European guideline on the management of Chlamydia trachomatis infections. Int J STD AIDS. 2016;27(5):333-48.
27. Nwokolo NC, Dragovic B, Patel S, Tong CY, Barker G, Radcliffe K. 2015 UK national guideline for the management of infection with Chlamydia trachomatis. Int J STD AIDS. 2016;27(4):251-67.
28. Ross J, Evans C, Lyons D, Dean G, Cousins D, PPI representative United Kingdom National Guideline for the Management of Pelvic Inflammatory Disease (2019 Interim Update). Available from: https://www.bashhguidelines.org/media/1217/pid-update-2019.pdf.