Steroid in ARDS

Saurabh Maji

- Histology early in the course of ARDS reveals interstitial and alveolar edema, infiltration of cells into the alveolar spaces (neutrophils, macrophages and red blood cells), and alveolar epithelial and endothelial injury. The alveolar basement membranes often become denuded; hyaline membranes form

- Dysregulated inflammation, both in the endothelial and epithelial spaces, is a key driver of the pathogenesis of ARDS

J Clin Invest. Aug 1; 2012 122(8):2731–2740

- Ventilator-induced lung injury may further perpetuate both pulmonary and systemic inflammation

- Alveolar macrophages release pro-inflammatory cytokines, including neutrophil chemoattractants that promote neutrophilic activation and migration into the interstitial and alveolar spaces

- These activated neutrophils release pro-inflammatory molecules, which contribute to and perpetuate the inflammatory environmen

N Engl J Med. 2000; 342(18):1301–1308

- Vascular permeability increases as these products released by neutrophils interrupt tight junctions and promote alveolar cell death, with loss of the normal function of the endothelial barrier

Annual review of pathology. 2011; 6:147–163

- Degree of pulmonary and systemic inflammation, as measured by cytokine concentrations in the alveolar compartment and in serum, have been shown to be associated with severity and outcome in ARDS

Crit Care Clin. Jul; 2011 27(3):661–683

- After the initial phase of ARDS, recovery may occur quickly, with reabsorption of the edema fluid, removal of the cellular infiltrates, and reparative epithelial proliferation with restoration of the alveolar barrier

- some patients with ARDS, recovery is complicated by persistent inflammation and fibroproliferation. Along with capillaries, fibroblasts proliferate in the alveolar and interstitial spaces, leading to collagen deposition and fibrosis

Chest. 2010; 107(1):196–200

Pharmacologic effects of corticosteroids

- Glucocorticoid is a potent anti-inflammatories which act primarily by binding to cytoplasmic glucocorticoid receptors. Once bound, the glucocorticoid-receptor complexes regulate the transcription of glucocorticoid-response elements (GRE) such as nuclear factor receptor-κβ (NF-κβ)

- The transcription of many pro-inflammatory cytokines (including interleukins-1α, -1β, -2, -3, -5, -6, -8 and -12; tumor necrosis factor α; and interferon γ) is modulated by NF-κβ

Minerva anestesiologica. Jun; 2010 76(6):441–447.

- Additionally, glucocorticoids act synergistically with natural anti-inflammatory cytokines, such as interleukin-4, -10, 13, and interleukin-1 receptor antagonist.

- Glucocorticoids also have actions on fibrotic pathways, inhibiting fibroblast proliferation and decreasing collagen deposition

- In addition to anti-inflammatory glucocorticoids have profound metabolic effects, including inducing gluconeogenesis, increasing serum glucose levels, and altering protein, fat and bone metabolism

Randomized trials of methylprednisolone for ARDS prevention

AUTHOR	Patients	intervention	Number	Outcome (steroid)	Outcome(control)	conclusion
Schein et al	Septic shock	MP 30 mg/kg; DX 6 m/kg,	59 enrolled, 42 without ARDS	ARDS 4/16 (MP) 3/13 (DX)	ARDS 2/13	Steroid treatment did not affect complement levels
Weigelt et al	Hypoxemic respiratory failure	MP 30 mg/kg q6	81 enrolled	ARDS 25/39Died 18/39	ARDS 14/42Died 13/42	Increased infectious complication in MP group
Bone et al	Septic shock	MP 30 mg/kg q6 hours for 24 hour	304	ARDS 50/152Died by day 14 26/50 (ARDS only	ARDS 38/152Died by day 14 23/38 (ARDS only)	
Luce et al	Septic shock	MP 30 mg/kg q6 hours for 24 hours	87 enrolled, 75 with sepsis	ARDS 13/38Died 22/38	ARDS 14/37Died 20/37	Stopped early (safety)

Early methylprednisolone treatment for septic syndrome and the adult respiratory distress syndrome

- Prospective, randomized, double-blind, placebo-controlled study
- 19 centers and 382 patients
- Effect of methylprednisolone sodium succinate (MPSS) on the septic syndrome
- Patients with the presumptive diagnosis of sepsis were identified
- Based on the presence of fever or hypothermia (temperature greater than 38.3 degrees C or less than 35.5 degrees C, rectal), tachypnea (greater than 20 bpm), tachycardia (greater than 90 bpm) and the presence of one of the following indices of organ dysfunction: a change in mental status, hypoxemia, elevated lactate levels or oliguria

Chest. 2010Dec;92(6):1032-6

- Either MPSS 30 mg/kg or Placebo, was given in four 20-minute infusions six hours apart and was initiated within two hours of the presumptive diagnosis of sepsis

- Development and reversal of the adult respiratory distress syndrome (ARDS) was followed and resulted in data on 304 of the 382 randomized patients

- A trend toward increased incidence of ARDS was seen in the MPSS group 50/152 (32 percent) compared to the placebo group 38/152(25 percent) p = 0.10

- Significantly fewer MPSS patients reversed their ARDS 15/50 (31 percent) compared to placebo 23/38 (61 percent) p = 0.005

- The 14-day mortality in patients with ARDS treated with MPSS was 26/50 (52 percent) compared to placebo 8/22 (22 percent) p = 0.004

- Conclude that early treatment of septic syndrome with MPSS does not prevent the development of ARDS. Additionally, MPSS treatment impedes the reversal of ARDS and increases the mortality rate in patients with ARDS

Chest. 2010 Dec;92(6):1032-6

Ineffectiveness of High-dose Methylprednisolone in Preventing Parenchymal Lung Injury and Improving Mortality in Patients with Septic Shock[1–3]

JOHN M. LUCE, A. BRUCE MONTGOMERY, JAMES D. MARKS, JOAN TURNER, CRAIG A. METZ, and JOHN F. MURRAY

- Prospective, randomized, double-blind study
- Determine whether high-dose methylprednisolone could prevent parenchymal lung injury, including the adult respiratory distress syndrome (ARDS), or improve mortality when administered early in septic shock.
- Inclusion criteria:(1) an increase in temperature of 1.5 degrees C and a decrease in systolic blood pressure of 20 mm Hg or more from baseline values (in already hospitalized patients), or (2) a temperature greater than 38.5 degrees C or less than 35.5 degrees C and a systolic blood pressure of less than 90 mm Hg (in newly admitted patients).

Am Rev Respir Dis. Jul; 2011 138(1):62–68.

- Exclusion criteria: (1) had severe immunodeficiency, (2) were less than 18 or greater than 76 yr. of age, (3) had multilobar roentgen graphic infiltrates, or (4) were already receiving corticosteroids

- Eighty-seven patients enrolled in the study received either methylprednisolone, 30 mg/kg per dose, or mannitol placebo for a total of 4 doses every 6 h, following the presumptive diagnosis of septic shock

- Of these patients, 75 ultimately were determined on the basis of culture results to have actually had septic shock at the time of entry

CHARACTERISTICS (MEAN ± SEM) OF PATIENTS WITH CONFIRMED SEPTIC SHOCK ON STUDY ENROLLMENT

	Received MPSS (*n = 38*)	Received Placebo (*n = 37*)
Age, yr	50 ± 2.5	53 ± 2.5
Men, n	26	31
Women, n	12	6
Temperature < 35.5° C, n	10	9
Temperature > 38.5° C, n	24	27
Pneumonia or other presumed intrathoracic infection, n	13	15
Peritonitis or other presumed intraabdominal infection, n	14	11
Alcoholic liver disease by history or physical examination, n	10	9
Blood urea nitrogen, mg/dL	30.0 ± 3.1	28.1 ± 3.3
Creatinine, mg/dL	2.1 ± 0.2	1.8 ± 0.3
Creatinine > 2.0 mg/dL, n	15	12
Albumin, mg/dL	2.7 ± 0.2	2.6 ± 0.1
Total bilirubin, mg/dL	2.1 ± 0.5	2.4 ± 0.5
Receiving mechanical ventilation, n	26	15*
Receiving vasopressors, n	18	15

Definition of abbreviation: MPSS = methylprednisolone sodium succinate.

* $p < 0.05$.

ADULT RESPIRATORY DISTRESS SYNDROME (ARDS) AND MORTALITY (MEAN ± SEM) IN PATIENTS WITH CONFIRMED SEPTIC SHOCK

	Received MPSS (*n = 38*)	Received Placebo (*n = 37*)
Developed ARDS, n	13	14
Time to onset of ARDS from clinical suspicion of septic shock, days	0.8 ± 0.3	1.0 ± 0.4
Resolved ARDS, n	4	2
Time to resolution of ARDS from onset of ARDS, days	11.0 ± 1.7	6.5 ± 0.5*
Died with ARDS, n	9	12
Died without ARDS, n	13	8
Total mortality, n	22	20

Definition of abbreviations: MPSS = methylprednisolone sodium succinate.

* $p < 0.05$.

PLASMA COMPLEMENT LEVELS (MEAN ± SEM) IN PATIENTS WITH CONFIRMED SEPTIC SHOCK

	Hours					
	0		12		24	
	MPSS	Placebo	MPSS	Placebo	MPSS	Placebo
C3a des Arg, ng/ml	951 ± 135	834 ± 121	818 ± 133	996 ± 193	913 ± 182	861 ± 186
n	31	32	20	21	18	22
C5a des Arg, ng/ml	12.7 ± 1.3	13.2 ± 1.5	13.5 ± 1.5	12.8 ± 0.9	11.4 ± 0.8	13.1 ± 1.1
n	31	32	20	21	18	22

Definition of abbreviation: MPSS = methylprednisolone sodium succinate.

- Conclusion: These results suggest that methylprednisolone neither prevents parenchymal lung injury nor improves' mortality when given early to patients with septic shock, perhaps because it does not inhibit complement activation

Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis

John Victor Peter, physician,[1] Preeta John, lecturer,[2] Petra L Graham, lecturer,[3] John L Moran, senior consultant,[4] Ige Abraham George, lecturer,[5] Andrew Bersten, professor[6]

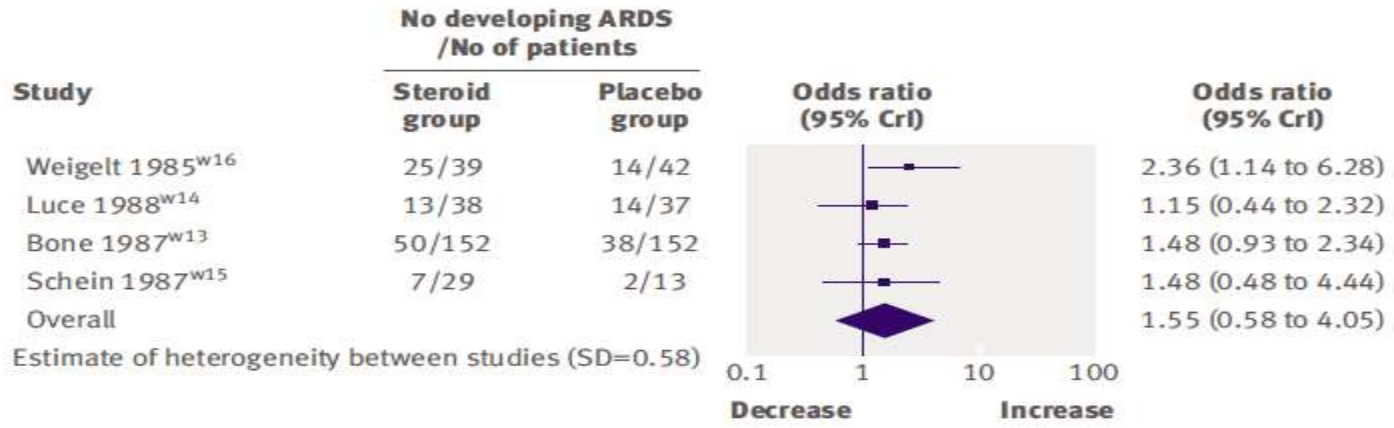

Fig 2 | Effect of preventive steroids on proportion of patients developing acute respiratory distress syndrome (ARDS)

There is an 86.6% probability that high dose steroid therapy may instead increase the incidence of ARDS

BMJ. May 3; 2011 336(7651):1006–1009

Pre-hospital use of inhaled corticosteroids and inhaled beta agonists and incidence of ARDS: A population-based study

Asif Muhammad Mangi[1], Vikas Bansal[1], Guangxi Li[2], Matthew S. Pieper[2], Ognjen Gajic[2], Emir Festic[1*]

- Retrospective cohort study of adult patients from Olmsted County, Minnesota admitted to the hospital with at least one predisposing condition for ARDS from 2001-2008
- The association with pre-hospital use of inhaled corticosteroids and inhaled beta agonists was evaluated using univariate and multivariate analyses.
- Primary outcome was ARDS and secondary outcome was hospital mortality

Acta Medica Academica 2015;44(2):109-116

Demographic and clinical characteristics of the patients (n=2,429)

Age (year, median IQR)	71 (53-83)
Male sex (%)	1,295 (53)
White race (%)	2,156 (89)
Asthma and/or COPD (%)	1101 (45)
Charlson score, median (IQR)	3 (1-4)
APACHE III score, median (IQR)	52 (34-72)
Inhaled corticosteroid users (%)	564 (23)
Inhaled beta agonist users (%)	626 (26)
Inhaled corticosteroid & beta agonist users (%)	354 (15)

- Result: Out of 2429 hospitalized adult patients with at least one risk factor for ARDS, 10.5% of those taking and 14% of those not taking inhaled corticosteroids developed ARDS (OR 0.72; 0.53-0.97; $p<0.03$)

- Inhaled beta agonists showed similar unadjusted protective effect; 9.7% of users and 14.4% of non-users developed ARDS (OR 0.64; 0.48-0.86; $p=0.003$)

- After adjusting for risk factors, comorbidities and severity of illness in the multiple logistic regression model, use of inhaled beta agonists, but not inhaled corticosteroids, remained independently associated with decreased risk of ARDS (OR 0.48; 0.31-0.72; $p<0.001$ versus 0.87; 0.57-1.29; $p=0.49$)
- The estimated protective effects were more pronounced among patients with pneumonia compared to those without pneumonia

Acta Medica Academica 2015;44(2):109-116

Steroid in early ARDS

Author	Patients	Intervention	ARDS definition	Number enrolled	Outcome: steroids	Outcome: control	Notes
Bernard et al	ARDS, risk factor, no shock	MP 30 mg/kg MP q 6 for 24 hours	CXR: bilateral infiltratesHypoxemia:	99	45-day mortality: 30/50	45-day mortality: 31/49	Stopped early for futility. No diff in infection
Annane et al	Septic shock, ARDS	HC 50mg q6 hours for 7 days, plus FC 50 mcg qd	AECC criteria with PaO2:FIO2 ratio <200	300 with sepsis, 177 with ARDS, 129 nonresponders	28-day mortality: 49/8533/62 (non-responders	28-day mortality 62/9250/75 (non-responders	Post-hoc secondary analysis of RCT
Meduri et al	ARDS, first 72 hours	MP 1 mg/kg load then 1 mg/kg/d infusion for 14 days	AECC definition	91	Hospital mortality: 15/63VFDs at 28: 16.5	Hospital mortality: 12/28VFDs at 28: 8.7	Primary endpoint: reduction in lung injury score 2:1 randomization protocol

High-dose corticosteroids in patients with the adult respiratory distress syndrome

- prospective, randomized, double-blind, placebo-controlled trial of methylprednisolone therapy in 99 patients with refractory hypoxemia, diffuse bilateral infiltrates on chest radiography and absence of congestive heart failure documented by pulmonary-artery catheterization

N Engl J Med. 2012 Dec 17;317(25):1565-70

- The causes of ARDS included sepsis (27 percent), aspiration pneumonia (18 percent), pancreatitis (4 percent), shock (2 percent), fat emboli (1 percent), and miscellaneous causes or more than one cause (42 percent)

- Fifty patients received methylprednisolone (30 mg per kilogram of body weight every six hours for 24 hours), and 49 received placebo according to the same schedule

- No statistical differences between groups in these characteristics upon entry or during the five days after entry
- Forty-five days after entry there were no differences between the methylprednisolone and placebo groups in mortality (respectively, 30 of 50 [60 percent; 95 percent confidence interval, 46 to 74] and 31 of 49 [63 percent; 95 percent confidence interval, 49 to 77]; P = 0.74) or in the reversal of ARDS (18 of 50 [36 percent] vs. 19 of 49 [39 percent]; P = 0.77)

- Infectious complications were similar in the methylprednisolone group (8 of 50 [16 percent]) and the placebo group (5 of 49 [10 percent]; P = 0.60)

- Conclusion: patients with established ARDS due to sepsis, aspiration, or a mixed cause, high-dose methylprednisolone does not affect outcome

N Engl J Med. 2012 Dec 17;317(25):1565-70

Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock

- Placebo-controlled, randomized, double-blind, parallel-group trial performed in 19 intensive care units in France from October 9, 2007, to February 23, 2010

- Three hundred adult patients who fulfilled usual criteria for septic shock were enrolled after undergoing a short corticotropin test

- Patients were randomly assigned to receive either hydrocortisone (50-mg intravenous bolus every 6 hours) and fludrocortisone (50- micro g tablet once daily) (n = 151) or matching placebos (n = 149) for 7 days

- MAIN OUTCOME MEASURE:

Twenty-eight-day survival distribution in patients with relative adrenal insufficiency (nonresponders to the corticotropin test)

- There were 229 nonresponders to the corticotropin test (placebo, 115; corticosteroids, 114) and 70 responders to the corticotropin test (placebo, 34; corticosteroids, 36)

- In nonresponders, there were 73 deaths (63%) in the placebo group and 60 deaths (53%) in the corticosteroid group (hazard ratio, 0.67; 95% confidence interval, 0.47-0.95; P =.02).
- Vasopressor therapy was withdrawn within 28 days in 46 patients (40%) in the placebo group and in 65 patients (57%) in the corticosteroid group (hazard ratio, 1.91; 95% confidence interval, 1.29-2.84; P =.001).

- There was no significant difference between groups in responders. Adverse events rates were similar in the 2 groups

- 7-day treatment with low doses of hydrocortisone and fludrocortisone significantly reduced the risk of death in patients with septic shock and relative adrenal insufficiency without increasing adverse events

Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome

- Retrospective analysis of a placebo-controlled, randomized, double-blind trial of low doses of corticosteroids in septic shock
- Nineteen intensive care units in France

- Among the 300 septic shock patients enrolled, we selected those meeting standard criteria for ARDS at inclusion

- Seven-day treatment with 50 mg of hydrocortisone every 6 hrs and 50 microg of 9-alpha-fludrocortisone once a day

Crit Care Med. 2012 Jan;34(1):22-30

- There were 177 patients with ARDS (placebo, n = 92; corticosteroids, n = 85) including 129 (placebo, n = 67; corticosteroids, n = 62) nonresponders and 48 (placebo, n = 25; corticosteroids, n = 23) responders
- In nonresponders, there were 50 deaths (75%) in the placebo group and 33 deaths (53%) in the steroid group (hazard ratio 0.57, 95% confidence interval 0.36-0.89, p = .013; relative risk 0.71, 95% confidence interval 0.54-0.94, p = .011)
- The number of days alive and off the ventilator was 2.6 +/- 6.6 in the placebo group and 5.7 +/- 8.6 in the steroid group (p = .006)

- There was no significant difference between groups in responders.
- There was no significant difference between groups in the two subsets of patients without ARDS.
- Adverse events rates were similar in the two groups

conclusion

- This post hoc analysis shows that a 7-day treatment with low doses of corticosteroids was associated with better outcomes in septic shock-associated early ARDS nonresponders, but not in responders and not in septic shock patients without ARDS

Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial

Randomized, double-blind, placebo-controlled trial

ICUs of five hospitals in Memphis

Ninety-one patients with severe early ARDS (</= 72 h), 66% with sepsis

Patients were randomized (2:1 fashion) to methylprednisolone infusion (1 mg/kg/d) vs placebo. The duration of treatment was up to 28 days. Infection surveillance and avoidance of paralysis were integral components of the protocol.

Chest. 2013 Apr;131(4):954-63

OUTCOME :The predefined primary end point was a 1-point reduction in lung injury score (LIS) or successful extubation by day 7

In intention-to-treat analysis, the response of the two groups (63 treated and 28 control) clearly diverged by day 7, with twice the proportion of treated patients achieving a 1-point reduction in LIS (69.8% vs 35.7%; $p = 0.002$) and breathing without assistance (53.9% vs 25.0%; $p = 0.01$)

Treated patients had significant reduction in C-reactive protein levels, and by day 7 had lower LIS and multiple organ dysfunction syndrome scores

Treatment was associated with a reduction in the duration of mechanical ventilation ($p = 0.002$), ICU stay ($p = 0.007$), and ICU mortality (20.6% vs 42.9%; $p = 0.03$)

Treated patients had a lower rate of infections ($p = 0.0002$), and infection surveillance identified 56% of nosocomial infections in patients without fever

conclusion

Methylprednisolone-induced down-regulation of systemic inflammation was associated with significant improvement in pulmonary and extrapulmonary organ dysfunction and reduction in duration of mechanical ventilation and ICU length of stay

Do glucocorticoids decrease mortality in acute respiratory distress syndrome? A meta-analysis

RITESH AGARWAL, ALOK NATH, ASHUTOSH N. AGGARWAL AND DHEERAJ GUPTA

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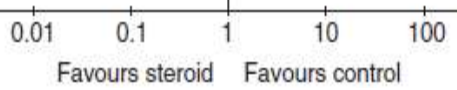
Outcome: 01 Glucocorticoids in early ARDS

Study or subcategory	Favours Steroid n/N	Favours Control n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
Bernard *et al.*[7]	30/50	31/49		41.10	0.87 (0.39–1.96)
Lee *et al.*[6]	1/12	7/12		10.65	0.06 (0.01–0.68)
Annane *et al.*[17]	54/85	67/92		48.25	0.65 (0.34–1.23)
Total (95% CI)	147	153		100.00	0.57 (0.25–1.32)

Total events: 85(Favours Steroid), 105(Favours Control)
Test for heterogeneity: $\chi^2 = 4.23$, d.f. = 2 ($P = 0.12$), $I^2 = 52.7\%$
Test for overall effect: $Z = 1.30$ ($P = 0.19$)



Respirology (2007) 12, 585–590

- Despite the lack of clear evidence, the American College of Critical Care Medicine issued a recommendation in 2008 that “moderate dose glucocorticoids should be considered in the management strategy of patients with early severe ARDS (PaO2:FIO2<200)”, with a grade 2B.

- In the recent Surviving Sepsis Campaign guidelines, no recommendations were made in this regarding the use of steroids in ARDS

Crit Care Med. Jun; 2008 36(6):1937–1949

Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome

- Multicenter, randomized controlled trial of corticosteroids in patients with persistent ARDS

- 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

N Engl J Med. 2012 Apr 20;354(16):1671-84

- RESULT:
- 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

- There were interesting differences between the treatment groups, however. Patients randomized to steroids liberated from mechanical ventilation sooner than those on placebo (14 days versus 23 days, p=0.006) and had significantly more ventilator free days at both 28 and 180 days. Yet, there was no difference in ICU length of stay between the groups, and return to mechanical ventilation was significantly more likely among patients randomized to steroids (20 versus 6, p=0.008)

- 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

Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial

- Randomized, double-blind, placebo-controlled trial
- Twenty-four patients with severe ARDS who had failed to improve lung injury score (LIS) by the seventh day of respiratory failure were selected
- Sixteen patients received methylprednisolone and 8 received placebo. Methylprednisolone dose was initially 2 mg/kg per day and the duration of treatment was 32 days. Four patients whose LIS failed to improve by at least 1 point after 10 days of treatment were blindly crossed over to the alternative treatment.

JAMA. 2013 Jul 8;280(2):159-65

- Primary outcome measures were improvement in lung function and mortality

- Secondary outcome measures were improvement in multiple organ dysfunction syndrome (MODS) and development of nosocomial infections

- At study entry (day 9 [SD, 3] of ARDS, the 2 groups had similar LIS, ratios of PaO2 to fraction of inspired oxygen (FIO2), and MODS scores

- By day 10 for methylprednisolone vs placebo were as follows: reduced LIS (mean [SEM], 1.7 [0.1] vs 3.0 [0.2]; P<.001); improved ratio of PaO2 to FIO2 (mean [SEM], 262 [19] vs 148 [35]; P<.001); decreased MODS score (mean [SEM], 0.7 [0.2] vs 1.8 [0.3]; P<.001); and successful extubation (7 vs 0; P=.05)

- For the treatment group vs the placebo group, mortality associated with the intensive care unit was 0 (0%) of 16 vs 5 (62%) of 8 (P=.002) and hospital-associated mortality was 2 (12%) of 16 vs 5 (62%) of 8 (P=.03). The rate of infections per day of treatment was similar in both groups, and pneumonia was frequently detected in the absence of fever
- CONCLUSIONS:In this study, prolonged administration of methylprednisolone in patients with unresolving ARDS was associated with improvement in lung injury and MODS scores and reduced mortality.

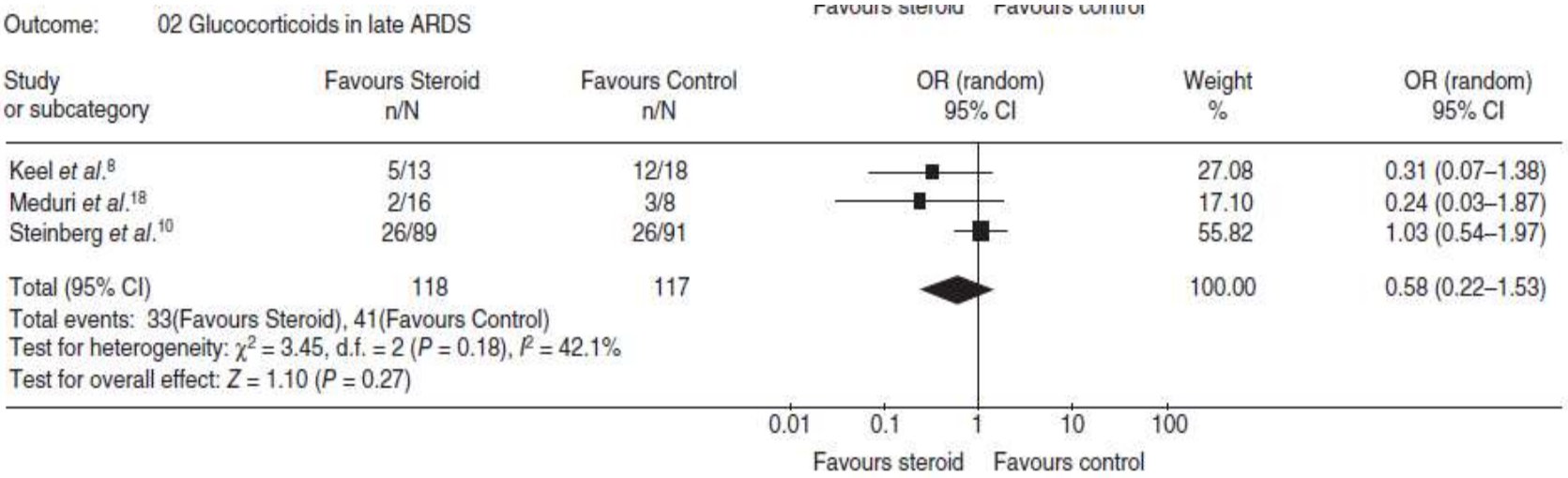
Pitfalls..

- First, the sample size is very small, with only 8 patients in the placebo group. This brings into question the statistical stability of the results, raising the likelihood of false positives
- Second, half of the placebo group were crossed over and began receiving methylprednisolone on study day 10, late into the course of ARDS
- All deaths in the placebo group occurred after crossover; it is unclear what role very late treatment with methylprednisolone might have played in patient outcome
- Third, an ICU mortality of over 60% is considerably higher than expected from a late ARDS population

Do glucocorticoids decrease mortality in acute respiratory distress syndrome? A meta-analysis

RITESH AGARWAL, ALOK NATH, ASHUTOSH N. AGGARWAL AND DHEERAJ GUPTA

Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Sector-12, Chandigarh, India



Respirology (2007) 12, 585–590

- American College of Critical Care Medicine recommends consideration of steroid treatment for unresolving ARDS before day 14, new randomized controlled trials are needed to increase certainty of efficacy, inform patient choice and timing of treatment, duration of therapy and approach to taper, and effect of treatment on long-term patient outcomes

American College of Critical Care Medicine.
Crit Care Med. Jun; 2011 36(6):1937–1949

Overview of meta-analyses of steroids and ARDS

Author	Inclusion criteria	Strata	Effects of steroids on outcome	Conclusion
Agarwal et al	RCT or observational cohorts of patients with ARDS treated with steroids	Early and late ARDS	Early: OR 0.57 (0.25–1.32)Late: OR 0.58 (0.22–1.53)	"Current evidence does not support a role for corticosteroids in the early or late stages of the disease"
Meduri et al	RCT of ≥ 7 days of treatment with steroids for ARDS	Study size, duration of ARDS <14 days and duration of therapy > 7 days (including subgroups)	OR 0.84 (0.68–1.04)ARDS<14 days: OR 0.78 (0.64–0.96)ARDS<14 days and Rx> 7 days: OR: 0.62 (0.43–0.90)	Prolonged glucocorticoid treatment substantially and significantly improves meaningful patient-centered outcome variable, and has a distinct survival benefit when initiated before day 14 of ARDS"

Overview of meta-analyses of steroids and ARDS

Author	Inclusion criteria	Strata	Effects of steroids on outcome	Conclusion
Peter et al	RCT of steroid for ARDS prevention or treatment	Prevention and treatment	Prevention: OR 1.55 (0.58–4.05)Treatment: 0.62 (0.23–1.26)	"A definitive role of corticosteroids in the treatment of ARDS is not established. A possibility of reduced mortality and increased ventilator free days with steroids started after the onset of ARDS was suggested"
Tang et al	RCTs and cohort studies that used low dose steroids to treat ARDS	Cohort and RCT	Overall: OR 0.62 (0.43–0.91)Cohort: OR 0.66 (0.43–1.02)RCT: 0.51 (0.24–1.09)	"The use of low-dose corticosteroids was associated with improved mortality and morbidity outcomes without increased adverse reactions. The consistency of results in both study designs and all outcomes suggests they are an effective treatment for ARDS.

Overview of meta-analyses of steroids and ARDS

Author	Inclusion criteria	Strata	Effects of steroids on outcome	Conclusion
Lamontagne et al	RCTs of steroids for ARDS, limited to ARDS < 14 days at enrollment	Definition of ARDS	OR 0.79 (0.61–1.01)	"Our analysis suggests that low-dose corticosteroid therapy administered within 14 days of disease onset may reduce all-cause mortality in patients with ARDS… [but] the mortality benefits we recorded rely on analyses of subgroups, which are both inconsistent and imprecise."

TO CONCLUDE

- No studies support the use of corticosteroids for the prevention of ARDS
- High dose and short course treatment with steroids does not improve the outcomes of patients with ARDS
- There is compelling data that low dose and prolonged treatment with steroids improves pulmonary physiology in patients with ARDS, but additional studies are needed to recommend treatment with steroids for ARDS