

**ARDS Clinical Trials Network “Efficacy and Safety of Corticosteroids for Persistent Acute Respiratory Distress Syndrome.” *NEJM*, 2006; 354(16):1671-1684.**

**Definition** Acute onset of bilateral pulmonary infiltrates; PaO<sub>2</sub>/FiO<sub>2</sub><200; Absence of left atrial hypertension; pulmonary arterial wedge pressures <18 cm of water. (American-European consensus committee 1994)

**Injury follows two distinct phases:**

- Early, exudative phase: usually 5-7 days
- Fibrotic (persistent) phase: >7 days

**Corticosteroids Rx and ARDS**

- Bone Chest 1987, showed early, high dose, short course of corticosteroids increased mortality
- Biffi Am J Surgery, 1995, Moderate doses of corticosteroids as salvage therapy improved lung injury scores
- Maduri JAMA 1998, a RCT showed methylprednisolone (2mg/kg/day) in persistent ARDS decreased mortality, improved multi-organ system dysfunction, P/F ratios, with similar infection rates (24 pts).

**Hypothesis**

The use of moderate-dose methylprednisolone in patients with persistent Acute Respiratory Distress Syndrome would improve clinical outcomes without increasing complications.

**Study Design**

Study type: Multi-Center, Randomized, Double-blinded, Placebo-controlled

Setting: ARDS Network, 12 clinical sites, 42 hospitals

Time period: Patients recruited from 8/97 to 11/03

Inclusion Criteria:

- Intubated, receiving mechanical ventilation
- 7-28 days AFTER onset of ARDS (as defined above)
- persistent bilateral pulmonary infiltrates
- P:F ratio <200 on day of enrollment

Exclusion Criteria: undrained abscess, intravascular infection, disseminated fungal infection, new nosocomial pneumonia with less than 72hours of antibiotics, ongoing septic shock, age <13, participation in other trials within 30 days, pregnancy, burns requiring skin graft, AIDS, Treatment with steroids >300mg prednisone or equivalent within 21days or 15mg/d within 7days, cytotoxic chemotherapy within 3 weeks, pre-existing condition with predicted 6 month mortality >50%, severe chronic respiratory disease, bone marrow or lung transplant, severe chronic liver disease, known or suspected adrenal insufficiency, vasculitis or diffuse alveolar hemorrhage, refusal of the attending physician.

Randomization: 4123 screened, 3464 eligible, 180 enrolled

- N=89 randomized to steroid (intervention) group: all doses mixed in 50mL of D5W
  - Intervention: Methylprednisolone 2mg/kg x 1 then 0.5mg/kg q6hr x 14days then 0.5mg/kg q12hr x 7days
    - taper to off over 4 days if patient survived 21 day course and still required mechanical ventilation
    - taper to off over 2 days if pt breathing without assist for 48hr or signs of shock or fungal infection
- N=91 randomized to placebo group:
  - Placebo: 50mL of 5% dextrose in water given for entire dosing schedule seen above

Weaning: Pre-specified parameters for weaning: assessed daily and if acceptable sat on 50% FiO<sub>2</sub> could start PS trials

Statistical Power: Originally powered for 400 patients for 85% power to detect 15% mortality difference, repowered for 180 later in study.

Outcomes: Primary Outcome: 60 day mortality

Secondary Outcomes: number of ventilator free days in first 28 days, number of days without organ failure during the first 28 days, number of infectious complications during the first 28 days, and markers of inflammation and fibroproliferation on study day 7.

## The evidence

	Placebo Group (CER)	Methylprednisolone Group (EER)	Relative Risk (RR)	Relative Risk Reduction (RRR)	Absolute Risk Reduction (ARR)	Number Needed to Treat (NNT)
60 Day Mortality	26/91	26/89 (p=1.0)	1.02	-0.02	-0.006	166.7
180 Day Mortality	29/91	28/89 (p=1.0)	0.99	0.01	0.004	250

	Placebo Group	Methylprednisolone Group	Absolute Risk Difference	Number Needed to Harm (NNH)
Number of serious events associated with myopathy or neuropathy	0/91	9/89 (p=0.001)	0.10	9.9
60 Day Mortality from >14days of ARDS Onset	2/25	8/23 (p=0.02)	0.267	3.7
180 Day Mortality from >14days of ARDS Onset	3/25	10/23 (p=0.01)	0.315	3.17

### Primary Outcome:

#### 60 day Mortality

- No significant difference, 28.6% in placebo group and 29.2% in methylprednisolone group (p = 1.0)
- 60 day Mortality from >14 days from ARDS onset: 8% in the placebo group and 35% in the methylprednisolone group (p=0.02)

### Secondary Outcomes:

#### Ventilator Free Days during the first 28 days

- 6.8 days in the placebo group and 11.2 in the methylprednisolone group (p<0.001)

#### Days without Organ Failure during the first 28 days

- Significant only for Cardiovascular Failure with p=0.04, not significant for coagulation abnormalities, hepatic failure, or renal failure

#### Number of Infectious Complications during the first 28 days

- 43 infections in 30 patients in the placebo group and 25 infections in the methylprednisolone group (p=0.14)

#### 180 Day Mortality

- No significant difference, 31.9% in placebo group and 31.5% in methylprednisolone group (p = 1.0)

#### Ventilator Free Days at Day 180

- 149 days in the placebo group and 159 in the methylprednisolone group (p=0.04)

#### 180 Day Mortality from >14 days from ARDS onset

- 12% in the placebo group and 44% in the methylprednisolone group (p=0.01)

## Comments

- In patients with persistent ARDS, the use of moderate-dose corticosteroids did not improve survival.
- This study has been criticized because only 5% of eligible patients were enrolled, delayed initiation of corticosteroids and that corticosteroids may have been tapered too rapidly, and gender differences between the cohorts.
- Study also complicated by changes in clinical practice, such as low tidal volumes for ventilatory support and tight blood glucose control.