



# Enfermedades Infecciosas y Microbiología Clínica

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## Editorial

### *Neisseria gonorrhoeae* infection: State of the art

### Infección por *Neisseria gonorrhoeae*: Puesta a punto

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Gonorrhea, a condition on the rise with high associated morbidity and the possibility of sequelae, has become a major public health problem worldwide with considerable socio-economic consequences. In 2012 in Europe, 50,341 new cases of gonorrhea were reported, with an increase of 58% since 2008.<sup>1</sup> Accordingly, the European Centre for Disease Prevention and Control (ECDC) has coordinated the enhanced surveillance of sexually transmitted infections (ESSTI). And as part of this project, the European gonococcal antimicrobial surveillance program (Euro-GASP) was established in 2004.

Over the past several years, *Neisseria gonorrhoeae* has developed resistance to all the antimicrobials used in its treatment. First, it became resistant to sulfonamides, followed by penicillin, tetracycline and ciprofloxacin. Currently, the extended-spectrum cephalosporins (ESC), ceftriaxone (intramuscular) and cefixime (oral), are the only available first-line monotherapy options for gonorrhea in most settings. However, during the last decade, susceptibility to these antibiotics has decreased and clinical treatment failure has been reported, starting in 2000 in Japan and spreading worldwide in subsequent years.<sup>2–6</sup> Even though, high values of MIC for these antibiotics are not always related to treatment failure, being this one of the reasons for which there is not a consensus about clinical breakpoints for *N. gonorrhoeae*.

Today, the majority of European<sup>7</sup> guidelines recommend ceftriaxone 500 mg intramuscularly in combination with azithromycin 1 g single oral dose as first-line treatment for all uncomplicated gonorrhea cases. The dual treatment aims to mitigate against the selection of gonococci with reduced susceptibility to cephalosporins. It is important to clarify that there is no

evidence for antimicrobial synergy between ceftriaxone and either azithromycin or doxycycline. The main reason for recommending dual therapy is the difficulty for *N. gonorrhoeae*, as well as for other bacteria, to develop simultaneous resistance to two different antimicrobial classes, meaning that dual treatment creates a pharmacological barrier to the emergence of isolates exhibiting resistance to one component of the recommended therapy.

In 2013, the Euro-GASP<sup>1</sup> reported decreased susceptibility (DS) (>0.125 mg/L) to cefixime in 4.7% of isolates in Europe, a value found to be much higher among the strains received from Spain (15.1%). Moreover, of the 7 isolates showing decreased susceptibility to ceftriaxone (>0.125 mg/L), 6 were from Spain. This represents an increase compared to 2012 data, when the rate of decreased susceptibility to cefixime was 3.9% and only 3 isolates showed DS to ceftriaxone.

More alarming was the detection of the first three extremely-drug resistant (XDR) gonococcal isolates, in Japan<sup>3</sup> in 2009, France<sup>5</sup> in 2010 and Spain<sup>8,9</sup> in 2011. Fortunately since then no other strains have been isolated with high-level resistance to ceftriaxone.

*N. gonorrhoeae* has used all the known mechanisms to develop resistance, and those that affect cephalosporins are alteration of its main target, PBP2, through acquisition of *penA* mosaic alleles and non-mosaic *penA* alleles mutations; alteration of PBP1 through mutations in *ponA* gene; over expression of efflux pump MtrC-D-E though alterations in its repressor; and point mutations in *penB* which codes the major outer membrane porin, PorB1b.

In the study published by Cobo et al.<sup>10</sup> in this edition, the authors determined antimicrobial susceptibility of 65 gonococcus isolated from January 2012 to October 2014. Based on CLSI clinical breakpoints, they detected one isolate resistant to ceftriaxone and cefixime, but according to EUCAST breakpoints, they found 4 isolates resistant to cefixime (6.1%) and 3 isolates to ceftriaxone (4.6%). These results highlight the lack of consensus in this field.

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Also, 64.6% of the gonococcus was resistant to ciprofloxacin and 60–70% to tetracycline. No isolate was resistant to spectinomycin. These results are similar to those published by Serra-Pladevall et al. in 2011,<sup>11</sup> in which among 100 strains, they found 4% with decreased susceptibility to ceftriaxone and 11% to cefixime according to EUCAST breakpoints, but according CLSI breakpoints no strain showed decreased susceptibility to cefixime and only three to ceftriaxone.

Spectinomycin does not seem a good option for empirical first-line treatment because the difficulties in acquiring this antibiotic in most countries, the fear of rapidly selected resistance and its reduced effectiveness at clearing pharyngeal infections. If in the future *N. gonorrhoeae* continues to decrease susceptibility to ESCs, we can face an era of untreatable gonorrhea.

Detection of local sexual networks can help to target interventions toward places and population groups that are at high risk for STI acquisition. However, interventions in *N. gonorrhoeae* transmission networks are difficult, in part due to the high number of anonymous sexual contacts and/or reluctance to reveal sexual partners.<sup>12</sup> Molecular epidemiology techniques, as NG-MAST and MLST, have been used over time to study outbreaks and to identify individuals within the same sexual network. Molecular typing combined with epidemiological data can provide better insight into *N. gonorrhoeae* transmission patterns, which can help to improve intervention strategies.<sup>13</sup>

As described in the study by Cobo et al.,<sup>10</sup> the most frequent sequence types were ST1407 followed by ST5405, ST7192, ST2992 and ST5120. Although the STs distribution varies in each country and in each area, according Chisholm et al. in 2010,<sup>14</sup> G-1407 was the most prevalent genogroup (23%) among *N. gonorrhoeae* strains isolated in the 21 European countries. The NG-MAST clone ST1407, together with the MLST clone ST7363, were responsible for all confirmed cases of therapeutic failure with cefixime, and 3 of the 5 cases of failure with ceftriaxone. These two clones are the most widespread and they have demonstrated a considerable capacity to develop high-level resistance to cefixime and ceftriaxone.<sup>15</sup> As described by Chisholm et al., ST2992 was the second most prevalent ST in Europe and in Spain, and it was statistically associated with men who have sex with men (MSM).

Due to this alarming situation, it is crucial to keep monitoring *N. gonorrhoeae* antimicrobial susceptibility, to examine all gonococcal strains causing treatment failure or showing *in vitro* high-levels of ESC resistance, to identify its resistance determinants and establish appropriate MIC breakpoints for ESC resistance (together with

pharmacokinetic/pharmacodynamic simulations). Also it is essential to continue to update the treatment guidelines and keep the healthcare professionals aware of the current situation.

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