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## Corticosteroids in ARDS: A Counterpoint

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## Corticosteroids in ARDS

### A Counterpoint

To the Editor:

The review article by Calfee and Matthay (March 2007)<sup>1</sup> provides an incomplete picture of the recent literature on prolonged glucocorticoid treatment in ARDS. Five randomized trials (n = 518) have been published investigating prolonged glucocorticoid (hydrocortisone, 200 to 240 mg/d; methylprednisolone, 1 mg/kg/d) treatment in early acute lung injury (ALI) [ $\text{PaO}_2/\text{fraction of inspired oxygen (FIO}_2) < 300$ ];<sup>2</sup> early ARDS ( $\text{PaO}_2/\text{FIO}_2 < 200$ );<sup>3,4</sup> and unresolving ARDS (methylprednisolone, 2 mg/kg/d).<sup>5,6</sup> These trials consistently reported that prolonged glucocorticoid treatment was associated with significant improvement in  $\text{PaO}_2/\text{FIO}_2$ ,<sup>2-6</sup> and a significant reduction in markers of systemic inflammation,<sup>2-6</sup> BAL neutrophilia,<sup>6,7</sup> duration of mechanical ventilation,<sup>2-6</sup> and ICU stay.<sup>2,4-6</sup> The magnitude of reduction in duration of mechanical ventilation (ventilator-free days) is shown in Table 1, and is far greater than the reduction observed with the recommended low-tidal-volume ventilation<sup>8</sup> or conservative strategy of fluid management.<sup>9</sup>

Overall, glucocorticoid treatment appears most effective when started at a lower dosage (1 mg/kg/d) early in the course of ALI-ARDS.<sup>2,4</sup> Mortality is overall improved with prolonged glucocorticoid treatment (91 of 276 patients; 33%; vs 111 of 242 patients; 46%; relative risk [RR], 0.76; 95% confidence interval [CI], 0.62 to 0.93; p = 0.007), and the benefits are more significant when treatment is initiated before day 14 of ARDS (84 of 252 patients; 33%; vs 108 of 216 patients; 50%; RR, 0.71; 95% CI, 0.50 to 0.87; p = 0.001). The mortality benefit with glucocorticoid treatment is greater than the benefit observed with low-tidal-volume ventilation (9%).<sup>8</sup> with number needed to treat to save one life of 6 for treatment initiated before day 14.

Finally, the conclusion of the ARDS network trial<sup>6</sup> that methylprednisolone treatment increases mortality in patients randomized after day 14 is challenged by the large imbalances in baseline characteristics (control vs methylprednisolone) in this small subgroup of patients for age (45 ± 13 years vs 52 ± 24 years), male gender (56% vs 35%), trauma (20% vs 13%), pneumonia (28% vs 44%), serum creatinine (1.0 ± 0.8 mg/dL vs 1.3 ± 1.3 mg/dL), APACHE (acute physiology and

chronic health evaluation) III score (79 ± 22 vs 87 ± 25), compliance (26 ± 15 cm H<sub>2</sub>O vs 18 ± 7 cm H<sub>2</sub>O; p = 0.02), and lung injury score (2.7 ± 1.2 vs 3.7 ± 0.87; p = 0.001) [mean ± SD] that likely accounted for the uncharacteristically low mortality in the control group (8% vs 36%). These factors should be taken into consideration in analyzing the role of glucocorticoid treatment in ARDS, and should stimulate additional clinical investigation of this inexpensive and highly effective antiinflammatory therapy.

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**Table 1—Effect of Glucocorticoid Treatment on Ventilator-Free Days to Day 28\***

Source/Year	Placebo	Glucocorticoid	p Value
Meduri et al <sup>5</sup> /1998	3.5 ± 6.2	11 ± 6.8	0.02
Confalonieri et al <sup>2</sup> /2005	10.1 ± 10.2	22 ± 6.3	0.001
Annane et al <sup>3</sup> /2006	3.1 ± 6.9	4.9 ± 8.4	0.09
NHLBI ARDS <sup>6</sup> †/2006	6.8 ± 8.5	11.2 ± 9.4	0.001
Meduri et al <sup>4</sup> /2007	8.7 ± 10.2	16.5 ± 10.1	0.001

\*Data are presented as mean ± SD.

†NHLBI ARDS = National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network.

and the acute respiratory distress syndrome: the Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342:1301–1308

9 Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354:2564–2575

## Response

To the Editor:

Meduri et al highlight the nature of the ongoing debate over the value of corticosteroids in acute lung injury/ARDS. The study by Confalonieri and colleagues<sup>1</sup> was not included in our review because the study population had severe pneumonia, not ARDS. The retrospective study by Annane et al<sup>2</sup> was a secondary analysis of a randomized controlled trial of corticosteroids in septic shock; benefit was noted in the subgroup of patients with sepsis-associated ARDS who failed to respond to a corticotropin stimulation test. The benefits of corticosteroids in this group likely derive from their beneficial effects in the overall population of nonresponders in this study rather than from an effect specific to ARDS; no statistical test of interaction between corticosteroid therapy and ARDS was reported in the article. In addition, while *post hoc* subgroup analysis may be useful for hypothesis generation, generalizing the findings to patient treatment can be perilous.<sup>3</sup> The 2007 study by Meduri et al was not published at the time of our review; however, this trial<sup>4</sup> has significant limitations as well. For one, the majority of patients randomized to placebo who remained on mechanical ventilation at day 9 of the study were crossed over to open-label methylprednisolone, making outcomes analysis after that point (such as mortality and ventilator-free days) very difficult to interpret. In our review,<sup>5</sup> we focused on the largest and most rigorous trial on this issue: the prospective, randomized controlled trial performed by the ARDS Network, which demonstrated no mortality benefit to corticosteroids.<sup>6</sup> We agree that the size of the subgroup of patients randomized after day 14 in this study is small, and that conclusions drawn from this subgroup, albeit a prespecified one, should be tempered by this consideration; however, most of the baseline imbalances cited by the letter were not statistically significant.

We also question the validity of the authors' approach of pooling data from the five studies cited in their letter. Since the trials did not have similar inclusion criteria (*ie*, ARDS vs pneumonia, early vs late ARDS), they would be poor candidates for a traditional metaanalysis.<sup>7</sup> Moreover, the authors do not describe their meta-analysis methods (*ie*, fixed vs random-effects model, statistical tests for heterogeneity). For these reasons, we also disagree with their calculation of a number needed to treat based on this data. The heterogeneity of prior studies was a primary driving force behind the creation of the ARDS Network's large randomized controlled trial, which has rendered the most definitive verdict in this field.

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## Steroids in Early ARDS

To the Editor:

We admire the endurance of Dr. Meduri et al<sup>1</sup> in completing their ARDS study (April 2007). However, during the 10 years that passed after the start of this study there have been important changes in daily ICU practice. In the control arm, with 46% catecholamine-dependent patients, no steroids were administered in the first week. With the spread of the Surviving Sepsis Campaign,<sup>2</sup> most patients in the control arm and probably several in the treatment arm would nowadays have received low-dose steroids (100 to 300 mg/24 h). We wonder how much of the beneficial results of the study are attributable to undertreatment of the control patients. Surprisingly Dr. Annane, one of the advocates of low-dose steroid treatment in septic shock, did not mention this item in the accompanying editorial.<sup>3</sup> We can imagine the enthusiasm for steroids, but the study by Meduri et al<sup>1</sup> does not justify the unconditional title of the editorial. Even Dr. Meduri advises a further study with stratification to minimize the risks of mismatching as occurred in this study.

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## Steroids for ARDS

### Still an Open Issue

To the Editor:

The recent study by Dr. Meduri and colleagues (April 2007)<sup>1</sup> 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: 80% 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 ascribed to the greater number of patients with CDS in the control group. Other apparent benefits may also be biased since the high mortality in the placebo group drastically reduces the number of patients who may improve despite the lack of treatment.

The authors should reanalyze their data after removing the patients with CDS at baseline. Although this would be *post hoc* subgroup analysis, it is apparently the only way to eliminate the biases caused by the inclusion of the patients with CDS.

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## Low-Dose Steroids in ARDS

To the Editor:

We read the article by Meduri et al<sup>1</sup> 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,<sup>2</sup> 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.<sup>3</sup> 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.<sup>4,5</sup> 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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# Methylprednisolone Infusion in Early Severe ARDS

## It Is Pretty, But Is It Art?

To the Editor:

Despite the recent advances in the care of critically ill patients,<sup>1</sup> ARDS is still a clinical condition associated with high mortality rates. In this clinical scenario, while most interventions to date have focused on the prevention of morbidity with ventilator-induced lung injury and pneumonia, no therapeutic intervention is indisputably associated with improved outcomes.

Corticosteroids have been used for the treatment of ARDS for the last 20 years; however, their benefits are still unproven.<sup>2</sup> Discrepancy of results from clinical trials may be explained by different doses and duration of administration, as well as patient selection and an excess of morbidity imposed by steroid-related side effects. However, the recent study by Meduri and coworkers<sup>3</sup> sheds some new light on ARDS pharmacotherapy by demonstrating clinical improvement based on possible immunomodulatory effects of the steroid infusion, thus hastening the resolution of lung injury and organ failures. Common aspects among all studies showing benefits of steroids<sup>3,4</sup> were the use of relatively lower doses, early infusion, and the selection of an extremely severely ill population. Moreover, these "successful" prospective studies had also similar limitations, the foremost one being a relatively small sample size with limited power for the detection of important outcomes (eg, hospital mortality). Therefore, these results must be viewed with caution because the morbidity burden associated with corticosteroids cannot be underestimated and a recent large multicenter clinical trial<sup>5</sup> failed to show any significant improvement in the outcomes of patients with ARDS and severe sepsis (as disclosed by the results of the Corticus Study).

In conclusion, we believe that corticosteroids cannot be widely recommended for critically ill patients. Although Dr. Meduri's results<sup>3</sup> are promising, a prospective multicenter trial is absolutely necessary before corticosteroids can be routinely recommended for the treatment of severe ARDS.

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# Methylprednisolone Infusion in Early Severe ARDS

To the Editor:

The current state of the literature surrounding the value of glucocorticoids in ARDS is riddled with complexity and conflict.<sup>1,2</sup> As such, we were surprised by the tone and conclusions of the editorial<sup>3</sup> accompanying Dr. Meduri's recently published study<sup>4</sup> on the value of methylprednisolone infusion in early severe ARDS. There are significant and fundamental design issues surrounding this study (notably absent from the editorial) that make it difficult to draw definitive conclusions regarding the role of this agent. The patients were randomized in a 2:1 fashion in favor of methylprednisolone. The incidence of catecholamine-dependent shock in the placebo group was nearly twice that of the methylprednisolone group (46.4% vs 23.8%,  $p = 0.03$ ), yet no clear analysis was presented controlling for this fact. Ten of the 15 control patients (67%) who remained on mechanical ventilation at day 9 received open-label methylprednisolone because their lung injury scores had not improved. The proportion of patients requiring mechanical ventilation at 28 days was not statistically different between the two groups. The likelihood of surviving the hospital admission was also not different between the two groups. Given the aforementioned problems with this study and the limited interpretability of the results (as well as recent recommendations by other important leaders in the field<sup>1</sup>), we do not feel that the use of glucocorticoids can be promoted as a "standard of care" for patients with ARDS at this time.

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## Response

To the Editor:

Dr. Savel and colleagues correctly argue that recommendations for practice may not rely exclusively on the results of a

single trial. For this reason, my recommendation for the routine use of low-dose corticosteroids in combination with secondary prophylaxis in patients with acute lung injury/ARDS was based on strong experimental and translational data and the consistent findings of five randomized controlled trials.<sup>1</sup> One may argue that these five trials were relatively small in size and that not all of the studies showed a significant survival benefit. However, a metaanalysis integrating the outcome data of these trials shows that prolonged glucocorticoid treatment initiated before day 14 of ARDS is associated with a significant reduction in mortality (84 of 252 patients [33%] vs 108 of 216 patients [50%]; relative risk, 0.71; 95% confidence interval, 0.50 to 0.87;  $p = 0.001$ ). What should clinicians do when no large randomized controlled trial is available and a metaanalysis of small sized trials shows significant reduction in mortality that can also be supported by biological plausibility? It is this author's opinion that while waiting for a large-scale trial to investigate mortality as a primary end point, patients with acute lung injury/ARDS should be treated with low-dose corticosteroids because this treatment undoubtedly reduces morbidity and the duration of mechanical ventilation. Additionally, potential glucocorticoid side effects can be prevented by strict surveillance for superinfection and blood glucose control, further increasing the treatment benefit/risk ratio. Regarding the internal validity of the trial of Meduri and colleagues,<sup>2</sup> having a treatment allocation based on 2:1 principle is not a problem, assuming that placebo-treated patients will behave roughly similarly. That more patients in the placebo group were in shock was due to chance, and per-protocol analysis failed to reproduce this imbalance in the proportion of vasopressor-dependent patients. In addition, this would suggest that the positive effects of methylprednisolone in this population were unlikely entirely related to shock reversal. As far as mechanical ventilation is concerned, the proportion of patients receiving mechanical ventilation at day 28 was affected by the introduction of open-label methylprednisolone in those failing to improve (8% vs 36%,  $p = 0.002$ ). Most importantly, the difference in mechanical ventilation-free days at day 28 ( $16.5 \pm 10.1$  days vs  $8.7 \pm 10.2$  days,  $p = 0.001$ ) underscores the significant impact of treatment on disease resolution and supports my argument for the routine use of this protocol in conjunction with measures demonstrated to reduce morbidity associated with glucocorticoids.

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## There Is No Illumination in Speculation

### Additional Data in Support of Methylprednisolone Treatment in ARDS

To the Editor:

The perceptive observations outlined in the five letters provide the opportunity to do the following: (1) introduce additional data showing how methylprednisolone treatment improved organ dysfunction irrespective of underlying shock; (2) clarify the impact of open-label methylprednisolone treatment on data interpretation; (3) expand on the relationship between biological response and reduction in lung injury score (LIS); (4) explain the use of a 2:1 randomization; (5) review the consistent positive findings of five randomized trials in acute lung injury (ALI); and (6) correct the mistaken reporting of mortality in the text.

### SHOCK AT BASELINE AND PRIMARY OUTCOME

The Web repository<sup>1</sup> of the article included the results of a series of stepwise logistic regression analyses adjusting for the effect of confounders and baseline differences (including pressors) on the primary variable of the study. When controlling for confounders and baseline differences, treatment effect remained significant ( $p = 0.002$ ). Among patients with and without shock, improvement in the primary variable was observed: methylprednisolone vs placebo, 67% vs 23% ( $p = 0.03$ ) and 71% vs 47% ( $p = 0.09$ ), respectively.

Although intention-to-treat analyses are standard for large randomized trials, smaller phase 2 trials may be biased by protocol violations or withdrawals, and a “per-protocol” analysis is recommended to reflect scientific methods of the protocol.<sup>2</sup> In the per-protocol analysis of this study ( $n = 79$ ),<sup>1</sup> the blinded data safety monitoring board removed an equal proportion of patients in each group, including eight patients with shock (reported in the article). The findings of the per-protocol analysis are shown in Tables 1, 2. At study entry, the two groups had similar proportions of patients with shock, and by day 7 the treated group had twice the proportion of patients alive and improved (87% vs 42%; relative risk [RR], 2.1; 95% confidence interval [CI], 1.3 to 3.4;  $p < 0.001$ ).<sup>1</sup> The significant findings observed by day 7 in the intention-to-treat and per-protocol analysis were similar, increasing confidence in the trial results.<sup>2</sup> In conclusion, the positive effects of treatment were not significantly affected by the presence of shock at study entry or undertreatment of this subgroup.

### IMPACT OF OPEN-LABEL METHYLPREDNISOLONE ON NONIMPROVERS

The statement that open-label treatment obscured detection of harm caused by steroid (Fremont and Rice<sup>3</sup>) is not supported by the findings of our study or the literature.<sup>1,4,5</sup> In our study, open-label treatment was not associated with deterioration in lung function, while a 1-point reduction in LIS was observed in 60% of patients. One patient had neuromuscular weakness, improved LIS, was extubated on ARDS day 27, and survived hospital admission. Infections developing before, during, and after open-label methylprednisolone were amply reported in the article.<sup>2</sup>

Similar to our original study,<sup>4</sup> the ARDS Network Trial<sup>5</sup> found that methylprednisolone treatment of unresolving ARDS was

**Table 1—Per-Protocol Analysis, Baseline Patient Characteristics\***

Variables	Methylprednisolone (n = 55)	Placebo (n = 24)	p Value
Age, yr	49.6 ± 15.5	53.3 ± 15.9	0.34
Male gender	30 (54.6)	11 (45.8)	0.48
White race	35 (63.6)	17 (70.8)	0.26
APACHE III score at ICU entry	58.9 ± 19	55.0 ± 20	0.43
Sepsis-induced ARDS	35 (63.6)	17 (70.8)	0.53
Bacteremia	14 (25.5)	7 (29.2)	0.73
Catecholamine-dependent shock	11 (20.0)	8 (33.3)	0.21
Postsurgical ARDS	20 (36.4)	11 (45.8)	0.43
LIS	3.23 ± 0.07	3.14 ± 0.10	0.44
PaO <sub>2</sub> /FIO <sub>2</sub>	117.4 ± 52	129.2 ± 40	0.28
Multiple organ dysfunction syndrome score	1.91 ± 0.8	1.92 ± 0.9	0.97
C-reactive protein level, mg/dL	25.4 ± 9	28 ± 9	0.27
Adrenal insufficiency	13 (23.6)	5 (20.8)	0.85

\*Data are presented as No. (%) or mean ± SEM. APACHE = acute physiology and chronic health evaluation.

associated with a significant improvement in lung mechanics and PaO<sub>2</sub>/fraction of inspired oxygen (FIO<sub>2</sub>) and a significant reduction in plasma interleukin-6, BAL neutrophilia, duration of mechanical ventilation, and ICU stay. Combining the survival data from the three trials (Fig 1)<sup>1,4,5</sup> for patients randomized before day 14 (n = 245), methylprednisolone treatment significantly reduced mortality (35 of 144 patients [24%] vs 40 of 101 patients [39%]; RR, 0.62; 95% CI, 0.43 to 0.90; p = 0.01). In these three trials,<sup>1,4,5</sup> methylprednisolone treatment increased ventilation-free days at day 28 by 5.6 days (95% CI, 3.5 to 7.7; p < 0.0001). These data suggest that the late introduction (day 7 to day 9) of open-label methylprednisolone treatment in patients with unresolving ARDS likely favored the control group and decreased the effect size (in comparison to control subjects) observed after day 7 in those randomized to methylprednisolone.

#### IMPROVEMENT IN LIS AND OUTCOME

Multiple studies (n = 15, including the original trial by Bernard and collaborators<sup>6</sup>; reviewed by Meduri<sup>7</sup>) have shown that improvement in LIS or its components by day 7 of ARDS correlates with improved survival. Reversal of hypoxemia (PaO<sub>2</sub>/FIO<sub>2</sub> ratio > 300) by day 7 was associated with significantly lower mortality rates (43% vs 97%, p < 0.001).<sup>5</sup> Similarly, we reported that improvement in LIS by day 7 correlated with improved hospital survival (R = 0.59; p < 0.001).<sup>1</sup> Even the cited ARDS Network Trial<sup>9</sup> reported that low tidal volume ventilation led to a reduction in systemic inflammation and improvement in PaO<sub>2</sub>/FIO<sub>2</sub> ratio by day 7 despite a lower PaO<sub>2</sub>/FIO<sub>2</sub> value at baseline.

Activation of the glucocorticoid receptor by endogenous or exogenous glucocorticoids is the most important down-regulator of inflammation. The significant physiologic and laboratory improvement in pulmonary and extrapulmonary organ function observed by study day 7 reflects the positive modulatory effects of prolonged methylprednisolone administration on nuclear factor-κB-mediated pathways (inflammation, coagulation, and tissue repair) that affect histologic and physiologic changes at the tissue level.<sup>9</sup> Translational research has shown that prolonged methylprednisolone in ARDS is associated with a significant reduction in pulmonary and circulating levels of markers of inflammation and fibrogenesis not shown by any other intervention.<sup>10</sup> Consequently, the accelerated resolution of respiratory failure observed during prolonged methylprednisolone treatment of early ARDS led to a significant increase in mechanical ventilation-free days by day 28 (16.5 ± 10.1 days vs 8.7 ± 10.2 days, p = 0.001),<sup>1</sup> which is

similar to those previously reported in unresolving ARDS by our group (16 ± 2 days vs 6 ± 2 days, p = 0.005)<sup>4</sup> and the ARDS Network (11.2 ± 9.4 days vs 6.8 ± 8.5 days, p < 0.001).<sup>5</sup> This effect is far greater than the one observed with the recommended low tidal volume ventilation<sup>5</sup> or conservative strategy of fluid management.<sup>11</sup>

#### RATIONALE FOR USING A 2:1 RANDOMIZATION

Unequal randomization is useful when trying to gain knowledge about the response to a new drug or, in this case, a new application for an old drug. In an efficacy study with a 2:1 randomization scheme, the higher number of subjects exposed to treatment may result in a narrower CI and improve the precision of the treatment effect. This design requires more patients to achieve the same power and effect as would be necessary with a 1:1 randomization design, and therefore does not bias the study toward methylprednisolone.

#### RISKS/BENEFITS OF PROLONGED GLUCOCORTICOID TREATMENT: RESULTS OF FIVE RANDOMIZED TRIALS

Five randomized trials (n = 518) have investigated prolonged glucocorticoid treatment (hydrocortisone, 200 to 400 mg/d; methylprednisolone, 1 mg/kg/d) in early ALI (PaO<sub>2</sub>/FIO<sub>2</sub> < 300),<sup>12</sup> early ARDS (PaO<sub>2</sub>/FIO<sub>2</sub> < 200),<sup>1,13</sup> and unresolving ARDS (methylprednisolone, 2 mg/kg/d).<sup>4,5</sup> These trials consistently reported that treatment was associated with significant improvement in PaO<sub>2</sub>/FIO<sub>2</sub>,<sup>1,4,5,12,13</sup> and a significant reduction in markers of systemic inflammation,<sup>1,4,5,12,13</sup> BAL neutrophilia,<sup>5,14</sup> duration of mechanical ventilation,<sup>1,4,5,12,13</sup> and ICU stay.<sup>1,4,5,12</sup>

For decades, intensivists have routinely administered higher daily doses of methylprednisolone for acute exacerbation of asthma or COPD and carefully balanced the important anti-inflammatory effect of treatment with potential complications. The most reliable data on actual complication rates associated with prolonged glucocorticoid treatment (in low-to-moderate doses) is from randomized trials in sepsis<sup>15,16</sup> and ARDS.<sup>1,4,5,12,13</sup> Similar to findings in septic shock,<sup>15,16</sup> glucocorticoid treatment in ARDS was not associated with increased rates of GI bleeding or nosocomial infections.<sup>1,4,5,12,13</sup> Glycemic spikes observed when glucocorticoids are administered as a bolus,<sup>5</sup> are mitigated when

**Table 2—Per-Protocol Analysis, Outcome Measures on or by Study Day 7\***

Variables	Methylprednisolone (n = 55)	Placebo (n = 24)	p Value
Extubated or with a $\geq$ 1-point reduction in LIS†	41 (74.6)	9 (37.5)	0.002
Patients breathing without assistance	32 (58.2)	7 (29.2)	0.02
LIS‡	2.03 $\pm$ 1.3	2.72 $\pm$ 0.1	< 0.001
PaO <sub>2</sub> /FIO <sub>2</sub> ‡	268.6 $\pm$ 21	179.8 $\pm$ 21	0.003
Mechanical ventilation-free days‡	2.11 $\pm$ 2.0	0.96 $\pm$ 1.3	0.009
Multiple organ dysfunction syndrome score	0.69 $\pm$ 0.9	1.71 $\pm$ 1.3	0.02
C-reactive protein level, mg/dL	2.7 $\pm$ 0.8	13.4 $\pm$ 0.8	< 0.001
Patients with new infection§	9 (16.4)	8 (33.3)	0.09
Patients with ventilator-associated pneumonia	3 (5.5)	5 (20.8)	0.051
Survivors	52 (94.5)	20 (83.3)	0.19
Patients with unresolving ARDS treated with open-label methylprednisolone (2 mg/kg/d)†	4 (7.3)	10 (41.7)	< 0.001

\*Data are presented as No. (%) or mean  $\pm$  SEM.

†The proportion of patients alive and improved for methylprednisolone vs placebo: 87% vs 42% (p < 0.001).

‡Lung injury score and in PaO<sub>2</sub>/FIO<sub>2</sub> values obtained in patients remaining on mechanical ventilation.

they are administered as an infusion.<sup>1,17</sup> Finally, systemic inflammation-associated neuromuscular weakness is uncommon with low-dose steroids if concomitant paralysis is avoided.<sup>1,12</sup> Neuro-muscular weakness is a known independent predictor of prolonged weaning,<sup>18</sup> yet the ARDS Network trial reported that among the 43 patients with weakness, those randomized to methylprednisolone (n = 25) had a significant (p = 0.003) and sizeable (11 days) reduction in duration of mechanical ventilation (Table 7, supplemental appendix).<sup>5</sup> Finally, when glucocorticoid treatment is initiated before day 14 of ARDS (n = 468),<sup>1,4,5,12,13</sup> mortality is significantly decreased (84 of 252 patients [33%] vs 108 of 216 patients [50%]; RR, 0.71; 95% CI, 0.50 to 0.87; p = 0.001), with 6 patients needed to treat to save one life.

### INCORRECT REPORTING OF MORTALITY

We express regret for an error in reporting “mortality” that has unfortunately generated misunderstanding (Segel<sup>19</sup>). The results for survival reported in the Tables and Figures are correct. In the text, however, the word *mortality* was used incorrectly in place of *survival* four times.

The text on page 956 should read, “Survival by day 7 for patients with catecholamine-dependent shock was similar (80% vs 76.9%).” Twelve of 15 patients (80%) and 10 of 13 patients (76.9%) with shock survived to day 7 in the treated and control

groups, respectively. The text on page 957 should read, “ICU survival 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). In per-protocol analysis (Web repository), ICU survival for patients with catecholamine-dependent shock was 90% vs 71% (p = 0.07).” The number of patients with shock who survived ICU admission was 11 of 15 patients (73%) and 6 of 13 patients (46%) in the treated and control groups, respectively. The text on page 958 should read, “Survival rates at 2, 6, and 12 months were 76% vs 61% (p = 0.13), 67% vs 46% (p = 0.07), and 63.5% vs 46%, respectively.”

In conclusion, methylprednisolone treatment has a strong benefit/risk ratio when it is applied in conjunction with measures demonstrated to reduce morbidity associated with glucocorticoids.<sup>1,4</sup> These measures include the following: (1) intensive infections surveillance, (2) avoidance of paralytic agents, and (3) avoidance of rebound inflammation with premature discontinuation of treatment that may lead to physiologic deterioration and reintubation. Correct use of this inexpensive and highly effective antiinflammatory therapy is associated with a significant improvement in patient-centered outcome variables, irrespective of shock, and decreases health-care cost associated with ARDS.<sup>20</sup> The relevance of these findings to public health and health-care economics urges investment in clinical investigation of this inexpensive and highly effective antiinflammatory therapy.

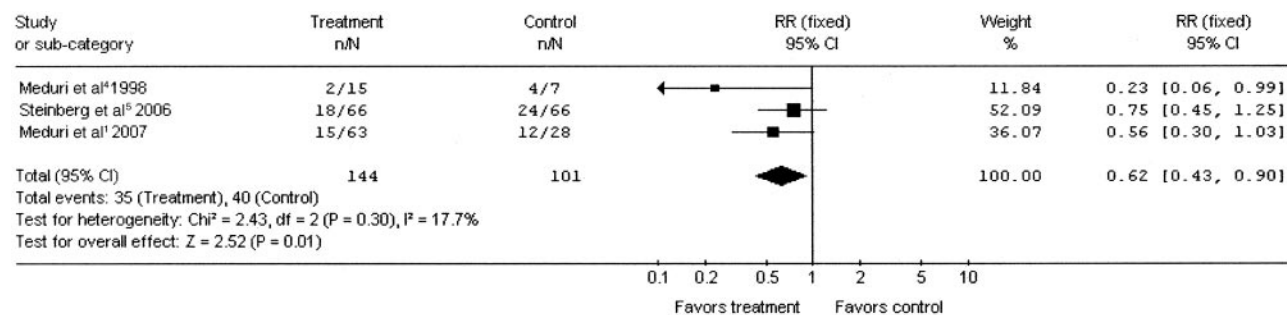


FIGURE 1. Effects on survival of prolonged glucocorticoid treatment initiated before day 14 of ARDS. Mortality was the primary outcome in two of the three trials.<sup>4,5</sup> Mortality is reported as hospital mortality<sup>1,4</sup> or 60-day mortality.<sup>5</sup> Figure provided by Professor D. Annane, Université de Versailles Saint-Quentin en Yvelines, Garches, France. df = degree of freedom.

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## Vancomycin Dosing for Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia

To the Editor:

We read the study by Jeffres and colleagues<sup>1</sup> (October 2006) with interest and were intrigued with the conclusion that trough concentrations  $> 15 \mu\text{g/mL}$  may not offer any advantage over traditional targets. This retrospective study was not adequately powered to detect differences between traditional and aggressive trough concentrations. Therefore, a statistically insignificant result is only inconclusive and not a negative finding.

With substantial imbalances between nonsurvivors and survivors, assessments of the variable in question in both analyses are impossible. Nonsurvivors were older with higher APACHE (acute physiology and chronic health evaluation)-II scores and had greater frequencies of bacteremia, end-stage renal disease, mechanical ventilation, and vasopressors. The trough concentration  $\geq 15 \mu\text{g/mL}$  group had higher APACHE-II scores and more patients receiving mechanical ventilation and vasopressors (a factor significantly associated with mortality in the multivariate analysis). Is it plausible that sicker patients receiving trough concentration  $\geq 15 \mu\text{g/mL}$  have the same risk of death as less ill patients receiving lower vancomycin trough concentrations?

The unavailability of minimum inhibitory concentrations made it impossible to calculate the area under the inhibitory curve values, although the accompanying editorial<sup>2</sup> stated these were calculated. Disk diffusion does not adequately identify *Staphylococcus aureus* with reduced vancomycin susceptibility.<sup>3</sup> While most isolates likely had an minimum inhibitory concentration  $\leq 0.5 \mu\text{g/mL}$ , we will never know for certain. Therefore, pharmacodynamic target attainment rates cannot be compared.

While vancomycin may not display pharmacokinetic qualities of the optimal agent for methicillin-resistant *S aureus* pneumonia, prospective, randomized trials comparing vancomycin target concentrations will hopefully provide some definitive answers to the role of aggressive vancomycin dosing for this disease. The major issue is that vancomycin has not had a fair comparison. Unfortunately, this study had the worst possible result, as it did not definitively conclude anything.<sup>1</sup> However, this study and the accompanying editorial suggest that the time for optimizing vancomycin dosing is over and clinicians should use "better" agents.

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## Methicillin-Resistant *Staphylococcus aureus* Pneumonia Treatment

### Do Not Confuse Pharmacokinetics and Pharmacodynamics

To the Editor:

We have read with great interest the article in a recent issue of *CHEST* (October 2006) by Jeffres et al,<sup>1</sup> which suggested that aggressive dosing strategies for vancomycin (eg, trough concentrations > 15 mg/L) may not offer any advantage over traditional dosing targets (range, 5 to 15 mg/L) in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) health-care-associated pneumonia. A lack of response to treatment with vancomycin in patients infected with MRSA, and in patients infected with vancomycin intermediate-resistant *S aureus* (VISA) and heterogeneous VISA (hVISA),<sup>3</sup> has been increasingly reported despite apparent *in vitro* susceptibility (minimum inhibitory concentration [MIC], 2 mg/L).<sup>2,3</sup> Moreover, MRSA isolates that show reduced susceptibility to vancomycin (MIC, 2 mg/L) are highly prevalent among strains that cause invasive infections.<sup>2</sup>

In the study by Jeffres et al,<sup>1</sup> the tested staphylococci exhibited a mean vancomycin zone diameter > 14 mm and would therefore be considered fully susceptible. Nevertheless, disk diffusion is not an acceptable method for testing of the vancomycin susceptibility of *S aureus*, specifically for the detection of VISA or hVISA.<sup>3,4</sup> Thus, the authors may not have excluded the idea that a lack of response to treatment was not associated with a high vancomycin MIC for MRSA (2 mg/L) or VISA/hVISA.

Unbound trough serum concentrations of vancomycin that are four to five times the MIC or 24-h area under the curve/MIC ratio of 400 were shown to be the pharmacodynamic parameters that best correlated with a successful clinical outcome.<sup>5</sup> Considering that vancomycin is 50% protein-bound in serum and that lung concentrations will not exceed 20 to 30% of the serum concentrations,<sup>5</sup> a trough serum concentration level of 15 to 25 mg/L may be adequate for the treatment of MRSA with a MIC at the breakpoint for susceptibility (2 mg/L), with a concentration of 30 to 40 mg/L being required for the treatment of VISA/hVISA pneumonia. Unfortunately, Jeffres et al<sup>1</sup> did not consider the potential

impact of variations in MRSA MICs on differences in outcome. Thus, it still seems appropriate to continue monitoring vancomycin serum levels in order to ensure effective therapeutic concentrations until the results of well-designed prospective clinical studies, including vancomycin MIC determinations, become available.

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## Appropriate Pharmacokinetic Index for Outcome in *Staphylococcus aureus* Pneumonia

To the Editor:

We read with interest the study by Jeffres and colleagues (October 2006)<sup>1</sup> investigating the relationship between vancomycin pharmacokinetic (PK) indices and outcome in patients with confirmed *Staphylococcus aureus* pneumonia. This study did not find a correlation between vancomycin area under the curve (AUC) ( $\geq 400$   $\mu\text{g}/\text{h}/\text{mL}$ ) and hospital mortality in patients with *S aureus* pneumonia. While the authors acknowledge that previous clinical studies show an association between vancomycin PK indices and patient outcomes, they do not further clarify that the AUC/minimum inhibitory concentration (MIC) ratio and not AUC alone, as evaluated in the current study, has correlated better with patient outcomes in those studies.<sup>2,3</sup> Although this correlation is not evidenced in all studies<sup>4,5</sup> evaluating this relationship, the AUC/MIC ratio is the best parameter predicting

vancomycin activity against *S aureus* in an animal infection model.<sup>6</sup> The authors in the current study acknowledge the lack of isolate MIC values from study patients and further state that although Kirby Bauer zone sizes from isolates between survivors and nonsurvivors did not differ, this may not mean the MIC values were similar.<sup>7</sup> In short, the MIC distribution in this study is not known. Undetermined MICs, however, could have resulted in significant AUC/MIC differences between groups that were not appreciated by study methodology.

The authors also question the recommendation of achieving vancomycin trough concentrations  $\geq 15 \mu\text{g/mL}$  as a predictor of outcome, yet trough concentrations are a reasonable surrogate marker for AUC as reinforced by the authors' calculations showing a significant correlation between trough levels and AUC values. Trough levels therefore may be of value in predicting an AUC/MIC ratio, again, provided the isolate MIC is known.

In conclusion, this study is severely limited by lack of MIC data that preclude the determination with certainty that an appropriate index has no correlation to mortality. We do agree with the authors' assessment that there is a need for a prospective randomized study to assess vancomycin exposure on mortality in ICU patients. This should be conducted using a more appropriate and previously identified index, the AUC/MIC ratio.

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## Response

To the Editor:

We would like to thank Dr. Moine and colleagues for their interest in our article focusing on the outcomes of patients with bronchoscopically proven methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia treated with vancomycin. We appreciate their important concern regarding the limitations of the disk-diffusion method to identify vancomycin-intermediate *S aureus* (VISA) or heteroresistant VISA strains.<sup>1</sup> Additionally, we also acknowledge the reports<sup>2,3</sup> associating poor outcomes in patients with infections caused by MRSA that have a vancomycin minimum inhibitory concentration (MIC)  $> 1.5 \mu\text{g/mL}$ . However, the point that MRSA isolates with MIC values  $\geq 2 \mu\text{g/mL}$  are highly prevalent varies from report to report and likely from institution to institution. The SENTRY Antimicrobial Surveillance Program database evaluated 35,458 *S aureus* isolates from 1998 to 2003 and determined both the vancomycin MIC of 50% of isolates and vancomycin MIC of 90% of isolates to be  $1 \mu\text{g/mL}$ .<sup>1</sup> The percentage of isolates with an MIC of  $2 \mu\text{g/mL}$  was  $< 8\%$  in each year evaluated, and this value was stable from year to year. More recently, the Surveillance Network data for 2005 found 16.4% of approximately 240,000 *S aureus* isolates had an MIC  $\geq 2 \mu\text{g/mL}$ .<sup>4</sup> The patient populations in the studies associating high vancomycin MICs with poor outcomes were small, isolated samples with heterogeneous baseline demographics, and as such likely do not represent the patient population of an academic medical center as described in our study.

Targeting pharmacodynamic end points such as unbound trough concentrations four to five times the MIC or an area under the curve (AUC):MIC ratio of 400 to achieve microbiological eradication or successful clinical outcome is also subject to debate, particularly if the MRSA isolate has an MIC  $\geq 1.5 \mu\text{g/mL}$ . First, the data supporting achievement of a vancomycin AUC:MIC ratio  $\geq 350$  is based on a sample of 33 patients with lower respiratory tract infections caused by MRSA that was isolated from sputum samples.<sup>5</sup> Eradication of MRSA from a sputum culture may or may not be related to hospital mortality in patients with pneumonia. Furthermore, all isolates in this study had MICs of  $0.5 \mu\text{g/mL}$  and  $1.0 \mu\text{g/mL}$ , and therefore this association should not be made for strains with an MIC  $\geq 1.5 \mu\text{g/mL}$ . More recently, clinical response rates were significantly lower in a group of patients with MRSA infections caused by isolates with MICs  $\geq 1.5 \mu\text{g/mL}$  compared to a group with MICs  $< 1 \mu\text{g/mL}$  (62% vs 85%,  $p = 0.02$ ) despite achieving a trough concentration of four to five times the MIC.<sup>2</sup> We clearly acknowledge in the discussion of our article that variability in the MIC distribution could have occurred between survivors and nonsurvivors thus impacting our findings. Interestingly, Monte Carlo

simulation of our data reveals 0% probability of achieving an AUC:MIC ratio  $\geq 400$  with either low-dose (trough  $< 15 \mu\text{g}/\text{mL}$ ) or high-dose (trough  $\geq 15 \mu\text{g}/\text{mL}$ ) in MRSA isolates with an MIC of  $2 \mu\text{g}/\text{mL}$ .<sup>6</sup> Further, based on this simulation, optimizing the vancomycin AUC:MIC ratio may only be of consequence in isolates with an MIC of  $1 \mu\text{g}/\text{mL}$ .

We agree with the statement Drs. Potoski and Paterson identifying a correlation between trough serum concentrations and AUC values; however, neither parameter was correlated with a successful outcome in our patient population. Dr. Hall and Ms. Adams-Huet postulate that increasing the serum vancomycin trough concentration in sicker patients may put them on equal footing regarding risk of death as less sick patients receiving lower serum trough concentrations. We attempted to answer this question through logistic regression analysis. If the above question were true, serum trough concentrations and/or APACHE (acute physiology and chronic health evaluation) II scores would have been identified as predictors of outcome in this patient population. The two variables associated with mortality were COPD and vasopressor administration.

It is becoming increasingly apparent that targeting vancomycin pharmacodynamic end points in patients with pneumonia caused by an MRSA isolate with an MIC  $\geq 1.5 \mu\text{g}/\text{mL}$  is a strategy that may not improve outcomes and could lead to increased toxicity.<sup>2,7</sup> Vancomycin may still be an option in MRSA pneumonias that have an MIC  $\leq 0.5 \mu\text{g}/\text{mL}$ ; however, alternative agents such as linezolid or tigecycline, and in the near future ceftobiprole, dalbavancin, and telavancin, should be considered if the MIC is  $> 1 \mu\text{g}/\text{mL}$ .

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## Corticosteroids in ARDS: A Counterpoint

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