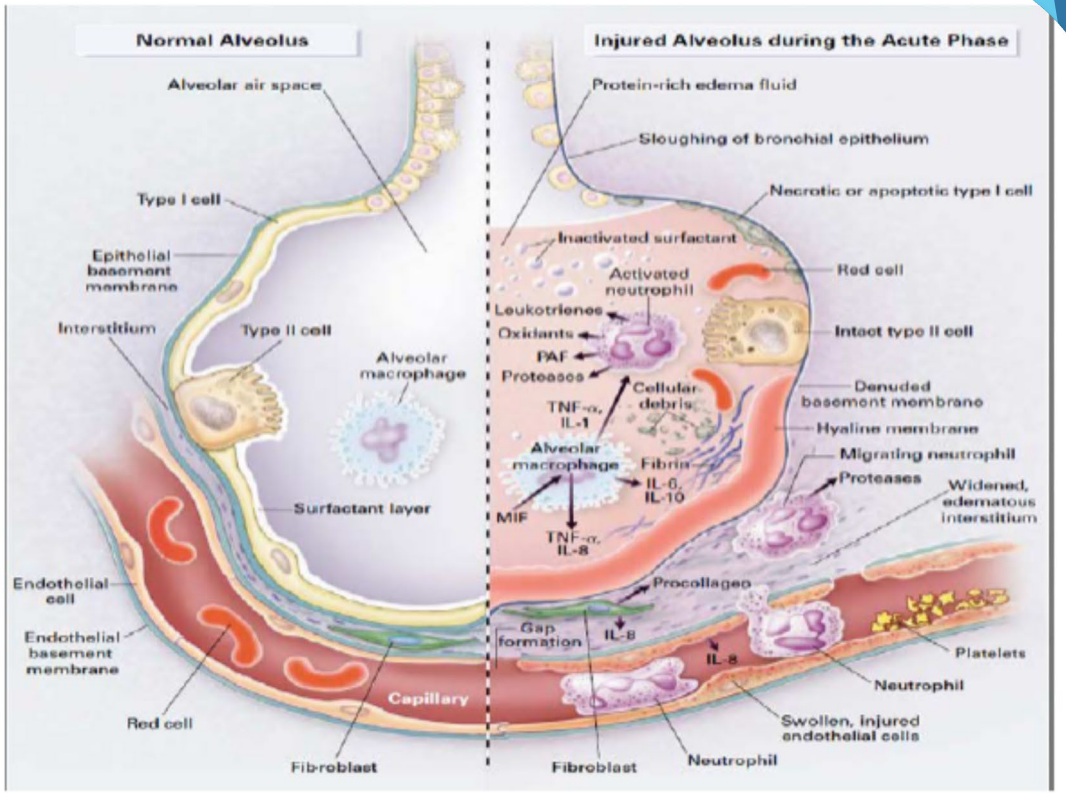
Pediatric Acute Respiratory Distress Syndrome (pARDS)

Kari Wellnitz, MD

October 2022

Overview: what is ARDS?

- Clinical syndrome characterized by diffuse inflammation in the lung
- Results in significant hypoxemia from endothelial injury to the pulmonary vasculature and alveolar epithelial injury
- No definitive diagnostic test (i.e. biomarker) which is present in all cases (even histopathology inconsistent)



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Epidemiology and Diagnosis

1994 American-European Consensus Conference (AECC) Definition

	AECC Definition	Patho Physiologic Concept
Timing	Acute onset	Differentiate from Chronic Disease
ALI vs. ARDS	ALI: PaO_2/FiO_2<300 ARDS: PaO_2/FiO_2<200	Severity of Disease
Oxygenation	$PaO_2/FiO_2 \leq 300$ mmHg (regardless of PEEP)	No tie to FRC/EELV
Chest Radiograph	Bilateral infiltrates seen on frontal chest radiograph	Differentiate from Lobar process
PAWP	PAWP ≤ 18 mmHg when measured or no clinical evidence of left atrial hypertension	Not explained by Heart Failure
Risk Factor	None	Cause for endothelial or epithelial injury

Final Berlin Definition of ARDS

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 $<$ Pa_{O_2}/F_{IO_2} $\leq$ 300 mm Hg with PEEP or CPAP $\geq$5 cm H_2O[c]
Moderate	100 mm Hg $<$ Pa_{O_2}/F_{IO_2} $\leq$ 200 mm Hg with PEEP $\geq$5 cm H_2O
Severe	Pa_{O_2}/F_{IO_2} $\leq$ 100 mm Hg with PEEP $\geq$5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; F_{IO_2}, fraction of inspired oxygen; Pa_{O_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: [Pa_{O_2}/F_{IO_2} × (barometric pressure/760)].

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

Limited validation in pediatric patients

Pediatric Acute Respiratory Distress Syndrome: Consensus Recommendations From the Pediatric Acute Lung Injury Consensus Conference

The Pediatric Acute Lung Injury Consensus Conference Group

Pediatric Critical Care Medicine

PALICC pARDS Definition (2015)

Age	Exclude patients with peri-natal related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	**Non Invasive mechanical ventilation**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	Mild	Moderate	Severe
	Full face-mask bi-level ventilation or CPAP ≥5 cm H_20 [2] PF ratio ≤ 300 SF ratio ≤ 264 [1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI < 16 7.5 ≤ OSI < 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
Special Populations				
Cyanotic Heart Disease	Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease. [3]			
Chronic Lung Disease	Standard Criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.[3]			
Left Ventricular dysfunction	Standard Criteria for age, timing and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction.			

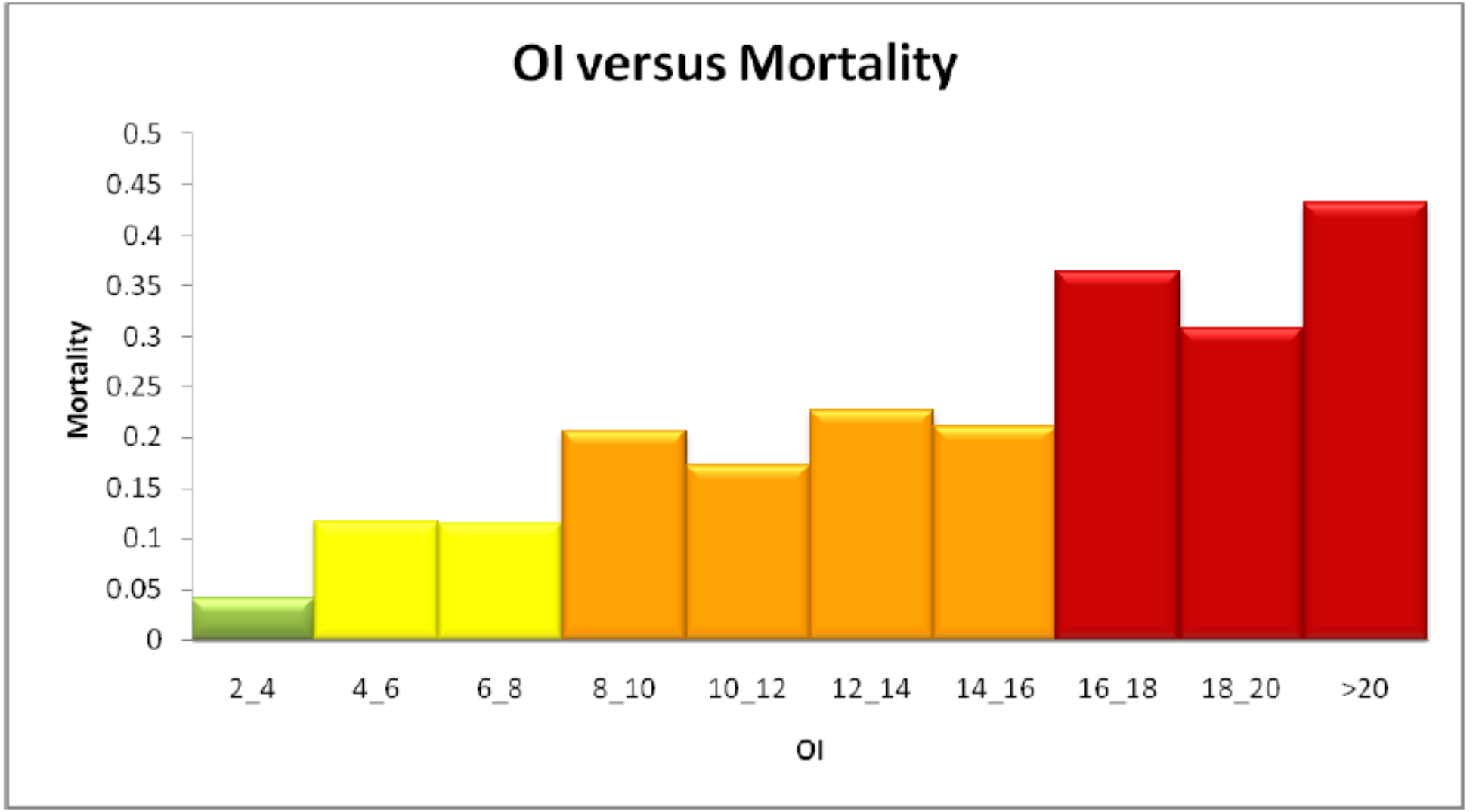
Oxygenation Index and Oxygen Saturation Index

- **Oxygenation index (OI):** (FiO_2 x Mean Airway Pressure x 100)/ PaO_2

No arterial line?

- **Oxygen saturation index (OSI):** (SpO_2 x Mean Airway Pressure x 100)/ PaO_2

Why use OI in pediatric ARDS definition?



How useful is the pediatric definition?

Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study

Robinder G Khemani, Lincoln Smith, Yolanda M Lopez-Fernandez, Jeni Kwok, Rica Morzov, Margaret J Klein, Nadir Yehya, Douglas Willson, Martin C J Kneyber, Jon Lillie, Analia Fernandez, Christopher J L Newth, Philippe Jouvet, Neal J Thomas, on behalf of the Pediatric Acute Respiratory Distress syndrome Incidence and Epidemiology (PARDIE) Investigators and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network*

- The PALICC definition identified more children as having PARDS than the Berlin definition
- PALICC PARDS severity groupings improved the stratification of mortality risk, particularly when applied 6 h after PARDS diagnosis.

[1] If PaO_2 not available, wean FiO_2 to maintain SpO2 ≤ 97% to calculate OSI
[2] Given lack of available data, for patients on an oxygen blender, flow for at risk calculation = FiO_2 * FlowRate (L/min) (e.g. 6L/min flow at 0.35 FiO_2 = 2.1 L/min)

At Risk for pARDS

Age	Exclude patients with peri-natal related lung disease		
Timing	Within 7 days of known clinical insult		
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload		
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease		
Oxygenation	**Non Invasive mechanical ventilation**		**Invasive mechanical Ventilation**
	Nasal mask CPAP or BiPAP	Oxygen via mask, nasal cannula or High Flow	Oxygen supplementation to maintain SpO_2 ≥ 88% but OI < 4 or OSI < 5[1]
	FiO_2 ≥ 40% to attain SpO_2 88-97%	SpO_2 88-97% with oxygen supplementation at minimum flow[2]: < 1 year: 2 L/min 1 – 5 years: 4 L/min 5 – 10 years: 6 L/min >10 years: 8 L/min	

pARDS: Triggers and Timing

- Most commonly presents at the time of hospital/ICU admission
  - Remainder of cases identified within the first week following admission
  - Very rapid progression to PARDS may be seen in transfusion related acute lung injury, neurogenic pulmonary edema, near drowning

Epidemiology in Children

First Author (reference)	Goh (87)	Costil (88)	Dahlem (4)	Flori (26)	ANZICS (5)
# Centers	Single center-2 yr	Multicenter-2 yrs	Single center	2 center-2, 4 yrs	Multicenter-1 yr
Entry criteria	LIS-AECC (ARDS)	MV, FIO_2 0.5, CXR	AECC and MV	AECC	AECC and MV
Number of patients	n = 21	n = 123	n = 44	n = 320	n = 117
Frequency (% admissions)	4.2%	2%	4%	NA	2.2%
Etiology	Sepsis 43% Pneumonia 33%	Pneumonia 65% Sepsis 16%	Sepsis 34% RSV 16%	Pneumonia 35% Sepsis 13%	LRTI (56%) Sepsis 19%
Mortality	62% (ARDS)	60%	27% (ARDS 31%)	22% (ARDS 29%)	35% (ARDS 39%)
Mortality predictors	P/F ratio MOF PRISM score	P/F ratio	P/F ratio MOF PRISM score	P/F ratio MOF pH	P/F ratio and OI MOF pH

- 2-4% of all PICU admissions have ALI/ARDS
- Mechanically ventilated children (>12-24h)
  - ARDS: 2-7%
  - ALI: 6-10%
- LRTI most common trigger
- Indirect Lung Injury from Sepsis also common, with worse prognosis (? More likely MODS)
- RCT versus observational data mortality range 8-30%
  - RCTs: 8% (prone); 28% (Calfactant–with BMT); 14% (Calfactant–no BMT)
  - Observational: Lopez-Fernandez (28%), Flori (23%), Erickson (30%), Khemani (20%, 22%)

Randolph 2009, 2003, Farias 2004, Dahlem 2003, Erickson 2007, Curley 2005, Willson 2005, Lopez-Fernandez 2012, Flori 2005, Khemani 2009, 2014

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	Survivors (n=587)	Non-survivors (n=121)	Total (n=708)	Mortality (%)	p value*
PARDS risk factor					
Pneumonia or lower respiratory tract infection	393 (67%)	52 (43%)	445 (63%)	12%	<0·0001
Sepsis	95 (16%)	41 (34%)	136 (19%)	30%	<0·0001
Aspiration	47 (8%)	13 (11%)	60 (8%)	22%	0·33
Trauma	24 (4·1%)	3 (2%)	27 (4%)	11%	0·60
Drowning	2 (<1%)	4 (3%)	6 (1%)	67%	0·0092
Non-septic shock	4 (1%)	6 (5%)	10 (1%)	60%	0·0026
Other	22 (4%)	2 (2%)	24 (3%)	8%	0·41

Lancet Respiratory Medicine, 2019-02-01, Volume 7, Issue 2, Pages 115-128

	Odds ratio (95% CI)	p value
Severe PARDS at onset	3·04 (1·89–4·87)	<0·0001
Middle-income country	2·85 (1·56–5·22)	0·0008
PARDS risk factor of pneumonia	0·48 (0·30–0·76)	0·0022
PARDS risk factor of non-septic shock	10·9 (2·56–46·5)	0·0012
PARDS risk factor of drowning	12·7 (2·0–79·4)	0·0078
Immune suppression	6·3 (3·6–11·2)	<0·0001

All variables adjusted for individual paediatric intensive care unit as a random effect in the hierarchical model. Vasoactive medication was not considered for inclusion in this model, since data was only available for 621 of 708 patients. PIM 3 score was also not included because PF ratio and immune suppression are components of the score, and the primary goal was to evaluate whether PARDS severity is independently associated with mortality (which has significant overlap with PF ratio). The ratio of generalised χ^2 to degrees of freedom is 0·85, indicating that the variability in data has been properly modelled, with no residual over dispersion. PARDS=paediatric acute respiratory distress syndrome. PIM 3=paediatric index of mortality 3. PF ratio=ratio of partial pressure of oxygen (PaO_2) to fractional concentration of oxygen (FiO_2).

Table 4: **Independent risk factors for mortality at PARDS diagnosis**

PARDIE continued….

- Of the 708 patients that met PALICC criteria for pARDS, only 208 (32%) met Berlin criteria.
  - **Mortality 17%** in those meeting **PALICC** definition **vs 27%** in those meeting Berlin criteria
- Based on hypoxaemia severity at PARDS diagnosis, **mortality was similar** among those who were **non-invasively ventilated and with mild or moderate PARDS** (10-15%), but **higher for those with severe PARDS** (33% [54 of 165; 95% CI 26-41]).
- **50% (80 of 160) of non-invasively ventilated patients** with PARDS were **subsequently intubated**, with **25%** (20 of 80; 95% CI 16-36**) mortality.**
- By **use of PALICC PARDS definition, severity of PARDS at 6 h after initial diagnosis** (area under the curve [AUC] 0·69, 95% CI 0·62-0·76) **discriminates PICU mortality better than severity at PARDS diagnosis** (AUC 0·64, 0·58-0·71**), and outperforms Berlin severity groups at 6 h** (0·64, 0·58-0·70; p=0·01).

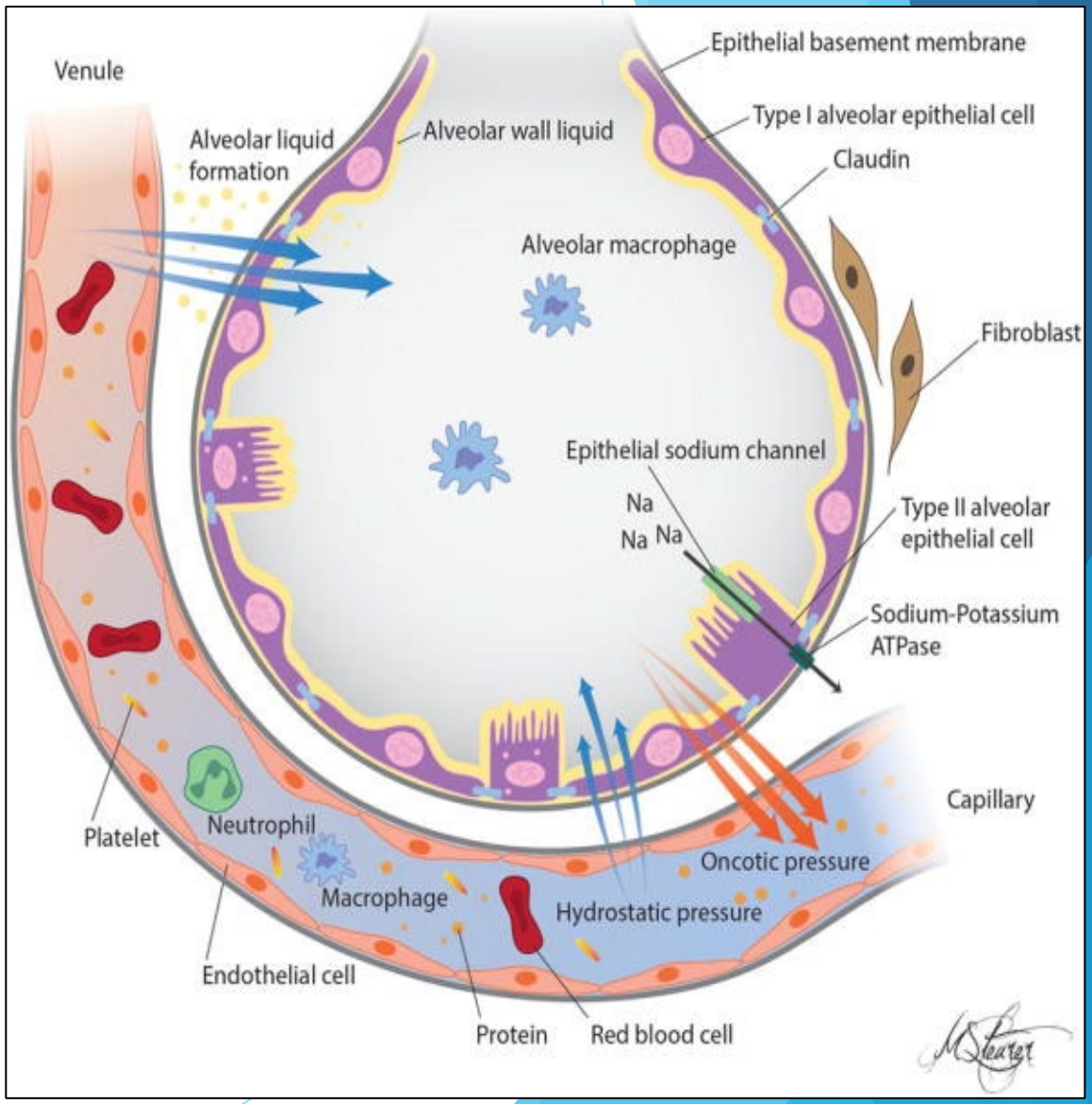
Pathophysiology of pARDS

Hallmark Symptoms of pARDS Pathophysiology

- Hypoxemia (due to shunt)
- Poor respiratory system compliance
- Decreased FRC
- Diffuse process
- Alveolar and interstitial edema
- Epithelial injury
- Increased alveolar dead space

Normal Lung

- Intact epithelial-endothelial barrier and pulmonary circulation allow for formation of **alveolar wall liquid (AWL)** while **maintaining the air-filled, fluid-free, status of the alveoli**
- The AWL **facilitates gas exchange** and is a medium for **dispersal of surfactant and alveolar macrophages**, which is essential for maintaining alveolar stability and host defenses.
- **Intact sodium-dependent vectorial transport** across type II alveolar epithelial cells **regulates the removal of excess alveolar fluid**



Pathophysiology of pARDS

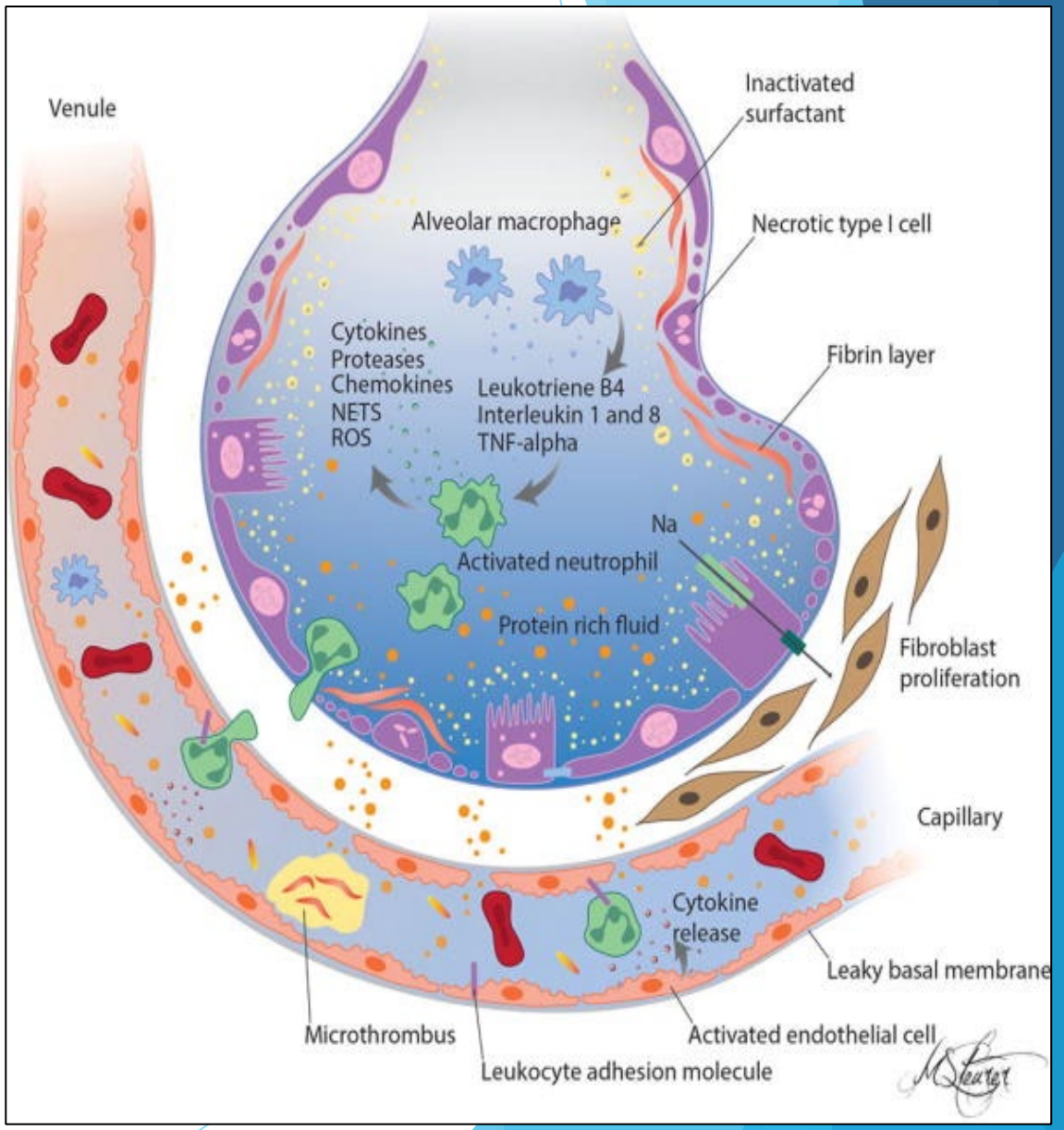
- **Loss of epithelial and endothelial barrier integrity and function**→ increased permeability

- In presence of **proinflammatory mediators and activated endothelium, leukocytes traffic into the pulmonary interstitium and alveoli**

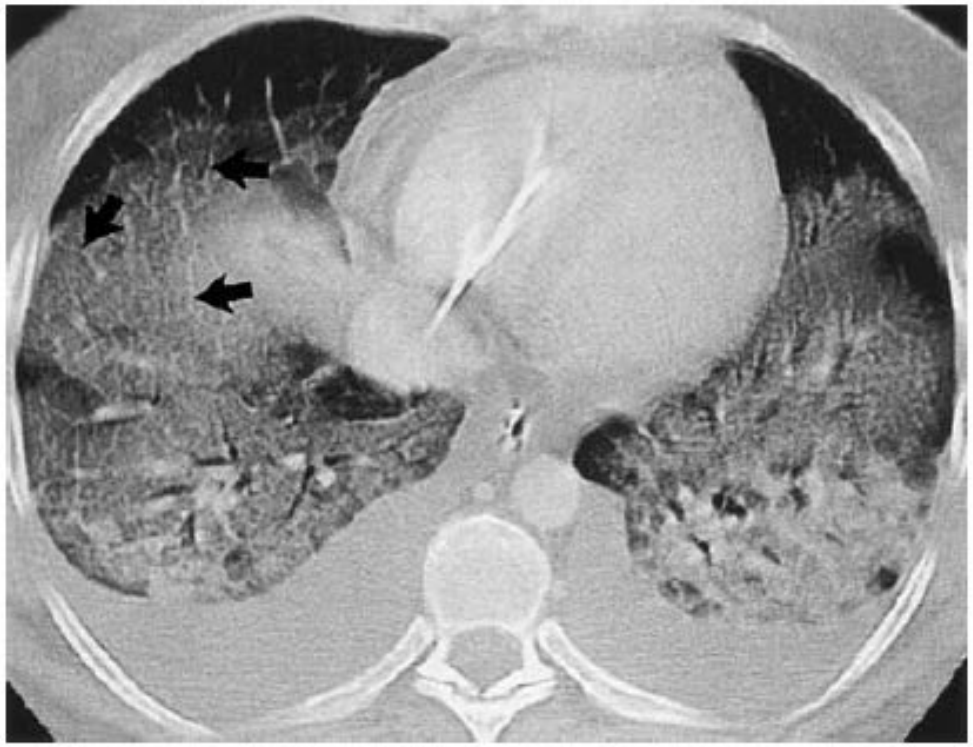
- **Activation of coagulation cascade and deposition of fibrin** in capillaries and alveoli

- **Surfactant depletion and degradation**→ large increases in surface tension and loss of alveolar shape and integrity

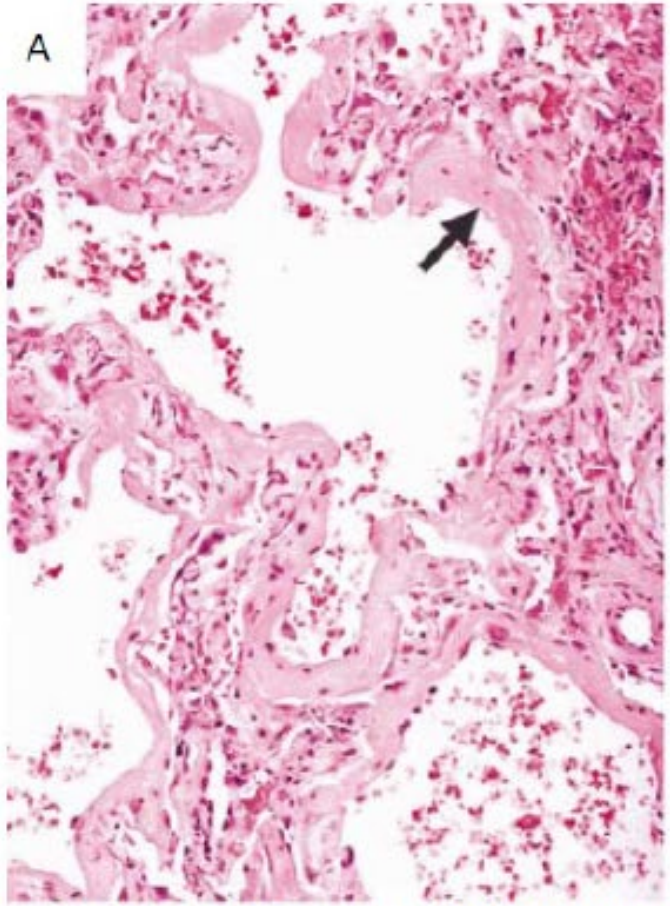
- **Recovery is preceded by fibroblast proliferation**



Phases of ARDS–Acute (Exudative) Phase



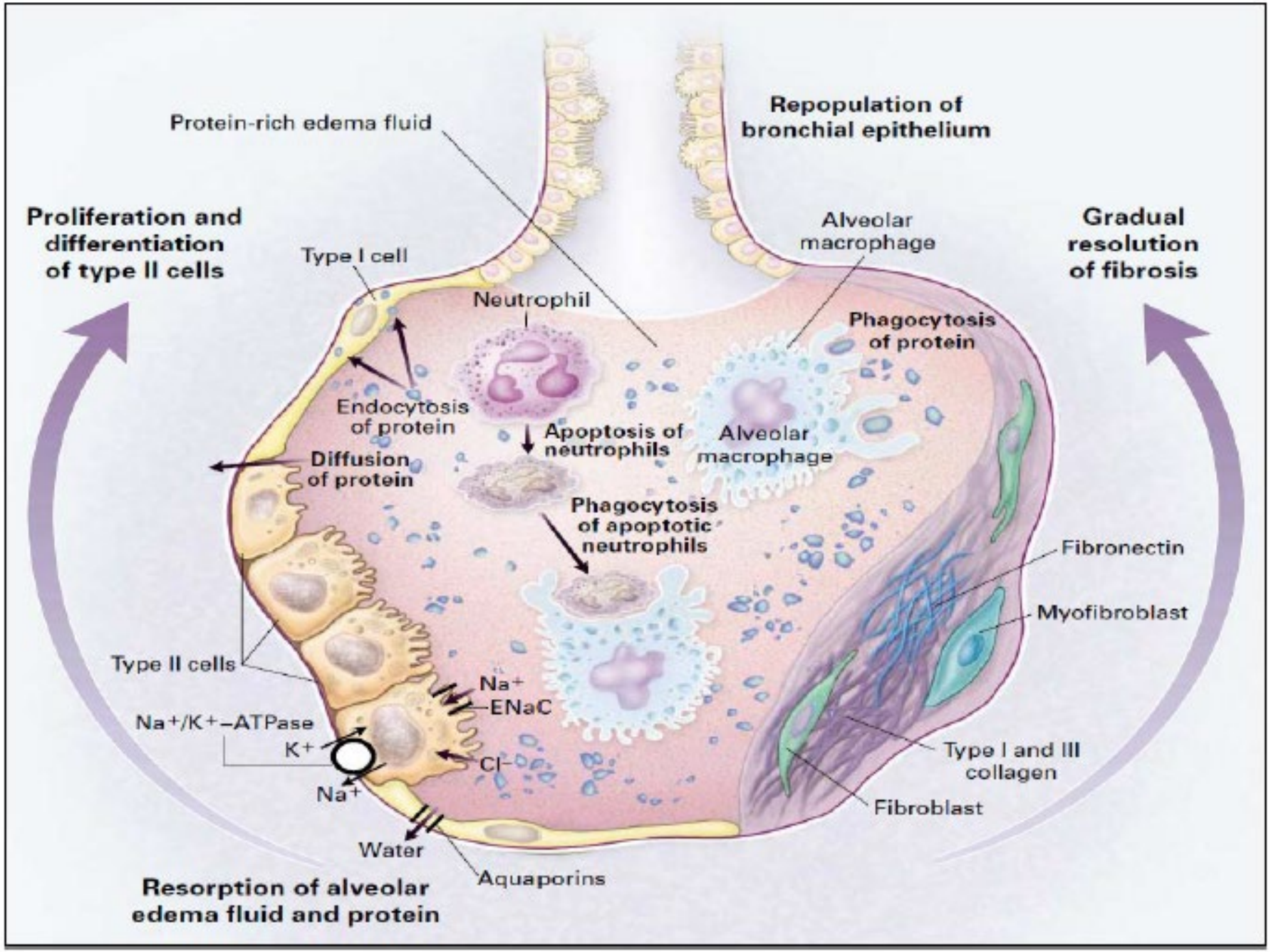
Rapid onset
Edema, effusions, patchy infiltrates on chest film or CT. Mostly in dependent regions of lungs, with relative sparing of other areas radiographically, although may be substantial inflammation.



Diffuse alveolar damage, PMNS, macrophages and hyaline membranes, edema in alveolar spaces, disruption of alveolar epithelium

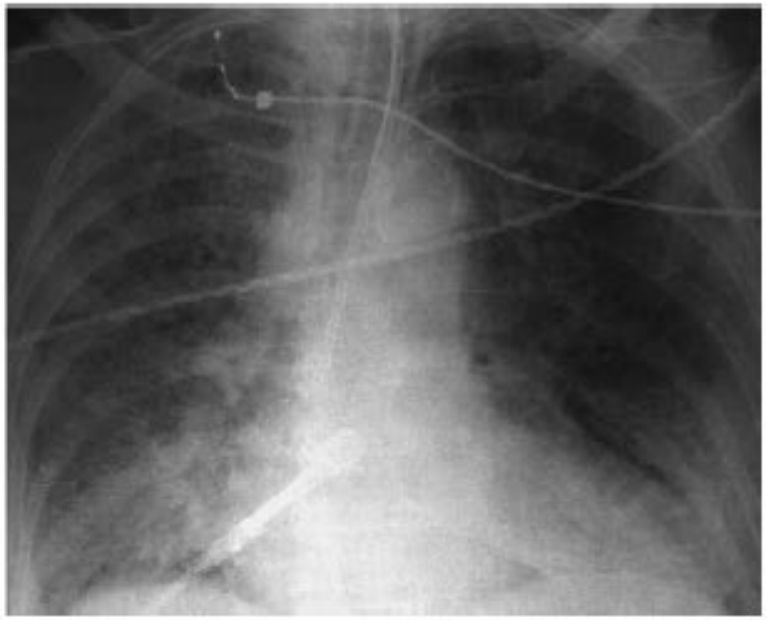
Ware 2000.

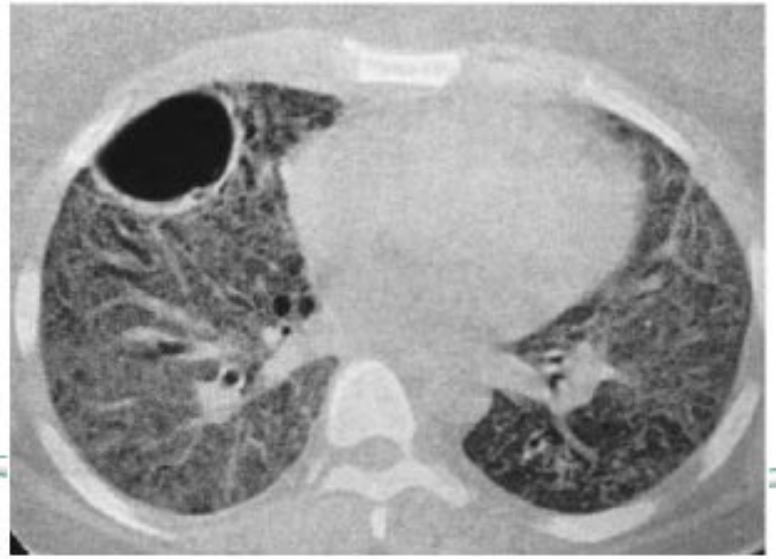
Society of Critical Care Medicine

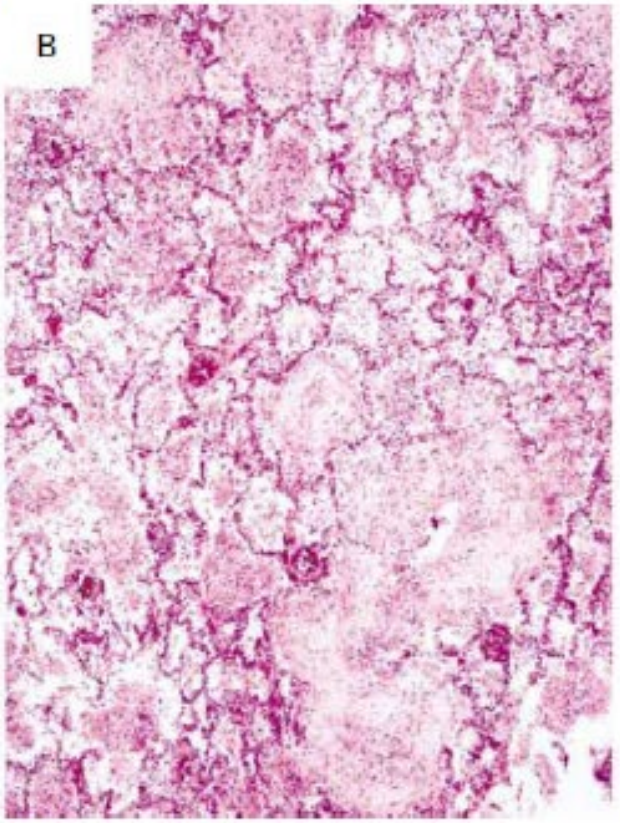

Protein-rich edema fluid
Repopulation of bronchial epithelium
Proliferation and differentiation of type II cells
Gradual resolution of fibrosis
Type I cell
Alveolar macrophage
Neutrophil
Phagocytosis of protein
Endocytosis of protein
Apoptosis of neutrophils
Alveolar macrophage
Diffusion of protein
Phagocytosis of apoptotic neutrophils
Fibronectin
Myofibroblast
Type II cells
Na+
ENaC
Na+/K+–ATPase
K+
Cl–
Na+
Type I and III collagen
Fibroblast
Water
Aquaporins
Resorption of alveolar edema fluid and protein

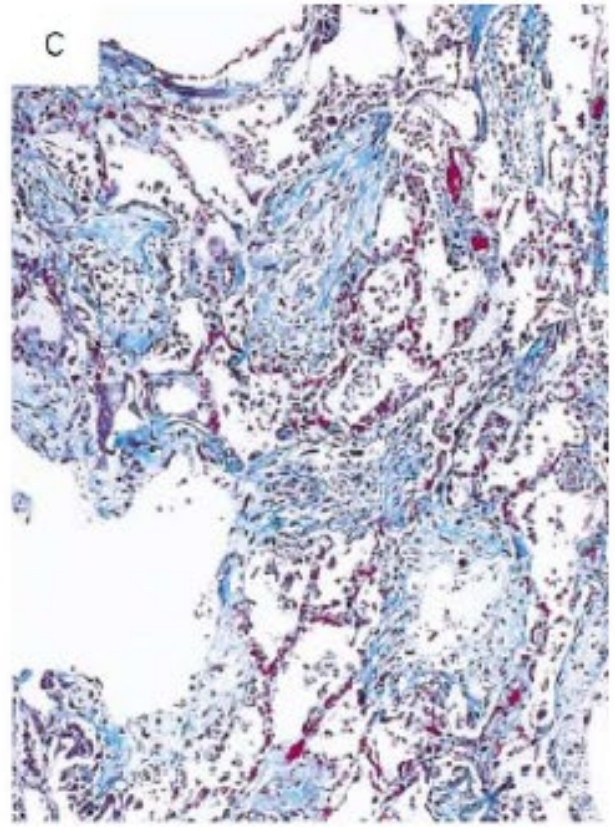
Ware 2000

Phases- Fibrosing Alveolitis









Persistent Hypoxemia, increased dead space, worsening compliance, some pulm htn Linear opacities on CXR- evolving fibrosis. CT- diffuse interstitial opacities, bullae. Acute and Chronic Inflammation, Fibrosis.

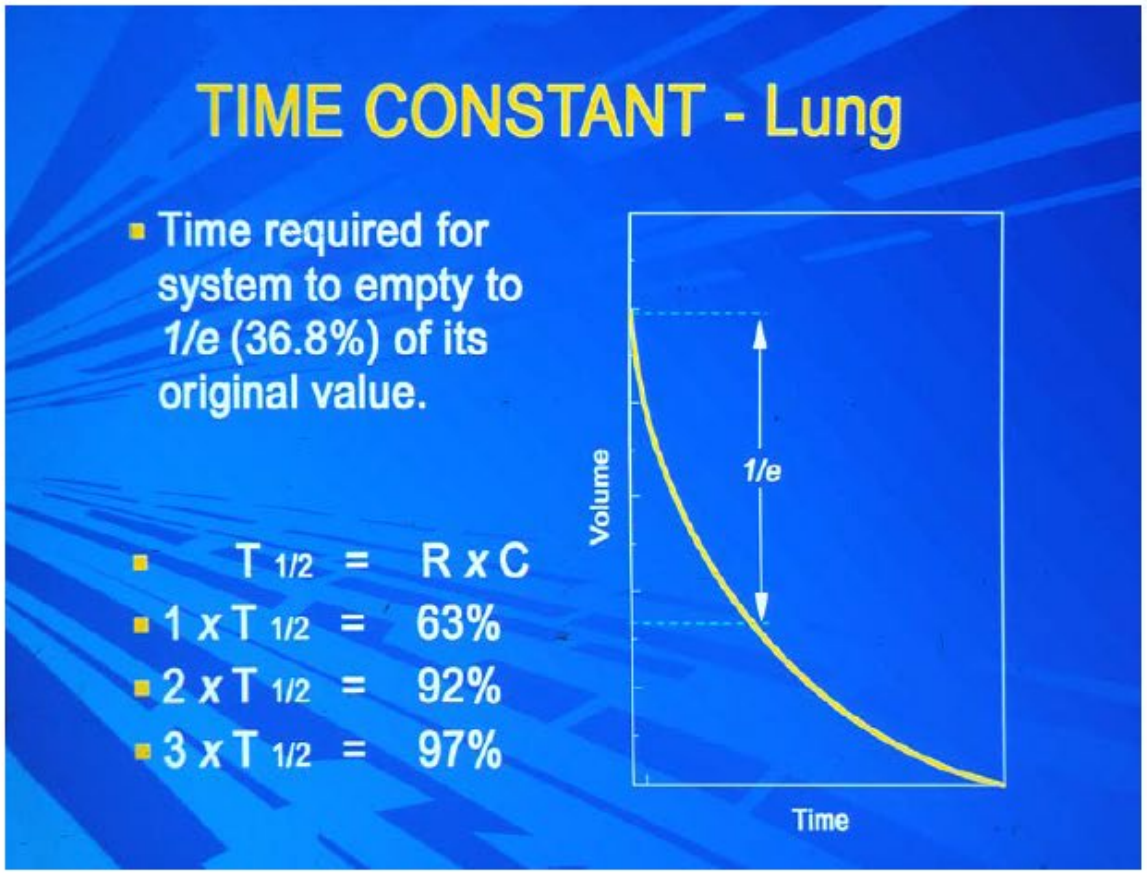
Ware 2000

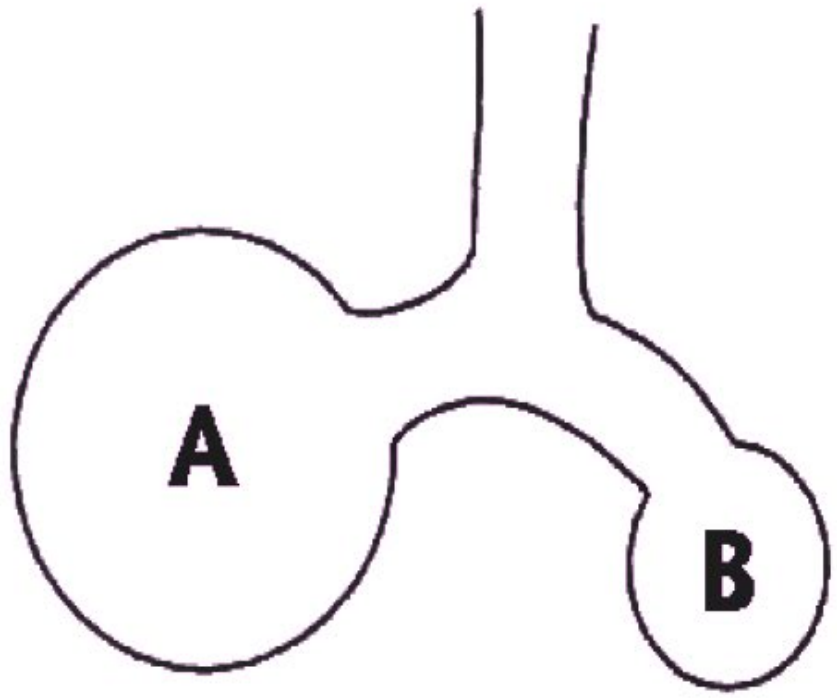
What About Ventilator Induced Lung Injury?

- Toxic effects of high fractions of inspired oxygen
- High volume or pressure relating to increased permeability and edema in the injured lung
- Capillary stress failure from over distention
- Cyclic opening and closing of atelectatic alveoli
- Alveolar overdistention plus cyclic opening and closing leads to increase in pro-inflammatory cytokines

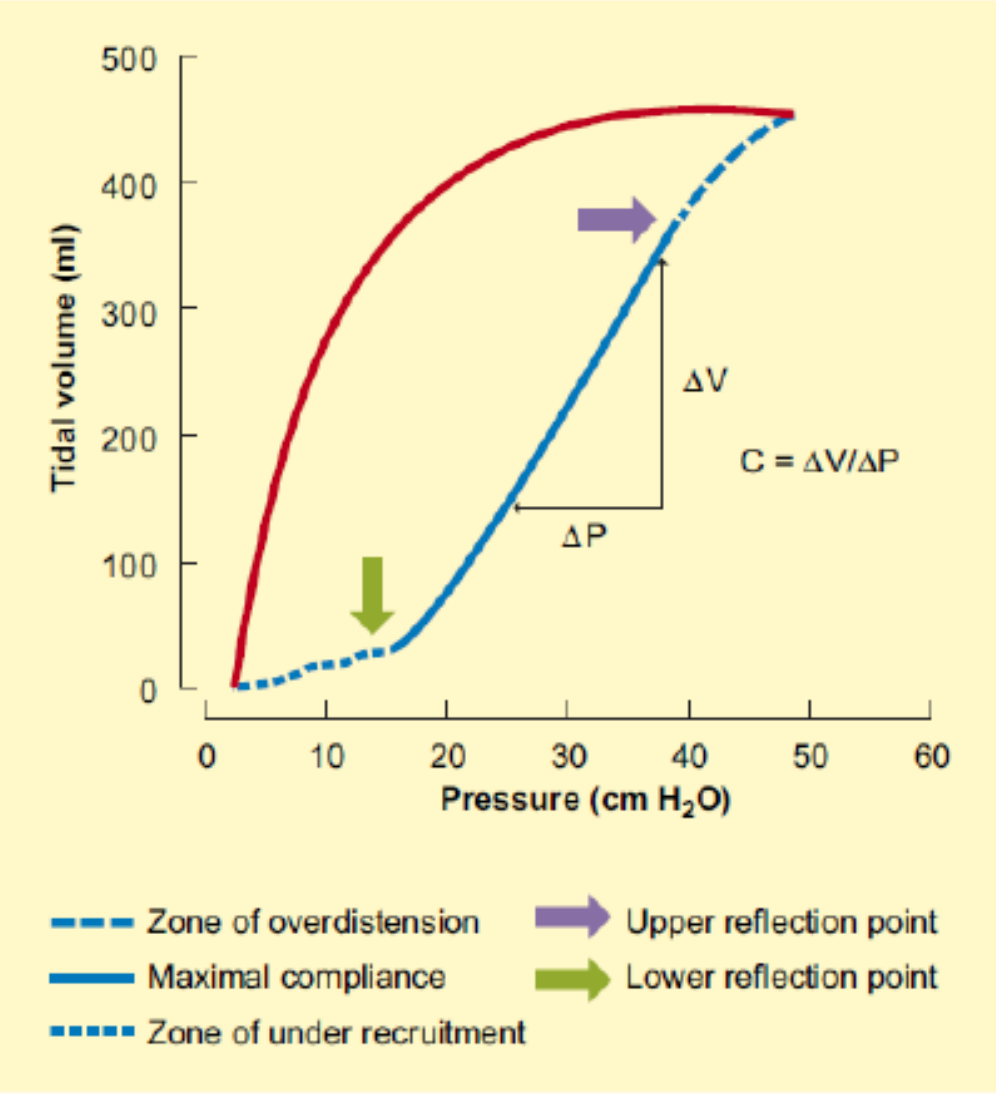
Ware 2000.

In an attempt to inflate lung unit B, Lung Unit A becomes exposed to higher tidal volume and becomes over-distended.





Ventilating in a Safe Zone



- Lower inflection point
  - Alveolar closing pressure below this
  - Apply enough PEEP
- Upper inflection point
  - Risk for over distention above
  - Limit pressure/volume

Based on quasi-static/static V-P curve

Khemani, Bart, Newth 2007.

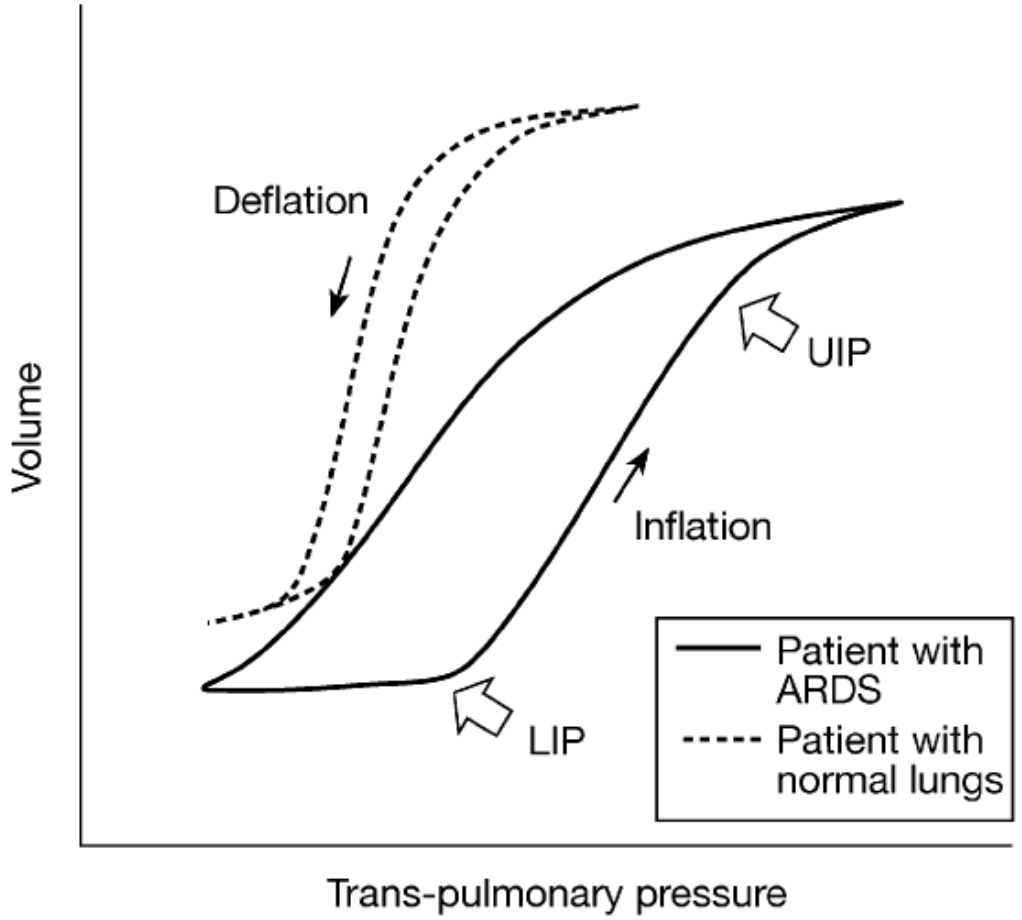


Fig 3 Schematic representation of a static pressure–volume curve of the respiratory system from a patient with normal lungs and from a patient with ARDS. The patient with ARDS has a lower functional residual capacity, decreased compliance and increased hysteresis. Note the lower and upper inflection points of the inspiratory limb in the patient with ARDS. LIP=lower inflection point; UIP=upper inflection point.

Mechanical Ventilation in pARDS

- Current management based primarily on data derived from adult studies
- Lung protective strategies
  - Low tidal volumes
  - Minimize peak pressures/permissive hypercapnia
  - Higher PEEPs

VENTILATORY STRATEGIES DURING CONVENTIONAL VENTILATION

Tidal Volume Delivery

Recommendations:

3.2.1 In any mechanically ventilated pediatric patient, we recommend in controlled ventilation to use tidal volumes in or below the range of physiologic tidal volumes for age/body weight (i.e., 5 to 8 mL/kg predicted body weight [PBW) according to lung pathology and respiratory system compliance. *Weak agreement (88% agreement)*

3.2.2 We recommend to use patient-specific tidal volumes according to disease severity. Tidal volumes should be 3–6 mL/kg PBW for patients with poor respiratory system compliance and closer to the physiologic range (5–8 mL/kg ideal body weight) for patients with better preserved respiratory system compliance. *Weak agreement (84% agreement)*

Adult Data on VT

- 5 RCTs comparing high vs low VT strategies
  - 3 have shown no benefit on mortality or VFD
    - Mean of 10.2-10.6 ml/kg vs 7.2-7.3 ml/kg
  - 2 trials with benefit were closer to 6 vs 12
    - The mean tidal volume of the control group in both of these studies increased by 17-18% after randomization, with increases in the plateau pressures of 4-6 cm H_20
    - Successful trials not only limited V_T, but also limited plateau pressure to <30 cmH_20

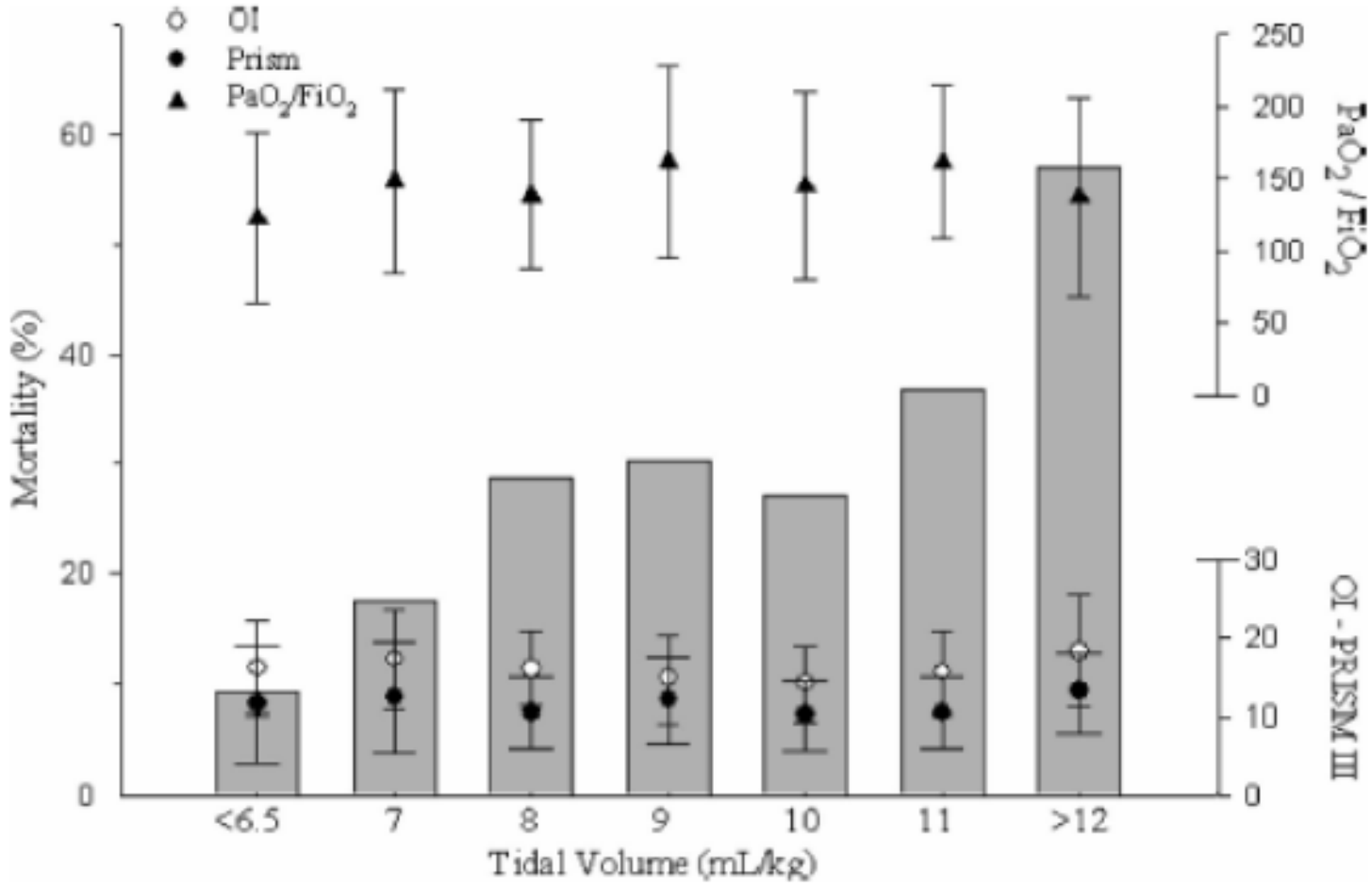
Low tidal volume: 2000 NEJM ARDS Network study

- "In patients with acute lung injury and the acute respiratory distress syndrome, mechanical ventilation with a **lower tidal volume** than is traditionally used results in **decreased mortality** and **increases the number of days without ventilator use.**"

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

Pediatric Historical Data
VT 11-12 ml/kg Harmful



Albuali 2007.

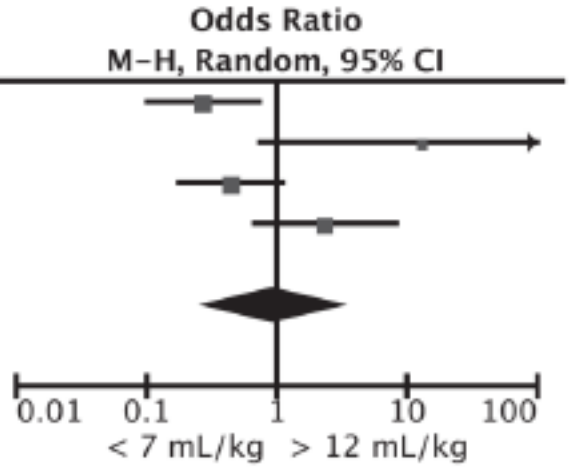
Tidal Volume and Mortality in Mechanically Ventilated Children: A Systematic Review and Meta-Analysis of Observational Studies*

Critical Care Medicine
December 2014 • Volume 42 • Number 12

Pauline de Jager, MD[1]; Johannes G. M. Burgerhof, MSc[2]; Marc van Heerde, MD, PhD[3]; Marcel J. I. J. Albers, MD, PhD[4]; Dick G. Markhorst, MD, PhD[3]; Martin C. J. Kneyber, MD, PhD[1,3,5]

Study or Subgroup	< 7 mL/kg Events	Total	> 10 mL/kg Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Albuali 2007	38	140	11	19	29.6%	0.27 [0.10, 0.72]
Erickson 2007	27	79	0	12	13.3%	13.10 [0.75, 229.60]
Flori	7	43	28	92	30.2%	0.44 [0.18, 1.12]
Khemani 2009	44	181	3	25	26.9%	2.36 [0.67, 8.25]
Total (95% CI)		**443**		**148**	**100.0%**	**0.94 [0.25, 3.52]**
Total events	116		42			

Heterogeneity: $Tau^2 = 1.28$; $Chi^2 = 12.80$, df = 3 (P = 0.005); $I^2 = 77\%$
Test for overall effect: Z = 0.09 (P = 0.93)



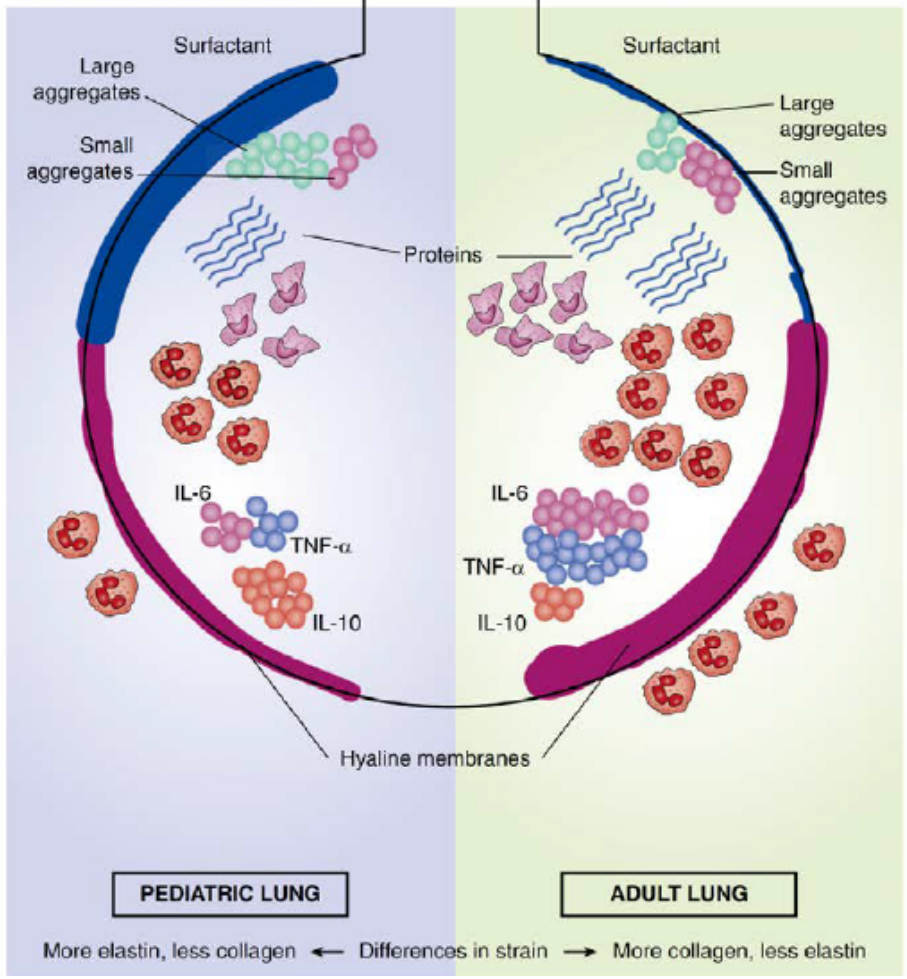
- Multitude of subgroup analysis exploring various V_T cut points
- No clear relationship between V_T and mortality, regardless of ARDS severity

Ventilator-induced Lung Injury

Similarity and Differences between Children and Adults

Martin C. J. Kneyber[1,2,3], Haibo Zhang[1,4,5,6], and Arthur S. Slutsky[1,5]

American Journal of Respiratory and Critical Care Medicine Volume 190 Number 3 | August 1 2014



- Supra physiologic V_T harmful in pediatric animal models, but **younger animals less susceptible** than older animals to VILI
- Relatively **more surfactant** production in pediatric versus adult lung with high V_T
- **Fewer inflammatory cytokines** in pediatric versus adult lung with high $_{VT}$
- Difference in **elastin and collagen** in pediatric versus adult lung
- **Higher endothelial injury** and coagulopathy in pediatric animal models of high V_T

VENTILATORY STRATEGIES DURING CONVENTIONAL VENTILATION

Tidal Volume Delivery

Recommendations:

3.2.1 In any mechanically ventilated pediatric patient, we recommend in controlled ventilation to use tidal volumes in or below the range of physiologic tidal volumes for age/body weight (i.e., 5 to 8 mL/kg predicted body weight [PBW) according to lung pathology and respiratory system compliance. *Weak agreement (88% agreement)*

3.2.2 We recommend to use patient-specific tidal volumes according to disease severity. Tidal volumes should be 3–6 mL/kg PBW for patients with poor respiratory system compliance and closer to the physiologic range (5–8 mL/kg ideal body weight) for patients with better preserved respiratory system compliance. *Weak agreement (84% agreement)*

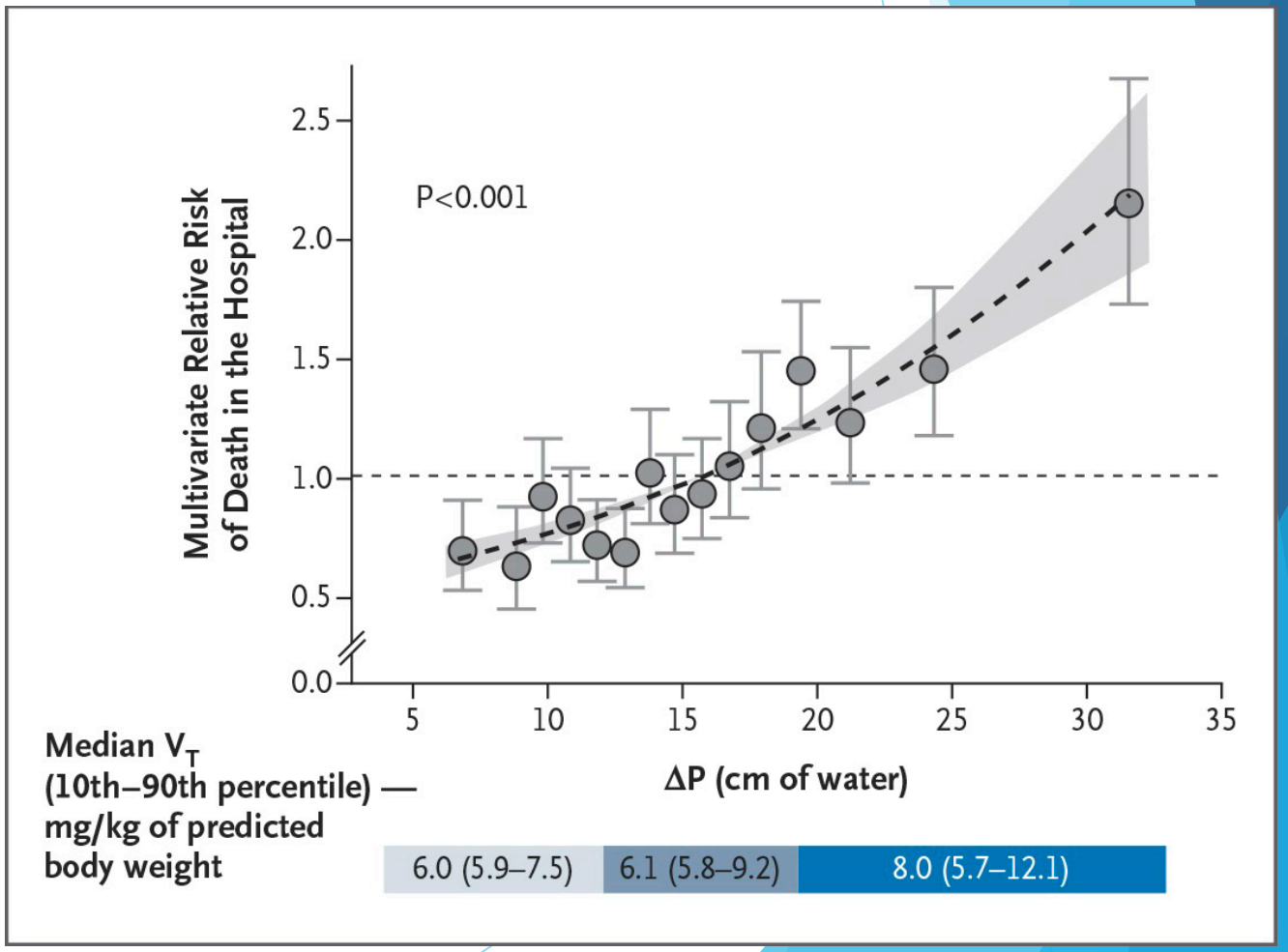
Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

Marcelo B.P. Amato, M.D., Maureen O. Meade, M.D., Arthur S. Slutsky, M.D.,

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 372;8 NEJM.ORG FEBRUARY 19, 2015

- Driving pressure (ΔP) = Plateau pressure- PEEP
- $=V_T/C_{RS}$
  - Index of the "functional" size of the lung



PIP and Mortality in PARDS

	Baseline All $n = 398$	Baseline Survived $n = 318$	Baseline Died $n = 80$	P value
Blood gas				
$PaCO_2$	45 (38, 53)	44 (38, 52)	46.5 (38, 57)	0.14
PaO_2	75 (61, 92)	77 (64, 94)	63.5 (53.5, 80)	<0.01
pH	7.35 (7.27, 7.40)	7.35 (7.29, 7.41)	7.29 (7.20, 7.36)	<0.01
BE	−2.1 (−5.3, 1.5)	−1.55 (−4.7, 1.85)	−4.6 (−8.8, −0.3)	<0.01
Vent support				
FiO_2	0.6 (0.4, 1)	0.5 (0.4, 0.9)	0.8 (0.5, 1)	<0.01
MAP	11 (9, 15)	11 (9, 14)	14 (9, 17)	<0.01
PIP	26 (22, 30.5)	26 (22, 30)	30 (24, 34)	<0.01
PEEP	6 (4, 8)	6 (4, 8)	8 (4, 10)	<0.01
V_T	7.45 (5.79, 9.14)	7.6 (5.86, 9.22)	7.04 (5.46, 8.74)	0.13
Injury marker				
PF ratio	138 (83, 192)	149 (95, 200)	80 (60, 147)	<0.01
OI	8.1 (5.1, 15.3)	7.4 (4.8, 13.1)	14.3 (7.9, 24.4)	<0.01
CRS	0.38 (0.27, 0.50)	0.38 (0.28, 0.51)	0.36 (0.23, 0.47)	0.086
LIS	2.33 (2, 3)	2.33 (1.67, 3)	3 (2.33, 3.33)	<0.01

PIP not associated with mortality when controlling for PF ratio

Intensive Care Med (2009) 35:1428–1437

Ventilatory Support in Children With Pediatric Acute Respiratory Distress Syndrome: Proceedings From the Pediatric Acute Lung Injury Consensus Conference

Peter C. Rimensberger, MD[1]; Ira M. Cheifetz, MD, FCCM[2]; for the Pediatric Acute Lung Injury Consensus Conference Group

Inspiratory Pressure

Recommendation:

3.2.3 In the absence of transpulmonary pressure measurements, we recommend an inspiratory plateau pressure limit of 28 cm H_2O, allowing for slightly higher plateau pressures (29–32 cm H_2O) for patients with increased chest wall elastance (i.e., reduced chest wall compliance). *Weak agreement (72% agreement)*

What About PEEP?

- Attempt to titrate PEEP above closing pressure
  - Controversy: PEEP of best compliance, PEEP where TPP is zero, where VD/VT lowest, oxygenation best?
  - Many adult studies showing CT evidence of increased lung recruitment with high PEEP strategies (but only some patients are recruitable)
- What is the evidence? Is there benefit for even higher PEEP versus "low" PEEP strategy?
  - No good pediatric evidence

Adult ARDSnet PEEP Trial

Table 1. Summary of Ventilator Procedures in the Lower- and Higher-PEEP Groups.*

Procedure	Value
Ventilator mode	Volume assist/control
Tidal-volume goal	6 ml/kg of predicted body weight
Plateau-pressure goal	≤30 cm of water
Ventilator rate and pH goal	6–35, adjusted to achieve arterial pH ≥7.30 if possible
Inspiration:expiration time	1:1–1:3
Oxygenation goal	
PaO_2	55–80 mm Hg
SpO_2	88–95%
Weaning	Weaning attempted by means of pressure support when level of arterial oxygenation acceptable with PEEP ≤8 cm of water and FiO_2 ≤0.40

Allowable combinations of PEEP and FiO_2†

Lower-PEEP group														
FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18–24
Higher-PEEP group (before protocol changed to use higher levels of PEEP)														
FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0	
PEEP	5	8	10	12	14	14	16	16	18	20	22	22	22–24	
Higher-PEEP group (after protocol changed to use higher levels of PEEP)														
FiO_2	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0				
PEEP	12	14	14	16	16	18	20	22	22	22–24				

ARDSnet PEEP

Table 4. Main Outcome Variables.*

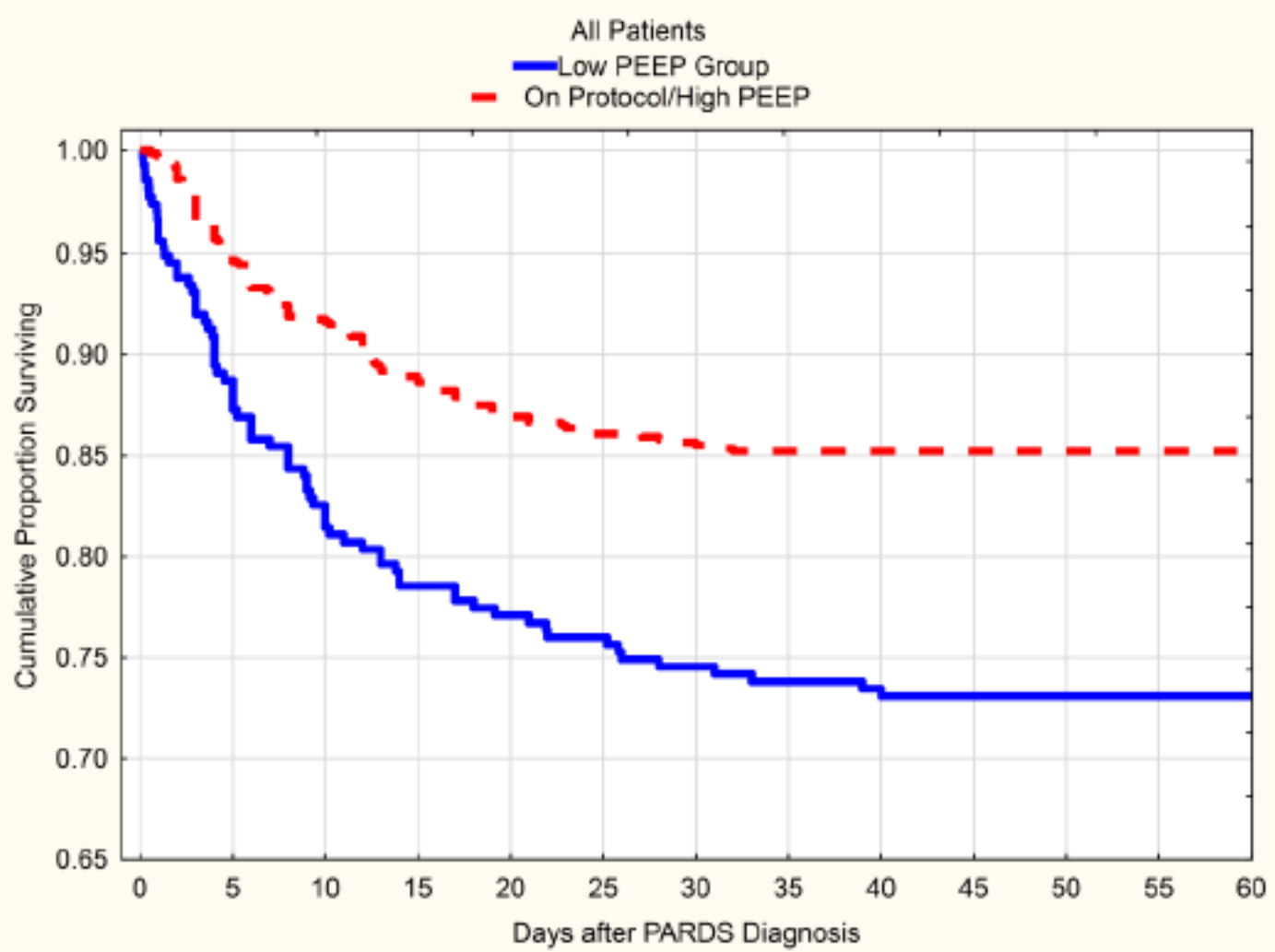
Outcome	Lower-PEEP Group	Higher-PEEP Group	P Value
Death before discharge home (%)†			
Unadjusted	24.9	27.5	0.48
Adjusted for differences in baseline covariates	27.5	25.1	0.47
Breathing without assistance by day 28 (%)	72.8	72.3	0.89
No. of ventilator-free days from day 1 to day 28‡	14.5±10.4	13.8±10.6	0.50
No. of days not spent in intensive care unit from day 1 to day 28	12.2±10.4	12.3±10.3	0.83
Barotrauma (%)§	10	11	0.51
No. of days without failure of circulatory, coagulation, hepatic, and renal organs from day 1 to day 28	16±11	16±11	0.82

- "No benefit" for high vs. lowPEEP
- "Low PEEP" is still pretty high by some standards

Am J Respir Crit Care Med. 2018 Jan 26. doi: 10.1164/rccm.201707-1404OC. [Epub ahead of print]

PEEP Lower Than the ARDS Network Protocol is Associated with Higher Pediatric ARDS Mortality.

Khemani RG[1], Parvathaneni K[2,3], Yehya N[4], Bhalla AK[5], Thomas NJ[6], Newth CJL[7].



PEEP lower than ARDSNet protocol independently associated with higher mortality OR 2.05 (95% CI 1.32,3.17)

Positive End-Expiratory Pressure

Recommendations:

3.3.1 We recommend moderately elevated levels of PEEP (10–15 cm H_2O) titrated to the observed oxygenation and hemodynamic response in patients with severe PARDS. *Weak agreement (88% agreement)*

3.3.2 We recommend that PEEP levels greater than 15 cm H_2O may be needed for severe PARDS although attention should be paid to limiting the plateau pressure as previously described. *Strong agreement*

3.3.3 We recommend that markers of oxygen delivery, respiratory system compliance, and hemodynamics should be closely monitored as PEEP is increased. *Strong agreement*

3.3.4 We recommend that clinical trials should be designed to assess the effects of elevated PEEP on outcome in the pediatric population. *Strong agreement*

Beyond the Ventilator: Management of Pediatric ARDS

Fluid Management

- Several observational (prospective and retrospective)pediatric trials demonstrating association with mortality and VFDs
- Adult RCT examining restrictive vs liberal fluid strategies, improvement in VFDs
- Other studies looking at albumin plus furosemide in adults who are hypoalbuminemic, no clear benefit on mortality of VFDs

Pediatric Prospective Observational Cohort Study

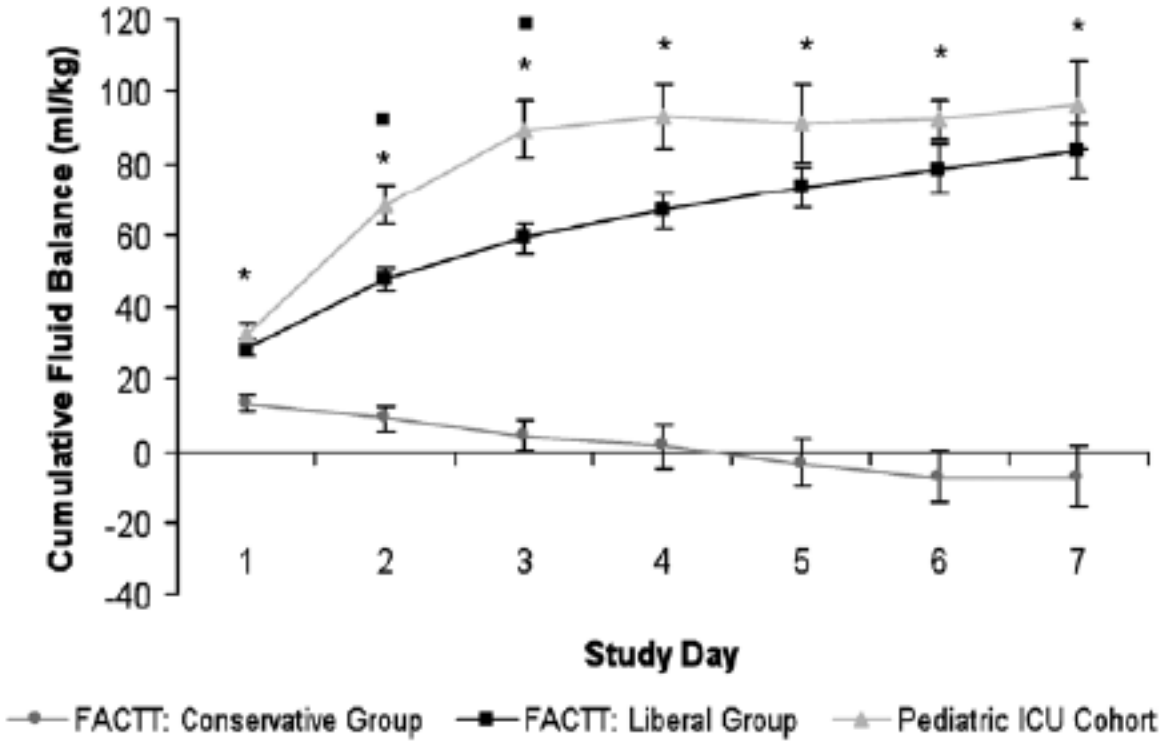


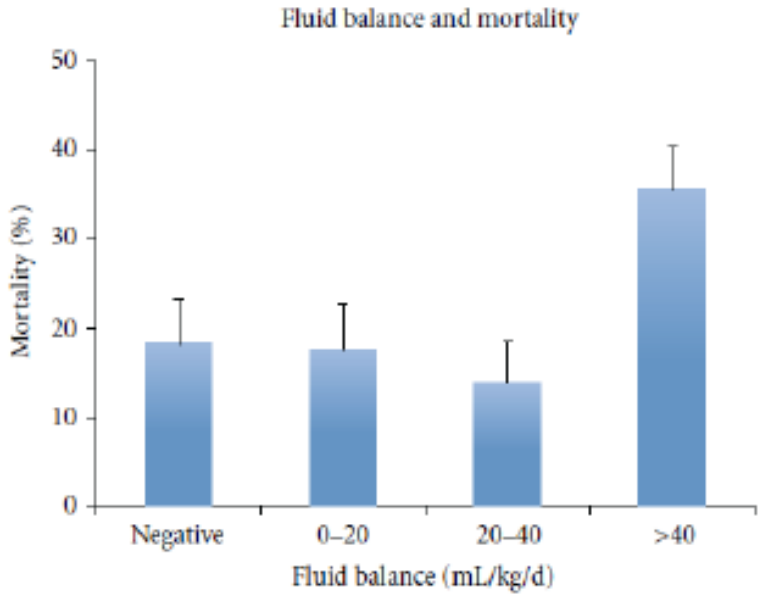
Table 3. Results of the multivariable analysis of factors associated with ventilator-free days

Clinical Covariates	Regression Coefficient	*p*
Cumulative day 3 fluid balance (mL/kg)	–0.02	.01
Pediatric Risk of Mortality III	–0.25	.03
Age (yrs)	–0.12	.35
Gender, male	0.16	.91
Race, white	–0.09	.95
Pao_2/Fio_2 at study entry	0.02	.08
Vasopressor use at study entry	–2.77	.08

Valentine *CCM* 2012.

Association between higher cumulative fluid balance and fewer ventilator free days

Pediatric Prospective Observational Cohort Study (Secondary Analysis)



TABLE

(a) Multivariate results for mortality

	Odds ratio (95% C.I.)	*P*-Value
PaO2/FiO2[1]	0.91 (0.82, 1.00)	.05
Other OSF[2]	1.90 (1.45, 2.49)	<.01
CNS Failure	7.46 (3.60, 15.45)	<.01
Fluid Balance[3]	1.08 (1.01, 1.15)	.02

TABLE 3

(a) Multivariate results for mortality, excluding patients with sepsis

	Odds ratio (95% C.I.)	*P*-Value
PaO2/FiO2[1]	0.88 (0.79, 0.99)	.03
Other OSF[2]	2.28 (1.60, 3.26)	<.01
CNS Failure	6.81 (2.94, 15.79)	<.01
Fluid Balance[3]	1.09 (1.00, 1.18)	.05

(b) Multivariate results for ventilator-free days, excluding patients with sepsis

	Coefficient (95% C.I.)	*P*-Value
PaO2/FiO2[1]	0.41 (0.11, 0.70)	<.01
Other OSF[2]	−2.92 (−3.98, −1.87)	<.01
CNS failure	−5.56 (−8.55, −2.57)	<.01
Fluid balance[3]	−0.21 (−0.42, −0.01)	.04

[1] PaO2/FiO2 measured in 20 point increases.
[2] Nonpulmonary, non-CNS organ system failure.
[3] Fluid Balance measured in 10 mL/kg/day increment.

Association between higher cumulative fluid balance and higher mortality and fewer ventilator free days

Flori Crit Care Rsch and Practice 2012.

Society of Critical Care Medicine
The Interactive Care Professionals

Fluid Management

5.4.1 We recommend that pediatric patients with PARDS should receive total fluids to maintain adequate intravascular volume, end-organ perfusion, and optimal delivery of oxygen. *Strong agreement*

5.4.2 After initial fluid resuscitation and stabilization, we recommend goal-directed fluid management. Fluid balance should be monitored and titrated to maintain adequate intravascular volume while aiming to prevent positive fluid balance. *Strong agreement*

5.4.3 We recommend that fluid titration be managed by a goal-directed protocol that includes total fluid intake, output, and net balance. *Strong agreement*

5.4.4 We recommend that clinical trials in PARDS should report their fluid management goals, strategy, and exposure. *Strong agreement*

5.4.5 We recommend that the reporting of fluid strategy and monitoring in clinical trials should be adequately explicit to allow comparison across studies (e.g., fluid bolus trigger, type of fluid, central venous pressure [CVP] goal, use of ultrasound, or impedance monitoring). *Strong agreement*

5.4.6 We recommend that clinical trials in PARDS should use a clinical protocol to guide fluid management. *Strong agreement*

5.4.7 We recommend that further studies are needed to definitively determine the optimal fluid management strategy in pediatric patients with PARDS. *Strong agreement*

Prone Positioning: Physiologic Rationale

- Changes in regional distribution of ventilation and perfusion (V/Q) matching
- Improves cephalo-caudal and dorsal-ventral distribution by shifting the weight of heart or mediastinal structures on sternum when prone, normalizing regional differences in pleural pressure (alveolar recruitment)
- Reduce inequalities in regional time constants- promoting more homogenous distribution of gas (minimize risk of VILI)

Prone Positioning–Severe ARDS

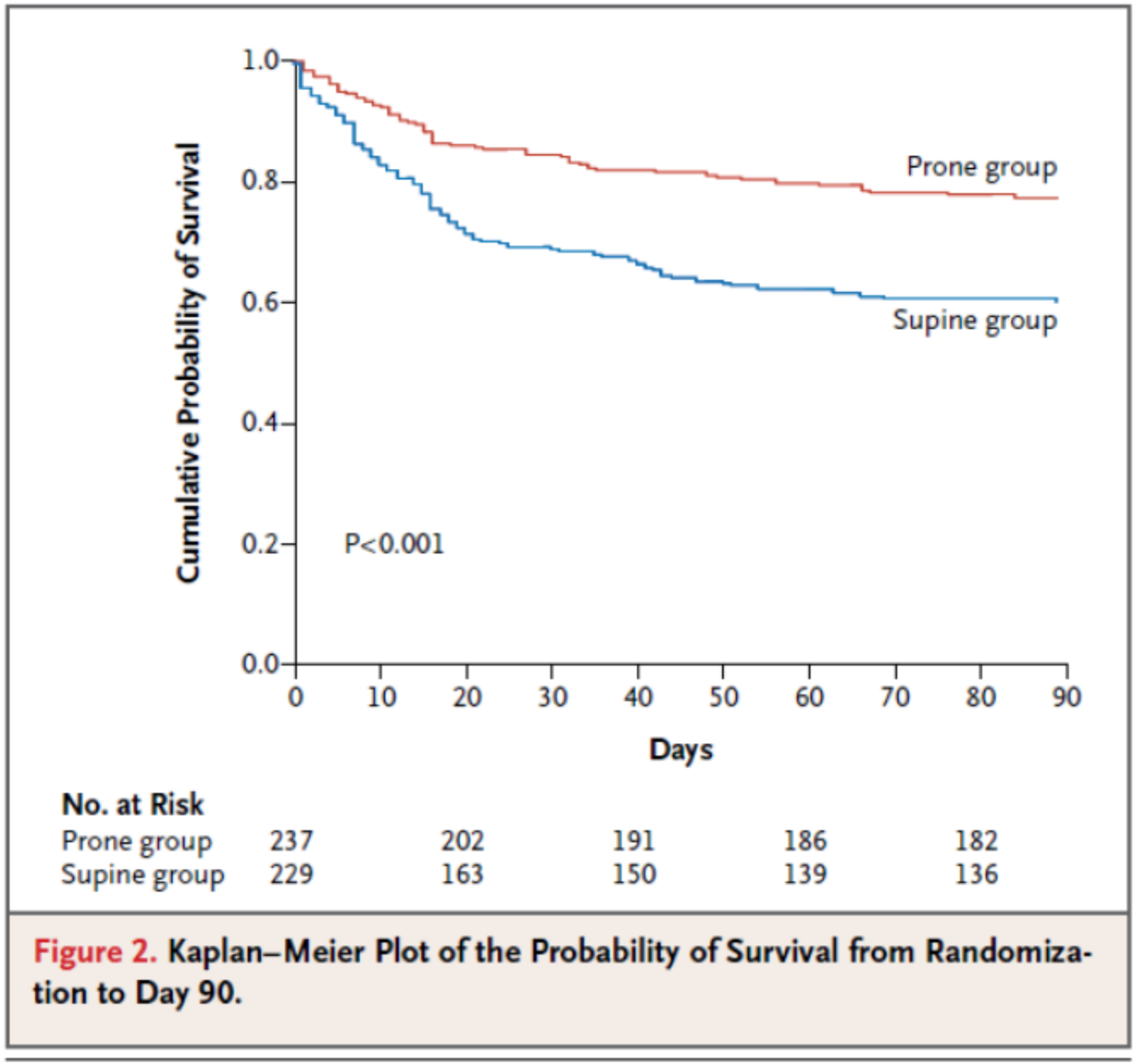


Figure 2. Kaplan–Meier Plot of the Probability of Survival from Randomization to Day 90.

Table 2. Ventilator Settings, Respiratory-System Mechanics, and Results of Arterial Blood Gas Measurements at the Time of Inclusion in the Study.*

Variable	Supine Group (N=229)	Prone Group (N=237)
Tidal volume (ml)	381±66	384±63
Tidal volume (ml per kg of PBW)	6.1±0.6	6.1±0.6
Respiratory frequency (breaths per min)	27±5	27±5
PEEP (cm of water)	10±4	10±3
F_{IO_2}	0.79±0.16	0.79±0.16
$Pplat_{RS}$ (cm of water)	23±5	24±5
Cst_{RS} (ml per cm of water)	35±15	36±23
Pao_2 (mm Hg)	80±18	80±19
Pao_2:F_{IO_2} (mm Hg)	100±20	100±30
$Paco_2$ (mm Hg)	52±32	50±14
Arterial pH	7.30±0.10	7.30±0.10
Plasma bicarbonate (mmol per liter)†	25±5	25±5

Guerin *NEJM* June 2013.

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Pediatric Prone Positioning Study

PF =150
OI=14-18
VT=6-8
PEEP=7-9

Prone for 20 Hours a Day for 7 days during acute phase of illness

Table 3. Primary and Secondary Outcome Variables*

Outcome	Supine (n = 50)	Prone (n = 51)	*P* Value†
No. of ventilator-free days from 1-28 d, mean (SD)	15.8 (8.5)	15.6 (8.6)	.91
Alive and ventilator-free on day 28, No. (%)	43 (86)	41 (80)	.45
Mortality, No. (%)	4 (8)	4 (8)	>.99
No. of days to recovery of lung injury, median (IQR)‡	5 (3-9)	4 (2-9)	.78
No. of days without failure of circulatory, neurological, coagulation, hepatic, and renal organs from 1-28 d, median (IQR)§	17 (7-22)	16 (9-22)	.88
Worse score from PICU admission to hospital discharge (or day 28), No. (%)‖			
PCPC	11 (22)	6 (12)	.16
POPC	14 (29)	8 (16)	.12

No improvement in clinically important outcomes, stopped early for futility
Very low mortality, 8%. Lowest reported in RCT for pediatric ARDS/ALI.

- Ventilator protocol, sedation protocol, extubation readiness test, nutrition

Curley 2005.

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Inhaled nitric oxide??

Recommendation:

4.1.1 iNO is not recommended for routine use in PARDS. However, its use may be considered in patients with documented pulmonary hypertension or severe right ventricular dysfunction. In addition, it may be considered in severe cases of PARDS as a rescue from or bridge to extracorporeal life support. When used, assessment of benefit must be undertaken promptly and serially to minimize toxicity and to eliminate continued use without established effect. Finally, future study is needed to better define its role, if any, in the treatment of PARDS. *Strong agreement*

Surfactant??

Recommendation:

4.2.1 At this time, surfactant therapy cannot be recommended as routine therapy in PARDS. Further study should focus on specific patient populations that may be likely to benefit and specific dosing and delivery regimens. *Strong agreement*

Prone positioning??

Recommendation:

4.3.1 Prone positioning cannot be recommended as routine therapy in PARDS. However, it should be considered an option in cases of severe PARDS. Further pediatric study is warranted, particular study stratifying on the basis of severity of lung injury. *Weak agreement*

ET suctioning??

Recommendations:

4.4.1 We recommend that maintaining a clear airway is essential to the PARDS patient. However, endotracheal suctioning must be performed with caution to minimize the risk of derecruitment. *Strong agreement*

4.4.2 There are insufficient data to support a recommendation on the use of either an open or closed suctioning system. However, in severe PARDS, consideration should be given to the technique of suctioning with careful attention to minimize the potential for derecruitment. *Strong agreement*

4.4.3 The routine instillation of isotonic saline prior to endotracheal suctioning is not recommended. However, the instillation of isotonic saline prior to endotracheal suctioning may be indicated at times for lavage to remove thick tenacious secretions. *Strong agreement*

Corticosteroids??

Recommendation:

4.6.1 At this time, corticosteroids cannot be recommended as routine therapy in PARDS. Further study should focus on specific patient populations that are likely to benefit from corticosteroid therapy and specific dosing and delivery regimens. *Strong agreement*

Throwing the kitchen sink at it???

Recommendations:

4.7.1 No recommendation for the use of the following ancillary treatment is supported: helium-oxygen mixture, inhaled or IV prostaglandins therapy, plasminogen activators, fibrinolytics, or other anticoagulants, inhaled β-adrenergic receptor agonists or ipratropium, IV N-acetylcysteine for antioxidant effects or intratracheal N-acetylcysteine for mobilizing secretions, dornase alpha outside of the cystic fibrosis population, and a cough assist device. *Strong agreement*

4.7.2 No recommendation for the use of stem cell therapy can be supported. It must be considered experimental therapy at this point. *Strong agreement*

Paralytic???

NMB

5.2.1 We recommend that if sedation alone is inadequate to achieve effective mechanical ventilation, NMB should be considered. When used, pediatric patients with PARDS should receive minimal yet effective NMB with sedation to facilitate their tolerance to mechanical ventilation and to optimize oxygen delivery, oxygen consumption, and work of breathing. *Strong agreement*

5.2.2 We recommend that, when used, NMB should be monitored and titrated to the goal depth established by the interprofessional team. Monitoring may include effective ventilation, clinical movement, and train-of-four response. *Strong agreement*

5.2.3 We recommend that if full chemical paralysis is used, the team should consider a daily NMB holiday to allow periodic assessment of the patient's level of NMB and sedation. *Strong agreement*

5.2.4 We recommend that clinical trials in PARDS should report their NMB goal, strategy, and exposure. *Strong agreement*

5.2.5 We recommend that the reporting of NMB strategy and monitoring in clinical trials should be adequately explicit to allow comparison across studies (e.g., type of NMB agent and use of steroids). *Strong agreement*

5.2.6 We recommend that further studies are needed to better understand the short- and long-term outcomes of NMB use. *Strong agreement*

Sedation:
Get to the "Goldilocks" Spot

Sedation

5.1.1 We recommend that pediatric patients with PARDS should receive minimal yet effective targeted sedation to facilitate their tolerance to mechanical ventilation and to optimize oxygen delivery, oxygen consumption, and work of breathing. *Strong agreement*

5.1.2 We recommend that valid and reliable pain and sedation scales should be used to monitor, target, and titrate sedation and to facilitate interprofessional communication. *Strong agreement*

5.1.3 We recommend that sedation monitoring, titration, and weaning should be managed by a goal-directed protocol with daily sedation goals collaboratively established by the interprofessional team. *Strong agreement*

5.1.4 We recommend that clinical trials in PARDS should report their sedation goal, strategy, and exposures. *Strong agreement*

5.1.5 We recommend that the reporting of sedation strategy and monitoring in clinical trials should be adequately explicit to allow comparison across studies. *Strong agreement*

5.1.6 We recommend that, when physiologically stable, pediatric patients with PARDS should receive a periodic assessment of their capacity to resume unassisted breathing (e.g., extubation) that is synchronized with sedative titration to an aroused state. *Strong agreement*

5.1.7 We recommend an individualized sedation weaning plan, guided by objective withdrawal scoring and assessment of patient tolerance that is developed by the clinical team and managed by the bedside nurse. *Strong agreement*

“Good Nutrition”

Nutrition

5.3.1 We recommend that pediatric patients with PARDS should receive a nutrition plan to facilitate their recovery, maintain their growth, and meet their metabolic needs. *Strong agreement*

5.3.2 We recommend that enteral nutrition, when tolerated, should be used in preference to parenteral nutrition. *Strong agreement*

5.3.3 We recommend that enteral nutrition monitoring, advancement, and maintenance should be managed by a goal-directed protocol that is collaboratively established by the interprofessional team. *Strong agreement*

5.3.4 We recommend that clinical trials in PARDS should report their nutritional/feeding goals, strategy, and exposure. *Strong agreement*

5.3.5 We recommend that the reporting of the nutrition strategy, exposure, and monitoring in clinical trials should be adequately explicit to allow comparison across studies (e.g., route, composition, calories delivered, use of additives, and time to reach nutrition goal). *Strong agreement*

Transfusion

5.5.1 In clinically stable children with evidence of adequate oxygen delivery (excluding cyanotic heart disease, bleeding, and severe hypoxemia), we recommend that a hemoglobin concentration of 7.0 g/dL be considered a trigger for RBC transfusion in children with PARDS. *Strong agreement*

5.5.2 We recommend that clinical trials in PARDS should report their blood product transfusion triggers, strategies, and exposures. *Strong agreement*

5.5.3 We recommend that the reporting of transfusion trigger, strategy, and monitoring in clinical trials should be adequately explicit to allow comparison across studies (e.g., whole vs packed RBCs, age of blood, use of leukoreduction, FFP, and platelets). *Strong agreement*

5.5.4 We recommend that clinical trials in PARDS should use a clinical protocol to guide blood product transfusion. *Strong agreement*

5.5.5 We recommend that further studies are needed to definitely determine the risks and benefits of transfusion in pediatric patients with PARDS. *Strong agreement*

NOTHING IS WORKING!!!!
Next stop: VV- or VA-ECMO

TABLE 1. Outcome of Pediatric Patients Who Receive Extracorporeal Membrane Oxygenation: Pediatric Respiratory Runs by Diagnosis

Diagnosis	Total Runs	Average Run Time	Longest Run Time	Survived	% Survived
Viral pneumonia	1,371	320	2,968	884	64%
Bacterial pneumonia	651	282	1,411	379	58%
Pneumocystis pneumonia	33	359	1,144	17	52%
Aspiration pneumonia	293	247	2,437	201	69%
ARDS, postoperative/trauma	183	248	935	114	62%
ARDS, not postoperative/trauma	530	305	3,086	285	54%
Acute respiratory failure, not ARDS	1,101	255	2,429	594	54%
Other	2,108	217	2,465	1,073	51%

ARDS = acute respiratory distress syndrome.

Run time is represented in hours. Data adapted from the International Registry of Extracorporeal Life Support Organization, July 2013, with permission.