

Updated global guidelines to treat infections with *Neisseria gonorrhoeae*

N. gonorrhoeae has developed resistance to all previous first-line antimicrobial treatments for gonorrhoea. Historically, the following were effective treatments for gonococcal infections, sulphonamides, penicillin, tetracycline, spectinomycin, fluoroquinolones, early generation cephalosporins and macrolides. Currently, at the global level, the third-generation, extended spectrum cephalosporin, ceftriaxone, given as high-dose monotherapy or together with azithromycin, is the only remaining option for first-line empirical antimicrobial therapy of gonorrhoea. However, in the past two decades, gonococcal strains with in-vitro and clinical resistance to ceftriaxone and azithromycin have emerged globally (Fifer H, et al).

Some extensively drug-resistant (XDR) gonococcal strains with ceftriaxone resistance in combination with high-level resistance to azithromycin have also been detected (Jennison AV et al). The emergence and international spread of multidrug-resistant and sporadic XDR gonococcal strains and treatment failures with ceftriaxone mean that gonorrhoea has become a major public health concern, with the future potential of untreatable gonorrhoea in certain circumstances and settings.

For this reason, the World Health Organization (WHO) has recommended that countries put in place antimicrobial susceptibility surveillance of *N. gonorrhoeae* locally, regionally and globally, and revitalized the WHO Global Gonococcal Antimicrobial Surveillance Programme (GASP). Additionally, WHO is currently expanding its Enhanced GASP (EGASP), which includes standardized and quality-assured protocols, epidemiological data, whole-genome sequencing (WGS) and, where feasible, tests of cure.

To respond to this persistent threat of *N. gonorrhoeae* becoming untreatable with the existing antimicrobial agents, WHO commissioned a systematic review to obtain evidence to stem the threat. In the updated systematic review of the literature there were 15 new studies (3 randomized controlled trials and 12 non-randomized and non-comparative studies), as well as the 41 studies which had been reviewed previously in 2016. The studies primarily involved individuals with confirmed gonorrhoea.

From the reviewed data it seemed that higher doses of parenteral ceftriaxone or oral cefixime may result in slightly greater cure rates (1–3 percentage points more), but cefixime may provide fewer cures. Combining ceftriaxone with dual therapy (azithromycin) probably does not increase cures. In addition, data from surveillance published from systematic reviews of the literature and from the WHO Gonococcal Antimicrobial Surveillance Programme found that ceftriaxone resistance is increasing in most countries, except in Europe, where introducing a ceftriaxone 500 mg dose in 2013 and subsequently increasing to ceftriaxone 1 gram was associated with a decrease in reported ceftriaxone resistance.

Furthermore, pharmacodynamic data suggested that ceftriaxone 1 g could eradicate most gonococcal strains except highly resistant strains of oropharyngeal infections. Thus, providing parenteral ceftriaxone 1 gram will provide cure for the majority of gonorrhoea cases and delay emergence and spread of multi-drug resistance, particularly ceftriaxone resistance.

In terms of undesirable effects, the evidence was inconsistent and did not show a pattern of greater adverse events with higher doses of ceftriaxone or cefixime. However, higher doses of intramuscular ceftriaxone may be more painful, and azithromycin 2 grams orally can result in gastrointestinal side-effects, especially when taken on an empty stomach.

As evidence found fewer cures with oral cefixime (even at 800 mg), a test of cure could be performed to verify cure, if possible. In settings in which a test of cure is not possible, combining therapy with a higher dose of azithromycin at 2 grams may ensure cure. Based on this, the dose of ceftriaxone was increased to 1 gram without azithromycin, the dose of cefixime was increased to 800 mg (with or without azithromycin, depending on whether or not a test of cure is feasible).

The doses of spectinomycin and gentamicin were unchanged from the previously recommended ones, with the addition of azithromycin 2 grams to ensure cure.

Recommendation for the treatment of genital, anorectal and oropharyngeal gonococcal infections (updated 2023)

Note: The WHO recommends that national or local antimicrobial resistance data determine the choice of therapy when available.

For adults and adolescents (including pregnant individuals) with genital, anorectal and/or oropharyngeal gonococcal infections, the WHO suggests:

1. ceftriaxone 1 gram intramuscularly as a single dose.

If ceftriaxone is not available or refused, the WHO suggests:

2. cefixime 800 mg orally, and performing test of cure.

If test of cure is not possible or when oropharyngeal infection is diagnosed or is a potential concern, the WHO suggests:

3. cefixime 800 mg orally plus azithromycin 2 g orally.

When resistance, allergy or availability of cephalosporins is a concern, the WHO suggests one of the following options:

4. spectinomycin 2 grams intramuscularly as a single dose plus azithromycin 2 g orally; or
5. gentamicin 240 mg intramuscularly as a single dose plus azithromycin 2 g orally.

Remarks: Ceftriaxone 1 gram intramuscularly may be painful. Therefore, discussion should be held with the individual regarding the option of providing lidocaine with the injection.

Azithromycin 2 grams may cause gastrointestinal side-effects, especially if taken on an empty stomach.

Re-treating gonococcal infections after treatment failure using recommended regimen.

For adults and adolescents (including pregnant individuals) with gonococcal infections for whom treatment has failed as evidenced by persistent symptoms or a positive test of cure, the WHO recommends that the possibility of reinfection or antimicrobial resistance be considered to

determine the choice of therapy. If treatment failure occurred and antimicrobial susceptibility testing data are available, the WHO suggests re-treating according to susceptibility results.

If treatment failure occurred after a WHO-recommended therapy and reinfection is assessed to be unlikely, the WHO suggests re-treating with a regimen not used previously from one of the following options and performing test of cure.

1. ceftriaxone 1 gram intramuscularly as a single dose plus azithromycin 2 g orally, only if ceftriaxone was not used previously;
2. spectinomycin 2 grams intramuscularly as a single dose plus azithromycin 2 g orally; or
3. gentamicin 240 mg intramuscularly as a single dose plus azithromycin 2 g orally.

Further reading

- i. Unemo M, Shafer WM. Antimicrobial resistance in *Neisseria gonorrhoeae* in the 21st century: past, evolution, and future. *Clin Microbiol Rev.* 2014;27:587–613. doi:10.1128/CMR.00010-14.
- ii. Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*. Geneva: World Health Organization; 2012. (<https://iris.who.int/handle/10665/44863>).
- iii. Unemo M, Seifert HS, Hook EW 3rd, Hawkes S, Ndowa F, Dillon JR. Gonorrhoea. *Nat Rev Dis Primers.* 2019;5:79. doi:10.1038/s41572-019-0128-6.
- iv. Wi T, Lahra MM, Ndowa F, Bala M, Dillon JR, Ramon-Pardo P et al. Antimicrobial resistance in *Neisseria gonorrhoeae*: global surveillance and a call for international collaborative action. *PLoS Med.* 2017;14:e1002344. doi:10.1371/journal.pmed.1002344.
- v. Unemo M, Lahra MM, Cole M, Galarza P, Ndowa F, Martin I et al. World Health Organization Global Gonococcal Antimicrobial Surveillance Program (WHO GASP): review of new data and evidence to inform international collaborative actions and research efforts. *Sex Health.* 2019;16:412–25. doi:10.1071/SH19023.
- vi. Unemo M, Lahra MM, Escher M, Eremin S, Cole MJ, Galarza P et al. WHO global antimicrobial resistance surveillance for *Neisseria gonorrhoeae* 2017–18: a retrospective observational study. *Lancet Microbe.* 2021;2:e627–36. doi:10.1016/S2666-5247(21)00171-3.
- vii. Fifer H, Natarajan U, Jones L, Alexander S, Hughes G, Golparian D et al. Failure of dual antimicrobial therapy in treatment of gonorrhoea. *N Engl J Med.* 2016;374:2504–6. doi:10.1056/NEJMc1512757.
- viii. Jennison AV, Whiley D, Lahra MM, Graham RM, Cole MJ, Hughes G et al. Genetic relatedness of ceftriaxone-resistant and high-level azithromycin resistant *Neisseria gonorrhoeae* cases, United Kingdom and Australia, February to April 2018. *Euro Surveill.* 2019;24:1900118. doi:10.2807/1560-7917.ES.2019.24.8.1900118.