

Epidemiological Alert

Extended-Spectrum Cephalosporin Resistance in *Neisseria gonorrhoeae*

2 February 2018

In light of increasing reports of extended-spectrum cephalosporin resistance in *Neisseria gonorrhoeae*, the Pan American Health Organization / World Health Organization (PAHO / WHO) recommends Member States to strengthen surveillance and laboratory diagnostic capacity in order to support the detection of cases, provide adequate treatment, and identify populations at high risk. Furthermore, prevention and timely management of cases are essential measures to mitigate antimicrobial resistance.

Background

Gonorrhea is listed as one of the prioritized sexually transmitted infections (STIs) that requires global action for control, due to its extraordinary ability to develop resistance to nearly all classes of antibiotics that are used for first-line empirical treatment. Antibiotics such as sulfanilamide, penicillin, tetracyclines, older macrolides (e.g. erythromycin), and fluoroquinolones are currently less recommended for gonorrhea treatment worldwide due to a high prevalence of gonococcal strains that are resistant to these antibiotics. Between 2005 and 2015, high levels of resistance to tetracycline, penicillin, ciprofloxacin in Latin America were noted according to the Latin American Surveillance Network of Antimicrobial Resistance data.⁽¹⁾

The extended-spectrum cephalosporins are now the last available antibiotics recommended for monotherapy for treating gonorrhea. Therefore there is an urgent need to prevent and control its resistance to retain gonorrhea as a treatable infection.

Gonorrhea (ICD 10 A54.0 –A54.2)

The infection is caused by *Neisseria gonorrhoeae*, transmitted through contact with exudates from mucous membranes of an infected individual; almost always as a result of oral, vaginal, and/or anal sex without condom.⁽²⁾

The incubation period ranges between 1 and 14 days, although it can be longer.⁽²⁾

Asymptomatic urogenital infections are frequently found, especially in women. If gonorrhea is not well treated, it may result in reproductive complications.⁽³⁾

Effective treatment ends communicability within hours.⁽²⁾

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Summary of the situation in the Americas

Ceftriaxone-resistant *Neisseria gonorrhoeae* (*N. gonorrhoeae*) has been reported in the Americas since 2007 and, as of October 2017, four countries and territories in the Region identified infections due to this microorganism: Argentina, Brazil, Canada and the United States.ⁱ

In **Argentina**, a *N. gonorrhoeae* isolate resistant to ceftriaxone and cefixime was detected in 2014 in a male with no underlying disease or recent travel history.⁽⁸⁾ It is reported that isolates with decreased susceptibility and resistance to extended-spectrum cephalosporins have increased from 2.3% to 7.9% between 2011 and 2015, most of them belonged to sequence type (ST) 1407 or closely related genotypes.⁽⁹⁾ This sequence type was associated with failures treatment in many countries and involved in isolates with high-level of resistance from France and Spain.

In **Brazil**, a total number of 7 isolates resistant to ceftriaxone were reported in 2007.⁽¹⁰⁾

In **Canada**, a ceftriaxone-resistant *N. gonorrhoeae* isolate was identified in an asymptomatic woman in 2017. Epidemiologic and genomic data suggested spread from Asia. The strain was resistant to ceftriaxone, cefixime, ciprofloxacin, and tetracycline and susceptible to azithromycin.⁽¹¹⁾

In the **United States of America**, 8 *N. gonorrhoeae* isolates were reported as resistant to azithromycin and 5 had decreased susceptibility to ceftriaxone in Hawaii in 2016.⁽¹²⁾ In Puerto Rico, a *N. gonorrhoeae* isolate with a high-level of resistance to ceftriaxoneⁱⁱ was reported in 2014.⁽¹³⁾

Even though, in recent years, some countries have reported a high level of resistance to azithromycin and decreased susceptibility to ceftriaxone, dual treatment of ceftriaxone and azithromycin still remains effective worldwide. As of now, one dual-therapy failure case has been reported in England in 2014.⁽¹⁴⁾

Advice to national authorities

As antimicrobial resistance is increasing globally and lately in the Region of the Americas, the Pan American Health Organization / World Health Organization advises its Member States to implement prevention and control actions to contain the spread of extended-spectrum cephalosporin resistant *N. gonorrhoeae* strains.

Prevention and adequate case management of gonorrhea have impact, both in reducing gonorrhea burden and mitigating resistance.⁽¹⁵⁾

ⁱCountries outside of the Region of the Americas that have reported ceftriaxone-resistant *N. gonorrhoeae* include Australia⁽⁴⁾, France⁽⁵⁾, Japan⁽⁶⁾, and Spain⁽⁷⁾.

ⁱⁱ With inhibition zone diameter=9 mm by disk diffusion method

A series of guidance for health authorities is presented below.

Surveillance

Surveillance is one of the key components of national antimicrobial resistance prevention and control strategies, and it should be strengthened, alongside laboratory capacity, to support the detection of asymptomatic infections and treatment failures, as well as to identify communities and populations at high risk.

The following is recommended as part of **surveillance** strengthening:

- Monitor gonococcus resistance at the national level through a strong collaboration between national HIV/AIDS/STI programs and national reference laboratories.
- Strategies for the detection of asymptomatic infections among risk groups and vulnerable population should be developed and criteria for defining cases of treatment failures should be established according to local context.
- When treatment failure is detected, clinicians either take samples for culture and antimicrobial susceptibility testing, or refer the patient for laboratory examination and testing.
- Strains presenting extended-spectrum cephalosporin resistance should be sent to a reference laboratory for confirmation, and any suspected treatment failures should be promptly reported to local health officials to ensure rapid response.
- Extended-spectrum cephalosporin-resistant *N. gonorrhoeae* should be reported to the Member State International Health Regulations (IHR) National Focal Point and, based on the risk assessment, the WHO IHR Contact Point should be notified.

Specific recommendations pertaining to **laboratory capacity** for extended-spectrum cephalosporin resistant *N. gonorrhoeae* detection:

- Strengthen national laboratory capacity through quality assurance and use of WHO reference strains.⁽¹⁶⁾
- Monitor the decrease of susceptibility to ESCs by determining the minimum inhibitory concentration.
- If possible, improve the surveillance and knowledge through participating of national or regional molecular studies and determining mechanisms of resistance to extended-spectrum cephalosporins.

Clinical management

- Treatment decision should be based on the local epidemiology of antimicrobial resistance. Clinicians should be constantly updated on gonococcal treatment recommendations as these evolve due to shifts in antimicrobial resistance patterns.

- The choice and dosage of single therapy (ceftriaxone, cefixime or spectinomycin) should be based on local resistance data. However, in settings with no quality-assured local antimicrobial resistance (AMR) surveillance data, dual therapy (ceftriaxone plus azithromycin or cefixime plus azithromycin) is recommended.
- When treatment failure is suspected, the patient should be retreated with the recommended local regime unless reinfection is discarded. Clinical samples should be obtained before retreatment and sent to a laboratory for microbiology diagnostics and susceptibility test.
- A patient with confirmed treatment failure should be retreated according to the WHO recommendations.⁽¹⁷⁾
- Sexual contact tracking and clinical evaluation should be prioritized in treatment failure cases and when isolates demonstrate decreased susceptibility to cephalosporin.
- To prevent disease transmission, patients treated for gonorrhoea should be advised to practice safer sex. All persons who receive a diagnosis of gonorrhoea should be tested for other STIs, including chlamydia, syphilis, and HIV.
- If a pregnant woman is infected with extended-spectrum cephalosporin-resistant *N. gonorrhoeae*, consultation with an infectious disease specialist is recommended to decide on treatment options.

Risk Communication

- Raise public awareness and promote safer sex practices to prevent STIs.ⁱⁱⁱ
- Inform health workers, institutions, and non-governmental organizations working in the prevention and control of STIs about the risks associated with extended-spectrum cephalosporin-resistant *N. gonorrhoeae*.

ⁱⁱⁱ Safer sexual practice includes correct and consistent use of male or female condoms, non-penetrative sex, reducing the number of sexual partners, and postponing sexual debut. http://www.unaids.org/sites/default/files/media_asset/2015_terminology_guidelines_en.pdf

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Related links

- WHO. WHO guidelines for the treatment of *Neisseria gonorrhoeae*:
<http://www.who.int/reproductivehealth/publications/rtis/gonorrhoea-treatment-guidelines/en/>
- United States Centers for Control and Prevention (CDC). Gonococcal infections:
<https://www.cdc.gov/std/tg2015/gonorrhea.htm>
- WHO. Strategies and laboratory methods for strengthening surveillance of sexually transmitted infection 2012:
<http://www.who.int/reproductivehealth/publications/rtis/9789241504478/en/>
- WHO. Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus:
<http://www.who.int/reproductivehealth/publications/rtis/9789241505840/en/>