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Methylprednisolone Infusion in Early Severe ARDS*
Results of a Randomized Controlled Trial
G. Umberto Meduri, MD, FCCP; Emmel Golden, MD; Amado X. Freire, MD, MPH, FCCP; Edwin Taylor, MD; Muhammad Zaman, MD; Stephanie J. Carson, RN; Mary Gibson, RN; and Reba Umberger, RN, MS

**Objective:** To determine the effects of low-dose prolonged methylprednisolone infusion on lung function in patients with early severe ARDS.

**Design:** Randomized, double-blind, placebo-controlled trial.

**Setting:** ICUs of five hospitals in Memphis.

**Participants:** Ninety-one patients with severe early ARDS (<72 h), 66% with sepsis.

**Interventions:** Patients were randomized (2:1 fashion) to methylprednisolone infusion (1 mg/kg/d) vs placebo. The duration of treatment was up to 28 days. Infection surveillance and avoidance of paralysis were integral components of the protocol.

**Main outcome measure:** The predefined primary end point was a 1-point reduction in lung injury score (LIS) or successful extubation by day 7.

**Results:** In intention-to-treat analysis, the response of the two groups (63 treated and 28 control) clearly diverged by day 7, with twice the proportion of treated patients achieving a 1-point reduction in LIS (69.8% vs 35.7%; p = 0.002) and breathing without assistance (53.9% vs 25.0%; p = 0.01). Treated patients had significant reduction in C-reactive protein levels, and by day 7 had lower LIS and multiple organ dysfunction syndrome scores. Treatment was associated with a reduction in the duration of mechanical ventilation (p = 0.002), ICU stay (p = 0.007), and ICU mortality (20.6% vs 42.9%; p = 0.03). Treated patients had a lower rate of infections (p = 0.0002), and infection surveillance identified 56% of nosocomial infections in patients without fever.

**Conclusions:** Methylprednisolone-induced down-regulation of systemic inflammation was associated with significant improvement in pulmonary and extrapulmonary organ dysfunction and reduction in duration of mechanical ventilation and ICU length of stay.

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**Key words:** ARDS; duration of mechanical ventilation; glucocorticoid treatment; infections; systemic inflammation

**Abbreviations:** APACHE = acute physiology and chronic health evaluation; Fio2 = fraction of inspired oxygen; LIS = lung injury score; MODS = multiple organ dysfunction syndrome; PEEP = positive end-expiratory pressure

In ARDS, the evolution of systemic and pulmonary inflammation in the first week of mechanical ventilation determines the physiologic progression (resolving vs unresolving) and outcome of the disease.1–3 The lung injury score (LIS) quantifies the physiologic respiratory impairment in ARDS through the use of a 4-point score based on the levels of positive end-expiratory pressure (PEEP), ratios of PaO2 to fraction of inspired oxygen (Fio2), the static lung compliance, and the degree of infiltration present on chest radiograph.4 Patients failing to improve the LIS or its components by day 7 of ARDS (unresolving ARDS), contrary to improvers, have persistent elevation in circulating and BAL levels of inflammatory cytokines and chemokines, markers of alveolocapillary membrane permeability and fibrogenesis (dysregulated systemic inflammation),1–3 and a higher mortality.5–7

We have previously shown1,2,8 that systemic inflammation-induced glucocorticoid receptor resistance and/or insensitivity is an acquired, generalized process central to the pathogenesis of unresolving ARDS that is potentially reversed by quantitatively adequate and prolonged glucocorticoid supplemen-
with parallel significant improvement in lung injury and multiple organ dysfunction syndrome (MODS) scores. Treatment was associated with a significant reduction in duration of mechanical ventilation and ICU mortality. Three additional randomized trials investigating prolonged glucocorticoid treatment in acute lung injury and ARDS were published showing a significant reduction in levels of inflammatory markers and duration of mechanical ventilation.

Since the direction of the systemic inflammatory response (regulated vs dysregulated) is established early in the course of the disease, we tested the hypothesis that prolonged administration of low-dose methylprednisolone (1 mg/kg/d) initiated in early ARDS (within 72 h of diagnosis) downregulates systemic inflammation and leads to earlier resolution of pulmonary organ dysfunction and a reduction in duration of mechanical ventilation and ICU stay. The present trial substantially differs from a prior study with negative findings that investigated, in 100 patients with early ARDS, a 1-day treatment with high-dose (120 mg/kg) methylprednisolone. Preliminary results of the per-protocol analysis of this study have been reported in abstract form.

**Materials and Methods**

**Patients**

This investigation was conducted between April 1997 and April 2002 in the medical and surgical ICUs of Baptist Memorial Hospital at University of British Columbia on May 6, 2010

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Results

Figure 1 shows progress through the phases of the trial. Data are reported as intention to treat for methylprednisolone vs placebo groups. Over the study period, the number of patients recruited each year was as follows: 10, 23, 25, 18, 11, and 4 patients. The baseline characteristics of each group at study entry were similar (Table 1), with the exception of a higher proportion of patients with catecholamine-dependent shock in the control group. In per-protocol analysis (Web repository) the distribution of patients with catecholamine-dependent shock was similar (20% vs 33%; p = 0.21). Extrapulmonary organ dysfunction included cardiovascular (57% vs 68%; p = 0.35), renal (21% vs 25%; p = 0.70), hepatic (13% vs 24%; p = 0.33), and hematologic (16% vs 7%; p = 0.33). Sixty-three patients initially received methylprednisolone, and 28 received placebo. Previously defined criteria for persistent ARDS by Ferguson and collaborators were still present at 24 h in most patients (Table 1).

Changes in LIS and C-reactive protein levels during the first 7 days of the study are shown in Figure 2. By study day 7 (Table 2), the response of the two groups clearly diverged; the methylprednisolone-treated group had twice the proportion of patients with a 1-point reduction in LIS (69.8% vs 35.7%; p = 0.002) and breathing without assistance (54.0% vs 25.0%; p = 0.01). Significant differences were also observed for PaO₂/FIO₂ ratio, mechanical ventilation-free days, and MODS score. Single-organ dysfunction by day 7 included pulmonary (40% vs 74%; p = 0.004), cardiovascular (12% vs 37%; p = 0.006), renal (18% vs 37%; p = 0.06), hepatic (9% vs 30%; p = 0.03), and hematologic (13% vs 15%; p = 1.00). Improvement by day 7 correlated with survival by day 7 (R = 0.41; p < 0.001) and hospital survival (R = 0.59; p < 0.001). Mortality by day 7 for patients with catecholamine-dependent shock was similar (80% vs 76.9%). Those with relative adrenal insufficiency had a lower response to methylprednisolone (50% vs 80%; p = 0.05), while among control subjects, adrenal insufficiency also affected the proportion of improvement (14% vs 47%; p = 0.19); however, these numbers were too small to detect a statistical difference.

By study day 7, infection surveillance identified 22 nosocomial infections in 19 patients. In methylprednisolone-treated patients, 7 of 13 infections (54%) were identified in the absence of fever. 2 ventilator-associated pneumonias, 3 catheter-related infections,
ARDS. Of the 15 control patients receiving methylprednisolone (2 mg/kg/d) for unresolving ARDS criteria at 24 h was defined as a Pa
¶If a component MODS value was missing at study entry, the MODS score was imputed when the component value was obtained within 24 h.
‡Scores can range from 0 to 299, with higher scores indicating more severe illness.25
§Extrapulmonary sources of sepsis are reported. Methylprednisolone: endocarditis, catheter-related infection, extra-abdominal abscess, pancreatic abscess, urosepsis (n = 2); peritonitis, and other. Placebo: endocarditis, perforated viscus (n = 2), endometritis, necrotizing fascitis, wound infection, and other. Other conditions precipitating ARDS are reported: methylprednisolone (n = 16); acute pancreatitis (n = 3); multiple blood transfusion (n = 3); postcoronary artery bypass surgery complications (n = 2); near drowning (n = 2); hemorrhagic shock, sickle-cell chest syndrome, abruptio placentae, postpartum complications, and other (n = 2). Placebo: acute myocardial infarction, dissecting aortic aneurysm, mesenteric ischemia, and other. Hospital mortality for conditions precipitating ARDS (methylprednisolone vs placebo): pulmonary infection (n = 5; 21% vs n = 6; 60%), aspiration of gastric contents (n = 2; 18% vs n = 1; 20%), extrapulmonary sepsis (n = 3; 50% vs n = 2; 29%), and other (n = 1; 7% vs n = 0.0%). Extrapulmonary sepsis associated with hospital death is reported. Methylprednisolone: urosepsis, peritonitis, and endocarditis. Placebo: necrotizing fascitis and wound infection.
¶¶See text for definition of LIS and MODS score, and adrenal insufficiency. Additional components for LIS are reported for methylprednisolone vs placebo: static compliance (30.2 ± 8.0 cm H 2O vs 29.6 ± 8.0 cm H 2O; p = 0.74) and chest radiograph score (3.90 ± 0.30 vs 3.89 ± 0.31; p = 0.87). Delivered tidal volume was similar between the two groups (668 ± 157 mL vs 658 ± 141 mL; p = 0.8).
¶¶¶If a component MODS value was missing at study entry, the MODS score was imputed when the component value was obtained within 24 h. Unimputed MODS scores were 1.1 (p = 0.87). Delivered tidal volume was similar between the two groups (668 ± 157 mL vs 658 ± 141 mL; p = 0.8).
*All but one (Hispanic) of the remaining 34 patients were African American.
**Data are presented as mean ± SD or No. (%). At study entry, C-reactive protein levels were available in 80 patients (n = 56 vs 24) and complete APACHE III data were not available in 3 patients (2 receiving methylprednisolone and 1 receiving placebo).

### Table 1—Baseline Patient Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Methylprednisolone (n = 63)</th>
<th>Placebo (n = 28)</th>
<th>p Value (n = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>50.1 ± 15.3</td>
<td>53.2 ± 15.3</td>
<td>0.38</td>
</tr>
<tr>
<td>Male gender</td>
<td>34 (54.0)</td>
<td>13 (46.4)</td>
<td>0.51</td>
</tr>
<tr>
<td>White ethnic group†</td>
<td>37 (58.7)</td>
<td>20 (71.4)</td>
<td>0.25</td>
</tr>
<tr>
<td>APACHE III score at ICU entry†</td>
<td>60.2 ± 20.2</td>
<td>57.9 ± 21.0</td>
<td>0.63</td>
</tr>
<tr>
<td>Conditions precipitating ARDS¶¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>26 (41.3)</td>
<td>12 (42.9)</td>
<td>0.80</td>
</tr>
<tr>
<td>Aspiration of gastric content</td>
<td>13 (20.6)</td>
<td>5 (17.9)</td>
<td>0.76</td>
</tr>
<tr>
<td>Sepsis (extrapulmonary)</td>
<td>8 (12.7)</td>
<td>7 (25.0)</td>
<td>0.22</td>
</tr>
<tr>
<td>Other</td>
<td>16 (25.4)</td>
<td>4 (14.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Direct cause of ARDS</td>
<td>44 (71.0)</td>
<td>16 (59.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>Sepsis-induced ARDS</td>
<td>42 (66.7)</td>
<td>19 (67.8)</td>
<td>0.91</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>14 (22.2)</td>
<td>6 (21)</td>
<td>0.93</td>
</tr>
<tr>
<td>Catecholamine-dependent shock</td>
<td>15 (23.8)</td>
<td>13 (46.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Postsurgical ARDS</td>
<td>22 (34.9)</td>
<td>12 (42.9)</td>
<td>0.47</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3.21 ± 0.41</td>
<td>3.11 ± 0.41</td>
<td>0.27</td>
</tr>
<tr>
<td>PEEP, cm H 2O</td>
<td>13 ± 5.0</td>
<td>11.2 ± 4.0</td>
<td>0.08</td>
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<tr>
<td>PaO2/FiO2 ratio</td>
<td>118.4 ± 51.2</td>
<td>125.9 ± 38.6</td>
<td>0.44</td>
</tr>
<tr>
<td>MODS score¶¶</td>
<td>2.1 ± 0.8</td>
<td>2.2 ± 1.1</td>
<td>0.54</td>
</tr>
<tr>
<td>C-reactive protein level, mg/dL</td>
<td>25.0 ± 8.8</td>
<td>26.4 ± 10.1</td>
<td>0.55</td>
</tr>
<tr>
<td>Baseline cortisol level, µg/dL</td>
<td>21.9 ± 1.8</td>
<td>25.9 ± 1.8</td>
<td>0.21</td>
</tr>
<tr>
<td>Adrenal insufficiency¶¶</td>
<td>16 (25.4)</td>
<td>7 (25.0)</td>
<td>0.88</td>
</tr>
<tr>
<td>Persistent ARDS at 24 h#</td>
<td>44 (72.2)</td>
<td>21 (84)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

*A data are presented as mean ± SD or No. (%). At study entry, C-reactive protein levels were available in 80 patients (n = 56 vs 24) and complete APACHE III data were not available in 3 patients (2 receiving methylprednisolone and 1 receiving placebo).

### Table 1—Baseline Patient Characteristics*

Of the 15 control patients receiving methylprednisolone (2 mg/kg/d) for unresolving ARDS criteria at 24 h was defined as a Pa
¶If a component MODS value was missing at study entry, the MODS score was imputed when the component value was obtained within 24 h.
‡Scores can range from 0 to 299, with higher scores indicating more severe illness.25
§Extrapulmonary sources of sepsis are reported. Methylprednisolone: endocarditis, catheter-related infection, extra-abdominal abscess, pancreatic abscess, urosepsis (n = 2); peritonitis, and other. Placebo: endocarditis, perforated viscus (n = 2), endometritis, necrotizing fascitis, wound infection, and other. Other conditions precipitating ARDS are reported: methylprednisolone (n = 16); acute pancreatitis (n = 3); multiple blood transfusion (n = 3); postcoronary artery bypass surgery complications (n = 2); near drowning (n = 2); hemorrhagic shock, sickle-cell chest syndrome, abruptio placentae, postpartum complications, and other (n = 2). Placebo: acute myocardial infarction, dissecting aortic aneurysm, mesenteric ischemia, and other. Hospital mortality for conditions precipitating ARDS (methylprednisolone vs placebo): pulmonary infection (n = 5; 21% vs n = 6; 60%), aspiration of gastric contents (n = 2; 18% vs n = 1; 20%), extrapulmonary sepsis (n = 3; 50% vs n = 2; 29%), and other (n = 1; 7% vs n = 0.0%). Extrapulmonary sepsis associated with hospital death is reported. Methylprednisolone: urosepsis, peritonitis, and endocarditis. Placebo: necrotizing fascitis and wound infection.
¶¶See text for definition of LIS and MODS score, and adrenal insufficiency. Additional components for LIS are reported for methylprednisolone vs placebo: static compliance (30.2 ± 8.0 cm H 2O vs 29.6 ± 8.0 cm H 2O; p = 0.74) and chest radiograph score (3.90 ± 0.30 vs 3.89 ± 0.31; p = 0.87). Delivered tidal volume was similar between the two groups (668 ± 157 mL vs 658 ± 141 mL; p = 0.8).
¶¶¶If a component MODS value was missing at study entry, the MODS score was imputed when the component value was obtained within 24 h. Unimputed MODS scores were 1.1 (p = 0.87). Delivered tidal volume was similar between the two groups (668 ± 157 mL vs 658 ± 141 mL; p = 0.8).
#Persistent ARDS criteria at 24 h was defined as a PaO2/FiO2 ratio ≤ 200 on PEEP and standardized ventilatory management.26 Includes 82 patients (n = 57 vs 25) with available arterial blood gas values on day 1.

1 urinary tract infection, and 1 wound infection. Treated patients had a trend toward decreased incidence of ventilator-associated pneumonia (p = 0.06).

Between day 7 and day 9, 14 patients failed to meet predefined criteria for improvement in LIS (8% vs 36%; p = 0.002) and received open-label methylprednisolone (2 mg/kg/d) for unresolving ARDS.9 Of the 15 control patients receiving mechanical ventilation on day 9, 5 patients met criteria for improvement in LIS, and 10 nonimprovers received open label methylprednisolone (2 mg/kg/d) for unresolving ARDS.

As shown in Table 3, the treatment group had a significant reduction in duration of mechanical ventilation, length of ICU stay, and ICU mortality; a trend toward significant reduction in hospital mortality (p = 0.07) was observed. 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). In per-protocol analysis (Web repository), ICU mortality for patients with catecholamine-dependent shock was 90% vs 71% (p = 0.07). Among survivors, the treatment group had a significant reduction in duration of mechanical ventilation (median, 5.5 days [range, 4 to 8.5 days] vs 9.5 days [range, 6 to 20 days]; p = 0.004), ICU stay (median, 7.5 days [range, 6 to
12 days] vs median, 16 days [range, 9.5 to 25.5 days]; p = 0.001), and hospital stay (median, 14 days [range, 10 to 20 days] vs median, 30 days [range, 13.5 to 61.5 days]; p = 0.005). Figures 3, 4 show Kaplan-Meier probability estimates for continuation of mechanical ventilation and survival curves, respectively. After study day 14, 3 patients (5%) in the treatment group and 10 patients (36%) in the control group remained on mechanical ventilation (p = 0.0001). Mortality 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% (p = 0.13), respectively.

Complications and infections observed during treatment are shown in Table 4. One hundred thirty-five bronchoscopies with BAL were performed during the study: 83 at study entry, 21 during the first week, and 31 after day 7. The treated patients had a significantly lower rate of infections. In the treatment group, among the 27 infections developing after day 7, 16 infections (60%) were identified in the absence of fever: 3 ventilator-associated pneumonias, 3 catheter-related infections, 4 urinary tract infection, 2 intra-abdominal infections, 2 primary bacteremia, 1 sinusitis, and 1 other. Three of the five patients with neuromuscular weakness (Table 4) were receiving mechanical ventilation for > 10 days; the control patients received open-label methylprednisolone for unresolving ARDS. One of five patients with neuromuscular weakness, randomized to methylprednisolone, was a nonsurvivor.

**Discussion**

This is the first randomized controlled trial investigating the efficacy and safety of low-dose prolonged methylprednisolone administration in early ARDS. This study tested a pathophysiologic model that placed dysregulated systemic inflammation at the pathogenetic core of ARDS, and evaluated the effect of prolonged low-dose glucocorticoid treatment on biological and physiologic responses related to inflammation. The surrogate marker for pulmonary inflammation was LIS; the markers for systemic inflammation were C-reactive protein and MODS. The findings of this study support our original hypothesis that down-regulation of systemic inflammation with early introduction of prolonged glucocorticoid treatment hastens resolution of pulmonary organ dysfunction in ARDS. The findings in the intention-to-treat and per-protocol analysis (Web repository) were similar.

By study day 7, the response to prolonged methylprednisolone infusion at a dosage of 1 mg/kg/d was remarkable, with twice the proportion of patients randomized to methylprednisolone achieving the primary end point of a 1-point reduction in LIS and breathing without assistance. Treated patients had a significant reduction in C-reactive protein levels and by study day 7 had, in comparison to control patients, significantly lower LIS and MODS score and more ventilator-free days. After day 7, comparison between the two groups was skewed by the fact that 10 of the 15 control patients (67%) remaining on mechanical ventilation received open-label methylprednisolone (2 mg/kg/d) for unresolving ARDS. Patients randomized to methylprednisolone treatment had a significant reduction in duration of mechanical ventilation and ICU length of stay. Improvement on day 7 was not significantly affected by the baseline imbalance in the proportion of patients with catecholamine-dependent shock, and correlated with ICU and hospital survival. The survival difference observed during hospitalization was preserved after 1 year.

Innate or treatment-induced down-regulation of systemic inflammation is important to the resolution of sepsis and ARDS. All randomized trials of sepsis and ARDS with positive findings reported a significant reduction in circulating levels of inflammatory cytokines and/or C-reactive protein.
homeostasis. At the cellular level, glucocorticoids exert their effects by activating cytoplasmic heat shock protein-complexed glucocorticoid receptors, which in turn interact with activated nuclear factor-κB to prevent DNA binding and subsequent transcriptional activity. Using an *ex vivo* model of systemic inflammation, we reported that naïve peripheral blood leukocytes exposed to longitudinal plasma samples collected during prolonged methylprednisolone treatment of unresolving ARDS exhibited a progressive increase in cytoplasmic binding of glucocorticoid receptor to nuclear factor-κB, and a concomitant reduction in nuclear factor-κB DNA binding and transcription of tumor necrosis factor-α.

over time. Glucocorticoids as end-effectors of the hypothalamic-pituitary-adrenal axis are the most important physiologic inhibitors of inflammation, affecting hundreds of genes involved in stress-related homeostasis. At the cellular level, glucocorticoids exert their effects by activating cytoplasmic heat shock protein-complexed glucocorticoid receptors, which in turn interact with activated nuclear factor-κB to prevent DNA binding and subsequent transcriptional activity. Using an *ex vivo* model of systemic inflammation, we reported that naïve peripheral blood leukocytes exposed to longitudinal plasma samples collected during prolonged methylprednisolone treatment of unresolving ARDS exhibited a progressive increase in cytoplasmic binding of glucocorticoid receptor to nuclear factor-κB, and a concomitant reduction in nuclear factor-κB DNA binding and transcription of tumor necrosis factor-α.

### Table 2—Outcome Measures on Study Day 7*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Methylprednisolone (n = 63)</th>
<th>Placebo (n = 28)</th>
<th>Relative Risk (95% Confidence Interval) [n = 91]</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extubated or with ≥ 1-point reduction in LIS†</td>
<td>44 (69.8)</td>
<td>10 (35.7)</td>
<td>1.96 (1.16–3.30)</td>
<td>0.002</td>
</tr>
<tr>
<td>Patients breathing without assistance</td>
<td>34 (54.0)</td>
<td>7 (25.0)</td>
<td>2.16 (1.09–4.26)</td>
<td>0.01</td>
</tr>
<tr>
<td>LIS† (mean ± SE)</td>
<td>2.14 ± 0.12</td>
<td>2.68 ± 0.14</td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>PaO₂/FIO₂ ratio in ventilated patients (mean ± SE)</td>
<td>256 ± 19</td>
<td>170 ± 21</td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>PEEP, cm H₂O</td>
<td>10.1 ± 4.6</td>
<td>12.9 ± 5.3</td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Mechanical ventilation-free days‡</td>
<td>2.2 ± 2.1</td>
<td>1.1 ± 1.9</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>MODS score‡ (mean ± SE)</td>
<td>0.90 ± 1.1</td>
<td>1.9 ± 1.4</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Patients with MODS score &gt; 1</td>
<td>33 (54.1)</td>
<td>23 (85.2)</td>
<td>0.64 (0.48–0.84)</td>
<td>0.005</td>
</tr>
<tr>
<td>C-reactive protein level, mg/dL</td>
<td>2.9 ± 4.1</td>
<td>13.1 ± 6.8</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Cortisol level, μg/dL</td>
<td>5.7 ± 2.1</td>
<td>18.0 ± 1.6</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Patients with new infection‡</td>
<td>10 (15.9)</td>
<td>8 (28.6)</td>
<td>0.56 (0.25–1.26)</td>
<td>0.16</td>
</tr>
<tr>
<td>Patients with ventilator-associated pneumonia‡</td>
<td>4 (6.4)</td>
<td>6 (21.4)</td>
<td>0.30 (0.09–0.97)</td>
<td>0.06</td>
</tr>
<tr>
<td>Survivors‡</td>
<td>56 (88.9)</td>
<td>22 (78.6)</td>
<td>1.13 (0.92–1.40)</td>
<td>0.21</td>
</tr>
<tr>
<td>Patients with unresolving ARDS treated with open-label methylprednisolone at 2 mg/kg/d‡</td>
<td>5 (7.9)</td>
<td>10 (35.7)</td>
<td>0.22 (0.08–0.59)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. No. (%) unless otherwise indicated.
†LIS, PaO₂/FIO₂ ratio, and PEEP values from patients receiving mechanical ventilation on study day 7. Additional components for LIS are reported for methylprednisolone vs placebo: static compliance (33.9 ± 11.5 cm H₂O vs 31.9 ± 17.7 cm H₂O; p = 0.69) and chest radiograph score (3.0 ± 1.3 vs 3.4 ± 1.1; p = 0.26). The number of ventilator-free days was defined as the number of days on which a patient breathed without assistance, if the period of unassisted breathing lasted at least 48 consecutive h. The number was counted as 0 if the patient died before day 28.
‡If MODS value was missing on study day 7, the MODS score was imputed using the last available component value. The unimputed MODS scores were 0.6 ± 0.8 vs 1.3 ± 0.9 (p = 0.007).
§Three treated patients and one control patient had two infections. Extrapulmonary infections (methylprednisolone vs placebo) included urinary tract infections (n = 3 vs 1), catheter-related infections (n = 4 vs 0), intra-abdominal abscess (n = 0 vs 1), primary bacteremia (n = 0 vs 1), sinusitis (n = 1 vs 0), and wound infection (n = 1 vs 0).
¶If the LIS failed to improve LIS (see text for definition) between study days 7 and 9, the patient left the treatment arm of the study to receive unblinded methylprednisolone therapy (2 mg/kg/d) for unresolving ARDS following a previously reported protocol.

### Table 3—Duration of Mechanical Ventilation and Length of Stay; ICU and Hospital Mortality*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Methylprednisolone (n = 63)</th>
<th>Placebo (n = 28)</th>
<th>Relative Risk (95% Confidence Interval) [n = 91]</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of mechanical ventilation, d‡</td>
<td>5 (3–8)</td>
<td>9.5 (6–19.5)</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Mechanical ventilation-free days to day 28‡</td>
<td>16.5 ± 10.1</td>
<td>8.7 ± 10.2</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Length of ICU stay, d</td>
<td>7 (6–12)</td>
<td>14.5 (7–20.5)</td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>Survivors of ICU admission</td>
<td>50 (79.4)</td>
<td>16 (57.4)</td>
<td>1.39 (0.98–1.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>13.0 (8–21)</td>
<td>20.5 (10.5–40.5)</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Survivors of hospital admission</td>
<td>48 (76.2)</td>
<td>16 (57.1)</td>
<td>1.33 (0.94–1.89)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. No. (%), and median (interquartile range) unless otherwise indicated.
‡The proportion of patients remaining on mechanical ventilation on study day 14 and day 28 (methylprednisolone vs placebo) was 4 (6.4%) vs 12 (42.9%) (p < 0.001) and 3 (4.7%) vs 4 (14.2%) (p = 0.20), respectively.
¶The number of ventilator-free days was defined as the number of days a patient breathed without assistance, if the period of unassisted breathing lasted at least 48 consecutive h. The number was counted as 0 if the patient died before day 28.
and interleukin-1β. These findings provided mechanistic evidence of the pharmacologic efficacy of methylprednisolone in ARDS.

Dosage and duration of administration are fundamental variables that considerably affect the response to a pharmacologic intervention and must be taken into account in designing a trial and in analyzing the literature. Our study design differs from an older trial with negative findings that investigated a daily methylprednisolone dose of 120 mg/kg and limited duration of administration to 24 h. In sepsis trials, a linear relation has been reported between dose and/or duration and survival (p < 0.02), with increased survival at lower doses with prolonged treatment, but increased mortality at higher doses with brief treatment. Moreover, methylprednisolone at high dose (15 to 30 mg/kg/d), but not low dose, is associated with measurable immunosuppression.

In ARDS, the circulating half-life of methylprednisolone (1 mg/kg) varies from 3.8 to 7.2 h, with greatly diminished effects (irrespective of dosage) expected after 24 to 36 h. Experimental and clinical literature support the concept that duration of exposure to glucocorticoids is critical to achieving regulation of cytokine production and demonstrable therapeutic benefits. In experimental models of acute lung injury, glucocorticoid administration was shown to be effective in decreasing edema and lung collagen formation with prolonged treatment, while premature withdrawal rapidly negated the positive effects of therapy. In patients with unresolving ARDS, premature discontinuation of methylprednisolone administration was associated with physiologic deterioration that responded favorably to reinstatement of treatment. In the recent ARDS network study, the large benefits observed during methylprednisolone treatment of unresolving ARDS (27% relative risk reduction in mortality; 10 days reduction in duration of mechanical ventilation [p = 0.006]) were partially lost after premature discontinuation of study drug (within 4 days of extubation) and likely accounted for the higher rate of reintubation (9% vs 28%; p = 0.006).

Since the 1950s, it has been appreciated that a serious threat to the recovery of patients receiving prolonged glucocorticoid treatment is failure to recognize infections in the presence of a blunted febrile
response. In our prior study, four of nine pneumonia cases were identified by surveillance bronchoscopy in treated patients without fever. In the present study, 23 of 40 nosocomial infections (56%) including 5 of 10 ventilator-associated pneumonia cases were identified by infection surveillance in treated patients without fever. These findings underscore the need for strict infection surveillance in the management of patients receiving prolonged glucocorticoid treatment. Among the 73 patients (including 10 control nonimprovers) who received methylprednisolone, 3 patients (4%) had prolonged neuromuscular weakness and delayed weaning. The percentage incidence is lower than that reported in the ARDSnet study and is likely related to the lower dose of methylprednisolone and the limited use of neuromuscular blocking agents.

Many of the positive results of this trial are similar to those reported in randomized studies investigating prolonged glucocorticoid treatment in acute lung injury and ARDS. Improvement in gas exchange and reduction in duration of mechanical ventilation were previously reported for patients with early acute lung injury, septic shock-induced ARDS, and unresolved ARDS. Both trials showed that earlier introduction of prolonged...
methylprednisolone treatment was associated with a higher rate of clinical improvement. In the ARDS network trial,\(^9\) however, large imbalances in baseline characteristics for patients randomized after day 14 (age, gender, pneumonia, trauma, creatinine, APACHE [acute physiology and chronic health evaluation] III, compliance, and lung injury score) likely affected the lower mortality in the control group (8\% vs 36\%). In a study by Lee et al.,\(^4\) prolonged methylprednisolone (2 mg/kg/d) treatment in patients with early ARDS following thoracic surgery was associated with, in comparison to historical controls, a significant reduction in duration of mechanical ventilation, ICU stay, and hospital mortality.

The reduction in C-reactive protein observed during treatment is comparable to the reduction reported for patients with community-acquired pneumonia and acute lung injury,\(^11\) and is similar to the reduction in systemic inflammation shown in other randomized studies.\(^9,12,13\) Resolution of cardiac dysfunction is consistent with the beneficial effect of prolonged glucocorticoid treatment on shock reversal in septic patients.\(^33\) In agreement with reports on sepsis\(^33\) and unresolving ARDS,\(^8,13\) prolonged glucocorticoid treatment was not associated with increased risk of infections, and our data add clinical relevance to the new understanding of the immunoenhancing role of low-dose glucocorticoids.\(^29,45\)

Study limitations are attributed primarily to the small sample size and imbalances among patients with catecholamine-dependent shock that may have biased the estimate of the treatment effect on mortality, and a larger randomized trial is necessary to support the mortality findings of this study. Additional limitations include previously reported limitations in chest radiograph scoring in patients with ARDS,\(^46\) failure to incorporate a weaning procedure, and failure to strictly monitor implementation of ventilator protocol.

In conclusion, the findings of this study provide evidence that glucocorticoid treatment-induced down-regulation of systemic inflammation in ARDS is associated with a significant improvement in pulmonary and extrapulmonary organ dysfunction and a reduction in duration of mechanical ventilation and ICU length of stay. The approximate cost of 28 days of therapy was $240. A larger trial is necessary to confirm the mortality findings of this study. In a future trial, we recommend adding stratification by shock at study entry, and strict implementation and monitoring of a ventilator and weaning protocol.

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METHODS

Exclusion and Exit Criteria

Exclusion criteria included enrollment in any other investigation, extensive burns, organ transplant recipients, active life-threatening fungal infection, moribund state (i.e., not expected to live more than 6 h), terminal illness with life expectancy of less than 3 months, positive HIV status, cytotoxic therapy within 3 weeks, malignancy with estimated 6-month mortality greater than 50%, severe chronic liver disease (Child-Pugh Class C score greater than 10 points), prehospitalization Karnofsky Performance Status Scale score less than or equal to 50, greater than 200% of ideal body weight, major gastrointestinal bleeding within the last 3 months, underlying disease requiring more than 0.5 mg/kg/day of
methylprednisolone equivalent (e.g., asthma), and primary care physician not fully committed to aggressive support of the patient at the time of randomization.

Patients exited the study if potentially life-threatening complications of corticosteroid therapy developed, such as gastrointestinal bleeding, perforated viscus, or fungal infection at more than two sites. An independent Data Safety Monitoring Committee (DSMC) reviewed exited patients, safety data, deaths, and assessed eligibility for analysis.

Randomization

The study statistician used a random-number generator to create randomization tables for each institution for both medical and surgical patients. The randomization schedule was 2:1 (methylprednisolone: placebo) in blocks of 3 and remained double blinded. The randomization assignments were provided in sealed envelopes for each institution, and the pharmacist maintained records on a study log. At each interim analysis, the study pharmacist provided patient assignments directly to the study statistician for analysis.

Protocol

In conformity with ethical principles that guide clinical critical care research (reviewed in reference 1), we incorporated steps into the protocol to maximize benefits and to minimize risks (prevent complications associated with glucocorticoid treatment) to participants. If the patient failed to achieve the predefined criteria for improvement in LIS between study days 7 and 9, the
patient left the treatment arm of the study to receive unblinded methylprednisolone therapy for unresolving ARDS following a previously reported protocol. Methylprednisolone was given daily as intravenous push every 6 hours (one fourth of the daily dose) and changed to a single oral dose when oral intake was restored. A loading dose of 2 mg/kg was followed by 2 mg/kg/day from day 1 to day 14, 1 mg/kg/day from day 15 to day 21, 0.5 mg/kg/day from day 22 to day 28, 0.25 mg/kg/day on days 29 and 30, and 0.125 mg/kg/day on days 31 and 32. If the patient was extubated prior to day 14, treatment was advanced to day 15 of drug therapy and tapered according to schedule. Despite the limitations of our original small trial, the study provided strong evidence of biological and physiological improvement during methylprednisolone administration, and the study protocol (including infection surveillance and avoidance of paralysis) became standard of practice at our institution. Additional studies (reviewed in the Discussion) have since then corroborated our original data. By introducing open label methylprednisolone to nonimprovers, we recognized that mortality would be affected, and for this reason the primary end point of the study was improvement in LIS by day 7.

Failed or delayed recognition of nosocomial infections in the presence of a blunted febrile response represents a serious threat to the recovery of patients receiving prolonged glucocorticoid treatment. The study protocol incorporated (i) surveillance bronchoscopy with bilateral BAL at 5- to 7-day intervals in intubated patients (without contraindication), and (ii) a systematic diagnostic protocol if patients developed fever or had an increase in immature neutrophil count (≥
10%) or minute ventilation (≥ 30%). Finally, the use of neuromuscular blocking agents was strongly discouraged, since the combination of prolonged methylprednisolone administration in conjunction with neuromuscular blocking agents may lead to prolonged neuromuscular weakness and delayed weaning.

**Definitions**

The precipitating cause of ARDS was classified as either direct or indirect lung injury. Shock was defined as the presence of a systolic arterial blood pressure ≤ 90 mm Hg that did not resolve with rapid fluid administration and that required vasopressors. An infection was classified as definitive by previously described strict diagnostic criteria. The diagnosis of pneumonia was established by recovering microorganisms in quantitative bacterial cultures of bronchoalveolar lavage at a growth ≥ 10,000 CFU/ml.

For patients remaining intubated on study day 7, improvement in lung function was defined as (i) a reduction in LIS ≥ 1 point, and (ii) a day 7 LIS ≤ 2.0 (for study entry LIS ≤ 2.9) or ≤ 2.5 (for study entry LIS ≥ 3.0). The LIS includes two measurements related to mechanical ventilation (PEEP and Cst); for this reason, patients extubated on or by day 7 and with unassisted breathing for the subsequent 48 h were considered improvers. Resolution of individual organ dysfunction followed expert panel recommendations. The number of ventilator-free days was defined as the number of days alive on which a patient breathed without assistance, if the period of unassisted breathing lasted at least 48 consecutive hours.
Statistical Analysis

The question that this clinical trial sought to answer was whether adding methylprednisolone to the standard treatment of patients with early ARDS showed an improvement over the standard treatment alone. The primary treatment differences were expected to occur within the first 7 days, and the primary outcome variable was improvement in LIS by study day 7 (see outcome definitions). This study was conducted as a group sequential clinical trial with continuation or termination determined by periodic inspection as data were accumulated.14

At the first interim analysis (50 patients), the DSMC recommended continuing the trial and at the second interim analysis (71 patients) recommended recruitment of approximately 20 patients. At the third analysis (91 patients), there was a significant difference in LIS improvement on day 7 (69.8% vs. 35.7%; P = 0.002; Power of 0.87). The study was analyzed as intention-to-treat. Intention-to-treat analyses are standard for large trials, however, smaller trials may be biased by protocol violations, withdrawals, or missing data, and a “per protocol” analysis is recommended to reflect scientific methods of the protocol.15 Before breaking the blind, cases were reviewed by the DSMC for inclusion in a preplanned per protocol analysis. All statistical calculations were performed using the SAS System for Windows (Version 9.0, SAS Institute, Cary, NC, USA). Significance was defined as a 2-tailed test with an alpha of .05.
Baseline data between groups were compared with the Student’s t-test for continuous data and the Cochran-Mantel-Haenszel $\chi^2$ test for categorical data. For 2x2 tables where any cell contained fewer than five observations or expected cell counts were fewer than five, Fisher’s exact 2-tailed test was used. When needed, data were log transformed to meet parametric assumptions. For continuous data not normally distributed, Wilcoxon rank-sum 2-tailed normal approximation test was used for group comparisons. Parametric statistics were used when a normal distribution was achieved with log transformation. For continuous variables assessed over time, least-squared means for both groups at each time were compared with planned contrasts by repeated-measures analysis of variance. Survival and duration of mechanical ventilation curves for each treatment group were estimated using the Kaplan Meier method and compared using the log-rank test. Time was censored at death and removal from mechanical ventilation for each group.

Several variables that could potentially confound improvement in LIS were assessed post-hoc using Cochran-Mantel-Haenszel $\chi^2$ test. These variables included hospital site, age > 63, gender, severity of illness (ICU admission APACHE III score), baseline C-reactive protein (1st and 4th quartiles), adrenal function, use of pressors, medical vs. surgical patients, presence of chronic cardiovascular comorbidities, and septic cause of ARDS. C-reactive protein level was the only confounding variable detected at baseline (odds ratio change by 10%). There was no change in the direction of treatment effect when confounding was present.
We performed a series of stepwise logistic regression analyses to assess the effect of confounders and baseline differences on day 7 LIS improvement that included all of these variables and pressors at infusion. The variables retained in the model were treatment, ICU admission APACHE III, adrenal insufficiency, baseline C-reactive protein level, and gender. The treatment effect remained significant at 0.007 in the best-fit model (lowest -2 Log Likelihood and highest Homer-Lemshow goodness of fit). Although not retained in the stepwise model, we assessed models including baseline pressors and septic cause of ARDS in further regression models. The best fit model included treatment, ICU admission APACHE III, adrenal insufficiency, C-reactive protein level, gender, and pressors, once we accounted for 14 missing variables (11 C-reactive protein levels and 3 APACHE III) by imputing group means (Homer-Lemshow goodness of fit 0.58) and the type 3 treatment effect remained significant at 0.002.

**Per Protocol Analysis**

This analysis most closely reflects the scientific model underlying the study design.\(^\text{15}\) The reasons for excluding patients in per protocol analysis are shown in Figure 1. The proportion of patients excluded in the methylprednisolone group was similar to the control group and to proportions reported in a recent ARDS trial.\(^\text{18}\) Eight of the twelve patients removed for per protocol analysis (Figure 1) had catecholamine-dependent shock leading to a similar distribution in the two groups (20% vs 33%; \(P = 0.21\)). Similar to the intention-to-treat analysis, by day 7, the methylprednisolone-treated group had
twice the proportion of patients with a 1-point reduction in LIS (74.6% vs. 37.5%; P = 0.002) and breathing without assistance (58.2% vs. 29.2%; P = 0.02). By day 7, a 50% reduction in C-reactive protein level was achieved in 97.6% vs. 58.8% (P < 0.001). Duration of mechanical ventilation (5 (4-8) vs 7 (6-17); P = 0.008) and length of ICU stay (7 (6-12) vs. 14 (7-20); P = 0.02) were similar to intention-to-treat analysis. ICU survival [90.2% vs. 71.4%; P = 0.07; relative risk (95%CI) = 1.26 (0.95-1.68)] showed a trend toward significance, while no significant change was seen in hospital mortality [86.3% vs. 71.4%; P =0.18; relative risk (95%CI) = 1.21 (0.90-1.62)].
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Methylprednisolone Infusion in Early Severe ARDS* Results of a Randomized Controlled Trial
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