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Editorial

Impact of microbial resistance on therapeutic decisions in sexually transmitted infections☆

Impacto de la resistencia microbiana en las decisiones terapéuticas de las infecciones de transmisión sexual

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Sexually transmitted infections (STIs) are a constant challenge. They have become increasingly common, largely due to an increase in sexual relations among young people and the existence of core groups. In Spain, according to data from the *Red Nacional de Vigilancia Epidemiológica de las Enfermedades Transmisibles* [National Epidemiological Surveillance Network for Communicable Diseases], between 2005 and 2015 (latest available data) the gonorrhoea rate rose from 2.91 to 11.14, and the syphilis rate from 3.39 to 8.37 per 100,000 population, which gives us an idea of the size of the problem.

At the same time, we have witnessed considerable advances in the field of diagnosis thanks to the implementation of highly sensitive molecular biology techniques. The downside, however, is that they have encouraged us to abandon the classic culture techniques. This is of particular concern in the case of gonococcus, because not culturing means we lose the ability to perform susceptibility tests, which help orientate the individual treatment, and determine the epidemiology of the circulating resistance patterns, an essential factor for establishing empirical treatment guidelines. *Neisseria gonorrhoeae* (*N. gonorrhoeae*) has become resistant to all the antimicrobial agents we have been accustomed to administering as monotherapy, and there is now a very real risk that within a few years gonorrhoea will be untreatable. In an attempt to avoid, or at least delay, this scenario and preserve the activity of the last effective antimicrobial agents, the therapeutic guidelines advocate the use of dual therapy to reduce the likelihood of strains developing with simultaneous mutations to both antibiotics. The current recommendations advise the simultaneous administration of ceftriaxone and azithromycin, both with high rates of susceptibility, but not free of resistance. The spread of strains resistant to ceftriaxone has been a recognised problem for years, and is known to exist in Spain; we have to remember that two of the first three European strains resistant to third-generation cephalosporins were isolated in 2011 in Barcelona.[1]

Azithromycin is also a source of concern. Gonococcus has developed resistance that may compromise the efficacy of dual therapy, and *Mycoplasma genitalium (M. genitalium)* has also developed resistance, which in turn affects treatment guidelines for non-gonococcal urethritis (NGU).

It is evident that the emergence of resistance affects therapeutic decisions, and knowledge of susceptibility patterns therefore becomes essential. To contribute to this, two articles have been published in the current issue of this journal that provide us with very relevant information which may help decision-making in clinical practice.

In the first of the two, Fuertes de Vega et al.[2] studied the susceptibility patterns of gonococci isolates for a period of over five years in a tertiary hospital in Barcelona, and analysed the relationship of those patterns with the epidemiological and behavioural characteristics of the infected patients, with the aim of identifying patients at risk of suffering from resistant gonorrhoea. The authors detected a resistance rate of 9.1% to third-generation cephalosporins in the strains studied (10 strains). This finding was striking,

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particularly in view of the fact that, according to the latest surveillance reports available on the antimicrobial susceptibility of gonococcus in Europe,[3] out of 1932 gonococci studied in 2013, seven strains resistant to ceftriaxone were found (0.004%) and in 2014, out of 2015 gonococci, five strains were found to be resistant (0.003%). It seems therefore that, at least in Barcelona, ceftriaxone resistance is not uncommon, and hopefully their finding will motivate other research groups in Spain to carry out similar studies to expand our knowledge base, as we would be facing a serious problem if this resistance became generalised. The WHO establishes that the antimicrobial agents used as the first line in empirical treatment must be capable of curing 95% of infected patients,[4] and the data presented in this work surpass that number. Other even stricter criteria have been proposed, such as considering the lower limit of the 95% CI, or that sensitive strains represent 97%, or even 99%, of the total.[5]

There are no easy solutions to deal with multidrug-resistant gonococci, and novel approaches are therefore being tried, such as the use of oral antiseptic mouthwashes[6] to try to reduce the pharyngeal focus that is considered to generate resistance. The partially protective effects against gonococcal infection of the meningococcal B vaccine are also encouraging, which opens up new avenues of investigation.[7]

However, until the vaccine becomes a reality and new rapid techniques determine the resistance patterns at the "patient's bedside", physicians have to ask themselves how to identify patients infected with a resistant gonococcus. In an attempt to answer that question, the authors focused their study on a search for epidemiological and behavioural characteristics of patients which might be associated with antimicrobial resistance. They found infections caused by resistant strains to be associated with heterosexual men, in the older age groups, with concurrent STI and risky sexual behaviour, with the STI and risky behaviour probably indicators of previous antimicrobial treatments that may have led to the development of resistance. These findings are interesting because they provide physicians in the clinic with useful and practical evidence for identifying patients at high risk of suffering from multidrug-resistant gonorrhoea, and they do so in our environment, which means they have even more added value.

M. genitalium infections also pose an additional challenge. *M. genitalium* is known to cause urethritis, and there is increasing evidence of its role in cervicitis and pelvic inflammatory disease, which signifies an important advance in understanding these infections. In other extragenital locations, such as the rectum, the role of *M. genitalium* is still subject to debate, as it may sometimes be the result of self-inoculation, as was demonstrated in *Chlamydia trachomatis* (*C. trachomatis*) in women. Cultures in selective media for mycoplasma are not capable of recovering this pathogen, and it can only be detected by specific molecular biology techniques that many laboratories do not include in their portfolio of services, in some cases due to lack of knowledge of the actual prevalence of *M. genitalium*.

The article published in this journal by Asenjo et al.[8] addresses this issue, and their data obtained in the Autonomous Region of Madrid from urine samples from patients who attended general clinics or Accident and Emergency with symptoms of STI show a prevalence of 3.34%: 6.62% in males and 0.96% in females. These data add to those recently published by Barberá et al. in Barcelona,[8] where the prevalence was 10% in patients attending an STI unit. Different series published in other countries report a prevalence from 0.5% to 3.3%, in line with what was found by our group in Asturias (unpublished data). The data provided by Asenjo et al.[8] show that the prevalence of infection by *M. genitalium* is behind that of *C. trachomatis*, but ahead of *N. gonorrhoeae*, with these being pathogens for which the need for systematic analysis is beyond question. The authors advocate routine detection of *M. genitalium*, which is becoming easier to perform in laboratories thanks to the commercialisation of PCR techniques in multiple formats. What is not so easy to determine is the existence of resistance; as it cannot be cultured, we have to resort to the genomic detection of mutations through amplification and subsequent sequencing. We have been aware for some time of the existence of therapeutic failures with azithromycin, the treatment of choice. We have also been aware, as reported in a meta-analysis[9] in 2015, that the overall frequency of failures increases with time; it has risen from 14.7% in studies published before 2009 to 33% in studies published since then. It therefore appears to be important that we know the prevalence of resistance to macrolides in Spain, and that issue is also addressed in this article; they report resistance in 20% of the strains studied, below the 35% reported by Barberá et al. in their series.[10] Azithromycin is the cornerstone in the treatment of STIs. It is used in infections caused by *C. trachomatis* and *M. genitalium*, and in the dual therapy against gonococcus. Generalisation of resistance may compromise our ability to cure these infections. To the data on *M. genitalium* from Asenjo et al.,[8] we have to add those on gonococcus from Fuertes de Vega et al.,[2] who in their series in Barcelona found that 12.1% of strains had intermediate susceptibility and 5.2% were resistant to azithromycin.

We should perhaps ask ourselves what we are doing wrong to be witnessing the loss of another very important therapeutic weapon. In the United Kingdom (UK), the increased resistance of gonococci is attributed to the very common administration of azithromycin at a dose of 1 g to treat *C. trachomatis* infections diagnosed through the screening programme carried out in the UK and the fact that, in cases where there is co-infection with gonococcus, it exposes the patient to non-lethal doses that facilitate the development of resistance.[11] Similar rationales have been made for *M. genitalium*,[12] and here we have to take into consideration the fact that azithromycin accumulates inside the cells, so obviously has complex pharmacokinetics, and that with the 1 g regimens, we could be subjecting *M. genitalium* to insufficient doses that encourage the development of resistance.[13]

All this has led us to reconsider the dose of 1 g of azithromycin for the treatment of non-gonococcal urethritis (NGU). Using 100 mg of doxycycline every 12 h for 7 days, which is the first-line treatment for NGU in the European guideline,[14] has the advantage of being effective against *C. trachomatis*, but has poorer efficacy against *M. genitalium* and cannot be used in pregnant women. The second option, especially if the presence of *M. genitalium* is demonstrated, is to use azithromycin in an extended regimen, which administers a total of 1.5 g over five days, 500 mg on the first and 250 mg on the following four days, which seems to decrease the chances of inducing resistance and is more effective than doxycycline. A total dose of 2 g has also been proposed, divided into 1 g on the first day and 250 mg on the following four days. The difficulty with these extended regimens is ensuring patient adherence to the treatment, a not-insignificant problem in STI clinics. The 2016 European guideline for *M. genitalium* infections includes these questions,[15] and proposes as first line the extended regimen of 1.5 g of azithromycin over 5 days, citing 500 g of josamycin every 8 h for 10 days as an alternative and, as second line, moxifloxacin for 7–10 days. However, none of these regimens solves the problem of patient adherence, and added to that are problems of price, teratogenic potential in pregnant women and the already proven emergence of resistance to fluoroquinolones.[10] Another possibility would be pristinamycin, which is marketed in France and the USA, and it could be second line, although the problem is the price and 1 g has to be given every 6 h for 10 days. One option for the future could be solithromycin, a fluoroketolide with superior activity against *M. genitalium* than macrolides, doxycycline and quinolones, and which is also active against gonococcus and *C. trachomatis*.[16]

We see once again the constant challenge posed by STIs, for which we have no easy solutions. The possibility of following the example of gonococcal infection and giving dual therapy for NGU has been raised on various occasions, but solutions may also be on the horizon, thanks to the development of rapid diagnostic techniques that will not only tell us, "at the patient's bedside", the aetiology of the infection, but will also determine the presence of resistance mechanisms against available antimicrobial agents, which will help us administer effective targeted treatments.

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