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., 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. 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 infection 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.

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). In addition, clustering costs within main diagnosis groups should be accounted for (eg, via comparisons within the same main diagnosis only). 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, comorbidities that cannot plausibly occur as a consequence of an infection should be used for risk adjustment. 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. Because C. difficile infections chiefly influence length of stay, which is a major driver of costs, the estimates likely substantially underestimate the true effect. 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.

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.

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. Another part of the estimates consisted of the difference between the costs of a patient being admitted to the hospital for C. difficile and the costs of a patient with a different disease but a similar comorbidity set.

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