

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The 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;354:1671-84.

ON-LINE SUPPLEMENTARY APPENDIX

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ADDITIONAL METHODS

Exclusion Criteria

The criteria for exclusion were: undrained abscess; intravascular infection; disseminated fungal infection; new nosocomial pneumonia with less than 72 hours of antibiotics; ongoing septic shock; age less than 13 years; participation in other trials within 30 days; pregnancy; burns requiring skin grafting; acquired immunodeficiency syndrome; treatment with corticosteroids (greater than 300 mg prednisone (or its equivalent) cumulative dose within 21 days or greater than 15mg/day within 7 days prior to enrollment); cytotoxic therapy within 3 weeks; pre-existing condition with estimated 6-month mortality greater than 50 percent; severe chronic respiratory disease; bone marrow or lung transplantation; severe chronic liver disease; known or suspected adrenal insufficiency; vasculitis or diffuse alveolar hemorrhage; or refusal of the attending physician.

Prospective Infection Monitoring

Infections were categorized as “serious infections” and “other infections”. Each were monitored for separately. Serious infections were defined as new, life-threatening, nosocomial infections. This included all serious infections occurring at least 48 hours after enrollment until day 28 post-enrollment or until 7 days after completion of study drug administration, whichever came first. This was done to address, to some degree, the issue of infections being counted that were not present at time of enrollment and makes the assumptions that immunosuppression due to steroids would take at least 48 hours to develop and would not last more than 7 days after discontinuation of a short course of corticosteroids. More than one occurrence of the same type of serious infection was recorded as long as the second episode met the criterion for being a new infection, specifically that it must occur at least 72 hours after a prior episode has met its criteria for ending as defined for each entity in the protocol.

Serious infections (see Appendix A in the on-line protocol for definitions of each infection):

(a) Bacteremia (due to a known pathogen with or without signs or symptoms), (b) Disseminated fungal infection, (c) Nosocomial pneumonia, (d) Peritonitis not associated with peritoneal dialysis, (e) Septic shock, (f) Wound infection requiring extensive debridement and/or healing by secondary intention, (g) Meningitis, (h) Empyema, (i) Abdominal or other deep tissue abscess, (j) Disseminated viral infections (e.g., VZV, HSV)

Other Infections (see Appendix A in the on-line protocol for definitions of each infection):

(a) *C. difficile* colitis, (b) Indwelling vascular line infection, (c) Oral or mucosal candidiasis, (d) Peritonitis associated with peritoneal dialysis, (e) Sinus infection, (f) Skin infection including non-disseminated viral infection, (g) Septic arthritis, (h) Urinary tract infection, (i) Other infections not listed above or as serious infections.

Plasma and Bronchoalveolar Lavage Fluid

Bronchoalveolar lavage fluid (BALF) and EDTA-plasma were obtained at study entry and day 7. The EDTA-plasma and cell-free supernatants from BALF were aliquoted and frozen at -70°C for subsequent analysis. Measurements included BALF leukocyte counts, procollagen peptide Type III (PIIIP) (RIA-Gnost-PIIIP, CIS Biointernational, Gif-Sur-Yvette, Cedex, France, via CIS-US, Inc., Bedford, MA), and interleukin-8 (IL-8) (Quantikine, R&D Systems, Minneapolis, MN), and plasma interleukin-6 (IL-6) (Luminex, fluorescent beads, R&D Systems, Minneapolis, MN). Logarithmic transformation was used for day 0 and day 7 plasma and BALF biological marker concentrations.

TABLE 4 (SUPPLEMENTARY APPENDIX)

Table 4. Baseline Characteristics of the Patients Randomized Within 7-13 Days and 14-28 Days From ARDS Onset		
Characteristic	Days 7-13 (N = 132)*	Days 14-28 (N = 48)*
Age (Mean±SD)	49.2±17.2	48.7±19.4
Male gender	50.8%	45.8%
Days in hospital before study entry (Mean±SD)	10.5±5.8	17.5±5.1
Days from ARDS onset to study entry (Mean±SD)	9.4±2.0	16.6±2.7
# Non-Pulm/CNS OF (Mean±SD)	0.6±0.7 (123)	0.8±0.8 (43)
Lung Injury Category		
Trauma	11.4%	16.7%
Sepsis	16.7%	29.2%
Multiple Transfusion	1.5%	0.0%
Aspiration	17.4%	14.6%
Pneumonia	39.4%	35.4%
Other	13.6%	4.2%
Radiographic Quadrants (Mean±SD)	3.9±0.4	3.9±0.4
APACHE III score (Mean±SD)	87.3±29.9	82.7±23.8
Glasgow coma score (Mean±SD)	8.4±4.6	9.0±4.1
BP: Systolic (Mean±SD)	123.0±23.3	120.2±20.4
Albumin (Mean±SD)	2.0±0.5 (116)	1.9±0.5 (41)
Glucose (Mean±SD)	153.3±67.3	129.8±47.6
Bilirubin (Mean±SD)	1.5±3.2 (118)	0.9±1.2 (41)
Highest creatinine (Mean±SD)	1.4±1.4 (128)	1.1±1.1 (45)
WBC (Mean±SD)	14801±7923	14169±6739 (46)
HCT (Mean±SD)	30.0±4.6	28.9±3.2 (46)
Arterial pH (Mean±SD)	7.4±0.1 (128)	7.4±0.1 (46)
FiO2 (Mean±SD)	0.6±0.2	0.6±0.2
PaO2 (Mean±SD)	71.3±13.4 (125)	67.5±11.8 (45)
PaCO2 (Mean±SD)	53.2±17.1 (128)	51.9±17.4 (46)
PaO2/FiO2 (Mean±SD)	125.0±43.2 (125)	126.9±34.2 (45)
Plateau Pressure (Mean±SD)	33.8±8.8 (98)	35.1±12.3 (33)
Cstat (Mean±SD)	24.6±10.4 (93)	22.5±12.3 (31)
Lung Injury Score (Mean±SD)	3.1±1.0 (90)	3.2±1.1 (30)
Tidal Volume [mL/kg PBW] (Mean±SD)	7.3±2.0 (116)	7.2±2.1 (36)
PEEP (Mean±SD)	13.3±5.0	10.8±5.1
Total Minute Ventilation (Mean±SD)	12.9±4.6 (130)	12.0±3.4 (47)

Legend for Table 4

*Number for each group for whom the results were available unless noted in parentheses

Abbreviations: Non-pulm/CNS OF, non-pulmonary/central nervous system organ failure; APACHE III score, Acute Physiology and Chronic Health Evaluation III score³⁶; BP, blood pressure; WBC, white blood cell count; HCT, hematocrit; Cstat, static compliance of respiratory system (tidal volume divided by the difference between end-expiratory and end-inspiratory pressures); PBW, predicted body weight; PEEP, positive end expiratory pressure.

FIGURE 4 (SUPPLEMENTARY APPENDIX)

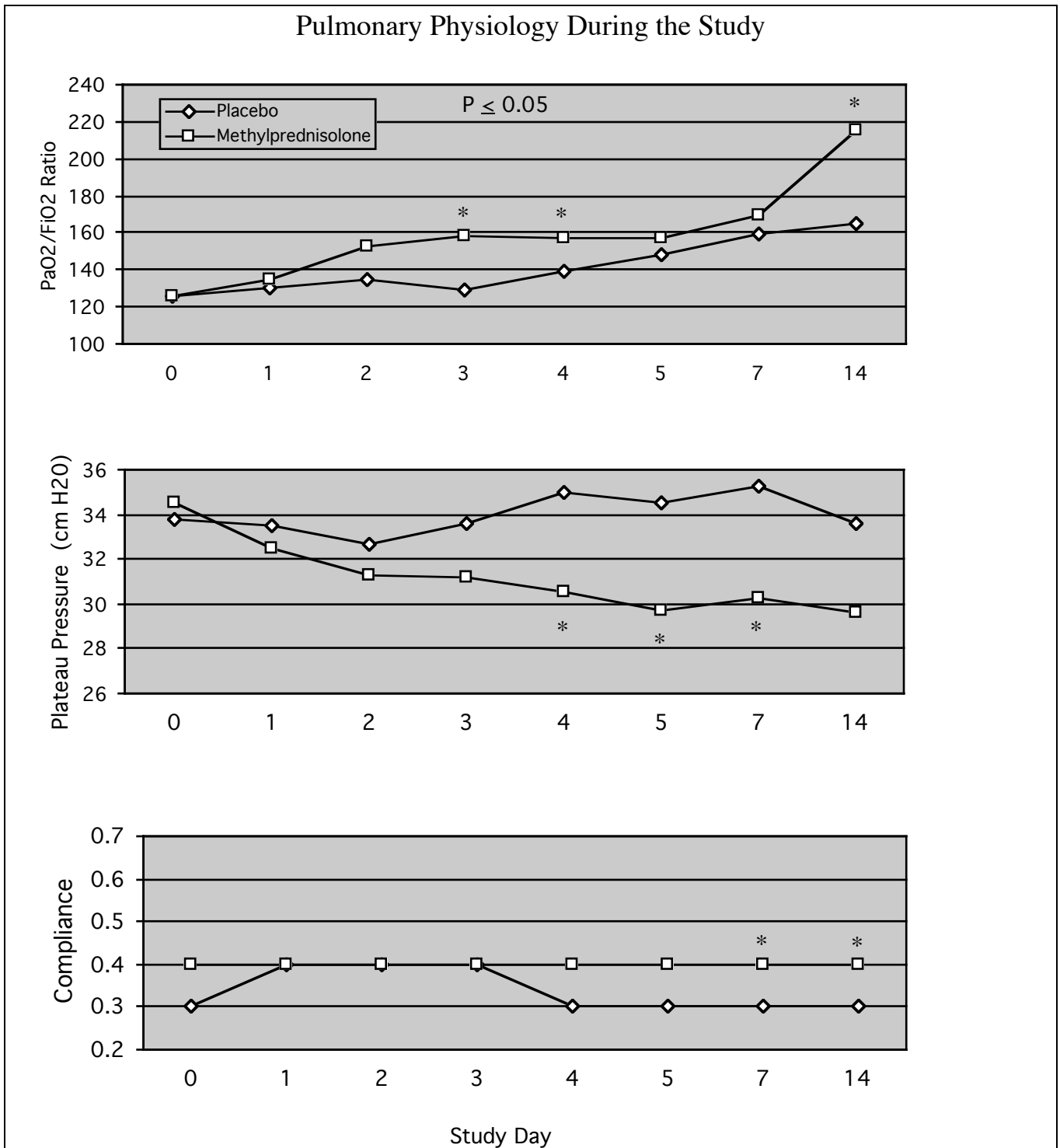


FIGURE 5 (SUPPLEMENTARY APPENDIX)

Mean Blood Glucose Levels During the Study

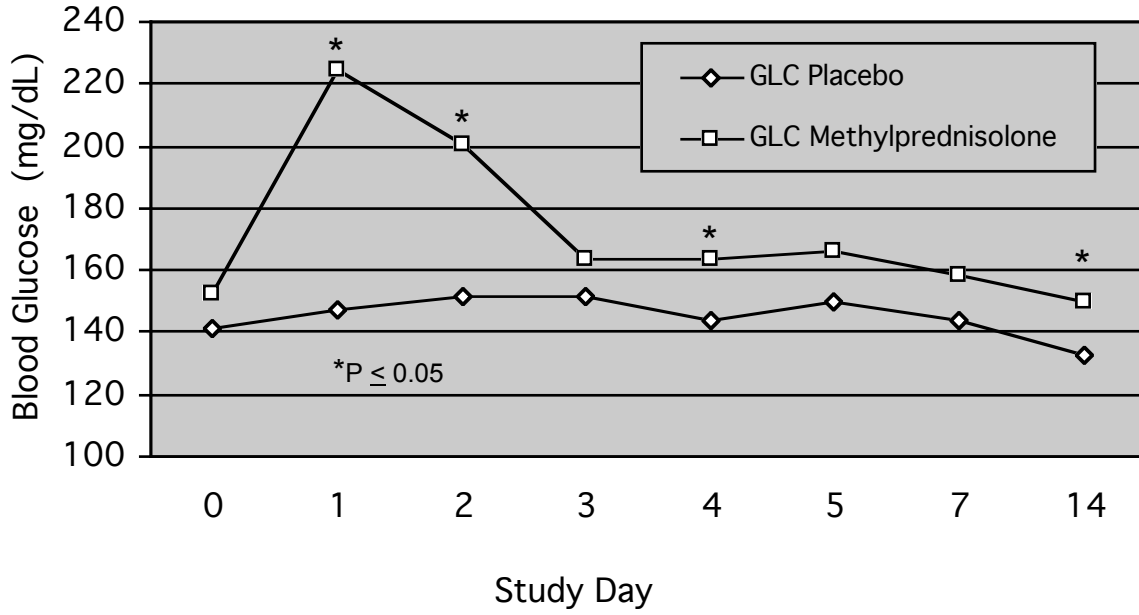


FIGURE 6 (SUPPLEMENTARY APPENDIX)

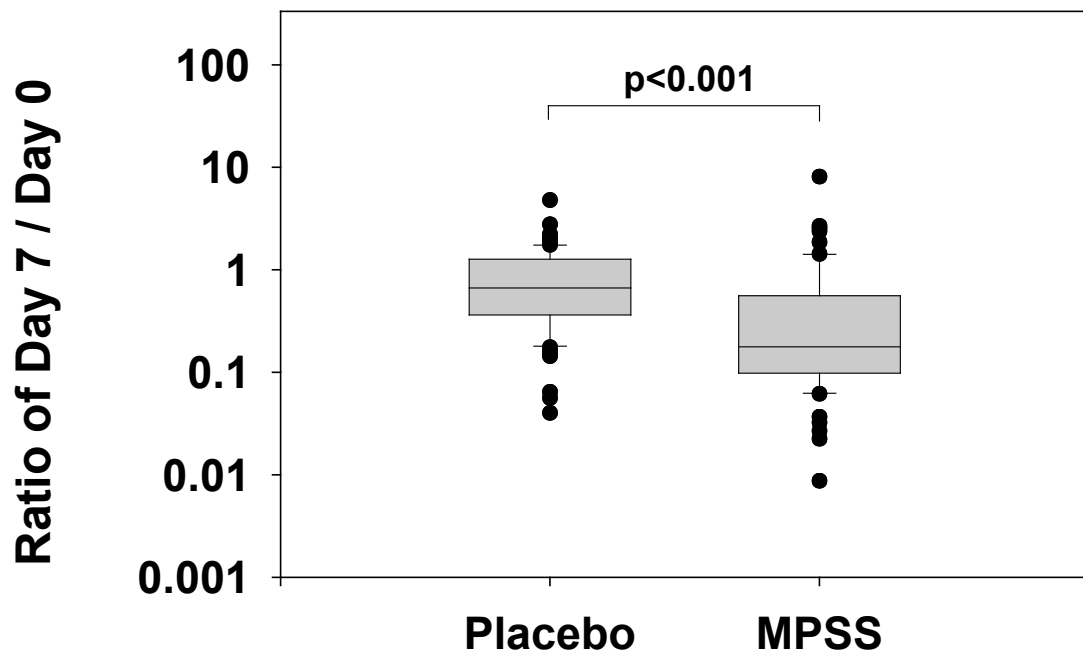


Figure 6: Effect of MPSS on Change in Plasma IL-6. The changes in plasma IL-6 concentrations (ratio of study day 7 / day 0 for individual patients with paired samples, n=122) were compared for the placebo vs. MPSS groups (median change 0.71 vs 0.18, $p < 0.001$ by independent sample T-test on log-transformed data). MPSS significantly reduced plasma IL-6 concentrations from study day 0 to day 7.

FIGURE 7 (SUPPLEMENTARY APPENDIX)

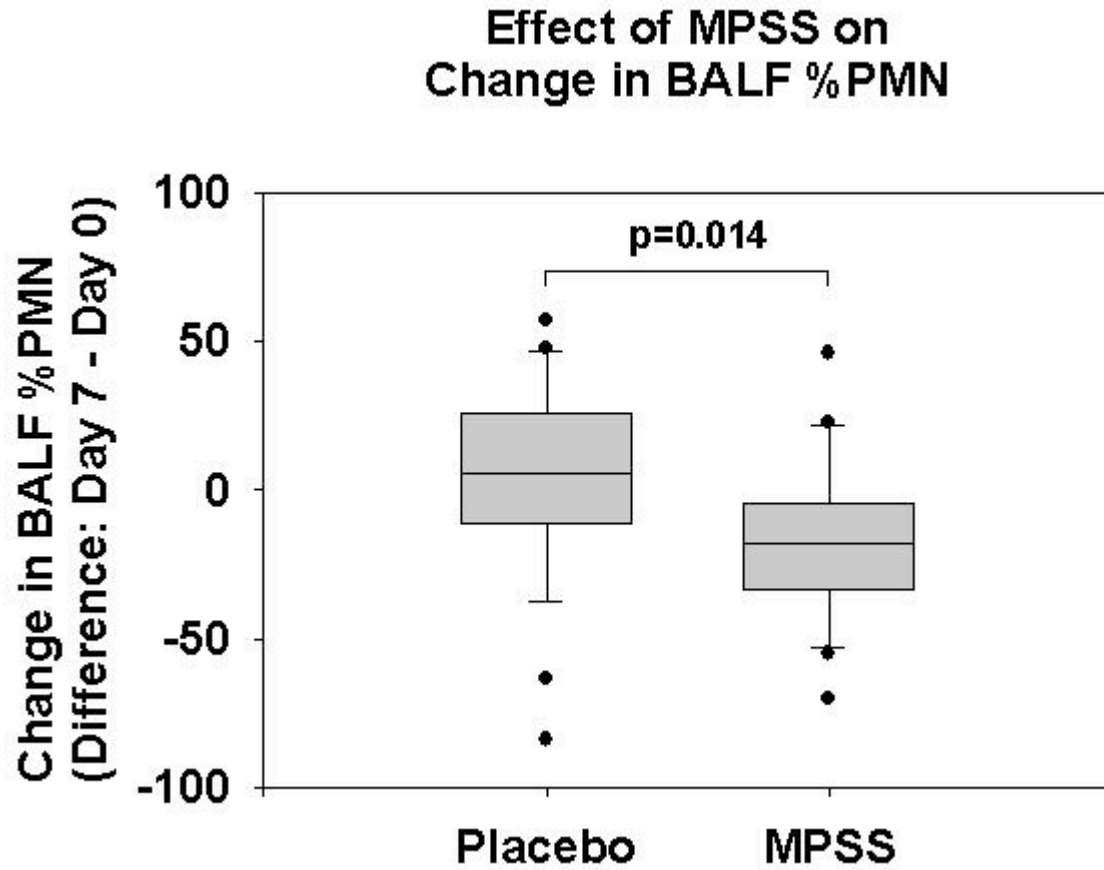


Figure 7: Effect of MPSS on Change in Bronchoalveolar Lavage Neutrophils. The changes in percentage of neutrophils in bronchoalveolar lavage (difference of study day 7 and day 0) for individual patients with paired samples, n=122) were compared for the placebo vs. MPSS groups. MPSS significantly reduced bronchoalveolar lavage neutrophils from study day 0 to day 7.

FIGURE 8 (SUPPLEMENTARY APPENDIX)

Blood Pressure During the Study

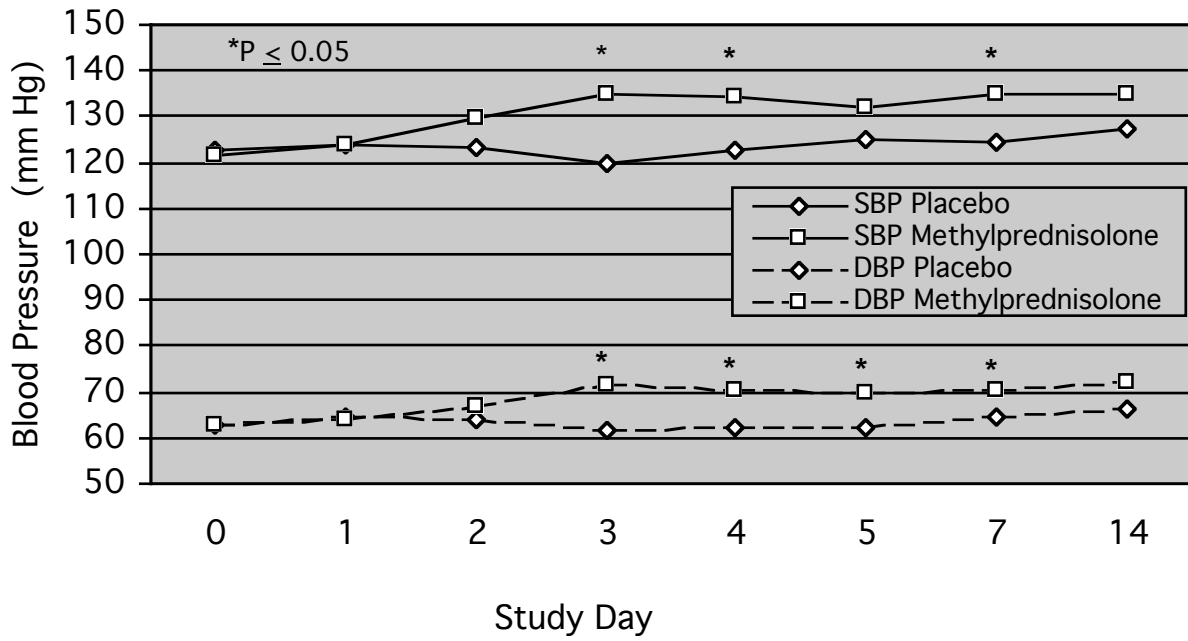


TABLE 5 (SUPPLEMENTARY APPENDIX)

A Comparison of Corticosteroid Dosing in Prior Studies and the Current ARDS Network Trial

First Author/Site/Year	Dosing Schedule	Taper
Ashbaugh (Seattle, 1985) ⁸	1-2 mg/kg MPSS* q6°	Yes, after “clinical response”, or d/c if no clinical response
Biffl (Denver, 1995) ¹³	1-2 mg/kg MPSS q6°	Yes, based on “clinical response”
Braude (London, 1992) ¹⁵	60 mg/day prednisolone qd	Not described; received for at least 14 days
Hooper (Phoenix, 1990) ¹⁴	125-250 mg MPSS q6°	Yes, after 3-4 days “as clinically tolerated”
Meduri (Memphis, 1994) ³¹	0.5-0.75 mg/kg MPSS q6°	No, not until after extubation
Keel (Zurich, 1998) ¹⁶	Not well defined in Methods. 100-250 mg MPSS for 1-3 days, then 80-180 mg MPSS	Yes, for up to 19 days but not specifically defined
Meduri (Memphis, 1998) ¹⁸	0.5 mg/kg MPSS q6° x 14d, then 0.25 mg/kg MPSS q6° x 7d, then 0.125 mg/kg MPSS q6° x 7d	Yes, 4 day taper after day 28 unless extubated early
ARDS Network (Multicenter, 2005)	0.5 mg/kg MPSS q6° x 14d, then 0.5 mg/kg q12° x 7d	Yes, 4 day taper after day 21, unless extubated early

*MPSS - methylprednisolone

TABLE 6 (SUPPLEMENTARY APPENDIX)

A Comparison of Treatment Windows in Prior Studies and the Current ARDS Network Trial

First Author/Site/Year	Average Duration of ARDS Prior to Treatment with Steroids	Range of ARDS Duration Prior to Treatment with Steroids
Ashbaugh (Seattle, 1985) ⁸	12 days	6 – 22 days
Biffi (Denver, 1995) ¹³	16 days	12 - 26 days
Braude (London, 1992) ¹⁵	24 days	NA
Hooper (Phoenix, 1990) ¹⁴	11 days	4 – 40 days
Meduri (Memphis, 1994) ³¹	15 days	Not defined; standard deviation was 7.5 days around the mean
Keel (Zurich, 1998) ¹⁶	15 days	5 – 44 days
Meduri (Memphis, 1998) ¹⁸	9.2 days	7 - 21 days
ARDS Network (Multicenter, 2005)	11.3 days	7 – 28 days

TABLE 7 (SUPPLEMENTARY APPENDIX)

Association of Treatment Group and Weakness with Duration of Mechanical Ventilation

Group	Duration of Mechanical Ventilation*
Not weak, Placebo (n=44)	16 (9-30.5)
Not weak, Steroids (n=38)	8.5 (5-21)
Weak, Placebo (n=18)	26 (14-38)
Weak, Steroids (n=25)	15 (12-22)

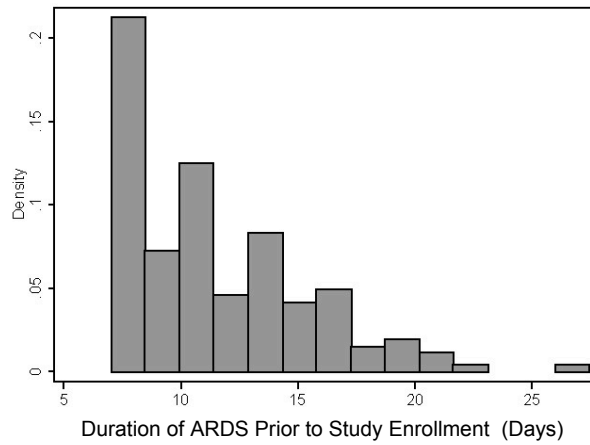
* Median days, interquartile range

Legend for Table 7

The table shows the median and interquartile values for duration of mechanical ventilation by group, stratified by treatment group and presence of weakness. The population was all patients who survived 60 days (the at-risk group for weakness). Both treatment group and weakness were significantly associated with duration of mechanical ventilation (p=0.003 for both)

FIGURE 9 (SUPPLEMENTARY APPENDIX)

Frequency Distribution of Duration of ARDS Prior to Enrollment

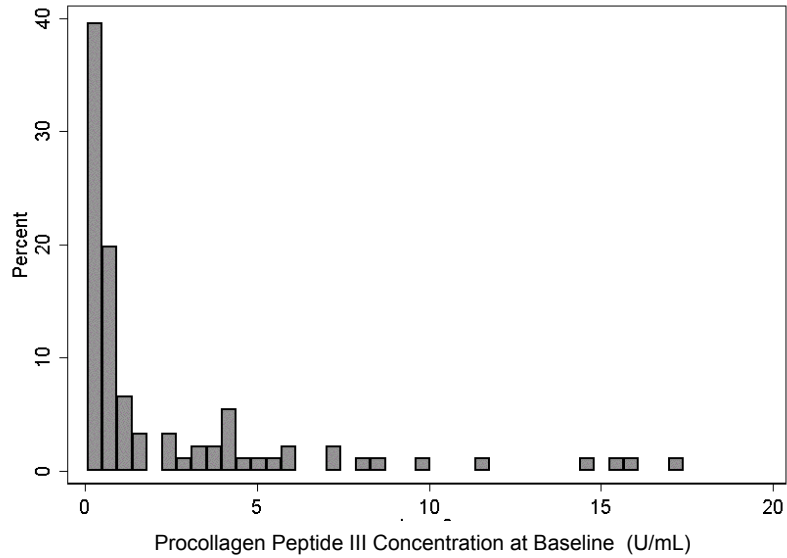


Legend for Figure 9

The figure shows the frequency distribution of duration of ARDS prior to enrollment in the study. The horizontal axis is the number of days prior to enrollment in study and the vertical axis is the number of enrolled subjects.

FIGURE 10 (SUPPLEMENTARY APPENDIX)

Frequency Distribution of Baseline Level of Procollagen Peptide III in Bronchoalveolar Lavage



Legend for Figure 10

The figure shows the frequency distribution of baseline (Study Day 0) procollagen III peptide in bronchoalveolar lavage fluid. The horizontal axis is the procollagen III peptide level (U/mL) and the vertical axis is the percent of subjects.