BRAZILIAN JOURNAL OF MICROBIOLOGY XXX (2017) XXX–XXX

BRAZILIAN JOURNAL OF MICROBIOLOGY

http://www.bjmicrobiol.com.br/

Review

Antimicrobial resistance in *Neisseria gonorrhoeae*: history, molecular mechanisms and epidemiological aspects of an emerging global threat

*Ana Paula Ramalho da Costa Lourenço, Késia Thaís Barros dos Santos, Beatriz Meurer Moreira, Sergio Eduardo Longo Fracalanzza, Raquel Regina Bonelli**

Institute of Microbiology, Universidade Federal do Rio de Janeiro, 21941-902 Rio de Janeiro, RJ, Brazil

ARTICLE INFO

Article history:
Received 9 November 2016
Accepted 5 June 2017
Available online xxx

Associate Editor: Marina Baquerizo

Keywords:
Neisseria gonorrhoeae
Surveillance
Resistance mechanisms

ABSTRACT

Neisseria gonorrhoeae is the agent of gonorrhea, a sexually transmitted infection with an estimate from The World Health Organization of 78 million new cases in people aged 15–49 worldwide during 2012. If left untreated, complications may include pelvic inflammatory disease and infertility. Antimicrobial treatment is usually effective; however, resistance has emerged successively through various molecular mechanisms for all the regularly used therapeutic agents throughout decades. Detection of antimicrobial susceptibility is currently the most critical aspect for *N. gonorrhoeae* surveillance, however poorly structured health systems pose difficulties. In this review, we compiled data from worldwide reports regarding epidemiology and antimicrobial resistance in *N. gonorrhoeae*, and highlight the relevance of the implementation of surveillance networks to establish policies for gonorrhea treatment.

Neisseria gonorrhoeae infections: symptoms, surveillance and treatment

The gonococcal disease

N. gonorrhoeae is the etiological agent of gonorrhea, the second most frequently reported sexually transmitted infection (STI) in the world. This bacterium typically colonizes and infects the genital tract in men and women, but may be found in additional body sites such as the rectal and oropharyngeal mucosa, with or without clinically evident infection.[1]

Gonorrhea is usually symptomatic in men, most often as urethritis, with pain or burning sensation during urination, urethral discharge, and painful testicles. In contrast, women

* *Corresponding author.*
E-mail: raquel.bonelli@micro.ufrj.br (R.R. Bonelli).

http://dx.doi.org/10.1016/j.bjm.2017.06.001

Please cite this article in press as: Lourenço AP, et al. Antimicrobial resistance in *Neisseria gonorrhoeae*: history, molecular mechanisms and epidemiological aspects of an emerging global threat. *Braz J Microbiol.* (2017), http://dx.doi.org/10.1016/j.bjm.2017.06.001

develop symptomatic gonococcal cervicitis less frequently, presenting a slight increase in vaginal discharge, and rare vaginal bleeding unrelated to periods, or pain and a burning sensation when urinating. The absence of symptoms in men and women can lead to sustained infections. Complicated gonorrhea may cause infertility.[2]

Surveillance programs around the world

A report from the World Health Organization (WHO) indicated the occurrence of 78 million new cases of gonococcal infection in people aged 15–49 worldwide during 2012.[3] Despite the high rate of incidence, just a few countries, including the United States (U.S.), Canada, members of the European Union (EU), and Australia conduct broad surveillance programs on gonorrhea. Additionally, some countries from Latin-America and the Caribbean region (LAC), and countries from Western Pacific Region (WPR) and South East Asian Region (SEAR) joined the Gonococcal Antimicrobial Surveillance Program (GASP) that was conducted by WHO in the early 1990s. Since antimicrobial resistance is the main challenge associated with this microorganism, published reports emphasize the antimicrobial susceptibility profile of isolates. However, analysis of published data can be challenging, considering the breakpoints to define resistance vary across different surveillance programs. Regardless of this limitation, resistance is clearly an emerging phenomenon.

United States

In the U.S., the Centers for Disease Control and Prevention (CDC) supports the Gonococcal Isolate Surveillance Project (GISP). This program analyzes the first 25–30 *N. gonorrhoeae* isolates collected from men with gonococcal urethral-syndrome in sentinel laboratories located in five regions of the U.S. monthly. Surveillance includes analysis of demographic and clinical data, and antimicrobial susceptibility.[4] In recent years, the southern region reported the highest rate of gonorrhea, reaching 131.4 cases per 100,000 individuals in 2014.[5] The CDC estimates 820,000 new gonorrhea cases per year throughout the country.[6]

The STI Surveillance Network in the U.S. indicated higher incidence rates of gonorrhea in men who have sex with men (MSM) of any age, followed by men who have sex with women (MSW), and women, in 2014.[5] The network also reported that the risk of gonococcal infection declines with age, with most cases occurring in individuals under the age of 24.[5] In regards to antimicrobial resistance, GISP data has shown that nearly 30% of the isolates obtained from MSM, and 12% of those obtained from MSW were resistant to ciprofloxacin, with a minimum inhibitory concentration (MIC) $\geq 1\ \mu g/mL$ in 2014.[7] Irrespective of the sexual partners gender, in that same year, 0.7% of the isolates ($n = 38$) presented a decrease in cefixime susceptibility (MIC $\geq 0.25\ \mu g/mL$), and 2.5% showed azithromycin MIC alert values (MIC $\geq 2\ \mu g/mL$) (Table 1).[7] Moreover, a genomic epidemiology study with 236 GISP isolates obtained in 2009–2010 has shown that an *N. gonorrhoeae* cluster with decreased susceptibility to extended-spectrum cephalosporins (ESC) spread predominantly among MSM during those years.[8]

Canada

The National Surveillance Program (NSP) in Canada, implemented in 1985, provides data from different provinces across the country regarding *N. gonorrhoeae* antimicrobial susceptibility. Provincial public health laboratories (PL) send resistant isolates or isolates not submitted to antimicrobial susceptibility testing to the National Microbiology Laboratory (NML). In 2014, 2101 of 3089 *N. gonorrhoeae* isolates cultured in the PL were sent to NML. Interestingly, contrasting with other countries, NSP data showed a consistent diminishing trend in the ESC reduced susceptibility rates (from 7.6% in 2011 to 3.1% in 2014). However, regarding azithromycin, resistance rates rose from 0.4% in 2011 to 2.3% in 2014.[9]

Europe

In Europe, the extent of *N. gonorrhoeae* surveillance varies in different countries, according to national public health policies. However, data compiled from 21 countries composing the European GASP (Euro-GASP) conducted by the European CDC (ECDC) reported 50,001 cases in 2013.[10] Euro-GASP has two surveillance modules: one decentralized, based on the communication of antimicrobial susceptibility test (AST) results to ECDC; and the other centralized. In this case, participating laboratories send isolates to the Public Health England (London) for AST.[10]

In the most recent Euro-GASP report, each country was required to make a contribution of 100–200 isolates (depending on the number of gonorrhoeae cases detected by the national protocols), obtained during April/May and October/November 2013. With this sampling strategy, the number of isolates included in the study, compared to the total reported cases in each country, varied from less than 1% (in consequence of high incidence levels or very efficient surveillance) to more than 100% (when under-reporting from the national protocols occurred). For instance, the United Kingdom (U.K.), with a well-established national surveillance program, reported the most cases, 32,377 in 2013, followed by the Netherlands ($n = 4171$), Spain ($n = 3314$), and Hungary ($n = 1526$); while Portugal reported only 116 cases in the same year, and Germany did not provide any information on this matter. Notwithstanding such differences, these six countries contributed to the Euro-GASP analysis with similar number of isolates, varying from 88 in Hungary to 240 in the U.K. Considering such a heterogeneous collection, data compiled showed in Europe, in addition to the U.S., MSM as the main group at risk of developing gonorrhea. However, in contrast to the predominant age group in the U.S., most cases reported for European citizens were with individuals over the age of 25.[10]

Concerning detection of resistance, the Euro-GASP adopts breakpoints set by The European Committee on Antimicrobial Susceptibility Testing (EUCAST), which are lower than the values adopted by the U.S.[4,11,12] With this caveat in mind, the Euro-GASP reported ciprofloxacin and azithromycin resistance rates of 53% and 5%, respectively, among 1994 isolates studied in the program during 2013.[10] In contrast, for cefixime,

Please cite this article in press as: Lourenço AP, et al. Antimicrobial resistance in *Neisseria gonorrhoeae*: history, molecular mechanisms and epidemiological aspects of an emerging global threat. *Braz J Microbiol.* (2017), http://dx.doi.org/10.1016/j.bjm.2017.06.001