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Methylprednisolone: Likely an Effective Treatment in Acute Respiratory Distress Syndrome

To the Editor:

We read with interest the article published in a recent issue of *Critical Care Medicine* by Fielding-Singh et al (1) on treatment adjuncts in acute respiratory distress syndrome (ARDS). We wish to comment on the section dealing with glucocorticoid treatment since it differs from the findings and recommendations of the 2017 Corticosteroid Guideline Task Force of the Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (2). The analysis to support the Task Force's efforts (2) was limited to nine randomized controlled trials (RCTs) that investigated methylprednisolone ($n = 322$) (3) and hydrocortisone ($n = 494$) treatment in ARDS for a duration of at least 7 days. The Task Force found moderate quality/certainty of evidence for a reduction in the duration of mechanical ventilation (mean difference, 7.06 d; 95% CI, 3.19–10.93) and improved survival (relative risk, 0.64; 95% CI, 0.46–0.89) and therefore made a conditional recommendation for methylprednisolone treatment (2). Except for hyperglycemia, glucocorticoid treatment was not associated with increased risk for neuromuscular weakness, gastrointestinal bleeding, or nosocomial infections (very low certainty evidence) (2).

We wish to address three points raised by the authors: 1) inconsistency in meta-analyses, 2) ARDS network Late Steroid Rescue Study (LaSRS) findings, and 3) clinical application.

1) Inconsistency in meta-analyses: The “mixed” results reported by meta-analyses (1) are explained by those (references 95, 97–99 in the article by Fielding-Singh et al [1]) that incorporated RCTs in the 1980s investigating short-term (24–48 hr) massive daily methylprednisolone doses (120 mg/kg), an obsolete intervention discredited by the present pathophysiologic understanding of ARDS and dose-response studies.

2) ARDS network LaSRS findings: The LaSRS RCT (reference 89 in the article by Fielding-Singh et al [1]), was underpowered to demonstrate a difference in mortality. The sample size was adjusted after 2 years from 400 to 200 patients, and the anticipated relative reduction in mortality changed from 30% to 50% (unachievable) without justification. Yet, despite this limitation, there were important improvements in all secondary outcomes including a sizable reduction in duration of mechanical ventilation in survivors (11.8 fewer days; 95% CI, 10.7–3.9) (4). Importantly, post hoc analysis examining those randomized after day 13 (control group mortality 8%), demonstrated no apparent mortality difference ($p = 0.325$) after adjustments for large baseline imbalances

(5). A similar post hoc analysis of the data provided evidence of efficacy even in this late administration subgroup (4).

3) Clinical application: In ARDS, reduction in duration of mechanical ventilation is an important outcome as it has been associated with decreased short-term and long-term morbidity and mortality. The SCCM Task Force made a conditional recommendation for starting methylprednisolone (protocol outlined in Supplemental Digital Content 5 in [2]). Patients and families should be provided with factual information about this high benefit/risk treatment. An initial bolus may be considered to achieve maximal glucocorticoid receptor saturation to be followed by an infusion to maintain steady state (2). Delaying treatment until refractory hypoxemia occurs and removal of treatment based on a nondefined lack of improvement by day 3 is not supported by the literature and not included in the Guidelines' protocol (Supplemental Digital Content 5 in [2]). Tapering is essential to preserve improvements and achieve gradual recovery of the suppressed hypothalamic-pituitary-adrenal axis (3). Finally, there is no contraindication to using methylprednisolone in conjunction with a 2 days duration of neuromuscular blockade.

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The authors reply:

We thank Meduri et al (1) for their letter. In our opinion, the literature does not support the conditional recommendation made by the 2017 Corticosteroid Guideline Task Force (2), recent article published in *Critical Care Medicine*. Responding to each of the points raised in the letter:

1) Inconsistency in meta-analysis: We agree with Meduri et al (1) that meta-analyses in this area suffer from significant methodologic heterogeneity. This issue extends to the Task Force's analysis. The quoted relative risk of 0.64 comes from an analysis within the 2017 Guidelines that includes nine trials—five of which have either a high risk of bias or serious methodologic concerns.

The guidelines contain a similar analysis limited to four studies assessed to be at lower risk of bias; however, even in these studies, there are methodologic issues. One study was a retrospective analysis of a randomized controlled trial in patients with septic shock, with benefit found only in the subset of patients who failed to respond to corticotropin (3). In another, a majority of patients randomized to placebo who remained on mechanical ventilation on day 9 were crossed over to methylprednisolone, making subsequent outcomes challenging to interpret (4). The I^2 for the primary analysis was 50%, suggesting approximately 50% of variation across studies results from heterogeneity. In our view, positive meta-analysis findings incorporating only a handful of small studies should be considered of lower value than large, rigorously conducted randomized controlled trials.

2) ARDS Network LaSRS findings: The highest quality evidence available on corticosteroids in acute respiratory distress syndrome (ARDS) remains the ARDS Network Late Steroid Rescue Study (LaSRS) randomized controlled trial (5). Although the trial may have been underpowered to detect small mortality differences, the identical 60-day mortality in corticosteroid-treated and placebo patients (29%) is not suggestive of significant benefit. Furthermore, the LaSRS trial uncovered potentially significant downsides associated with corticosteroids in ARDS. As summarized in reference 5 cited by the letter (1), the appropriate test for statistical interaction demonstrated ample cause for concern about the risks of starting corticosteroid therapy more than 2 weeks after ARDS onset.

3) Clinical application: In the 2017 guidelines and in the letter, the presented protocol appears to derive from a 2007 trial reported by Meduri et al (4). As we noted above, this trial has significant limitations. Based on these limitations and the lack of other corroborating evidence for this specific regimen, we do not believe the evidence supports this protocol. We also disagree that “there is no contraindication to using methylprednisolone in conjunction with a 2 days duration of neuromuscular blockade.” Although there may not be a definitive contraindication, results of the LaSRS trial suggested an association between neuromuscular weakness and corticosteroid use (4); given the known association between neuromuscular blockade and weakness, avoiding the combination of corticosteroids and neuromuscular blockade when feasible seems prudent.

In summary, the debate regarding the use of corticosteroids in ARDS continues, largely due to the overall limited and conflicting evidence available. There are reasons for optimism, but in our view, additional large multicenter randomized controlled trials are needed before more definitive recommendations for their use can be made.

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