Septic Shock Should Be Included in Multivariable Models Analyzing the Effect of Empirical Antibiotic Therapy on Mortality

To the Editor—In a recent issue of Clinical Infectious Diseases, McGregor et al. [1] reviewed the methods used to analyze the association between antibiotic therapy and mortality among bacteremic patients. We completely agree with the concerns stated by these authors regarding the frequency of incorrect reports of multivariable analysis and, most worrisome, the possible misuse of these statistical methods. More than 15 years ago, Concato et al. [2] first highlighted the need for improvements in the reporting and conducting of multivariable analysis in medical literature. This issue has remained in the limelight but has been unsolved [3, 4].

From a statistical point of view, multivariable models can be used in 2 different ways: (1) to develop predictive models that estimate the likelihood of an outcome for a given patient from a set of observations (e.g., APACHE or Fine score) and (2) to analyze the specific effect of a variable on a particular outcome while adjusting for differences in other factors [5–7] (e.g., to assess the influence of empirical therapy on mortality among bacteremic patients [descriptive models]). When logistic regression analyses are conducted in this descriptive manner, considering all potential confounders, the specific recommendation made by McGregor et al. [1], which emphasizes considering septic shock as an intermediate variable and, therefore, not adjusting for this factor in multivariable analyses in which the effect of antibiotic therapy on mortality is assessed among bacteremic patients. An intermediate variable is defined as “a variable in a causal pathway that causes variation in the dependent variable and is itself caused to vary by the independent variable” [8]. In light of this definition, it is quite obvious that presentation with septic shock cannot vary by empirical therapy; thus, it should not be considered to be intermediate between the exposure to a given empirical antibiotic regimen (independent variable) and the outcome (dependent variable). On the contrary, presenting with septic shock may modify general management or specific antibiotic treatment, and some antibiotics are preferably used in patients experiencing septic shock [9]. Consequently, the possibility of septic shock being an either positive or negative potential confounder of the association between empirical therapy and mortality cannot be dismissed. For instance, an antibiotic preferably used to treat patients with septic shock would be penalized in a multivariable analysis evaluating mortality. Imagine a cohort of bacteremic patients in which subjects with septic shock were mostly treated with carbapenems. If septic shock were not included in the multivariable model, treatment with carbapenems may be incorrectly considered to be a risk factor for mortality. In summary, we consider that not adjusting for septic shock in multivariable models analyzing the effect of empirical antibiotic therapy on mortality may lead to incorrect conclusions.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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References

Reply to Leibovici and Paul and to Marcos et al.

To the Editor—We thank Leibovici and Paul [1] and Marcos et al. [2] for their interest in our article [3]. Both critiques presented interesting issues that highlight the need for high-quality epidemiologic studies of the association between appropriate antibiotic therapy and mortality among bacteremic patients.

Leibovici and Paul [1] expressed several comments regarding the differences between traditional meta-analyses and systematic reviews of epidemiologic methods. We agree that a free-text search would likely have had greater sensitivity than did the Medical Subject Heading term search that we used; however, we believe that our search method, which achieved high specificity, was sufficient for the purposes of our study. Our systematic review aimed to evaluate methodologies in the hope of providing useful insight into the optimal epidemiologic methods for evaluating the association between appropriate antibiotic therapy and patient mortality among bacteremic patients. If our article had been a meta-analysis aimed at estimating a...
pooled measure of effect, a higher-sensitivity search would certainly have been the best choice.

With regard to the criticisms that we included publications that may have had overlapping study populations and that we did not provide estimates of the measure of effect observed in the studies that we reviewed, we again refer to the primary aim of our review. Because our focus was on evaluating study methods, we did not discriminate between publications with total or partial overlaps in the study population, nor did we feel that it was necessary to include observed measures of effect. We agree that, in the case of meta-analyses, it is critical not to include publications that are based on the same study and to provide measures of effect (as a pooled estimate of the measure of effect) for the association being evaluated.

In reference to the criticisms that we included studies that contradicted our study inclusion and/or exclusion criteria or that we mistakenly categorized a study as not having performed a multivariable analysis, we can only reassure that we made every effort to abide by the criteria that we set and to ensure the accuracy and integrity of our publication. The publication that Leibovici and Paul [1] referenced included a multivariable analysis of appropriate therapy and septic shock [4]; however, this association was not the subject of interest for our review. Thus, we were correct in our determination that this study lacked a multivariable analysis of the association between appropriate antibiotic therapy and mortality.

Finally, we agree that there are additional methodological issues that could have been addressed. However, because of space limitations, we focused on the specific epidemiologic subjects that were of particular importance to studies of appropriate therapy and mortality among bacteremic patients.

Marcos et al. [2] disagreed with our recommendation that investigators should not statistically adjust for septic shock in studies of the appropriateness of antibiotic therapy and mortality among bacteremic patients. The authors contended that septic shock is not an intermediate variable in the causal pathway between antibiotic therapy and mortality. In contrast, we believe that septic shock is an intermediate variable; thus, adjusting for septic shock would result in an attenuated estimate of effect of appropriate antibiotic therapy on mortality. Among bacteremic patients, the development of septic shock is in the causal pathway to mortality. Furthermore, patients receiving inappropriate antibiotic therapy may be more likely to experience a worsening progression of bacteremia, including the development of septic shock and, ultimately, death. Thus, there is a need to study the association between appropriate antibiotic therapy and mortality. We do, however, acknowledge the exception that, in some instances, therapy may be initiated after the onset of septic shock.

In this situation, septic shock may be associated with the receipt of more-aggressive therapy; thus, investigators should consider controlling for potential confounding by indication using either design or statistical analysis techniques [5–8]. This point of contention highlights the need for researchers to stipulate the causal model that they are using to guide their multivariable analyses, as well as the time at which time-dependent covariates are measured [9, 10].

In summary, we agree that a meta-analysis of the association between appropriate antibiotic therapy and mortality would be both informative and useful, but at present, the methodological heterogeneity among existing studies would render such an analysis uninformative. It is our hope that our review will provide guidance for the design and analysis of future research and, thus, allow for a future meta-analysis of studies that have a high degree of internal validity and generalizability.

Acknowledgments

Potential conflicts of interest. J.C.M. and J.P.F: no conflicts.

References


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Clinical Infectious Diseases 2007;45:1401–2
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Strengthening Adult and Adolescent Immunization: A Policy without a Home

To the Editor—The American Academy of Family Physicians is a strong advocate for widespread provision of Advisory Committee on Immunization Practices–recommended vaccines to children, ado-