Con: Corticosteroids Are Not Indicated for Treatment of Acute Lung Injury from H1N1 Viral Pneumonia

Severe viral pneumonia has been recognized for decades as an important cause of acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) (1), and therefore it is not surprising that the A/H1N1 2009–2010 influenza pandemic was associated with substantial morbidity and mortality from acute respiratory failure (2, 3). In addition to antiviral therapy and other supportive measures, many clinicians administered corticosteroids to patients with ALI/ARDS, hoping that steroid therapy would reduce lung inflammation and improve clinical outcomes (4). However, no randomized clinical trials have been performed to test the potential benefit or harm of steroid therapy for ALI/ARDS from acute viral pneumonia.

In this issue of the *Journal*, two articles (pp. 1200–1206 and 1207–1214) report the results of steroid therapy in critically ill patients with proven or strongly suspected H1N1 viral infection (5, 6). Since neither study was a randomized clinical trial, the investigators used several analytic techniques to adjust for differences in the steroid-treated versus non–steroid-treated patients to compare clinical outcomes. Given the acute nature of the H1N1 influenza pandemic, a prospectively designed, randomized clinical trial of steroids was not feasible.

The study by Brun-Buisson and colleagues (5) focused on patients with ARDS. To try to eliminate potential differences between patients who received steroid therapy and those who did not, all analyses were restricted to individuals who were not chronic steroid users. To avoid differences in timing of steroid administration, patients who received steroids more than 14 days after the diagnosis of ARDS were also not included. The final cohort was made up of 208 patients, and steroid therapy was associated with death both in the unadjusted analysis (34% versus 17%, $P = 0.004$) and also in the propensity score-adjusted analysis (hazard ratio, 2.82; 95% confidence interval [CI], 1.5–5.4; $P = 0.002$). Early steroid therapy ($\leqslant$ 3 d of mechanical ventilation) was associated with higher mortality. Patients who received steroids had more hospital-acquired pneumonia and a trend for longer duration of mechanical ventilation.

In the study by Kim and coworkers (6), 245 critically ill patients were included in the cohort; of these, 136 patients met criteria for ARDS. The crude 90-day mortality for patients who received steroids was higher than in the patients who did not receive steroids (58% versus 27%, $P < 0.001$). As in the Brun-Buisson study, the steroid-treated group was more likely to develop bacterial pneumonia or invasive fungal infection, and had significantly prolonged ICU stays. However, in contrast to the Brun-Buisson study, there were significant differences between the steroid-treated and untreated groups; specifically, severity of illness scores and the incidence of prior corticosteroid use, underlying immunosuppressive conditions, and mechanical ventilation were all higher in the steroid-treated group. The authors used two statistical methods to control for these differences, multivariable adjustment (in which the analysis is controlled for variables that are different between the two groups, and which can include the propensity score) and propensity score matching (in which patients who received steroids are matched to participants who did not). In the propensity score–matched analysis, steroid treatment was associated with an increase in 90-day mortality (odds ratio [OR], 2.63; 95% CI, 1.43–4.82). Of note, only 130 of the original 245 patients could be matched, resulting in 65 matched pairs and highlighting differences between the steroid-treated and untreated groups.

In the subgroup of 136 patients with ARDS, while steroid use was associated with an increased risk of death in the crude analysis, the association was no longer statistically significant in the adjusted or propensity-matched analyses, likely because of issues of power. Specifically, substantial differences between steroid-treated and untreated patients persisted and only 70 of the initial 136 patients with ARDS could be matched, resulting in 35 matched pairs; the point estimate in the propensity-matched analysis suggests that steroids were associated with an increased risk of death (OR, 2.28), but the result is no longer statistically significant. The conclusion from this study, therefore, was that steroids are associated with an increased risk of complications and of death in a critically ill population with H1N1, and that these trends persist in the subgroup of patients with ARDS. Along with the results of the Brun-Buisson study, in aggregate, these studies provide data that corticosteroid therapy may be harmful in the setting of ALI/ARDS from H1N1 viral pneumonia, perhaps by increasing viral load and predisposing to secondary infection (7).

There is one omission from both studies that deserves particular comment. Neither study provided data on how the patients were mechanically ventilated. Lung protective ventilation is the standard for treating patients with ALI/ARDS because of the evidence that it reduces mortality (8). Thus, it is important that all clinical studies and trials provide data on this issue, in part because lung protective ventilation is a major factor in determining clinical outcomes (9). We can assume that probably some degree of lung protective ventilation was used in these patients, but the data were not provided on how well and how consistently lung protective ventilation was applied, and the analyses could not be adjusted for potential differences in the application of mechanical ventilation between steroid-treated and untreated patients.

The use of steroids for ARDS from a variety of clinical disorders has been addressed in several clinical trials. We believe that the weight of evidence does not favor the use of steroids in patients with ARDS (10), although there are still some who believe steroids may have value (11). One limitation of most prior trials has been the inclusion of ARDS patients with multiple and heterogeneous clinical disorders, including pneumonia, nonpulmonary sepsis, aspiration of gastric contents, and major trauma. The two articles in this issue of the *Journal* illustrate the value of studying therapeutic modalities for ARDS in the context of a specific cause of acute lung injury, in this case severe viral pneumonia, albeit with the limitation that these are observational studies, not randomized clinical trials. As noted above, there are limitations to interpreting observational studies that depend on a multivariable or a propensity-matched analysis to adjust for potential differences between the two groups, because these analytic techniques cannot adjust for all the variables that might contribute to clinical outcomes or for residual confounding. For example, it is possible that clinicians used steroids in the sickest patients, thus biasing the results against the possibility that steroid therapy would be beneficial; the standard criticism of multivariable or propensity-matched analyses is that controlling for severity of illness scores as a surrogate for "more sick" may not fully adjust for differences between the groups. Furthermore, the timing and dose of corticosteroid therapy was not controlled in either study.

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However, the Brun-Buisson analysis in particular attempted to control for these differences by restricting the analysis to a subgroup of patients who did not have chronic conditions requiring steroid administration, and analyzing mortality in treatment groups based on the timing of steroid administration.

Finally, do the results of these two studies provide sufficient evidence to persuade clinicians to avoid using steroids in patients with ARDS from viral pneumonia? In spite of the limitations noted, both studies reported harm with steroid administration. Therefore, our view is that steroids should not be used in viral pneumonia, unless and until new research provides data that they are beneficial for the treatment of ARDS from viral pneumonia. These data should come from a randomized, double-blind clinical trial to avoid issues of confounding that cannot be addressed in an observational study. In our view, it will probably be more productive to focus future trials on testing new antiviral therapies. In addition, clinicians should focus on the rigorous institution of lung-protective ventilation, which is known to have survival benefit and is not associated with an increased risk of complications (8).

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