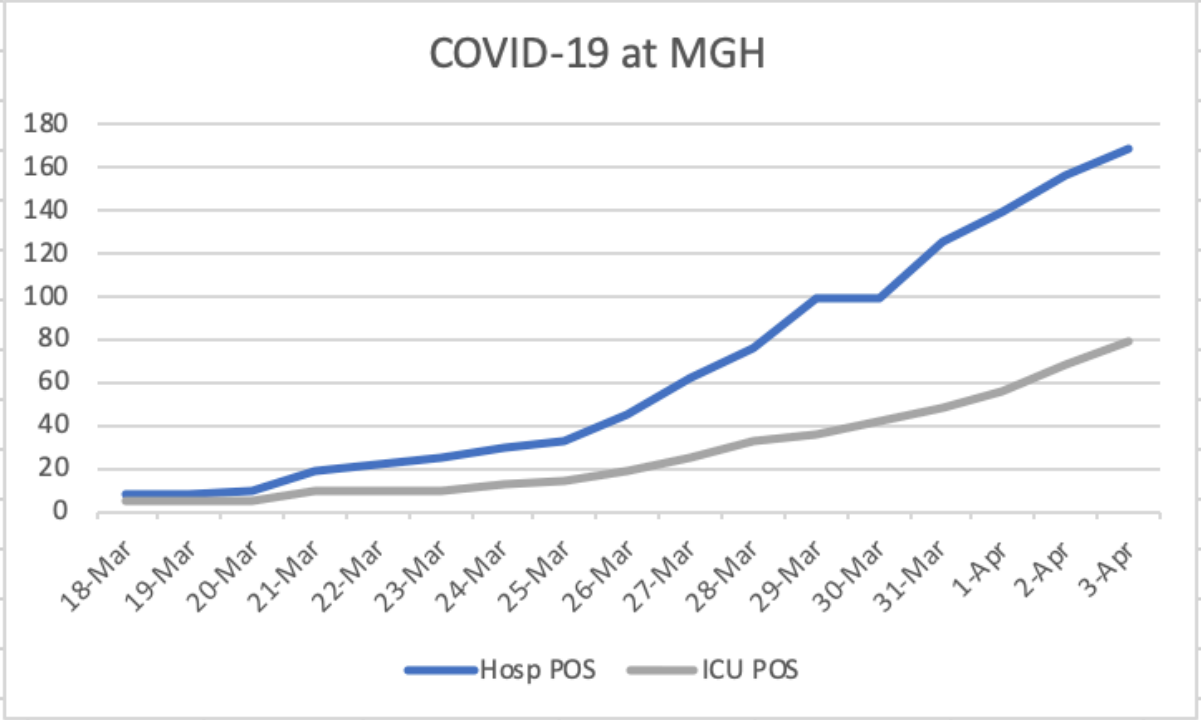
ICU Management ofCOVID 19

Corey Hardin MD, PhD

April , 2020

4/4/20	ICU Total	Blake7 MICU	Blake12 ICU	Ellison9 CCU	Ellison4 SICU	Lunder6 NICU	Blake8 CSICU	Bigelow 6 PICU	E14 Burn ICU	Lunder7 NICU	Lunder9 NICU
COVID+ ICU	**78**	15	14	13	14	11	1	5	4	1	0
RISK ICU	**7**	1	0	0	1	3	1	0	0	1	0
COVID+ ICU Intubated	**74**	14	14	13	14	9	1	5	4		
RISK ICU Intubated	**5**	1	0	0	1	3	0	0	0		
Open Neg Pressure Beds	**11**	0	1	1	0	1	1	1	-	6	



Respiratory Failure and COVID-19

- Somewhere between 5-10% of hospitalized patients with COVID-19 require critical care
  (*Yang et. al.* ***Lancet Respiratory Medicine****, Grasselli et. al* **JAMA 2020**)

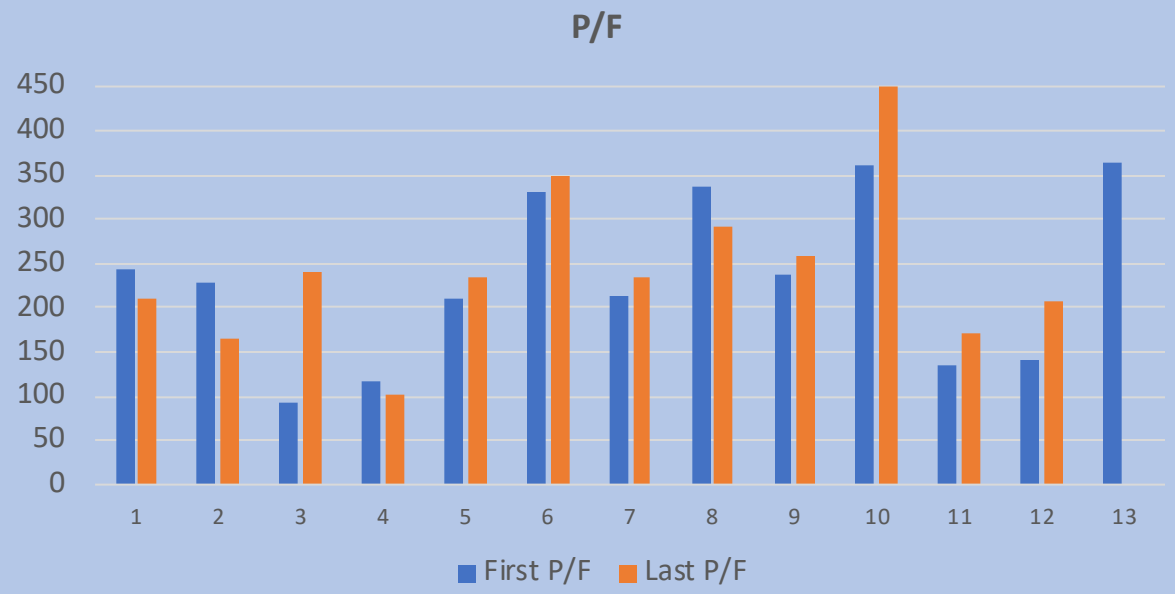
- AGE > 60, lymphopenia, elevated CRP, elevated IL-6 all associated with worse outcome
  (from Runa et. al. **ICM** 2020 ?hyperinflammatory phenotype -> Calfee et al. **Lancet Respir. Med** 2014)

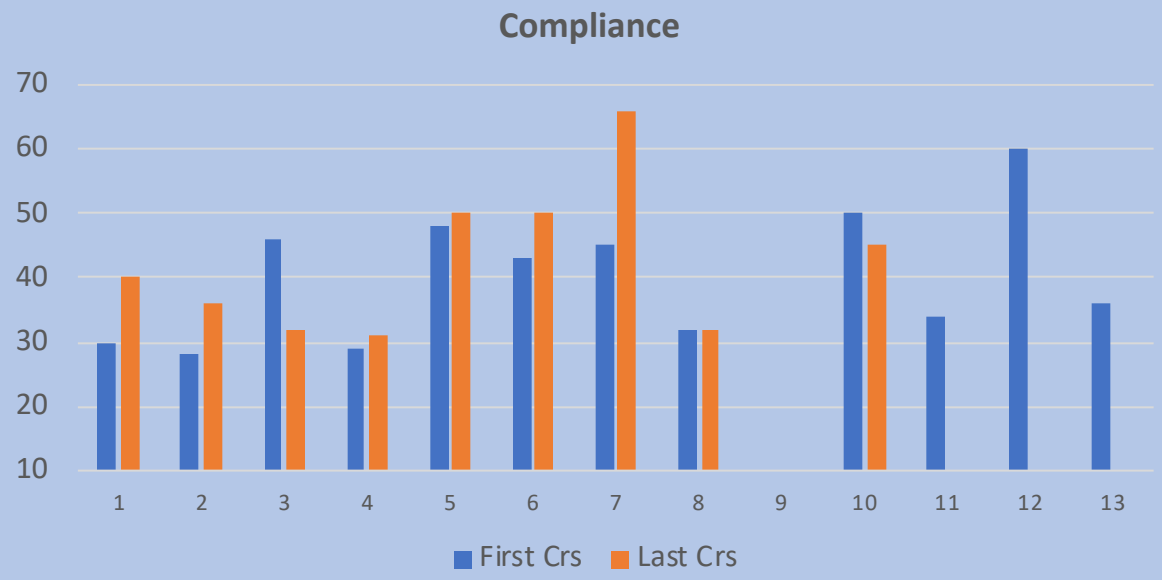
- Median time from presentation to ICU admission is ~10 days

- Critical illness and ARDS can present with rapid decompensation:
  - Rapid increase in f_iO_2
  - Progressive findings on chest imaging
  - Progressive lymphopenia

What brings patients to the ICU?

An Emerging Profile ARDS in the setting of COVID-19





Initial PEEP: 10.1 $\pm$ 1.6 cmH_2O
Initial ΔP: 10.9 $\pm$ 1.2 cmH_2O

Initial airways resistance: 4.8 $\pm$ 1.3 $cmH_2O/L/s$
Average airways resistance: 4.5 $\pm$ 1.1 $cmH_2O/L/s$

Initial static compliance: 40.1 $\pm$ 5.7 mL/cmH_2O
Average static compliance: 42.0 $\pm$ 5.6 mL/cmH_2O

Moderate compliance deficit
Hypoxemia ranges from mild to severe
Responsive to MODERATE PEEP

Data courtesy of David Ziehr MD

Covid-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome

Luciano Gattinoni, Silvia Coppola, Massimo Cressoni, Mattia Busana and Davide Chiumello

Published Online:

MGH COVID-19 Experience

- Moderate compliance deficit (C_{rs} 40)
- P:F not terrible on moderate PEEP (150-200 on PEEP 8-12)

Lung Safe (JAMA 2016)

- P_{plat} 22.6 -23.7 on PEEP 8-10
- P/F:
  - Mild (n=714) 246
  - Mod (n=1106) 149
  - Sev (n=557) 75

Severe ARDS has always been the less common presentation

Berlin Definition of ARDS

	Acute Respiratory Distress Syndrome		
Timing	Within 1 week of a known clinical insult or new/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 (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present		
	Mild	**Moderate**	**Severe**
Oxygenation [b]	**200<PaO_2/FiO_2≤ 300** with PEEP or CPAP ≥ 5 cmH_2O[c]	**100<PaO_2/FiO_2≤200** with PEEP ≥ 5 cmH_2O	**$PaO_2/FiO2$≤100** with PEEP ≥ 5 cmH_2O

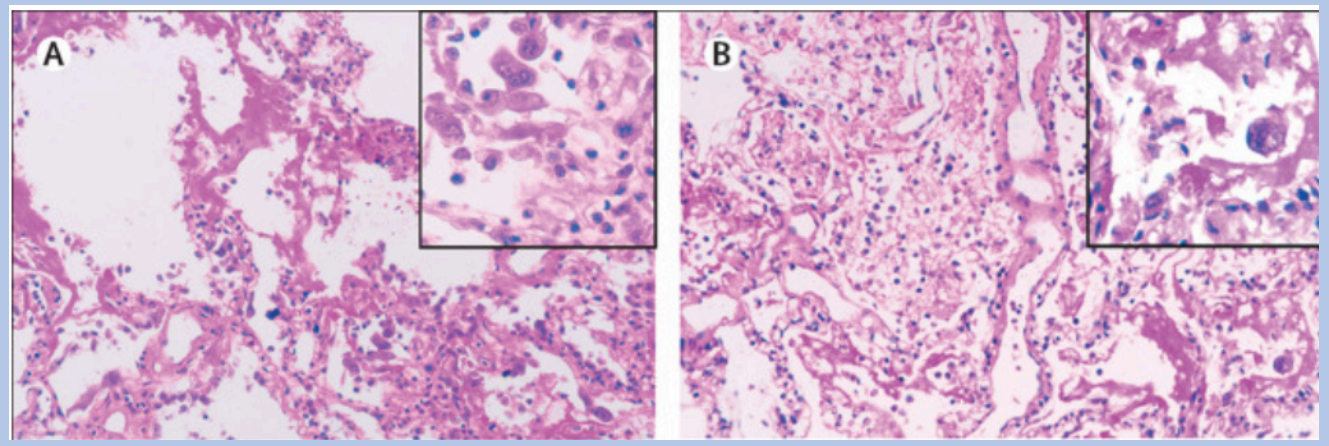
eSUPPLEMENT
1) Radiographs of consensus interpretations of radiographics
2) Consensus case vignettes of “fully explained” by cardiac failure of fluid overload

Ferguson et al ICM 2012

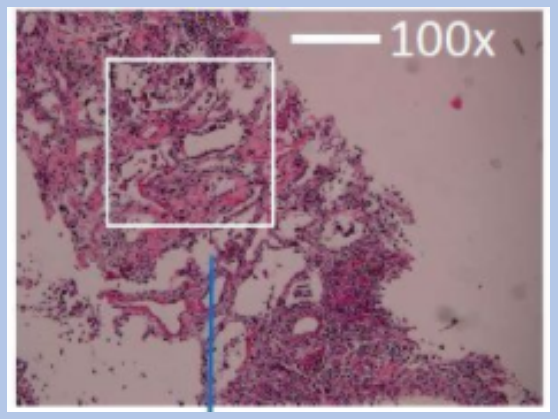
Lowest Pao_2:Fio_2 ratio during mechanical ventilation — median (IQR)‡	
Day 1	142 (94–177)
Day 2	139 (112–171)
Day 3	134 (108–171)
Infection analyses — no. positive/total no.	
Blood cultures	0/20
Sputum cultures	0/15
Influenza A	0/23
Influenza B	0/23
Respiratory syncytial virus	0/23
Extended-spectrum respiratory viruses	0/21
Chest radiography findings — no./total no. (%)§	
Clear	0/23
Bilateral infiltrates	23/23 (100)
Pleural effusion	0/23
Computed tomography findings — no./total no. (%)	
Bilateral ground-glass opacification	4/5 (80)
Nodules	1/5 (20)
Pleural effusions	0/5

Bhatraju et. al. NEJM 2020

Available Pathology from COVID-19 is Consistent with Diffuse Alveolar Damage



Xu et. , Lancet Respir. Med , 8:420-422



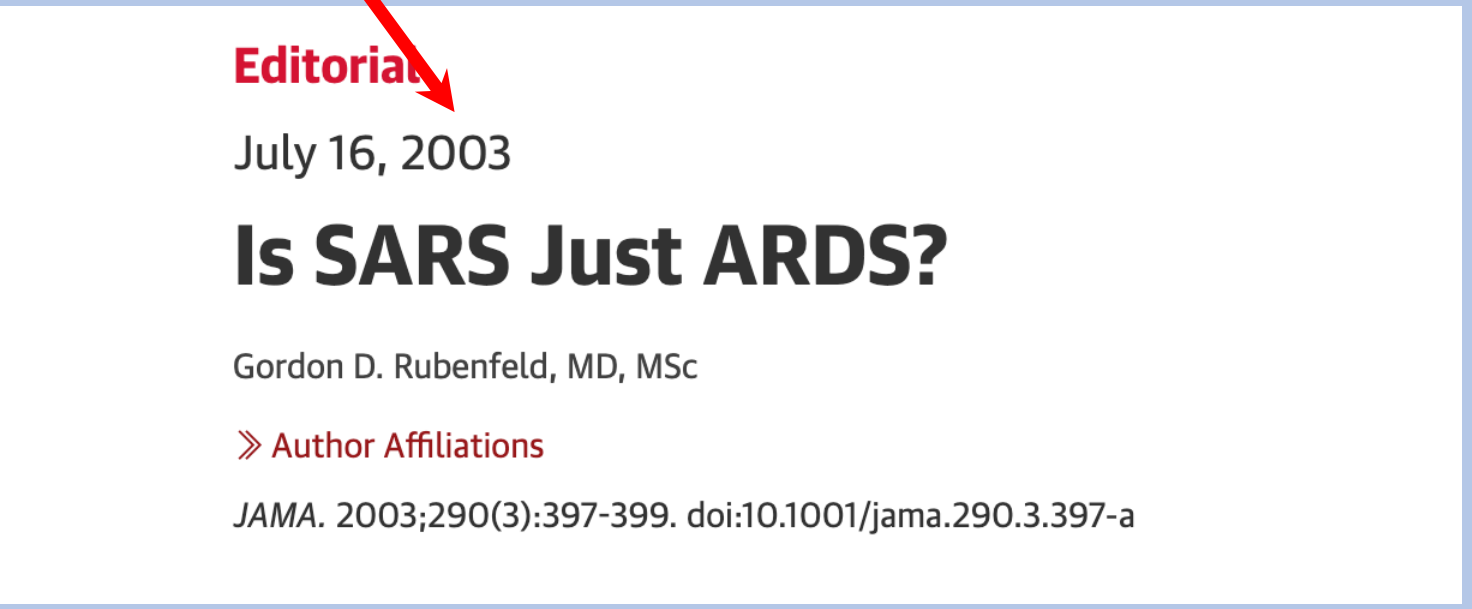
Zhang et. all Ann. Int Med 2020

- Loss of penumocytes
- Hyaline membranes
- Consistent with Diffuse Alveolar Damage (DAD)

Unpublished autopsy series from Seattle:

9/12 pts with DAD

3 years after ARMA (ARDSnet 1)



Editorial

July 16, 2003

Is SARS Just ARDS?

Gordon D. Rubenfeld, MD, MSc

» Author Affiliations

JAMA. 2003;290(3):397-399. doi:10.1001/jama.290.3.397-a

- SARS-CoV-1 and SAR-CoV-2 ~80% sequence homology
- Same mechanism – S protein binds ACE2 receptor
- Same clinical presentation

Toronto series 38 pts with critical illness 2/2 SARS (SARS-CoV-1)

- Risks similar to SARS-CoV-2:
  - Age > 50
  - CAD, DM
  - CRP,LDH,DK
- Vt > 8cc/kg , 6 pts 1 survivor
- Vt < 6cc/kg, 23 pts, 15 survivors
- No difference in survival with steroid treatment

Non-standard ARDS care can result in excess mortality

COVID-19 is ARDS

	Acute Respiratory Distress Syndrome		
Timing	Within 1 week of a known clinical insult or new/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 (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present		
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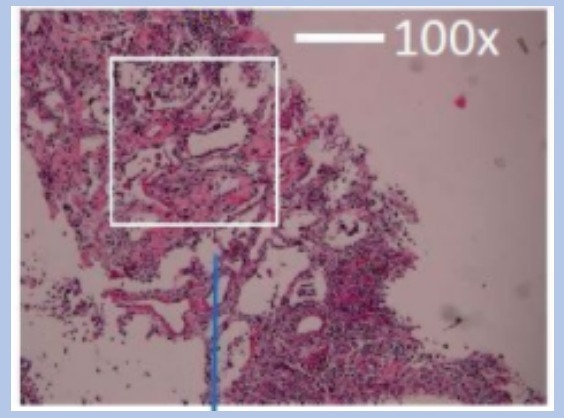
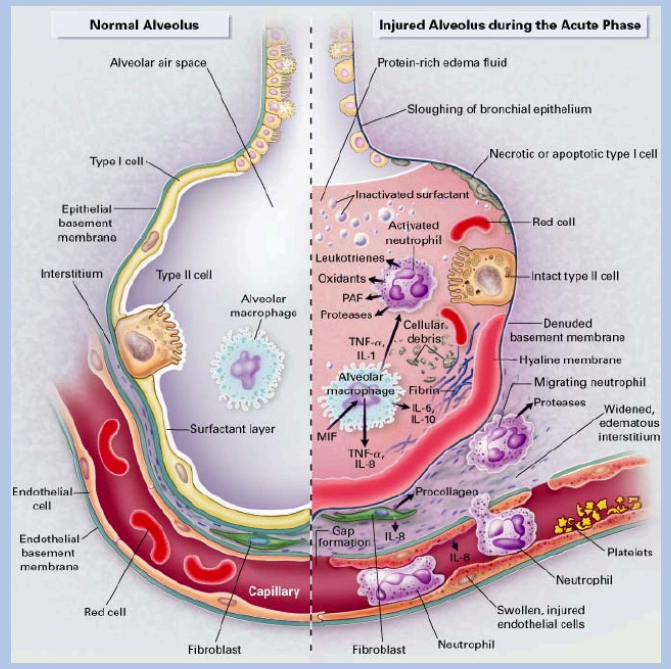


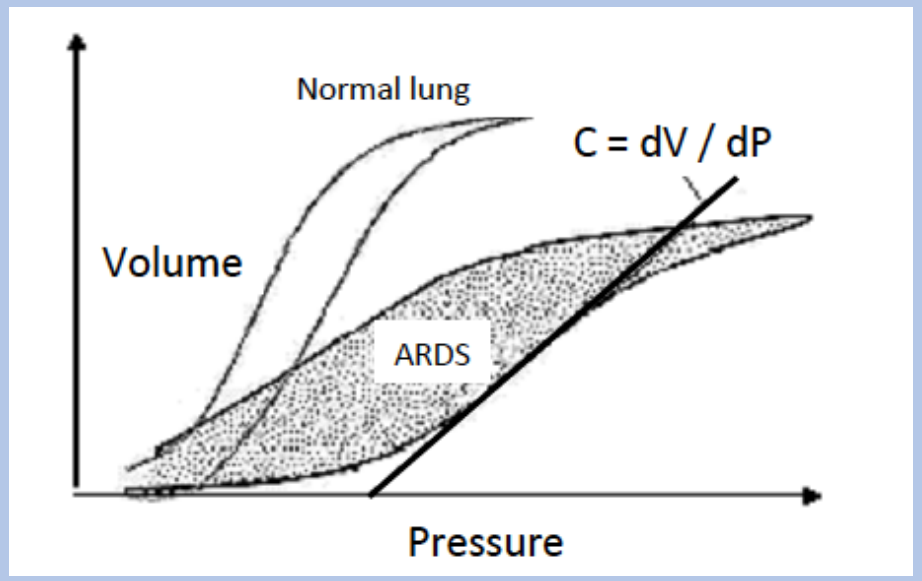
- Acute onset hypoxemia with P:F < 300
- Bilateral infiltrates
- Not caused by heart failure
- DAD

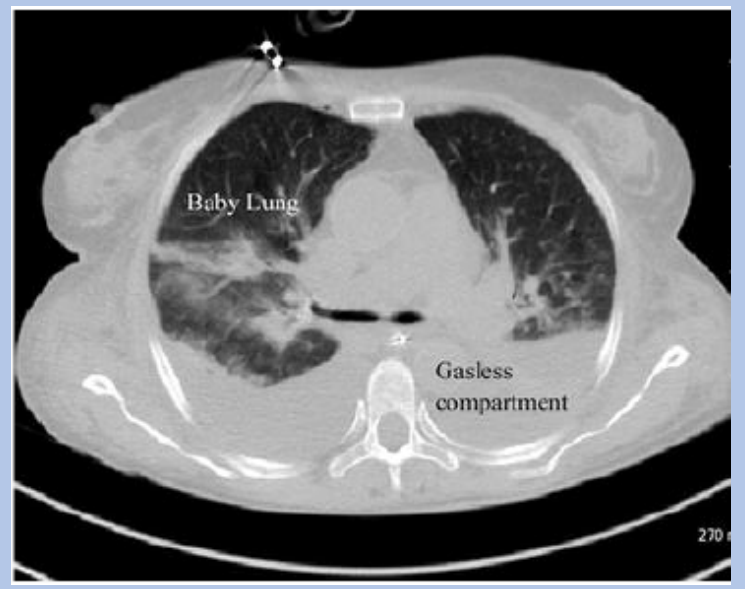
Respiratory Failure in COVID-19 is ARDS

Pathophysiology of ARDS



Ware and Mathay 2000





Gattinoni, L et al. ICM 2016

- Increased permeability of alveolar-capillary interface
- Surfactant dysfunction -> alveolar instability. Cellular apoptosis

- Alveolar instability = increase in opening pressure of some units
- Other units may have preserved mechanics

- Collapse of unstable units -> shunt (perfusion without ventilation) -> hypoxemia
- Remaining 'Baby Lung' may be over-distended by usual V_t

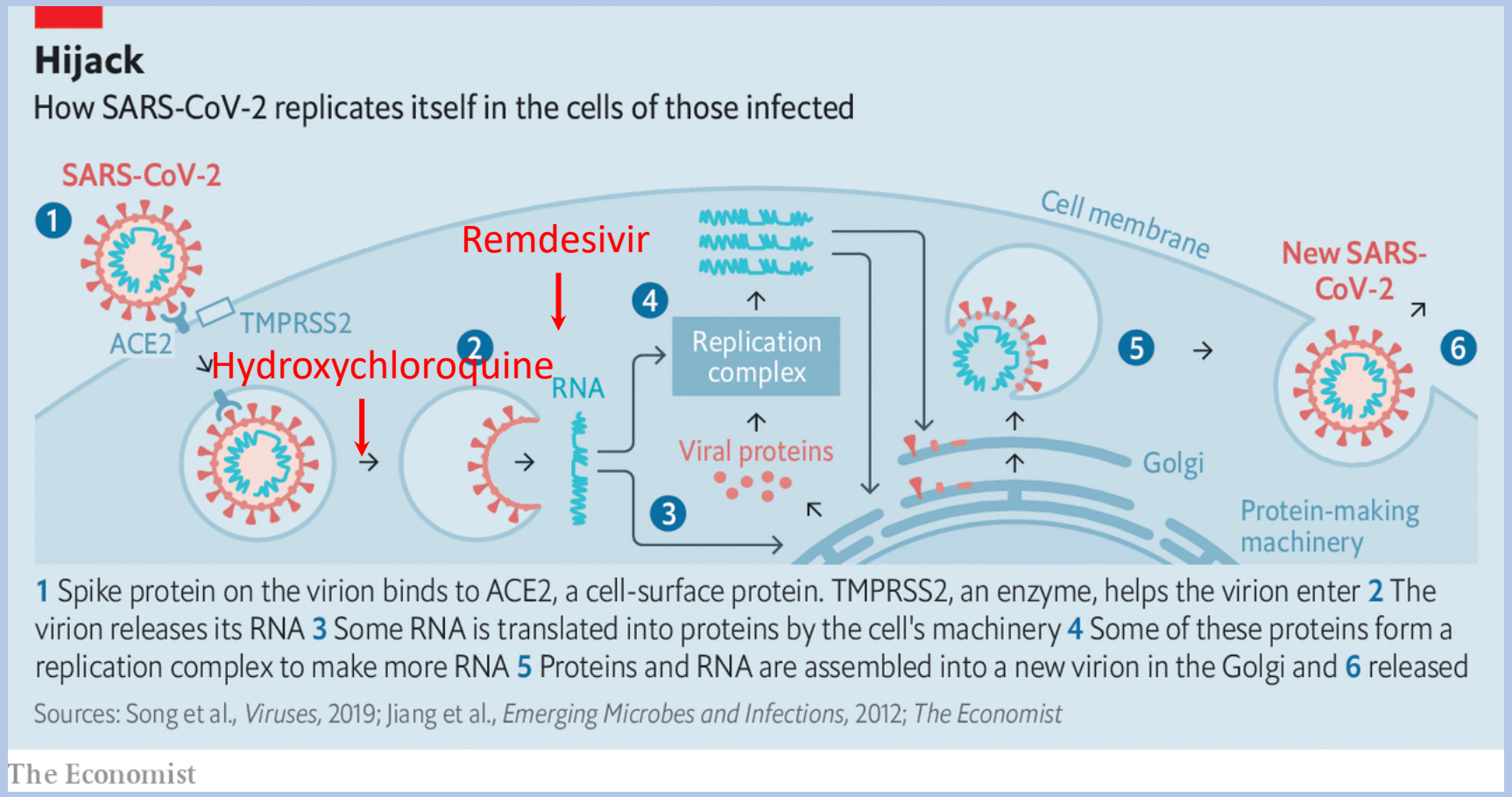
Management of ARDS

Drug Trials for Sepsis/ARDS: No Specific Rx

- nitric oxide
- surfactant/perflourocarbon
- corticosteroids
- prostaglandin E1
- lysophylline
- ibuprofen
- procysteine
- anticytokine/antiendotoxin
- ketoconazole
- streptokinase
- neutrophil elastase inhibitor
- $sPLA_2$ Inhibitor
- rhAPC
- Albuterol/salmeterol
- furosemide
- Cisatricurium
- Heparin
- IL-1 receptor antagonism

- In general – no specific therapy for ARDS.
- No proven therapy for ARDS in the setting of COVID-19

Novel Agents for COVID-19



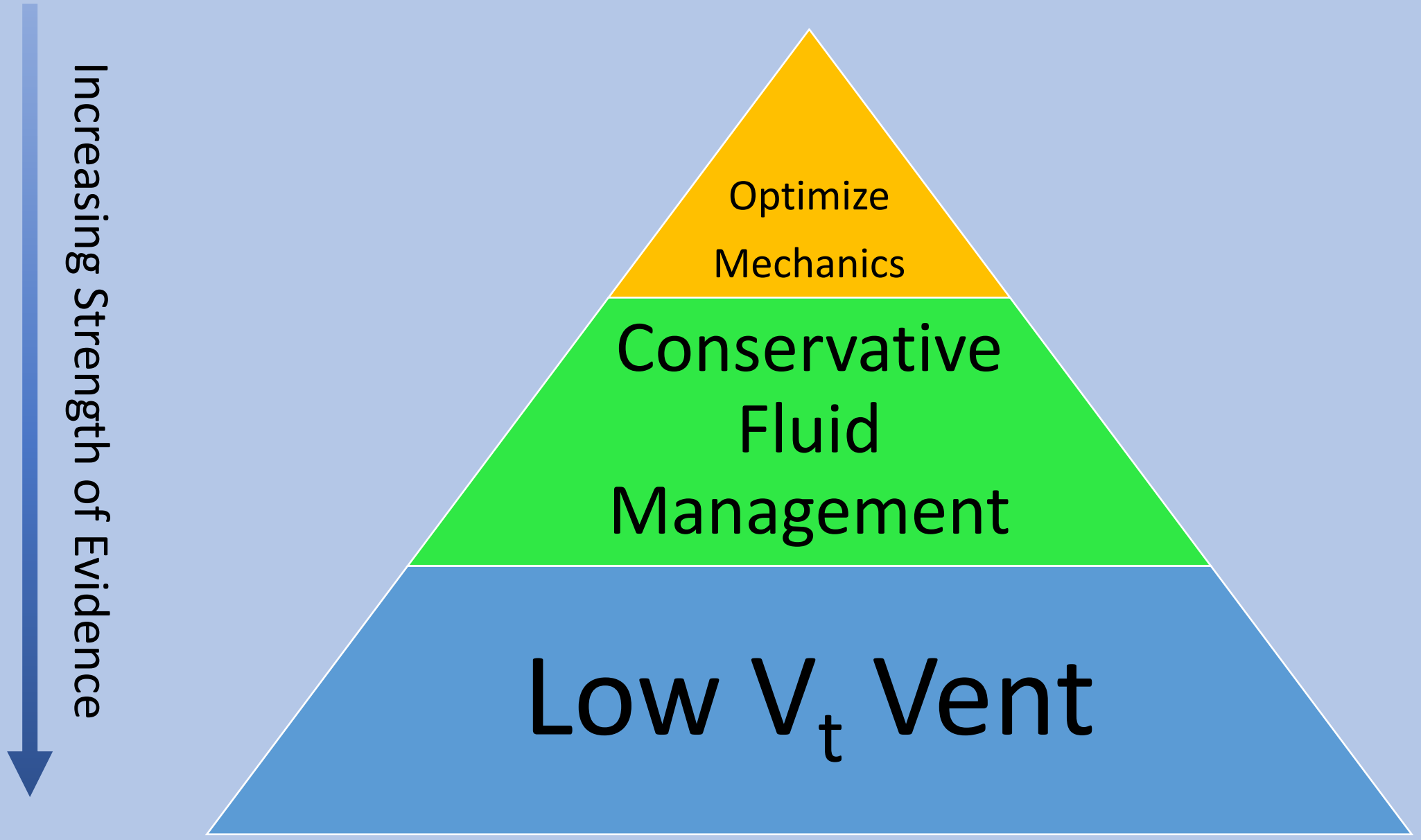
- **Remdesivir**: RNA polymerase inhibitor. Inhibits SARS-1 in animal models. Trials ongoing
- **Hydroxychloroquine:** Dramatic results reported in small study with questionable methodology (Gautret et. al)
- (Molina et. al (https://doi.org/10.1016/j.medmal.2020.03.006) same dosing, 11 patients, no effect on viral replication
- **Statin** – (Calfee Lancet Respir Medicine 2018) Reanalysis of HARP-2 data in inflammatory subtype showed lower mortality. Overall study neg.

Novel Agents for COVID-19

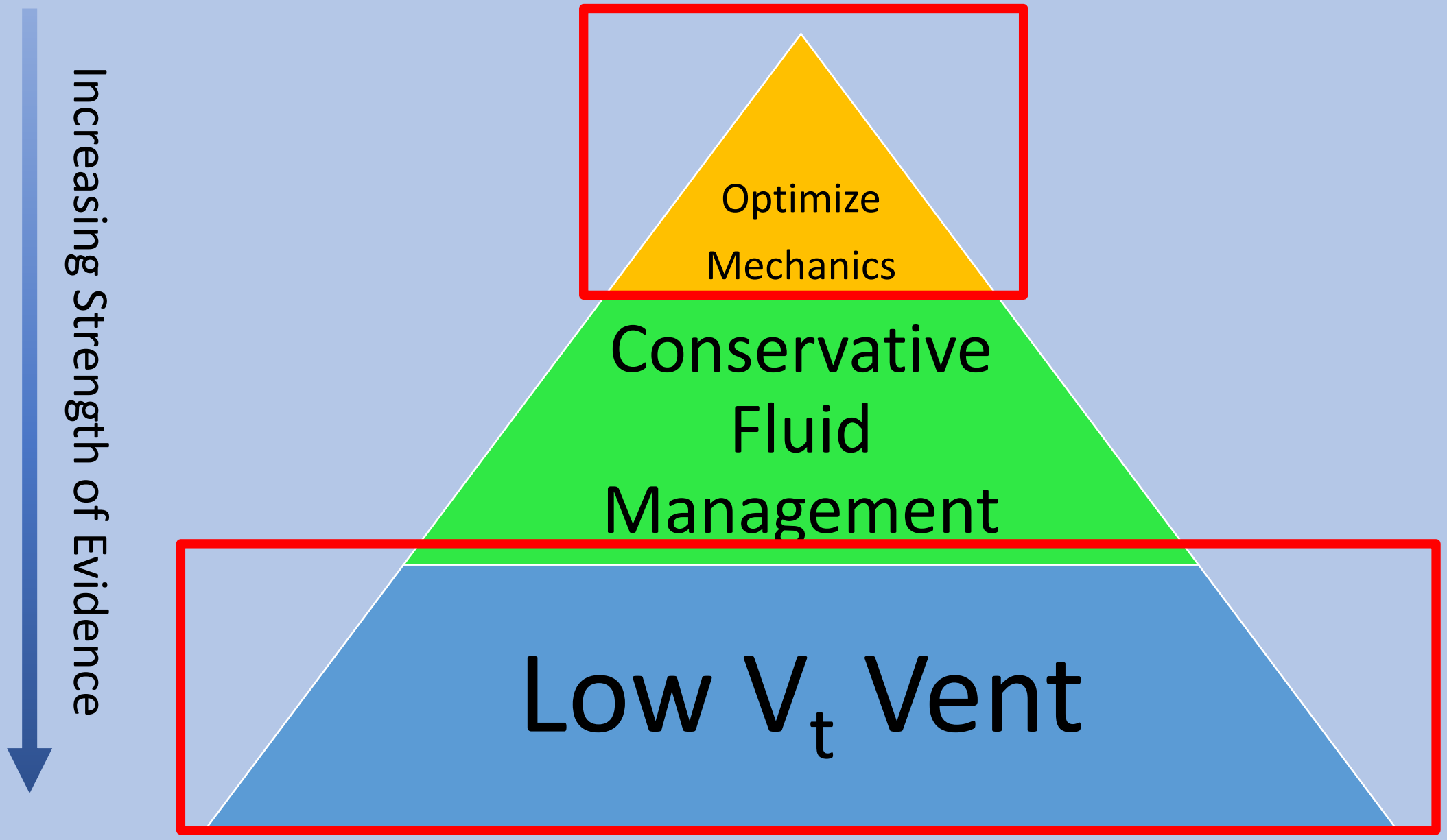
- There are no evidenced–based therapies for SARS-CoV-2 infection or COVID-19.
- Anti-infectives usually improve outcome in ARDS/Sepsis – trials ongoing
- Speculative approaches:
  - Anti-cytokine therapies – failed already in sepsis/ARDS
  - Anticoagulation – failed already in ARDS
  - Steroids – failed in late ARDS, harm in flu, SARS, MERS

Care for COVID-19 will be largely supportive

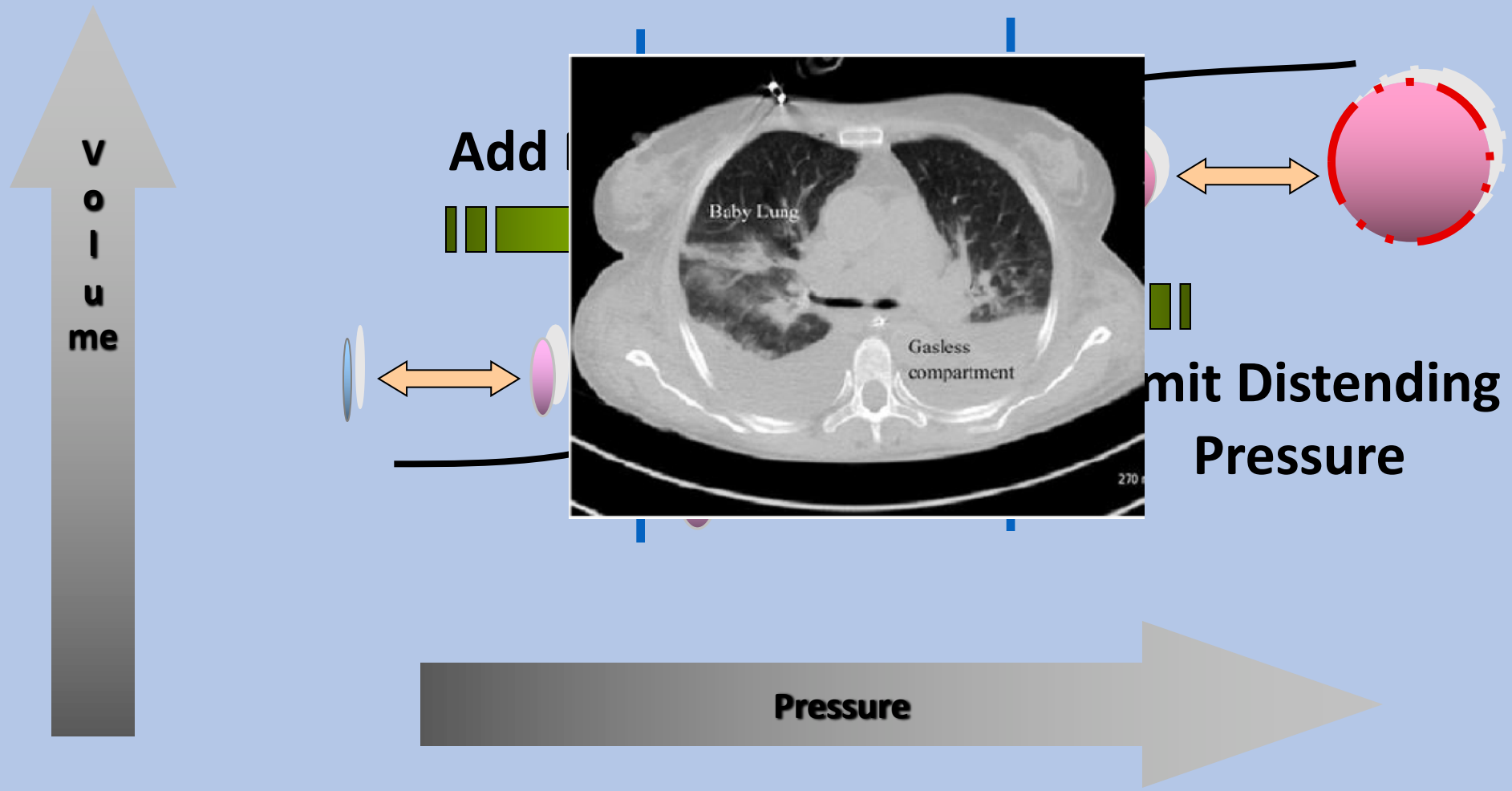
Cornerstones of ARDS Management



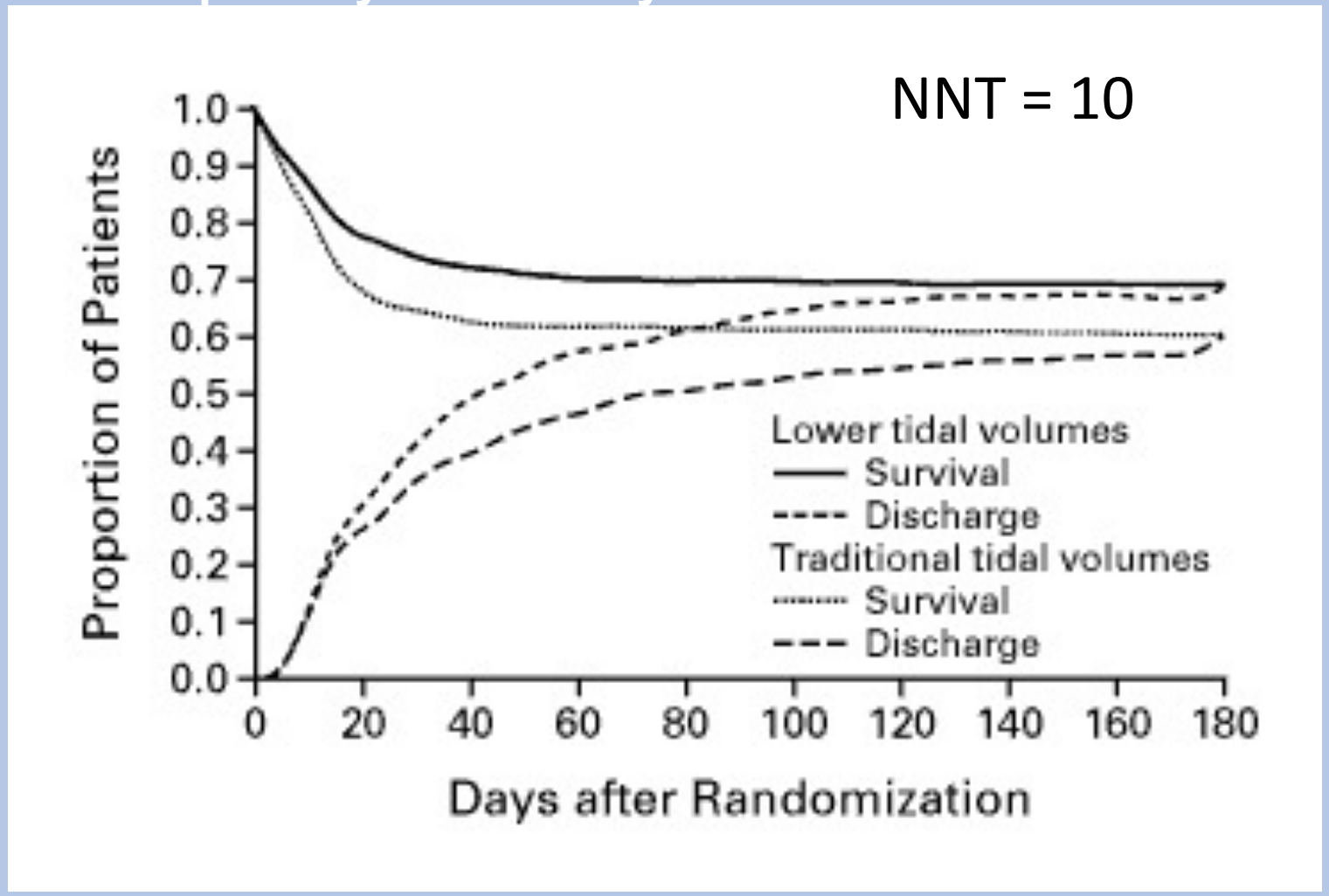
Cornerstones of ARDS Management



“Lung Protective” Ventilation



Probability of Survival and of Being Discharged Home and Breathing without Assistance during the First 180 Days after Randomization in Patients with Acute Lung Injury and the Acute Respiratory Distress Syndrome.



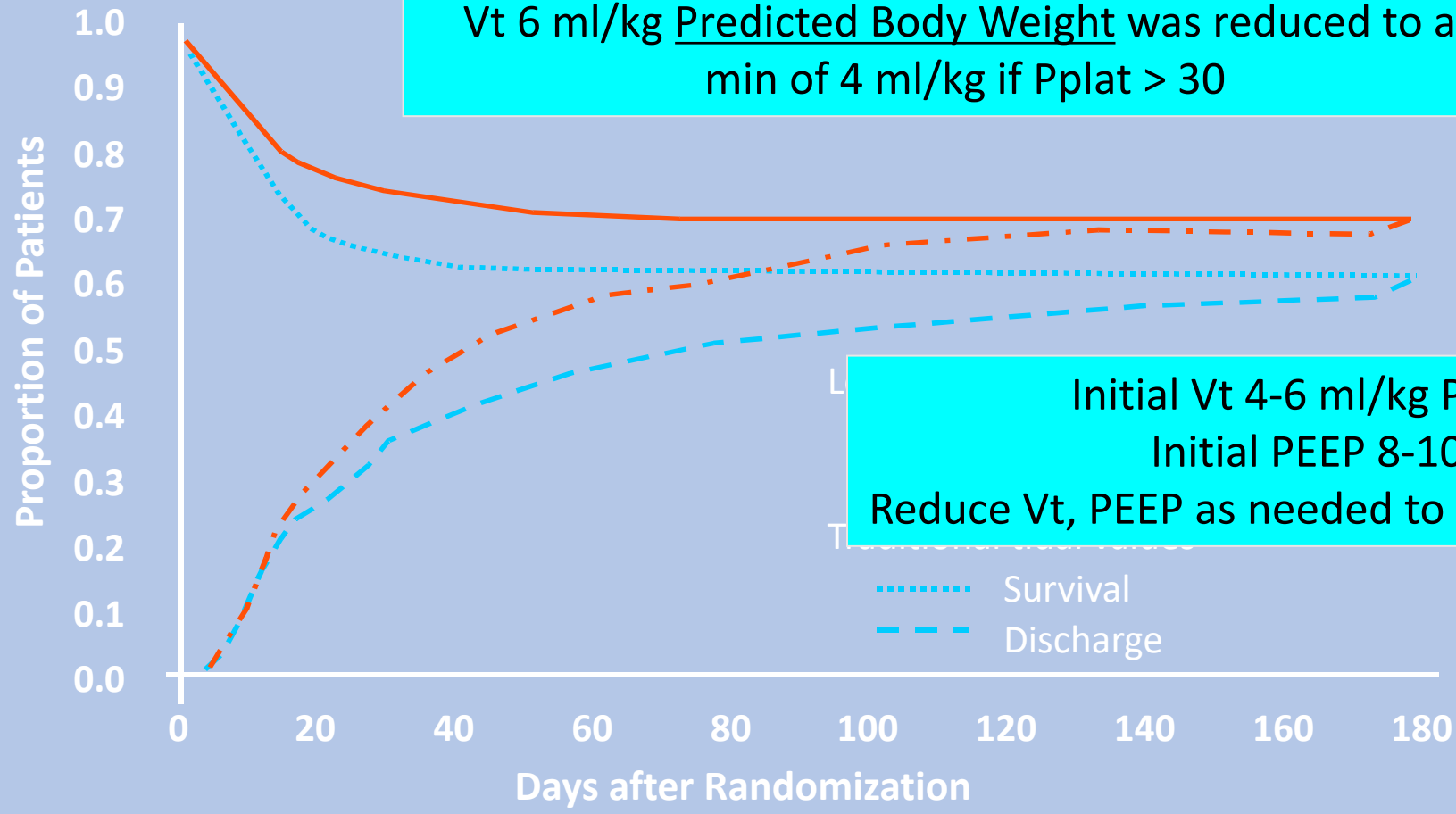
The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342:1301-1308.

The NEW ENGLAND JOURNAL of MEDICINE

ARDS Net I

Airway pressure *and* Volume Limited Strategy

Vt 6 ml/kg Predicted Body Weight was reduced to a min of 4 ml/kg if Pplat > 30

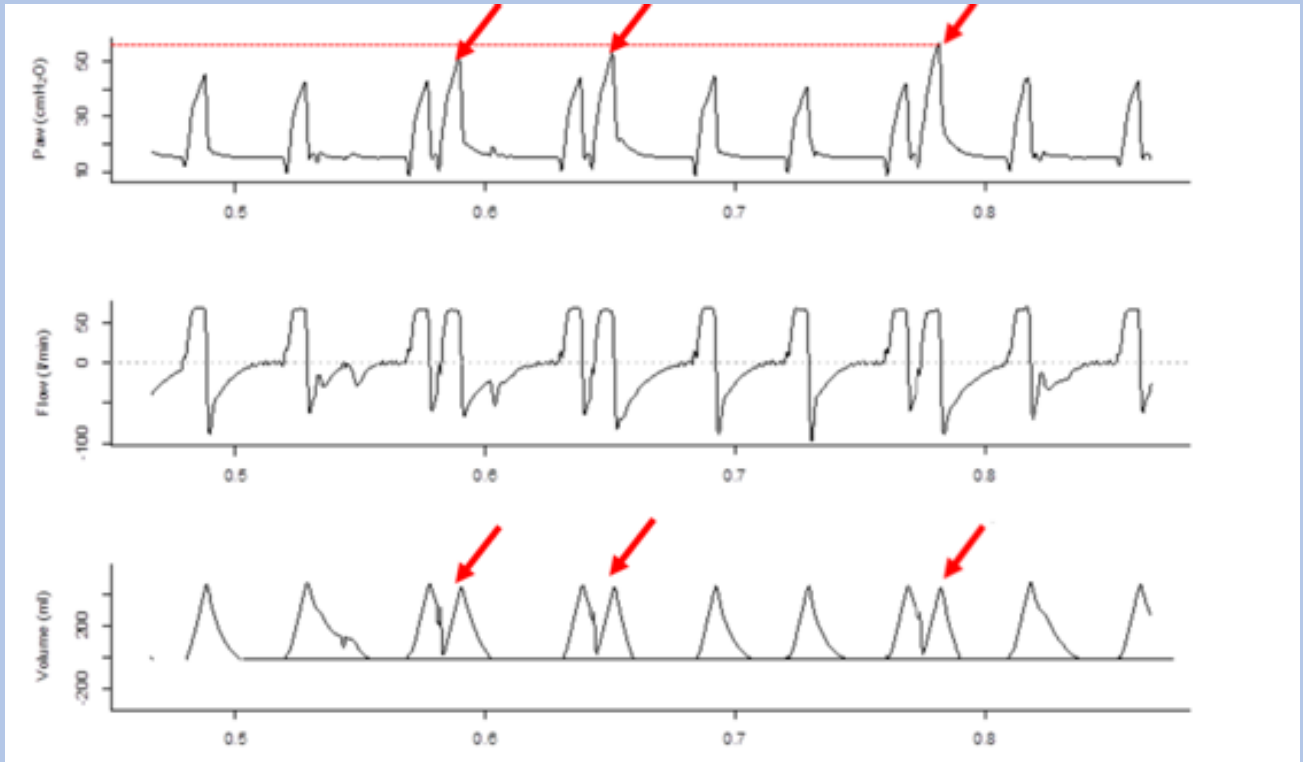


Initial Vt 4-6 ml/kg PBW
Initial PEEP 8-10
Reduce Vt, PEEP as needed to reach Pplat<30

ARDS Net *N Engl J Med* 2000.

Low tidal volume ventilation is not free

- High respiratory drive and low minute ventilation = dysynchrony

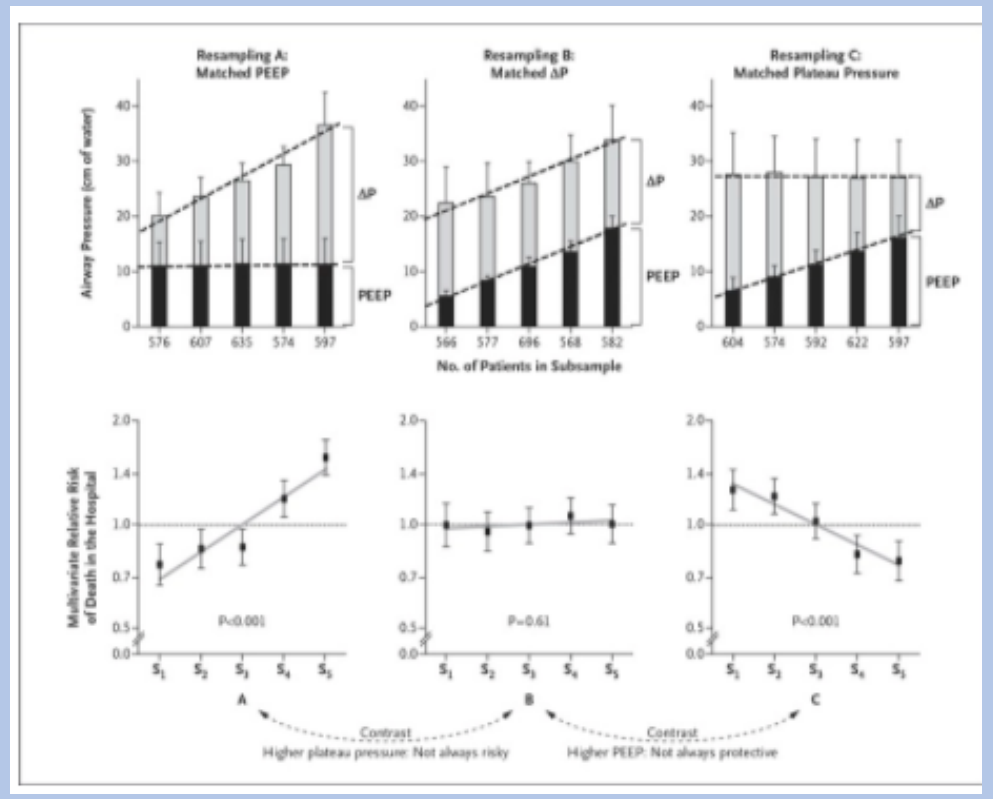


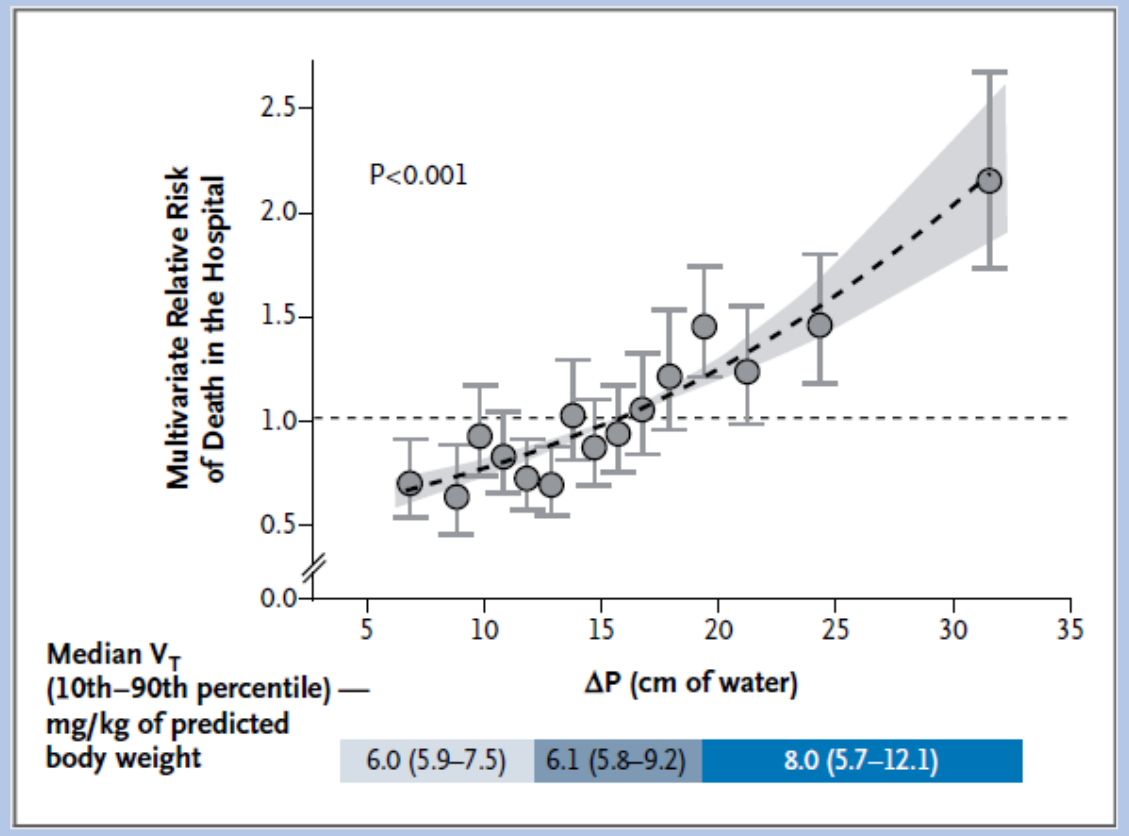
- Trade off is vent compliance vs sedation
- Low V_t will require sedation/paralytic
- Low V_t is the single most established therapy in all of critical care
- Okay to increase sedation:
  - Propofol
  - Dilaudid (fent,morphine)
  - Midaz (Ketamine)
  - Paralytics prn

JAMA. 2017;318(14):1335-1345

Driving Pressure

$\Delta P = P_{plat} - PEEP$. Since $C_{rs} = V_t/\Delta P$, ΔP is tidal volume scaled by compliance





Amato, NEJM 2015

PEEP Titration Methods

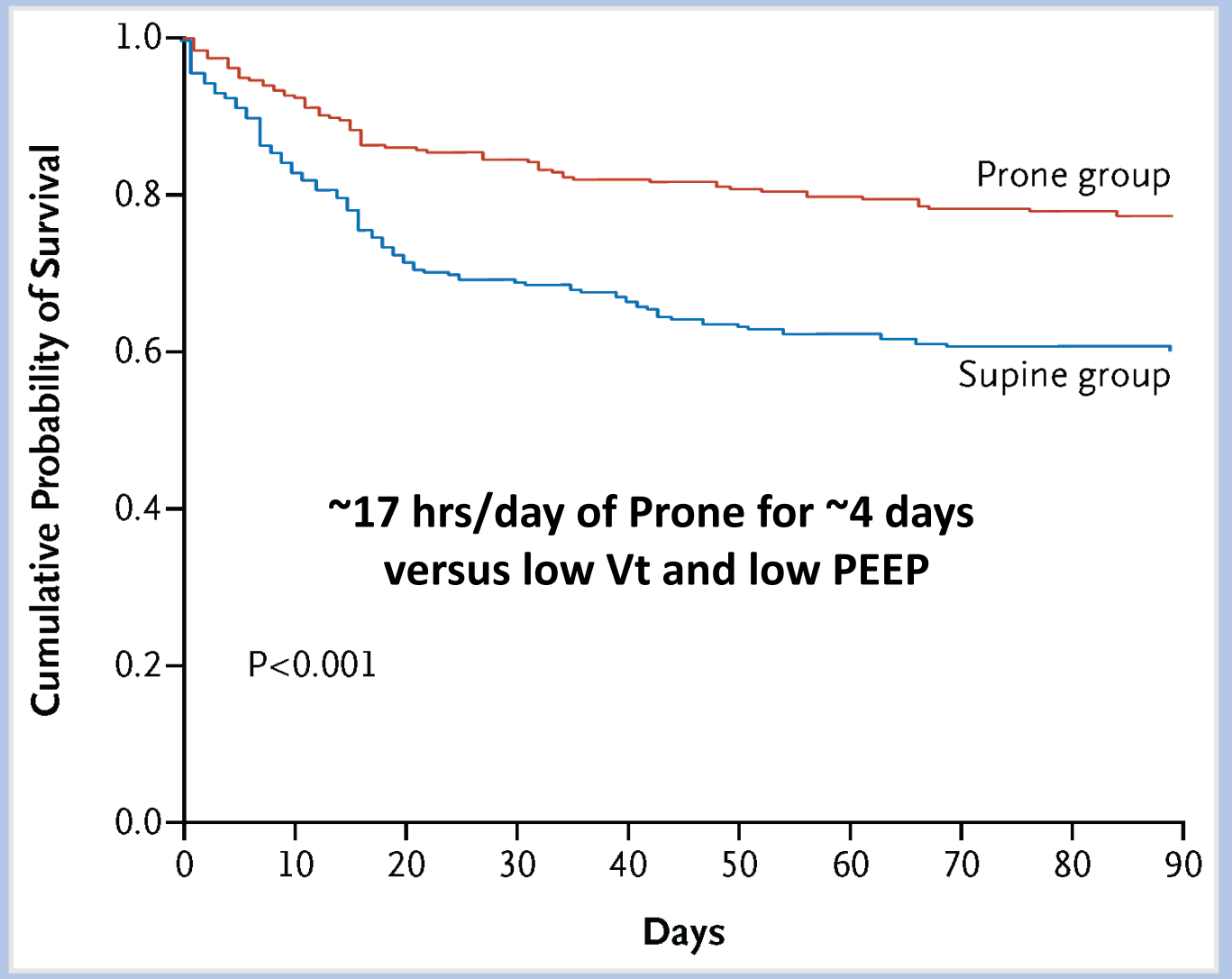
- Multiple methods published
- None superior
- Likely harm associated with aggressive recruitment in unselected patients (ART). Avoid repeated recruitment maneuvers
- COVID-19 Pts so far with relatively preserved mechanics
- Can optimize PEEP via ARDSnet table:

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

What about Prone?



Guerin NEJM 2013

Prone positioning improves survival in severe ARDS: a pathophysiologic review and individual patient meta-analysis

L. GATTINONI [1, 2], E. CARLESSO [2], P. TACCONE [1], F. POLLI [2], C. GUÉRIN [3], J. MANCEBO [4]

TABLE II.—*Mortality rate of patients with severe hypoxemia (i.e., PaO_2/FIO_2 <100 mmHg) in the different trials (prone vs. supine group).*

	Prone-supine II 2009 [20] Prone *vs.* Supine	Mancebo J *et al.* 2006 [18] Prone *vs.* Supine	Guérin C *et al.* 2004 [16] Prone *vs.* Supine	Prone-Supine I 2001 [15] Prone *vs.* Supine
N. of patients	74 *vs.* 76	43 *vs.* 29	90 *vs.* 75	53 *vs.* 46
28-day mortality	37.8% *vs.* 46.0%	41.9% *vs.* 58.6%	47.8% *vs.* 53.3%	60.4% *vs.* 65.2%
ICU Mortality	+8% *vs.* 55.3%	+17% *vs.* 65.5%	+6% *vs.* 61.3%	+5% *vs.* 65.2%
Last follow-up mortality	*vs.* 63.2%	*vs.* 72.4%	*vs.* 65.3%	*vs.* 76.1%

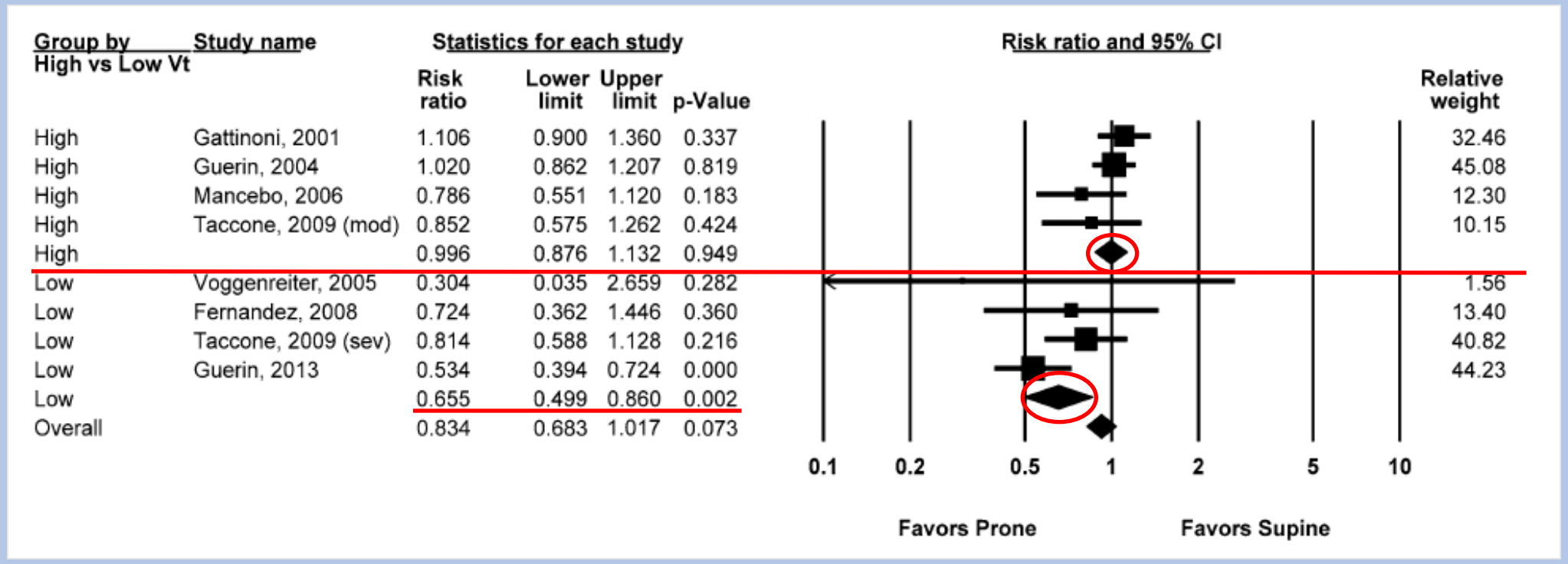
Minerva Anestesiologica 2010

Intensive Care Med (2014) 40:332–341
DOI 10.1007/s00134-013-3194-3

SYSTEMATIC REVIEW

Jeremy R. Beitler
Shahzad Shaefi
Sydney B. Montesi
Amy Devlin
Stephen H. Loring
Daniel Talmor
Atul Malhotra

Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis



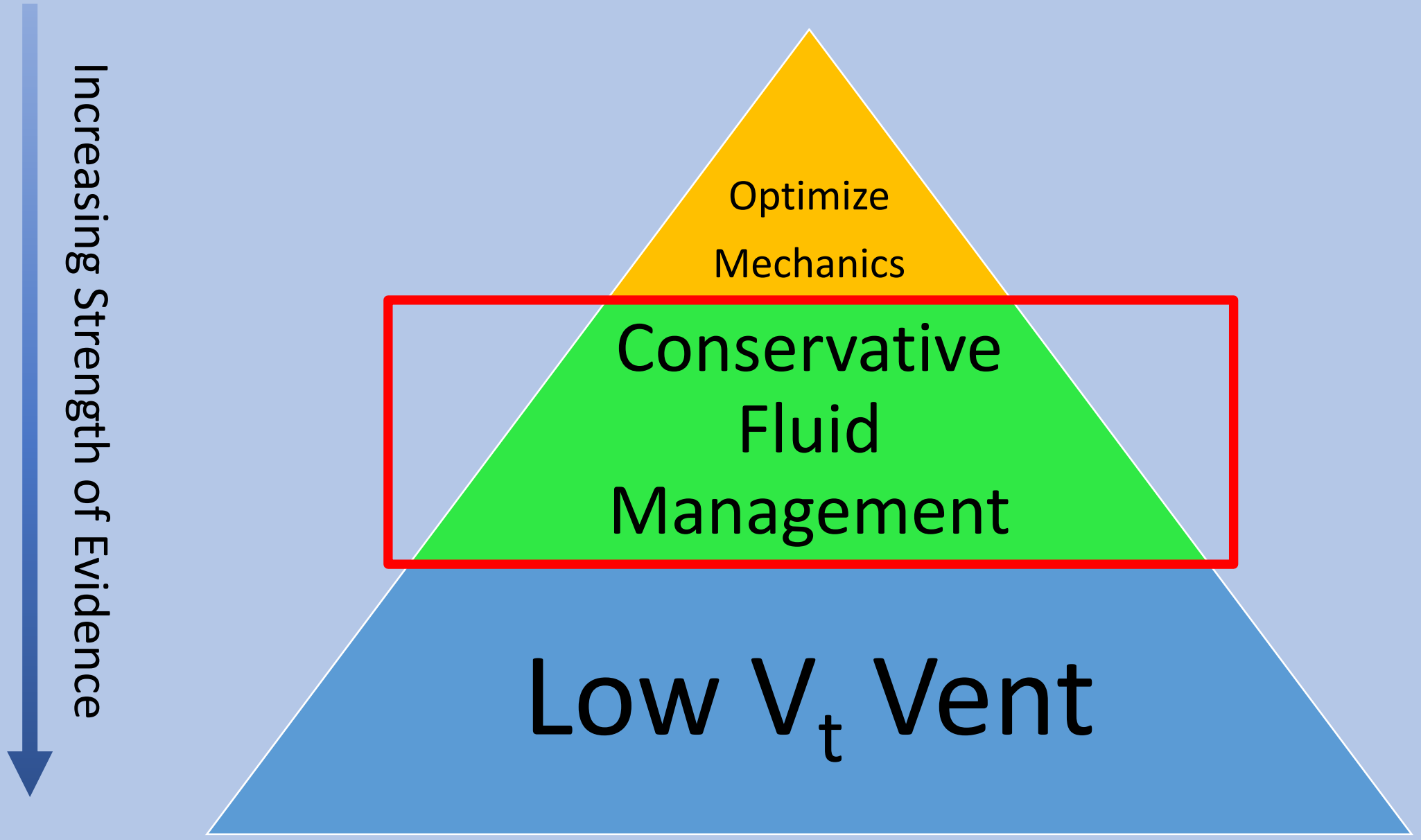
Prone Position

- **Protocol available on Apollo**
- **Safe with few contraindications (unstable spine, sternum)**
- **Consider early, P:F < 150 and not responding to initial attempts to set PEEP**
- **Longer periods in prone are safe and effective – re-supine qAM, less frequently if labile**
- **If P:F > 150 mmHg on 10 or less of PEEP after 2hrs supine can leave supine**
- **Consider PEEP adjustment prior to supine attempt**

Prone Position

- **Prone position only shown to benefit with low Vt vent**
- **Large percentage of COVID-19 getting proned in ICU**
- **But…safe, many centers experimenting in non-intubated**
- **MGH protocol for non-intubated patients approved this week and available on Apollo:**
  - **1 hr prone on admit, RR, SpO2, L/min pre and post**
  - **Encourage prone “more often than not” thereafter**
  - **Escalating O2 – 1 hr prone, mandatory 1 hr re-assess**

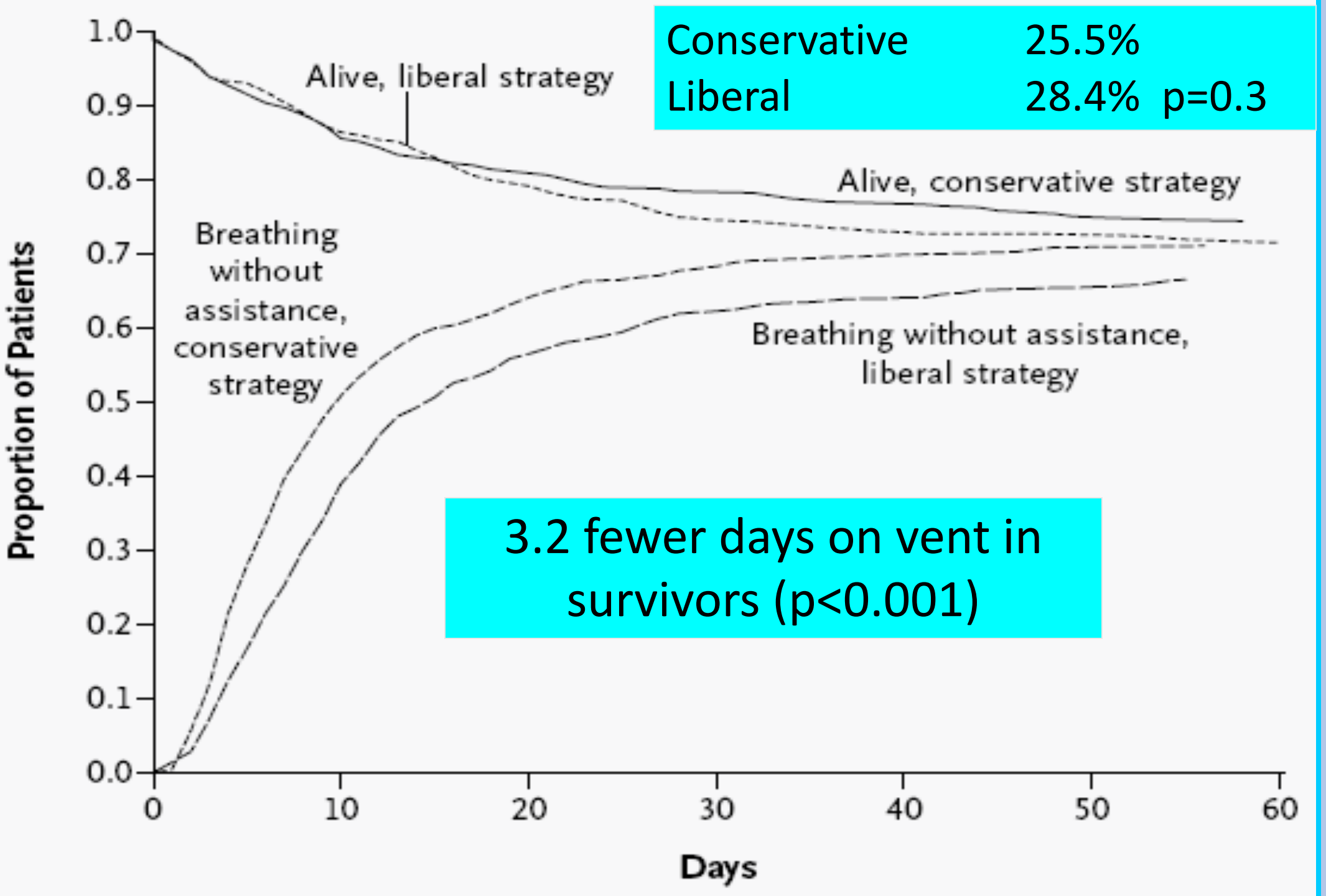
Cornerstones of ARDS Management



Volume Overload is Harmful in ARDS

- High pulmonary vascular pressures and flow
  - May lead to stress failure of capillaries
- Reduction in PAOP a/w improved survival
- EVLW targeted therapy a/w less fluid administration and improved survival
- Hypoproteinemia a/w ARDS and mortality in sepsis
- Diuresis after shock reversal shortens time on vent

West *J Appl Physiol* 2000; Hotchkiss et al AJRCCM 2000;
Humphrey et al. Chest 1990; Mitchell et al. Am Rev Respir Dis 1992
Mangialardi RJ, et al. *CCM* 2000, ARDSnet FACTT NEJM 2006


Conservative 25.5%
Liberal 28.4% p=0.3
Alive, liberal strategy
Alive, conservative strategy
Breathing without assistance, conservative strategy
Breathing without assistance, liberal strategy
3.2 fewer days on vent in survivors (p<0.001)
Proportion of Patients
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
40
50
60
Days

FACTT: Protocol…short form

- <u>When shock-free -> Post-resuscitation fluid management</u>
  - No maintenance fluids
  - Diuretics to *normalize* CVP until off-vent, **as tolerated**
  - Hold diuretic for rising creatinine and/or active urine sediment
  - If patient becomes hypotensive with small increases in PEEP consider hypovolemia.

Shock in COVID-19

- Management is not different than usual distributive shock (levo/vaso, assess for fluid responsiveness)
- Comparatively little multiple organ failure:

Wuhan

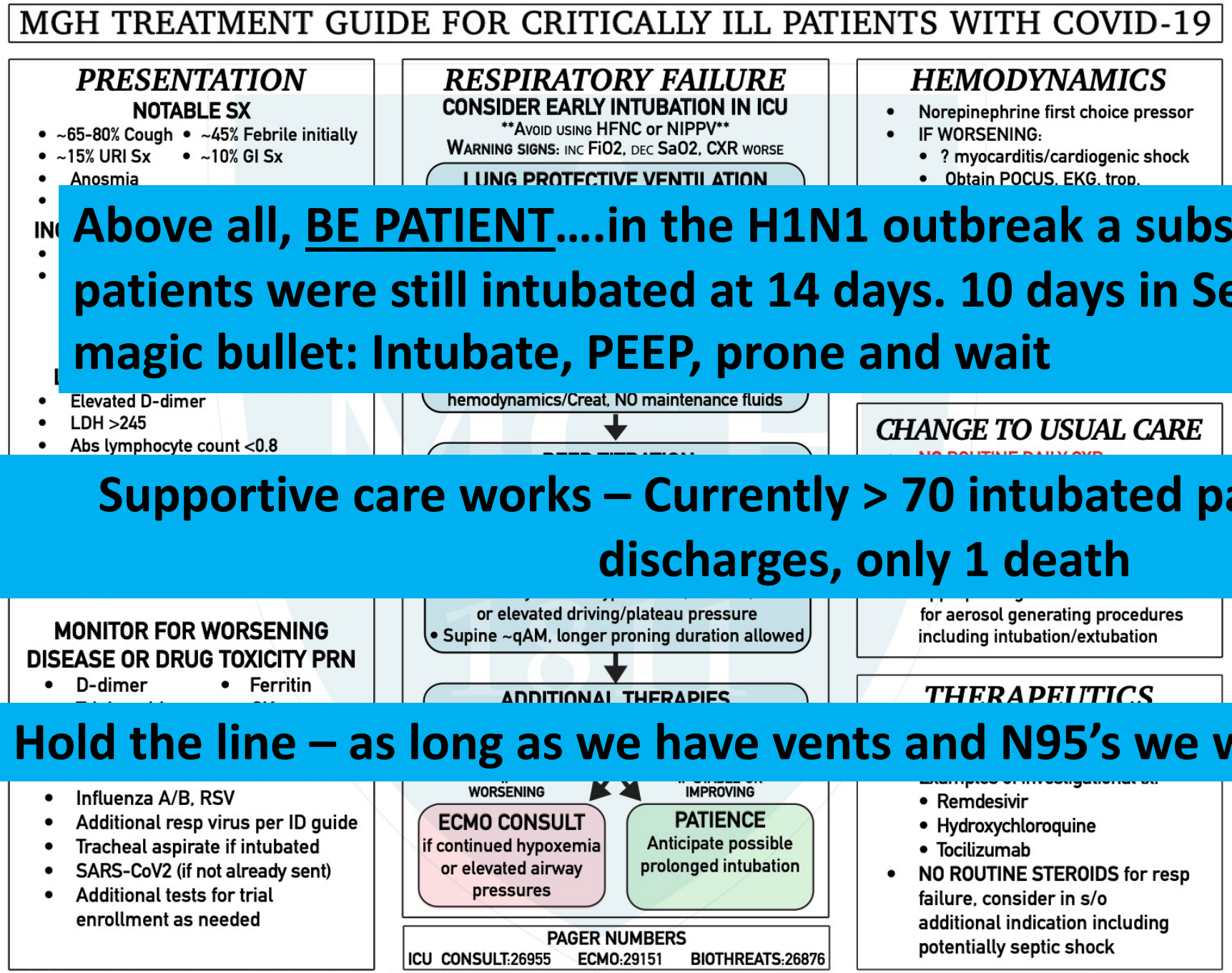
High flow nasal cannula	17 (85%)	16 (50%)	33 (63·5%)
Mechanical ventilation	7 (35%)	30 (94%)	37 (71%)
Non-invasive	6 (30%)	23 (72%)	29 (56%)
Invasive	3 (15%)	19 (59%)	22 (42%)
Prone position ventilation	2 (10%)	4 (12·5%)	6 (11·5%)
Extracorporeal membrane oxygenation	1 (5%)	5 (16%)	6 (11·5%)
Renal replacement therapy	1 (5%)	8 (25%)	9 (17%)
Vasoconstrictive agents	2 (10%)	16 (50%)	18 (35%)
Antiviral agents	13 (65%)	10 (31%)	23 (44%)
Antibacterial agents	19 (95%)	30 (94%)	49 (94%)
Glucocorticoids	14 (70%)	16 (50%)	30 (58%)
Immunoglobulin	9 (45%)	19 (59%)	28 (54%)

Lancet Respir Med 2020

Seattle

Vasopressors	17/24 (71)
Echocardiogram completed	9/24 (38)
Echocardiogram showing new left ventricular dysfunction	0/9

- Variable reports of late myocarditis (7% in one Chinese series)
- Diagnostic criteria not clearly met (“By review of chart”)
- One MGH case now on VA ECMO with isolated cardiogenic shock
- Consider CvO2, EKG, lactate,exam, POCUS is new shock



Above all, BE PATIENT….in the H1N1 outbreak a substantial proportion of patients were still intubated at 14 days. 10 days in Seattle. There is no magic bullet: Intubate, PEEP, prone and wait

Supportive care works – Currently > 70 intubated patients. To date, 8 discharges, only 1 death

Hold the line – as long as we have vents and N95's we will get patients better

Take Home Points

- Standard lung protective ventilation: **Vt 4-6ml/kg PBW**; focus on goals: **Pplat**
- Prone early, prone long
- R/O cardiogenic
- management when out of shock
- Therapeutics unproven, best in context of trial

MGH Protocol for management of COVID-19:

http://apollo.massgeneral.org/coronavirus/wp-content/uploads/sites/78/2020/03/MGH-Critical-Care-of-COVID-19-Protocol.pdf

http://apollo.massgeneral.org/coronavirus/wp-content/uploads/sites/78/2020/03/Covid19_ICU_RX_SUMMARY_FIGURE.pdf

MGH Protocol for Prone Ventilation:

http://apollo.massgeneral.org/coronavirus/wp-content/uploads/sites/78/2020/03/Prone-Positioning-Guideline.clean-1.pdf

Questions?