

Treatment of *N. gonorrhoeae* in response to the discontinuation of spectinomycin: Alternative treatment guidance statement

Revised
July 2017

Issue

The Public Health Agency of Canada (PHAC) has been informed that manufacturing of spectinomycin has been discontinued. This antimicrobial is therefore no longer available through Health Canada's Special Access Program (SAP).

Spectinomycin is recommended in the *Canadian Guidelines on Sexually Transmitted Infections* (CGSTI) as part of an alternate [combination therapy](#) for anogenital *Neisseria gonorrhoeae* infection, in individuals with contraindications to first-line treatment (i.e., cephalosporins given in combination with azithromycin or doxycycline).

In the face of increasing [antimicrobial resistance in *Neisseria gonorrhoeae*](#), the discontinuation of spectinomycin has the potential to limit gonorrhea prevention and control efforts in Canada by further restricting treatment options.

This guidance statement for alternative treatments for gonococcal infections was developed in consultation with the CGSTI [Expert Working Group](#) based on Canadian epidemiology and a [rapid evidence review](#).

Pre-treatment considerations

If culture was not done at the initial visit and is available through your local laboratory, a pre-treatment swab for culture should ideally be submitted for antimicrobial susceptibility testing.

- Due to the significance in reported resistance to ciprofloxacin (39% of Canadian isolates tested in 2015 were resistant), quinolones such as ciprofloxacin and levofloxacin are no longer recommended for treating gonococcal infections in Canada, unless:
 - antimicrobial susceptibility testing is available and quinolone susceptibility is demonstrated
- OR
- regional/local quinolone resistance rates are known to be under 5%
- AND
- a test of cure (ideally using culture) can be performed.

Alternate treatment for adults and youth with anogenital *N. gonorrhoeae* infections

Patients with cephalosporin-resistant *N. gonorrhoeae* or a history of anaphylactic reaction to penicillin or allergy to cephalosporins

- **Azithromycin** 2 g in a single oral dose PLUS **gentamicin** 240 mg IM¹ in 2 separate 3-mL injections of 40 mg/mL solution
 - Gentamicin 240 mg IV infused over 30 minutes may be considered as an alternative route of administration when the IM route is not feasible.
 - Azithromycin should not be used as monotherapy as resistance has been reported.²⁻⁵

Refer to the section below on [literature related to potential alternative treatments](#) for more information.

Patients with macrolide-resistant *N. gonorrhoeae* or a history of anaphylactic reaction to macrolides, and with contraindications to cephalosporins

- **Gentamicin** 240 mg IM^{6,7} in 2 separate 3-mL injections of 40 mg/mL solution
 - Gentamicin 240 mg IV infused over 30 minutes may be considered as an alternative route of administration when the IM route is not feasible.

Patients should be treated with combination therapy whenever possible.

- Where azithromycin is not used, **doxycycline** 100 mg orally twice daily for 7 days should be provided unless contraindicated or there is documented tetracycline resistance.

Quinolone treatment regimens

- **Azithromycin** 2 g in a single oral dose PLUS **ciprofloxacin** 500 mg in a single oral dose⁸⁻¹⁰
OR
- **Azithromycin** 2 g in a single oral dose PLUS **gemifloxacin** 320 mg in a single oral dose¹

Note:

At the time of publication, gemifloxacin was not available on the Canadian or US market. In the future, gemifloxacin is expected to be marketed in the US, at which time it will be made accessible through Health Canada's Special Access Program (SAP).

Follow-up

- All patients treated with an alternative regimen should have a test of cure (from all positive sites), using cultures taken **3–7 days** after the completion of therapy.
 - If NAAT is the only choice for test of cure, it should be done **2–3 weeks** after treatment to avoid false-positive results due to the presence of non-viable organisms.
- Repeat screening for individuals with a gonococcal infection is recommended 6 months post-treatment.

Supporting evidence for treatment recommendations

Antimicrobial resistance in *N. gonorrhoeae*

- Gonococcal infections have shown progressive resistance to penicillin, tetracyclines, quinolones, and more recently to third generation oral and injectable cephalosporins (the current first-line treatments).
- Recent resistance rates in Canada (unpublished data from NML):
 - The proportion of azithromycin-resistant (MIC \geq 2 mg/L) *N. gonorrhoeae* isolates has increased from 3.3% (127/3,809) in 2014 to 4.7% (109/4,109) in 2015 (the majority of azithromycin resistant isolates have been identified in central Canada).
 - Isolates with decreased susceptibility to cefixime (MIC \geq 0.25 mg/L) increased from 1.1% (42/3,809) in 2014 to 1.9% (80/4,190) in 2015.
 - Isolates with decreased susceptibility to ceftriaxone (MIC \geq 0.125 mg/L) increased from 2.7% (101/3,809) in 2014 to 3.5% (146/4,190) in 2015.
 - Tetracycline resistance increased from 47.3% (1,809/3,809) in 2014 to 56.4% (2,364/4,190) in 2015.
 - There is currently no reported resistance to gentamicin (MIC \geq 32 mg/L) in Canada, but approximately 95% of isolates exhibit intermediate susceptibility (MIC 8-16 mg/L) to gentamicin.
- No data on gemifloxacin resistance are available for Canadian isolates.

Literature related to potential alternative treatments

- A two-arm prospective study comparing the safety and efficacy of gentamicin 240 mg IM plus azithromycin 2 g in a single oral dose vs. gemifloxacin 320 mg orally plus azithromycin 2 g in a single oral dose reported cure rates of 100% for all sites of infection (anogenital, pharyngeal and rectal) with the gentamicin/azithromycin regimen, and 99.5% with the gemifloxacin/azithromycin regimen (*N. gonorrhoeae* was isolated from one urethral swab collected at a follow-up visit).¹
- There is a randomized controlled trial underway in the UK comparing ceftriaxone 500 mg IM vs. gentamicin 240 mg IM in combination with azithromycin 1 g in a single oral dose.¹¹ Preliminary results of this trial are anticipated later in 2017.
- Cure rates of 62-98% with gentamicin monotherapy have been reported in two systematic reviews.^{6,7}
- Cross resistance between gemifloxacin and ciprofloxacin has been reported, but one study reported that gemifloxacin had better activity against isolates with reduced susceptibility to ciprofloxacin.¹²

References

- (1) Kirkcaldy RD, Weinstock HS, Moore PC, Philip SS, Wiesenfeld HC, Papp JR, et al. The efficacy and safety of gentamicin plus azithromycin and gemifloxacin plus azithromycin as treatment of uncomplicated gonorrhoea. *Clin Infect Dis* 2014 Oct 15;59(8):1083-1091.
- (2) Young H, Moyes A, McMillan A. Azithromycin and erythromycin resistant *Neisseria gonorrhoeae* following treatment with azithromycin. *Int J STD AIDS* 1997 May;8(5):299-302.
- (3) Habib AR, Fernando R. Efficacy of azithromycin 1g single dose in the management of uncomplicated gonorrhoea. *Int J STD AIDS* 2004 Apr;15(4):240-242.
- (4) Yuan LF, Yin YP, Dai XQ, Pearline RV, Xiang Z, Unemo M, et al. Resistance to azithromycin of *Neisseria gonorrhoeae* isolates from 2 cities in China. *Sex Transm Dis* 2011 Aug;38(8):764-768.
- (5) Katz AR, Komeya AY, Soge OO, Kiaha MI, Lee MV, Wasserman GM, et al. *Neisseria gonorrhoeae* with high-level resistance to azithromycin: case report of the first isolate identified in the United States. *Clin Infect Dis* 2012 Mar;54(6):841-843.
- (6) Dowell D, Kirkcaldy RD. Effectiveness of gentamicin for gonorrhoea treatment: systematic review and meta-analysis. *Sex Transm Infect* 2012 Dec;88(8):589-594.
- (7) Hathorn E, Dhasmana D, Duley L, Ross JD. The effectiveness of gentamicin in the treatment of *Neisseria gonorrhoeae*: a systematic review. *Syst Rev* 2014 Sep 19;3:104-4053-3-104.
- (8) Echols RM, Heyd A, O'Keeffe BJ, Schacht P. Single-dose ciprofloxacin for the treatment of uncomplicated gonorrhoea: a worldwide summary. *Sex Transm Dis* 1994 Nov-Dec;21(6):345-352.
- (9) Moran JS. Ciprofloxacin for gonorrhoea--250 mg or 500 mg? *Sex Transm Dis* 1996 Mar-Apr;23(2):165-167.
- (10) Moran JS, Levine WC. Drugs of choice for the treatment of uncomplicated gonococcal infections. *Clin Infect Dis* 1995 Apr;20 Suppl 1:S47-65.
- (11) Brittain C, Childs M, Duley L, Harding J, Hepburn T, Meakin G, et al. Gentamicin versus ceftriaxone for the treatment of gonorrhoea (G-TOG trial): study protocol for a randomised trial. *Trials* 2016;17:10.1186/s13063-016-1683-8.
- (12) Pottumarthy S, Fritsche TR, Jones RN. Activity of gemifloxacin tested against *Neisseria gonorrhoeae* isolates including antimicrobial-resistant phenotypes. *Diagn Microbiol Infect Dis* 2006 Feb;54(2):127-134.