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Letter to the Editor

Mycoplasma genitalium and fluoroquinolone resistance: From genotype to phenotype☆,☆☆

Mycoplasma genitalium *y resistencia a fluoroquinolonas: del genotipo al fenotipo*

Dear Editor,

We have read with great interest the abridged original "Targeted antibiotic therapy in *Mycoplasma genitalium* (MG) infections: analysis of mutations associated with resistance to macrolides and fluoroquinolones", published by Piñeiro et al.,[1] in which the prevalence of resistance to macrolides (16.3%) and fluoroquinolones (7.9%) is documented in a well-characterised cohort of 313 patients with MG infection. The work provides relevant information on the management of MG infection, even so, we would like to make some considerations.

On the one hand, in relation to the results obtained from the targeted therapy, a significant number of MG infections without initial mutations (13.9%) end up developing resistance after treatment with the macrolide azithromycin. This fact, in addition, is much more marked when azithromycin is used in single doses with respect to the extended regimen (31.3% *vs.* 7.0%; $p < 0.001$), which has already been described previously although with less consistency.[2] In this line, we would like to highlight a recent study conducted by Read et al., where a sequential strategy with doxycycline followed by the targeted antibiotic for MG, either azithromycin or fluoroquinolone moxifloxacin, is used for the treatment of non-gonococcal urethritis.[3] Thus, the previous use of doxycycline, together with higher doses of azithromycin, achieved resistance selection in only 2.6% of MG infections. It is also worth mentioning that the use of doxycycline in dual therapy could reduce the occurrence of resistance in MG.[4]

Finally, we would like to expand the study of resistance to fluoroquinolones exposed by Piñeiro et al. In a research study published by our group,[5] resistance-associated mutations were detected in 8.3% of infections, similar to the few studies carried out in other parts of Europe and presented in the supplementary table of the article by Piñeiro et al. (7.1%). However, as the authors point out, the presence of missense mutations in *parC* is not always associated with a therapeutic failure with fourth-generation fluoroquinolones, such as moxifloxacin (remember that other fluoroquinolones such as levofloxacin or ciprofloxacin are ineffective against MG).[4,6] There are few studies that correlate the presence of these mutations with the *in vivo* and *in vitro* activity of moxifloxacin. In 2013, Couldwell et al. recorded the first cases of therapeutic failure associated with the S83I mutation in ParC (MG numbering).[7] Later, Murray et al. observed similar events associated with the S83I and S83R mutations.[8] Finally, in a recent *in vitro* susceptibility study, Hamasuna et al. relate the S83I mutation, and subtly the D87Y mutation, with an increase in the minimum inhibitory concentration (MIC) of moxifloxacin.[6] In addition, from an enzymatic-structural point of view, mutations in the S83 and D87 amino acids of ParC in MG can affect the antibiotic–enzyme interaction and thus confer resistance to moxifloxacin.[9] In this sense, we consider that only the mutations in S83 and D87, and perhaps the D82N mutation due to its proximity to the antibiotic target region, should be considered as associated with resistance to fluoroquinolones in the study by Piñeiro et al. In contrast, the A69T mutations (previously described,[6] and not associated with an increase in the MIC of moxifloxacin), S95N (conservative change) and T101I (far from the target region) should not *a priori* be included in the above estimate. This would give a prevalence of mutations associated with fluoroquinolone resistance of 4.9–5.6%, and not 7.9%, as stated in Piñeiro et al. It would also be interesting if the authors could clarify which mutation in ParC was associated with the only therapeutic failure to moxifloxacin that they recorded (first well documented case in Spain).

On the other hand, the presence of mutations in GyrA (especially in M95 and D99), although it has been associated with therapeutic failure,[7] could have a less important effect associated with a reduction in the susceptibility of the bacterium to fluoroquinolone.[6,9]

Currently, in Spain, due precisely to the lack of therapeutic alternatives, infections that do not respond to macrolides should probably be treated with moxifloxacin, regardless of mutations in *parC* or *gyrA*. Doxycycline, pristinamycin (not marketed in Spain) or the fourth generation fluoroquinolone sitafloxacin (not marketed in Spain, with increased activity against MG) could be some alternatives.[2,4,6,10]

Conflicts of interest

None.

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How to limit bias in quasiexperimental studies☆

Cómo limitar los sesgos en estudios cuasiexperimentales

Dear Editor,

In the abridged original entitled "Dual prophylaxis with teicoplanin added to cefazolin in the prevention of prosthetic joint infection",[1] the authors try to demonstrate in a retrospective work the effectiveness of this regimen in the reduction of prosthetic joint infections caused by gram-positive cocci in primary and elective surgery of hip and knee arthroplasty. We would like to thank the authors for their contribution, and, while it is true that prophylaxis with beta-lactams plus teicoplanin could be considered in some situations, there is no quality evidence in the literature that supports the use of dual prophylaxis.[2–8] The authors recognise the limitations of their work as it is not a randomised study. However, in order to evaluate the effectiveness of an intervention in a quasi-experimental study, it is desirable, in addition to the usual bivariate analyses, to take into account other factors that have not been considered and which are frequent with before–after studies, such as mean regression, maturation effect and confounding variables. Regression to the mean is a phenomenon whereby when results are at their extreme points, they are most likely about to start the way back to a midpoint and, therefore, the change could have occurred without the intervention. The maturation effect is another phenomenon whereby the results obtained are due to changes that patients experience over time or seasonal cycles. To reduce the probability of these two phenomena occurring, it is necessary to observe the trend of the outcome variable before the intervention, and to make a longer observation after the intervention or the change of regimen to verify that there is neither a tendency to the mean nor a maturation effect. Confounding factors are frequent in all before-after studies, especially if the work is retrospective. In the work in question, a logistic regression would have made it possible to control various confounding factors, such as the Charlson index and transfusions, which were significantly more frequent in the control group, or colonisation by methicillin-resistant *Staphylococcus aureus* which, although without significant differences, occurred in twice as many patients in the control group. In this type of work, it is also desirable to reflect the adherence to preventive measures that have been proven to be effective in preventing surgical infection such as the decolonisation of *S. aureus* carriers, the adequate preparation of patients (hygiene, shaving, disinfection of the skin), the control of perioperative blood glucose, adherence to antibiotic prophylaxis used or changes in surgical practice (drainage, etc.). The "standard" logistic regression in this type of study does not estimate the trend or the slope of the changes after an intervention, so the results obtained may be biased and the changes in time (trend) may not be detected. Segmented regression techniques make it possible to estimate the association between an intervention and the outcome variable controlling for confounding factors, and estimate the changes in the mean at different levels (interception) and trends (slopes). The limitations of these statistics are that they require data from multiple time intervals before and after the intervention (≥10 observations/model and parameter to be studied) to avoid over-adjustments, but it is possible to have ≥24 observations (e.g. 12 months before and 12 months after the intervention). Potential stationary changes can even be detected.

Quasi-experimental studies are widely used to observe the impact of certain interventions in the prevention and treatment of osteoarticular infection due to the difficulty of conducting randomised clinical trials, so it is important that they are carried out with an appropriate methodology. Otherwise, biased results may lead to inappropriate clinical practice. We encourage all researchers to take these concepts into account when designing and analysing the results of a quasi-experimental work. We believe that the results of this study may encourage conducting a randomised trial, but should not lead to a change in clinical practice.

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