Commentary

Antimicrobial resistance and patient outcomes: the hazards of adjustment

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See related research by Zavascki *et al.*, http://ccforum.com/content/10/4/R114

Abstract

Outcomes studies of infections with resistant bacteria often do not account appropriately for intermediate variables – events in the causal pathway between the exposure and the outcome – when controlling for confounders. We discuss how failure to distinguish between confounders and intermediate variables can bias the analysis, and we address methods of approaching this issue.

Antimicrobial resistance in invasive infections is associated with adverse outcomes, including increased mortality, increased length of stay, and increased hospital costs [1-4]. A number of reasons have been suggested for this observation: a delay in institution of effective therapy, inferior definitive therapy as compared with that available for susceptible bacteria, and greater virulence of some resistant strains [3-5]. *Pseudomonas aeruginosa*, although inherently resistant to numerous antibiotics, appears to be no exception to this phenomenon: a number of studies have demonstrated an association between still broader resistance and mortality in infections caused by this pathogen [6,7].

In the previous issue of *Critical Care*, Zavascki and colleagues report the results of a prospective cohort study of mortality associated with hospital-acquired pneumonia caused by *P. aeruginosa* [8]. The authors looked specifically at the effect on outcome of the production of metallo-β-lactamase (MBL), a group of carbapenamases that hydrolyze all β-lactam antibiotics with the exception of aztreonam. In crude analysis of 150 patients, MBL production was significantly associated with increased 30-day mortality, with a nearly twofold relative risk. In multivariable analysis, MBL production remained a significant predictor of mortality until inclusion of the variable 'appropriate antimicrobial therapy', which caused MBL production to lose its significance. The authors postulate that the collinearity between these two covariates demonstrates that MBL production leads to the administration of inappropriate therapy, which in turn increases mortality.

Another way to describe this phenomenon is that appropriateness of therapy is an intermediate variable; that is, a variable in the causative pathway between infection with a resistant organism (the exposure) and mortality (the outcome). Accordingly, infection with an MBL producer leads to inappropriate therapy, which in turn leads to increased mortality. This scenario is a prime example of how adjustment for intermediate variables may bias the association between exposure and outcome, often reducing its magnitude and even depriving it of statistical significance. In the case of inappropriate therapy and resistance, Zavascki and colleagues have correctly presented both models (with and without the variable appropriateness of therapy), and plausibly concluded that MBL production leads to increased mortality by causing a delay in appropriate therapy [8].

Zavascki and colleagues, however, do not account for adjustment for the variables 'severe sepsis/septic shock' and 'bacteremia' in the same manner. These are also intermediate variables, in the causative pathway between the exposure and the outcome. The methodologic flaw of adjusting for intermediate variables without accounting for them as such is common to many outcome studies of infections in seriously ill patients [9-11], and may bias the results [12,13].

Control for confounding variables is crucial in analysis of outcomes studies, as factors such as the patient demographics, the severity of underlying illness, and the comorbid conditions may be closely associated with both the exposure (e.g. resistance, infection) and the outcome studied (e.g. death, length of stay, cost). Failure to adjust for such

APACHE = Acute Physiology and Chronic Health Evaluation; MBL = metallo-β-lactamase.

confounders will bias the results and may lead to erroneous conclusions. Adjustment for these confounders may be accomplished using validated tools such as the Acute Physiology and Chronic Health Evaluation (APACHE) score when studying the effect of intensive care unit events (such as acquisition of a resistant pathogen) on outcomes (such as mortality) [14].

Treating a confounder as an intermediate variable, or conversely, treating an intermediate variable as a confounder, may lead to false results. How, then, do we differentiate between the two? Both intermediate variables and confounders are associated with the outcome. The intermediate variable, however, unlike the confounder, is caused by the exposure. In the case of resistant hospital-acquired pneumonia, it is plausible that the natural course of the disease would entail pneumonia followed by bacteremia, leading to sepsis, septic shock, and consequent death. Nonintermediate variables such as the Charlson score, by contrast, predate the infection and are therefore not in the temporal pathway between infection and death.

A more subtle problem arises when an intermediate variable is itself a confounder. An example of this potential pitfall occurs when adjusting for physiological scores measured at the time of the onset of the infection. Recording the APACHE score at the onset of infection is problematic since the patient may already demonstrate signs of infection. In such a case, the APACHE score itself, utilized by the investigator to adjust for confounding, becomes an intermediate variable. The APACHE score should ideally be recorded before any signs of infection appear, but such data are often not available.

In constructing multivariable models in outcomes studies, the investigators must identify which of the included covariates are intermediate variables. These variables must be accounted for in the analysis in a way that accounts for their being intermediate [12,15]. Our suggestion for a way to manage such analyses is to run the model with and without each intermediate variable, individually and together, in order to determine as accurately as possible the true independent predictors of the outcome under study.

Zavascki and colleagues, in the first reported outcomes study of MBL production in patients with hospital-acquired pneumonia, have appropriately accounted for the intermediate variable of inappropriate therapy, and thereby provided a plausible explanation for the effect of resistance on mortality via its effect on appropriateness of therapy [8]. We stand to gain even more insight into the effect of resistance on mortality if further analyses of these data take appropriate account of the additional intermediate variables of sepsis/septic shock and bacteremia. As multidrug resistance is an emerging threat among critically ill patients, future studies will be required to quantitate its effect in infections within this patient population. Analyses that deal appropriately with intermediate variables, including sepsis, shock, and physiological scores at time of infection, stand to provide the most valid information.

Competing interests

The authors declare that they have no competing interests.

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