Updates in Critical Care

2020 Annual Chapter Meeting, Washington ACP

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ACP American College of Physicians Leading Internal Medicine, Improving Lives | Washington Chapter

Outline

Sepsis and Septic Shock
The ongoing debate about Vitamin C

Acute Respiratory Distress Syndrome
Dexamethasone

COVID-19
Management of Respiratory Failure, VTE Prophylaxis in the ICU, Therapeutics

Questions

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SEPSIS

Vitamin C, Hydrocortisone, and Thiamine

Vitamin C in Sepsis

2017 - Study makes headlines as treatment for sepsis

CHEST

Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock

A Retrospective Before-After Study

CrossMark

PODCAST

Paul E. Marik, MD, FCCP; Vikramjit Khangoora, MD; Racquel Rivera, PharmD; Michael H. Hooper, MD; and John Catravas, PhD, FCCP

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Vitamin C in Sepsis

2017 - Study makes headlines as treatment for sepsis

Treatment and Rationale

Vitamin C
(Ascorbic Acid)
1.5 g IV Q6Hr

- Deficient in patients with sepsis
- Beneficial antioxidant effects
- Maintains endothelium integrity, preserving microcirculatory flow
- Required for production of catecholamines and cortisol production

Hydrocortisone
50mg IV Q6Hr

- Synergistic effects with Vit. C
- Assists with uptake of Vitamin C into cells
- Prior studies suggest either Vitamin C or Hydrocortisone alone have no benefit.

Thiamine
200mg IV Q12Hr

- Deficient in patients with sepsis
- Intended to mitigate kidney injury and oxalate formation associated with high dose of Vitamin C

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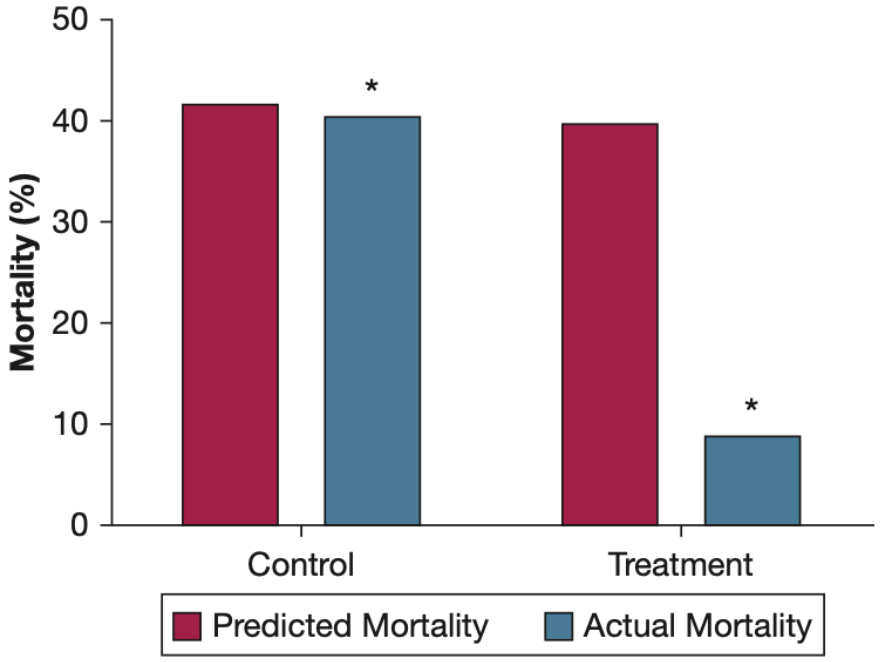
Vitamin C in Sepsis

Before and after unblinded cohort study

Variable	Control (n=47)	Treated (n=47)
Hospital Mortality	40.4%	8.5%
ICS LOS	4	4
Hours on vasopressors	55	18
Renal Replacement Therapy for AKI	33%	10%
SOFA* reduction at 72hr	0.9	4.8

*SOFA = Sequential Organ Failure Assessment Score



Marik PE et al. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. Chest. 2017 Jun;151(6):1229-1238.

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Vitamin C in Sepsis

Takeaways from the 2017 Vitamin C, Hydrocortisone, and Thiamine study

- Very low quality of evidence
- Results appropriately met with skepticism
- More studies are needed

However:

- Seemingly low risk of harm with potential benefit
- A lot of media coverage
- Variable implementation

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Vitamin C in Sepsis: CITRIS-ALI Study

JAMA | Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure

The CITRIS-ALI Randomized Clinical Trial

Alpha A. Fowler III, MD; Jonathon D. Truwit, MD; R. Duncan Hite, MD; Peter E. Morris, MD; Christine DeWilde, RN, PhD; Anna Priday, BS, MS;

- Randomized, double blinded, placebo-controlled, in 7 ICUs
- Population: 167 patients with Sepsis and ARDS for less than 24hr
- Intervention: Vitamin C Infusion (50mg/kg Q 6Hr)
- Primary Outcome:
  - Change in SOFA score at 96hr
  - Reduction in plasma biomarkers of inflammation (CRP) and vascular injury (thrombomodulin)
- Secondary Outcome (46 total)
  - All-cause mortality at day 28

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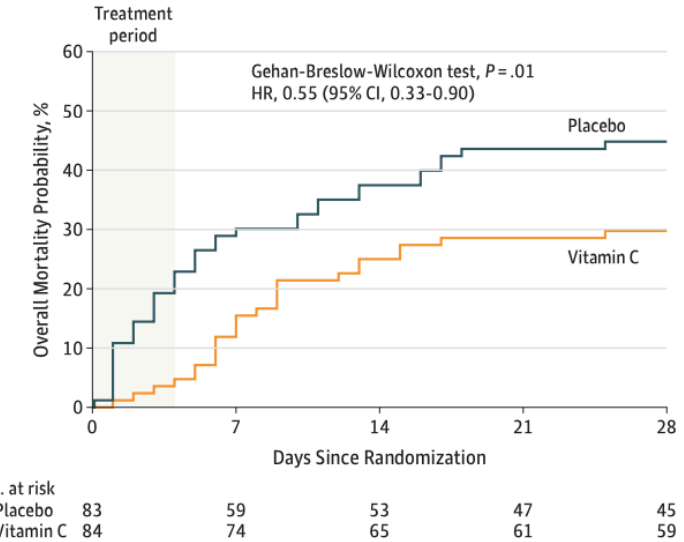
Alpha A. Fowler III, MD; Jonathon D. Truwit, MD; R. Duncan Hite, MD; Peter E. Morris, MD; Christine DeWilde, RN, PhD; Anna Priday, BS, MS;

- Primary Outcome:
  - No significant difference in SOFA score or biomarkers
- Secondary Outcome: Improved 28-day Mortality
  - Placebo: 46.3% (38/82)
  - Treatment: 29.8% (25/84)

Mortality result does not account for multiple comparisons and differences in baseline characteristics. Intended only for design of future trials

Primary endpoints may be affected by survivorship bias

Figure 3. All-Cause Mortality From Randomization (Day 0) to Day 28 Among Patients With Sepsis-Associated Acute Respiratory Distress Syndrome



Fowler AA 3rd, et al. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. JAMA. 2019 Oct 1;322(13):1261-1270.

Vitamin C in Sepsis: VITAMINS

The VITAMINS Trial

JAMA | Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock

The VITAMINS Randomized Clinical Trial

Tomoko Fujii, MD, PhD; Nora Luethi, MD; Paul J. Young, MBChB, PhD; Daniel R. Frei, BSc, MBChB; Glenn M. Eastwood, PhD; Craig J. French, MB, BS;

Fujii T, VITAMINS Trial Investigators. Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock: The VITAMINS Randomized Clinical Trial. JAMA. 2020 Feb 4;323(5):423-431.

Vitamin C in Sepsis: VITAMINS

The VITAMINS Trial

211 patients
Septic shock
<24hr admission to ICU

Vitamin C 1.5g IV q6 hr AND
Hydrocortisone 50mg IV q6 hr

Time alive and free of vasopressors:
122 hr
28-d Mortality: 23%
90-d Mortality: 29%

Hydrocortisone 50mg IV q6 hr

Time alive and free of vasopressors:
124 hr
28-d Mortality: 20%
90-d Mortality: 25%

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Vitamin C in Sepsis: VITAMINS

The VITAMINS Trial

Take Home:

No benefit in this study to support combination of vitamin C, thiamine, and hydrocortisone compared to hydrocortisone alone

Critics of the VITAMINS study point out that treatment was often late in the patient's course compared to 2017 study and other small positive studies, thus early use may ultimately have benefit.

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Vitamin C in Sepsis: Summary

Should we use Vitamin C, Hydrocortisone, and Thiamine early in patients with sepsis?

PRO

- Small before and after studies in multiple hospitals suggest a benefit
- CITRIS-ALI found a mortality benefit in patients with ARDS and Sepsis treated with high dose Vitamin C
- Seems to have no evidence of harm
- If used, should only be used early.

CON

- The small studies that have shown benefit are vulnerable to biases and confounders
- Largest randomized control trials so far are negative on primary end points.
- Better evidence may be coming

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Vitamin C in Sepsis

If you use high dose Vitamin C, point of care glucometers will overestimate glucose readings. . . .

- **Risk of missed cases of hypoglycemia**
- **Risk of insulin administration for high glucose readings and subsequent iatrogenic hypoglycemia**
- **Must rely on lab for glucose measurement**

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Acute Respiratory Distress Syndrome

Steroids: When and How?

Steroids in ARDS

Recent recommendations

- ARDS for steroid-responsive process (e.g. eosinophilic pneumonia)
- Refractory sepsis (as an alternative indication)
- Community acquired pneumonia if
  - FiO2 > 50%

    AND
  - One of the following: pH < 7.3, Lactate > 4, CRP >150
- Patients with moderate to severe ARDS failing standard therapies (as long as started before day 7)

Traditional regimen:

Methylprednisolone 1 mg/kg/day for 21-28 days, then taper

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Steroids in ARDS: The DEXA-ARDS Trial

The DEXA-ARDS Trial

Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial

Jesús Villar, Carlos Ferrando, Domingo Martínez, Alfonso Ambrós, Tomás Muñoz, Juan A Soler, Gerardo Aguilar, Francisco Alba,

- Multicenter RCT in Spain
- 277 patients with ARDS, P:F < 200 after 24 hr of Mechanical Ventilation
- Dexamethasone 20mg IV daily for 5 days, followed by 10mg daily for 5 days

Villar J et al; dexamethasone in ARDS network. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020 Mar;8(3):267-276.

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Steroids in ARDS: The DEXA-ARDS Trial

	Dexamethasone group (n=139)	Control group (n=138)	Between-group difference (95% CI)	p value
Ventilator-free days at 28 days	12·3 (9·9)	7·5 (9·0)	4·8 (2·57 to 7·03)	<0·0001
All-cause mortality at day 60	29 (21%)	50 (36%)	−15·3% (−25·9 to −4·9)	0·0047
ICU mortality	26 (19%)	43 (31%)	−12·5% (−22·4 to −2·3)	0·0166
Hospital mortality	33 (24%)	50 (36%)	−12·5% (−22·9 to −1·7)	0·0235
Actual duration of mechanical ventilation in ICU survivors, days	14·2 (13·2)	19·5 (13·2)	−5·3 (−8·4 to −2·2)	0·0009
Actual duration of mechanical ventilation in survivors at day 60, days	14·3 (13·3)	20·2 (14·0)	−5·9 (−9·1 to −2·7)	0·0004
Adverse events and complications*				
Hyperglycaemia in ICU	105 (76%)	97 (70%)	5·2% (−5·2 to 15·6)	0·33
New infections in ICU	33 (24%)	35 (25%)	1·6% (−8·5 to 11·7)	0·75
Barotrauma	14 (10%)	10 (7%)	2·8% (−4·0 to 9·8)	0·41

Data are n (%) or mean (SD). ICU=intensive care unit. *Data included the period from randomisation to day 10 (for hyperglycaemia) and from randomisation to ICU discharge (for new infections and barotrauma).

Table 2: **Outcomes, adverse events, and complications**

Outcome

- Reduced duration of Mechanical Ventilation
- Appears to reduce mortality
- No difference in rates of hyperglycemia or adverse events

Take Home

- It's one study, and it has some criticisms.
- Further supports the use of steroids in ARDS – earlier than most of us have adopted in our practice
- This is higher than the dose we are using in our COVID patients

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COVID-19

COVID Critical Care: Respiratory Support

Non-invasive respiratory support

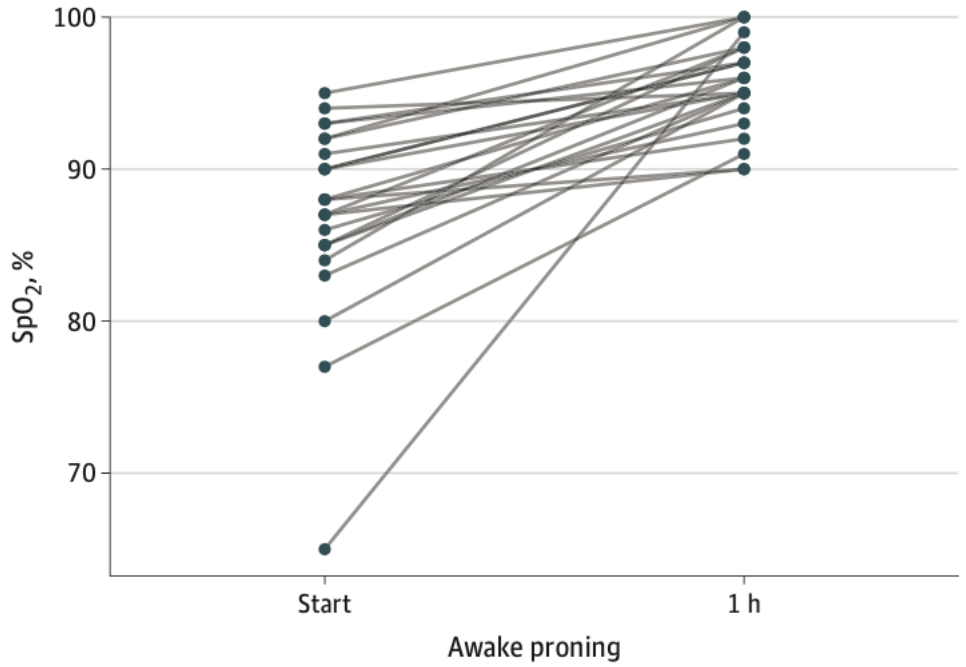
High Flow Oxygen

CPAP

Non-invasive positive pressure ventilation (BiPap)

Awake Prone Positioning

Figure. Oxyhemoglobin Saturation (Spo_2) 1 Hour After Initiation of the Prone Position in Awake, Nonintubated Patients With COVID-19



Spo_2 before and 1 h after initiation of the prone position in awake, nonintubated patients with COVID-19 severe hypoxemic respiratory failure (n = 25).

Coppo A, et al. Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study. Lancet Respir Med. 2020 Aug;8(8):765-774.

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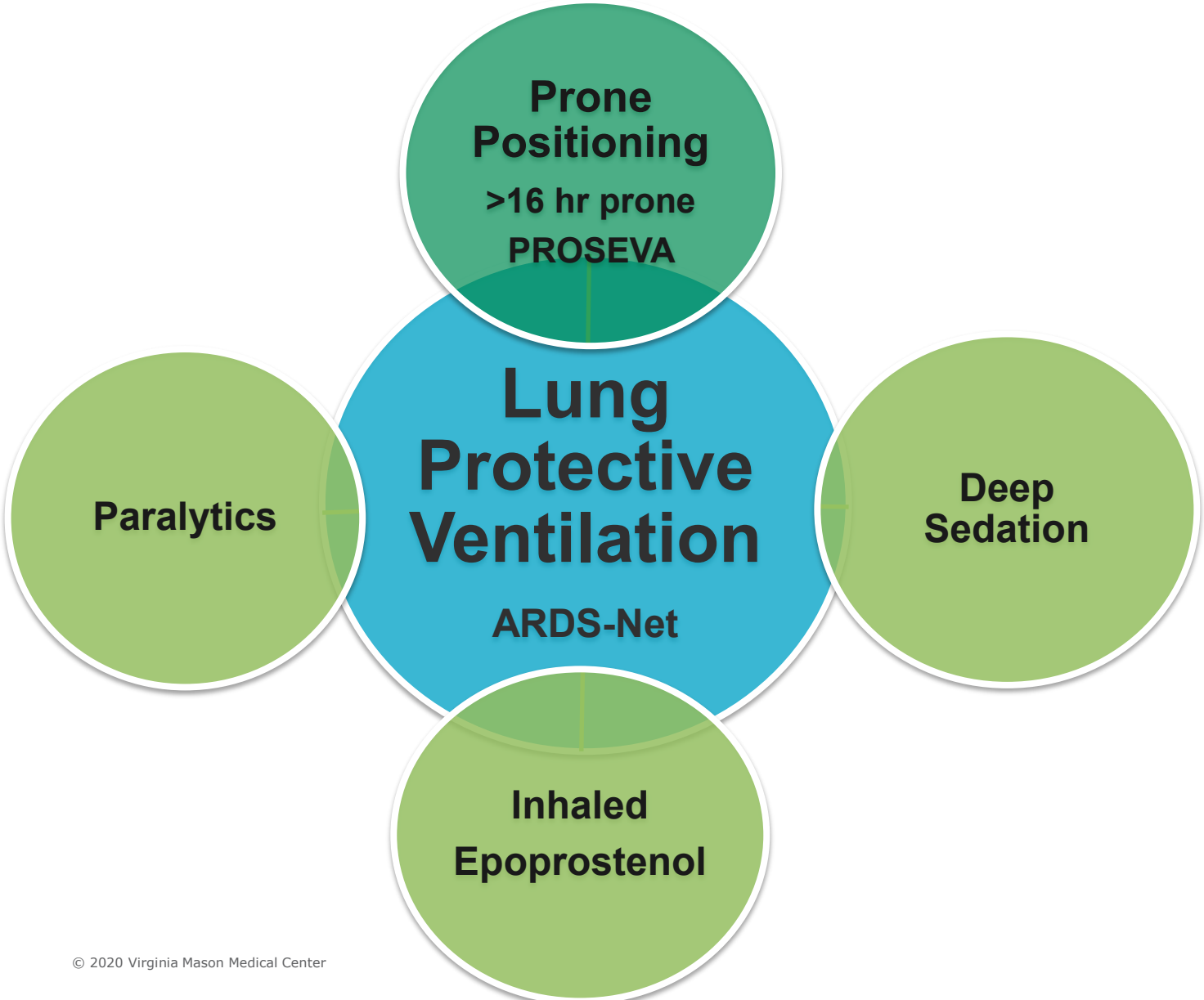
COVID Critical Care: Ventilator Strategies



Our Experience

- Many prolonged courses of mechanical ventilation.
- Prone positioning may last for days (standard is 16 hr sessions)
- Complications of prolonged ventilation
  - Skin and tissue injury
  - encephalopathy following prolonged sedation
  - Critical illness weakness and myopathy

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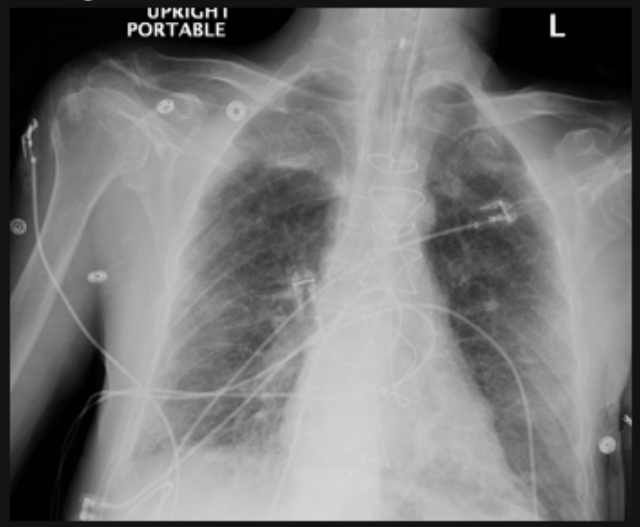
Day 1

Day 5



Day 5

Day 13

Day 21

Day 28

COVID Critical Care: VTE

Medical Ward

- May have increased risk of thrombotic events
- Standard VTE prophylaxis is appropriate

Intensive Care

- 25-43% of patients develop VTE despite standard prophylaxis
- Standard VTE Prophylaxis vs “intermediate” or therapeutic anticoagulation although evidence is limited

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COVID Critical Care: VTE

Coagulopathy and VTE Prophylaxis Guidelines for COVID-19 patients admitted to CCU for respiratory failure

D-dimer < 5.0	D-dimer > 5.0 (consider if continuous proning for > 48hr)	Diagnosed VTE (or high suspicion and unable to test)
Increased standard prophylactic dosing If CrCl > 30: BMI < 40: Enoxaparin 30 mg Q12hr BMI ≥ 40: Enoxaparin 40 mg Q12hr If CrCl ≤ 30: BMI < 40: Heparin 5,000 units Q8hr BMI ≥ 40: Heparin 7,500 units Q8hr	**Intermediate anticoagulation dosing** Screen for DVT with bilateral lower extremity duplex. Include upper extremity if central line present. Consider weekly exams until extubated and mobilizing. Consider CTPA if suspicion is high. If CrCl > 30: Enoxaparin 0.5 mg/kg Q12hr If CrCl ≤ 30: Heparin Low Intensity Protocol *Return to prophylactic dosing once extubated and mobilizing	**Full anticoagulation dosing** Heparin High Intensity Protocol or Enoxaparin 1 mg/kg Q12hr (CrCl > 30) Consider conversion to oral anticoagulation when nearing discharge from hospital. Continue anticoagulation for 3-6 months.

D-dimer 5.00 mcg/mL = 10x ULN.
Hold prophylactic or treatment anticoagulation if plts < 40, fibrinogen < 100, or active bleeding.

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COVID Critical Care: Treatments

Dexamethasone

6mg daily for up to 10 days

Remdesivir

5 or 10 day course – Recent conflicting studies

Convalescent Plasma

May be effective, readily available and low risk of harm

IL-6 Inhibitors

Tocilizumab – recent negative study

Antibody therapy

Under development by Eli Lilly and Regeneron

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REMDESIVIR – Recent conflicting results

NEJM – October 8, 2020
N=1000

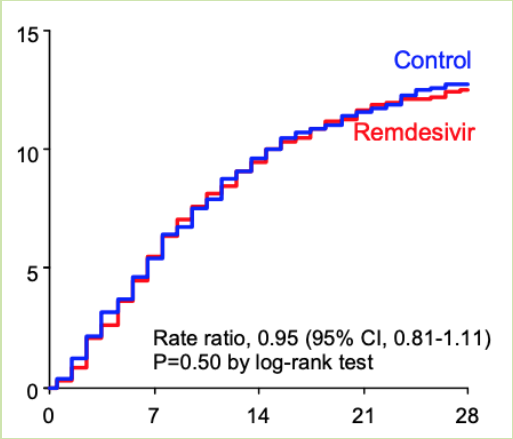
- SpO2 < 94% on RA
- RR > 24
- Supplemental Oxygen or Mechanical ventilation

	Placebo	Remdesvir 10 days
Days to recovery	**15**	**10**
Hospital Days	**17**	**12**
Mortality at day 29	**15%**	**11%**

- Shortens time to recover and hospital days
- Appears to reduce disease progression including need for mechanical ventilation

WHO SOLIDRITY Trial
October 15, 2020
N=11,266

- 405 Hospitals in 30 Countries
- Control vs Remdesivir, Hydroxychloroquine, Lopinavir and Interferon



- Appears to have no effect on mortality, initiation of ventilation and duration of hospital stay

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Summary: As many questions as answers

Vitamin C, Hydrocortisone, and Thiamine in Sepsis
Best evidence suggests no benefit

Vitamin C in ARDS and Sepsis
Signal toward benefit but not enough evidence yet

Early Dexamethasone in ARDS
Might be helpful. Not yet widely adopted

COVID-19
Supportive care, prone positioning, lung protective ventilation
Evolving recommendations for anticoagulation and therapeutics

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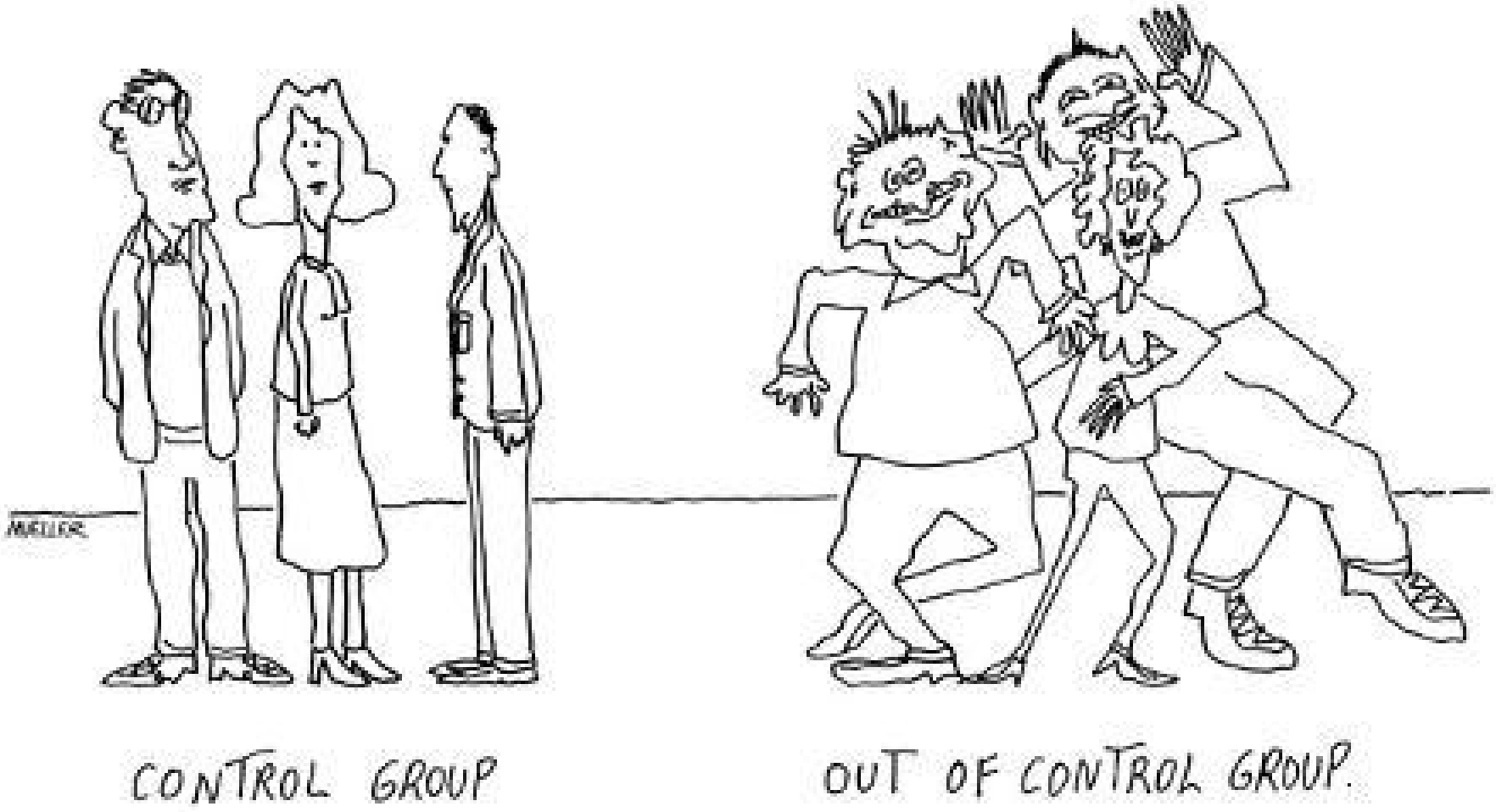
Questions?



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"We've lost control of our control group."

© Jonny Hawkins 2010

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