Seminar

Current Concepts

In ARDS

What I think is possible to cover in 40 minutes-

- Definition
- Management
  - Ventilatory strategies
    - Conventional LPV
    - Rescue therapy
  - Non Ventilatory strategies

Definition and Diagnosis

- First described by Ashbaugh and Petty-1967
- Case series of 12 patients

- Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967;2(7511):319-323.

- No valid definition for almost 25 years

Definition and Diagnosis contd..

- In 1994 AECC definition of ARDS
- Four key features
  - Acute
  - Hypoxemia
  - CXR
  - Non cardiogenic nature
- Broader term ALI- to include less severe disease

-Bernard GR et al. Am J Respir Crit Care Med. 1994;149(3 pt 1):818-824.

Definition and Diagnosis contd..

Why new definition is required?

1. What is acute?
2. Does PEEP affect P/F ratio?
3. CXR- Subjective- Can it be made more objective?
4. Requires RHC!!!

- Term ALI- “Exclusive” or “Inclusive”
- No severity stratification for ARDS

-Phua J Acute respiratory distress syndrome 40 years later: time to revisit its definition. Crit Care Med. 2008;36(10):2912-21.

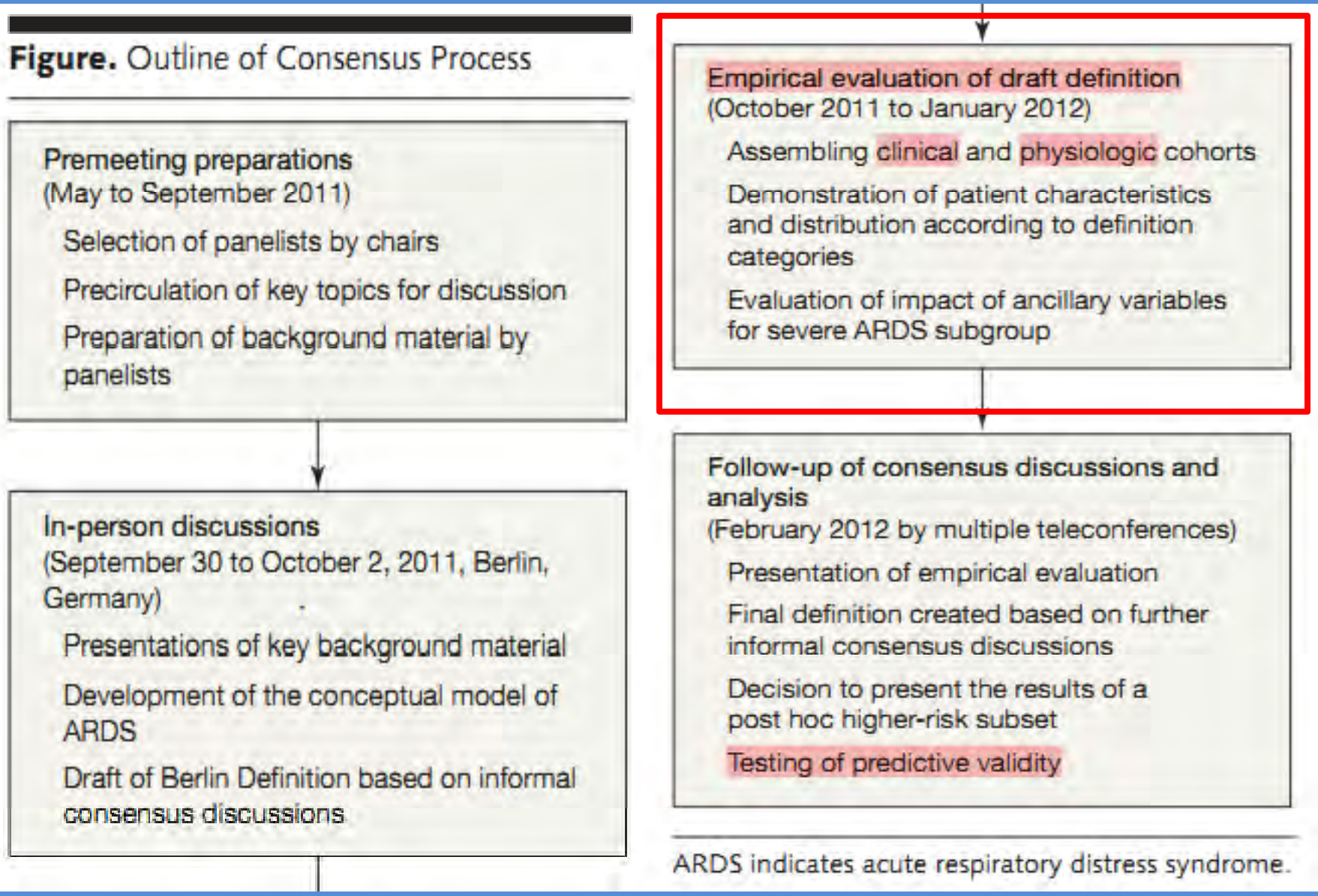
Definition and Diagnosis contd..

- ESICM with endorsement from ATS & Society of Critical Care Medicine – Convened an International expert panel
- First meeting in Berlin from Sep 30th to Oct 2nd 2011-Draft definition of ARDS
- Evaluated on 4000 patients of presumed ARDS for ability to predict short term mortality

-Rubenfeld et al JAMA. 2012;307(23):2526-33.
-Angus DC JAMA. 2012;307(23):2542-4.

Definition and Diagnosis contd..

Figure. Outline of Consensus Process



ARDS indicates acute respiratory distress syndrome.

-Rubenfeld et al JAMA. 2012;307(23):2526-33.

Definition and Diagnosis contd..

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < Pao_2/Fio_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	Pao_2/Fio_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; Fio_2, fraction of inspired oxygen; Pao_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

[a] Chest radiograph or computed tomography scan.

[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [Pao_2/Fio_2 × (barometric pressure/760)].

[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

-Rubenfeld et al JAMA. 2012;307(23):2526-33.

Other variables assessed-

Table 2. Exploration of Proposed Variables to Define Severe ARDS[a]

Severe ARDS Definition	Mild		Moderate		Severe	
	No. (%) of Patients	% Mortality (95% CI)	No. (%) of Patients	% Mortality (95% CI)	No. (%) of Patients	% Mortality (95% CI)
Consensus panel draft						
PaO_2/FIO_2 ≤100 mm Hg + chest radiograph of 3 or 4 quadrants + PEEP ≥10 cm H_2O + (C_{RS} ≤40 mL/cm H_2O or $\dot{V}E_{CORR}$ ≥10 L/min)	220 (22)	27 (24-30)	2344 (64)	35 (33-36)	507 (14)	45 (40-49)[b]
Consensus panel final						
PaO_2/FIO_2 ≤100 mm Hg	220 (22)	27 (24-30)	1820 (50)	32 (29-34)	1031 (28)	45 (42-48)[b,c]

Abbreviations: ARDS, acute respiratory distress syndrome; C_{RS}, compliance of the respiratory system; FIO_2, fraction of inspired oxygen; PaO_2, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure; $\dot{V}E_{CORR}$, corrected expired volume per minute.

[a] The moderate group includes patients with PaO_2/FIO_2 ≤200 mm Hg and patients with PaO_2/FIO_2 ≤100 mm Hg who do not meet the additional criteria for severe ARDS in the draft definition. All patients are receiving at least 5 cm H_2O PEEP and have bilateral infiltrates on chest radiograph.

[b] $P < .001$ comparing mortality across stages of ARDS (mild, moderate, severe) for draft and final definitions.

[c] $P = .97$ comparing mortality in consensus draft severe ARDS to consensus final severe ARDS definitions.

Angus DC JAMA. 2012;307(23):2542-4.

To conclude-

	AECC	Berlin
Duration	Vague	1 week
P/F ratio	<200	<300
Requires	RHC	Ventilator
Conceptually	Conservative/Restrictive	More liberal “INCLUSIVE”
Possibly both are complimentary to each other		

Current in Ventilatory strategies-

- Conventional LPV
- Unconventional
  - Higher PEEP
  - Recruitment
  - PCIRV
  - APRV
  - HFOV

Dawn of LTVV/LPV

How much to expect?

TABLE 4. MAIN OUTCOME VARIABLES.*

VARIABLE	GROUP RECEIVING LOWER TIDAL VOLUMES	GROUP RECEIVING TRADITIONAL TIDAL VOLUMES	P VALUE
Death before discharge home and breathing without assistance (%)	31.0	39.8	0.007
Breathing without assistance by day 28 (%)	65.7	55.0	<0.001
No. of ventilator-free days, days 1 to 28	12±11	10±11	0.007
Barotrauma, days 1 to 28 (%)	10	11	0.43
No. of days without failure of nonpulmonary organs or systems, days 1 to 28	15±11	12±11	0.006

ARR 8.8

ARR 10.7

*Plus–minus values are means ±SD. The number of ventilator-free days is the mean number of days from day 1 to day 28 on which the patient had been breathing without assistance for at least 48 consecutive hours. Barotrauma was defined as any new pneumothorax, pneumomediastinum, or subcutaneous emphysema, or a pneumatocele that was more than 2 cm in diameter. Organ and system failures were defined as described in the Methods section.

New Engl j of med 2000;342(18):1301-8

Does compliance at baseline predict response to LTV?

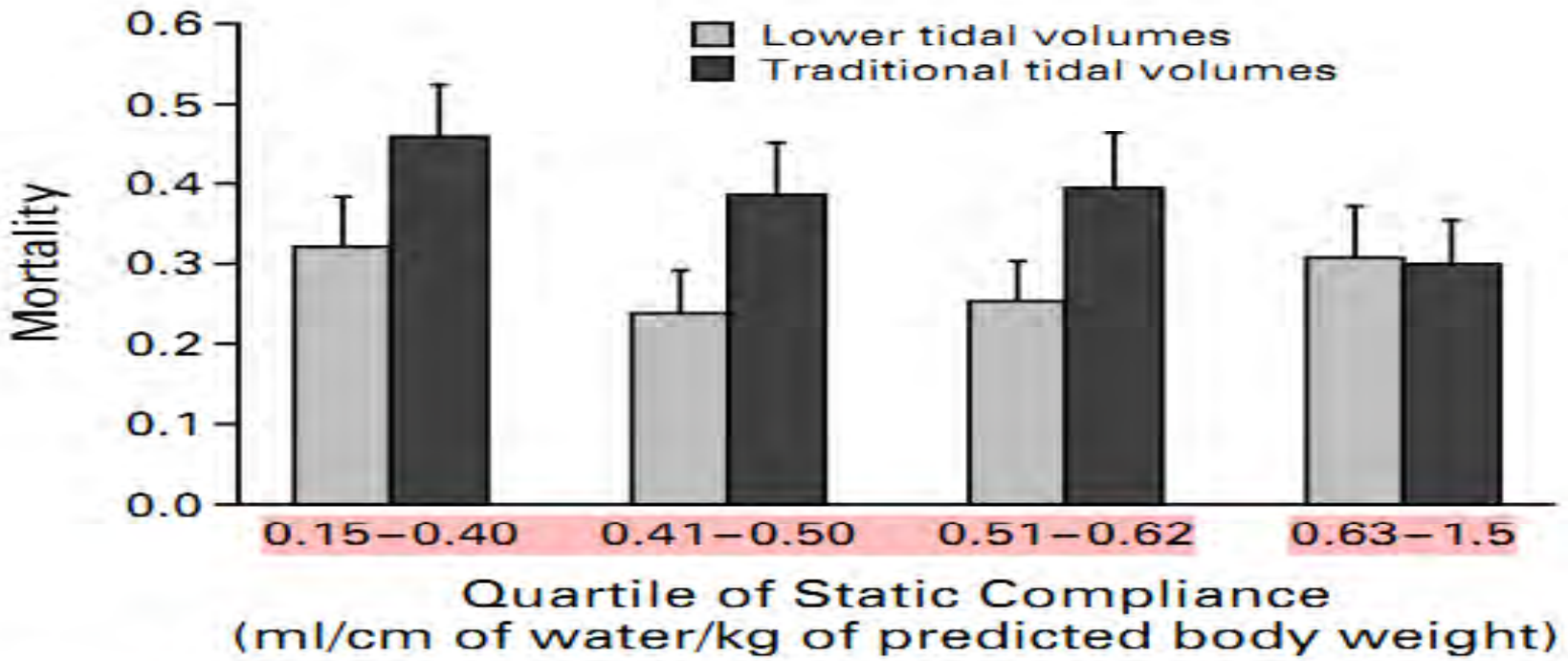


Figure 2. Mean (+SE) Mortality Rate among 257 Patients with Acute Lung Injury and the Acute Respiratory Distress Syndrome Who Were Assigned to Receive Traditional Tidal Volumes and 260 Such Patients Who Were Assigned to Receive Lower Tidal Volumes, According to the Quartile of Static Compliance of the Respiratory System before Randomization.

The interaction between the study group and the quartile of static compliance at base line was not significant ($P=0.49$).

New Engl j of med 2000;342(18):1301-8

- What does literature say about long term effects of LTVV

Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study

Dale M Needham *associate professor*[1 2], Elizabeth Colantuoni *assistant scientist*[3], Pedro A Mendez-Tellez *assistant professor*[4], Victor D Dinglas *research programme supervisor*[1], Jonathan E Sevransky *assistant professor*[1], Cheryl R Dennison Himmelfarb *associate professor*[6], Sanjay V Desai *assistant professor*[1], Carl Shanholtz *associate professor*[7], Roy G Brower *professor*[1], Peter J Pronovost *professor*[4 5 6]

Results 485 patients contributed data for 6240 eligible ventilator settings, as measured twice daily (median of eight eligible ventilator settings per patient; 41% of which adhered to lung protective ventilation). Of these patients, 311 (64%) died within two years. After adjusting for the total duration of ventilation and other relevant covariates, each additional ventilator setting adherent to lung protective ventilation was associated with a 3% decrease in the risk of mortality over two years (hazard ratio 0.97, 95% confidence interval 0.95 to 0.99, P=0.002). Compared with no adherence, the estimated absolute risk reduction in two year mortality for a prototypical patient with 50% adherence to lung protective ventilation was 4.0% (0.8% to 7.2%, P=0.012) and with 100% adherence was 7.8% (1.6% to 14.0%, P=0.011).

BMJ 2012;344:e2124 doi: 10.1136/bmj.e2124 (Published 5 April 2012)

- Does this mean we are able to save additional approximately 8.8% of ARDS patients, by resorting to LTVV?

- NO

Outcome- Then And Now-

Table 3 Demographic and ventilatory parameters at ARDS onset and outcome measures in main studies reporting ARDS incidence using AECC definition

	Valta et al. [8]	Luhr et al. [9]	Bersten et al. [23]	Rubenfeld et al. [10]	Linko et al. [21]	Li et al. [22]	Current study
Study period	3 years (1993–1995)	8 weeks (Oct–Nov 1997)	2 months (Oct–Nov 1999)	1 year (April 1999–July 2000)	8 weeks (April–June 2007)	8 years (2001–2008)	1 year (Nov 2008–Oct 2009)
Study design	Retrospective	Prospective	Prospective	Prospective	Prospective	Retrospective	Prospective
ARDS cases/100,000 population	4.9	13.5 (as reported), 11.3 (calculated by us)	28	58.7	5.0	33.8 (as 2008 only)	7.2
Age, years (mean ± SD or median)	45 ± 2	61 ± 16	62 ± 18	Not reported	61 (50–72)	64 (51–80)	58 (41–73)
Tidal volume (ml/kg BW)	8.2 ± 0.4 (measured BW)	8.3 ± 2.7 (measured BW)	9.7 ± 1.9 (measured BW)	Not reported, 10.2 ± 2.6 (from Ref. [40]) (predicted BW)	8.6 (7.3–9.9) (predicted BW)	Not reported	7.2 ± 1.1 (predicted BW)
PEEP (cmH_2O)	7.8 ± 0.6 (estimated by us)	6.1 ± 3.3	6.3 ± 2.8	Not reported	8 (6–10)	Not reported	9.3 ± 2.4
Plateau pressure (cmH_2O)	Not reported	Not reported	25 ± 6.6	Not reported	Not reported	Not reported	26 ± 4
PaO_2/FiO_2 (mmHg)	123 ± 7	130 ± 37	Not reported	Not reported	Not reported	Not reported	114 ± 40
Pneumothorax after initiating MV (%)	12	Not reported	10.1	Not reported	Not reported	Not reported	8.1
ICU mortality (%)	43	Not reported	30.4	Not reported	Not reported	Not reported	42.7
Hospital mortality, %	42.0	Not reported	Not reported	41.1	Not reported	45% (in 2008)	47.8
28-day mortality	–	–	34.4	–	–		–
90-day mortality		41.2	–	–	47 (ALI/ARDS)		–

Villar J et. al. 2011 The ALIEN study, Intensive Care Med 37:1932–1941

Experience at Our Centre-

Etiology and Outcomes of Pulmonary and Extrapulmonary Acute Lung Injury/ARDS in a Respiratory ICU in North India*

Ritesh Agarwal, DM; Ashutosh N. Aggarwal, DM, FCCP; Dheeraj Gupta, DM, FCCP; Digamber Behera, MD, FCCP; and Surinder K. Jindal, MD, FCCP

tion was available. All patients received mechanical ventilation (Hamilton Amadeus; Bonaduz, GR, Switzerland) using the protocol followed by the ARDS Network low-tidal volume ventilation strategy using ideal body weight to calculate tidal volumes.[9] However, if plateau pressures (Pplat) exceeded 30 cm H_2O or if the pH decreased to < 7.3, the tidal volumes were increased or the positive end-expiratory pressure (PEEP) was decreased, as applicable.[10] The baseline characteristics such as age and gender,

-Chest 2006;130:724-729

Experience at Our Centre-

Table 3—*Risk Factors Affecting Outcome of ALI/ARDS Patients in the RICU (Multivariate Logistic Regression Model)*

Variables	Survivors (n = 94)	Nonsurvivors (n = 86)	Crude OR (95% CI)	Adjusted OR (95% CI)
Age,* yr Mean (SD)	41 (19)	45 (18)	1.01 (0.99–1.03)	
Female sex,†	47 (50)	30 (34.9)	0.54 (0.29–0.98)‡	0.49 (0.25–0.94)‡
ARDSexp patients,†	24 (25.5)	33 (38.4)	1.82 (0.96–3.43)§	1.6 (0.8–3.2)
Pplat at admission,* cm H_2O	22 (6)	23 (7)	1.02 (0.96–1.1)	
PEEP at admission,* cm H_2O	7 (3)	8 (4)	1.1 (0.97–1.3)	
SOFA score‖	7 (2–18)	10 (3–21)	1.18 (1.08–1.29)¶	1.18 (1.07–1.3)¶
Δ SOFA score‖	0 (0–8)	0.5 (0–15)	1.21 (1.07–1.36)¶	1.24 (1.09–1.41)¶

groups (5 days [interquartile range (IQR), 6 days] vs 5 days [IQR, 9.5 days], respectively, in patients with ALI/ARDSp and ALI/ARDSexp; p = 0.4). The hospital mortality rate was 47.8% and was not significantly different between the two groups (ALI/ARDSp group, 43.1%; ALI/ARDSexp group, 57.9%; p = 0.06). Multivariate analysis showed the following risk factors for death in the ICU: female

-Chest 2006;130:724-729

Possible reasons

- LTV in clinical practice is yet to be accepted universally
- Mortality is affected predominantly by other components, especially sepsis and MODS
- Previous studies also used TV to the tune of 7-9ml/Kg and not 12 ml/Kg as was used in ‘Tidal volume trial’

To conclude

- LTV Ventilation has definite mortality benefit, both in short and long term and needs to be accepted and used routinely
- Our practice-
  - To start with 6 ml/Kg IBW and titrate according to SpO2 and Pplat at bedside

How do I know my patient will require more than usual?

1. P/F ratio <100
2. PEEP >15 – Attributable mortality 16%
3. Inability to maintain Pplat <30 cmH2O despite a Vt 4 mL/kg IBW
4. Oxygenation Index [(FIO2 X mPaw X 100)/PaO2] - > 30
5. Little improvement in P/F ratio after 24 hours of LPV – ***Mortality 53-68%***
6. Development of barotrauma

-Esan A. et al. CHEST 2010; 137(5): 1203 – 1216

- What next??

Wait- Is it really refractory hypoxemia?

- Check
  - Is the Vt appropriate?
  - Is there VP asynchrony?
  - Is there fluid overload/cardiogenic component?
  - Is there a device malfunction?

How do I go about refractory hypoxemia in severe ARDS?

Rescue therapy-

ECMO

96….95…..94….93…..92…

Higher PEEP …….

Recruitment maneuver

HFOV/HFPV

Prone positioning

APRV

Unconventional strategies

Physiological Rationale-

- Recruit collapsed but potentially recruitable alveoli
- Optimize V/P matching
- Without further increasing lung injury

Rationalization from Clinical trials-

- 16% of early deaths in ARDS are due to refractory hypxemia
- Most of the rescue therapies are proven to improve oxygenation

-Esan A. et al. CHEST 2010; 137(5): 1203 – 1216

Recruitment Maneuver-

Rationale-

1. ARDS lung is derecruited and recruitable

2. Concept of COP of the lung units
   - COP varies from relatively low to very high

3. Lung recruitment is beneficial
   - increase in the aerated lung mass- minimize the lung heterogeneity and to increase the size of the baby lung
   - Prevention of atelectatotrauma

Guerin et al. Annals of Intensive Care 2011,1 :9

Recruitment cont..

It is a transient increase in transpulmonary pressure intended to promote reopening of collapsed alveoli- function of lung inflation

Recruitment cont..

- Used to identify and utilize alveoli which are collapse but are potentially recruitable without further lung injury
- Useful only if patient is on modest PEEP
- Improvement in oxygenation- indicates PEEP being used was inadequate
- Should be followed by high PEEP to maintain benefits

Recruitment, Evidence-

- No properly conducted RCT
- Only Case series/ data from other ARDS studies
- No standard maneuver

-Esan A. et al. CHEST 2010; 137(5): 1203 – 1216

Recruitment, evidence-

Duration of hold-

- Early ARDS- most of the recruitment occurs during the first 10 s of a SI RM

- Hmodynamic impairment is significant after the tenth second of RM

-Arnal JM et al. Intensive Care Med, 2011;37:1588–1594

Conclusion-

Recruitment Maneuvers for Acute Lung Injury

A Systematic Review

Eddy Fan[1,2], M. Elizabeth Wilcox[1], Roy G. Brower[2], Thomas E. Stewart[1], Sangeeta Mehta[1], Stephen E. Lapinsky[1], Maureen O. Meade[3], and Niall D. Ferguson[1]

[1]Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada; [2]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland; and [3]Departments of Clinical Epidemiology and Biostatistics, and Medicine, McMaster University, Hamilton, Ontario, Canada

Rationale: There are conflicting data regarding the safety and efficacy of recruitment maneuvers (RMs) in patients with acute lung injury (ALI).
Objectives: To summarize the physiologic effects and adverse events in adult patients with ALI receiving RMs.
Methods: Systematic review of case series, observational studies, and randomized clinical trials with pooling of study-level data.
Measurements and Main Results: Forty studies (1,185 patients) met inclusion criteria. Oxygenation (31 studies; 636 patients) was significantly increased after an RM (Pa_{O_2}: 106 versus 193 mm Hg, $P = 0.001$; and Pa_{O_2}/F_{IO_2} ratio: 139 versus 251 mm Hg, $P < 0.001$). There were no persistent, clinically significant changes in hemodynamic parameters after an RM. Ventilatory parameters (32 studies; 548 patients) were not significantly altered by an RM, except for higher PEEP post-RM (11 versus 16 cm H_2O; $P = 0.02$). Hypotension (12%) and desaturation (9%) were the most common adverse events (31 studies; 985 patients). Serious adverse events (e.g., barotrauma [1%] and arrhythmias [1%]) were infrequent. Only 10 (1%) patients had their RMs terminated prematurely due to adverse events.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Conflicting data exist regarding the safety and efficacy of recruitment maneuvers in patients with acute lung injury. Recruitment maneuvers lead to a significant increase in oxygenation, with few serious adverse events.

What this Study Adds to the Field

Given the uncertain benefit of transient oxygenation improvements in patients with ALI and the lack of information on their influence on clinical outcomes, the routine use of RMs cannot be recommended or discouraged at this time. RMs should be considered for use on an individualized basis in patients with ALI who have life-threatening hypoxemia.

Fan et al. Am J Respir Crit Care Med;178:1156–1163.

Higher PEEP – Continuum of recruitment

Table 1—*Summary of Results of Three Randomized Controlled Trials of Lower vs Higher Levels of PEEP*

Study	Control Group	Experimental Group	Major Findings
ALVEOLI[39]	Volume assist-control. V_T = 6 mL/kg IBW; Pplat ≤ 30 cm H_2O. Combinations of PEEP and F_{IO_2} to maintain Pa_{O_2} (55-80 mm Hg) or Sp_{O_2} (88%-95%). PEEP on days 1-4 was 8.3 ± 3.2 cm H_2O. n = 273	Volume assist-control. V_T = 6 mL/kg IBW; Pplat ≤ 30 cm H_2O. Combinations of PEEP and F_{IO_2} to maintain Pa_{O_2} (55-80 mm Hg) or Sp_{O_2} (88%-95%). PEEP on days 1-4 was 13.2 ± 3.5 cm H_2O. In the first 80 patients, recruitment maneuvers of 35-40 cm H_2O for 30 s. n = 276	Higher Pa_{O_2}/F_{IO_2} ratio in high PEEP group (220 ± 89 vs 168 ± 66) on day 1. Higher compliance in the higher-PEEP group (39 ± 34 vs 31 ± 15 mL/cm H_2O) on day 1. Mortality before hospital discharge (low PEEP, 24.9%; high PEEP, 27.5%; P = .48). Ventilator-free days (low PEEP, 14.5 ± 10.4 d; high PEEP, 13.8 ± 10.6 d; P = .50). Incidence of barotrauma (low PEEP, 10%; high PEEP, 11%; P = .51).
LOV[27]	Volume assist-control. V_T = 6 mL/kg IBW; Pplat ≤ 30 cm H_2O. Combinations of PEEP and F_{IO_2} to maintain Pa_{O_2} (55-80 mm Hg) or Sp_{O_2} (88%-93%). PEEP on days 1-3 was 9.8 ± 2.7 cm H_2O. n = 508	Pressure control. V_T = 6 mL/kg IBW; Pplat ≤ 40 cm H_2O. Combinations of PEEP and F_{IO_2} to maintain Pa_{O_2} (55-80 mm Hg) or Sp_{O_2} (88%-93%). PEEP on days 1-4 was 14.6 ± 3.4 cm H_2O. Recruitment maneuvers after each disconnect from the ventilator of 40 cm H_2O for 40 s. n = 475	Higher Pa_{O_2}/F_{IO_2} ratio in higher-PEEP group (187 ± 69 vs 149 ± 61) on day 1. Higher Pplat in the high-PEEP group (30.2 ± 6.3 vs 24.9 ± 5.1). The higher-PEEP group had lower rates of refractory hypoxemia (4.6% vs 10.2%; P = .01), death with refractory hypoxemia (4.2% vs 8.9%; P = .03), and previously defined eligible use of rescue therapies (5.1% vs 9.3%; P = .045). Twenty-eight day mortality (high PEEP, 28.4%; low PEEP, 32.3%; P = .2). Incidence of barotrauma (high PEEP, 11.2%; low PEEP, 9.1%; P = .33).
EXPRESS[28]	Volume assist-control. V_T = 6 mL/kg IBW. Moderate PEEP (5-9 cm H_2O). n = 382	Volume assist-control. V_T = 6 mL/kg IBW. PEEP set to reach Pplat of 28-30 cm H_2O (14.6 ± 3.2 cm H_2O) on day 1. n = 385	Higher Pa_{O_2}/F_{IO_2} ratio in higher-PEEP group (218 ± 97 vs 150 ± 69) on day 1. Higher compliance in the high-PEEP group (37.2 ± 22.7 mL/cm H_2O vs 33.7 ± 14.3 mL/cm H_2O) on day 1. The increased PEEP group had higher median number of ventilator-free days (7 d vs 3 d; P = .04), organ failure-free days (6 d vs 2 d; P = .04), and use of adjunctive therapies. Incidence of barotraumas (high PEEP, 6.8%; low PEEP, 5.8%; P = .57).

-Esan A. et al. CHEST 2010; 137(5): 1203 – 1216

However…

- Higher PEEP was safe
- Sub group analysis of refractory hypoxemia group
  - Lesser numbers requiring salvage therapy(10 % vs. 20 %)
  - Alveoli trial was not based on identification of LIP & PEEP was arbitrarily set as per table
- Definite role in subset of patients with severe lung injury

- Briel M et al. JAMA. 2010;303(9):865-873

-Esan A. et al. CHEST 2010; 137(5): 1203 – 1216

Which patient will benefit?

- 30 minute trial of high PEEP
- B/L lung involvement
- Recruitable lung

Optimal PEEP- No clear evidence-

- Incremental or decremental PEEP
- Esophageal pressure- unreliable
- PV tool- LIP useful
- Stress Index-

-Esan A. et al. CHEST 2010; 137(5): 1203 – 1216

Stress index

-Esan A. et al. CHEST 2010; 137(5): 1203 – 1216

Combining above three strategies (LOVS)

Ventilation Strategy Using Low Tidal Volumes, Recruitment Maneuvers, and High Positive End-Expiratory Pressure for Acute Lung Injury and Acute Respiratory Distress Syndrome

A Randomized Controlled Trial

Results Eighty-five percent of the 983 study patients met criteria for acute respiratory distress syndrome at enrollment. Tidal volumes remained similar in the 2 groups, and mean positive end-expiratory pressures were 14.6 (SD, 3.4) cm H_2O in the experimental group vs 9.8 (SD, 2.7) cm H_2O among controls during the first 72 hours ($P < .001$). All-cause hospital mortality rates were 36.4% and 40.4%, respectively (relative risk [RR], 0.90; 95% confidence interval [CI], 0.77-1.05; $P = .19$). Barotrauma rates were 11.2% and 9.1% (RR, 1.21; 95% CI, 0.83-1.75; $P = .33$). The experimental group had lower rates of refractory hypoxemia (4.6% vs 10.2%; RR, 0.54; 95% CI, 0.34-0.86; $P = .01$), death with refractory hypoxemia (4.2% vs 8.9%; RR, 0.56; 95% CI, 0.34-0.93; $P = .03$), and previously defined eligible use of rescue therapies (5.1% vs 9.3%; RR, 0.61; 95% CI, 0.38-0.99; $P = .045$).

Meade MO et al. JAMA. 2008;299(6):637-645

PCIRV

Rationale

- Maintains recruitment
- More time for oxygenation
- Improves oxygenation

Problems

- Requires sedation and paralysis
- Uncomfortable
- Risk of Auto PEEP & haemodynamic compromise

- Evidence does not show any benefit over LPV

-Esan A. et al. CHEST 2010; 137(5): 1203 – 1216

APRV

- Conceptually continuum of IRV
- Separates 2 Pumps
- Recruitment- Maximizes benefit of PPV & SV
- Allows asynchrony without adverse effects on oxygenation
- Improves patient comfort
- Allows OLV at relatively low pressure swings

-Esan A. et al. CHEST 2010; 137(5): 1203 – 1216

APRV evidence

Author, yr	No of pt.	Mortality	comment
Putensen et al. 2001	30	20 vs 26%	Safe Comfortable for patient No mortality benefit over LPV Not recommended routinely
Verpula et al.	33	8 vs 14%	
Verpula et al.	58	17 vs 18%	

-Esan A. et al. CHEST 2010; 137(5): 1203 – 1216

HFOV

Rationale-

- Maintain open lung
- Minimal volume swings

Achieved by-

- Higher mean pressure
- Frequency increased to minimize fall in airway pressure
- Vt decreased to compensate for possible auto PEEP
- VT= dead space- oscillatory pattern

HFOV: Evidence-

Author, yr	No. of patients	Result	comment
Derdak et al. 2002	148	- No survival benefit - Improved oxygenation	Safe Efficacy compared to LPV needs to be proven Can be used as salvage therapy
Bollen et al. 2005	61 Stopped prematurely	No survival benefit	

- Derdak S, Mehta S, Stewart TE et al. Am J Respir Crit Care Med 2002;166:801-8.
- Bollen CW, van Well GT, Sherr y T et al. Crit Care 2005;9:R430-R9

When Caring for Critically Ill Patients, Do Clinicians Have a Responsibility to Be Innovative and Try Unproven Approaches When Accepted Approaches Are Failing?

Bruce K Rubin MEngr MD MBA FAARC and Kenneth P Steinberg MD

Table 1. Research Versus "Adventurism"

Research	Adventurism
Distinguishes helpful from unhelpful, or even harmful, therapies	Fails to advance knowledge
Vital to improving care	Unable to distinguish benefit from harm
Advances knowledge, even if it doesn't help the individual patient	Often leads to false conclusions
Generates evidence	Ignores evidence

To conclude

- Use what is available
- Use the one which you are well versed with
- When faced with a patient with refractory hypoxemia- Rescue strategy of ventilation may be life saving in individual patient and is worth trying for….
- However if no benefit is observed over few hours of trial- it should abandoned

Non ventilatory strategies

Rapid Rescue from hypoxemia-

1. Neuromuscular blockade
2. Inhaled vasoactive agents
3. Prone positioning
4. Extracorporeal life support

Gradual rescue from hypoxemia-

1. Conservative fluid management
2. Intravenous corticosteroids
3. Nutritional modification

- Raoof S, Goulet K, Esan A et al. CHEST 2010; 137(6): 1437 – 1448

Neuromuscular blockade

3 RCTs- Latest ACURASyS trial

- Significant improvement in oxygenation
- Benefit seen despite absence of VP asynchrony at baseline
- Lower concentrations of proinflammatory cytokines
- Survival benefit at 90 days- ACURASyS study

Problem-

- Critical care myopathy esp. with concurrent steroids

Present status-

- Can be used if first dose shows significant improvement, No major adverse events

- Papazian L, Forel JM, Gacouin A et al.; ACURASyS Study, N Engl J Med 2010;363:1107-16.
- Raoof S, Goulet K, Esan A et al. CHEST 2010; 137(6): 1437 – 1448

Inhaled NO

Rationale-

- Selective vasodilation- Improved V/Q matching
- lower PAP

Evidence- 5 RCTs, 1 systemic review, 1 metaanalysis-

- Transient improvement in oxygenation 24-96hrs
- No survival benefit or reduction in ventilator-free days

- Raoof S, Goulet K, Esan A et al. CHEST 2010; 137(6): 1437 – 1448

Inhaled NO

Problems-

- Cost
- Renal dysfunction
- Methemoglobinemia- rare at dose<80ppm

Present status-

- Can be used in refractory hypoxemia
- Discontinue if no benefit in 1 hour

- Raoof S, Goulet K, Esan A et al. CHEST 2010; 137(6): 1437 – 1448

Other vasoactive drugs

- IV Phenylephrine-
- Prostacyclins- Cheaper alternative to iNO
- Almitrine- Potentiates HPV
- Avoid systemic vasodilators
  - All conceptually sound
  - Imrove oxygenation in short term

- Raoof S, Goulet K, Esan A et al. CHEST 2010; 137(6): 1437 – 1448

Prone position: Physiological Rationale-

- Recruitment
- Redistribution of ventilation -enhanced V/Q matching
- Elimination of compression of the lungs by the heart
- Decreased shunt
- Improved compliance

- Girard TD, Bernard GR Chest 2007;131 (3):921-929.
- Guerin C, Badet M, Rosselli S et al. Intensive Care Med. 1999;25(11):1222-1230
- Raoof S, Goulet K, Esan A et al. CHEST 2010; 137(6): 1437 – 1448

Prone position: Evidence-

Table 1—*Summary of Four Randomized Trials on Prone Position*

	Gattinoni et al[68]	Guerin et al[69]	Mancebo et al[70]	Taccone et al[71]
No. of patients	304	791	136	343
Prone	152	413	76	168
Supine	152	378	60	174
Enrollment criteria	ALI	ALI	ARDS	ARDS
	$Pao_2/Fio_2 < 300$	$Pao_2/Fio_2 < 300$	$Pao_2/Fio_2 < 200$	$Pao_2/Fio_2 < 200$
Daily proning				
Planned	> 6 h/d	> 8 h/d	20 h/d	20 h/d
Actual	7 h/d	8 h/d	13 h/d	18-20 h/d
Number of days	10 d	4 d	10 d	28 d
Oxygenation	Improved	Improved	Improved	Improved
VAP	Not assessed	Reduced	Not reduced	Not assessed
Primary end point	10-d mortality	28-d mortality	ICU mortality	28-d mortality
Prone vs supine	21.1% vs 25%	32.4% vs 31.5%	43% vs 58%	31.0% vs 32.8%
	RR, 0.84	RR, 0.97	RR, 0.74	RR, 0.97
	95% CI, 0.56-1.27	95% CI, 0.79-1.19	95% CI, 0.53-1.04	95% CI, 0.84-1.13
	$P = .50$	$P = .77$	$P = .12$	$P = .72$

ALI = acute lung injury; RR = relative risk; VAP = ventilator-associated pneumonia.

- Raoof S, Goulet K, Esan A et al. CHEST 2010; 137(6): 1437 – 1448

Analyzing the latest trial- Prone-Supine II Study

- Only ARDS patients
- Stratification in moderate vs severe
- Prespecified ventilation protocol
- Early application <72 hrs
- Up to 20 hr/day

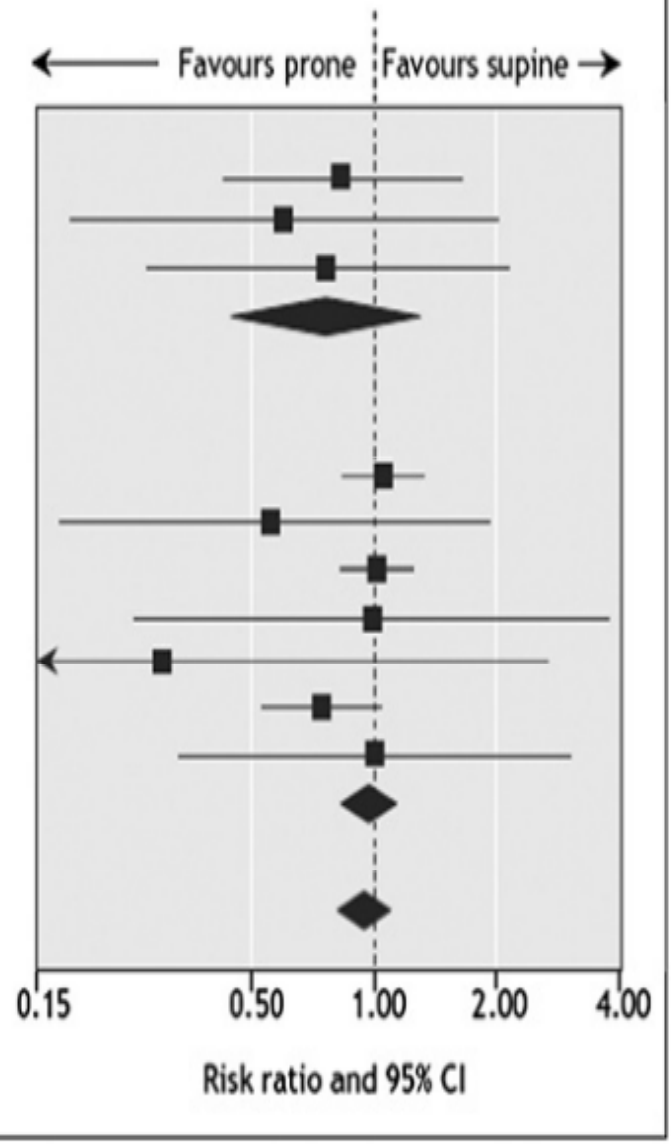
Results

- NO SURVIVAL BENEFIT
- More COMPLICATIONS
- Non significant trend towards survival benefit in severe group

Can be used in refractory patients with potential complications in mind

-Taccone P, Pesenti A, Latini R, et al;JAMA. 2009;302(18):1977- 1984.
- Raoof S, Goulet K, Esan A et al. CHEST 2010; 137(6): 1437 – 1448

Study	Prone, n/N	Supine, n/N	RR (95% CI)
Short-term prone positioning			
Leal et al[22]	5/8	6/8	0.83 (0.43-1.63)
Papazian et al[29]	3/13	5/13	0.60 (0.18-2.01)
Demory et al[32]	4/13	6/15	0.77 (0.28-2.14)
Subtotal	34	36	0.77 (0.46-1.28)
Overall effect p = 0.32. Heterogeneity I^2 = 0%.			
Prolonged prone positioning			
Gattinoni et al[23]	77/152	73/152	1.05 (0.84-1.32)
Beuret et al[24]	3/12	4/9	0.56 (0.17-1.91)
Guerin et al[27]	134/413	119/378	1.03 (0.84-1.26)
Curley et al[28]	4/51	4/51	1.00 (0.26-3.78)
Voggenreiter et al[30]	1/21	3/19	0.30 (0.03-2.66)
Mancebo et al[31]	33/76	35/60	0.74 (0.53-1.04)
Chan et al[34]	4/11	4/11	1.00 (0.33-3.02)
Subtotal	736	680	0.97 (0.85-1.11)
Overall effect p = 0.68. Heterogeneity I^2 = 0%.			
Overall	770	716	0.96 (0.84-1.09)
Overall effect p = 0.52. Heterogeneity I^2 = 0%.			



Dickinson S et al. Crit Care Clin 27 (2011) 511–523

ECMO in ARDS

3 RCTs in adults, total 330 patients

- First 2 trials, 110 patients- no mortality benefit
- CESAR trial- serious methodological flaws- significant mortality benefit- however conclusion is not possible
- Can be considered as rescue therapy in suitably selected patients

- Peek GJ, Mugford M, Tiruvoipati R, et al;Lancet. 2009;374:1351-1363.
- Raoof S, Goulet K, Esan A et al. CHEST 2010; 137(6): 1437 – 1448

ECMO in ARDS

Indications (as a temporary rescue measure)

- Acute
- Life threatening
- Reversible
- Unresponsive to conventional therapy
- Ventilation <7days
- Age <65 years
- $PO_2 / FiO_2 < 60$ (in spite of standard care)
- No significant comorbidities

- Raoof S, Goulet K, Esan A et al. CHEST 2010; 137(6): 1437 – 1448

Fluids- How much is better?

Comparison of Two Fluid-Management Strategies in Acute Lung Injury

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

RESULTS

The rate of death at 60 days was 25.5 percent in the conservative-strategy group and 28.4 percent in the liberal-strategy group (P=0.30; 95 percent confidence interval for the difference, –2.6 to 8.4 percent). The mean (±SE) cumulative fluid balance during the first seven days was –136±491 ml in the conservative-strategy group and 6992±502 ml in the liberal-strategy group (P<0.001). As compared with the liberal strategy, the conservative strategy improved the oxygenation index ([mean airway pressure × the ratio of the fraction of inspired oxygen to the partial pressure of arterial oxygen] × 100) and the lung injury score and increased the number of ventilator-free days (14.6±0.5 vs. 12.1±0.5, P<0.001) and days not spent in the intensive care unit (13.4±0.4 vs. 11.2±0.4, P<0.001) during the first 28 days but did not increase the incidence or prevalence of shock during the study or the use of dialysis during the first 60 days (10 percent vs. 14 percent, P=0.06).

CONCLUSIONS

Although there was no significant difference in the primary outcome of 60-day mortality, the conservative strategy of fluid management improved lung function and shortened the duration of mechanical ventilation and intensive care without increasing nonpulmonary-organ failures. These results support the use of a conservative strategy of fluid management in patients with acute lung injury. (ClinicalTrials.gov number, NCT00281268.)

But—

- Martin et al. failed to show significant difference in placebo and diuretics + albumin
- In another study they reported beneficial role of Albumin + Furosemide over furosemide alone especially in patients with hypoproteinemia

  - Martin GS et al. Crit Care Med. 2002;30 (10):2175-2182.
  - Martin GS et al. Crit Care Med. 2005;33(8):1681-1687.

- So what do we take from it?
- Difficult to say at present- till it is solved…

Table 2—*Simplified Algorithm for Conservative Management of Fluids in Patients With ALI, Based on Protocol Used in the FACTT

CVP, mm Hg (Recommended)	PAOP, mm Hg (Optional)	MAP ≥ 60 mm Hg and Not Receiving Vasopressors for ≥ 12 h	
		Average Urine Output < 0.5 mL/kg/h	Average Urine Output ≥ 0.5 mL/kg/h
≥ 8	> 12	Furosemide†; reassess in 1 h	Furosemide; reassess in 4 h
4–8	8–12	Fluid bolus as fast as possible‡; reassess in 1 h	Furosemide; reassess in 4 h
≤ 4	< 8	Fluid bolus as fast as possible‡; reassess in 1 h	No intervention; reassess in 4 h

(CHEST 2007; 131:913–920)

Steroids

❖ Early

- Improved oxygenation
- More ventilator free & shock free days

Metaanalysis by Tang BM et al.

- Lower overall relative risk for death, ICU LOS, and multiple organ dysfunction scale score
- No increase in infection, neuromyopathy, or major complications with corticosteroids.

- Meduri GU et al. JAMA. 1998;280(2):159- 165
- Tang BM et al. Crit Care Med. 2009;37(5):1594-1603
- Steinberg KP et al. N Engl J Med. 2006;354(16):1671- 1684.

Table 3
Methylprednisolone treatment of early ARDS and unresolving ARDS

Time	Administration form	Dosage
Early severe ARDS (PaO_2:FiO_2 <200 on positive end-expiratory pressure 10 cm H_2O)		
Loading	Bolus over 30 min	1 mg/kg
Days 1–14[abc]	Infusion at 10 mL/h	1 mg/kg/d
Days 15–21[ac]	Infusion at 10 mL/h	0.5 mg/kg/d
Days 22–25[ac]	Infusion at 10 mL/h	0.25 mg/kg/d
Days 26–28[ac]	Infusion at 10 mL/h	0.125 mg/kg/d
Unresolving ARDS (less than one-point reduction in lung injury score by day 7 of ARDS)		
Loading	Bolus over 30 min	2 mg/kg
Days 1–14[abc]	Infusion at 10 mL/h	2 mg/kg/d
Days 15–21[ac]	Infusion at 10 mL/h	1 mg/kg/d
Days 22–25[ac]	Infusion at 10 mL/h	0.5 mg/kg/d
Days 26–28[ac]	Infusion at 10 mL/h	0.25 mg/kg/d
Days 29–30[ac]	Bolus over 30 min	0.125 mg/kg/d

Marik PE et al. Crit Care Clin 27 (2011) 589–607