

6. Hamasuna R, Le PT, Kutsuna S, Furubayashi K, Matsumoto M, Ohmagari N, et al. Mutations in ParC and GyrA of moxifloxacin-resistant and susceptible *Mycoplasma genitalium* strains. *PLoS ONE*. 2018;13:e0198355.
7. Couldwell DL, Tagg KA, Jeoffreys NJ, Gilbert GL. Failure of moxifloxacin treatment in *Mycoplasma genitalium* infections due to macrolide fluoroquinolone resistance. *Int J STD AIDS*. 2013;24:822–8.
8. Murray GL, Bradshaw CS, Bissessor M, Danielewski J, Garland SM, Jensen JS, et al. Increasing macrolide and fluoroquinolone resistance in *Mycoplasma genitalium*. *Emerg Infect Dis*. 2017;23:809–12.
9. Aldred KJ, Kerns RJ, Osheroff N. Mechanism of quinolone action and resistance. *Biochemistry*. 2014;53:1565–74.
10. Kikuchi M, Ito S, Yasuda M, Tsuchiya T, Hatazaki K, Takashi M, et al. Remarkable increase in fluoroquinolone-resistant *Mycoplasma genitalium* in Japan. *J Antimicrob Chemother*. 2014;69:2376–82.

Miguel Fernández-Huerta^a, Judit Serra-Pladevall^a,
Juliana Esperalba^a, Mateu Espasa^{b,*}

^a Servicio de Microbiología, Hospital Universitario Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

^b Servicio de Microbiología, Corporació Sanitària Parc Taulí, Universitat Autònoma de Barcelona, Barcelona, Spain

* Corresponding author.

E-mail address: mespasa@tauli.cat (M. Espasa).

2529-993X/ © 2019 Elsevier España, S.L.U. and Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica. All rights reserved.

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.

References

1. Barbero-Allende JM, García-Sánchez M, Montero-Ruiz E, Vallés-Purroy A, Plasencia-Arriba MÁ, Sanz-Moreno J. Dual prophylaxis with teicoplanin and cefazolin in the prevention of prosthetic joint infection [Article in English, Spanish]. *Enferm Infecc Microbiol Clin*. 2019;37:588–91.
2. Sewick A, Makani A, Wu C, O'Donnell J, Baldwin KD, Lee GC. Does dual antibiotic prophylaxis better prevent surgical site infections in total joint arthroplasty? *Clin Orthop Relat Res*. 2012;470:2702–7.
3. Ponce B, Raines BT, Reed RD, Vick C, Richman J, Hawn M. Surgical site infection after arthroplasty: comparative effectiveness of prophylactic antibiotics: do surgical care improvement project guidelines need to be updated? *J Bone Joint Surg Am*. 2014;96:970–7.
4. Branch-Elliman W, Ripollone JE, O'Brien WJ, Itani KMF, Schweizer ML, Perencevich E, et al. Risk of surgical site infection, acute kidney injury, and *Clostridium difficile* infection following antibiotic prophylaxis with vancomycin plus a beta-lactam versus either drug alone: a national propensity-score-adjusted retrospective cohort study. *PLoS Med*. 2017;14:e1002340.
5. Liu C, Kakis A, Nichols A, Ries MD, Vail TP, Bozic KJ. Targeted use of vancomycin as perioperative prophylaxis reduces periprosthetic joint infection in revision TKA. *Clin Orthop Relat Res*. 2014;472:227–31.

[☆] Please cite this article as: del Toro López MD, Rodríguez-Baño J. Cómo limitar los sesgos en estudios cuasiexperimentales. *Enferm Infecc Microbiol Clin*. 2019. <https://doi.org/10.1016/j.eimc.2019.04.009>

6. Tornero E, García-Ramiro S, Martínez-Pastor JC, Bori G, Bosch J, Morata L, et al. Prophylaxis with teicoplanin and cefuroxime reduces the rate of prosthetic joint infection after primary arthroplasty. *Antimicrob Agents Chemother.* 2015;59:831–7.
7. Soriano A, Popescu D, García S, Bori G, Martínez JA, Balasso V, et al. Usefulness of teicoplanin for preventing methicillin-resistant *Staphylococcus aureus* infections in orthopedic surgery. *Eur J Clin Microbiol Infect Dis.* 2006;25:35–8.
8. Capdevila A, Navarro M, Bori G, Tornero E, Camacho P, Bosch J, et al. Incidence and risk factors for infection when teicoplanin is included for prophylaxis in patients with hip fracture. *Surgery.* 2016;17:381–4.

María Dolores del Toro López^{a,b,*}, Jesús Rodríguez-Baño^{a,b}

^a *Unidad Clínica de Enfermedades Infecciosas, Microbiología Clínica y Medicina Preventiva, Hospital Universitario Virgen Macarena, Sevilla, Spain*

^b *Departamento de Medicina, Universidad de Sevilla, Instituto de Biomedicina de Sevilla, Sevilla, Spain*

* Corresponding author.

E-mail address: mdeltoro@us.es (M.D. del Toro López).

2529-993X/ © 2019 Elsevier España, S.L.U. and Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica. All rights reserved.

Reply to “How to limit bias in quasiexperimental studies”[☆]



Respuesta a «Cómo limitar los sesgos en estudios cuasiexperimentales»

Dear Editor,

First, we would like to thank the authors of the letter “How to limit bias in quasi-experimental studies”¹ for the interest shown in our publication and their comments on it.

The goal of our work² is to describe our experience after replacing the prophylaxis recommended in the clinical practice guidelines for cephalosporin arthroplasty surgery,³ by a regimen of cefazolin + teicoplanin, after detecting that in our centre a high percentage of joint prosthesis infections were due to bacteria resistant to cephalosporins, particularly gram-positive, and to observe the favourable results obtained in other centres with the addition of a dose of teicoplanin to the usual dose of cephalosporin.⁴

We agree with the authors that inherent to such a study is a series of methodological limitations that must be taken into account when assessing their results and making decisions based on them. By using a historical comparison group, that of the patients immediately prior to the change in regimen, the study is subject to the possibility of bias. It is very true that, as a result of the lack of randomisation, there are some differences between the groups, such as a higher comorbidity index and a higher percentage of patients transfused in the comparison group. We do not believe that the difference in colonisation by methicillin-resistant *Staphylococcus aureus* is important because, although in relative value there were twice as many patients in the control group, the absolute number of patients is small (10 and 5 in each group, and it is not statistically significant) and all were decolonised prior to surgery (in fact, none of these patients suffered from an infection, so it does not affect the results). We did not mention the adherence to the rest of prophylactic measures because the only difference during the control period and the intervention period was the addition of teicoplanin, keeping the rest of the measures the same (hygiene, use of antiseptics, early removal of probes and drains, control of perioperative blood glucose, etc.).

We agree with the theoretical comments on the methodological or statistical aspects of the study, but most, if not all, of them are the result of having a sample size that, in our case, would take many years to achieve. Of course, a longer period of observation would be convenient to corroborate the results, limiting the bias mentioned by the authors, and making the result of the

intervention more robust. As the authors, we undertake to publish them when we have them.

Obviously, randomised clinical trials provide a better level of evidence and make it possible to avoid this bias. However, conducting them offers difficulties known by all and also raises the ethical question of whether to use a control group maintaining cefazolin, knowing that in our centre an important part of the bacteria that cause joint prosthesis infection are resistant to it, and thus subject these patients to an excess risk of infection when favourable experiences have already been reported by adding a dose of glycopeptide, with a favourable adverse effects profile.^{4,5}

In our opinion, beyond the statistical limitations, which we recognise, we believe that our work offers plausible results for two reasons. In the first place, the results are consistent, since adding an antibiotic that has activity specifically against methicillin-resistant gram-positive cocci exclusively reduces these infections and, on the other hand, gram-negative infections remain unchanged. On the other hand, it reproduces the results of other studies conducted with similar regimens.⁴

Whether or not this work should lead to a change in the usual clinical practice, each reader should evaluate it, in the event that it is useful to them if they have a problem similar to ours. Some authors already wonder if, given the epidemiological change of surgical infection in general, and prosthetic infection in particular, mainly referring to the increasing rate of resistance to antibiotics, current antibiotic prophylaxis guidelines (backed by clinical trials conducted in the last century) are still effective today.^{6,7} The methodological limitations can make our conclusions more or less debatable, but, undoubtedly, they do not discard them, until a work with similar or better methodology is published that refutes them.

Conflicts of interest

José María Barbero declares that he has received fees for conferences from the pharmaceutical company Angelini. Jose Sanz Moreno declares that he has received fees due to teaching and consultancy collaborations from the pharmaceutical companies Gilead, Viid and Janssen. All other authors declare that they have no conflicts of interest.

References

1. Del Toro López MD, Rodríguez-Baño J. Cómo limitar los sesgos en estudios cuasiexperimentales. *Enferm Infecc Microbiol Clin.* 2019;38:48–9.
2. Barbero-Allende JM, García Sánchez M, Montero-Ruiz E, Vallés Purroy A, Plasencia-Arriba MA, Sanz-Moreno J. Profilaxis dual con teicoplanina añadida a cefazolina en la prevención de la infección de prótesis articular. *Enferm Infecc Microbiol Clin.* 2019;37:588–91.

[☆] Please cite this article as: Barbero-Allende JM, Montero-Ruiz E, Vallés-Purroy A, Sanz-Moreno J. Respuesta a «Cómo limitar los sesgos en estudios cuasiexperimentales». *Enferm Infecc Microbiol Clin.* 2019;2020:46–47.