Excess Shock and Mortality in *Staphylococcus aureus* Related to Methicillin Resistance

Str—The study by Soriano et al. [1] provides additional information toward the goal of understanding the impact of antibiotic resistance on patient outcome. The study data are an important contribution to the growing body of literature on this subject; however, there are several points worth making with regard to the stated methodology and results of the study. For example, it should be noted that, in the cohort study, methicillin-resistant *Staphylococcus aureus* (MRSA) was found to be an independent risk factor for the development of shock. To determine predictors of mortality, the authors then used shock as a predictor in the nonconditional logistic regression analysis, even though their definition of “bacteremia” required the presence of clinically apparent signs and symptoms of sepsis, and even though their definition of “mortality” required that it be related to the episode of bacteremia. If shock is an intermediate step in the direct causal pathway between MRSA and mortality, then it is not a confounder and should not be controlled for in the logistic regression analysis [2]. In this instance, controlling for shock would be similar to controlling for coronary artery disease in a study that looks at the risk of cholesterol in the development of myocardial infarction and then concludes that cholesterol is not a risk factor for myocardial infarction.

In addition, an atypical method of performing a case-control study was used. The typical method is to select case patients on the basis of an outcome such as death, to compare the case patients with control subjects who are matched but who did not die, and then to look for predictors of the outcome. Soriano et al. [1] used MRSA and methicillin-susceptible *S. aureus* (MSSA) bacteremias as the outcomes, and they included shock and related mortality as predictors in the model, which is somewhat difficult to interpret. A strict interpretation of this model might be that future occurrences of death and shock are predictors of current MRSA bacteremia.

The authors state that, in the conditional logistic regression analysis of the case-control study, shock was no longer associated with MRSA bacteremia, although they cite an OR of 2.19. This is very similar to the OR of 1.94 that MRSA predicted shock in the nonconditional logistic regression analysis of the cohort study. The wider CIs found in the conditional logistic regression analysis probably reflect a loss of statistical power and were secondary to the smaller numbers of patients in the case-control study.

Finally, the authors state that the only real difference between the case-control and cohort studies was that there was better control for underlying disease in the case-control study. This overstates the power of matching. Matching is a tool that controls for confounding in the design stage of a study, whereas regression controls for confounding in the analysis stage. There is nothing inherently better about matching compared with multivariable regression analysis.

The authors conclude their report by stating that MRSA is not an independent risk factor for shock and mortality and that conclusions to the contrary may be related to an inherent methodological weakness of cohort studies. A different conclusion might be that the larger and more statistically powerful cohort study found a 2-fold increased risk of shock among patients with MRSA bacteremia and that it probably would have found a similar increased risk of mortality among these patients if shock had not been included in the logistic regression analysis model.

**Eli N. Perencevich**

*Department of Medicine, Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, Massachusetts*

---

**References**


---

**Reply**

Str—We agree with Dr. Perencevich that the results from our cohort study [1] suggest that methicillin-resistant *Staphylococcus aureus* (MRSA) is associated with mortality through the intermediate pathway of shock. This conclusion is presented in the Discussion section of our report [1]. If shock would not have been included in the model predicting mortality, the adjusted OR of death occurring when MRSA was involved would have been 2.48 (95% CI, 1.56–3.95) times the OR for death occurring when methicillin-susceptible *Staphylococcus aureus* (MSSA) was involved. Inclusion of shock as a predictor of...