LETTERS TO THE EDITOR

Novel Indicators for Enhancing the Clinical Outcome Metrics of Antimicrobial Stewardship Programs

To the Editor—One of the main challenges that face antimicrobial stewardship programs (ASPs) is proving their effect on the incidence of multidrug-resistant (MDR) microorganisms and the related mortality.[1] It can be especially difficult in centers with a limited incidence of bacterial resistance, where large samples may be required to demonstrate significant changes.[2] This might be a reason to assess the ecological impact of interventions through the incidence of all MDR isolations, including colonizations,[1] but such assessments may not reflect their effect on the incidence of clinical infections.

An educational ASP implemented in our hospital in 2011 proved to be effective in reducing the inappropriate use of antimicrobials as well as global antibiotic consumption in the center.[3] In a recent publication,[4] we were able to show that the sustained effect of our program on antibiotic use produced a reduction of the incidence and mortality of nosocomial bloodstream infections (BSIs) by MDR bacteria and *Candida* spp. To solve the aforementioned drawbacks, we employed an ecologic interrupted time-series study and pooled as a sole indicator the incidence of all MDR bacteria and *Candida* spp producing BSIs, considering that they all share as a preferential risk factor the previous exposure to antibiotics. Additionally, we measured the changes in crude death rate (deaths per 1,000 occupied bed days) of these infections.

We found several important advantages in these 2 novel indicators: (1) pooling several mechanisms of resistance in the same indicator improved the power of the sample to show the effects of the reduction of antibiotic pressure in the center; (2) assessing infections instead of colonization provided information on the clinical benefits of the intervention; and (3) measuring the absolute reduction in mortality using the crude death rate let us show the burden of mortality avoided by the program. This metric is relevant because reductions in the rate of mortality of infections can be difficult to prove when they depend on multiple factors that require complex patient-level analyses. But if antibiotic pressure (and subsequently bacterial resistance) is reduced in a center, a reduction in mortality in absolute terms should be expected, as shown in our article.[4]

Researchers interested in this approach should be aware of certain considerations. The pooled analysis of MDR does not replace the surveillance of specific mechanisms of resistance; otherwise, occasional outbreaks could pass unnoticed. It also requires an analysis of the possible influence on results of infection control programs coexisting with the ASP. In this case, if different interventions sequentially occur during the study period, a joinpoint regression analysis may allow researchers to establish mathematically (ie, not subjectively) when the inflection point occurs.[5] Regarding the assessment of mortality, precautions should also be adopted to prevent ecologic bias. For instance, the total number of cultures and incidence of susceptible bacteria should be measured because a decrease in the incidence of MDR-produced deaths could also be explained by a reduction in diagnostic tests or by general improvements in the prevention of infections. Antimicrobial stewardship programs aiming to reduce antibiotic consumption should also monitor the mortality produced by susceptible bacteria to ensure the safety of the intervention.

In conclusion, we propose 2 novel indicators that, used properly, could enhance the ability of ASP to prove their clinical and ecological impact in a feasible and objective way.

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José Molina, MD;[1]
Germán Peñalva, MD;[1]
José A. Lepe, PhD;[1]
Raquel Valencia, PhD;[1]
María V. Gil-Navarro, PhD;[2]
José M. Cisneros, PhD[1]

Affiliations: 1. Clinical Unit of Infectious Diseases, Microbiology and Preventive Medicine, Institute of Biomedicine of Seville (IBiS), University Hospital Virgen del Rocio, CSIC, University of Seville, Seville, Spain; 2. Clinical Unit of Pharmacy, Institute of Biomedicine of Seville (IBiS), University Hospital Virgen del Rocio, CSIC, University of Seville, Seville, Spain.

Address correspondence to José Miguel Cisneros Herreros, Clinica Unit of Infectious Diseases, Microbiology and Preventive Medicine, University Hospital Virgen del Rocío, Seville (Spain). Av/ Manuel siurot s/n 41013 Seville Spain (jmcisnerosh@gmail.com).

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Determining the Attributable Costs of *Clostridium difficile* Infections When Exposure Time Is Lacking: Be Wary of "Conditioning on the Future"

To the Editor—We would like to comment on a recent paper by Mehrotra et al,[1] which presents an investigation of the attributable costs of *Clostridium difficile* infection (CDI) in pediatric patients. While there is an increasing body of literature on the costs of CDI, this study focused on the much less investigated area of pediatric inpatients.[2] While more reliable estimates in this field are needed, we would like to stress the importance of considering the methodological particularities of hospital-acquired infection and the scope and limitations of routine data for such analyses. We briefly outline the distinction of infections types by acquisition because this has important implications for the appropriate calculation of the attributable costs.

From the hospital perspective, the economic burden of *C. difficile* infections can be divided into 3 components: (1) hospital-acquired infections, (2) community-acquired infections that were the main reason for hospitalization, and (3) community-acquired infections that were not the main reason for hospitalization.

(1) Hospital-acquired *C. difficile* infections are those that occur 48 hours or more after admission, and therefore, *C. difficile* was not the main reason for hospitalization (ie, the main diagnosis group is not 008.45). For estimating the additional costs, these patients must be compared to appropriate controls. When selecting controls, the time-dependent nature of hospital-acquired infections should be taken into account (eg, via time-to-exposure matching).[3] In addition, clustering costs within main diagnosis groups should be accounted for (eg, via comparisons within the same main diagnosis only).[4] Because main diagnoses are the retrospectively coded principal reason for hospitalization, this ensures baseline comparability and prevents matching patients that incur different costs irrespective of the *C. difficile* infection. Finally, only comorbidities that cannot plausibly occur as a consequence of an infection should be used for risk adjustment.[4,5] This is usually an issue when using routine data, which often lack a time stamp for secondary diagnoses, so that it is possible to control for an outcome rather than a risk factor, thereby artificially reducing the effect. The authors acknowledge the time dependency of hospital-acquired infection but are faced with the unavailability of exposure time. The proposed matching (or adjusting) for total length of stay, however, may not be a second-best solution because it is subject to "conditioning on the future" by controlling for an outcome. This condition violates major epidemiological principles for analysis of such data.[6] Because *C. difficile* infections chiefly influence length of stay, which is a major driver of costs, the estimates likely substantially underestimate the true effect.[7] In addition, these authors failed to consider cost clustering within main diagnosis group, and they only adjusted for a limited set of main diagnosis and comorbidities. Thus, baseline costs between cases and controls are not necessarily comparable.

(2) For calculating the burden of *C. difficile* infections that were the main reason for hospitalization (ie, the main diagnosis group is 008.45), no control group, no time-to-exposure matching, no cost clustering and/or risk adjustment are necessary. The (additional) cost of *C. difficile* infections within this patient group is just the total cost of hospitalization because, per definition, the patient would not have been admitted to the hospital without the infection.

(3) The last group consists of patients, with a *C. difficile* infection that was detected <48 hours after admission but was not the main reason for hospitalization (ie, the main diagnosis group is not 008.45). These patients should be compared to controls within the same main diagnoses and baseline risk adjustment should be used as discussed above. Time-to-exposure matching is not necessary.

The lack of the timing of infection not only leads to time-dependent bias, it also makes it impossible to distinguish between these 3 infection types. This causes 2 issues in the study. First, the hospital-acquired cases in the sample were subject to the time-dependent bias and their effect was therefore overestimated. Controlling for length of stay was not sufficient to obtain appropriate estimates. In addition, being unable to distinguish between the 3 types of infections and analyzing all *C. difficile* cases together can lead to blurred estimates because the estimates partly present the (overestimated) incremental cost for hospital-acquired *C. difficile*.

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