Did COVID Change Your ARDS Management: Exploring Evidence Based Strategies to Impact Outcomes

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Disclosures

- Consultant-Michigan Hospital Association Keystone Center
- Subject matter expert on CAUTI, CLABSI, HAPI, Sepsis, Safety culture for HRET/AHA
- Consultant and speaker bureau
  - Stryker's Sage business
  - LaJolla Pharmaceutical
  - Potrero Medical
- Baxter Advisory Board

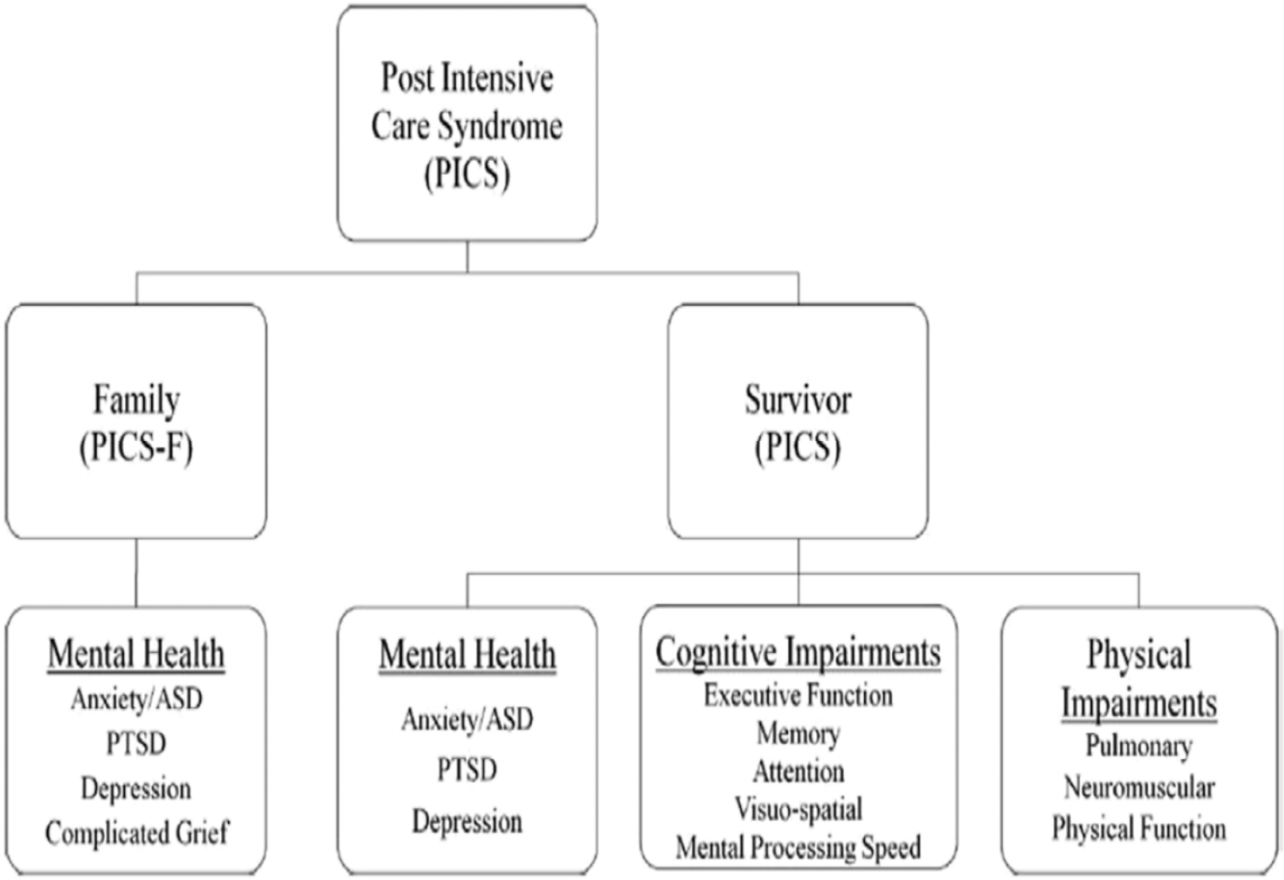
Objectives

- Discuss strategies for early recognition of patients with ARDS and explain the pathophysiologic manifestations seen in ARDS
- Apply the 8 P's of supportive evidence-based care practices for patients with ARDS
- Summarize the latest research that demonstrate an impact on short- and long-term outcomes for the ARDS patient.

Surviving

Thriving

Post Intensive Care Syndrome/ Post COVID Long Haulers



Harvey M, Davidson J. Crit Care Med, 2016;44(2):381-385

The Berlin ARDS Definition

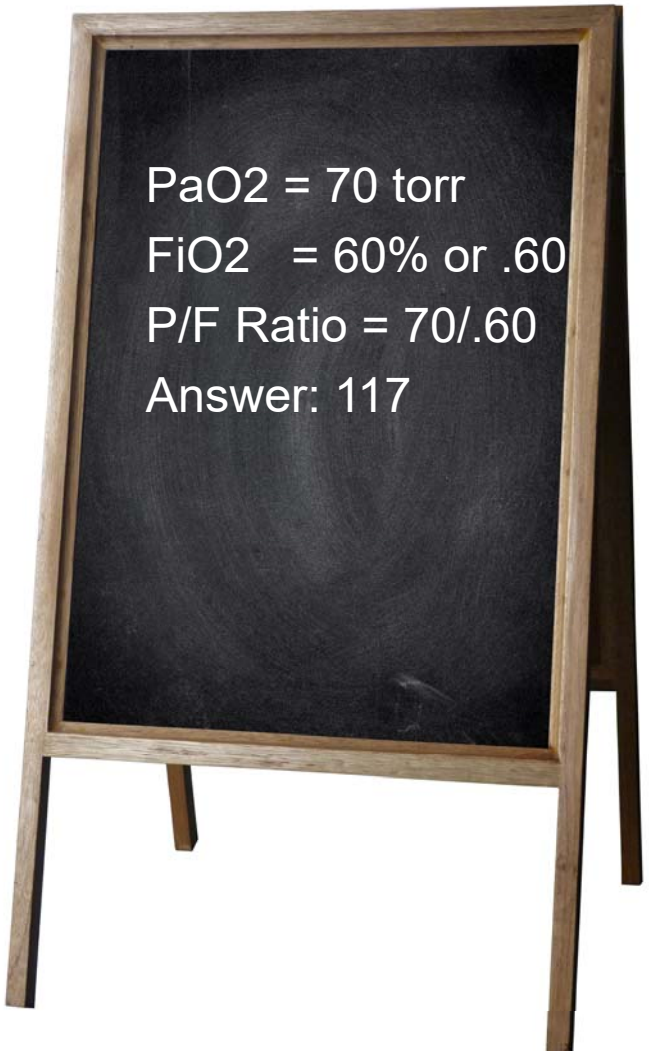
TIMING	Within 1 week of a known clinical insult or new/worsening respiratory symptoms
CHEST IMAGING (X-RAY OR CAT SCAN)	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
ORIGIN OF EDEMA	Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factors present

	MILD	MODERATE	SEVERE
OXYGENATION	<200 PaO_2/FiO_2 or ≤300 with PEEP/CPAP ≥5 cm H_2O	<100 PaO_2/FiO_2 or ≤200 with PEEP ≥5 cm H_2O	≤100 PaO_2/FiO_2 with PEEP ≥5 cm H_2O
MORTALITY	27% (24% to 30%)	32% (29% to 34%)	45% (42% to 48%)

Ferguson ND, et al. *Intensive Care Med*. 2012;38(10):1573-1582.
Dharia A, et al. *ICU Director*. 2012;3(6):287-292.

PaO_2/FiO_2 Ratio

- User friendly tool
- Crude assessment of the severity of lung injury
- Used in the definition of ARDS
  - Mild
  - Moderate
  - Severe



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Epidemiology, Patterns of Care & Mortality in ICU's in 50 Countries

- Large observational study to understand the global impact of severe acute respiratory failure (LUNG SAFE)
- Winter 2014: Four consecutive weeks
- 459 ICUs from 50 countries across 5 continents
- Primary outcome measure: ARDS incidence
  - Secondary measures: assessment of clinical recognition, application of vent management, use of adjunct interventions and outcomes for ARDS

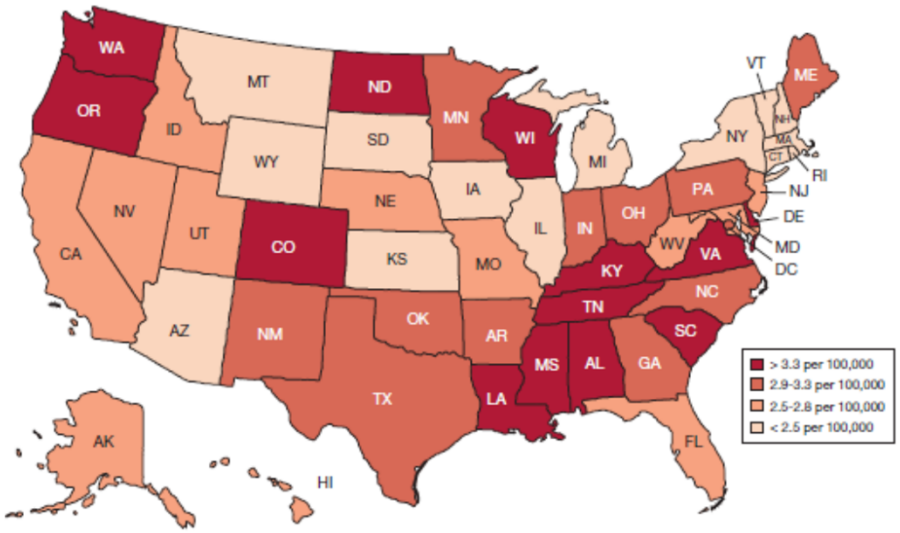
10% incidence of ARDS, 78% within 48hrs are mechanically ventilated

Bellaini G, et al. JAMA, 2016;315(8):788-800

ARDS Prevalence & Mortality By Type & Location

Type of ARDS	Prevalence	Hospital Mortality
Mild	30%	34.9%
Moderate	46.6%	40.3%
Severe	23.4%	46.1%

Greater incidence, 10% of ICU admissions, under recognized and higher mortality
ARDS occurs in 1 of every 10 patients in ICU's around the world



Mortality for ARDS in US stagnate
Higher rates:
↑in Blacks & Hispanics
↑Males and low income patients

Bellaini G, et al. JAMA, 2016;315(8):788-800
Parcha V, et al. Chest 2020 22:s0012-3692

Predisposing Conditions Associated with ARDS

Direct Injury

- Inhalation injuries
- Pneumonitis
- Virus
- Pulmonary Contusion
- Oxygen Toxicity
- Drugs:
- Radiation

Indirect Injury

- Sepsis
- Hyperinflammatory
- Multiple Transfusions (TRALI)
- Shock
- Multisystem Trauma
- Pulmonary Embolism
- Fat Embolism
- Pancreatitis
- Intracranial Hypertension
- Burns
- Bypass Surgery
- DIC

Focus on Sub-Phenotypes to target therapy better

Matthay MA, 2019; Primer 5;18. www.nature.com

COVID-What's Different in Incidence, Mortality, Pathophysiology

- Systematic review: Small sample size studies
- Examined ARDS incidence from January to June 2020 among hospitalized COVID 19 patients:
  - 33% develop ARDS
  - 26% required transfer to ICU
  - 16% MV
  - 45% mortality in ICU ARDS COVID patients
- Mortality rate: 39% (23%-56%)

Tzotzos SJ, et al. Critical Care. 2020;24:516
Hasan SS, et al. Expert Rev Respir Med. 2020;14(11):1149-1163

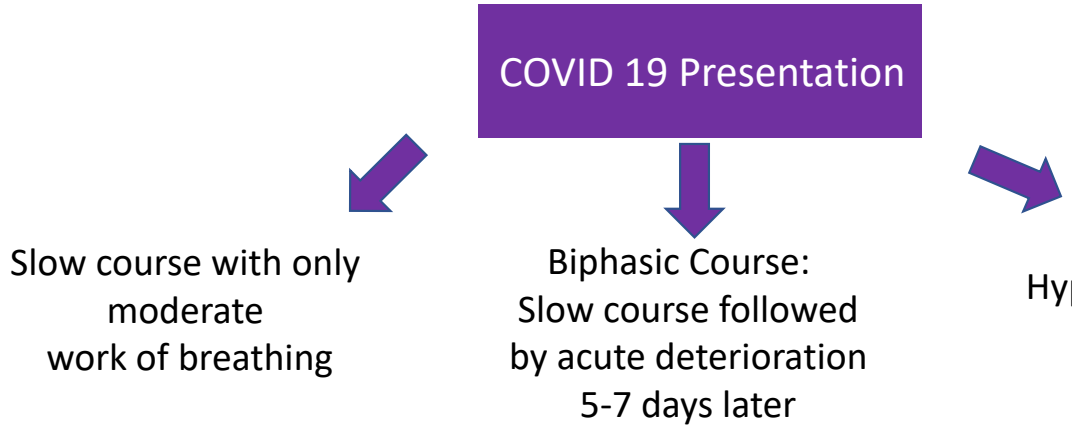
Pathophysiologic Characteristics in ARDS

- A permeability defect described as a diffuse, non-uniform injury to the alveolar epithelium and alveolar capillary membrane (mediator/biotrauma & ventilator induced)
- Ventilator induced lung injury: overdistenison injury caused by higher tidal volumes and higher transpulmonary pressures. This may induce cytokine release
- Direct injury to pulmonary circulation (mediator/biotrauma & ventilator induced)
- Defect in the body's ability to transport and utilize O_2 at tissue level

Blondonnet R, e tal. Disease Markers, 2016; open access
Manimala R, et al. Current Respiratory Medicine Reviews, 2015;11(3):231-235
Walkey AJ, et al. AnnalsATS, 2017;14(Supp 4): s271-s279

COVID Pathophysiology

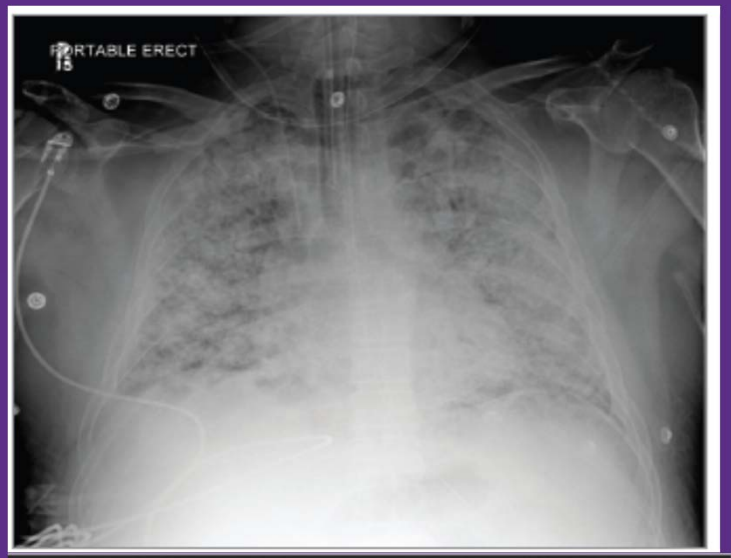
- More delayed onset
- Hyper inflammatory response
- Similar diffuse alveolar damage
- Higher thrombus burden in the pulmonary capillaries/Increase deadspace
- Abolition of hypoxic pulmonary vasoconstriction



Welker C, et al. Journal of Cardiothoracic and Vascular Anesthesia. 2021 in press
Grasselli G, et al. Lancet Respiratory, 2020;8:1201-1208

Clinical Manifestations

- Refractory hypoxemia
- Pulmonary shunting
- Diffuse alveolar and interstitial infiltrates
- Decreased lung compliance
- Pulmonary hypertension
- Other organ system failures



Fan E, et al. JAMA, 2018;319(7):698-710

The Eight P's of ARDS Treatment

- PREVENTION
- PEEP
- PUMP
- PIPES
- PARALYSIS
- POSITION
- PROTEIN
- PROTOCOL

9th For COVID 19: PHARMACOLOGY

PREVENTION

Preventing the Invasion

- VAE/VAC/IVAC & Probable VAP-Increase risk of death in COVID
- CLA-BSI-higher rates seen nationally with COVID
- SSI
- CA-UTI

Pickens CO, et al. *medRxiv.* 2021:2021.2001.2012.20248588
https://www.tarrn.org/covid
Rouze A, et al. Intensive Care Med. 2021 Feb;47(2):188-198
Buetti N, et al. Intensive Care Med. 2021 https://link.springer.com/article/10.1007/s00134-021-06346-w

PEEP

POSITIVE END EXPERIATORY PRESSURE

Strategies for Ventilating the ARDS Lung: Protect From Injury

- Oxygen exposure
- Pressure (Barotrauma)
- Volume (Volutrauma & Biotrauma)
- Shear forces (Reopening & closing of alveoli) (Atelectrauma & Biotrauma)

ATS & SCCM Guidelines for Mechanical Ventilation of ARDS Patients

- Strong recommendation for:
  - Using lower tidal volumes (4-8ml/kg PBW) & lower inspiratory pressures (plateau pressures < 30 cm H2O
  - Severe ARDS prone positioning for > 12 h/d
  - Against the routine use of HFOV
- Conditional recommendation
  - Higher PEEP's
  - Recruitment maneuvers

Additional evidence needed for ECMO

Amer J of Respir & Crit Care Med, 2017:195(9):1253-1263

Lung Protective Ventilation

Target may be too low

Goal: Pplat = ≤ 30 cm H2O, PaO2=55-88mmHg or SpO2 =88%-95%, start at PEEP of 5cm H2O

http://www.ardsnet.org/tools.shtml

Lower PEEP/higher FiO2

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO_2	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24

Higher PEEP/lower FiO2

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16

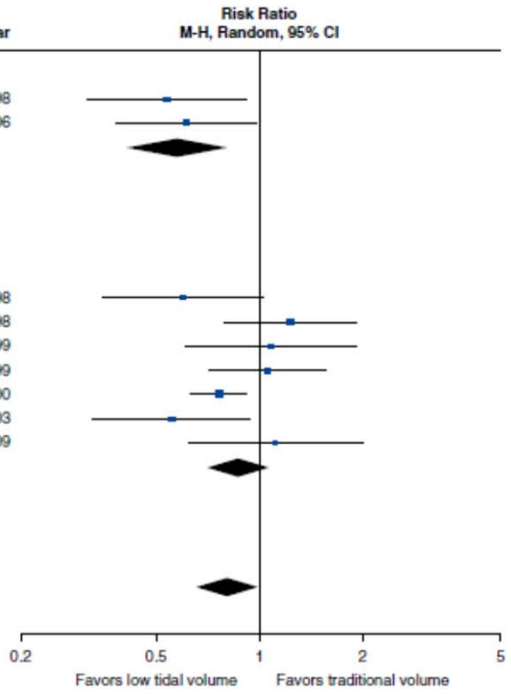
FiO_2	0.5	0.5-0.8	0.8	0.9	1.0	1.0
PEEP	18	20	22	22	22	24

Barrot L, et al. New England J of Medicine, 2020;382(11):999-1008

Low Tidal Volume

- 7 RCT's
- 1481 patients

Study or Subgroup	Low tidal volume Events	Total	No low tidal volume Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Open Lung							
Amato 1998	11	29	17	24	9.0%	0.54 [0.31, 0.91]	1998
Villar 2006	17	50	25	45	10.6%	0.61 [0.38, 0.98]	2006
Subtotal (95% CI)		**79**		**69**	**19.6%**	**0.58 [0.41, 0.82]**	
Total events	28		42				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.14$, df = 1 (P = 0.71); $I^2 = 0\%$							
Test for overall effect: Z = 3.07 (P = 0.002)							
No Open Lung							
Wu 1998	12	32	15	24	8.7%	0.60 [0.35, 1.03]	1998
Brochard 1998	27	58	22	58	11.7%	1.23 [0.80, 1.89]	1998
Brower 1999	13	26	12	26	8.3%	1.08 [0.62, 1.91]	1999
East 1999	36	103	32	97	13.0%	1.06 [0.72, 1.56]	1999
ARDSNet 2000	133	427	174	425	21.4%	0.76 [0.63, 0.91]	2000
Orme 2003	15	60	27	60	9.3%	0.56 [0.33, 0.93]	2003
Sun 2009	16	43	14	42	8.0%	1.12 [0.63, 1.99]	2009
Subtotal (95% CI)		**749**		**732**	**80.4%**	**0.87 [0.70, 1.08]**	
Total events	252		296				
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 11.12$, df = 6 (P = 0.08); $I^2 = 46\%$							
Test for overall effect: Z = 1.26 (P = 0.21)							
Total (95% CI)		**828**		**801**	**100.0%**	**0.80 [0.66, 0.98]**	
Total events	280		338				
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 14.93$, df = 8 (P = 0.06); $I^2 = 46\%$							
Test for overall effect: Z = 2.18 (P = 0.03)							
Test for subgroup differences: $Chi^2 = 3.82$, df = 1 (P = 0.05); $I^2 = 73.8\%$							



Walkey AJ, et al Ann Am Thorac Soc. 2017 Oct;14(Supplement_4):S271-S279.

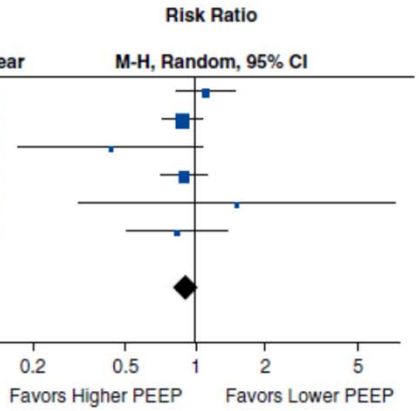
EBR & Meta-analysis: High Peep vs. Low PEEP

- 8 trials, 2,728 patients
- Mean PEEP in higher 15.1 (±3.6 cm)
- Mean PEEP in lower 9.1 (± 2.7cm)
- No difference in mortality, barotrauma, new organ failure or VFD's

	High		Low			Risk Ratio		Risk Ratio
Study or Subgroup	Mortality Events	Total Patients	Mortality Events	Total Patients	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Brower *et al.*, 2004	76	276	68	273	19.2%	1.11 [0.83, 1.46]	2004	
Meade *et al.*, 2008	135	475	164	508	40.8%	0.88 [0.73, 1.06]	2008	
Talmor *et al.*, 2008	5	30	12	31	1.9%	0.43 [0.17, 1.07]	2008	
Mercat *et al.*, 2008	107	385	119	382	31.1%	0.89 [0.72, 1.11]	2008	
Hodgson *et al.*, 2011	3	10	2	10	0.6%	1.50 [0.32, 7.14]	2011	
Kacmarek *et al.*, 2016	22	99	27	101	6.4%	0.83 [0.51, 1.36]	2016	
Total (95% CI)		**1275**		**1305**	**100.0%**	**0.91 [0.80, 1.03]**		
Total events	348		392					

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.09$, df = 5 (P = 0.41); $I^2 = 2\%$

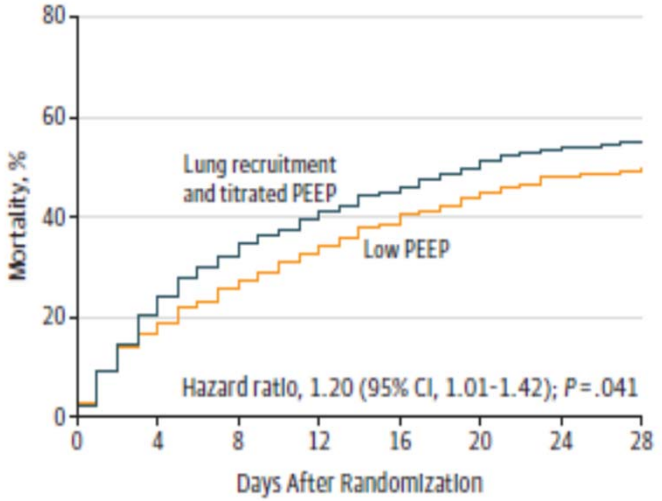
Test for overall effect: Z = 1.46 (P = 0.14)



Walkey AJ, et al. AnnalsATS, 2017;14(Supp 4):s297-s303

Effect of Lung Recruitment & Titrated PEEP vs Low PEEP on Mortality (ART Trial)

- Multi-center RCT, 120 ICU's, 9 countries, 1010 patients
- Maneuver: RM with incremental PEEP titration, then PEEP set at 23cm and ↓ by 3cm till 11cm based on compliance. Once reached added 2cm-best PEEP. Follow by additional recruitment maneuver
- After PaO2/FiO2 stabilize or ↑ then PEEP ↓ 2 cm every 8 hrs
- Small # didn't received RM due to hypotension
- Higher # with barotrauma in RM group
- PEEP diff btwn groups thru day 7 was 3-4 cm



No. at risk								
Lung recruitment and titrated PEEP	501	397	340	303	276	254	233	225
Low PEEP	509	423	378	343	312	286	264	260

PEEP indicates positive end-expiratory pressure.

Cavalcanti AB, et al. JAMA, 2017;318(14):13351345

PHARLAP:
An Open Lung Strategy including Permissive Hypercapnia, Alveolar Recruitment and Low Airway Pressure in ARDS patients

- A Multi-center RCT in 5 countries/Phase II trial
- Objective: Determine whether maximal ling recruitment strategies reduce VFD versus Low V_t and moderate PEEP
- Enrollment stopped after publication of ART
- 115/340 planned enrolled were analyzed
- Results:
  - △ No difference
    - VFD
    - Mortality
    - Barotrauma
  - △ Intervention group
    - Increase rate of new cardiac arrythmias
    - Reduced use of hypoxemic adjunctive therapies

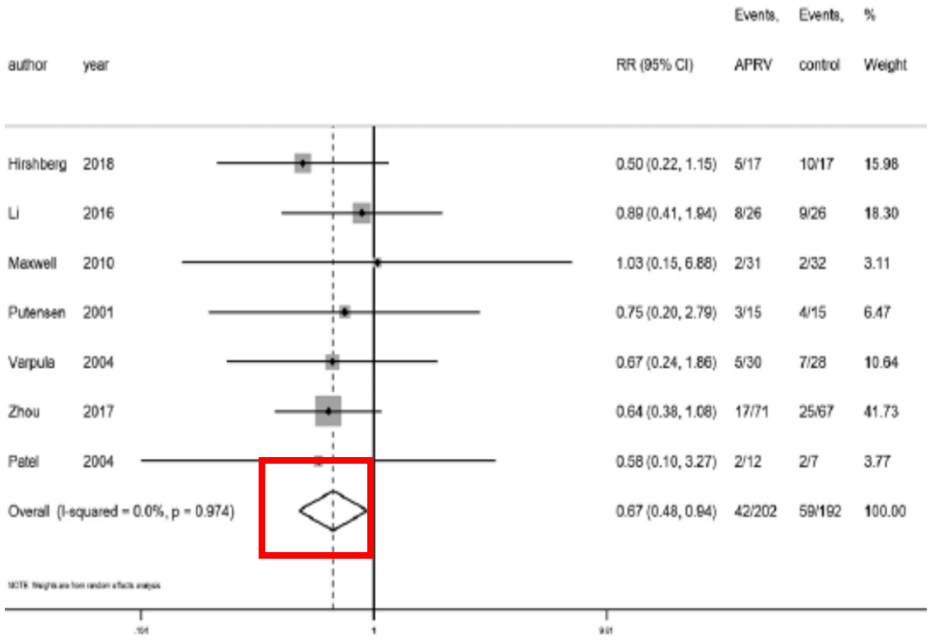
Hodgson CL, et al. Am J Respir Crit Care Med. 2019 Dec 1;200(11):1363-1372.

Adjunctive Strategies

- APRV
- HFOV
- ECMO
- $ECCO_2$ (experimental)
  - The strategy of altar protective lung ventilation with extracorporeal CO2 removal for new onset moderate to severe ARDS (SUPERNOVA) trial
  - Protective ventilation with Veno venous lung assist in respiratory failure (REST) trial

APRV:
Airway Pressure Release Ventilation vs any Ventilator Mode

- 7 RCT's
- 412 patients
- Mean measured TV in APRV group: 7.47 ml/kg, vs. 7.45 ml/kg
- Improvement in day 3 PaO2/FiO2 ratio
- No difference in:
  - Initial rescue treatments
    - inhaled pulmonary vasodilators
    - prone positioning
    - ECMO
- Barotrauma only reported in three studies (no difference)

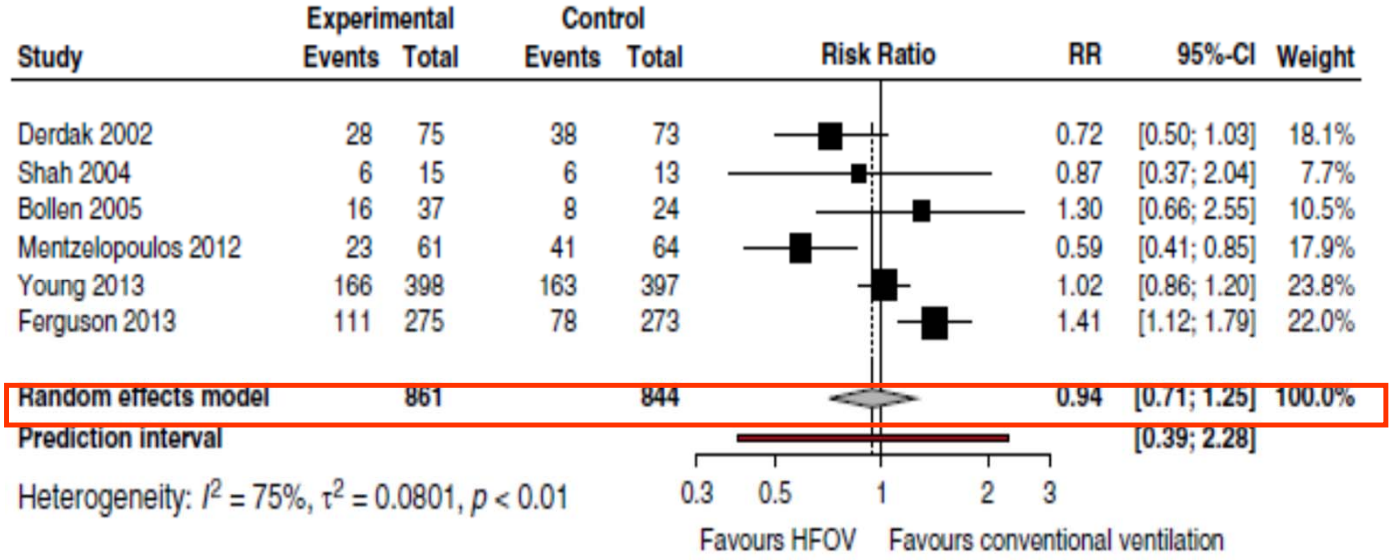


Needed a larger sample to prevent false positive in primary outcomes (614 patients)

Lim J, et al. Crit Care Med. 2019 Dec;47(12):1794-1799.

High Frequency Oscillation: EBR & Meta-analysis

- Six trials with 1715 patients
- No difference in barotrauma rates



In an individual patient meta-analysis, those with ARDS with P/F ratios < 65mmhg may see a benefit.

(Meade MO, et al. AJRCCM,2017;196(6):727-733

Goligher EC, et al. AnnalsATS, 2017;14(suppl 4):s289-s296

EOLIA Trial

- Multicenter, International, RCT
- Method: Compared early VV ECMO or continued conventional ventilator therapy and measure 60-day mortality in patients with severe forms of ARDS
- Cross over to ECMO was possible for conventional group who had refractory hypoxemia
- Results:
  - Mortality: 35% in ECMO versus 46% in control (p< 0.09)
  - Crossover to ECMO avg 6.5 days-28% of control / Mortality 57%

Combes A, et al. New Engl J of Med. 2018;378(21):1965-75

ARDS Trails (non-COVID)

- Implementation of Computerized Clinical Decision Support for Mechanical Ventilation of Patients With Acute Respiratory Distress Syndrome
- Careful Ventilation in ARDS (COVID 19) -740 pts
- Individualized Positive End-expiratory Pressure Guided by End-expiratory Lung Volume in the Acute Respiratory Distress Syndrome (IPERPEEP)- 174pt, not yet recruiting
- Early PReserved SPONtaneous Breathing Activity in Mechanically Ventilated Patients With Acute Respiratory Distress Syndrome - The PReSPON Randomized Controlled Trial—using APRV
  - Recruitment ongoing-target 840 patients

PIPES
&
PUMP

Measures to Improve Oxygen Delivery

Measures to Improve O_2 Delivery

- Fluid Management
  - Balanced fluids vs. Saline
  - Dry vs. Wet

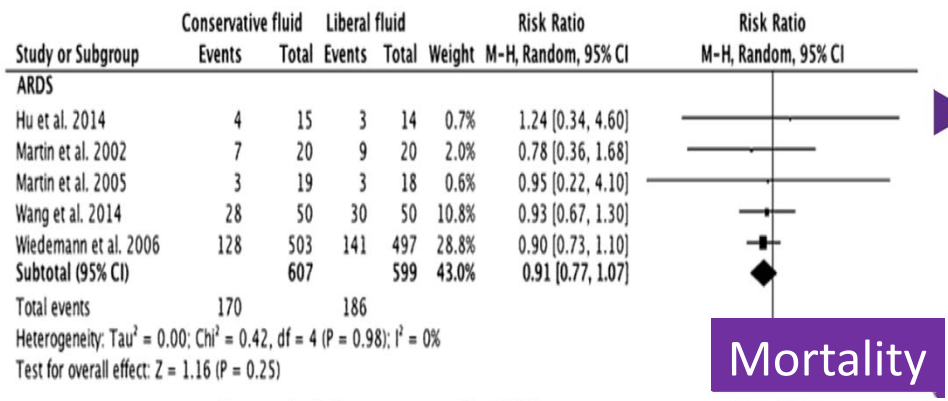
SMART Trial:
Balanced Fluids vs .9 % Normal Saline

- The rate of death, new dialysis, or renal dysfunction lasting through hospital discharge was significantly lower with balance fluids

Semler MW, et al. N Engl J Med. 2018;378[9]:819

Conservative/ Deresuscitation vs. Liberal Fluid For ARDS Following Critical Phase

- 11 RCT's
- 2051 patients
- Results:
  - No difference in mortality
  - ↑ VFD 1.82 days
  - ↓ LOS 1.9 days



Study or Subgroup	Conservative fluid Events	Total	Liberal fluid Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ARDS						
Hu et al. 2014	4	15	3	14	0.7%	1.24 [0.34, 4.60]
Martin et al. 2002	7	20	9	20	2.0%	0.78 [0.36, 1.68]
Martin et al. 2005	3	19	3	18	0.6%	0.95 [0.22, 4.10]
Wang et al. 2014	28	50	30	50	10.8%	0.93 [0.67, 1.30]
Wiedemann et al. 2006	128	503	141	497	28.8%	0.90 [0.73, 1.10]
Subtotal (95% CI)		**607**		**599**	**43.0%**	**0.91 [0.77, 1.07]**
Total events	170		186			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.42$, df = 4 (P = 0.98); $I^2 = 0\%$
Test for overall effect: Z = 1.16 (P = 0.25)

Risk Ratio M-H, Random, 95% CI

Mortality

Study or Subgroup	Conservative fluid Mean [Days]	SD [Days]	Total	Liberal fluid Mean [Days]	SD [Days]	Total	Weight	Mean Difference IV, Random, 95% CI [Days]
Chen and Kollef. 2015	5.5	9.4	41	7.4	12.9	41	6.5%	
Zhang et al. 2015	9	17.9	168	10.3	18.7	182	10.3%	
Hjortrup et al. 2016	21.4	9.7	75	19.8	11.1	76	13.3%	
Martin et al. 2005	10.3	8	20	8	8	20	6.4%	
Wiedemann et al. 2006	14.6	11.2	503	12.1	11.1	497	51.6%	
Richard et al. 2015	12.7	18.7	30	9.7	16.3	30	2.1%	
Benakatti et al. 2014	15.8	10.8	54	12.1	9.4	47	9.8%	
Total (95% CI)			**891**			**893**	**100.0%**	

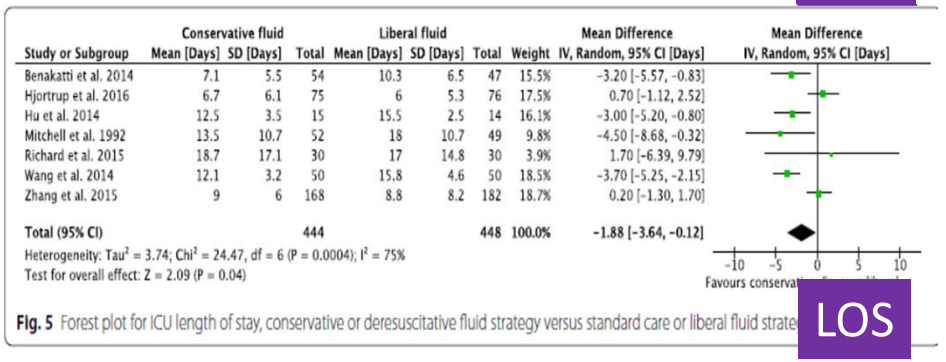
Heterogeneity: $Tau^2 = 0.33$; $Chi^2 = 6.63$, df = 6 (P = 0.36); $I^2 = 9\%$
Test for overall effect: Z = 2.78 (P = 0.005)

Mean Difference IV, Random, 95% CI [Days]

10 5 0 -5 -10
Favours conservative

VFD

Fig. 4 Forest plot for outcome of ventilator-free days



Study or Subgroup	Conservative fluid Mean [Days]	SD [Days]	Total	Liberal fluid Mean [Days]	SD [Days]	Total	Weight	Mean Difference IV, Random, 95% CI [Days]
Benakatti et al. 2014	7.1	5.5	54	10.3	6.5	47	15.5%	-3.20 [-5.57, -0.83]
Hjortrup et al. 2016	6.7	6.1	75	6	5.3	76	17.5%	0.70 [-1.12, 2.52]
Hu et al. 2014	12.5	3.5	15	15.5	2.5	14	16.1%	-3.00 [-5.20, -0.80]
Mitchell et al. 1992	13.5	10.7	52	18	10.7	49	9.8%	-4.50 [-8.68, -0.32]
Richard et al. 2015	18.7	17.1	30	17	14.8	30	3.9%	1.70 [-6.39, 9.79]
Wang et al. 2014	12.1	3.2	50	15.8	4.6	50	18.5%	-3.70 [-5.25, -2.15]
Zhang et al. 2015	9	6	168	8.8	8.2	182	18.7%	0.20 [-1.30, 1.70]
Total (95% CI)			**444**			**448**	**100.0%**	**-1.88 [-3.64, -0.12]**

Heterogeneity: $Tau^2 = 3.74$; $Chi^2 = 24.47$, df = 6 (P = 0.0004); $I^2 = 75\%$
Test for overall effect: Z = 2.09 (P = 0.04)

Mean Difference IV, Random, 95% CI [Days]

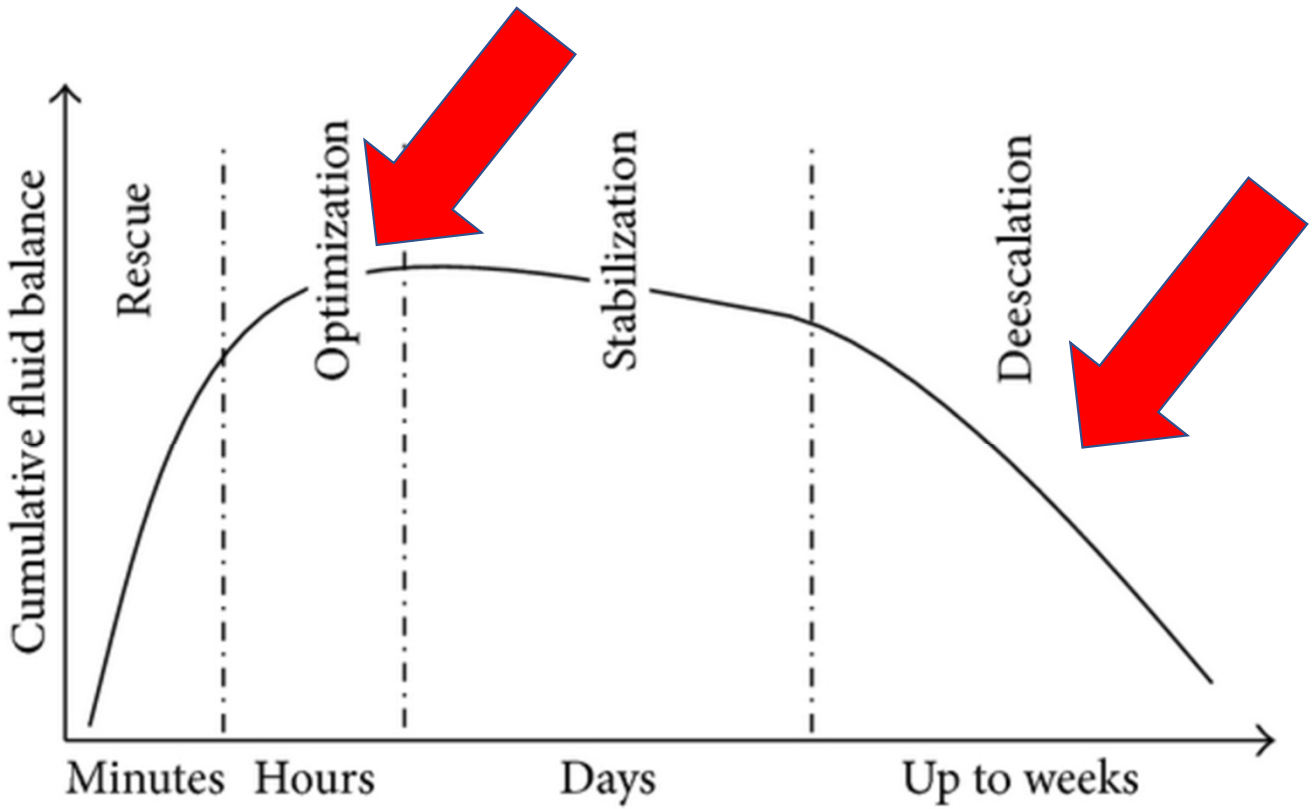
-10 -5 0 5 10

LOS

Fig. 5 Forest plot for ICU length of stay, conservative or deresuscitative fluid strategy versus standard care or liberal fluid strate

Silversides JA, et al. Intensive Care Med, 2017;43:155-170

4 Phases of Fluid Resuscitation



https://www.researchgate.net/figure/Four-phases-of-hemodynamic-treatment-in-relation-to-cumulative-fluid-balance_fig1_287977953

FRESH Trial

- 13 US and UK Hospitals
- Non-blinded RCT
- n = 124 patients
  - 83 treatment vs. 41 Usual Care
  - 2:1 enrollment
- Enrolled in the ER
  - Refractory septic shock
  - < 3L of fluid administered
- PLR with dynamic measure of SV change
  - Used to guide decision of fluid vs. vasopressors for clinical hypoperfusion
  - Over the next 72 hours of care, or ICU discharge
- Hypoperfusion defined as:
  - MAP < 65
  - Persistent hyperlactemia
  - Cryptic shock – lactate > 4 without hypotension

Douglas I et al. Fluid Response Evaluation in Sepsis Hypotension and Shock: A Randomized Clinical Trial, *CHEST* (2020)

Primary endpoint

- **Decreased 72-hour Fluid Balance** (p=0.02)
  - △ Treatment Group: 0.65 L +/- 2.85 L
  - △ Control Group: 2.02 L +/- 3.44 L
- Favoring Treatment Group: -1.37 L

- 43% fluid responsive on initial PLR
- 33% fluid responsive between 48 – 72 hours
- 18% never fluid responsive

Douglas I et al. Fluid Response Evaluation in Sepsis Hypotension and Shock: A Randomized Clinical Trial, *CHEST* (2020)

Secondary Endpoints

- **Renal Replacement Therapy (RRT)** p = 0.04
  - △ Treatment Group 5.1%
  - △ Control Group 17.5 %
- **Mechanical Ventilation** p = 0.04
  - △ Treatment Group 17.7%
  - △ Control Group 34.1%
- **ICU LOS** p = 0.11
  - △ Treatment Group 3.31
  - △ Control Group 6.22
- **Discharge Home** p = 0.035
  - △ Treatment Group 63.9%
  - △ Control Group 43.9 %

Douglas I et al. Fluid Response Evaluation in Sepsis Hypotension and Shock: A Randomized Clinical Trial, *CHEST* (2020)

Timing & Amount of Fluid Administration is Key

- Start as early as possible the administration of volume if warranted-more conservative for patients not in shock
- Control the efficacy of volume expansion with predefined goal-oriented therapy
- More fluid early, less fluid later
- Consider deresuscation if warranted after hemodynamically stable

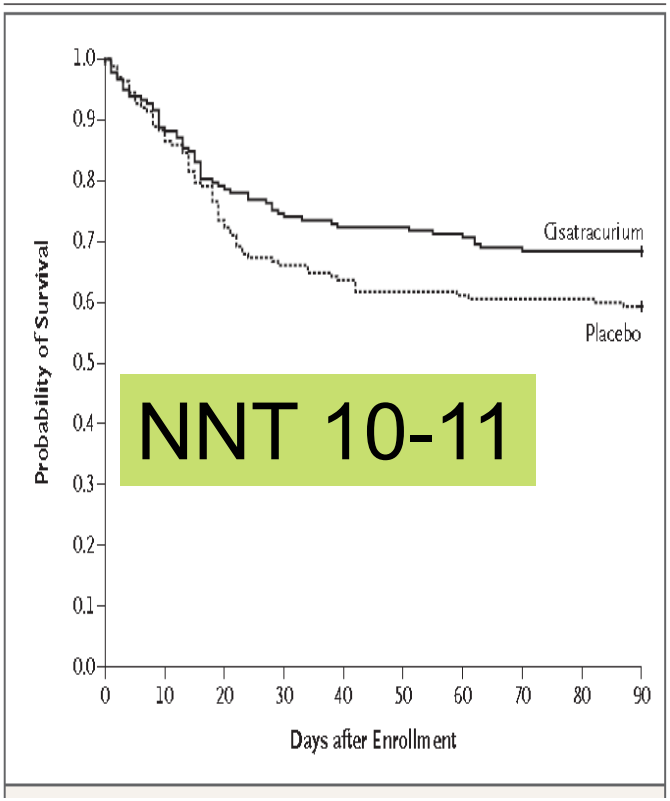
PARALYSIS

Neuromuscular Blockade in Early ARDS

- Multicenter, double blind trial
- 340 patients with ARDS within 48hrs of admitted to ICU
- ARDS defined as P/F ratio of < 150 ≥ PEEP 5cm & Vt of 6-8 ml/kg PBW
- Randomized to receive 48hrs of cisatracurium or placebo
- Study did not use train of 4

Results:

- After risk adjustment NMB group showed improved mortality at 90 days (31.6% vs. 40.7%)
- Also significant at 28 days
- ↑time off vent
- No difference in muscle weakness



Papazian L, et al. N Engl J Med. 2010;363(12):1107-16

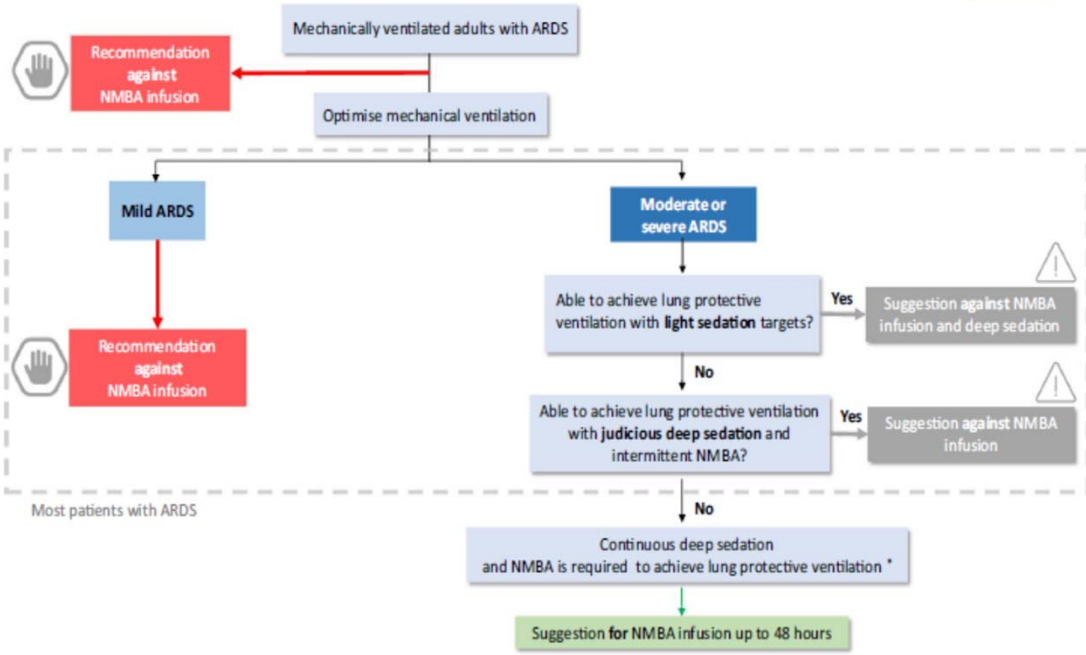
ROSE Trial

- 1006 moderate to severe ARDS patients
- Randomized to 48hrs Cisatracurium/deep sedation or usual care
- Vent strategies similar in both group (use of higher PEEP)
- Trial stopped for futility at 2nd analysis
- Results:
  - 90-day follow-up
  - 42.5% of the intervention group vs 42.8% of the control group died before hospital discharge (between group difference -0.3%, 95% CI -6.4 to 5, *P*=0.93)
  - During hospital stay intervention group had more;
    - Adverse cardiovascular events
    - Less active

Moss M, et al. Petal Network. NEJM, 2019;380(21):1997-2008

Rapid Practice Guideline: NMBA in ARDS Patients

- 20 international experts/12 countries
- Overall certainty in the evidence was low
- 1 Recommendation:
  - Against routine use of NMBA infusions in adults with ARDS before optimizing mechanical ventilation & assessing ARDS severity
- 2 suggestions:
  - If NMBA required to facilitate LPV, suggest intermittent doses with judicious deep sedation over NMBA infusion & deep sedation
  - If clinician determines continued need for NMBA and deep sedation, suggest continuous for 48hrs over intermittent



Alhazzani W, et al. Intensive Care Medicine 2020;46:1977-1986

POSITION

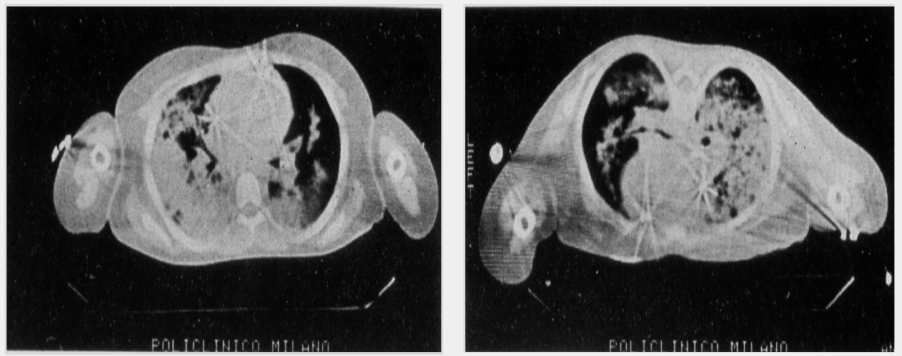
ATS & SCCM Guidelines for Mechanical Ventilation of ARDS Patients

- Strong recommendation for:
  - Using lower tidal volumes (4-8ml/kg PBW) & lower inspiratory pressures (plateau pressures < 30 cm H2O
  - Severe ARDS prone positioning for > 12 h/d
  - Against the routine use of HFOV
- Conditional recommendation
  - Higher PEEP's
  - Recruitment maneuvers

Amer J of Respir & Crit Care Med, 2017:195(9):1253-1263

Prone positioning was only used in 19% of patient with severe ARDS

Bellaini G, et al. JAMA, 2016;315(8):788-800



A1 Supine A2 Prone

Gattinoni L. et al. Anesthesiology 1991;74:15-23

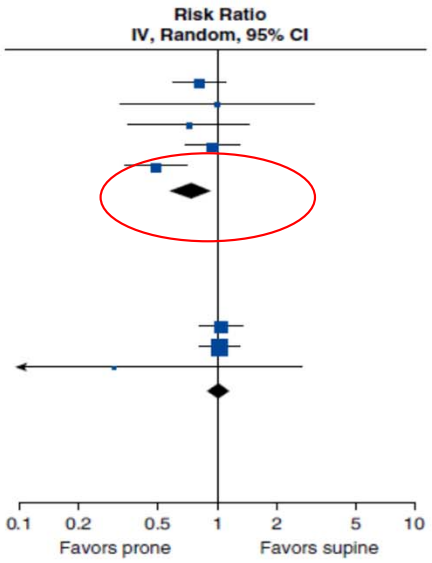
European Prevalence Study: Use of PP for mild 5.9%, moderate 10.3%, severe 32.9%

Guerin C, et al. Intensive Care Med, 2018;44(1):22-37

Prone Meta-Analysis

- 8 RCT's
- 2129 total adult patients
- Subgroup analyses found lower mortality with > 12 hours duration prone for patients with moderate to severe ARDS
- Prone positioning was associated with higher rates of endotracheal tube obstruction and pressure sores

Study or Subgroup	Prone Events	Prone Total	Supine Events	Supine Total	Weight	Risk Ratio IV, Random, 95% CI
≥12h Prone						
Mancebo *et al.* 2006	38	76	37	60	28.5%	0.81 [0.60, 1.10]
Chan *et al.* 2007	4	11	4	11	5.7%	1.00 [0.33, 3.02]
Fernandez *et al.* 2008	8	21	10	19	12.0%	0.72 [0.36, 1.45]
Taccone *et al.* 2009	52	166	57	172	27.9%	0.95 [0.69, 1.29]
Guerin *et al.* 2013	38	237	75	229	25.8%	0.49 [0.35, 0.69]
Subtotal (95% CI)		**511**		**491**	**100.0%**	**0.74 [0.56, 0.99]**
Total events	140		183			
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 8.53$, df = 4 (P = 0.07); $I^2 = 53\%$						
Test for overall effect: Z = 2.06 (P = 0.04)						
<12h Prone						
Gattinoni *et al.* 2001	70	152	67	152	40.0%	1.04 [0.82, 1.34]
Guerin *et al.* 2004	134	413	119	378	59.5%	1.03 [0.84, 1.26]
Voggenreiter *et al.* 2005	1	21	3	19	0.5%	0.30 [0.03, 2.66]
Subtotal (95% CI)		**586**		**549**	**100.0%**	**1.03 [0.88, 1.20]**
Total events	205		189			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.24$, df = 2 (P = 0.54); $I^2 = 0\%$						
Test for overall effect: Z = 0.36 (P = 0.72)						
Test for subgroup differences: $Chi^2 = 3.92$, df = 1 (P = 0.05), $I^2 = 74.5\%$						



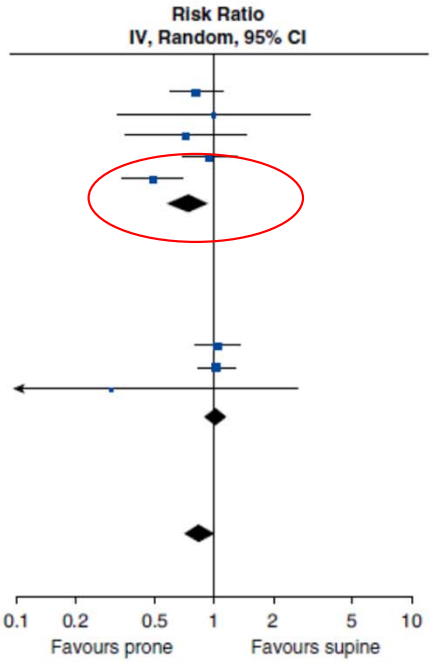
Overall Mortality

Munshi L, et al. AnnalATS, 2017;14(4):s280-s288

Prone Meta-Analysis: Sub-Groups

- Moderate to Severe ARDS vs. Mild ARDS

Study or Subgroup	Prone Events	Prone Total	Supine Events	Supine Total	Weight	Risk Ratio IV, Random, 95% CI
Moderate to Severe ARDS						
Mancebo *et al.* 2006	38	76	37	60	17.0%	0.81 [0.60, 1.10]
Chan *et al.* 2007	4	11	4	11	3.2%	1.00 [0.33, 3.02]
Fernandez *et al.* 2008	8	21	10	19	6.9%	0.72 [0.36, 1.45]
Taccone *et al.* 2009	52	168	57	174	16.6%	0.94 [0.69, 1.29]
Guerin *et al.* 2013	38	237	75	229	15.3%	0.49 [0.35, 0.69]
Subtotal (95% CI)		**513**		**493**	**59.1%**	**0.74 [0.56, 0.99]**
Total events	140		183			
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 8.51$, df = 4 (P = 0.07); $I^2 = 53\%$						
Test for overall effect: Z = 2.06 (P = 0.04)						
All ARDS						
Gattinoni *et al.* 2001	70	152	67	152	19.1%	1.04 [0.82, 1.34]
Guerin *et al.* 2004	134	413	119	378	20.9%	1.03 [0.84, 1.26]
Voggenreiter *et al.* 2005	1	21	3	19	0.9%	0.30 [0.03, 2.66]
Subtotal (95% CI)		**586**		**549**	**40.9%**	**1.03 [0.88, 1.20]**
Total events	205		189			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.24$, df = 2 (P = 0.54); $I^2 = 0\%$						
Test for overall effect: Z = 0.36 (P = 0.72)						
Total (95% CI)		**1099**		**1042**	**100.0%**	**0.84 [0.68, 1.04]**
Total events	345		372			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 16.94$, df = 7 (P = 0.02); $I^2 = 59\%$						
Test for overall effect: Z = 1.60 (P = 0.11)						
Test for subgroup differences: $Chi^2 = 3.93$, df = 1 (P = 0.05), $I^2 = 74.6\%$						

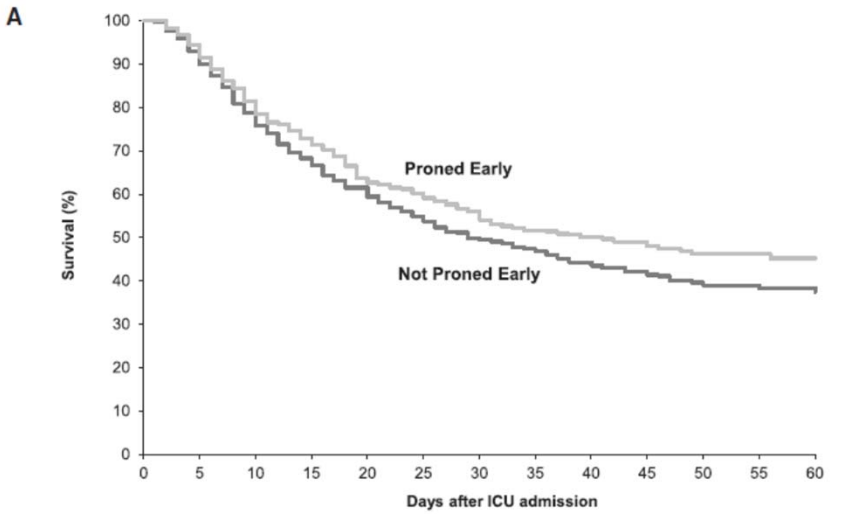


Greater incidence of pressure injuries and ET tube obstruction in prone vs supine.

Munshi L, et al. AnnalATS, 2017;14(4):s280-s288

Prone Positioning in COVID 19 Patients

- Data from study & treatment of outcomes in critical ill patients with COVID
- 68 hospitals
- Patients with p/f ratio < 200mmHg initiated prone positioning or not within first 2 days of ICU admission
- Results
  - 2338 eligible pts: 30% proned
  - Lower in-hospital mortality if proned early

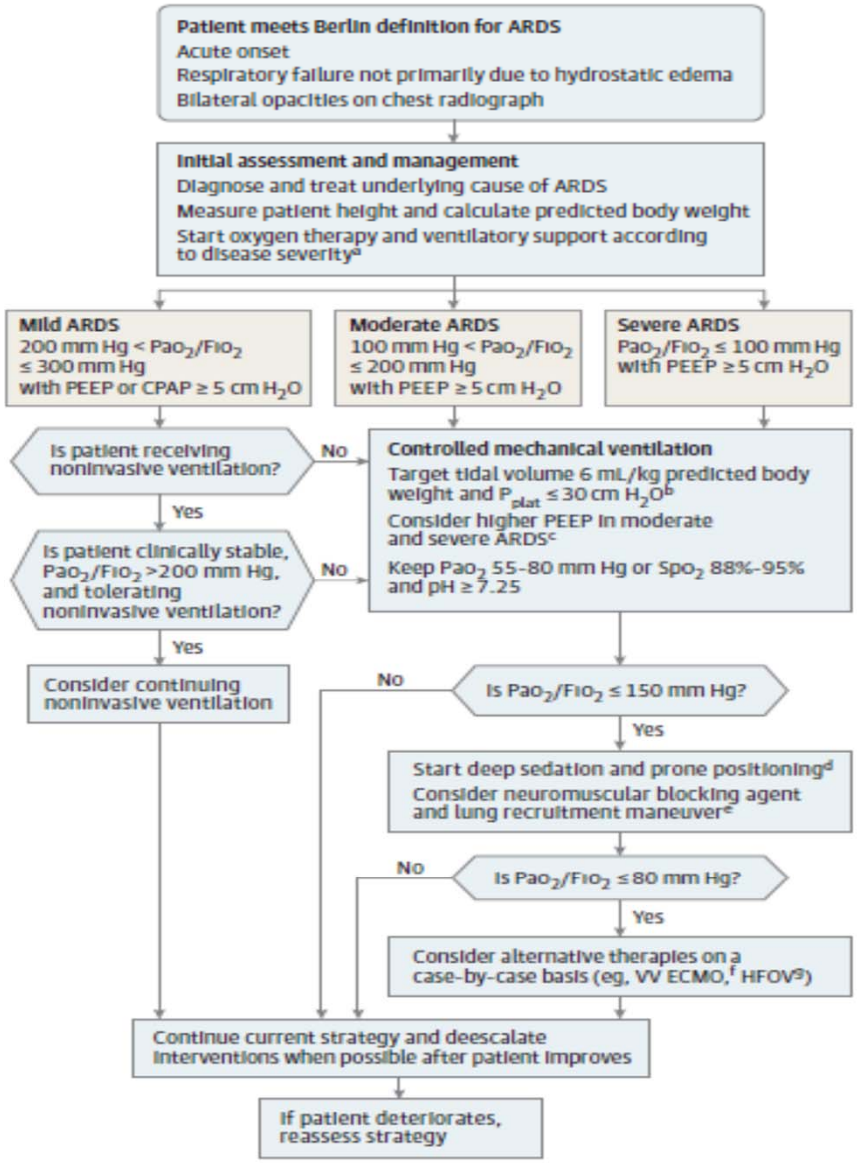


No. at risk

	Day 0	Day 10	Day 20	Day 30	Day 40	Day 50	Day 60
Proned	702	566	387	243	126	59	22
Not Proned	1636	1258	755	421	215	105	52

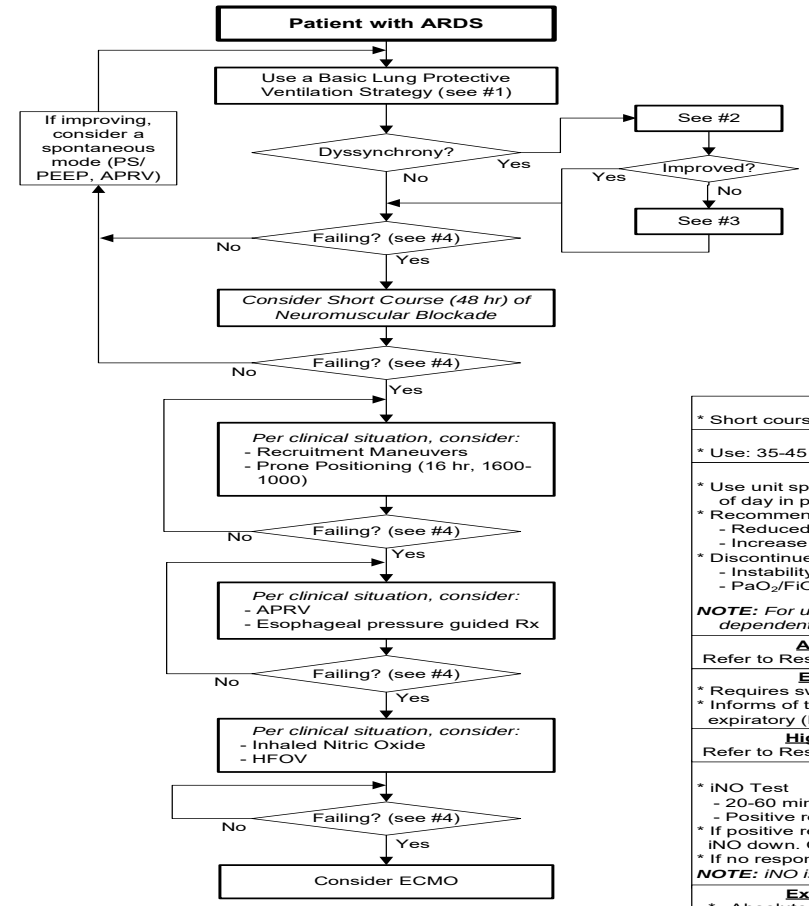
Mathews KS, et al. Critical Care Medicine 2021 April online

Sample ARDS Treatment Algorithm



Overview of ARDS Ventilator Management Strategies

University Hospital Respiratory Care
University of Michigan Hospitals & Health Centers



See back for general comments & recommended reading

1: Basic LPVS
- ARDS Network ventilation strategy:
  a. Using VCV or PCV and targeting VT 4-6 mL/kg PBW
  b. Maintain Pplat ≤30 cm H_2O
  c. PEEP/FiO_2 per table (see back page)

2: Pt-Vent Dyssynchrony, Step 1
- Initial strategy should be to:
  a. Assess potential to treat with pharmacologic agents (eg. sedation, NMB agents), and
  b. Consider minor ventilator adjustments (eg, flow rate & pattern, inspiratory pause)
- If above does not work, consider increasing VT 1 mL/kg (max 8 mL/kg), provided Pplat ≤28-30 cm H_2O

3: Pt-Vent Dyssynchrony, Step 2
- Consider a variable flow pressure breath mode of ventilation:
  a. Volume Control+
  b. Pressure Control Ventilation

4: Criteria for Failing LPVS
- PaO_2 <55 torr on FiO_2 =1.0 and Pplat >30 cm H_2O on VT =4 mL/kg PBW

Neuromuscular Blockade
* Short course (48 hrs) associated with mortality benefit in RCT

Recruitment Maneuvers
* Use: 35-45 cm H_2O X 20 sec, or PCV with 40/20 for 2 minutes

Prone Positioning
* Use unit specific rotation frequency, but evidence suggests majority of day in prone position, if tolerated
* Recommend a 48 hr trial, stop if no improvement, as evidenced by:
  - Reduced FiO_2 by 0.10
  - Increase PaO_2/FiO_2 by 30
* Discontinue when:
  - Instability
  - PaO_2/FiO_2 >150; reduced FiO_2 of 0.60

NOTE: *For unilateral lung process, consider placing 'good lung' in dependent position to improve V/Q ratio and oxygenation*

Airway Pressure Release Ventilation (APRV)
Refer to Respiratory Care policy

Esophageal Pressure (Pes) Guided Therapy
* Requires switch to AVEA ventilator & placement of Pes catheter
* Informs of transpulmonary end-inspiratory (Ptp-plat) and end-expiratory (Ptp-PEEP) pressures

High Frequency Oscillatory Ventilation (HFOV)
Refer to Respiratory Care policy (policy follows Oscillate protocol)

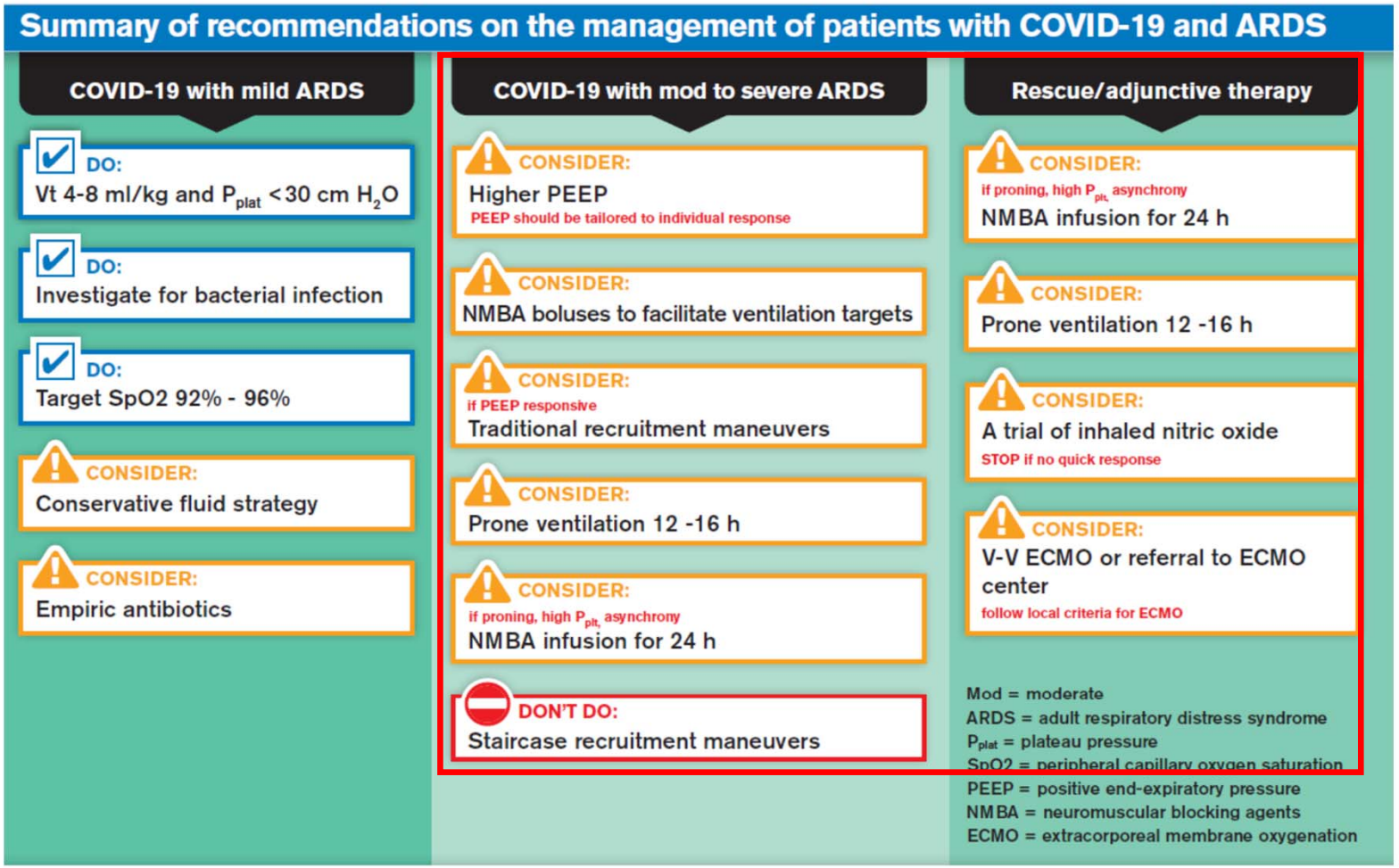
Inhaled Nitric Oxide (iNO)
* iNO Test
  - 20-60 minute test on 20 ppm
  - Positive response: increase in PaO_2/FiO_2 of >10
* If positive response, reduce to 10 ppm, then FiO_2 to 0.6, then titrate iNO down. Consider flolan or iloprost, per Respiratory Care Policy
* If no response, discuss with team to consider stopping

NOTE: *iNO is a very costly drug compared to alternatives*

Extracorporal Membrane Oxygenation (ECMO)
* Absolute contraindications: irreversible pulmonary process and inability to anticoagulate
* Evaluate, but lower survival if on vent 7-10 days pre-ECMO

7/25/16 (modified for SICU)

COVID-19 Resources



Society of Critical Care Medicine
The Intensive Care Professionals

Surviving Sepsis Campaign

ESICM
The European Connection

PROTEIN (NURTITION)

SSCM Nutritional Guidelines (2016)

- Initiate enteral nutrition (EN) within 24−48 hours following the onset of critical illness and admission to the ICU and increase to goals over the first week of ICU stay. For ARDS-either trophic or full EN
- Take steps as needed to reduce risk of aspiration or improve tolerance to gastric feeding
- Do not use gastric residual volumes as part of routine care to monitor ICU patients on EN
- Start parenteral nutrition early when EN is not feasible or sufficient in high-risk or poorly nourished patients
- No specific recommendation for ARDS/Severe ALI=EN formula with anti-inflammatory lipid

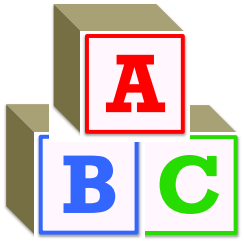
Taylor B, et al. Crit Care Med, 201644(2):390-438

Synopsis of the recommendations for the patients with COVID-19 requiring intensive care as per ASPEN guidelines (May 26, 2020)

Recommendation 1	Nutrition assessement	RDs are recommended to perform a dedicated nutrition-focussed physcial assessment and plan out a safe nutrition protocol
Recommendation 2	Timing of nutrition delivery	Whenever possible, early EN is always preferred with some exceptions (escalating vasopressors, high positive respiratory support, GI symptoms, or bowel ischemia)
Recommendaton 3	Method of nutrition delivery	-Feeding via nasogastric tube is an easy to execute methods that require minimal expertise. -A prokinetic agent can be used as a second step in case of GI intolerance. -Postpyloric EN deliery route is only used in cases when above strategies have failed. -A continous rather than bolus EN is recommended.
Recommendation 4	Nutrition goal and adjustments	-Initiate at low dose (hypocaloric or trophic), slowly advancing to full-dose EN over 1st week (target: 15–20 kcal/kg
Recomendation 5	Formula selection	-Standard high-protein (>20% protein) polymeric isosmotic enteral formula. -A fibre-free formula in cases with significant GI dysfunction
Recommendation 6	Monitoring nutrition tolerance	EN tolerance should be done by daily physical examination and chart reivew to confirm the passage of stool and gas. -Gastric residual volume monitoring is not an ideal indicator for detection of delayed gastric emptying and aspiration risk.
Recommendation 7	Patients with prone position	-Nasogastric tube can be used for EN in proned patients. -Use of postpyloric tube placement in COVID-19 should be limited as much as possible due to the likelihood of exposure to the procedure-performing healthcare providers. -Recommended to keep the patients in reverse trendelenberg position to reduce the aspiration.
Recommendation 8	ECMO and nutrition therapy	-No strong data available for nutrition of COVID-19 patients in ECMO support. -ASPEN recommends low-dose EN for COVID-19 patients on ECMO with slow advancement and close monitoring for enteral feed intolerance.

Journal of Parenteral and Enteral Nutrition, Volume: 44, Issue: 8, Pages: 1439-1446, First published: 16 August 2020, DOI: (10.1002/jpen.1996)

PROTOCOL/ BUNDLE DRIVEN CARE



Assess & Manage Pain, Awake and Breathing Coordination:

- ↓Duration of mechanical ventilation
- ↓Duration of coma
- ↓Mortality

Manage pain first, Choose light sedation & avoid benzos

- ↓Duration of mechanical ventilation
- ↓Mortality
- ↓Delirium

Delirium monitoring & management

- ↑ Delirium detection

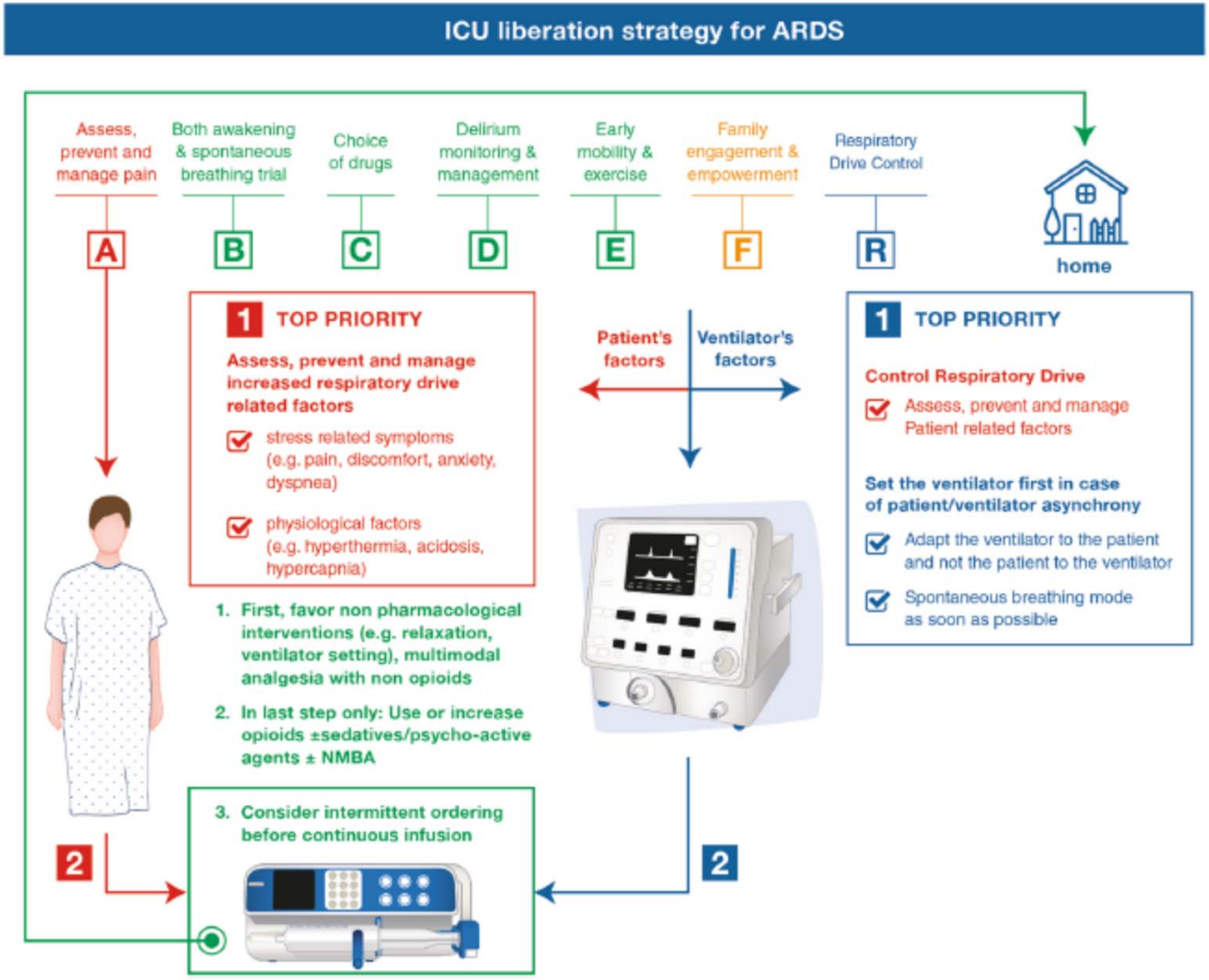
Early Mobility & Environment

- ↓Duration of delirium
- ↓Disability
- ↓ICU Length of Stay
- ↓Rehospitalization/Mortality

Family Engagement

Respiratory Drive Control

Morandi et al Curr Opin Crit Care 2011;17:43-9
Vasilevskis et al Crit Care Med 2010;38:S683-91
Vasilevskis et al Chest 2010;138:1224-1233
Zaal et al, ICM 2013;39:481-88
Colombo et al, Minerva Anest 1012;78:1026-33
Chanques G, et al. Intensive Care Medicine. 2020 Dec;46(12):2342-2356.

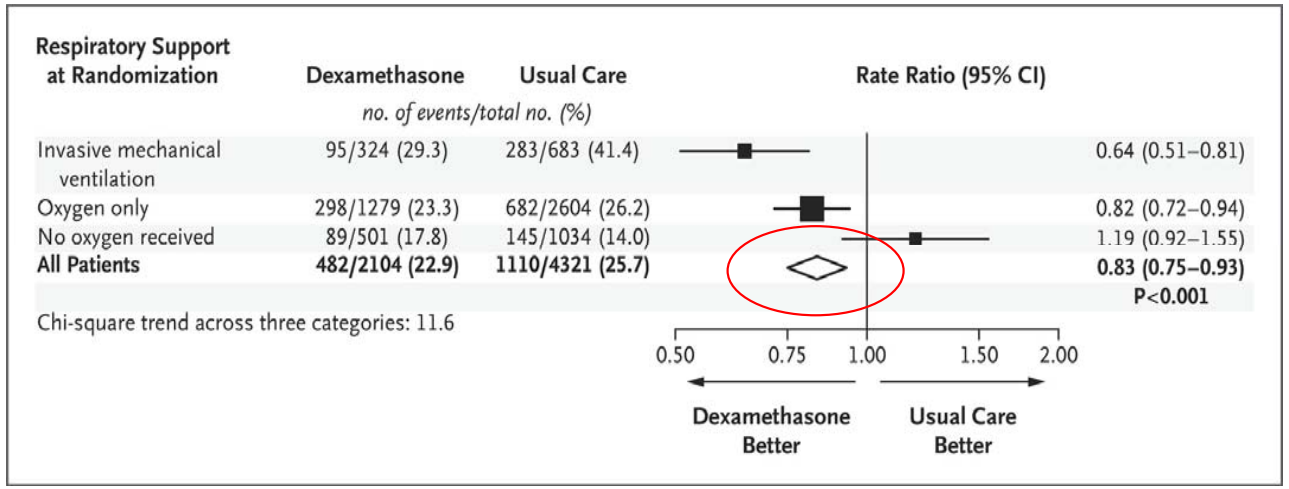


Chanques G, et al. Intensive Care Medicine. 2020 Dec;46(12):2342-2356.

PHARMACOLOGICAL TREATMENT

Recovery Trial: Dexamethasone in Hospitalized COVID Patients

- Controlled open label trial
- Hospitalized COVID patients
  - 2104 randomized to steroid: 6mg x1 daily for 10 days
  - 4321 randomized to usual care



Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.92–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.6

The Recovery Collaborative Group. *New England Journal of Medicine.* 2020;384(8):693-704.

Recovery Trial: Tocilizumab (Preliminary Results)

- Monoclonal antibody
  - Binds to receptor of IL-6
- Randomized open label trial
- COVID patients with
  - Hypoxia O2 sat < 92% on RA
  - Evidence of systemic inflammation (CRP ≥75mg/L)
- Randomized to usual care or usual care & Tocilizumab (400-800 mg dose IV base on weight, repeated on 12-24hrs if condition not improved

- Results : 4116 patients
  - 562 (14% on MV)
  - 1686 (41% on Noninvasive resp support
  - 1868 (45% no resp support)
- 82% of patients receiving steroids at randomization
- Mortality
  - Tocilizumab-29% p=0.007
  - Usual care-33%
- Better benefit in those receiving steroid & tolcilzumab
- Less likely to received mechanical ventilation

Recovery Collaborative Group. https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1

Case Study

- Mr. T is a 44-year-old male 88kg (PBW 75kg) male 6 feet 2 inches. Patient has a week history of fever and chills. He was exposed to a person in the family with COVID. His past medical hx. Is benign. He presents to the ED with a fever 39.5°C complaining of inability to catch his breath. His initial vital signs HR 120, RR 40/min, BP 90/65 with an O2 sat of 92% on room air. Initial labs:
  - ABG: pH 7.19, PaCO2 22, PaO2 55, SaO2 92%, Bicarb 16 /initial
  - Lactic acid: 3.5
  - WBC's: 24,000 with a left shift
  - Platelets: 75,000
  - Electrolytes WNL
  - Chest x-ray shows bilateral infiltrates
  - Patient is intubated, place on a ventilator with V_t 525, AC 26, FiO2 of 100%,PEEP 5 & transferred to the ICU

Does the patient meet the diagnostic criteria for ARDS? If so, what type category of hypoxemia does he present

A. mild

B. moderate

C. severe

C. Severe

Patient continues to experience problems with oxygenating. The PEEP is now at 15cm H2O.

What would be the next step in supportive care to maximize his oxygenation?

A. recruitment maneuver followed by PEEP of 24

B. ECMO

C. Prone positioning

D. High frequency oscillation ventilation

C. Prone Positioning

Post ICU Discharge & Long Term: How Do We Help?

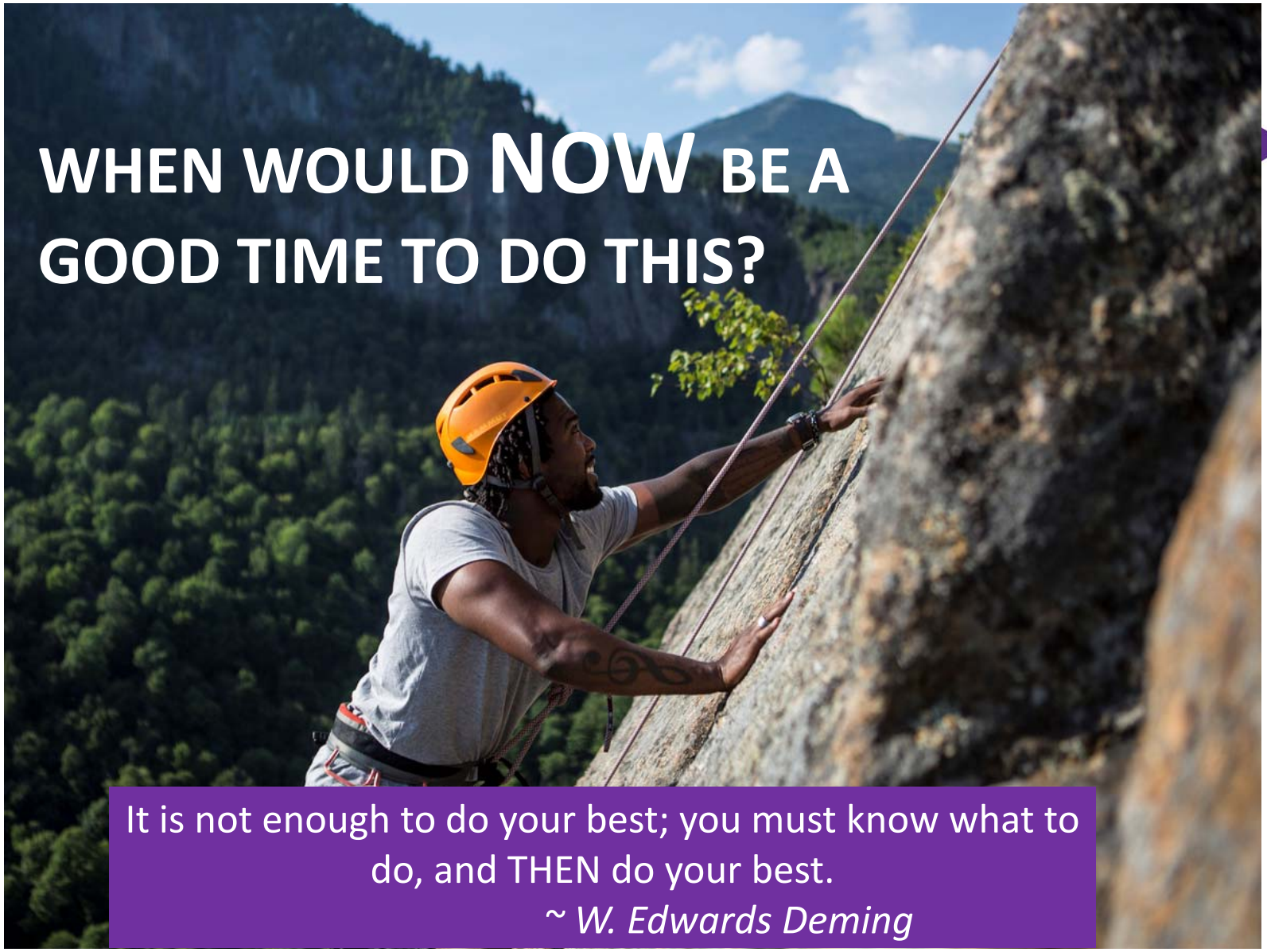
Long Term Follow Up: Managing Medical Complexity

- Understanding baseline health and functional status are important determinants of subsequent morbidity after critical illness
- Critical illness erodes baseline health and increases medical complexity
- Specialized inpatient and longitudinal interprofessional and multidisciplinary team-based care
- Case complexity necessitates the simultaneous, integrated, multipronged approach that is dynamic and extends over years until outcome or functional status stabilizes

Formal Patient/Family Center Follow-Up After ARDS

Herridge MS, Am J Respir Crit Care Med, 2017;196(11):1380-1384

- Preventing Progression
- Confirming practices with larger studies
- New Pharmacological agents
- Models for long term follow up
- ?


WHEN WOULD NOW BE A GOOD TIME TO DO THIS?
It is not enough to do your best; you must know what to do, and THEN do your best.
~ W. Edwards Deming

Questions

kvollman@comcast.net