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CLINICAL COMMENTARY

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Steroid treatment in ARDS: a critical appraisal of the ARDS network trial and the recent literature

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Abstract *Objectives:* To compare the design and results of randomized trials investigating prolonged glucocorticoid treatment (≥ 7 days) in patients with acute lung injury–acute respiratory distress syndrome (ALI–ARDS), and review factors affecting response to therapy, including the role of secondary prevention. *Design:* Trials were retrieved from the Cochrane Central Register of Controlled Trials (CENTRAL). Two investigators collected data on study characteristics, treatment intervention, and outcomes. The methodological quality of trials was determined and data were analyzed with Review Manager 4.2.3. *Measurements and results:* Five selected trials ($n = 518$) consistently reported significant improvement in gas exchange, reduction in markers of inflammation, and decreased duration of mechanical ventilation and intensive care unit stay (all $p < 0.05$). Two early small clinical trials showed marked reductions in the relative risk (RR) of death with glucocorticoid therapy (RR = 0.14, 95% CI 0.04–0.53; $p = 0.004$, $I^2 = 0\%$). Three subsequent larger trials, when combined, although nominally beneficial, did not reproduce the marked reductions observed in the earlier trials (RR = 0.84; 95% CI 0.68–1.03; $p = 0.09$, $I^2 = 9.1\%$), but achieved a distinct reduction in the RR of death in the larger subgroup of patients ($n = 400$) treated before day 14 of ARDS [82/214 (38%) vs. 98/186 (52.5%), RR = 0.78; 95% CI 0.64–0.96; $p = 0.02$, $I^2 = 0\%$]. *Conclusions:* Prolonged glucocorticoid treatment substantially and significantly improves meaningful patient-centered outcome variables, and has a distinct survival benefit when initiated before day 14 of ARDS.

Keywords Acute respiratory distress syndrome · Glucocorticoid treatment · Duration of mechanical ventilation · Mortality

Introduction

In acute respiratory distress syndrome (ARDS), the evolution of systemic and pulmonary inflammation in the first week of mechanical ventilation determines the physiological progression (resolving vs. unresolving) and outcome of the disease [1–3]. Patients failing to improve the lung injury score (LIS) or its components by day 7 of ARDS (unresolving ARDS), contrary to those who are improving, have persistent elevation in circulating and bronchoalveolar lavage (BAL) levels of inflammatory cytokines and chemokines, markers of alveolocapillary membrane permeability and fibrogenesis (dysregulated systemic inflammation) [1–4], and a higher mortality [5–7].

Translational research has provided evidence that insufficient glucocorticoid receptor (GR)-mediated inhibition of proinflammatory transcription factor nuclear factor-κB (NF-κB) is a central pathogenetic mechanism of dysregulated systemic and pulmonary inflammation in ARDS and is potentially reversed by quantitatively and temporally adequate prolonged glucocorticoid administration [1, 2, 8]. In a small randomized trial, prolonged methylprednisolone (2 mg/kg/day) administration led to rapid, progressive, and sustained reductions in plasma and BAL inflammatory cytokines, chemokines, and procollagen levels with parallel improvement in LIS and multiple organ dysfunction syndrome score (MODS) [2, 8–10] Treatment was associated with significant reductions in duration of mechanical ventilation and in intensive care unit (ICU) mortality [9]. Despite its limitations [11], this trial provided proof of concept for methylprednisolone treatment in ARDS [4, 8, 10], justifying a larger confirmatory trial that was conducted over 6 years by the ARDS Clinical Trials Network [12]. During this period, three additional randomized trials were conducted (Table 1) to investigate prolonged glucocorticoid treatment in early acute lung injury (ALI) (PaO_2:$FiO_2 < 300$) [13] and ARDS (PaO_2:$FiO_2 < 200$) [14, 15]. Cumulative data from these trials involving a total of 518 patients provide

Table 1 Randomized trials investigating prolonged glucocorticoid treatment in acute lung injury and ARDS

Study, year	Confalonieri et al. [13] 2005	Annane et al. [14] 2006	Meduri et al. [15] 2007	Meduri et al. [9] 1998	Steinberg et al. [12] 2006
Methodological quality[a]	11.5	14.5	13.5	13	14.5
Number of patients	46	177	91	24	180
Timing of ALI/ARDS	Early ALI	Early ARDS	Early severe ARDS	Unresolving ARDS	Unresolving ARDS
Randomized > day 14	0	0	0	2	48
Patient population	Community-acquired pneumonia	Medical–surgical septic shock[b]	Medical–surgical	Medical–surgical	Medical–surgical
Initial daily treatment[c]	Hydrocortisone 240 mg	Hydrocortisone 200 mg Fludrocortisone 50 μg	Methylprednisolone 1 mg/kg	Methylprednisolone 2 mg/kg	Methylprednisolone 2 mg/kg
Duration of treatment (days)	7	7	Up to 28	Up to 32	Up to 25
Primary outcome	Improvement in PaO_2:FiO_2 by day 8	28-day mortality	Improvement in LIS by day 7	ICU mortality	60-day mortality
Imbalance in baseline characteristics[d]	Yes	No	Yes	No	Yes
Infection surveillance[e]	N.A.	N.A.	Yes	Yes	No
Study limitations	See [d]	Post-hoc analysis Short duration of treatment	Open-label treatment for non improvers[f]	Blind cross-over for non improvers[f]	Discontinuation of study drug 48 h after extubation

LIS, lung injury score.

[a]The methodological quality of trials was determined by two authors (GUM and DA) using the "Methodologic Quality Form: The Efficacy and Adverse Effects of Corticosteroids in Sepsis and Septic Shock" [41], which includes the following criteria: patient selection, patient characteristics at baseline; randomization; blinding; intervention; contamination; co-intervention; explicit description of complications; withdrawal; intention-to-treat and adherence to protocol; and explicit diagnostic criteria. Any disagreement between the two authors was resolved by discussion with the other authors. We contacted authors for clarification where necessary.

[b]Post-hoc analysis of a subgroup of 177 patients with ALI–ARDS from a published trial of vasopressor-dependent septic shock [42].

[c]A loading dose was administered in four trials: hydrocortisone 200 mg [13], methylprednisolone 1 mg/kg [15], and methylprednisolone 2 mg/kg [9, 12]. Two trials administered the study drug as an infusion [13, 15].

[d]Imbalance in baseline characteristics: noninvasive positive pressure ventilation versus conventional ventilation [13] vasopressor-dependent shock [14, 15] and for severable variables in patients randomized on or after day 14 of ARDS (see Table 4) [12].

[e]Infection surveillance for patients that received greater than 7 days of treatment. N.A. = not applicable.

[f]Reference [38] provides data indicating the blinded (to randomization) administration of open label methylprednisolone treatment to nonimprovers favored the control group and decreased the effect size (in comparison to controls) observed in those randomized to methylprednisolone.

Table 2 Difference in study protocol between the two unresolving ARDS trials

	Meduri et al. [9], 1998	Steinberg et al. [12], 2006
Study entry		
Randomized after day 14 of ARDS	8%	27%
Severity of ARDS at study entry	LIS ≥ 2.5 and < 1 point reduction in LIS from day 1	PaO_2:FiO_2 < 200
Elevated BAL procollagen	100%	60%
Infection surveillance	Implemented[a]	Not required
During treatment		
Neuromuscular blocking agent use	Not allowed	42%
Infection surveillance	Implemented*	Daily exam
Tapering 48 h after extubation	Up to 18 days	0.5 -1.5 days
Patient receiving methylprednisolone 2 mg/kg/day	Day 1–7 = 1 mg/kg/day Day 8–14 = 0.5 mg/kg/day Day 14–18 = 0.25-0.125 mg/kg/day	Day 1 = 1 mg/kg/day, Day 2 = 0.5 mg/kg/day
Patient receiving methylprednisolone 1 mg/kg/day	Complete the 7-day course Day 8–14 = 0.5 mg/kg/day Day 14–18 = 0.25-0.125 mg/kg/day	Day 1 = 0.5 mg/kg/day Day 2 = 0.25 mg/kg/day
Patient receiving methylprednisolone 0.5 mg/kg/day	Complete the 7-day course Day 8-12 = 0.25-0.125 mg/kg/day	Discontinue

[a]Infection surveillance included (1) bronchoscopy with bilateral BAL prior to study entry and at 5- to 7-day intervals in intubated patients (without contraindication) and (2) a systematic diagnostic protocol if patients developed fever or had an increase in immature neutrophil count (≥ 10%) or minute ventilation (≥ 30%).

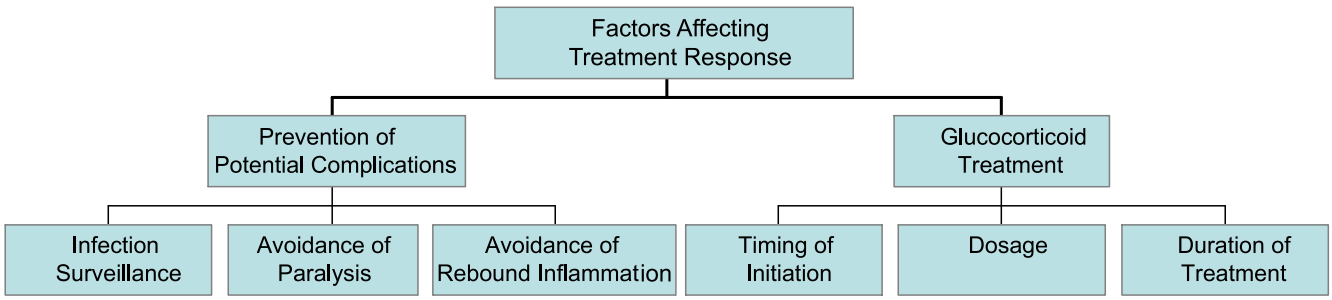

Fig. 1 Factors affecting response to glucocorticoid treatment

a broader understanding of the effects of glucocorticoid treatment in ALI–ARDS.

The purpose of this commentary is to highlight differences in study design between the two unresolving ARDS trials [10, 12] (Table 2) and to evaluate critically the findings of the ARDS Network trial [12]. This analysis considers previously reviewed factors affecting response to prolonged glucocorticoid administration (Fig. 1) [16] and the results of the other randomized trials [9, 13–15].

Methods for data extraction and analysis

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library (issue 2, 2007), using the search terms "acute lung injury," "acute respiratory distress syndrome," "acute respiratory failure," "steroids," "adrenal cortex hormones," "glucocorticoids," and "corticosteroids." We also searched the following electronic databases using the topic search terms in combination with a search strategy for identifying trials developed by The Cochrane Collaboration: (1) MEDLINE (1966 to May 2007) using the same search terms.

Data were extracted by one author (G.U.M.) and checked by another author (D.A.). Then they were entered onto the Review Manager 4.2.3 version by one author using the double-entry option (D.A.) and checked by another author (G.U.M.). For each outcome measure, we computed 2 × 2 tables summarizing the number of people who experienced the event or outcome in each comparison group and the total number in each group. These tables were organized so that a beneficial effect of treatment was associated with a relative risk (RR) < 1. We performed intention-to-treat analyses. We performed all statistical calculations using Review Manager 4.2.3. We calculated a weighted treatment effect (using the fixed effect model) across trials. The results were expressed as RRs with 95% confidence intervals (CI) for dichotomous outcomes (i. e., mortality), and weighted mean difference (WMD, 95% CI) for continuous outcomes (i. e., mechanical ventilation-free

days). We considered methods based on the random effects model only in the case of heterogeneity (i. e., 10% level of statistical significance for the chi-squared test for homogeneity). To identify potential sources of heterogeneity (when the chi-squared test for homogeneity yielded a probability value < 0.10), we sought to conduct a subgroup analysis based on size of the study (small vs. larger), timing of initiation of treatment (before day 14 from the onset of ALI–ARDS), and duration of treatment (greater than 1 week).

Findings during treatment

Table 3 shows the results of the ARDS network trial during treatment. In agreement with all other trials, prolonged glucocorticoid treatment was associated with significant improvement in PaO_2:FiO_2 ratio [9, 13–15] and significant reduction in markers of systemic inflammation [8, 13–15], BAL neutrophilia [4], duration of mechanical ventilation [9, 13, 15], and ICU stay [9, 13, 15]. In the five trials [9, 12–15], glucocorticoid treatment increased the number of mechanical ventilation-free days at day 28 (4.42 days; 95% CI 2.93–5.90; $p < 0.001$). However, there was significant heterogeneity across the studies ($Chi^2 = 15.36$, $p = 0.004$). Subgroup analysis based on studies that investigated only treatment (methylprednisolone) of greater than 1 week's duration ($n = 295$) [9, 13, 15] showed a distinct increase in the number of mechanical ventilation-free days (WMD = 5.59 days, 95% CI 3.49–7.68; $p < 0.001$) without heterogeneity ($Chi^2 = 2.18$, $p = 0.34$) across the studies (Fig. 2). This effect was far greater than the one observed with the recommended low tidal volume ventilation (12 ± 11 vs. 10 ± 11; $p = 0.007$) [17] or conservative strategy of fluid management (14.6 ± 0.5 vs. 12.1 ± 0.5; $p < 0.001$) [18].

Findings after rapid tapering of treatment

In the ARDS network trial, the large benefits observed during methylprednisolone treatment of unresolving ARDS

Table 3 Findings of the ARDS network trial [12][a]

	Methylprednisolone ($n = 89$)	Placebo ($n = 91$)	p value
Findings before discontinuation of treatment			
Change in plasma IL-6 by day7	−0.71	−0.18	< 0.001
Change in BALF % neutrophils by day7	−18.00	+5.75	0.02
PaO_2:FiO_2 on day 14	215.4 ± 114.7	164.8 ± 54.9	0.02
Static compliance (cm H_2O) on day 14	40 ± 20	30 ± 10	0.01
Died during initial assisted breathing	17 (19%)	24 (26%)	0.3
Initially weaned to unassisted breathing	72 (81%)	65 (71%)	0.006
Duration (days) of mechanical ventilation (mean)	14.1 ± 1.7	23.6 ± 2.9	0.006
Discharged home after initial wean	55 (62%)	45 (49%)	0.006
Findings after discontinuation of treatment			
Returned to assisted breathing	20 (28%)	6 (9%)	0.008
Died following return to assisted breathing	8 (40%)	3 (50%)	1.0
Overall findings			
Ventilator-free days at day 28	11.2 ± 9.4	6.8 ± 8.5	< 0.001
ICU-free days at day 28	8.9 ± 8.2	6.2 ± 7.8	0.006
Suspected or probable pneumonia (%)	6	14	0.05
Number of serious infections/Number of patients	25/20	42/30	0.14
Episodes of shock after study entry	6	17	0.03
Neuromyopathy	30%	20%	0.2
Serious events associated with myopathy or neuropathy[b]	9	0	0.001

[a]Dr. Marek Ancukiewicz (Massachusetts General Hospital, Boston) graciously provided previously unpublished data.
[b]Criteria for serious events associated with myopathy or neuropathy are not defined in the text of the manuscript.

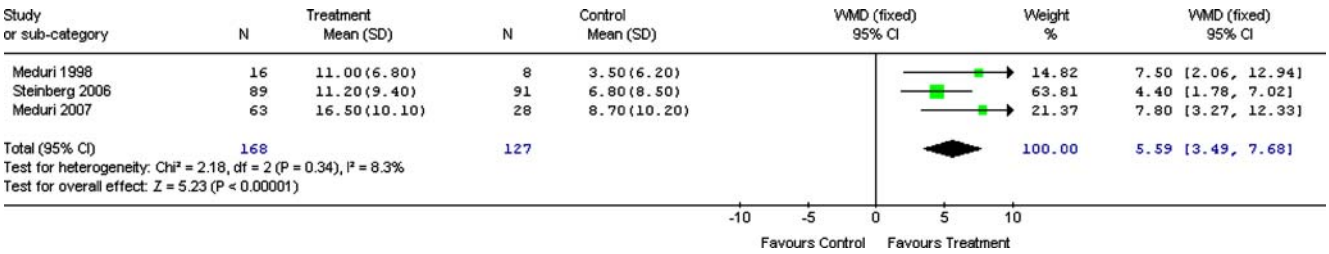

Fig. 2 Effects of prolonged methylprednisolone treatment on mechanical ventilation-free days at day 28

(10 days' reduction in duration of mechanical ventilation; 27% relative reduction in mortality; 21% relative increase in patients discharged home after initial weaning) were partially lost with protocol-driven rapid tapering of the study drug after 48 h of unassisted breathing (Table 2). It is important to underscore that, in ARDS, systemic and pulmonary inflammation continue for weeks and extend well beyond extubation [8]. The circulating half-life of methylprednisolone varies from 3.8 to 7.2 h, with greatly diminished effects expected 24–36 h after discontinuing treatment [19–21]. Moreover, exposure to glucocorticoids leads to significant reduction in glucocorticoid receptor number and binding capacity (reviewed in [2]). Ample evidence demonstrates that rapid tapering of glucocorticoid treatment may lead to rebound inflammation–fibroproliferation [10, 20, 22–27] and an exaggerated cytokine response to infection [28]. In experimental ALI, prolonged glucocorticoid administration decreased edema and lung collagen formation, while early withdrawal rapidly negated the positive effects of therapy [22–24]. In unresolving ARDS, early discontinuation of methylprednisolone administration was associated with physiological deterioration [10, 25, 26] that improved following reinstitution of treatment [25, 26]. Likewise, in patients with septic shock, early glucocorticoid discontinuation was associated with physiological deterioration [20, 27]. In the ARDS network trial, methylprednisolone was removed within 3–4 days of extubation and likely contributed, as acknowledged by the authors, to the deterioration in PaO_2:FiO_2 ratio and higher rate of reintubation (35% with shock and probable treatment-induced relative adrenal insufficiency) and associated mortality (Table 3) [12]. In other trials [9, 13–15], longer duration of methylprednisolone treatment following extubation – similar to the treatment of respiratory failure associated with asthma or chronic obstructive lung disease (COPD) – was not associated with a relapse of ARDS.

Findings for patients randomized after day 14

Although the ARDS network trial reported substantial and significant positive results for most secondary variables (Table 3), the trial is portrayed as negative partly because of the increased mortality observed in the subgroup of patients randomized to methylprednisolone after day 14 of ARDS. This small subgroup, however, had large imbalances in baseline characteristics (Table 4) for age, gender, pneumonia, trauma, serum creatinine, APACHE III, compliance, and lung injury score that likely accounted for the uncharacteristically low mortality in the control group (8% vs. 36%). Prior studies have shown that risk factors for higher mortality in ARDS include age [29–31], female gender [32], sepsis [29], APACHE score [30, 31, 33, 34], and lung injury score [33], while trauma is associated with lower mortality [29, 35]. As shown in Table 4, the control group had – among all four subgroups – the lowest values for age, pneumonia, APACHE III, creatinine, and lung injury score and the highest values for trauma and compliance. In contrast, the treated group had – among all subgroups – the highest values for age, female gender, pneumonia, and lung injury score and the lowest value for compliance. These imbalances and the small size of the subgroup directly challenge the conclusion of the ARDS network trial that "starting methylprednisolone therapy more than two weeks after the onset of ARDS

Table 4 Imbalance in baseline characteristics between methylprednisolone-treated and control patients

Treatment initiation	7–13 days		14–28 days	
Variable	Placebo ($n=66$)	Methylprednisolone ($n=66$)	Placebo ($n=25$)	Methylprednisolone ($n=23$)
60-day mortality unadjusted	36%	27%	8.0 ± 5.4%	34.8 ± 9.9%[a]
60-day mortality adjusted	N.A	N.A	11.2 ± 7.2%	28.0 ± 7.5%[b]
Age, years	51 ± 17	47 ± 13	45 ± 13	52 ± 24
Male gender	59%	42%	56%	35%
Trauma	11%	12%	20%	13%
Pneumonia	42%	36%	28%	44%
APACHE III score	87 ± 31	88 ± 28	79 ± 22	87 ± 25
Creatinine (mg/dl)	1.4 ± 1.4	1.4 ± 1.4	1.0 ± 0.8	1.3 ± 1.3
Compliance (cmH_2O)	24 ± 10	25 ± 10	26 ± 15	18 ± 7*
Lung injury score	3.1 ± 0.9	3.1 ± 1.0	2.7 ± 1.2	3.7 ± 0.8*

[a]Significance: 60-day mortality ($p=0.035$); compliance ($p=0.07$); lung injury score ($p=0.02$). Additional significant differences for patients randomized after day 14 (placebo vs. methylprednisolone) included patients with LIS > 2.5 (60% vs. 90%; $p=0.025$).
[b]Dr. Marek Ancukiewicz (Massachusetts General Hospital, Boston) graciously provided previously unpublished data and statistical analysis for the ARDS Network. Mortality was adjusted by fitting, in 48 patients enrolled after day 14 of ARDS, baseline APACHE III, age, plateau pressure, number of organ failures, baseline A-a DO_2. Using the logistic regression coefficients, the two predictions were calculated, on all 48 patients assuming first all patients received placebo, then all patients received methylprednisolone. These predictions were averaged and confidence intervals were obtained using bootstraps. Adjusted mortality is 11 ± 7 vs. 28 ± 7.5 ($p=0.57$). When lung injury score (data available in 30 of 45 patients) were also included, the adjusted mortality is 11 ± vs. 28 ± 9 ($p=0.22$).

may increase the risk of death" [12]. When mortality was adjusted (Table 4) fitting in the regression model, some variables found different at baseline [APACHE III, age, plateau pressure, number of organ failures, alveolar–arterial O_2 difference (A-a DO_2)], the 60-day mortality decreased to $11.2 \pm 7.2\%$ vs. $28.0 \pm 7.5\%$, and significance ($p = 0.57$) was lost (personal communication: Dr. Marek Ancukiewicz, Massachusetts General Hospital, Boston, MA, USA).

Preventive measures to decrease complications associated with glucocorticoid treatment

As shown in Fig. 1, implementing measures to prevent complications associated with glucocorticoid treatment affects overall response and is fundamental to minimizing imbalances in risk exposure between groups. Failed or delayed recognition of nosocomial infections in the presence of a blunted febrile response represents a serious threat to the recovery of patients receiving prolonged glucocorticoid treatment [16]. In a randomized trial, therefore, inclusion of infection surveillance – for those receiving treatment greater than 7 days' duration – is essential to minimize the potential bias generated by under-diagnosed infections on morbidity and mortality. In the two randomized trials [9, 15] that incorporated infection surveillance (Table 1), nosocomial infections were frequently (56%) identified in the absence of fever. After randomizing patients to methylprednisolone, researchers performed 79 bronchoscopies with bilateral BAL every 5–7 days and identified 19 cases of ventilator-associated pneumonia, 9 in afebrile patients [9, 15]. Although the ARDS Network trial reported a lower rate of clinically identified ventilator-associated pneumonia in treated patients; the protocol did not incorporate infection surveillance, making it impossible to estimate the impact of undiagnosed infections on outcome.

The combination of glucocorticoids and neuromuscular blocking agents versus steroids alone significantly increases the risk for prolonged neuromuscular weakness [36]. For this reason, the use of neuromuscular blocking agents is strongly discouraged in patients receiving concomitant glucocorticoid treatment, particularly when other risk factors are present (sepsis, aminoglycosides, etc.). In the ARDS Network trial, although all groups had similar exposure to paralytic agents (49% vs. 42%; $p = 0.30$), those randomized to methylprednisolone had a higher rate of serious events associated with myopathy or neuropathy (Table 3) [12]. ICU-acquired paresis is a known independent predictor of prolonged weaning [37]. However, among the 43 patients with weakness, those randomized to methylprednisolone ($n = 25$) had a significant ($p = 0.003$) and sizable (11 days) reduction in duration of mechanical ventilation (Table 7, supplementary appendix) [12].

Randomization of patients with undetectable procollagen in BAL

Persistent ARDS is characterized by ongoing inflammation, parenchymal cell proliferation, and disordered deposition of collagen, all of which may be responsive to glucocorticoid therapy [12]. Yet, in the ARDS Network trial, procollagen – a marker of fibrogenesis – was undetectable in 40% of BAL samples. In the previous late ARDS study [10], all patients with unresolving ARDS had a progressive increase in plasma and BAL procollagen type I and III until randomization to methylprednisolone. Lack of procollagen in BAL is more indicative of resolved ARDS, a condition that would not benefit from late introduction of anti-inflammatory anti-fibrotic treatment. This might explain why, in the ARDS network trial [12], those with no or low BAL procollagen levels in contrast to those with elevated procollagen levels had a poor response to methylprednisolone treatment.

Effect of prolonged glucocorticoid treatment on mortality

The analysis for mortality is limited by the significant heterogeneity across the five trials ($Chi^2 = 9.22$, $p = 0.06$). In these trials, glucocorticoid treatment reduced short-term mortality in models with fixed effects [91/276 (33%) vs. 111/242 (46%), RR = 0.76, 95% CI 0.62–0.93; $p = 0.007$]. Subgroup analysis for size of the study (Fig. 3) showed little heterogeneity within the two small studies [9, 13] and within the three larger trials [12, 14, 15]. The two early small clinical trials ($n = 68$) [9, 13] showed marked reductions in RR of death with glucocorticoid therapy [2/39 (5%) vs. 11/31 (35%), RR = 0.14, 95% CI 0.04–0.53; $p = 0.004$, $I^2 = 0\%$]. The three subsequently published larger clinical trials, when combined ($n = 448$) [12, 14, 15], although nominally beneficial, did not reproduce the marked reductions observed in the earlier trials [89/237 (37.5%) vs. 1000/211 (47%), RR = 0.84; 95% CI 0.68–1.03; $p = 0.09$, $I^2 = 9.1\%$], but achieved a distinct reduction in the RR of death in the larger subgroup ($n = 400$) of patients treated before day 14 of ARDS [82/214 (38%) vs. 98/186 (52.5%), RR = 0.78; 95% CI 0.64–0.96; $p = 0.02$, $I^2 = 0\%$]. We interpret these data to indicate that treatment initiation before day 14 of ALI–ARDS has a beneficial effect on mortality. This is supported by the fact that when analyzing the three trials investigating methylprednisolone for greater than 1 week's treatment (the form of treatment most likely to be used in ARDS) initiated before day 14 of ARDS ($n = 245$), mortality was equally decreased [35/144 (24%) vs. 40/101 (40%), RR = 0.62, 95% CI 0.43–0.90; $p = 0.01$, $I^2 = 17.7\%$] [38].

In conclusion, we have reviewed some of the salient differences in two trials investigating the effectiveness of

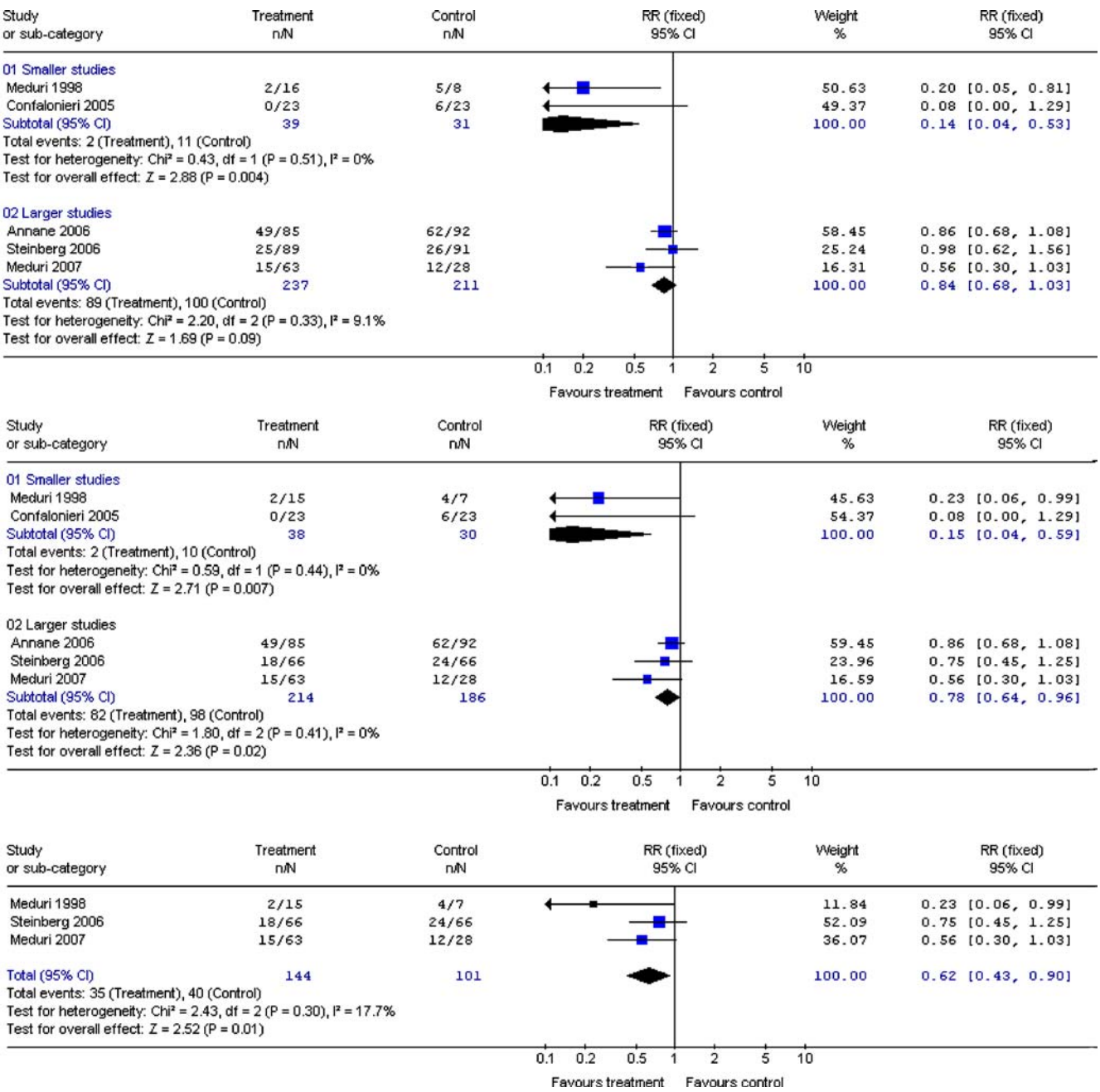

Fig. 3 Effects of prolonged glucocorticoid treatment on ARDS survival. The *top panel* reports data for all five randomized trials. The *middle panel* reports data for all five randomized trials after removing patients randomized after day 14. The *bottom panel* reports data for the three randomized trials that investigate prolonged methylprednisolone treatment of greater than 1 week's duration after removing patients randomized after day 14. This figure is reproduced with permission from [38]. Mortality was the primary outcome in three of the five studies [9, 12, 14]. One of these studies [14] investigated the efficacy of low-dose hydrocortisone in septic shock patients with ARDS by post-hoc analysis of a previously completed trial. Mortality is reported as 28-day [14], hospital [9, 13, 15], or 60-day [12]

prolonged methylprednisolone treatment in unresolving ARDS [9, 12]. Both trials [9, 12], similar to others [13, 15], reported a significant biological and physiological improvement during methylprednisolone treatment resulting in a significant reduction in duration of mechanical ventilation. None of the glucocorticoids trials reported an increased rate of infection, while two reported a reduction [12, 15]. The more rapid resolution of ALI–ARDS,

observed in all five randomized trials, might have a positive impact on long-term physical function and survival [15, 39]. In the ARDS network trial, premature removal of an effective treatment likely accounted for the higher rate of reintubation and loss of early survival benefits [12]. Moreover, the conclusion that methylprednisolone treatment increases mortality in patients randomized after day 14 is challenged by the large imbalances in baseline characteristics in this small subgroup of patients and the loss of significance when mortality is adjusted for baseline differences. The number of patients ($n = 518$) recruited in the above-referenced randomized trials is similar to those included in randomized trials for status asthmaticus ($n = 507$), COPD ($n = 511$), or *P. jiroveci* pneumonia ($n = 352$) [40]. Taken together, the results of five randomized studies [9, 12–15] provide evidence of efficacy in ALI–ARDS (accelerated resolution of ARDS with significant reduction in duration of mechanical ventilation and ICU stay) with a favorable risk profile when secondary prevention is implemented. These measures include (1) intensive infection surveillance, (2) avoidance of paralytic agents, and (3) avoidance of rebound inflammation with premature discontinuation of treatment that may lead to physiological deterioration and reintubation.

Correct use of prolonged glucocorticoid treatment is associated with a substantial and significant improvement in meaningful patient-centered outcome variables, and a distinct survival benefit when treatment is initiated before day 14 of ARDS (Fig. 3). The findings recently reported with low-dose methylprednisolone (1 mg/kg/day) in early severe ARDS [15] should be replicated in a larger trial of patients with ALI–ARDS. The new trial should have mortality as the primary end-point, avoid internal crossover, and incorporate secondary prevention measures (infection surveillance and avoidance of paralysis and rebound inflammation) to minimize potential complications associated with glucocorticoid treatment. Similarly, clinicians should integrate secondary prevention measures when using prolonged glucocorticoid treatment in patients with ARDS. We hope that this commentary will generate interest on this important topic and stimulate additional clinical investigation of this inexpensive and highly effective anti-inflammatory therapy.

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