Are Corticosteroids Useful in Late-Stage Acute Respiratory Distress Syndrome?

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Summary

The acute respiratory distress syndrome (ARDS) is characterized by intense inflammation and alveolar-capillary disruption that can progress to a state of unresolving inflammation and disordered fibrosis, referred to as fibroproliferative, late-stage, or persistent ARDS. These pathophysiologic features may be responsive to corticosteroids, but early high-dose, short-duration therapy was proven ineffective. More recently, several small and one moderate-size multicenter randomized controlled trial (RCT) investigated low-to-moderate-dose prolonged corticosteroid treatment. The RCT and meta-analysis consistently demonstrated improved oxygenation and shorter duration of mechanical ventilation with methylprednisolone. The largest RCT also revealed less pneumonia and shock, and shorter intensive care unit (ICU) stay, but more cases of severe myoneuropathy, with methylprednisolone. There were virtually identical 60-day and 180-day mortality rates for methylprednisolone and placebo in the largest RCT. Sub-group analysis of that study showed significantly higher mortality with methylprednisolone than with placebo when enrollment occurred > 13 days after onset of ARDS, but small sample size and differences in subject characteristics probably confound those results. Most meta-analyses demonstrated trends toward better survival with methylprednisolone, and, when restricted to patients enrolled in RCTs who received prolonged administration of methylprednisolone that was initiated within the first 14 days of ARDS, one meta-analysis demonstrated better survival with corticosteroids. Importantly, the aforementioned studies have methodological limitations, and the number of subjects enrolled was small. Experts differ in their recommendations regarding corticosteroids for late-stage ARDS, although one consensus group supported a "weak" recommendation of low-to-moderate-dose corticosteroids for ARDS of < 14 days duration. If corticosteroids are administered, infection surveillance, avoidance of neuromuscular blockers, and gradual taper of corticosteroids are recommended. *Key words: acute lung injury; ALI; acute respiratory distress syndrome; ARDS; corticosteroids, late; fibroproliferative*. [Respir Care 2010;55(1):43–52. © 2010 Daedalus Enterprises]

Introduction

The acute respiratory distress syndrome (ARDS) was described more than 40 years ago and remains a challenging clinical syndrome with high risk for prolonged hypoxemic respiratory failure and fatal outcome.[1] Clinical features of ARDS include acute onset (ie, < 7 d) after a pulmonary (such as pneumonia) or extra-pulmonary (such as sepsis) insult, bilateral pulmonary infiltrates on chest radiograph, absence of left atrial hypertension with elevated filling volumes, and hypoxemia (ie, ratio of P_{aO_2} to fraction of inspired oxygen [F_{IO_2}] < 200 mm Hg).[2] The same criteria, except with less severe hypoxemia (ie, P_{aO_2}/F_{IO_2} < 300 mm Hg) is referred to as acute lung injury (ALI).[2] The ARDS/ALI syndrome is characterized by intense inflammation and alveolar capillary membrane disruption, leading to high-protein-content pulmonary edema early in its course.[3]

ARDS can take one of several pathways, leading either to rapid recovery or to ongoing pulmonary inflammation and disorganized fibrosis.[3,4] This "fibroproliferative" (late) stage complicates the course of many patients with ARDS, and is accompanied by ongoing hypoxemia, fever, leukocytosis, and pulmonary inflammation, without evidence of infection, and with increased risk of fibrosis and air leaks.[4] This unresolving form of ARDS has been an important target for prevention and for effective management, because the clinical course is often complicated and long, and may be followed by functional impairment in survivors. Given the ongoing inflammatory response and prominent disorganized fibrosis in late-stage ARDS, various anti-inflammatory and immune-modulatory agents have been studied. Among these, glucocorticoids have had the longest and most controversial attention. Corticosteroids have numerous actions that mitigate inflammation, including reducing the extravasation of plasma through intercellular junctions of the capillary, inhibiting the adhesion and migration of leukocytes across the capillary wall, inhibiting leukocyte inflammatory genes, and blocking transcription of pro-inflammatory proteins via nuclear factor kappa B.[5]

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Drs Sessler and Gay presented a version of this paper at the 44th RESPIRATORY CARE Journal Conference, "Respiratory Care Controversies II," held March 13-15, 2009, in Cancún, Mexico.

The authors have disclosed no conflicts of interest.

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Variables that influence the impact of corticosteroids include the timing of drug administration relative to the onset of ARDS (before, during the early stage, or during the late stage of ARDS); the specific pharmacologic agent (methylprednisolone, dexamethasone, or hydrocortisone); dose (low, moderate, or high dose); and duration (short vs long duration). We will focus primarily on corticosteroids for late-stage ARDS, although a more comprehensive overview is presented as well.

Clinical Trials of Corticosteroids in ARDS

Early studies, published in the 1980s, focused on whether corticosteroids prevented ARDS after insults (eg, septic shock) with a high likelihood of leading to ARDS.[6-9] Those randomized controlled trials (RCTs) employed high-dose corticosteroids (typically 1–8 doses of 30 mg/kg methylprednisolone) for short durations (≤ 48 h). In comparison to placebo, corticosteroids resulted in either no difference[7,8] or *increased* the incidence[6] of ARDS. Meta-analysis of those studies demonstrated no difference in the likelihood of ARDS with high-dose short-duration corticosteroids (odds ratio [OR] 1.55, 95% confidence interval [CI] 0.58–4.05).[10] Similarly, high-dose, short-duration methylprednisolone (30 mg/kg intravenous every 6 h, 8 doses) to patients with early-phase ARDS was ineffective, compared to placebo, with no difference in survival or in reversal of ARDS between the groups.[9]

More recent RCTs examined low-to-moderate doses (methylprednisolone 1–2 mg/kg/d to start) for longer duration (average 25–32 d), with gradual tapering. Some studies examined initiating therapy early in the course of ARDS, whereas others addressed late-stage ARDS. In an RCT with 91 subjects, in which methylprednisolone 2 mg/kg/d was begun within 3 days of onset of severe ARDS, Meduri and colleagues[11] found that, compared to placebo, corticosteroids significantly improved multiple outcomes, including: lower Lung Injury Score and Multiple Organ Dysfunction Syndrome (MODS) score, shorter duration of mechanical ventilation, shorter ICU stay, lower ICU mortality, and lower infection rate. However, methodological issues, including 2:1 randomization and crossover of nonresponders at 10 days to open-label methylprednisolone, have provoked controversy regarding the validity of the results. Other limitations of the study are discussed below.

Clinical Trials of Corticosteroids for Late-Stage ARDS

The primary issue under discussion in this paper is the value of corticosteroids in patients with late-stage ARDS. Typically, late-stage refers to treatment begun ≥ 7 days after onset of ARDS; however, divergent results among those in whom treatment was initiated during the second week of ARDS, versus after the second week,[12] has

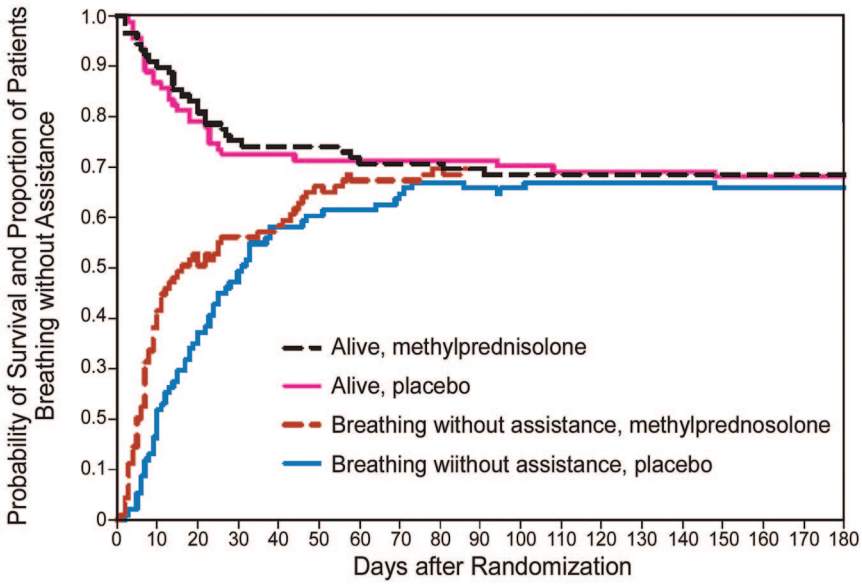

Fig. 1. Probability of survival and the proportion of patients with persistent acute respiratory distress syndrome who became able to breathe without assistance during the first 180 days after randomization. (From Reference 12, with permission.)

prompted different recommendations for 7–13 days into ARDS versus > 13 days. The debate topic posed to us for this Journal Conference was "Are steroids useful in late-stage ARDS?" In this section we describe the study designs, major results, and authors' conclusions of the key RCTs, and our pro/con discussion follows. Similarly, the results and authors' interpretations of the meta-analyses are reported first, with our pro/con discussion following.

Two RCTs have direct bearing on the use of corticosteroids in late-stage ARDS,[12,13] and these will be critically discussed. Additionally, a number of cohort studies, related RCTs, and analyses of multiple related studies have been presented in systematic reviews and meta-analyses, and these will also be examined.[10,14-16] Finally, expert panel recommendations will be reviewed.[17]

In 1998, Meduri and colleagues[13] reported the results of a small RCT in which 24 patients with severe ARDS that had failed to resolve after 7 days of mechanical ventilation were randomized to receive methylprednisolone, with an initial dose of 2 mg/kg/d, then tapered (16 patients) or placebo (8 patients), with a treatment duration of 32 days. Four patients whose lung injury failed to improve after 10 days of treatment were then blindly crossed over to alternative treatment, according to the a priori design (all were in the placebo group). An explicit infection-surveillance protocol was employed. The primary outcomes were improvement in lung function and mortality. There was significant improvement in Lung Injury Score, P_{aO_2}/F_{IO_2}, and MODS score, and successful extubation by study day 10 in the methylprednisolone group, compared to the placebo group. The methylprednisolone group had lower ICU mortality (0% vs 62%, $P = .002$) and hospital-associated mortality (12% vs 62%, $P = .03$) than the placebo group. There was no difference in infection rate per treatment day. As in their other study,[11] Meduri et al used an unconventional randomization of 2:1, and non-responders were crossed over to the other treatment arm, potentially contaminating longer-term outcomes. The authors concluded that prolonged administration of methylprednisolone in patients with unresolving ARDS was associated with improvement in lung injury and MODS scores and reduced mortality.

The ARDS Network investigators designed an RCT to compare placebo to methylprednisolone, starting at 2 mg/kg/d, then tapered (additional discussion on tapering follows), with initiation of treatment between 7 and 28 days of ARDS onset. The primary outcome was mortality at 60 days, and secondary outcomes were number of ventilator-free days and organ-failure-free days, biochemical markers, and infectious complications.[12] The 180 patients enrolled into the 2 treatment groups had similar baseline characteristics, and were critically ill, with an average P_{aO_2}/F_{IO_2} of 126 mm Hg and an average Acute Physiology and Chronic Health Evaluation (APACHE) III score of 86.

There was no significant difference in 60-day hospital mortality (29.2% in the methylprednisolone group vs 28.6% in the placebo group) or 180-day mortality (31.5% vs 31.9%).[12] The methylprednisolone group had significantly more ventilator-free days during the first 28 days (11.2 d vs 6.8 d, $P < .001$) and over 180 days (159 d vs 149 d, $P = .04$). Figure 1 shows the Kaplan-Meier curves for probability of survival and proportion of patients surviving without ventilatory assistance over 180 days. The methylprednisolone patients were able to breathe without assis-

Table 1. Major Findings and Assessment of Benefit or Harm for Key Outcomes and Physiologic Parameters in Patients With ARDS, Randomized to Methylprednisolone (vs Placebo) in the Corticosteroid for Late-Stage ARDS Clinical Trial (ARDS Network)[12]

Parameter	Major Findings	Benefit or Harm?
Survival	No difference in 60-day or 180-day mortality ($P > .99$)	Neutral
Duration of mechanical ventilation	More ventilator-free days through day 28 ($P < .001$) and through day 180 ($P = .04$)	Benefit
	Shorter duration of mechanical ventilation ($P = .006$)	
ICU and hospital stay	More ICU-free days through day 28 ($P = .02$)	Benefit
Organ function	Less cardiovascular organ failure ($P = .04$)	Benefit
Adverse effects	Less pneumonia ($P = .05$)	Neutral
	Less shock ($P = .03$)	
	More frequent severe myoneuropathy ($P = .001$)	
	No difference in prospectively diagnosed ($P = .67$) or overall ($P = .20$) myoneuropathy	
Physiology	Higher P_{aO_2}/F_{IO_2} ($P < .05$)	Benefit
	Better lung compliance ($P < .05$)	
Cost, availability	Low cost, ready availability	Benefit

ARDS = acute respiratory distress syndrome
ICU = intensive care unit
F_{IO_2} = fraction of inspired oxygen

tance on average 10 days before the placebo patients (14 d vs 24 d of mechanical ventilation, $P = .006$). However, significantly more methylprednisolone patients required resumption of mechanical ventilation ($n = 20$ vs $n = 6$, respectively, $P = .008$), and shock ($n = 7$ vs $n = 0$) and myoneuropathy ($n = 9$ vs $n = 2$) were common underlying issues. Methylprednisolone increased the number of ventilator-free and shock-free days during the first 28 days, and improved oxygenation, respiratory-system compliance, and blood pressure, with fewer days of vasopressor therapy. Methylprednisolone was associated with significantly increased 60-day and 180-day mortality among patients enrolled at least 14 days after the onset of ARDS.

A subset of 91 patients enrolled in the ARDS Network RCT had bronchoscopy performed at baseline, with measurement of procollagen peptide type III in bronchoalveolar lavage (BAL) fluid.[12] Among the 46 patients with low (< median) baseline BAL procollagen peptide type III, the 23 randomized to methylprednisolone had higher 60-day mortality (35%) than did the placebo patients (8%) ($P = .03$). In contrast, there was a trend ($P = .10$) toward lower mortality with methylprednisolone (4%) than placebo (19%) in patients with high baseline BAL procollagen peptide type III. Such biochemical markers may improve patient selection for therapy, depending upon the results of future studies.

The ARDS Network authors concluded that their results do not support the routine use of methylprednisolone for persistent ARDS, despite the improvement in cardiopulmonary physiology, and that starting methylprednisolone more than 2 weeks after ARDS onset may increase the risk of death.[12] The pro and con analyses of this pivotal study are presented below, and Table 1 summarizes the major findings.

Meta-analyses of Clinical Trials

Since the results of individual studies on corticosteroids in ARDS have been controversial, experts have sought to provide a rationale for treatment recommendations by performing systematic reviews and meta-analyses. Virtually all recent analyses focused on low-to-moderate-dose therapy administered over a prolonged period. Since there are only 2 RCTs of corticosteroids for late (≥ 7 d) ARDS, some of these analyses examined broader questions, such as initiation of therapy between ARDS days 1 and 14. Further, some included non-randomized cohort studies. Peter et al[10] pooled 5 low-dose and high-dose studies and found a nonsignificant trend (OR 0.62, 95% CI 0.23–1.26) toward benefit of therapeutic steroids on mortality. Corticosteroids increased the number of ventilator-free days, compared to controls, in 3 studies, and was not associated with greater risk of infection.[10] They concluded that a definitive role for corticosteroids in ARDS in adults is not established, but that a possibility of lower mortality and more ventilator-free days with corticosteroids started after the onset of ARDS was suggested.

In their analysis of 3 studies of glucocorticoids in late ARDS, Agarwal et al[14] found a nonsignificant trend that favors glucocorticoids for mortality (OR 0.58 95% CI 0.22–1.53). They concluded that current evidence does not support a role for corticosteroids in the management of late-stages ARDS. They added that more research is required to establish the role of steroids in patients with late-stage ARDS, 7–14 d after onset.

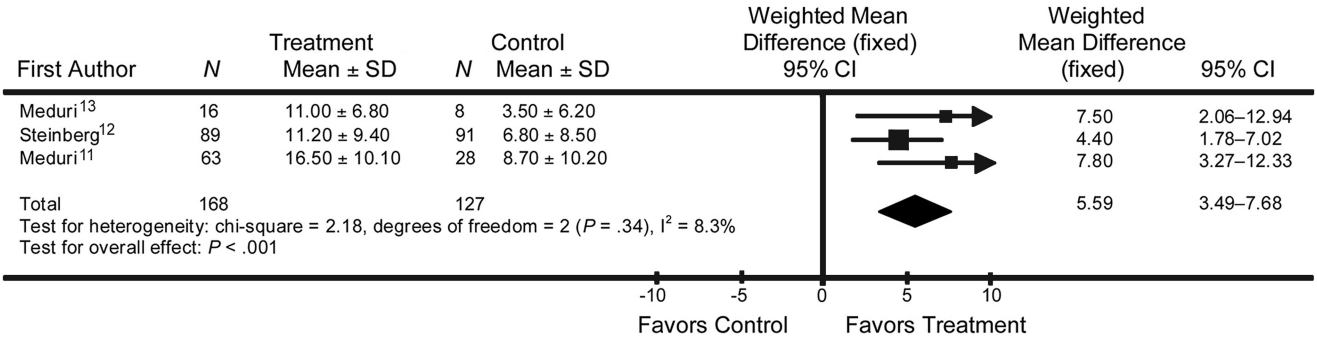

Fig. 2. Effects of prolonged methylprednisolone on mechanical-ventilation-free days at day 28. CI = confidence interval. (Adapted from Reference 15.)

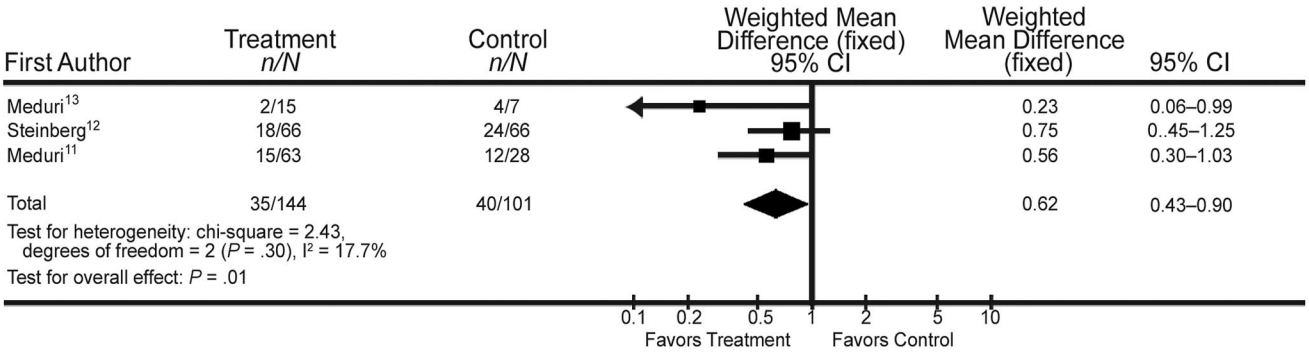

Fig. 3. Effects of prolonged glucocorticoid treatment on survival of acute respiratory distress syndrome, based on data from 3 randomized trials of methylprednisolone for > 1 week, after removing patients randomized after day 14. CI = confidence interval. (Adapted from Reference 15.)

Meduri et al[15] performed a meta-analysis of 3 placebo-controlled RCTs that used low-dose prolonged-duration methylprednisolone, and found significantly more ventilator-free days through day 28 (5.59 d, 95% CI 3.49–7.68 d, $P < .001$) (Fig. 2).[11-13] Working with the raw data gleaned from 3 placebo-controlled RCTs that specifically selected subjects with ARDS and who received methylprednisolone for > 1 week, after removing patients who were randomized after day 14, they found significantly ($P = .01$) lower mortality (risk ratio 0.62, 95% CI 0.43–0.90) with methylprednisolone (Fig. 3). It should be recognized that methodological concerns exist about the studies in these meta-analyses, and that combining studies with heterogeneous populations and treatments may not be valid.

Recently, Tang et al[16] meta-analyzed 5 cohort studies[18-22] and 4 RCTs[11,13,23,24] of low-to-moderate-dose, prolonged-duration corticosteroids, regardless of the time of initiation, and found significantly lower mortality with steroids (OR 0.62, 95% CI 0.43–0.91, $P = .01$) (Fig. 4), and fewer days on mechanical ventilation, greater improvement in MODS score, and higher P_{aO_2}/F_{IO_2}, but no difference in ICU stay, Lung Injury Score, infection rate, myoneuropathy, or all major adverse events. Table 2 summarizes the major findings of the meta-analysis by Tang et al[16] of prospective studies that examined low-to-moderate dose (0.5–2.5 mg/kg/d) methylprednisolone for ARDS, that were related to clinical outcomes and physiologic effects.

Consensus Recommendations

The consensus statement from an international task force by the American College of Critical Care Medicine includes evidence-based recommendations for corticosteroids in critically ill adults.[17] It concludes that:

> Moderate-dose glucocorticoids should be considered in the management strategy of patients with early severe ARDS ($P_{aO_2}/F_{IO_2} < 200$ mm Hg) and before day 14 in patients with unresolving ARDS. The role of glucocorticoid treatment in acute lung injury and less severe ARDS ($P_{aO_2}/F_{IO_2} > 200$ mm Hg) is less clear.

That recommendation has a grade of 2B, which they define as a "weak" recommendation with "moderate quality evidence," which has the general implication, "weak recommendation: best action may differ depending on circumstances or patients or societal values."

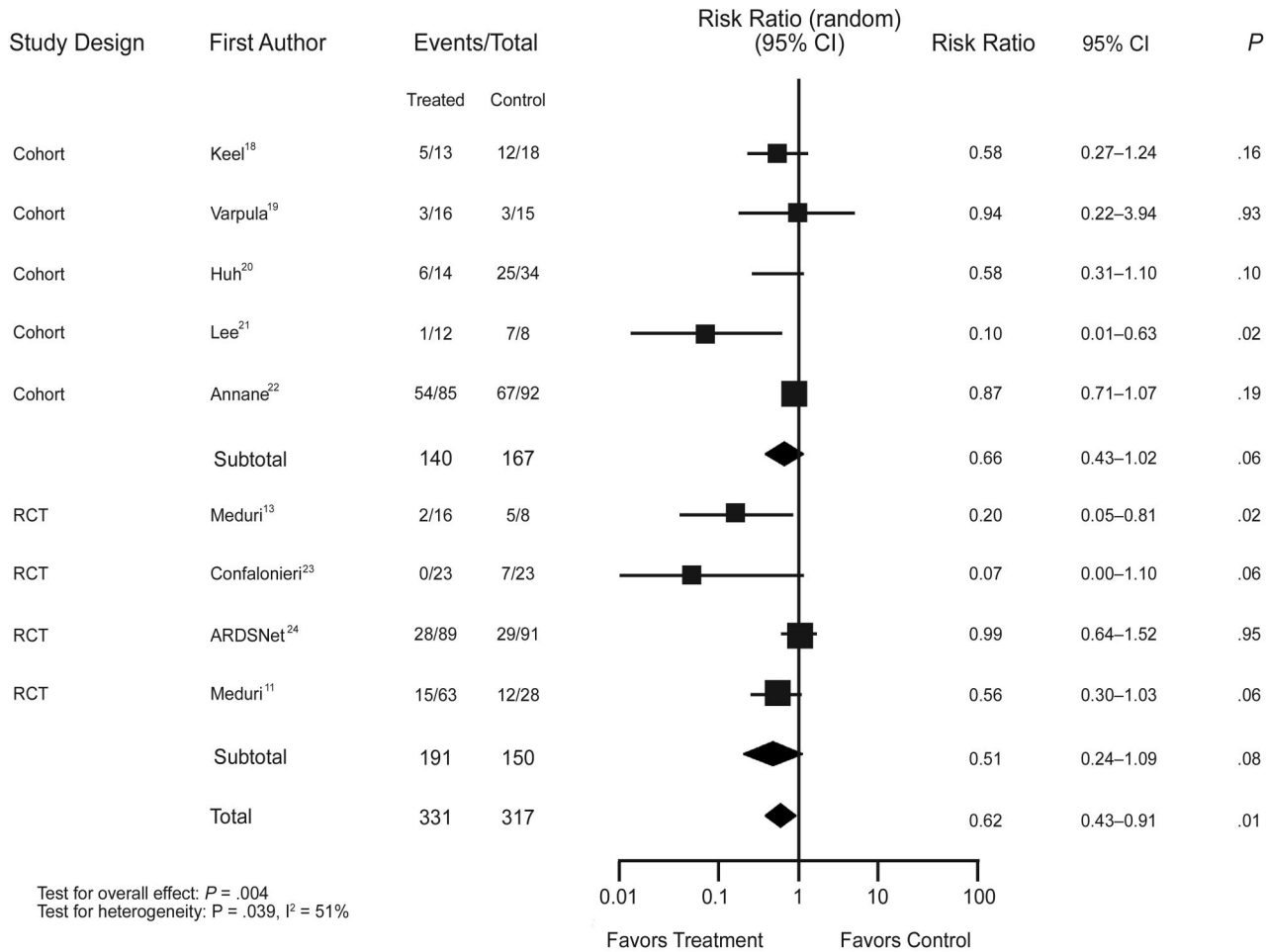

Fig. 4. Effect of steroids on mortality in acute respiratory distress syndrome (ARDS). CI = confidence interval. RCT = randomized controlled trial. ARDSNet = Acute Respiratory Distress Syndrome Network. (Adapted from Reference 16.)

Pro: Corticosteroids Are Useful for Late-Stage ARDS

To determine if an intervention is useful, one must consider safety and efficacy, using the highest-level evidence available. Beneficial and harmful effects of the intervention must be considered. While survival is the ultimate benefit and the outcome variable most often considered for critically ill patients, in fact, relatively few of the hundreds of medications and other interventions that clinicians use daily are strictly based upon this standard. Additional important outcomes and other factors that influence a clinician's decision to use an intervention in the ICU setting include: (1) how rapidly the patient recovers, often expressed as ICU stay or hospital stay; (2) outcomes directly related to the clinical course of the target disorder, reflected in incidence or duration of mechanical ventilatory support; (3) function of other vital organs, depicted by measures of organ function, such as MODS score; and (4) potential adverse effects of the intervention.

Additionally, improvement of the underlying organ injury following the intervention can result in physiologic improvement such as better oxygenation or improved lung compliance in the case of ARDS. While these improvements may not, by themselves, benefit the outcomes outlined above, they may permit adjustments in potentially injurious or costly interventions. For example, by improving gas exchange, one may reduce F_{IO_2}, reduce positive end-expiratory pressure, and/or avoid or more quickly discontinue hypoxemia rescue treatments. such as prone positioning or inhaled nitric oxide, that also have costs and risks.

It is noteworthy, however, that such physiologic improvements do not always coincide with outcome benefits. For example, the mortality benefit associated with low-tidal-volume ventilation in ARDS is not accompanied by a physiologic benefit (ie, improved oxygenation).[24] Finally, the cost and availability of the intervention should be considered. Table 1 summarizes the major findings and

Table 2. Major Findings and Assessment of Benefit or Harm for Key Outcome and Physiologic Parameters in Patients With ARDS Who Received Low-to-Moderate-Dose Corticosteroids (vs Placebo) in Prospective Cohort and Randomized Controlled Trials, in the Meta-analysis by Tang et al[16]

Parameter	Major Findings	Benefit or Harm?
Survival	Lower mortality indicated by 4 RCTs and 5 cohort studies ($P = .01$)	Benefit
Duration of mechanical ventilation	More ventilator-free days ($P = .03$)	Benefit
ICU and hospital stay	Trend for shorter ICU stay ($P = .09$)	Neutral
Organ function	Better Multiple Organ Dysfunction Syndrome score ($P < .001$)	Benefit
Adverse effects	No difference in infection ($P = .48$)	Neutral
	No difference in neuromyopathy ($P = .62$)	
	No difference in all major adverse events ($P = .45$)	
Physiology	Higher P_{aO_2}/F_{IO_2} ($P = .01$)	Benefit
	No difference in Lung Injury Score ($P = .14$)	

ARDS = acute respiratory distress syndrome
RCT = randomized controlled trial
ICU = intensive care unit
F_{IO_2} = fraction of inspired oxygen

assessment of benefit or harm for key outcomes, including survival, duration of mechanical ventilation, ICU and hospital stay, organ function, adverse effects, physiology, and cost/availability from the ARDS Network RCT.[12] Table 2 summarizes the most comprehensive meta-analysis of low-to-moderate-dose (0.5–2.5 mg/kg/d) methylprednisolone for ARDS, by Tang et al.[16]

Survival

In the ARDS Network RCT by Steinberg et al[12] there was no difference in either 60-day or 180-day mortality for the entire population (see Fig. 1, and Table 1). In contrast, Meduri and colleagues[13] detected an ICU and hospital mortality benefit with methylprednisolone in late-stage ARDS. Meta-analyses restricted to RCTs of low-dose corticosteroids for late-stage ARDS revealed a trend toward lower mortality, compared to placebo.[14] The point in time at which corticosteroids are begun in late-stage ARDS may influence outcomes. Steinberg et al[12] found significantly ($P = .02$) higher 60-day mortality with methylprednisolone (versus placebo) in the subset of patients enrolled > 13 days after ARDS onset, whereas no difference was seen between the treatment arms in patients enrolled 7–13 days after ARDS onset.

A closer look at these data, however, reveals that the subset of patients enrolled at > 13 days were very small: 25 received placebo and 23 received methylprednisolone. Further, the 60-day mortality among the placebo patients enrolled > 13 days after ARDS onset was strikingly low (8%), in comparison to 35% in the methylprednisolone patients enrolled at > 13 days, and 36% and 27% for patients receiving placebo and methylprednisolone, respectively, started 7–13 days after enrollment. This surprising finding of very low mortality is not likely the result of placebo treatment or harm from the steroids, but suggests imbalances in important baseline characteristics of these small subgroups. When adjusted for imbalances in baseline characteristics, the mortality difference lost significance ($P = .57$).[17] Whether corticosteroids are harmful when initiated > 13 days after ARDS onset will require further research, but it is reasonable to avoid them in this setting in current practice.

When considering only patients enrolled before day 14 of ARDS into an RCT, low-dose prolonged-duration corticosteroid is associated with significantly ($P = .01$) lower mortality (see Fig. 3),[14] though that finding is based on only 245 patients in 3 RCTs. When initiation of low-to-moderate-dose prolonged-duration corticosteroid is broadened to include early and late-stage ARDS, there is a significant ($P = .01$) mortality benefit (see Table 2).[15] Taken together, it is likely that low-to-moderate-dose prolonged-duration corticosteroid begun < 13 days after ARDS onset is associated with a survival benefit, but that corticosteroid initiation after ARDS day 13 might be harmful.

Duration of Mechanical Ventilation, ICU Stay, and Hospital Stay

There is consistency among the studies that corticosteroids lead to more rapid recovery from respiratory failure and shorter ICU stay. This was observed in the ARDS Network study, which found significantly more ventilator-free days at 28 days ($P < .001$) and 180 days ($P = .04$) and more ICU-free days ($P = .02$) at day 28.[12] Figure 1 is the Kaplan-Meier curve for "breathing without assistance,"

which shows a marked separation early in the course of the study. In fact, the mean duration of assisted ventilation was 14 days in the methylprednisolone group versus 24 days in the placebo group ($P = .006$). Accordingly, patients randomized to corticosteroids were liberated from ventilation 10 days earlier than the placebo patients—an improvement in duration of ventilation that exceeds virtually all other interventions tested via RCT, including low-tidal-volume ventilation,[24] conservative fluid management,[25] and daily interruption of sedation.[26]

In Figure 1, from the ARDS Network study, the "breathing without assistance" curves of the methylprednisolone and placebo groups are initially separate, but converge at about day 40.[12] Extubation failure was significantly ($P = .008$) more common in the methylprednisolone group, which accounts for these different patterns. It is instructive to examine the methylprednisolone tapering strategy as a potential contributing factor to extubation failure in the methylprednisolone group. Methylprednisolone was tapered over 4 days if > 21 days of methylprednisolone had been administered, but over only 2 days if the patient was able to breathe without assistance for > 48 hours, if septic shock developed, or if disseminated fungal infection was documented.[12] Critics have postulated that the rapid corticosteroid taper may have contributed to the high frequency of relapse of ventilatory failure in the methylprednisolone arm of the ARDS Network study. The findings of several other placebo-controlled corticosteroid studies support this hypothesis. In a previous single-center RCT, by Huang et al,[27] 75% of mechanically ventilated patients satisfied laboratory criteria for adrenal insufficiency, and ventilator weaning was significantly less frequently successful (69% vs 91%, $P < .05$) in patients who received placebo, versus corticosteroid (hydrocortisone).

Regarding patients with septic shock, there is consistency among the RCTs and meta-analyses that shock reversal is significantly faster with hydrocortisone than with placebo.[28,29] Further, Keh and colleagues[30] found hemodynamic deterioration when hydrocortisone was discontinued on day 4 of treatment for septic shock. Additionally, in a multicenter placebo-controlled RCT with patients with severe community-acquired pneumonia, Confalonieri et al[23] found that patients randomized to hydrocortisone had delayed-onset septic shock significantly less frequently (0% vs 52% in the placebo patients, $P < .001$). Finally, in the ARDS Network study,[12] shock was significantly less common (6% vs 17%, $P = .03$) in the methylprednisolone group.

In sum, there is compelling evidence that the mandated rapid methylprednisolone taper following successful extubation and in septic shock probably contributed to the high frequency of clinical deterioration and re-intubation.

Adverse Events

There were significantly fewer pneumonias (6% vs 14%, $P = .05$), and a trend toward fewer serious infections (22% vs 33%, $P = .14$) with methylprednisolone, compared to placebo. Shock was significantly less common (6% vs 17%, $P = .03$) with methylprednisolone. Corticosteroids have been linked to the development of myoneuropathy in the critically ill, particularly when administered concomitantly with neuromuscular blockers.[31] The ARDS Network investigators noted the presence of serious myoneuropathy in their study subjects, which prompted analysis by the data safety monitoring board and led to prospective monitoring and retrospective review.[12] Investigator-identified serious myoneuropathy was observed in 9% of the methylprednisolone patients, versus none of the placebo patients ($P = .001$). However, there was no difference in myoneuropathy rate between the groups in the prospective review (25% for methylprednisolone, 23% for placebo, $P = .67$) or in the combination data from retrospective and prospective reviews (30% methylprednisolone, 22% placebo, $P = .20$).[12] Avoidance of concomitant corticosteroids and neuromuscular blockade is recommended.

Analyzing data from controlled trials of low-to-moderate-dose corticosteroids, Tang et al found no difference in rates of infection, myoneuropathy, or all major adverse events with corticosteroids.[16] As a reflection of overall organ function, the MODS score was significantly better (lower, $P < .01$) with corticosteroid than with placebo in the most comprehensive and recent meta-analysis.[16] On balance, the adverse event profile is similar for corticosteroids and placebo.

Physiologic Manifestations

In the ARDS Network study, methylprednisolone was associated with better oxygenation, better lung compliance, and lower plateau pressure than placebo. Specifically, P_{aO_2}/F_{IO_2} was higher on days 3, 4, and 14 after enrollment, and lung compliance was better on days 7 and 14 after enrollment.[12] In the meta-analysis of 6 controlled trials, P_{aO_2}/F_{IO_2} was significantly ($P = .01$) higher with corticosteroids.[16]

Cost and Availability

In contrast to many other critical care medications and interventions, corticosteroids are inexpensive and readily available.

Con: Corticosteroids are Not Useful for Late-Stage ARDS

Despite being examined in multiple controlled trials, the role of corticosteroids in late-stage ARDS remains unproven. The total number of patients enrolled into RCTs that specifically focused on initiating therapy > 7 days after ARDS onset is limited to 204.[12,13] Further, there are serious methodological concerns and issues related to generalizability in those studies. Specifically, in their small (n = 24) RCT of methylprednisolone versus placebo for late-stage ARDS, Meduri et al[13] used several unconventional approaches. First, the randomization was 2 subjects to the methylprednisolone arm for every one subject in the placebo arm, which yielded only 8 placebo patients. Further, non-responders (ie, those who did not have sufficient improvement in Lung Injury Score by day 10 of treatment) were permitted to be crossed over to the other treatment arm, which further complicates interpretation of longer-term outcomes. Four placebo and zero methylprednisolone subjects crossed over. Beyond modest sample size, additional concerns regarding this RCT[13] include imbalances of catecholamine-dependent shock, which occurred more frequently in the placebo group (46% v 24%, $P < .03$), and failure to incorporate a weaning procedure and to strictly monitor implementation of a ventilator protocol. Also of considerable concern is the fact that this trial was terminated early because of the divergence in outcomes of the 2 groups; clinical investigators are well aware of the problems of stopping a clinical study early.

The ARDS Network RCT[12] was intended to settle the controversy surrounding the role of corticosteroids in late-stage ARDS. However, despite screening 4,123 patients at 25 hospitals over a > 6-year enrollment period, only 180 subjects were enrolled, which was considerably less than the original estimated sample size of 400 patients, in part as a result of slow enrollment. The observation that only 4% of available patients were recruited limits the trial results' general applicability. Additionally, there was a major change in clinical practice during that period: the ARDS Network's low-tidal-volume-ventilation study[24] was published in 2000, after which study patients were changed to low-tidal-volume ventilation.

The pivotal corticosteroid study found no survival difference and a very low likelihood that a larger study would have shown a difference. A significantly higher mortality rate at 60 days was detected, however, in the subset of patients who had initiation of methylprednisolone after 13 days of ARDS. While the small sample sizes and/or baseline imbalances between groups may have influenced the results, the possibility of harm from methylprednisolone in this setting cannot be excluded. Although randomization to methylprednisolone was associated with faster recovery from respiratory failure and extubation, this apparent benefit disappeared by day 40, as a result of significantly more frequent re-intubations. It is possible that a higher rate of severe myoneuropathy, as noted by the investigators, was responsible for deterioration resulting in re-intubation. Other explanations, such as recurrent shock and ventilatory failure that could have followed the rapid taper of methylprednisolone, while plausible, remain speculative explanations for the high rate of extubation failure.

Although meta-analyses have been performed to help provide guidance in this controversial area, several caveats are worth considering. First, meta-analysis will not correct for methodological shortcomings of the included clinical trials. Second, the meta-analyses that showed a mortality benefit encompassed a broader patient group (such as early-stage ARDS *and* late-stage ARDS),[15,16] included non-randomized trials along with RCTs,[16] and/or restricted subgroups (such as prolonged methylprednisolone therapy started < 14 d after onset of ARDS).[15] Those results do not directly address the value of corticosteroids in late-stage ARDS.

Finally, focus on surrogate markers, such as oxygenation, is potentially hazardous. For example, despite being associated with a clear mortality benefit, low-tidal-volume ventilation is not associated with better oxygenation, but, instead, with P_{aO_2}/F_{IO_2} similar to or lower than that with conventional tidal volume.[24] We must be wary of such physiologic markers, because they do not necessarily correspond to the important outcomes (eg, survival).[32]

Summary

The role of corticosteroids in unresolving (≥ 7 d) ARDS remains controversial. In the largest RCT, prolonged low-dose methylprednisolone had no mortality benefit, though it was associated with more rapid recovery from ARDS, resulting in more rapid weaning from mechanical ventilation, more ventilator-free days, and earlier discharge from the ICU, without more adverse effects, particularly when limited to starting methylprednisolone < 14 days after ARDS onset. Meta-analyses that broadened the time frame of initiation of prolonged low-to-moderate-dose corticosteroids to 1–14 days after ARDS onset indicate mortality benefit and other benefits, without more adverse effects, including myoneuropathy. Nevertheless, the number of patients enrolled in the studies upon which we base treatment decisions has been quite small. Proponents of prolonged low-to-moderate-dose corticosteroids emphasize that abrupt withdrawal of therapy should be avoided. Additional secondary preventive measures to employ if corticosteroids are administered include intensive infection surveillance, avoidance of paralytic agents, and avoidance of rebound inflammation from premature discontinuation of treatment, which may lead to physiologic deterioration and re-intubation.[17]

The role of corticosteroids in very late ARDS (> 14 days after ARDS onset) is uncertain, but the potential for harm cannot be excluded, based on the existing data, and such treatment is not recommended at this time.

More research is needed to clarify the role of methylprednisolone in all stages of ARDS. Finally, the value of biological markers, such as procollagen peptide type III in BAL fluid, as predictors of response to therapy should be explored as a potential aid in patient selection.

REFERENCES

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet 1967;2(7511):319-323.
2. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American European consensus conference on ARDS. definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149(3 Pt 1):818-824.
3. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000;342(18):1334-1349.
4. Meduri GU, Belenchia JM, Estes RJ, Wunderink RG, el Torky M, Leeper KV Jr. Fibroproliferative phase of ARDS. Clinical findings and effects of corticosteroids. Chest 1991;100(4):943-952.
5. Suter PM. Lung inflammation in ARDS: friend or foe? N Engl J Med 2006;354(16):1739-1741.
6. Weigelt JA, Norcross JF, Borman KR, Snyder WH 3rd. Early steroid therapy for respiratory failure. Arch Surg 1985;120(5):536-540.
7. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA. Early methylprednisolone treatment for septic syndrome and the adult respiratory distress syndrome. Chest 1987;92(6):1032-1036.
8. Luce JM, Montgomery AB, Marks JD, Turner J, Metz CA, Murray JF. Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. Am Rev Respir Dis 1988;138(1):62-68.
9. Bernard GR, Luce JM, Sprung CL, Rinaldo JE, Tate RM, Sibbald WJ, et al. High-dose corticosteroids in patients with the adult respiratory distress syndrome. N Engl J Med 1987;317(25):1565-1570.
10. Peter JV, John P, Graham PL, Moran JL, George IA, Bersten A. Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. BMJ 2008; 336(7651):1006-1009.
11. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. Chest 2007;131(4):954-963.
12. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, et al; ARDS Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006;354(16):1671-1684.
13. Meduri GU, Headley AS, Golden E, Carson SJ, Umberger RA, Kelso T, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. JAMA 1998;280(2):159-165.
14. Agarwal R, Nath A, Aggarwal AN, Gupta D. Do glucocorticoids decrease mortality in acute respiratory distress syndrome? A meta-analysis. Respirology 2007;12(4):585-590.
15. Meduri GU, Marik PE, Chrousos GP, Pastores SM, Arlt W, Beishuizen A, et al. Steroid treatment in ARDS: a critical appraisal of the ARDS network trial and the recent literature. Intensive Care Med 2008;34(1):61-69.
16. Tang BM, Craig JC, Eslick GD, Seppelt I, McLean AS. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. Crit Care Med 2009;37(5):1594-1603.
17. Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med 2008;36(6):1937-1949.
18. Keel Hauser M, Stocker R, Baumann PC, Speich R. Established acute respiratory distress syndrome: benefit of corticosteroid rescue therapy. Respiration. 1998;65(4):258-264.
19. Varpula T, Pettilä V, Rintala E, Takkunen O, Valtonen V. Late steroid therapy in primary acute lung injury. Intensive Care Med. 2000;26(5):526-531.
20. Huh JW, Lim CM, Jegal YJ, Lee SD, Kim WS, Kim DS, et al. The effect of steroid therapy in patients with late ARDS. Tuberc Respir Dis. 2002;52(4):376-384. [Korean]
21. Lee HS, Lee JM, Kim MS, Kim HY, Hwangbo B, Zo JI. Low-dose steroid therapy at an early phase of postoperative acute respiratory distress syndrome. Ann Thorac Surg. 2005;79(2):405-410.
22. Annane D, Sébille V, Bellissant E; Ger-Inf-05 Study Group. Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome. Crit Care Med. 2006; 34(1):22-30.
23. Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med 2005;171(3):242-248.
24. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342(18):1301-1308.
25. Widemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, et al; ARDS Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006; 354(24):2564-2575.
26. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342(20):1471-1477.
27. Huang CJ, Lin HC. Association between adrenal insufficiency and ventilator weaning. Am J Respir Crit Care Med 2006;173(3):276-280.
28. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358(2):111-124.
29. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating severe sepsis and septic shock. Cochrane Database Syst Rev 2004;(1):CD002243.
30. Keh D, Boehnke T, Weber-Cartens S, Schulz C, Ahlers O, Bercker S, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. Am J Respir Crit Care Med 2003;167(4): 512-520.
31. Leatherman JW, Fluegel WL, David WS, Davies SF, Iber C. Muscle weakness in mechanically ventilated patients with severe asthma. Am J Respir Crit Care Med 1996;153(5):1686-1690.
32. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med 1996;125(7):605-613.

Discussion

Moores: You alluded to genetic testing. Obviously, some of the people with persistent fibroproliferative ARDS have a different inflammatory response than those who do not, and an imbalance between the inflammatory and anti-inflammatory response. So, for whatever reason, they have a more pro-inflammatory response and an inadequate anti-inflammatory response. Could cytokine or inflammatory cell mediators in BAL, at day 3, 5, or 7, help us target who might benefit from corticosteroids? You mentioned that the ARDS Network trial did that.

Gay: Umberto Meduri has made a living out of this BAL sampling; if he doesn't have a BAL sample on someone in his ICU, he can't put them in the trial to try to answer that question.[1] But a lot of these observations are epiphenomena, and it's unclear if we can find mechanistically what's important, such as if interleukin-6 goes up or should we beat it down. The yin-and-yang complexity of the pro-inflammatory and anti-inflammatory response tells me that we need to know more about that position before we try to block something globally with steroids. That's where we're stuck now.

1. Meduri GU, Kohler G, Headley S, Tolley E, Stentz F, Postlethwaite A. Inflammatory cytokines in the BAL of patients with ARDS: persistent elevation over time predicts poor outcome. Chest 1995;108(5): 1303-1314.

MacIntyre: We keep talking about genetic markers and inflammatory mediators, and steroids in pharmacologic doses. What about taking a slightly different angle on this: the notion that in systemic inflammatory illnesses there is a relative adrenal insufficiency, so the role of steroids is not so much to suppress inflammation but, instead, as a replacement, if you will, for relative adrenal insufficiency. That might be the mechanism that gives us some benefit, even though it may not be a gross mortality benefit.

Sessler: This is a really challenging area. I've spoken with many investigators, and they say it is difficult to make a biochemical definition that really fits and makes sense. The gap, or the delta, of less than 9 μg/mL of cortisol after a supraphysiologic dose of ACTH [adrenocorticotropic hormone], is debated as to whether that is really a legitimate marker of critical-illness-related adrenal insufficiency.

There is evidence,[1] which I think is not widely appreciated, that, in septic shock, hydrocortisone increases catecholamine receptor activity on the vascular smooth muscle. The increase in arterial blood pressure is larger at each dose of norepinephrine or phenylephrine after 50 mg of hydrocortisone is administered, compared to placebo. So there may be factors separate from adrenal axis function. Regarding acute lung injury, the pro-inflammatory state that is attenuated by corticosteroids is certainly a separate issue. It's challenging to sort it all out; I'd be reluctant to hang my hat on the adrenal insufficiency piece of it.

1. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, et al; National Heart, Lung, and Blood Institute; Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006; 354(16):1671-1684.

Gay: I agree. In this literature it is so fascinating how you walk around with your house staff and you tell them what one study did this week and then you tell them what a very similarly designed trial did the next year; you really wonder what you're trying to teach people, because the data are not very consistent. Precision is what we're missing—the timing with this stuff: how big should the dose be? What is the target? I struggle with this.

Sessler: If I may go back to that first question. In the ARDS Network a very high BAL procollagenase peptide type III was a strong predictor of responsiveness to methylprednisolone: the 60-day mortality was less than 5%. But that was in a subgroup of only 24 patients.

Moores: Right. And it didn't necessarily mean that if you took the ones who didn't have a high procollagenase peptide III and randomized those—that's your question at that point.

Sessler: Right. The mortality was actually higher, although I don't think it reached statistical significance, at 35% with methylprednisolone, for the subgroup that had low BAL procollagenase peptide III. So I think markers like that are promising. I don't think those data say that that's the answer, and it's not commercially available, but if we can identify a marker like that, it would certainly help sort out who might be a good candidate.

Talmor: Are we ready for another clinical trial in this field, or do we have to go back to the drawing board and better identify who may benefit before we do that again?

Gay: I think we've learned something from the error of our ways. Fundamentally, very high dosages directed strictly at septic patients is a mistake. I don't think any of us will start out on day 1 giving steroids to everybody who has fever, tachycardia, and bilateral infiltrates. So the question becomes, what is the physiologic marker we're really looking for? I think the key outcome should be mortality. Ventilator-free days often translate to much more expensive care. The old doctrine that if they die early you get the full DRG [diagnosis-related group] is still out there, but, seriously, having them around longer to have more complications may not be another good end point to get hung up on.

So where do we go? Would I use steroids again? I certainly think there's going to be a time I use steroids again, whether focused on blood pressure phenomena, adrenal insufficiency, or lung remodeling from inflammation. But I think that without first being linked to some other mechanism that we can say steroids are modulating, we'd just be doing another expensive trial for limited gain.

Sessler: I believe the abrupt methylprednisolone taper may have produced an unintended effect, so ideally it deserves a repeat trial. There was substantial difficulty in enrolling patients in the first ARDS Network study.

Is the same thing going to happen as we saw in the CORTICUS[1] [Corticosteroid Therapy of Septic Shock] trial? In that study, enrollment was affected by the fact that there are so many believers in corticosteroids for sepsis. That is, many investigators said, "My equipoise is off in enrolling my patients in a study where half the patients are going to get placebo, because I'm convinced from my own practice that steroids have benefit." So, like we saw in CORTICUS, where the population was substantially different from every other sepsis study—instead of mostly medical patients, there were mostly surgical patients in CORTICUS. I suspect there would be enrollment difficulty in a repeat study of corticosteroids for ARDS if it were of similar design. That would be my primary concern about that trial.

If you have a study that doesn't show mortality benefit but does show other benefits, such as reduced ventilator duration—that I think do have value beyond being just "surrogate markers"—how are these results viewed? I think there are clearly factors that are surrogate markers. For example, better oxygenation seems nice, but it does not affect important outcomes. But some of the things I can prevent, such as having a lower likelihood of developing shock or secondary infections, or if I can get the patient out of the ICU faster and off the ventilator faster—I think that's an important positive outcome. Is that going to help me manage the patient in the bed in front of me? Yes, it is. I don't have to have a mortality benefit to use an intervention if it's safe and has some other secondary benefits that are beyond being a surrogate marker.

1. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008; 358(2):111-124.

Gay: I would say that the difficulty with that approach is that it tends to let a runaway locomotive out of the depot. That is, if it changes practice on the basis of just those surrogate markers and the take-home lesson is that this alone is a benefit, at least in some people, then you may improperly conclude that this has got to be good practice and continue this in a runaway fashion. It also loses sight of the fact that there are very few people enrolled in the trials, and the generalizability of these—I can often say, "Of course they would have never been in a trial at all"—and now I'm trying to generalize something to somebody who would have never gotten into that trial at all based on something that looked good as a surrogate marker. If that's a major practice change on that basis, then I think we're playing with fire. I think that certainly happened, and I'll claim to be a victim of that mentality with the trial by Meduri et al[1] when it first came out.

1. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Caron SJ, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. Chest 2007;131(4):954-963.

Epstein: Curt, you quoted the RCT by Huang and Lin[1] on adrenal insufficiency and weaning. I was struck by the extraordinarily high incidence of adrenal insufficiency in that study, which really differed from any other study that's been published. Was etomidate an exclusion criterion? Also, did they use a tight weaning protocol? Any study that looks at weaning outcome has to have weaning driven by a tight protocol.

1. Huang CJ, Lin HC. Association between adrenal insufficiency and ventilator weaning. Am J Respir Crit Care Med 2006; 173(3):276-80.

Sessler: It was a very high incidence of adrenal insufficiency, which they defined as less than 25 μg/mL for baseline hydrocortisone, and then the second step was response to ACTH, and they had to have a delta of less than 9 μg/mL for adrenal insufficiency. But since three quarters of the patients had adrenal insufficiency, it begs the question, did they get etomidate, which would certainly invalidate or confound that. It is interesting that, regardless of how you define it, a large percentage of patients who got placebo did not have as good weaning success. If they didn't have a standardized protocol for weaning (I would hope they would if the study was all about weaning) and adhere to it, it's still a provocative finding, considering that it was a single-center study. It is supportive, but I don't think it stands by itself.

Epstein: You quoted the American College of Critical Care Medicine's guidelines[1] and recommendations, and the author names didn't seem like a very balanced panel. I don't think there was a single ARDS Network member on the panel. I think we need to be careful about who are the authors of guidelines.

1. Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med 2008;36(6):1937-1949.

Sessler: I prefaced my comments about those guidelines by saying, "this was written by the true believers," because the familiar names of individu-

als who take the pro side are the authors, and that's why I showed it in my role as the pro presenter, acknowledging that the author list did omit ARDS Network investigators.

Epstein: To use your term, it was steroidophilic.

Sessler: Exactly.

Gay: The editorial[1] was written by Annane and titled "Just Do It," so it was hardly open-minded.

1. Annane D. Glucocorticoids for ARDS: just do it [editorial]. Chest 2007;131(4):945-946.

Sessler: Like I said: it's a wonderful debate.

Gentile: As an ARDS Network veteran, I can tell you that the 5% enrollment was because it was day 7: by then they were either better or dead. Enrolling for a study with 5 inclusion criteria and 35 exclusion criteria was a huge challenge, so that's why we ended up with 5%.

Fessler: We're in an unfortunate situation here. We've done large expensive phase-III trials to get phase-II data. If we're going to do another trial, I wonder who we should enroll, at what point we should enroll them, at what dose, and for what duration?

Gay: I think that having another agent involved with this, either as an immunomodulator or as another therapeutic agent, would give us a little better insight into what we're doing, rather than trying to guess at another 1,000-patient target and a different timing for the steroid.

MacIntyre: I think you'd be hard pressed to start a trial like this. Too many people believe that steroids are probably OK in moderate doses, they don't cost much, and the down sides are low, so why do I want to bother with a trial to prove a negative?

Sessler: If you centered a study on a surrogate marker, such as BAL procollagenase peptide III, and said, "we have reason to believe this is a good marker of which patients would probably benefit," and require that as an inclusion criteria, then it makes some sense because you've improved patient selection. In that setting you might have a realistic chance at enrollment. But with an open-ended approach, enrollment will be difficult. Recall that it was problematic 7 years ago, even with the study as it was. And the timing is another question. Now we have the Meduri study[1] that looks promising—recognizing the limitations of the study design—so people are going to be more interested to learn, say, whether to start corticosteroids on day 3. So that would be the other question that's different. The Meduri study is provocative but limited by its methodological issues.

1. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. Chest 2007;131(4):954-963.

Siobal: In terms of designing another study, that list of 30 exclusion criteria will probably grow, because the IRBs [institutional review boards] scrutinize our protocols now.

I'm on the fence here. We have occasionally used steroids as rescue treatment in patients in that 7-to-14 day window, possibly where nothing else is working, and I think it still happens in our ICUs.

Durbin: You didn't show data that steroids cause harm, so you're talking about finding out what group they might help more. So why not take the position that steroids are cheap and available, and if they don't hurt anybody, what's the harm in giving them?

Epstein: There may be subgroups that are harmed, so we have to be careful about doing that.

Sessler: We also have some patients who we don't know what wrong with them—some sort of acute lung injury, for instance, and we've ruled out infection. Some may have acute interstitial pneumonitis, which would traditionally be regarded as a steroid-responsive condition. Maybe that's a different thing, but I think it is what we're left with sometimes; that is, the undiagnosed etiology for somebody with ARDS who may have a steroid-responsive condition.