Prolonged glucocorticoid treatment in acute respiratory distress syndrome: Evidence supporting effectiveness and safety*

In this issue of *Critical Care Medicine*, Tang et al (1) provide a systematic review and meta-analysis of nine controlled studies (n = 648) evaluating the effectiveness of prolonged glucocorticoid treatment (PGCT) in patients with acute lung injury and acute respiratory distress syndrome (ARDS) (2–10). These studies (Table 1) consistently report a significant improvement in Pa_{O_2}:Fi_{O_2} (2–10) and a significant reduction in markers of systemic inflammation (2–10), multiple organ dysfunction score (2, 5, 6, 8–10), duration of mechanical ventilation (2,4–6,10), and intensive care unit length of stay (2, 3, 5, 6, 10) (all with p values <0.05) without an increased rate of complications. The reduction in duration of mechanical ventilation is two- to three-fold greater than the reduction reported with low tidal volume ventilation or the conservative strategy of fluid management (11, 12). The more rapid resolution of lung injury and multiple organ dysfunction scores observed in these trials could positively affect long-term physical recovery (13) and survival (5). The relevance of these findings to public health and healthcare economics urges investment in clinical investigation of this inexpensive and highly effective anti-inflammatory therapy.

Because of differences in study design and patient characteristics and the limited size of the studies (1–4), the cumulative mortality summary should be interpreted with some caution. Nevertheless, all four studies (2–5) (n = 334) investigating treatment initiated within 3 days of meeting acute lung injury and ARDS criteria showed a significant reduction in mortality, with an overall 24% absolute reduction in mortality (risk ratio, 0.69; 95% confidence interval, 0.56–0.84). Two of the five studies (6, 9) investigating treatment initiated after 5–7 days of meeting ARDS criteria showed a significant reduction in mortality, whereas three studies (7, 8, 10) found no difference in mortality, with an overall 15% absolute reduction in mortality (risk ratio, 0.75; 95% confidence interval, 0.55–1.02) that increased to 19% for the larger subgroup of patients (n = 233) randomized before day 14 of ARDS (risk ratio, 0.65; 95% confidence interval, 0.45–0.94) (6, 8–10). In the three studies without a mortality benefit (7, 8, 10), treatment was associated with significant early physiologic improvement; however, rapid dosage reduction (8) or premature removal after extubation (as acknowledged by the authors) (10) might have affected final outcome. In the ARDS Network trial, the treated group had—before removal of treatment—a noteworthy 9.5 days' reduction in duration of mechanical ventilation ($p = 0.006$) (10). The ARDS Network trial reported a lower mortality for patients (n = 132) randomized before day 14 (27% vs. 36%; $p = 0.14$) and higher mortality for patients (n = 48) randomized after day 14 of ARDS (8% vs. 35%; $p = 0.01$) (10). The latter subgroup, however, had large imbalances in baseline characteristics and an uncharacteristically low mortality in the control group, and the mortality difference lost significance ($p = 0.57$) when adjusting for these imbalances (14, 15).

Treatment decisions involve a tradeoff between benefits on the one hand and risks, burdens, and, potentially, costs on the other (16). As an aggregate (n = 648), absolute and relative reduction in mortality is substantial for all patients (18% and 35%) and even greater when treatment is initiated before day 14 of ARDS (21% and 38%). While awaiting a larger confirmatory trial in early acute lung injury and ARDS, this meta-analysis provides evidence of a sizable reduction in duration of mechanical ventilation and intensive care unit stay and a considerable survival benefit with the potential saving of one life for every four treated patients (1). In the United States alone, this could translate to tens of thousands of lives saved per year and several billion dollars in reduced healthcare expenditures (17). Furthermore, the low cost of off-patent methylprednisolone—in the United States approximately $240 for 28 days of intravenous therapy (5)—makes this treatment globally and equitably available.

In their systematic review, Tang et al (1) report that PGCT at low-to-moderate doses was not associated with an increased rate of major complications, including infections and neuromyopathy. This counterintuitive finding deserves further elucidation and provides an opportunity to debunk common fallacies about glucocorticoid treatment-associated complications. Most misconceptions originate from the findings of sepsis and ARDS trials conducted in the 1980s that investigated a massive daily dose of glucocorticoids (methylprednisolone, up to 120 mg/kg/day) over a short time interval (24–48 hours). The experimental model supporting this treatment protocol relied on the intravenous administration of a lethal bolus of lipopolysaccharide that could be offset only by administering an equally massive dose of glucocorticoids before or within a brief experimentally generated inflammatory window (18–20). This experimental model did not replicate human sepsis or acute lung injury and was discredited in the early 1990s (18). Since then, longitudinal measurements of inflammatory cytokines in ARDS patients have clearly shown that significant systemic and pulmonary inflammation persists 28 days into the disease process (21–24) and that PGCT (14–21 days) followed by slow tapering is essential to achieve and sustain biological resolution of the disease process (21, 25).

In recent years, substantial evidence has accumulated showing that systemic inflammation, the central pathogenetic process in ARDS (21, 22, 24), is also implicated in the type of morbidity—

***See also p. 1594.**

Key Words: acute respiratory distress syndrome; complications; duration of mechanical ventilation; glucocorticoid treatment; infection; mortality

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Table 1. Prolonged glucocorticoid treatment in ALI-ARDS: Overall mortality, improvement in markers of systemic inflammation, gas exchange, duration of mechanical ventilation, and ICU stay

Study	Hospital Mortality[a]	Reduction in Inflammation	Improvement in PaO_2:FiO_2	Reduction in MV Duration	Reduction in ICU Stay
Early ALI-ARDS (n = 334)	38% vs. 62%	3 of 3	4 of 4	4 of 4	3 of 3
Confalonieri (2)	0.0% vs. 30%	Yes	Yes	Yes	Yes
Lee (3)	8% vs. 88%	NA	Yes	Yes	Yes
Annane (4)	64% vs. 73%	Yes	Yes	Yes	NA
Meduri (5)	24% vs. 43%	Yes	Yes	Yes	Yes
Late ARDS (n = 314)	28% vs. 43%	5 of 5	5 of 5	2 of 3	2 of 3
Meduri (6)[b]	12% vs. 62%	Yes	Yes	Yes	Yes
Keel (7)	38% vs. 67%	Yes	Yes	NA	NA
Varpula (8)	19% vs. 20% (30 d)	Yes	Yes	No	No
Huh (9)	43% vs. 74%	Yes	Yes	NA	NA
Steinberg (10)[b]	29% vs. 29% (60 d)	Yes	Yes	Yes	Yes
Early and Late ARDS	34% vs. 52%	8 of 8	9 of 9	6 of 7	5 of 6

Early ALI-ARDS, treatment initiated within 3 days of meeting acute lung injury-acute respiratory distress syndrome criteria; Late ARDS, treatment initiated after 5–7 days of meeting ARDS criteria; NA, not available or not applicable; d, days; MV, mechanical ventilation; ICU, intensive care unit.

[a]Mortality is reported as hospital mortality unless specified otherwise in parenthesis; [b]Two trials reported mortality in patients randomized before day 14 of ARDS: Meduri et al (6) (13% vs. 57%), and Steinberg et al (10) (27% vs. 36%). Comparisons are reported as glucocorticoid-treated vs. control.

hyperglycemia (26), neuromuscular weakness (27), increased risk for nosocomial infections (28), and delirium (27)—that is otherwise attributable to glucocorticoid treatment. Two sets of consequences follow. First, in uncontrolled studies, when the use of glucocorticoid treatment is limited to the "rescue" of the sickest patients, it is difficult to separate disease from treatment-related complications. Second, treatment-induced downregulation of systemic inflammation could theoretically prevent, or partly offset, development and progression of these complications. The findings reported by Tang et al (1) add credit to a new line of reasoning that views control of systemic inflammation as indispensable to decreased short- and long-term morbidity in ARDS and sepsis. We review evidence accumulated in the last decade that supports this paradigm shift in our traditional thinking. Because of space limitations, we will address only the topic of infection and neuromuscular weakness.

None of the reviewed trials reported an increased rate of nosocomial infection (1, 29), whereas two reported a significant reduction (5, 10). In the ARDS network trial (10), the infection rate for treated and control groups was 31% vs. 47% (relative risk 0.59, 95% confidence interval 0.40–0.88), respectively. A prospective ARDS study investigating the longitudinal relationship between inflammatory cytokine levels (plasma and bronchoalveolar lavage) and infections (28) showed that nosocomial infections are an epiphenomenon of dysregulated systemic inflammation (28, 30), a finding supported by recent experimental evidence (31). It is now appreciated that bacteria have receptors for cytokines tumor necrosis factor-α and interleukin (IL)-1β and that exposure of bacteria to inflammatory cytokines enhances their growth and virulence (reviewed in Ref. 30). Although a moderate degree of local inflammation is required to control infection, high levels of inflammatory cytokines favor bacterial proliferation and virulence following a U-shaped response. When fresh isolates of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter* sps. obtained from patients with ARDS were exposed *in vitro* to a lower concentration (10–250 pg) of tumor necrosis factor-α, IL-1β, or IL-6—similar to the plasma values detected in ARDS survivors—extracellular and intracellular bacterial growth was not promoted, and human monocytic cells were efficient in killing the ingested bacteria (32, 33). On the contrary, when bacteria were exposed to higher concentrations of proinflammatory cytokines—similar to the plasma values detected in ARDS nonsurvivors—intracellular and extracellular bacterial growth was enhanced in a dose-dependent manner (32, 33). In separate parallel experiments, impairment in intracellular bacterial killing by activated monocytes correlated with the increased monocyte expression of proinflammatory cytokines, whereas restoration of monocyte killing function upon exposure to methylprednisolone coincided with the downregulation of the expression of tumor necrosis factor-α and IL-1β (34). In experimental sepsis, the magnitude of induced systemic inflammation affects macrophage-associated host antibacterial innate immunity and susceptibility to infection (31).

Glucocorticoid treatment has been proven beneficial and safe for a wide variety of infections (35). In experimental pneumonia, animals randomized to glucocorticoid treatment had a significant reduction in bacterial burden (bronchoalveolar lavage and lung tissue) and histologic severity of pneumonia (36) and improved survival (37). Two randomized trials in patients with septic shock (most caused by pneumonia) reported that hydrocortisone infusion—while decreasing circulating IL-6 and IL-8 levels and neutrophil spontaneous release of hydrogen peroxide (H_2O_2)—was associated with *ex vivo* preserved or increased (in comparison to placebo) monocyte and neutrophil phagocytosis and preserved respiratory burst (38, 39). The cumulative evidence indicates that in ARDS and severe sepsis, glucocorticoid-induced downregulation of life-threatening systemic inflammation improves innate immunity (38, 39) and provides an environment less favorable to intracellular and extracellular bacterial growth (34, 36).

A number of reports, including muscle histopathologic studies (40), support an association between systemic inflammation and critical illness neuromuscular abnormality (CINMA) (27). In this regard, downregulation of systemic inflammation in ARDS could potentially prevent development and progression of CINMA. A recent systematic review of the literature found no clear association between glucocorticoid treatment and electro-

physiologically proven CINMA in patients on mechanical ventilation (41). Because CINMA is recognized as an independent predictor of prolonged weaning (42) and ARDS trials consistently report a sizable and significant reduction in duration of mechanical ventilation (2,4–6,10), clinically relevant CINMA caused by glucocorticoid or glucocorticoid-induced hyperglycemia is unlikely.

The ARDS network study (10) reported nine serious, unspecified (not defined in the text of the article) events associated with myopathy or neuropathy among treated patients ($p = 0.001$). Specific information about these patients, however, was not provided. Because greater than 40% of patients in the ARDS network trial were exposed to neuromuscular blocking agents (NMBA), it is difficult to factor how much the combination NMBA–glucocorticoid affected this finding. In ventilated patients with severe asthma on PGCT, the use of glucocorticoids in combination with an NMBA was associated with a much higher incidence of muscle weakness than was the use of glucocorticoids alone (20 of 69 vs. 0 of 38, $p < 0.001$) (43). In the single study that identified by multivariate analysis a positive relationship between glucocorticoid treatment and CINMA, most patients were exposed to NMBA for 3 days (44). For this reason, the use of NMBA is strongly discouraged in ARDS patients receiving glucocorticoid treatment (15).

It can be argued that, lacking a large confirmatory trial proving a definitive mortality benefit, caution is warranted in recommending PGCT in ARDS. Weighting in favor of this approach are concerns related to glucocorticoid-induced complications, a line of reasoning that is weakened by the findings of this meta-analysis. As reviewed by Tang et al, cumulative findings from multiple controlled ARDS studies have consistently demonstrated that PGCT is associated with a sizable and significant improvement in meaningful patient-centered outcome variables and a distinct survival benefit. Subgroup analysis should be interpreted with some caution. Although the analysis by Tang et al did not find the dosage strategy to affect outcome, we believe that corticosteroids should be initiated early at a dose not exceeding 1 mg/kg/day of methylprednisolone in patients meeting criteria for severe ARDS (Pao_2: FIO_2 $\geq$200 on positive end-expiratory pressure of 10 cm H_2O) and within 72 hours in patients without severe ARDS but failing to improve by day 3. In patients failing to improve lung injury score after days 5–7, present data are limited to the study investigating a dose of 2 mg/kg/day of methylprednisolone. In all cases, duration of treatment should be 14–21 days before final tapering. Most important, PGCT has a strong benefit/risk ratio in ARDS when it is applied in conjunction with measures demonstrated to reduce potential morbidity associated with glucocorticoids (5, 6). These measures include i) intensive infection surveillance, ii) avoidance of paralytic agents, and iii) avoidance of rebound inflammation with premature discontinuation of treatment that may lead to physiologic deterioration and reintubation (5).

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How can severity scoring methods maintain clinical and temporal relevance with advances in critical care practice? Here's one way*

One dilemma facing users of risk-adjusted severity scoring as a surrogate for quality in the intensive care unit (ICU) is the difficulty in ensuring that predictive modeling accurately reflects advancements in clinical care, admission criteria, or other practice changes. Earlier in this decade, Glance et al (1), using the standardized mortality ratio (ratio of mortality predicted by a severity score to actual mortality) as a measure of ICU quality, hypothesized that existing individual scoring systems should consistently and reproducibly demonstrate high-quality or low-quality ICU outliers. While establishing that there was only a fair to moderate agreement among Acute Physiology and Chronic Health Evaluation II (2), Simplified Acute Physiology Score II (3), and Mortality Probability Admission Model (MPM_0-II) (4) in determining ICU quality outliers using the Project IMPACT (5) database, they also demonstrated an interesting, unintended finding: that most of the ICUs were, with apologies to Garrison Keillor and the Lake Wobegon effect (6), "above average" (i.e., of high quality).

Because the severity scoring methods used in the aforementioned study (1) were published 10–15 years prior, most clinicians would argue that skewing of the bell-shaped curve toward inflation of ICU quality is indicative of the prediction models losing their relevance as care practices change over time. Unfortunately, the only way to refine an exist-

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