The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 20, 2006 VOL. 354 NO. 16

Efficacy and Safety of Corticosteroids for Persistent Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

ABSTRACT

BACKGROUND

Persistent acute respiratory distress syndrome (ARDS) is characterized by excessive fibroproliferation, ongoing inflammation, prolonged mechanical ventilation, and a substantial risk of death. Because previous reports suggested that corticosteroids may improve survival, we performed a multicenter, randomized controlled trial of corticosteroids in patients with persistent ARDS.

METHODS

We randomly assigned 180 patients with ARDS of at least seven days' duration to receive either methylprednisolone or placebo in a double-blind fashion. The primary end point was mortality at 60 days. Secondary end points included the number of ventilator-free days and organ-failure–free days, biochemical markers of inflammation and fibroproliferation, and infectious complications.

RESULTS

At 60 days, the hospital mortality rate was 28.6 percent in the placebo group (95 percent confidence interval, 20.3 to 38.6 percent) and 29.2 percent in the methylprednisolone group (95 percent confidence interval, 20.8 to 39.4 percent; P=1.0); at 180 days, the rates were 31.9 percent (95 percent confidence interval, 23.2 to 42.0 percent) and 31.5 percent (95 percent confidence interval, 22.8 to 41.7 percent; P=1.0), respectively. Methylprednisolone was associated with significantly increased 60- and 180-day mortality rates among patients enrolled at least 14 days after the onset of ARDS. Methylprednisolone increased the number of ventilator-free and shock-free days during the first 28 days in association with an improvement in oxygenation, respiratory-system compliance, and blood pressure with fewer days of vasopressor therapy. As compared with placebo, methylprednisolone did not increase the rate of infectious complications but was associated with a higher rate of neuromuscular weakness.

CONCLUSIONS

These results do not support the routine use of methylprednisolone for persistent ARDS despite the improvement in cardiopulmonary physiology. In addition, starting methylprednisolone therapy more than two weeks after the onset of ARDS may increase the risk of death. (ClinicalTrials.gov number, NCT00295269.)

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N Engl J Med 2006;354:1671-84.

The acute respiratory distress syndrome (ARDS) is caused by an inflammatory injury to the lung that is characterized clinically by acute hypoxemic respiratory failure.[1] Pathologically complex changes in the lung are manifested by an early, exudative phase followed by proliferative and fibrotic phases.[2,3] Persistent ARDS is characterized by ongoing inflammation,[4,5] parenchymal-cell proliferation,[3] and disordered deposition of collagen,[3,6-8] all of which may be responsive to corticosteroid therapy.

Four trials of high-dose, short-course corticosteroids for early-phase ARDS failed to show improvements in survival.[9-12] Several reports from small case series suggested a benefit of moderate-dose corticosteroids in patients with persistent ARDS.[8,13-17] A single-center, randomized trial involving 24 patients who had had ARDS for seven or more days reported that moderate-dose corticosteroids improved lung function and survival.[18]

The risks associated with corticosteroids in these patients are unclear. Several studies involving patients with sepsis and ARDS have suggested that high-dose corticosteroids increase the risk of secondary infections,[11,12,19-21] yet a meta-analysis of moderate-dose corticosteroids for sepsis did not substantiate this observation.[22] Additional potential risks of corticosteroids include hyperglycemia, poor wound healing, psychosis, pancreatitis, and prolonged muscle weakness with impaired functional status.[23]

We conducted a multicenter randomized, controlled trial to determine the efficacy and safety of this therapy. Our hypothesis was that the administration of moderate-dose methylprednisolone to patients with persistent ARDS would improve clinical outcomes without significantly increasing complications.

Methods

Patients were enrolled from August 5, 1997, through November 17, 2003, at 25 hospitals of the National Heart, Lung, and Blood Institute (NHLBI) ARDS Clinical Trials Network (see the Appendix). The institutional review board of each hospital approved the trial. Written informed consent was obtained from patients or their surrogates. A complete description of the protocol and methods is available at www.ardsnet.org.

Patients

Patients who were intubated and receiving mechanical ventilation were eligible for enrollment 7 to 28 days after the onset of ARDS as previously defined.[1] The ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FIO_2) was adjusted for barometric pressure in Denver and Salt Lake City. Continuous mechanical ventilation and persistent bilateral infiltrates were required from the onset of ARDS to study entry. On the day of study entry, the PaO_2:FIO_2 ratio had to be less than 200. Exclusion criteria are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

Study Protocol

Patients were randomly assigned with the use of permuted blocks to receive either intravenous methylprednisolone sodium succinate (methylprednisolone) diluted in 50 ml of 5 percent dextrose in water or placebo (50 ml of 5 percent dextrose in water), stratified according to hospital. A single dose of 2 mg of methylprednisolone per kilogram of predicted body weight[24] was followed by a dose of 0.5 mg per kilogram of predicted body weight every 6 hours for 14 days, a dose of 0.5 mg per kilogram of predicted body weight every 12 hours for 7 days, and then tapering of the dose. Study drug was tapered over a period of 4 days if 21 days of treatment had been completed and the patient was unable to breathe without assistance for a period of 48 hours. Tapering occurred over a two-day period if disseminated fungal infection or septic shock developed or the patient was able to breathe for a period of 48 hours without assistance.

The protocol specified how patients were to be weaned from the ventilator. Patients were assessed daily for weaning readiness and weaned by pressure-support ventilation when acceptable arterial oxygenation could be maintained with the use of an FIO_2 of 0.5 or less.

Data on demographic characteristics, physiological characteristics, radiographic features, coexisting conditions, and medication were recorded at study entry and on days 1, 2, 3, 4, 5, 7, 14, 21, and 28. Patients were followed until they died, were discharged home while breathing without assistance, or day 180, whichever came first.

Patients were monitored daily for cardiovascular, renal, and hepatic failure and coagulation

abnormalities, as defined previously, for 28 days.[24] According to our definition, organs were considered failure-free after patients had been discharged from the hospital.

Any positive culture of material from a normally sterile site, when clinically available (cerebrospinal fluid, blood, pleural fluid, urine [$\geq 10^5$ colonies per milliliter]), as well as of bile and abdominal (peritoneal) fluid, was recorded. Data from weekly chart reviews were recorded if evidence of serious infections (e.g., nosocomial pneumonia, disseminated fungal infection, or sepsis) or other infections was present (a complete list of prospectively defined infections is provided in the Supplementary Appendix). Bronchoalveolar-lavage fluid and plasma were obtained at study entry and on day 7 and processed as previously described[25] (details are provided in the Supplementary Appendix). Plasma samples were stored in EDTA-treated tubes.

EVENTS OF NEUROMYOPATHY

Early in the course of the study, six adverse events of neuropathy, myopathy, or myositis were reported among patients in one treatment group. At the request of the data and safety monitoring board, we reviewed the charts of all 88 previously enrolled patients for evidence of neuromyopathy, as defined by the presence of the terms "myopathy," "myositis," "neuropathy," "paralysis," or "unexplained weakness" in the medical record. Clinically available information pertaining to neuromyopathy was collected from the charts of patients identified in this manner. The data and safety monitoring board and an NHLBI-appointed neurologist reviewed these data and recommended the continuation of the study. The charts of the final 91 patients who were enrolled were reviewed prospectively.

STATISTICAL ANALYSIS

The primary outcome was mortality 60 days after enrollment. Patients discharged home while breathing without assistance before 60 days were defined as survivors. The comparisons were conducted according to the intention-to-treat principle. We originally estimated that 400 patients would need to be enrolled for the study to have a statistical power of 85 percent to detect an absolute difference in mortality rates of 15 percent between groups (50 percent in the placebo group vs. 35 percent in the methylprednisolone group). After two years, we resized the study to detect a decrease in mortality from 40 percent to 20 percent because of survival data from our previous trial[24] and because the low rate of enrollment precluded timely completion of the original study. The modified sample calculation of 180 patients, approved by the data and safety monitoring board, provided the study with 85 percent power to detect this reduction in mortality at a two-sided significance level of 5 percent. Interim analyses were performed by the data and safety monitoring board after the enrollment of successive groups of approximately 60 patients with the use of symmetric stopping boundaries (two-sided $\alpha = 0.05$).

Secondary outcomes included the number of ventilator-free days (the number of days patients were alive and breathing without assistance) during the first 28 days,[24,26] the number of days without organ failure during the first 28 days, infectious complications during the first 28 days, and changes in markers of inflammation and fibroproliferation on study day 7. The following a priori determined covariates were examined for a treatment interaction: PaO_2:FIO_2, respiratory-system compliance, minute ventilation, time of entry after onset of ARDS (greater than 13 days vs. 7 to 13 days), number of nonpulmonary organs that failed, sepsis-initiated ARDS (vs. ARDS from other causes), and baseline levels of procollagen peptide type III. Two other covariates, tidal volume (expressed as milliliters per kilogram of predicted body weight) and date of enrollment, were added after the completion of the ARDS Clinical Trials Network tidal volume study.[24] Interactions were identified with the use of the Wald test and a logistic-regression model including main effects and interaction terms. Fatality rates were compared with use of Fisher's exact test. We calculated Wilson's confidence intervals.[27]

After the study was completed, an analysis revealed that 52 patients were still hospitalized and 12 patients were still receiving mechanical ventilation 60 days after enrollment. To obtain more complete information on outcomes, we reviewed patients' records to determine their hospital-discharge status up to 180 days after enrollment. This review was performed at each site by the site investigators without knowledge of patients' treatment assignments.

RESULTS

A total of 4123 patients were screened for the study, 659 (16 percent) of whom never met eligibility criteria. Of the remaining 3464 eligible patients, 180 (5 percent) were enrolled between day 7 and day 28 after the onset of ARDS: 91 were randomly assigned to the placebo group and 89 to the methylprednisolone group. The most common reason for exclusion was immunosuppression, which included the prior use of corticosteroids (22 percent) (Fig. 1). All patients had complete 180-day follow-up for survival status.

At baseline, the cohort was critically ill with severe ARDS as reflected by Acute Physiology and Chronic Health Evaluation III scores, PaO_2:FIO_2, partial pressure of arterial carbon dioxide, and respiratory-system compliance (Table 1). Except for the percentage of men, the baseline demographic and physiological variables did not differ significantly between groups (Table 1). Patients who were enrolled before our tidal volume study[24] was completed (in March 1999) had a mean (±SD) baseline tidal volume of 9.2±2.6 ml per kilogram of predicted body weight as compared with a value of 6.8±1.6 ml per kilogram of predicted body weight among patients enrolled after April 1, 1999 ($P<0.001$).

There was no significant difference in the 60-day hospital mortality rate, with 26 deaths in each group: 28.6 percent (95 percent confidence interval, 20.3 to 38.6 percent) in the placebo group and 29.2 percent (95 percent confidence interval, 20.8 to 39.4 percent) in the methylprednisolone group, for an absolute difference of 0.6 percent (95 percent confidence interval, –12.6 to 13.9 percent) favoring placebo (Table 2). At 180 days, 29 patients (31.9 percent) had died in the placebo group and 28 (31.5 percent) had died in the methylprednisolone group (Table 3).

The duration of ARDS before study entry and procollagen peptide type III levels at baseline were found to interact with treatment and mortality. Treatment with methylprednisolone was associated with a significantly increased mortality rate among patients who had had ARDS for more than 13 days before enrollment and a significantly decreased mortality rate among those with higher-than-median levels of procollagen peptide type III in bronchoalveolar-lavage fluid at baseline (Tables 2 and 3). None of the other interactions, including tidal volume ($P=0.63$) and date of enrollment ($P=0.34$), were significant. There were no significant differences between the group enrolled 7 to 13 days after the onset of ARDS and the group enrolled at least 14 days after the onset of ARDS, other than in the percentage of men and the positive end-expiratory pressure at baseline (13.3+5.0 and 10.8+5.1 cm of water, respectively; $P=0.004$) (Table 4 of the Supplementary Appendix).

The methylprednisolone group had significantly more ventilator-free days than the placebo group during the first 28 days (Table 2) as well as at 180 days (Table 3). Patients given methylprednisolone were able to breathe without assistance sooner than patients given placebo (14.1 days vs. 23.6 days, $P=0.006$) (Fig. 2). As compared with the placebo group, the methylprednisolone group also had significantly fewer days in the intensive care unit (ICU) during the first 28 days (Table 2), but not at day 180 (Table 3). Survivors in the placebo group spent more days receiving

Figure 1 (facing page). Enrollment and Possible Outcomes.

Eligibility criteria included the presence of ARDS for 7 to 28 days, continuous mechanical ventilation, persistent bilateral opacities on chest radiography, and a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of less than 200 on the day of enrollment. All patients were initially receiving mechanical ventilation. A large fraction of each group was initially able to breathe without assistance (the mean duration of assisted ventilation was 14 days in the methylprednisolone group and 24 days in the placebo group, $P=0.006$), but some patients in each group again required assisted ventilation after having breathed without assistance for at least 48 hours. Of these patients, some were once again able to breathe without assistance, but some died. The term "discharged home" was applied to patients who were able to breathe without assistance and returned to the same type of facility they had been in before hospitalization (e.g., home or a skilled nursing facility) before 180 days. The term "not home at 180 days" was applied to patients who either still needed breathing assistance or had not returned to the same type of facility they had been in before hospitalization by 180 days. We used Gray's test[28] to compare the cumulative incidence rates of death, discharge home, resumption of assisted ventilation, and freedom from the need for assisted ventilation among patients whose assisted-breathing history differed.

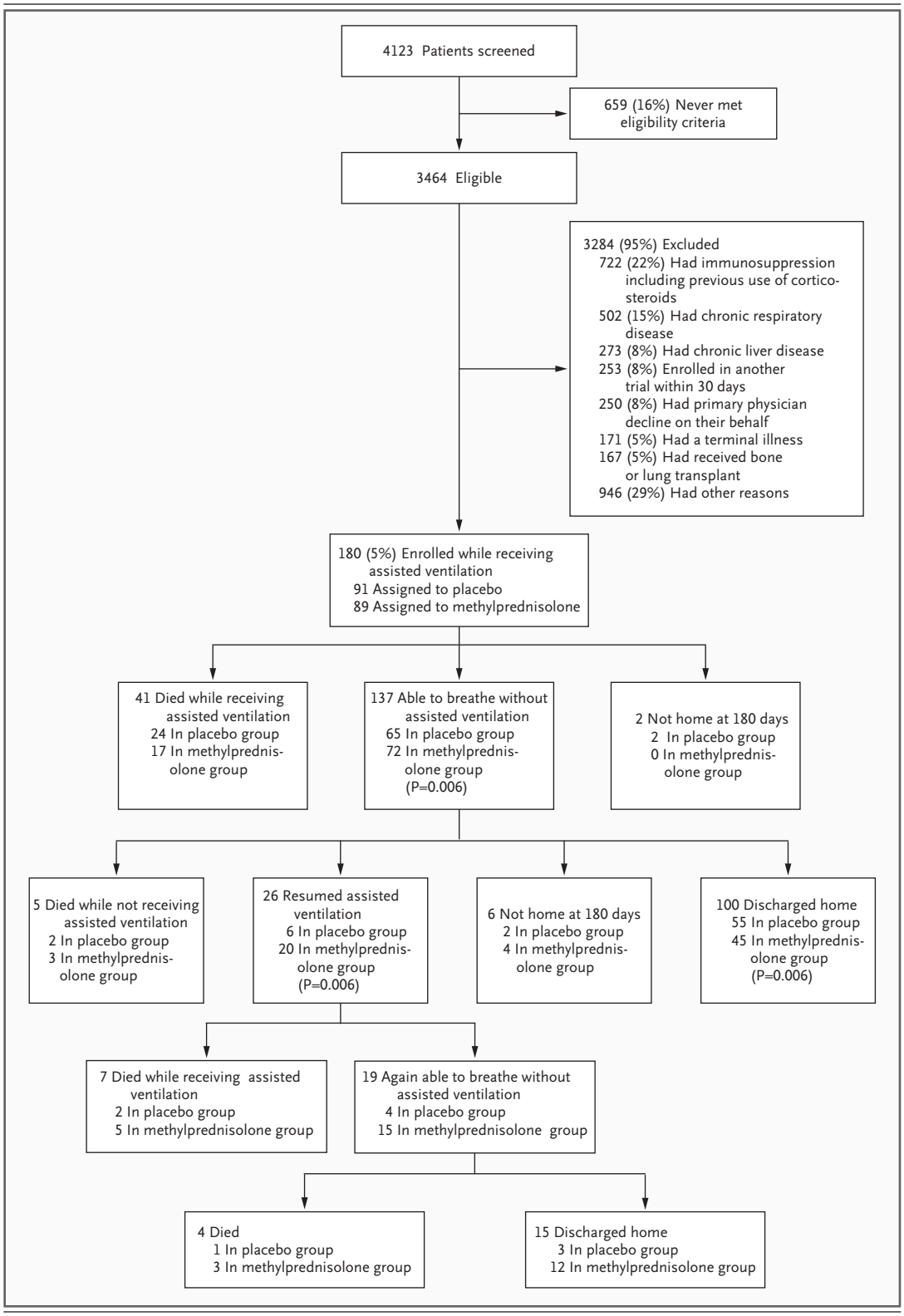

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Total Population		Randomization within 7–13 Days after ARDS Onset		Randomization within 14–28 Days after ARDS Onset	
	Placebo (N=91)	Methyl-prednisolone (N=89)	Placebo (N=66)	Methyl-prednisolone (N=66)	Placebo (N=25)	Methyl-prednisolone (N=23)
Age (yr)	49.2±16.5	49.0±19.0	50.7±17.4	47.8±16.9	45.2±13.0	52.5±24.2
Male sex (%)	58	40	59	42	56	35
Days in hospital before study entry	12.3±6.6	12.4±6.2	10.1±5.6	10.9±5.9	18.0±5.6	16.9±4.6
Days from ARDS onset to study entry	11.3±4.0	11.3±3.8	9.3±2.0	9.4±2.0	16.6±3.0	16.6±2.4
No. of nonpulmonary or CNS organ failures	0.6±0.8	0.7±0.7	0.6±0.8	0.6±0.6	0.9±0.8	0.8±0.9
No. of patients	85	81	64	59	21	22
Category of lung injury (%)						
Trauma	13	12	11	12	20	13
Sepsis	19	21	14	20	32	26
Multiple transfusions	1	1	1	2	—	—
Aspiration	18	16	20	15	12	17
Pneumonia	38	38	42	36	28	44
Other	11	11	12	15	8	0
Direct lung injury (%)†	56	54	62	52	40	61
Indirect lung injury (%)‡	44	46	38	48	60	39
No. of radiographic quadrants involved	3.9±0.4	3.9±0.4	3.9±0.4	3.8±0.5	3.8±0.5	4.0±0.0
No. of patients	91	89	66	66	25	23
APACHE III score§	84.6±29.4	87.6±27.5	86.8±31.6	87.9±28.4	78.8±22.2	86.9±25.3
Glasgow Coma score¶	8.8±4.5	8.4±4.5	8.7±4.7	8.1±4.5	8.9±3.9	9.1±4.5
Systolic blood pressure (mm Hg)	122.9±24.0	121.6±21.0	123.3±23.9	122.7±22.9	121.6±24.7	118.6±14.6
Albumin (g/dl)	2.0±0.5	1.9±0.5	2.0±0.5	1.9±0.6	2.0±0.5	1.9±0.4
No. of patients	80	77	61	55	19	22
Glucose (mg/dl)	141.6±52.8	152.8±72.6	146.4±57.1	160.2±76.0	127.9±35.3	131.6±58.2
No. of patients	89	89	66	66	23	23
Bilirubin (mg/dl)	1.2±2.0	1.5±3.5	1.3±2.2	1.8±4.1	0.9±1.0	0.9±1.3
No. of patients	81	78	62	56	19	22
Highest creatinine (mg/dl)	1.3±1.3	1.3±1.4	1.4±1.4	1.4±1.4	1.0±0.8	1.3±1.3
No. of patients	87	86	64	64	23	22
White-cell count (per mm^3)	13,874±7,140	15,401±8,041	13,519±7,032	16,083±8,586	14,893±7,509	13,444±5,951
No. of patients	89	89	66	66	23	23
Hematocrit	30.4±4.3	29.1±4.2	30.8±4.5	29.3±4.6	29.1±3.4	28.6±3.0
No. of patients	89	89	66	66	23	23
Arterial pH	7.4±0.1	7.4±0.1	7.4±0.1	7.4±0.1	7.4±0.1	7.4±0.1
No. of patients	88	86	65	63	23	23

Table 1. (Continued.)

Characteristic	Total Population		Randomization within 7–13 Days after ARDS Onset		Randomization within 14–28 Days after ARDS Onset	
	Placebo (N=91)	Methyl-prednisolone (N=89)	Placebo (N=66)	Methyl-prednisolone (N=66)	Placebo (N=25)	Methyl-prednisolone (N=23)
FiO_2	0.6±0.2	0.6±0.2	0.6±0.2	0.6±0.2	0.6±0.1	0.6±0.2
PaO_2 (mm Hg)	70±14	71±12	71.4±14.4	71.2±12.3	66.5±11.4	68.5±12.4
No. of patients	86	84	63	62	23	22
$PaCO_2$ (mm Hg)	53±16	53±18	52.5±16.2	53.8±18.1	53.1±17.3	50.7±17.8
No. of patients	88	86	65	63	23	23
PaO_2:FiO_2	126±40	126±42	125.4±42	124.6±44.7	125.5±34.4	128.4±34.6
No. of patients	86	84	63	62	23	22
Plateau pressure (cm of water)	33.8±9.7	34.5±10.0	33.2±8.1	34.4±9.5	35.2±13.1	35.0±11.7
No. of patients	65	66	47	51	18	15
Cstat‖	24.9±11.7	23.3±10.2	24.4±10.5	24.8±10.5	26.3±14.8	18.4±7.4
No. of patients	61	63	45	48	16	15
Lung Injury Score**	3.0±1.1	3.3±0.9	3.1±1.0	3.1±0.9	2.7±1.2	3.7±0.8
No. of patients	59	61	44	46	15	15
Tidal volume (ml/kg of predicted body weight)						
Total population	7.4±2.0	7.2±2.1	7.4±2.0	7.1±2.1	7.2±2.2	7.3±2.1
No. of patients	75	77	57	59	18	18
Enrolled before April 1, 1999	9.4±2.5	9.1±2.7	—	—	—	—
Enrolled on or after April 1, 1999	7.0±1.8	6.6±1.5	—	—	—	—
PEEP (cm of water)	12.3±4.7	12.9±5.6	12.9±4.7	13.6±5.2	10.8±4.4	10.8±5.9
Total minute ventilation (liters/min)	12.6±3.7	12.7±4.9	12.5±4.0	13.3±5.2	12.9±3.0	11.1±3.5
No. of patients	89	88	65	65	24	23

* Plus–minus values are means ±SD. Because of rounding, percentages may not total 100. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for bilirubin to micromoles per liter, multiply by 17.1. To convert values for creatinine to micromoles per liter, multiply by 88.4. CNS denotes central nervous system, FiO_2 fraction of inspired oxygen, PaO_2 partial pressure of arterial oxygen, $PaCO_2$ partial pressure of arterial carbon dioxide, and PEEP positive end-expiratory pressure.
† Direct lung injury included the categories of pneumonia and aspiration of gastric contents.
‡ Indirect lung injury included the categories of trauma, sepsis, transfusion, and other.
§ APACHE III denotes the Acute Physiology and Chronic Health Evaluation III; scores can range from 0 to 299, with higher scores indicating more severe illness.[29]
¶ Glasgow Coma Scale scores can range from 15 (normal) to 3 (deep coma).
‖ Cstat denotes the static compliance of the respiratory system, obtained by dividing the tidal volume by the difference between end-expiratory and end-inspiratory pressures.
** Lung Injury Scores can range from 0 to 4, with higher scores indicating more severe injury.

assisted ventilation than did survivors in the methylprednisolone group (P=0.006). There were no significant differences between groups in the median number of days spent in the ICU or the hospital at 180 days (Table 3). At 180 days after enrollment, 58 patients in the placebo group and 57 patients in the methylprednisolone group had been discharged home while breathing without assistance.

Ventilatory assistance was resumed in 26 pa-

Table 2. Primary and Secondary Outcomes and Adverse Events Defined A Priori According to the Protocol.*

Variable	Placebo (N=91)	Methylprednisolone (N=89)	P Value
60-Day mortality (%)	28.6	29.2	1.0
95% CI	20.8–38.6	20.8–39.4	
No. of ventilator-free days at day 28	6.8±8.5	11.2±9.4	<0.001
No. of organ-failure–free days			
Cardiovascular failure	17.9±10.2	20.7±8.9	0.04
Coagulation abnormalities	22.1±8.6	22.2±8.3	0.84
Hepatic failure	21.4±10.2	21.2±10.2	0.70
Renal failure	21.4±10.2	22.8±8.7	0.36
No. of ICU-free days at day 28	6.2±7.8	8.9±8.2	0.02
No. of serious adverse events associated with myopathy or neuropathy	0	9	0.001
Suspected or probable pneumonia (%)	14	6	0.05
No. of episodes of shock/no. of patients	17/15	6/5	0.03
No. of serious infections/no. of patients	43/30	25/20	0.14
Amylase on day 7 (U/liter)	73±50	125±131	0.003
Glucose on day 7 (mg/dl)	144.0±61.8	158.7±64.4	0.14
60-Day mortality according to time from ARDS onset			
7–13 Days (%)	36	27	0.26
No. of patients	66	66	
>14 Days (%)†	8	35	0.02
No. of patients	25	23	
60-Day mortality according to baseline BAL procollagen peptide type III level			
< Median (%)	9	35	0.03
No. of patients	23	23	
> Median (%)†	19	4	0.10
No. of patients	21	24	

* Plus–minus values are mean ±SD. Continuous variables were compared with the use of Student's t-test, and categorical variables with Fisher's exact test. Rank transformation was used for ventilator-free days, intensive care unit (ICU)–free days, and organ-failure–free days. CI denotes confidence interval, and BAL bronchoalveolar-lavage fluid.
† P=0.02 for the interaction with treatment-group assignment with the use of Wald's test.

tients: 6 in the placebo group and 20 in the methylprednisolone group (P=0.008) (Fig. 2). Seven of these patients had evidence of shock around the time assisted ventilation was resumed, all of whom were in the methylprednisolone group. Eleven of the 26 patients had evidence of neuromyopathy during their hospital course, 2 in the placebo group and 9 in the methylprednisolone group. The duration of ARDS before study enrollment (see Fig. 9 of the Supplementary Appendix) was not associated with a return to assisted ventilation; the 26 patients who resumed receiving assisted ventilation had enrolled a median of 10.5 days (interquartile range, 8 to 14) after the onset of ARDS, as compared with a median of 10.0 days (interquartile range, 8 to 14) after the onset of ARDS among the 154 patients who did not need to resume assisted ventilation (P=0.89).

Significant improvements in PaO_2:FIO_2 were observed in the methylprednisolone group on days 3 and 14 after enrollment. Plateau pressure was significantly lower in the methylprednisolone group on days 4, 5, and 7 after enrollment, as compared with the placebo group, whereas respiratory-system compliance was significantly improved on days 7 and 14 (Fig. 4 of the Supplementary Appendix).

As compared with the placebo group, the meth-

Table 3. Post Hoc Analyses of Outcomes and Adverse Events at 180 Days.*

Variable	Placebo (N=91)	Methylprednisolone (N=89)	P Value
180-Day mortality — %	31.9	31.5	1.0
95% CI	23.2–42.0	22.8–41.7	
No. of ventilator-free days at day 180			0.04
Median	149	159	
Interquartile range	0–167	13–173	
No. of ICU-free days at day 180			0.27
Median	150	152	
Interquartile range	0–164	13–168	
Survivors			0.006
Days of assisted ventilation up to 180 days			
Median	18	11	
Interquartile range	10–33	6–22	
Days of ICU stay up to 180 days			0.29
Median	20	17	
Interquartile range	11–31	10–31	
Days of hospitalization up to 180 days			0.73
Median	29	26	
Interquartile range	19–40	19–43	
Neuromyopathy — no./ total no. (%)			0.18
Retrospective review	10/43 (23)	15/44 (34)	
Prospective review	11/48 (23)	11/44 (25)	0.67
Overall	21/91 (22)	26/88 (30)	0.20
180-Day mortality according to time from ARDS onset			
7–13 Days — %	39	27	0.14
No. of patients	66	66	
>14 Days — %†	12	44	0.01
No. of patients	25	23	
180-Day mortality according to baseline BAL procollagen peptide type III level			
≤ Median — %	13	39	0.04
No. of patients	23	23	
> Median — %‡	24	4	0.05
No. of patients	21	24	

* Continuous variables were compared with the use of Student's t-test, and categorical variables with Fisher's exact test. Rank transformation was used for ventilator-free days and intensive care unit (ICU)–free days. CI denotes confidence interval, and BAL bronchoalveolar-lavage fluid.
† P=0.006 for the interaction with treatment-group assignment with the use of Wald's test.
‡ P=0.01 for the interaction with treatment-group assignment with the use of Wald's test.

ylprednisolone group had significantly more days without shock during the first 28 days. There were no significant differences between groups in the number of days without coagulation abnormalities or hepatic and renal failure (Table 2).

The mean serum glucose level was not significantly different between groups at baseline but was significantly higher in the methylprednisolone group than the placebo group on days 1 (Fig. 3), 2, and 4. The difference in means decreased from

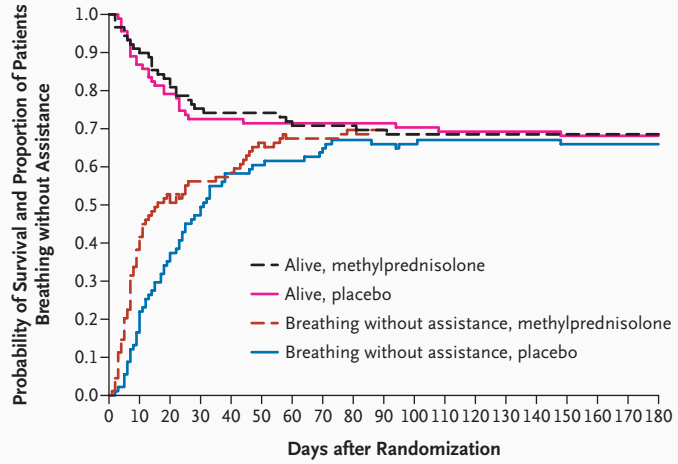

Figure 2. Probability of Survival and the Proportion of Patients with Persistent ARDS Who Became Able to Breathe without Assistance during the First 180 Days after Randomization.

At 180 days, 29 patients in the placebo group had died, 58 had been discharged home, and 4 had not been discharged home; the respective values in the methylprednisolone group were 28, 57, and 4. The status was known for all 180 patients at 180 days.

77.1 mg per deciliter (4.3 mmol per liter) on day 1 (95 percent confidence interval, 52.1 to 102.1 mg per deciliter [2.9 to 5.7 mmol per liter]) to 20.2 mg per deciliter (1.1 mmol per liter) on day 4 (95 percent confidence interval, 2.4 to 37.9 mg per deciliter [0.1 to 2.1 mmol per liter]) (Fig. 5 of the Supplementary Appendix).

Forty-three serious infections were diagnosed in 30 patients in the placebo group, as compared with 25 serious infections in 20 patients in the methylprednisolone group (P=0.14). The percentage of patients with suspected or probable pneumonia was lower in the methylprednisolone group than in the placebo group (P=0.05). There were 17 episodes of septic shock among 15 patients in the placebo group and 6 episodes among 5 patients in the methylprednisolone group (P=0.03).

Fifty-eight adverse events were reported: 25 in the placebo group and 33 in the methylprednisolone group (P=0.27). Serious adverse events of neuromyopathy were reported in nine patients, all of whom were in the methylprednisolone group (P=0.001 for the comparison with the placebo group). Chart review identified 48 patients with neuromyopathy: 21 in the placebo group and 27 in the methylprednisolone group (P=0.31). No significant difference in the incidence of neuromyopathy was detected by retrospective, as compared with prospective, chart review (26 of 88 patients, as compared with 22 of 92). Most patients (71 percent) with neuromyopathy had bilateral weakness of the arms and legs. Sensory deficits were reported in 17 percent of patients with neuromyopathy.

There was no significant difference in the percentage of patients exposed to neuromuscular-blocking agents in the placebo and methylprednisolone groups (49 percent and 42 percent, respectively; P=0.30). The duration of exposure to neuromuscular-blocking agents was generally short (median, 0 days; interquartile range, 0 to 2.5). The use of neuromuscular-blocking agents largely occurred before entry into the study: 34 percent of patients in the placebo group and 28 percent of patients in the methylprednisolone group received a neuromuscular blocker before study day 0. Exposure to neuromuscular-blocking agents was not significantly more common among patients who were identified as having neuromyopathy. Data on the association between treatment group and weakness with the duration of mechanical ventilation are given in Table 7 of the Supplementary Appendix.

As compared with the placebo group, the methylprednisolone group had significantly lower plasma interleukin-6 levels and neutrophil counts in bronchoalveolar-lavage fluid between day 0 and 7 (Fig. 6 and 7 of the Supplementary Appendix). Systolic and diastolic systemic arterial pressures were, for the most part, higher in the methylprednisolone group than in the placebo group beginning on study day 3 (See Fig. 8 of the Supplementary Appendix). The changes in procollagen peptide type III levels between day 0 and 7 did not differ significantly between the groups. Data on the distribution of baseline levels of procollagen peptide type III in bronchoalveolar-lavage fluid are given in Figure 10 of the Supplementary Appendix.

DISCUSSION

In this clinical trial of 180 patients with persistent ARDS, we found no beneficial effect of corticosteroids on survival in the hospital. Furthermore, the initiation of methylprednisolone 2 or more weeks after the onset of ARDS was associated with a significantly increased mortality rate at 60 and 180 days as compared with that in the placebo group.

However, corticosteroids improved cardiopulmonary physiology within three to seven days af-

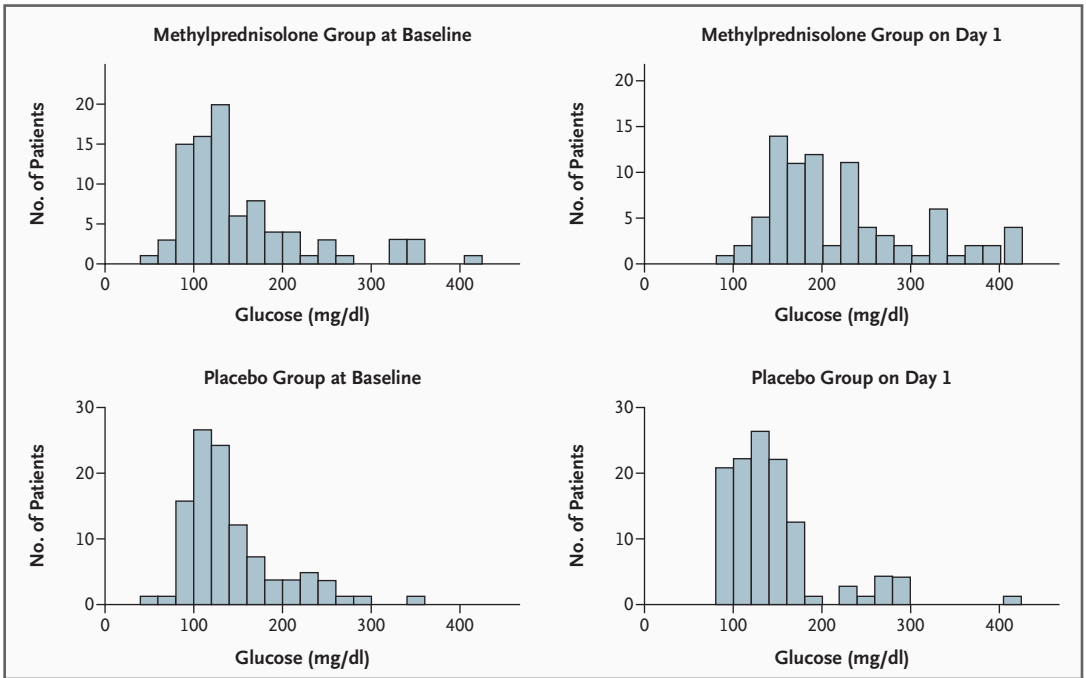

Figure 3. Frequency Distributions for Glucose Values Stratified According to Treatment Group at Baseline and on Study Day 1.

At baseline (study day 0), there was no significant difference in the distribution of average glucose levels. However, on study day 1, after the initiation of methylprednisolone, there were significantly more patients with higher glucose levels in the methylprednisolone group than in the placebo group, although there was still a large amount of overlap. We recorded the morning blood glucose level, defined as the value measured between 6 a.m. and 10 a.m. If more than one value was available during this reference period, the value obtained closest to 8 a.m. was recorded. To convert values for glucose to millimoles per liter, multiply by 0.05551.

ter their initiation and altered the course of ARDS. Treatment with methylprednisolone increased the number of ventilator-free days, ICU-free days, and shock-free days during the first 28 days. The number of days without assisted ventilation remained higher in the methylprednisolone group than in the placebo group at 180 days. The duration of hospitalization did not differ significantly between the groups at any time. Patients in the methylprednisolone group were able to breathe without assistance earlier than were patients in the placebo group, but they were also more likely to resume receiving assisted ventilation (28 percent vs. 9 percent, $P=0.006$).

The increased rate of return to assisted breathing appears to be an important reason why early physiological improvements in the methylprednisolone group did not translate to a survival advantage; 8 of the 20 methylprednisolone-treated patients who resumed receiving assisted ventilation died, as compared with 3 of 6 patients in the placebo group. Possible explanations for this effect include complications of corticosteroid therapy, such as neuromyopathy; complications related to the withdrawal of corticosteroids, including shock,[30] after patients were breathing without assistance; and pulmonary parenchymal causes of hypoxemic respiratory failure, such as recrudescence of fibroproliferation as a result of corticosteroid withdrawal.[30] Overall, shock was observed less often with methylprednisolone than with placebo, yet shock was common among patients who resumed receiving assisted ventilation. Neuromyopathy occurred at similar rates in the groups overall but also was common in patients who resumed receiving assisted ventilation. Given the small number of events, it is difficult to make causal inferences regarding why the resumption of assisted ventilation was more common in the methylprednisolone group.

An increased risk of secondary infections was reported in studies of high-dose corticosteroids for sepsis and early ARDS[11,12,19,20] but not in studies of more moderate doses.[22,31] We did not de-

tect an increased rate of nosocomial infections in the methylprednisolone group. There were more cases of nosocomial pneumonia, septic shock, and positive blood cultures in the placebo group. The lower rates of pneumonia and septic shock in the methylprednisolone group lead us to conclude that infections themselves do not explain the higher rate of return to assisted ventilation in this group.

Corticosteroids affect muscle function, but the effects of moderate-dose corticosteroids in critically ill patients are not well understood. Recent studies of patients receiving assisted ventilation have found a strong association between corticosteroid treatment and muscle weakness.[23,32] Although the overall rate of clinically suspected neuromyopathy was similar in our two groups, all nine reports of serious adverse events related to neuropathy or myopathy were in patients treated with methylprednisolone. One explanation for this disparity is that methylprednisolone increased the severity but not the incidence of neuromyopathy. The similar incidence in the two groups may also be explained by the presence of competing risks for neuromyopathy: corticosteroid-induced myopathy and hyperglycemia in the methylprednisolone group and protracted assisted ventilation in the placebo group.

We did not systematically assess nerve conduction or muscle function, and the study was underpowered to detect absolute differences in the incidence of neuromyopathy of less than 25 percent. Thus, the true rate and severity of neuromuscular abnormalities in either group are unknown. Despite these shortcomings, our results confirm that neuromyopathy is common in patients with persistent ARDS and raise concern that methylprednisolone may lead to an increase in clinically important neuromyopathy and its consequences.

The duration of ARDS before treatment significantly interacted with the effect of corticosteroids on survival. Patients who were enrolled at least 14 days after the onset of ARDS and who were randomly assigned to receive methylprednisolone had a significantly higher case fatality rate than similar patients who were assigned to receive placebo. Perhaps patients surviving at least 14 days of ARDS have less active fibroproliferation, as reflected by lower baseline lung levels of procollagen peptide type III (median, 0.4 vs. 0.9 U per milliliter; $P=0.01$), and are less responsive to corticosteroids. In prior studies purporting to show a benefit from corticosteroids, the median duration of ARDS was similar to the interval allowed before enrollment in our trial[8,13-16,18,33] and only two patients in our study had had ARDS longer than 21 days before enrollment (23 days and 26 days) (see Tables 5 and 6 of the Supplementary Appendix). Thus, the optimal timing, if it exists, of methylprednisolone therapy during the course of ARDS is unknown.

This study lasted seven years and spanned a period in critical care medicine in which there were substantial changes in practice. During this time, the use of low tidal volumes for ventilatory support in patients with ARDS,[24] tight blood glucose control,[34] corticosteroids for refractory septic shock,[31] drotrecogin-alfa for severe sepsis,[35] preventive strategies for ventilator-associated pneumonia,[36] and protocolized sedation with daily awakening[37] became part of evidence-based practice in the ICU. Although we cannot exclude the possibility that these interventions affected the outcome among patients enrolled in our study, we did not find an interaction between the time or baseline tidal volume and outcome with methylprednisolone. Average glucose levels were higher in the methylprednisolone group than in the placebo group at several points during the study. This disparity in glycemic control may have contributed to the mortality and neuromyopathy outcomes.

Although this study was not powered to detect relatively small treatment effects, we did not observe the magnitude of effect reported in a previous study.[18] Methylprednisolone did not increase infectious complications but may have increased the risk of neuromyopathy associated with critical illness. Our results do not provide support for the routine use of methylprednisolone in patients with persistent ARDS and suggest that methylprednisolone therapy may be harmful when initiated more than two weeks after the onset of ARDS.

APPENDIX

Participants in the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network were as follows (principal investigators and members of the steering committee are marked with an asterisk): **Investigators:** *Cleveland Clinic Foundation* — H.P. Wiedemann,* A.C. Arroliga, C.J. Fisher, Jr., J.J. Komara, Jr., P. Periz-Trepichio; *Denver Health Medical Center* — P.E. Parsons, *Denver Veterans Affairs Medical Center* — C. Welsh; *Duke University Medical Center* — W.J. Fulkerson, Jr.,* N. MacIntyre, L. Mallatratt, M. Sebastian, J. Davies, E. Van Dyne, J. Govert; *Johns Hopkins Bayview Medical Center* — J. Sevransky, S. Murray; *Johns Hopkins Hospital* — R.G. Brower, D. Thompson, H.E. Fessler,

S. Murray; *LDS Hospital* — A.H. Morris,* T. Clemmer, R. Davis, J. Orme, Jr., L. Weaver, C. Grissom, F. Thomas, M. Gleich (deceased); *McKay-Dee Hospital* — C. Lawton, J. D'Hulst; *MetroHealth Medical Center of Cleveland* — J.R. Peerless, C. Smith; *San Francisco General Hospital Medical Center* — R. Kallet, J.M. Luce; *Thomas Jefferson University Hospital* — J. Gottlieb, P. Park, A. Girod, L. Yannarell; *University of California, San Francisco* — M.A. Matthay,* M.D. Eisner, J. Luce, B. Daniel, R. Kallet; *University of Colorado Health Sciences Center* — E. Abraham,* F. Piedalue, R. Jagusch, P. Miller, R. McIntyre, K.E. Greene; *University of Maryland* — H.J. Silverman,* C. Shanholtz, W. Corral; *University of Michigan* — G.B. Toews,* D. Arnoldi, R.H. Bartlett, R. Dechert, R. Hyzy, C. Watts; *University of Pennsylvania* — P.N. Lanken,* J.D. Christie, B. Finkel, B.D. Fuchs, C.W. Hanson III, P.M. Reilly, M.B. Shapiro; *University of Utah Hospital* — R. Barton, M. Mone; *University of Washington–Harborview Medical Center* — L.D. Hudson,* T. Berry-Bell, G. Carter, C.L. Cooper, A. Hiemstra, R.V. Maier, M.J. Neff, K.P. Steinberg; *Utah Valley Regional Medical Center* — T. Hill, P. Thaut; *Vanderbilt University* — A.P. Wheeler,* G.R. Bernard, B. Christman, S. Bozeman, L. Collins, T. Swope, L.B. Ware; *Baylor College of Medicine–Ben Taub General Hospital*—K. Guntupalli,* V. Bandi, C. Pope; *Wake Forest University* — R.D. Hite,* P. Morris, A. Howard; **Clinical Coordinating Center:** *Massachusetts General Hospital, Harvard Medical School* — D.A. Schoenfeld,* B.T. Thompson, M. Ancukiewicz, D. Hayden, F. Molay, N. Ringwood, C. Oldmixon, A. Korpak, R. Morse; **National Heart, Lung, and Blood Institute Staff:** D.B. Gail, A. Harabin,* P. Lew, M. Waclawiw; **Steering Committee:** G.R. Bernard (chair); **Data and Safety Monitoring Board:** R.G. Spragg (chair), J. Boyett, J. Kelley, K. Leeper, M. Gray Secundy, A.S. Slutsky, B. Turnbull, G. Corbie-Smith; **Protocol Review Committee:** J.G.N. Garcia (chair), S.S. Emerson, S.K. Pingleton, M.D. Shasby, W.J. Sibbald.

REFERENCES

1. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149:818-24.
2. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000;342:1334-49.
3. Tomashefski JF Jr. Pulmonary pathology of the adult respiratory distress syndrome. Clin Chest Med 1990;11:593-619.
4. Steinberg KP, Milberg JA, Martin TR, Maunder RJ, Cockrill BA, Hudson LD. Evolution of bronchoalveolar cell populations in the adult respiratory distress syndrome. Am J Respir Crit Care Med 1994;150:113-22.
5. Park WY, Goodman RB, Steinberg KP, et al. Cytokine balance in the lungs of patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2001;164:1896-903.
6. Raghu G, Striker LJ, Hudson LD, Striker GE. Extracellular matrix in normal and fibrotic human lungs. Am Rev Respir Dis 1985;131:281-9.
7. Lamy M, Fallat RJ, Koeniger E, et al. Pathologic features and mechanisms of hypoxemia in adult respiratory distress syndrome. Am Rev Respir Dis 1976;114:267-84.
8. Ashbaugh DG, Maier RV. Idiopathic pulmonary fibrosis in adult respiratory distress syndrome: diagnosis and treatment. Arch Surg 1985;120:530-5.
9. 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;92:1032-6. [Erratum, Chest 1988;94:448.]
10. 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;138:62-8.
11. Bernard GR, Luce JM, Sprung CL, et al. High-dose corticosteroids in patients with the adult respiratory distress syndrome. N Engl J Med 1987;317:1565-70.
12. Weigelt JA, Norcross JF, Borman KR, Snyder WH III. Early steroid therapy for respiratory failure. Arch Surg 1985;120:536-40.
13. Biffl WL, Moore FA, Moore EE, Haenel JB, McIntyre RC Jr, Burch JM. Are corticosteroids salvage therapy for refractory acute respiratory distress syndrome? Am J Surg 1995;170:591-6.
14. Hooper RG, Kearl RA. Established ARDS treated with a sustained course of adrenocortical steroids. Chest 1990;97:138-43.
15. Braude S, Haslam P, Hughes D, MacNaughton P, Evans TW. Chronic adult respiratory distress syndrome — a role for corticosteroids? Crit Care Med 1992;20:1187-9.
16. Keel JB, Hauser M, Stocker R, Baumann PC, Speich R. Established acute respiratory distress syndrome: benefit of corticosteroid rescue therapy. Respiration 1998;65:258-64.
17. 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;100:943-52.
18. Meduri GU, Headley AS, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. JAMA 1998;280:159-65.
19. Sprung CL, Caralis PV, Marcial EH, et al. The effects of high-dose corticosteroids in patients with septic shock: a prospective, controlled study. N Engl J Med 1984;311:1137-43.
20. Cronin L, Cook DJ, Carlet J, et al. Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. Crit Care Med 1995;23:1430-9.
21. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 1987;317:653-8.
22. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. BMJ 2004;329:480.
23. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 2003;348:683-93.
24. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
25. Goodman RB, Strieter RM, Martin DP, et al. Inflammatory cytokines in patients with persistence of the acute respiratory distress syndrome. Am J Respir Crit Care Med 1996;154:602-11.
26. Schoenfeld DA, Bernard GR. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. Crit Care Med 2002;30:1772-7.
27. Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. Stat Sci 2001;16:101-33.
28. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Statist 1988;16:1141-54.
29. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system: risk prediction of hospital mortality for critically ill hospitalized adults. Chest 1991;100:1619-36.
30. Keh D, Boehnke T, Weber-Cartens 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;167:512-20.
31. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862-71.
32. De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA 2002;288:2859-67.
33. Meduri GU, Chinn AJ, Leeper KV, et al.

Corticosteroid rescue treatment of progressive fibroproliferation in late ARDS: patterns of response and predictors of outcome. Chest 1994;105:1516-27.
34. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001; 345:1359-67.
35. Bernard GR, Vincent J-L, Laterre P-F, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699-709.
36. Collard HR, Saint S, Matthay MA. Prevention of ventilator-associated pneumonia: an evidence-based systematic review. Ann Intern Med 2003;138:494-501.
37. 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;342:1471-7.