An Exploratory Reanalysis of the Randomized Trial on Efficacy of Corticosteroids as Rescue Therapy for the Late Phase of Acute Respiratory Distress Syndrome*

G. Umberto Meduri, MD[1]; Lisa Bridges, MSN, ACNP[1]; Reed A. C. Siemieniuk, MD[2,3]; Mehmet Kocak, PhD[4]

***See also p. 1011.**

[1]Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Memphis Veterans Affairs Medical Center, Memphis, TN.

[2]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada.

[3]Department of Medicine, University of Toronto, Toronto, ON, Canada.

[4]Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN.

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Dr. Meduri wrote the study and wrote the first draft of the report with the assistance of Ms. Bridges. Ms. Bridges standardized definitions and prepared the dataset. Drs. Siemieniuk and Kocak did the statistical analysis and collaborated in writing the article. All authors reviewed and approved the final report.

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For information regarding this article, E-mail: gmeduri@uthsc.edu

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Objectives: In the Acute Respiratory Distress Syndrome Network randomized controlled trial, methylprednisolone treatment was associated with increased return to mechanical ventilation with partial loss of early improvements. We hypothesize a causal relationship between protocol-driven rapid discontinuation of methylprednisolone post extubation and return to mechanical ventilation. To explore this possibility, we investigated the timing that events occurred in each treatment arm during active treatment intervention (efficacy) and after stopping therapy.

Design and Settings: Retrospective intention-to-treat analysis of multicenter randomized controlled trial.

Patients and Interventions: Patients were randomized to methylprednisolone (2 mg/kg/d) or placebo (89 vs 91). The target sample size was reduced post hoc and provided 80% power for an optimistic 50% mortality reduction.

Measurements and Main Results: Findings are reported as methylprednisolone versus placebo. By day 28, fewer patients died before achieving extubation (15.7% vs 25.3% and risk ratio, 0.62; 95% CI, 0.34–1.13), more achieved successful extubation (71.9% vs 49.5% and risk ratio, 1.45; CI, 1.14–1.85), time to successful extubation was shorter (hazard ratio, 2.05; CI, 1.42–2.96), and more were discharged alive from the ICU (65.2% vs 48.3%; risk ratio, 1.35; CI, 1.04–1.75). After treatment discontinuation, more methylprednisolone-treated patients returned to mechanical ventilation (26.6% vs 6.7%; risk ratio, 3.98; CI, 1.24–12.79)—consistent with reconstituted systemic inflammation in the presence of adrenal suppression. Participants returning to mechanical ventilation without reinstitution of methylprednisolone had increased risk of ventilator dependence and mortality. Despite loss of early benefits, methylprednisolone was associated with sizable and significant improvements in all secondary outcomes and reduction in serious complications (shock and severe infections).

Conclusions: During active intervention, methylprednisolone was safe and effective in achieving disease resolution. Our findings support rapid glucocorticoid discontinuation post extubation as likely cause of disease relapse. Gradual tapering might be necessary to

preserve the significant improvements achieved during methylprednisolone administration. (*Crit Care Med* 2018; 46:884–891)

Key Words: glucocorticoid treatment; reconstituted systemic inflammation; survival; tapering

In 2006, the acute respiratory distress syndrome (ARDS) network published the findings of the landmark randomized controlled trial (RCT) "Efficacy of Corticosteroids as Rescue Therapy for the Late Phase of Acute Respiratory Distress Syndrome (LaSRS)" investigating the effects of prolonged methylprednisolone treatment in patients with persistent ARDS (1). The LaSRS study, conducted from July 1997 to November 2003, was designed to validate the encouraging findings of translational and experimental research, several observational studies (reviewed in reference [1]), and a small pilot randomized trial (2). The LaSRS trial was initially designed to detect a 30% relative reduction in 60-day mortality with a sample size of 400 patients. On October 1999, because of low recruitment, the study was resized to 200 patients (LaSRS protocol Version V, June 2, 2000) and the anticipated relative reduction in 60-day mortality was increased accordingly from 30% to 50% (1). No justification was provided for the post hoc increase in expected effect size. The patient population was divided into early ($n = 132$—randomized on ARDS day 7–13) and late ($n = 48$—randomized on ARDS day 14–28) randomization subgroups.

The LaSRS study, perhaps unsurprisingly, did not detect a significant difference in the primary outcome. However, despite the small sample size, there were meaningful and significant improvements in all secondary outcomes, including an increase in ICU and mechanical ventilation (MV)–free days by day 28 and a reduction in markers of inflammation and serious complications (1). The RCT found overall no difference in 60- and 180-day hospital mortality and an increased unadjusted mortality (3) for the late randomization subgroup. The late randomization subgroup, however, had significant imbalances in baseline characteristics and an unusually low mortality (8%) in the control group (4). In a subsequent ancillary publication, the LaSRS authors reported that, after adjustments for baseline imbalances, there was no apparent mortality difference ($p = 0.325$) for those randomized after day 13 (3). The authors concluded that these findings "do not support the routine use of methylprednisolone for persistent ARDS despite the improvement in cardiopulmonary physiology." (1)

Although the study was probably destined to fail traditional hypothesis testing because of unrealistic effect size expectations, there may have been other contributors. The LaSRS protocol included "rapid tapering" (≤ 36 hr) of study treatment 48 hours after initial extubation, and in patients who deteriorated after stopping therapy, glucocorticoids were not reinstituted. The risk for untreated adrenal suppression (5) was not described in the protocol or the consent form. More methylprednisolone-treated patients rapidly returned to MV, and this was associated with increased ventilator dependence and mortality. The LaSRS article (1) and letters to the editor (6, 7) identified recrudescence of ARDS from premature discontinuation of study drug as a potential mechanism for the return to MV. However, no analysis was provided to support or negate this hypothesis.

We, therefore, conducted a retrospective analysis of the LaSRS RCT to evaluate outcome during study drug administration (treatment efficacy), and after rapid discontinuation of treatment post extubation. Our first hypothesis was that the antiinflammatory action of methylprednisolone during active treatment intervention—in comparison to placebo—was associated with earlier disease resolution and that delaying initiation of treatment by a few days (before or after ARDS day 14) should not have affected the response to intervention. Our second hypothesis was that the abrupt discontinuation of methylprednisolone resulted in reconstituted systemic inflammation, leading to increased chance of returning to MV and that failure to reinstitute glucocorticoid treatment leads to increased morbidity and mortality. Since the original LaSRS report provided conflicting results on neuromuscular weakness (1), its potential relationship with the return to MV was also explored. Finally, our findings are compared with similar ARDS RCTs (2, 8, 9) that have investigated prolonged methylprednisolone treatment and incorporated slow tapering after extubation.

METHODS

The NHLBI Biologic Specimen and Data Repository Information Coordinating Center kindly provided the ARDSnet02 Dataset and the Descriptive Report of Late Steroid Rescue Study (10). We received institutional review board approval for access to the dataset (Secondary Analysis of ARDSnet02 Limited Dataset—Institutional review Board: 382094-3). Data were available until 28 days of follow-up for most outcomes and therefore our primary analyses are restricted to 28 days. For components of the LaSRS protocol, definitions, methodology, preestablished outcome measurements, and statistical analysis, see **supplemental digital content** (Supplemental Digital Content 1, http://links.lww.com/CCM/D298).

Findings During Active Treatment Intervention (Efficacy)

Throughout this section, data are reported as methylprednisolone group ($n = 89$) versus placebo group ($n = 91$). By study day 7, methylprednisolone—in comparison to placebo—was associated with a significant 1) reduction in plasma interleukin (IL)–6 levels ($p < 0.001$) and percentage of neutrophils in bronchoalveolar lavage ($p = 0.014$) (1), and 2) increase in functional large aggregates surfactant (11). Ninety-four patients received study medication until the day of extubation: 59 of 89 (66.3%) versus 35 of 91 (38.5%). Mean time to discontinuation of treatment after extubation was 2.7 ± 1.4 versus 3.1 ± 1.2 days ($p = 0.17$). The total mean duration of therapy was approximately 2 weeks (12.3 ± 6.5 versus 13.9 ± 7.6 d; $p = 0.21$). Data on removal of study drug prior to extubation are provided in the supplemental digital content (Supplemental Digital Content 1, http://links.lww.com/CCM/D298).

Transitions between states by day 28 are shown in **Figure 1**. By day 28, 14 patients (15.7%) versus 23 (25.3%) died before initial extubation (risk ratio [RR], 0.62, 95% CI, 0.34–1.13), more patients in the methylprednisolone group achieved

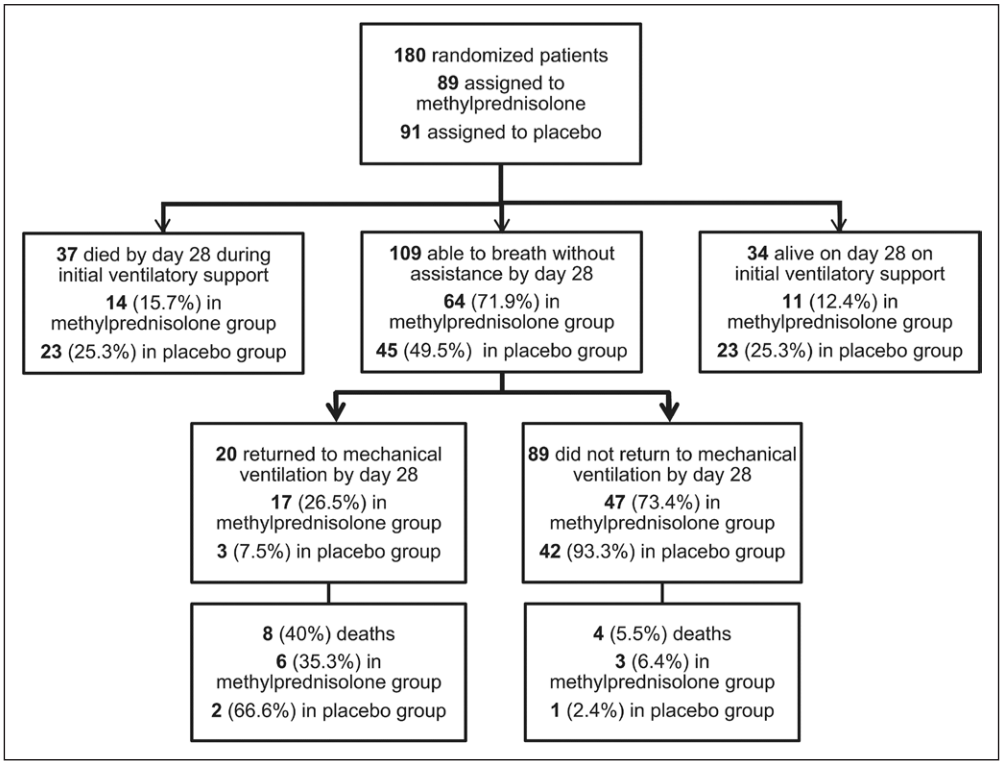

Figure 1. Flow diagram of those who achieved initial successful extubation and then returned to mechanical ventilation in the first 28 d of observation. After day 28, two patients in the methylprednisolone group and one in the placebo group that had achieved successful extubation returned to mechanical ventilation (survivors). An additional seven in the methylprednisolone group and 20 in the placebo group achieved successful extubation after day 28 (in all cases, the study treatment was completed before extubation); of those, one and two patients returned to mechanical ventilation, respectively.

successful extubation (64 [71.9%] vs 45 [49.5%] and RR, 1.45; CI, 1.14–1.85) and were discharged alive from the ICU (58 [65.2%] vs 44 [48.3%] and RR, 1.35; CI, 1.04–1.75). Results were similar for patients in the early and late randomization subgroups (**Fig. 2**). The methylprednisolone group achieved twice the extubation rate of the control group by day 28 (hazard ratio, 2.05; CI, 1.42–2.96) (**Fig. 3**) and a sizable reduction in duration of initial MV (14.1 ± 1.7 vs 23.6 ± 2.9 d; $p = 0.006$) (1).

Findings After Rapid Discontinuation of Study Treatment Post Extubation

Among patients who were successfully extubated, more patients in the methylprednisolone group returned to MV by day 28 (17/64 [26.6%] vs 3/45 [6.7%] and RR, 3.98; CI, 1.24–12.79) (Fig. 2). **Table 1** shows the characteristics and outcome of patients that did and did not return to MV. Most patients returning to MV were in the early randomization subgroup (14 vs 2). Patients returning to MV had a higher 60-day mortality than those nonreturning to MV (8/20 [40.0%] vs 4/89 [4.5%] and RR, 8.90; CI, 2.97–26.68) (Fig. 2). Patients in the methylprednisolone group who were discharged from the ICU were also more likely to return to ICU (14/58 [24.1%] vs 3/44 [6.8%] and RR, 3.54; CI, 1.08–11.56).

The methylprednisolone group had shorter mean time from extubation to return to MV (5.1 ± 1.1 vs 13.2 ± 5.4 d; $p = 0.006$) (10), and longer duration of additional MV in survivors (16.0 ± 4.1 vs 6.5 ± 3.3 d; $p = 0.77$) (10). Patients who returned to MV and survived (12 vs 3) contributed an additional 3.15 and 0.3 days to the total mean duration of MV of their respective treatment group.

Overall Response

By day 28, despite the negative impact on mortality ($n = 5$) and duration of MV (accounting for an additional 68.8 d in 12 survivors) for those returning to MV, the methylprednisolone group had a sizable increase in MV-free days (11.2 ± 9.4 vs 6.8 ± 8.5 d; mean difference, 4.4 d; 1.8–7.0 d) (1). Including the available data past day 28, 72 patients (79.1%) versus 65 (73.0%) achieved initial successful extubation, and 26 patients (20 vs 6; $p = 0.006$) eventually returned to MV (1). Despite increased return to MV in the methylprednisolone group, the mean total duration of MV (including return to MV) in survivors was 17.6 versus 29.4 days in the placebo group (11.8 fewer d; CI, 19.7–3.9) (10).

Unlike the late randomization subgroup, the randomization in the subgroup of patients diagnosed with ARDS within 14 days ($n = 132$) led to well-balanced baseline characteristics. Although return to MV contributed five of 18 deaths (28%) in the methylprednisolone versus one of 24 (4%) in the placebo group (**Table 1**), study treatment in early randomization group was associated with a 25% (18/66 [27.3%] vs 24/66 [36.4%] and RR, 0.75; CI, 0.45–1.24) and 31% (18/66 [27.3%] vs 26/66 [39.4%] and RR, 0.69; CI, 0.42–1.13) relative reduction in 60-day and 180-day mortality, respectively.

Overall, all but four deaths occurred in ventilator-dependent patients, and details are reported in the supplemental digital content (Supplemental Digital Content 1, http://links.lww.com/CCM/D298).

Safety Profile

Except for transient early (study days 1 and 2) bolus-associated hyperglycemia (**Supplemental Fig. 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/D299; legend, Supplemental Digital Content 1, http://links.lww.com/CCM/D298), methylprednisolone treatment was well tolerated and not associated with an increase in adverse effects. There were fewer serious complications including shock (5 [5.6%] vs 18 [19.8%] and RR, 0.28; CI, 0.11–0.73), pneumonia (6 [6.7%] vs 16 [17.6%] and RR, 0.38; CI, 0.16–0.94), bacteremia (22

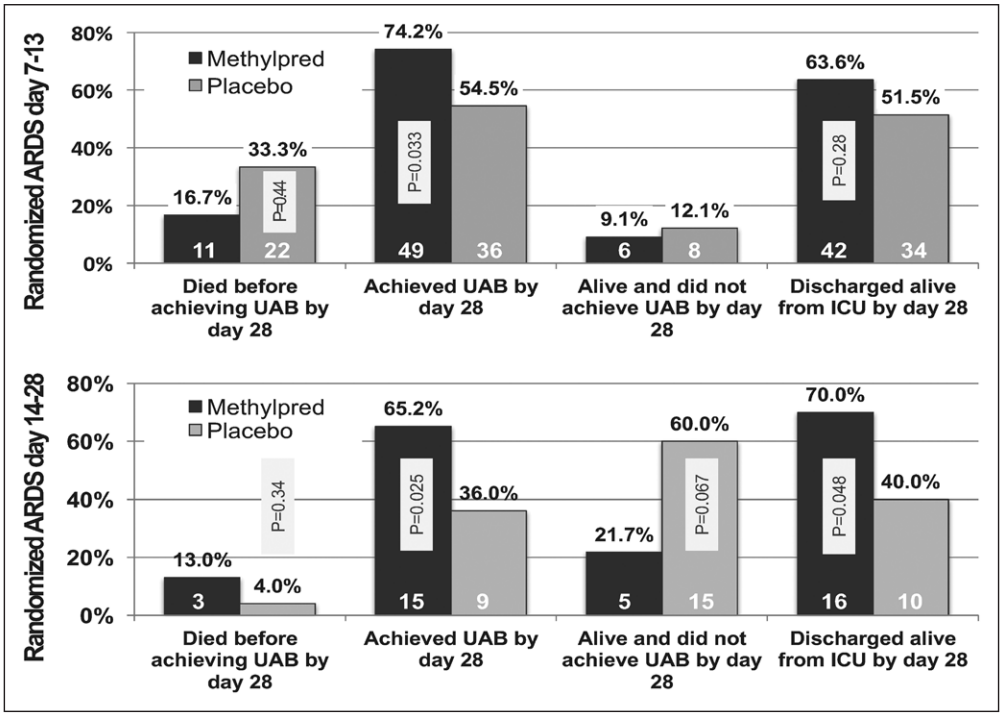

Figure 2. Events by day 28 in patients randomized on acute respiratory distress syndrome (ARDS) day 7–13 and 14–28. Patients ($n = 132$) in the early randomization group (ARDS day: 9.4 ± 2.0 vs 9.3 ± 2.0) had similar baseline characteristics. Among patients ($n = 48$) in the late randomization group (ARDS day: 16.6 ± 2.4 vs 16.6 ± 3.0), the methylprednisolone group had worsened static lung compliance (18. 4 ± 7.4 vs 26.4 ± 14.8; $p = 0.07$) and lung injury score (3.7 ± 0.8 vs 2.7 ± 1.2; $p = 0.02$) (1). In the late randomization group, all patients with age greater than 65 belonged to the methylprednisolone group (9 vs 0; $p = 0.002$) with all but one death (age 63 yr) belonging to this elderly cohort.

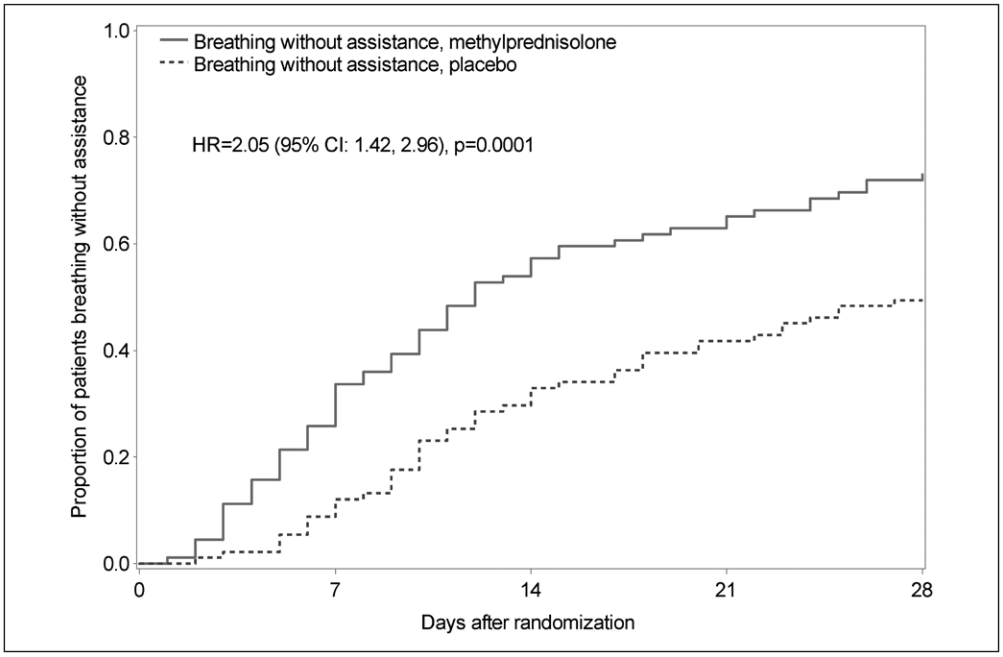

Figure 3. Probability of achieving successful extubation from randomization (methylprednisolone vs placebo) to study day 28. HR = hazard ratio.

[24.7%] vs 37 [40.6%] and RR, 0.60; CI, 0.39–0.94), and serious infections events (25 [28.0%] vs 43 [47.3%] and RR, 0.59; CI, 0.39–0.88) (1, 10). Serious infections included suspected/probable pneumonia (6 vs 16), possible pneumonia (11 vs 13), wound infection (0 vs 4), viral infection (0 vs 2), peritonitis (2 vs 0), fungal infection (3 vs 7), empyema (1 vs 1), and abscess (2 vs 0) (10). Pathogens causing pneumonia included *pseudomonas* species (13), enterococcus (2), other Gram-negative rods (11), *Staphylococcus aureus* (11), other Gram-positive cocci (4), and others (3). Wound infections were caused by candida (2), *pseudomonas* species (1), and others (1) (10).

The frequency of postrandomization neuromyopathy was similar in the two groups (21 vs 20), and among patients who achieved successful extubation by day 28 (22/64 [34.4%] vs 12/45 [27.7%]; $p = 0.41$). The frequency of neuromyopathy was also similar in patients who did (7/17 [41%] vs 0/3 [0%]; $p = 0.52$) and did not return to MV (16/47 [34.0%] vs 11/42 [26.2%]; $p = 0.49$). Among patients with neuromyopathy, the methylprednisolone group had shortened median duration of MV: 15 days (CI, 12–22) versus 26 (CI, 14–38), p value equals to 0.003. Detailed findings related to neuromuscular weakness and shock are reported in the supplemental digital content (Supplemental Digital Content 1, http://links.lww.com/CCM/D298).

DISCUSSION

The LaSRS RCT failed to achieve a significant improvement in the primary mortality outcome and is frequently quoted—in isolation of the updated literature—to negate a therapeutic benefit for prolonged glucocorticoid treatment in ARDS (12). Our analysis, however, demonstrates that, during active treatment (12.3 ± 6.52 d), methylprednisolone was associated with accelerated disease resolution achieving twice the extubation rate of control (hazard ratio, 2.05; CI, 1.42–2.96) (Fig. 3), and a sizable 9.5 days' reduction

TABLE 1. Outcome Among Patients That Achieved Initial Extubation by Day 28: Did Not Return Versus Returned to Mechanical Ventilation by Day 28

	Did Not Return to MV by Day 28 ($n = 89$)			Did Return to MV by Day 28 ($n = 20$)		
Variables	**Methylprednisolone**	**Placebo**	***p***	**Methylprednisolone**	**Placebo**	***p***
Patients achieving extubation by day 28, *n* (%)	47 (73.4)	42 (93.3)	0.011	17 (26.6)	3 (6.7)	0.008
Randomized on ARDS day 7–13	35 (71.4)	34 (94.4)	0.010	14 (28.6)	2 (5.7)	0.003
Randomized on ARDS day 14–28	12 (80.0)	8 (88.9)	1.00	3 (20.0)	1 (11.1)	0.34
Mean time to achieving initial successful extubation, d, mean ± SD	10.23 ± 6.7	13.5 ± 6.8	0.02	9.4 ± 6.9	9.0 ± 3.6	0.7
Shock after achieving initial successful extubation, *n* (%)	0 (0.0)	0 (0.0)		1 (5.9)	0 (0.0)	
Patients with neuromyopathy, *n* (%)	16 (34)	11 (26.2)	0.49	7 (41.2)	0 (0.0)	0.52
Time from extubation to removal of study drug, d, mean ± SD	2.66 ± 1.46	3.13 ± 1.16	0.17	2.80 ± 1.37	2.33 ± 2.08	0.86
Additional days on MV by study day 28 in survivors ($n = 14$), mean ± SD	NA	NA		5.73 ± 4.56	9.0 ± 7	
28-d mortality, *n* (%)[a]	3 (6.3)	1 (0.25)		5 (29.4)	1 (33.3)	
60-d mortality, *n* (%)[b]	3 (6.3)	1 (0.25)		6 (35.3)	2 (66.6)	

ARDS = acute respiratory distress syndrome, MV = mechanical ventilation, NA = not available.

[a]Belong to early randomization group.

[b]Additional two deaths (1 vs 1) belong to late randomization group.

in duration of initial MV (1). By day 28 (Fig. 2), fewer patients in the methylprednisolone group died before extubation and more patients were discharged alive from the ICU (65.2% vs 48.3% and RR, 1.35; CI, 1.04–1.75). These results are consistent with those of other RCTs investigating methylprednisolone in ARDS (2, 8, 9) (**Supplemental Table 1**, Supplemental Digital Content 3, http://links.lww.com/CCM/D300) (13). Furthermore, the point estimate of effect on mortality while on therapy (a reduction by approximately 10%) (Fig. 1) is consistent with the rest of the literature (nine RCTs) (**Supplemental Fig. 2**, Supplemental Digital Content 4, http://links.lww.com/CCM/D301; legend, Supplemental Digital Content 1, http://links.lww.com/CCM/D298), although the confidence interval in this single underpowered study included no effect. We have also found—in agreement with a prior report (14)—that methylprednisolone treatment was highly effective in both the early and late randomization subgroups (Fig. 2). By day 28, the improvements in secondary outcomes were superior to those of other ARDS network trials (15, 16), and contrasts with the lack of reduction in duration of MV reported in the landmark lower versus traditional tidal volumes RCT (median 8 d in both groups) (15). Our findings—in support of our first hypothesis—provide strong evidence of therapeutic efficacy during active intervention.

While glucocorticoids have a powerful antiinflammatory effect, this is achieved at the expense of reversible suppression of the hypothalamic-pituitary-adrenal (HPA) axis. The Food and Drug Administration package insert for methylprednisolone (Reference ID: 3032293; https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/011856s103s104lbl.pdf) warns that rapid discontinuation of treatment versus gradual reduction of the dosage—in the presence of a suppressed adrenal function—can lead to a reconstituted inflammatory response with clinical deterioration necessitating prompt reinstitution of treatment (5). For this reason, the true efficacy of methylprednisolone in critically ill patients is best evaluated during active treatment administration, and events following drug removal

must be addressed in relation to the modality of tapering and reinstitution of treatment in those with clinical deterioration.

The risk for glucocorticoid treatment-associated adrenal insufficiency in critically ill patients with dysregulated systemic inflammation is underappreciated. It has been shown that neither the total dose, the highest dose, nor the duration of glucocorticoid treatment is a significant predictor of HPA axis recovery (17). In the recent Reduction in the Use of Corticosteroids in Exacerbated chronic obstructive pulmonary disease trial that evaluated prednisone 40 mg daily for 5 or 14 days, adrenal suppression was detected at hospital discharge and at 30 days in 38% and 9% of patients, respectively, and without difference between 5 and 14 days glucocorticoid exposure (18).

Observational studies have shown that premature discontinuation of glucocorticoid treatment in patients with ARDS is associated with rapid clinical deterioration that resolves with reinstitution of treatment (19–21). Similar to the experimental literature (22, 23), critical care RCTs have shown that abrupt glucocorticoid discontinuation after a 3–7 days treatment was rapidly followed by a reconstituted inflammatory response (increased levels of inflammatory markers) with clinical relapse (return to MV, worsening multiple organ dysfunction) in approximately one third of patients (24–26). In the LaSRS trial, discontinuation of study drug 48 hours post extubation was associated with clinical relapse in one-quarter of methylprednisolone-treated patients. Several patients rapidly returned to MV (without reinstitution of study treatment) and fared poorly: they required additional days of MV and had a nine-fold increased risk of 60-day mortality ($p = 0.001$) in comparison to patients that did not return to MV

Based on preestablished criteria, several findings—in support of our second hypothesis—are consistent with recrudescence of ARDS from reconstituted systemic inflammation in the presence of untreated suppressed HPA axis and are reviewed in the supplemental digital content (Supplemental Digital Content 1, http://links.lww.com/CCM/D298). In addition, Supplemental Table 1 (Supplemental Digital Content 3, http://links.lww.com/CCM/D300), a comparison of the LaSRS trial versus three RCTs incorporating slow tapering (over 12–16 d) after extubation shows that increased return to MV was exclusive to the LaSRS methylprednisolone group ($p = 0.02$) (13).

Since the original LaSRS publication (1), support of biological plausibility for prolonged glucocorticoid treatment has increased (27–29). In 2008, an international multidisciplinary task force convened by the Society of Critical Care Medicine coined the term "critical illness-related corticosteroid insufficiency" (CIRCI) to define the central role played by the HPA axis and the activated glucocorticoid receptor alpha (GRα) complex in the pathogenesis of dysregulated systemic inflammation in critical illness and ARDS (30). Three major pathophysiologic events account for the neuroendocrine decompensation observed in CIRCI: 1) multilevel dysregulation of the HPA axis (correlating with circulating inflammatory cytokine levels), 2) altered cortisol metabolism, and 3) secondary generalized (circulating and tissue cells) reduction in GRα number/function with multifactorial tissue resistance to endogenous glucocorticoids (30).

Importantly, increasing GRα activation with quantitatively adequate and prolonged glucocorticoid supplementation can reverse CIRCI. In both experimental and clinical RCTs, prolonged glucocorticoid treatment was shown to restore GRα number and function leading to: 1) down-regulation of systemic and pulmonary inflammation and 2) resolution of ARDS (adaptive lung repair) (30, 31). Treatment was associated with a rapid, significant, and sustained reduction in circulating and bronchoalveolar lavage markers of inflammation, hemostasis, and tissue repair (27) and an increase in protein C levels (32) and functional surfactant (11). Furthermore, glucocorticoid treatment-associated down-regulation of systemic and pulmonary inflammation might lower the risk of developing nosocomial infections by 1) decreasing duration of MV, 2) achieving an inflammatory milieu less favorable to intra- and extracellular growth of bacterial pathogens frequently encountered in ARDS (*S. aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter* species) (33), and 3) improving opsonization-dependent phagocytic neutrophil function (34) and intracellular killing (35). Inflammation has a bidirectional effect on the growth of nosocomial pathogens; lower inflammatory cytokine levels—similar to values detected in ARDS survivors—suppress growth, while higher levels—similar to values detected in ARDS nonsurvivors—enhance bacterial growth in a dose-dependent manner (33). In lipopolysaccharide-activated immune cells exposed to graded doses of methylprednisolone, concentrations similar to the plasma levels (150–250 μg/mL) achieved in ARDS patients receiving methylprednisolone infusion (1 mg/Kg/d) (36) were associated with the greatest reduction in both intracellular bacterial growth and expression of tumor necrosis factor-α, IL-1β, and IL-6 (35).

Since the original LaSRS publication (1), six additional RCTs were published and incorporated in a systematic meta-analysis (Supplemental Fig. 2, Supplemental Digital Content 4, http://links.lww.com/CCM/D301; legend, Supplemental Digital Content 1, http://links.lww.com/CCM/D298; and **Supplemental Fig. 3**, Supplemental Digital Content 5, http://links.lww.com/CCM/D302; legend, Supplemental Digital Content 1, http://links.lww.com/CCM/D298) for the 2017 guidelines for the management of CIRCI in critically ill patients (29). The pooled relative risk estimate for hospital mortality with glucocorticoids from studies only at a low risk of bias was 0.83 (95% CI, 0.71–0.98), and independent of hospital mortality, treatment was associated with a seven days increase in ventilator-free days (mean difference 7.06 d, 95% CI 3.19–10.93) (Supplemental Digital Content 4 in [29]), leading to the conditional recommendation (moderate quality of evidence) for prolonged glucocorticoid treatment in patients with moderate to severe ARDS (treatment protocol in Supplemental Digital Content 5 in [29]) (29). Similar to the LaSRS trial, the aggregate data also show a reduced rate of nosocomial infections (120 [27.5%] vs 134 [35.3%] and RR, 0.78; CI, 0.63–0.95) in patients randomized to glucocorticoid treatment.

Glucocorticoid treatment is also associated with decreased risk for developing ARDS in patients with sepsis (37, 38). Other treatment interventions known to suppress nuclear factor-κB (statins and aspirin) have been investigated in RCTs directed at both prevention and treatment of ARDS with no apparent benefit (39, 40).

These interventions, however, may not achieve a timely and consequential antiinflammatory effect in critical illness (41, 42).

Future research directions include investigating modalities to improve cellular responsiveness to glucocorticoid administration, by correcting disorders associated with intracellular glucocorticoid resistance (43). In ARDS, CIRCI-associated dysregulated systemic inflammation is associated with oxidative stress (44) and subnormal plasma ascorbic acid concentrations (44), both known to cause glucocorticoid resistance. There is a multifaceted interplay between oxidative stress, ascorbic acid, and the activated GRα transcriptional control of mitochondrial proteins encoded by nuclear and mitochondrial DNA (45). Although GRα inducible gene expression is suppressed under oxidative stress conditions (46), ascorbic acid administration reverses oxidation of the GR restoring cellular glucocorticoid-responsiveness in oxidative conditions (46). Both ascorbic acid (47) and the GRα (48) are essential to endothelial cell homeostasis and the combination of glucocorticoids with ascorbic acid is superior to either one alone in protecting vascular endothelium critical to ARDS recovery (49). Additionally, glucocorticoids in a time- and concentration-dependent manner facilitate the uptake of ascorbic acid into the cell (50), providing the rationale for combination treatment (51). The findings of a recent retrospective before-after study in patients with septic shock (leading cause of ARDS) have generated momentum for increased research in this field (51).

The major limitation of this study is that our analyses are all post hoc and were not considered in the initial protocol. While it is possible that other unknown factors might have contributed to increased return to MV in the methylprednisolone group, it must be specific to the LaSRS treatment protocol or due to chance because this phenomenon was not seen in similar RCTs. The only key identifiable difference in the LaSRS treatment protocol was rapid discontinuation post extubation compared with several days-to-weeks in other RCTs.

To conclude, untreated reconstituted systemic inflammation following discontinuation of methylprednisolone post extubation likely explains the increased return to MV and associated morbidity/mortality in the methylprednisolone group. Further, the study was also underpowered to detect a realistic mortality reduction. Despite these problems, and contradicting the frequent misrepresentation of this trial (12), we found that methylprednisolone was highly effective during drug administration across the early and late randomization subgroups. The sizable improvements in important patient-centered outcomes were also accompanied by a significant reduction in serious complications (shock and serious infectious events).

These findings underscore how gradual tapering may be essential to 1) preserve early improvements (accelerated disease resolution), 2) sustain continuous resolution of inflammation with the restoration of tissue homeostasis (52), and 3) achieve gradual recovery of the suppressed HPA axis to forestall disease relapse from reconstituted systemic inflammation. Finally, any rapid deterioration after discontinuing glucocorticoids should prompt reinstitution of glucocorticoid therapy (5).

In the near future, improved knowledge of CIRCI should provide opportunities to investigate glucocorticoid administration in combination with interventions directed at increasing its intracellular sensitivity/response. Finally, the completion of a multicenter Spanish trial investigating dexamethasone (10 d duration including tapering) in patients with persistent early ARDS will provide valuable new data on the role of prolonged glucocorticoid treatment in ARDS (53).

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