Steroids for ARDS
Still an Open Issue

To the Editor:

The recent study by Dr. Meduri and colleagues (April 2007) regarding treatment of severe ARDS with steroids has critical flaws in the presentation and analysis of the data. The methylprednisolone and control groups differed significantly in the proportion of patients who had catecholamine-dependent shock (CDS) at baseline in the treatment group (15 of 63 patients, 23.8%) vs those in the control group (13 of 28 patients, 46.4%) \([p = 0.03]\). The authors state that mortality rates by day 7 for patients with catecholamine-dependent shock were similar in the treatment and control groups: 90% and 76.9%, respectively. This translates into 12 fatalities and 10 fatalities, respectively. This contradicts data in Table 2 that describe 56 survivors at 7 days in the treatment group and 22 survivors in the control group.

ICU mortality data are equally confusing. The text states that “ICU mortality for patients with catecholamine-dependent shock was 73% vs 46% \((p = 0.24)\), and for patients without shock was 81% vs 67% \((p = 0.29)\).” This contradicts data shown in Table 3 showing there were 50 survivors of ICU admission \((79.4\%)\) in the methylprednisolone group vs 16 survivors \((57.4\%)\) in the placebo group. These discrepancies need to be resolved.

Beyond the technical presentation of the data, the difference between the groups in the proportion of patients with CDS at baseline, and the extremely high mortality rate in this subgroup—apparently nearly 80% in both groups—render this study of questionable significance in its entirety. It is quite possible that the apparent mortality benefit from the treatment can be largely attributed to the greater number of patients with CDS in the control group. Other apparent benefits may also be biased since the technique of “periodic data inspection,” via unplanned interim analyses instead of a priori-defined evaluation points, allows a continuous look at the data with the ability to terminate the study early once a desired \(p\) value is met (which may not be significant at other times during the study). The authors fail to report key aspects of trial design, such as the planned sample size, the rules used in deciding to stop the trial, and adjusted estimates for interim analyses and early termination. Finally, although the authors report an intention-to-treat analysis, a significant percentage of control patients crossover and receive open-label methylprednisolone, effectively contaminating the control group and potentially obscuring the detection of any harm caused by steroids. Essentially, the study compares early vs delayed methylprednisolone treatment in patients with ARDS. With these limitations, the only reasonable conclusion that can be gleaned from this data is that the use of steroids in a small, unmatched cohort may have a beneficial effect on lung injury scores at day 7. Unfortunately, improvement in oxygenation and lung injury scores have not been found to correlate with clinical outcomes. Therefore, before incorporating methylprednisolone treatment into routine care of these patients, a larger, randomized, blinded, placebo-controlled study without crossover should be undertaken to better evaluate the effect of steroids in ARDS.

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Low-Dose Steroids in ARDS

To the Editor:

We read the article by Meduri et al regarding the early use of low-dose steroids in ARDS with great interest. Although the results appear promising, detailed evaluation reveals a few concerning issues that may have resulted in an exaggeration of the treatment effect. First, the characteristics of the two groups were not balanced at baseline, with the control group having twice the incidence of catecholamine-dependent shock. Since shock has been directly associated with both length of mechanical ventilation and mortality, this imbalance likely contributed to the differences in outcomes. Second, the technique of “periodic data inspection,” via unplanned interim analyses instead of a priori-defined evaluation points, allows a continuous look at the data with the ability to terminate the study early once a desired \(p\) value is met (which may not be significant at other times during the study). The authors fail to report key aspects of trial design, such as the planned sample size, the rules used in deciding to stop the trial, and adjusted estimates for interim analyses and early termination. Finally, although the authors report an intention-to-treat analysis, a significant percentage of control patients crossover and receive open-label methylprednisolone, effectively contaminating the control group and potentially obscuring the detection of any harm caused by steroids. Essentially, the study compares early vs delayed methylprednisolone treatment in patients with ARDS. With these limitations, the only reasonable conclusion that can be gleaned from this data is that the use of steroids in a small, unmatched cohort may have a beneficial effect on lung injury scores at day 7. Unfortunately, improvement in oxygenation and lung injury scores have not been found to correlate with clinical outcomes. Therefore, before incorporating methylprednisolone treatment into routine care of these patients, a larger, randomized, blinded, placebo-controlled study without crossover should be undertaken to better evaluate the effect of steroids in ARDS.

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