

# Best Practices for the Management of Severe COVID-19 Pneumonia

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- Medicine Residency: University of Washington
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- Clinical focus: Critical care
- Research focus: Quantitative imaging

# Disclosures

- Related to this presentation:
  - None
- Other:
  - Quantitative Imaging Solutions – owner/equity
  - Verona Pharmaceuticals – advisory board
  - Vertex Pharmaceuticals – consulting

# Objectives

- Brief review of the key aspects of critical care for patients with severe COVID-19 pneumonia:
  - That is the same as other patients with similar illnesses
  - That is different from other patients with similar illnesses
- Review COVID-19 pneumonia specific therapies

# Outline

- General principles
- Background
- Respiratory Failure
- Thrombosis
- COVID Specific Therapy
- Summary
- References

# General Principles



# General Principles

- The key tenets of the care of patients with severe COVID-19 pneumonia are the same as those for the care of all patients with severe respiratory illnesses
- Carefully consider study design, analysis and context prior to modifying standards of care
- Ongoing developments in COVID specific therapies continue to refine guidelines and improve outcomes

# General Principles

- While the role of COVID specific therapy is increasing, a patient's COVID status does not change the management of their:
  - Sepsis
  - Shock
  - Acute kidney injury
  - Gastrointestinal bleed
  - Stroke
  - Hyperglycemia/DKA
  - Acute coronary syndrome
  - Myocarditis
  - And others...





# Background

Image: [https://www.who.int/health-topics/coronavirus#tab=tab\\_1](https://www.who.int/health-topics/coronavirus#tab=tab_1)

# Background

## *Disease Severity Categories*

Severity Category	Description
Asymptomatic or presymptomatic	Individuals who test positive for SARS-CoV-2 using a virologic test but have no symptoms consistent with COVID-19
Mild illness	Individuals who have any of the various signs and symptoms of COVID-19 but do not have shortness of breath, dyspnea, or abnormal chest imaging
Moderate illness	Individuals who have SpO <sub>2</sub> <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO <sub>2</sub> /FiO <sub>2</sub> ) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%
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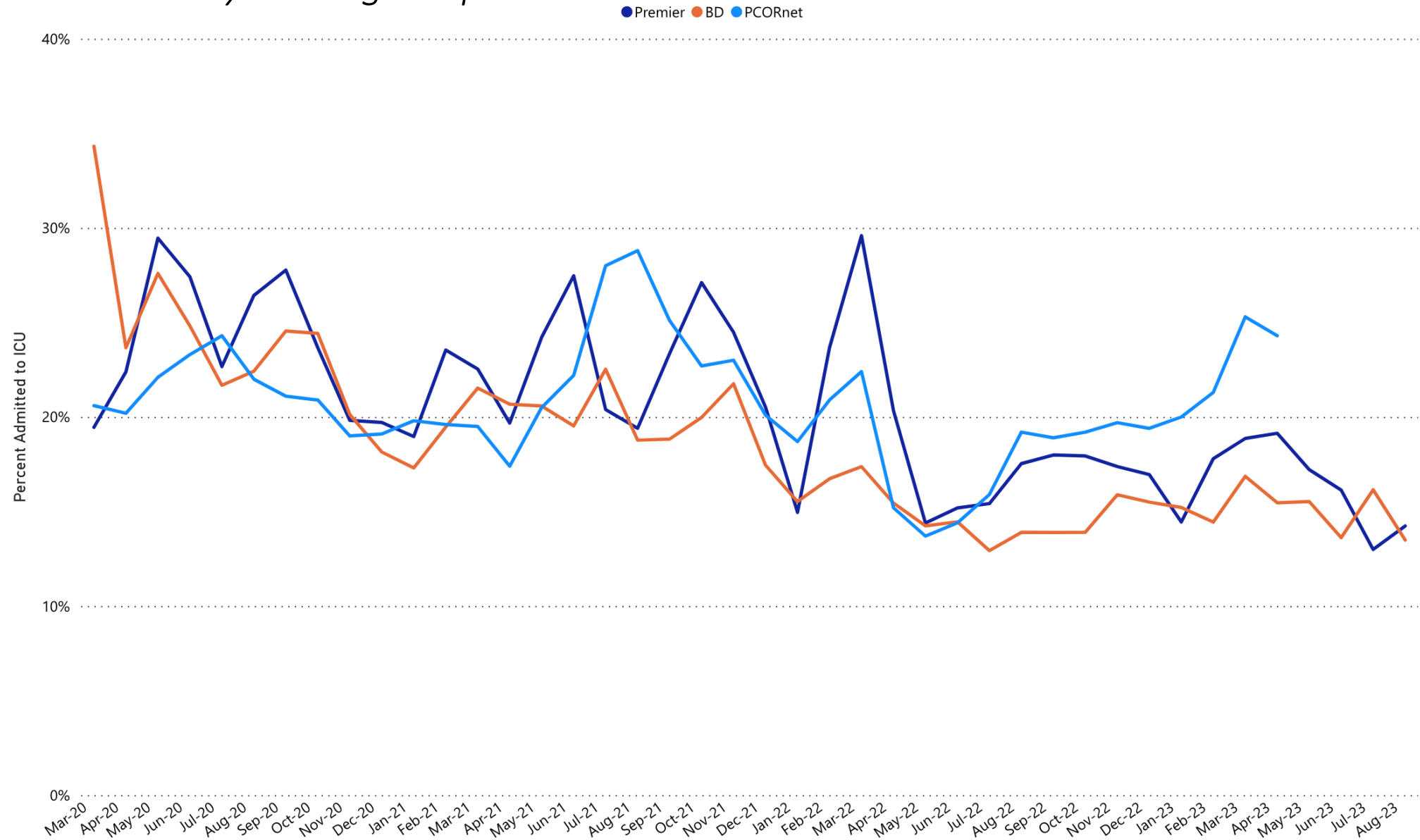
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# Background

## *Disease Severity Among Hospitalized Patients*



# Background

## *Causes of Death*

- Respiratory failure alone, 53%
- Circulatory failure alone, 7%
- Mixed respiratory and circulatory failure, 33%
- Unknown cause, 7%

Yang, Lancet Respir Med, 2020

Arentz, JAMA, 2020

Phua, Lancet Respir Med, 2020

Wu, JAMA, 2020

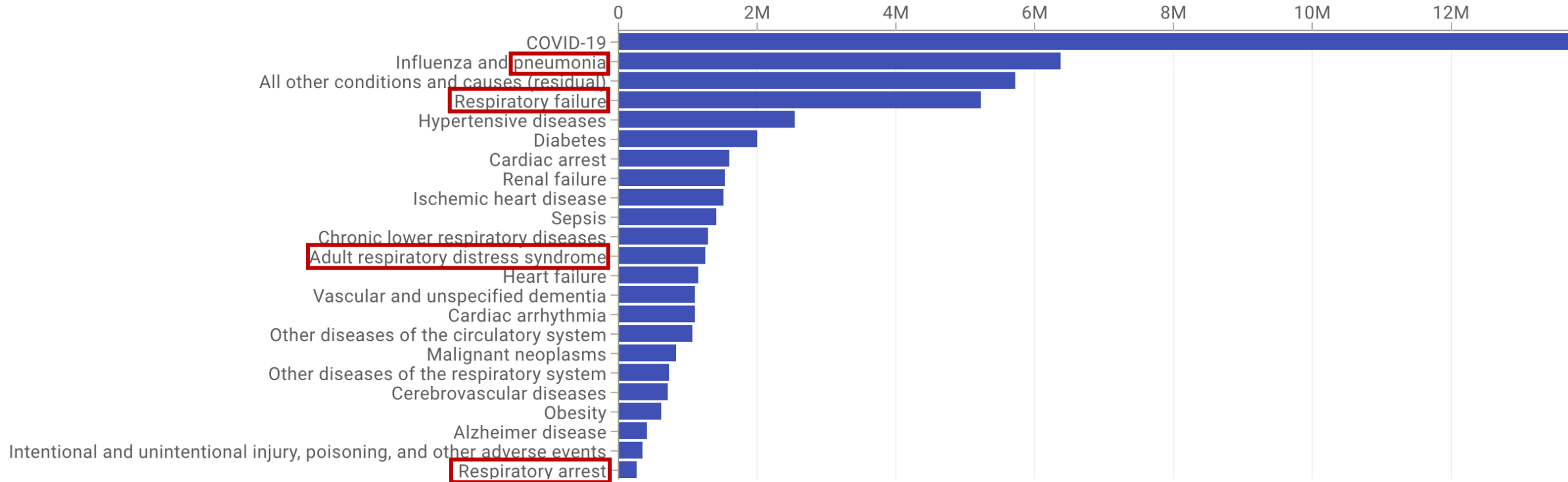
Cummings, Lancet, 2020

Ruan, Intensive Care Med, 2020



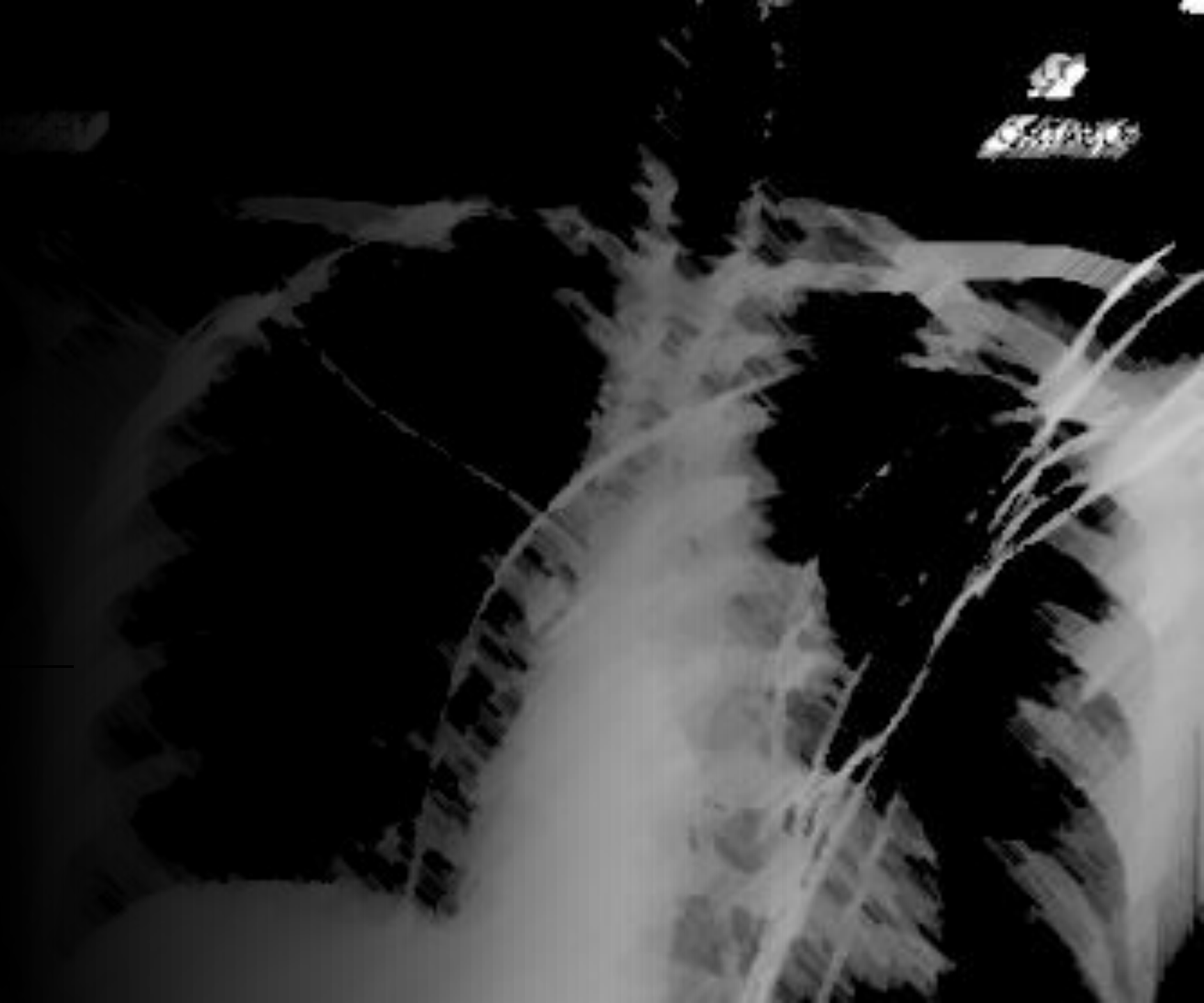
# Background

## *Causes of Death*





# Respiratory Failure





# Respiratory Failure

## *Pre-intubation*

- Primary challenges:
  - Hypoxemia
  - Infection control/prevention
  - Goals of care
- Oxygen delivery options:
  - Nasal cannula
  - Oxymizer
  - Venturi mask
  - Non-rebreather mask
  - High flow nasal cannula
  - Non-invasive positive pressure ventilation (CPAP/BiPAP)



# Respiratory Failure

## *Pre-intubation*

### **Nonmechanically Ventilated Adults With Acute Hypoxemic Respiratory Failure**

#### **High-Flow Nasal Cannula Oxygen and Noninvasive Ventilation**

##### *Recommendations*

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends starting therapy with HFNC oxygen; if patients fail to respond, NIV or intubation and mechanical ventilation should be initiated ([BIIa](#)).
- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy who do not have an indication for endotracheal intubation and for whom HFNC oxygen is not available, the Panel recommends performing a closely monitored trial of NIV ([BIIa](#)).

# Respiratory Failure

## *High flow nasal cannula (HFNC)*

- Concern for aerosol generation and healthcare worker transmission
- Likely can be used as in non-COVID-19 patients
  - Interstitial lung disease
  - Immunocompromised
  - Need for inhaled pulmonary vasodilator
- Conflicting data but may prevent need for intubation and time to recovery

# Respiratory Failure

## *High flow nasal cannula (HFNC)*

**JAMA**

**QUESTION** In patients with respiratory failure due to COVID-19, does the use of high-flow nasal cannula oxygen reduce the risk of mortality compared with standard oxygen therapy?

**CONCLUSION** This randomized clinical trial found that high-flow nasal cannula oxygen did not significantly reduce mortality at day 28 compared with standard oxygen therapy among patients with respiratory failure due to COVID-19.

### POPULATION

497 Men  
214 Women



Adults with respiratory failure due to COVID-19

Mean age: **61** years

### LOCATIONS

34 ICUs  
in France



### INTERVENTION



782 Patients randomized  
711 Patients analyzed

357

#### High-flow oxygen

Oxygen continuously delivered via large bore binasal prongs with gas flow of  $\geq 50$  L/min



354

#### Standard oxygen

Oxygen continuously delivered through a nonrebreathing mask, with oxygen flow set at  $\geq 10$  L/min

### PRIMARY OUTCOMES

Proportion of patients who died within 28 days following randomization

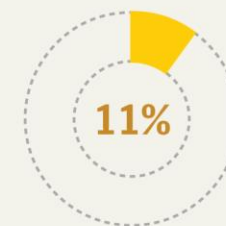
### FINDINGS

Mortality rate at day 28

**High-flow oxygen**  
36 of 357 patients



**Standard oxygen**  
40 of 354 patients



The results were not significant:

Absolute difference, **-1.2%**  
(95% CI, -5.8% to 3.4%);  $P = .60$

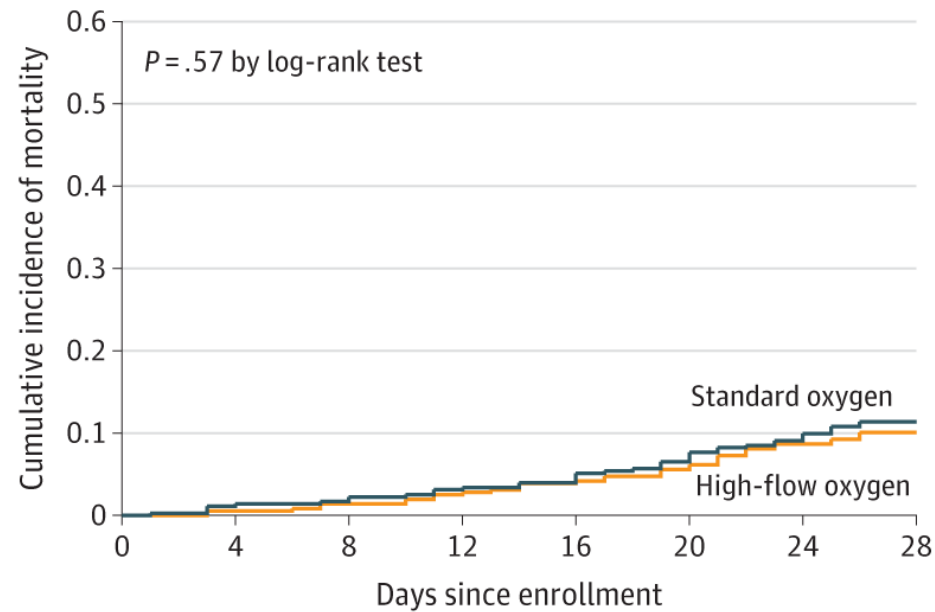
© AMA

Frat JP, Quenot JP, Badie J, et al; SOHO-COVID Study Group; REVA Network. Effect of high-flow nasal cannula oxygen vs standard oxygen therapy on mortality in patients with respiratory failure due to COVID-19: the SOHO-COVID randomized clinical trial. *JAMA*. Published September 27, 2022. doi:10.1001/jama.2022.15613

# Respiratory Failure

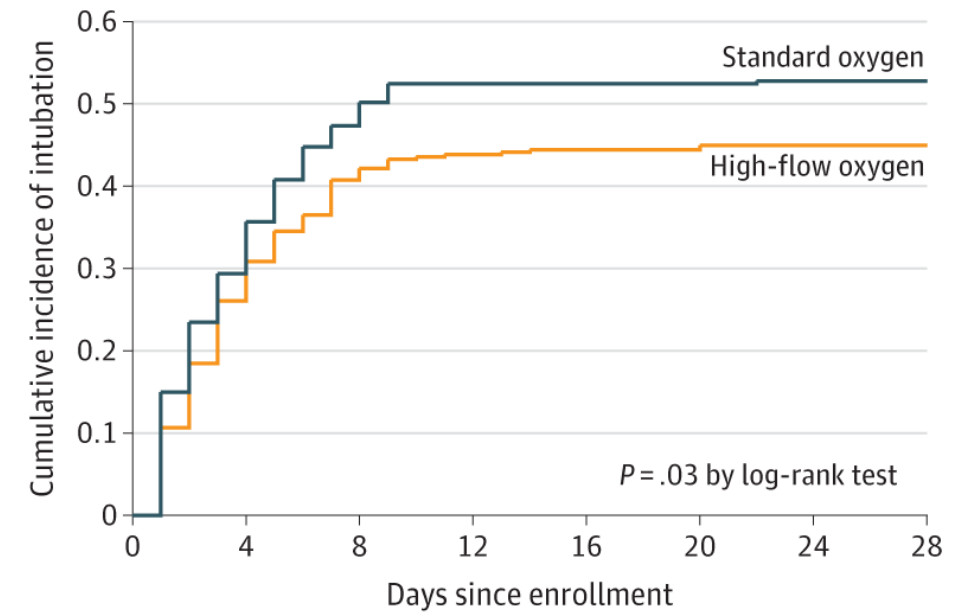
## *High flow nasal cannula (HFNC)*

**A** Cumulative incidence of mortality (primary outcome)



No. at risk								
High-flow oxygen	357	355	352	348	343	337	326	321
Standard oxygen	354	349	347	342	337	328	319	311

**B** Cumulative incidence of intubation (secondary outcome)



No. at risk								
High-flow oxygen	357	262	210	199	197	195	193	193
Standard oxygen	354	248	185	165	164	164	163	163



# Respiratory Failure

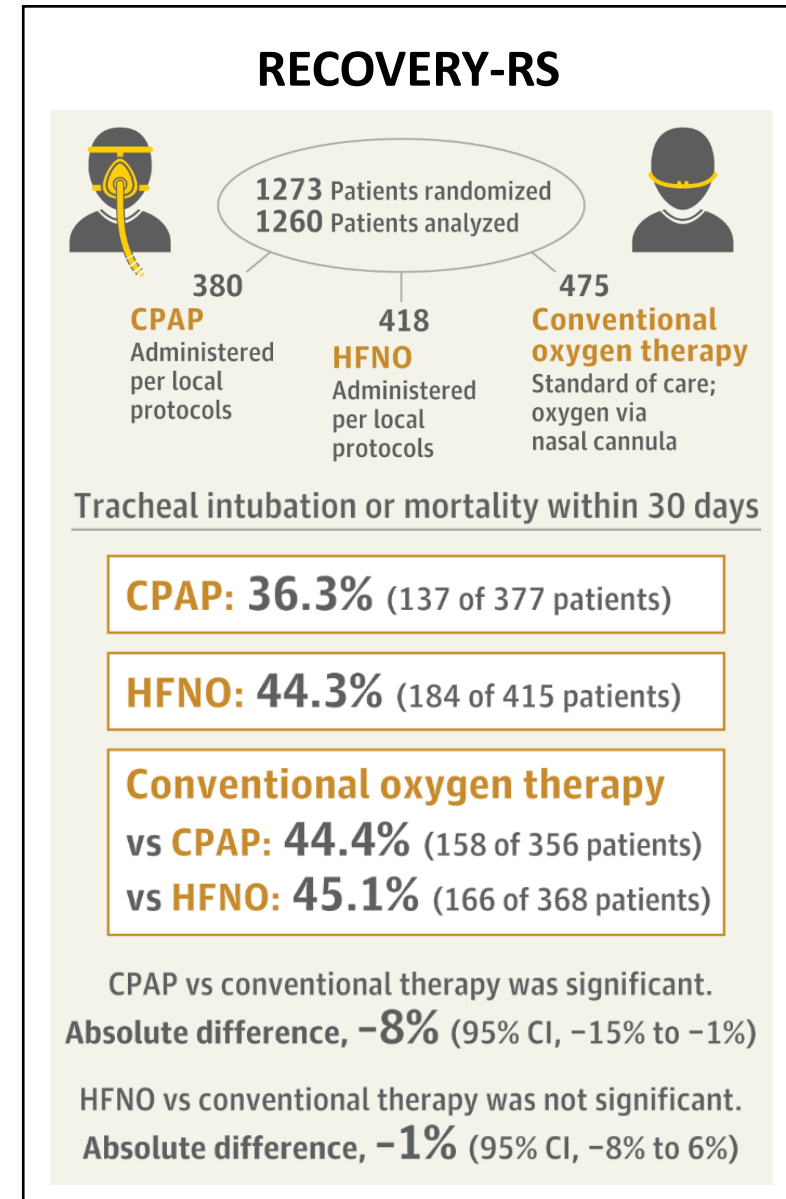
## *Non-invasive positive pressure*

- Should be used for the same indications as COVID-19 negative patients
  - Continuation of home use (e.g., OSA)
  - Acute pulmonary edema
  - COPD exacerbation
- If used
  - It should be considered aerosol generating procedure
  - If possible, use dual limb machine with HEPA filter and mask without anti-asphyxia valve
  - Ensure proper mask fit

Hui, Eur Respir J, 2019

Brusasco, Eur Respir J, 2021

Perkins, JAMA, 2022

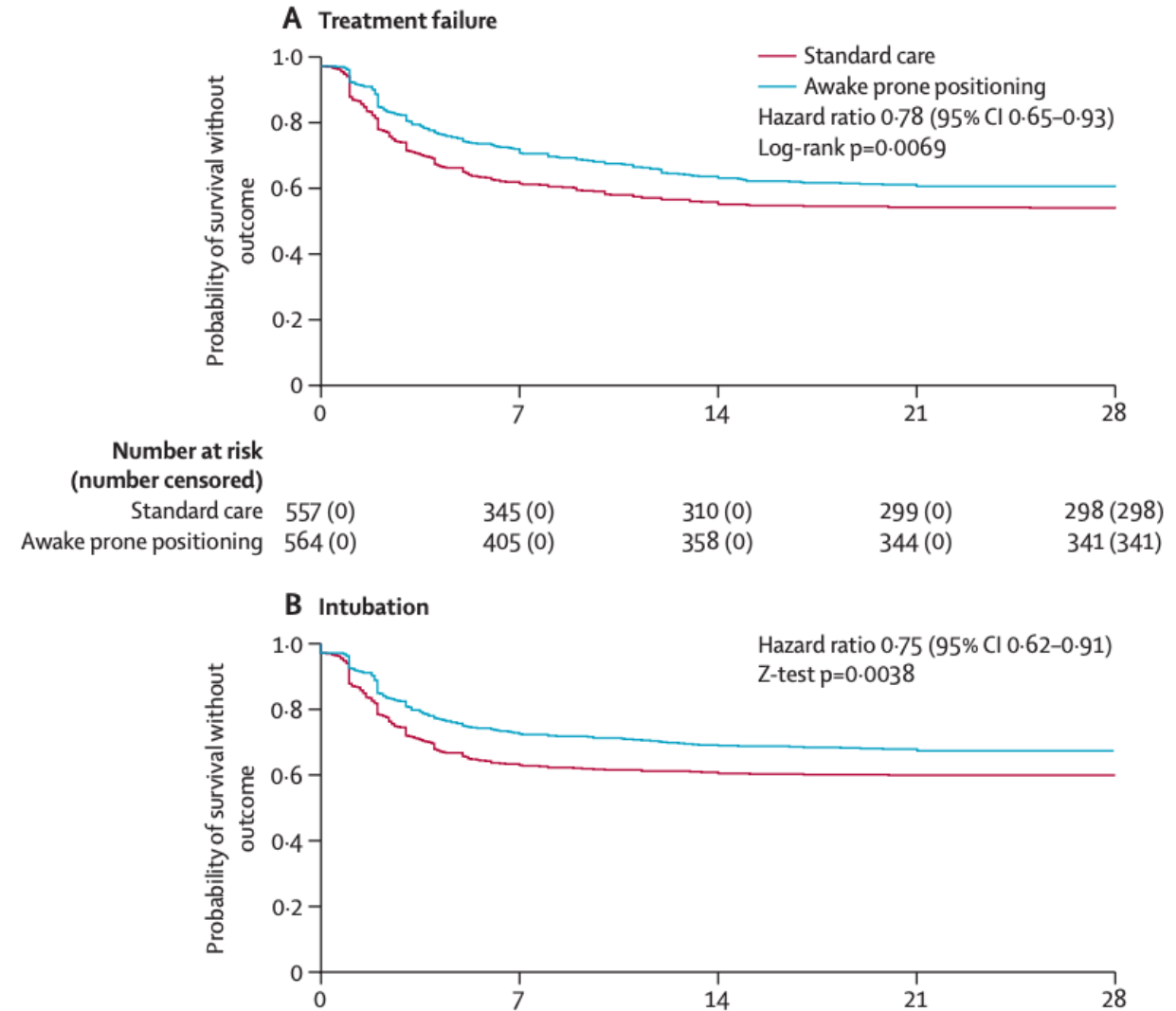


# Respiratory Failure

## *Pre-intubation*

### Self-proning

- Improves oxygenation and prevents intubation
- Can be used at any oxygen requirement
- Patient must be able to move independently
- Goal is 16 hours per 24 hours



Scaravilli, J of Critical Care, 2015

Elharrar, JAMA, 2020

Ding, Critical Care, 2020

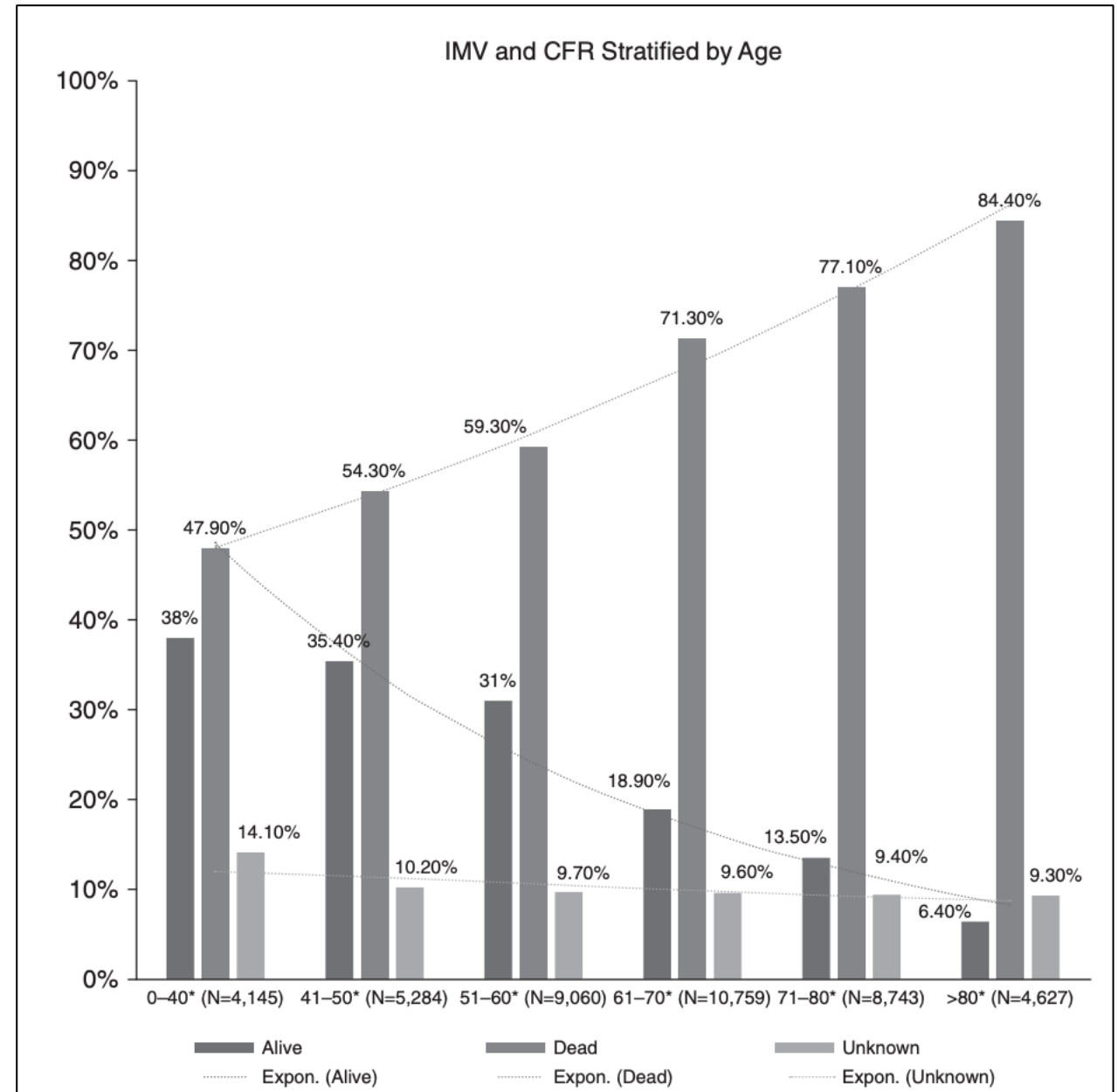
Ehrman, Lancet Respir Med, 2021



# Respiratory Failure

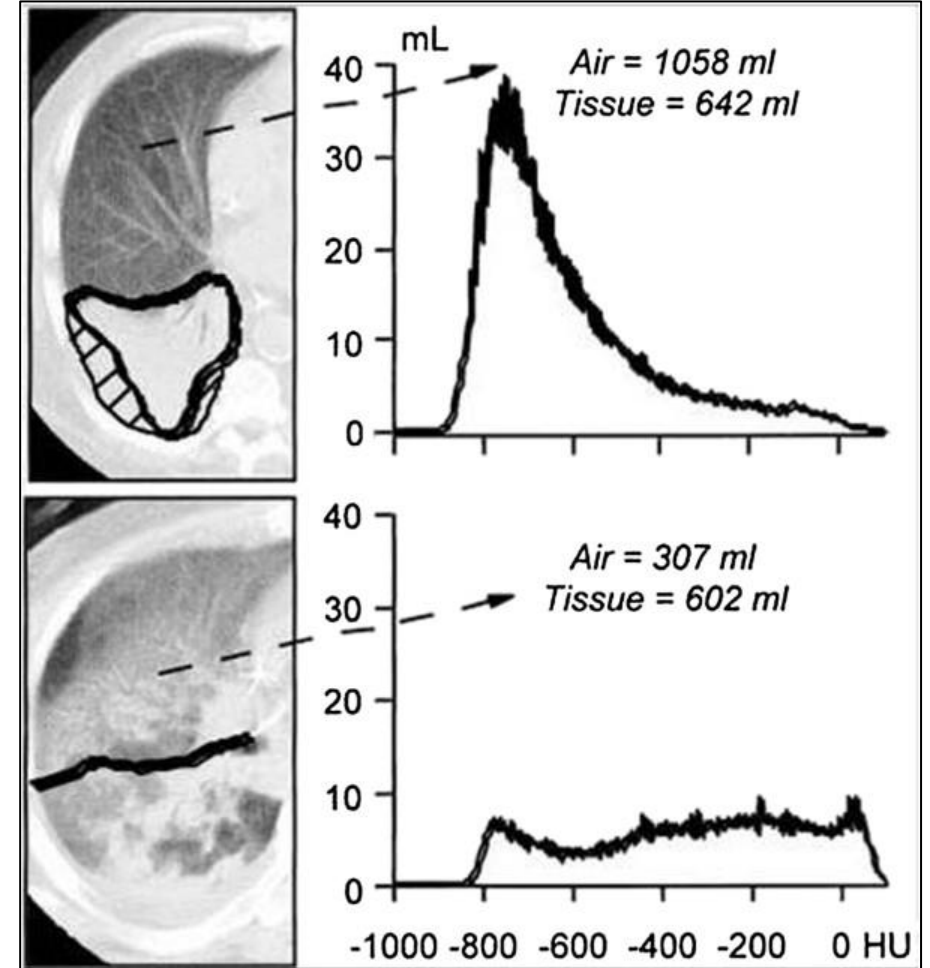
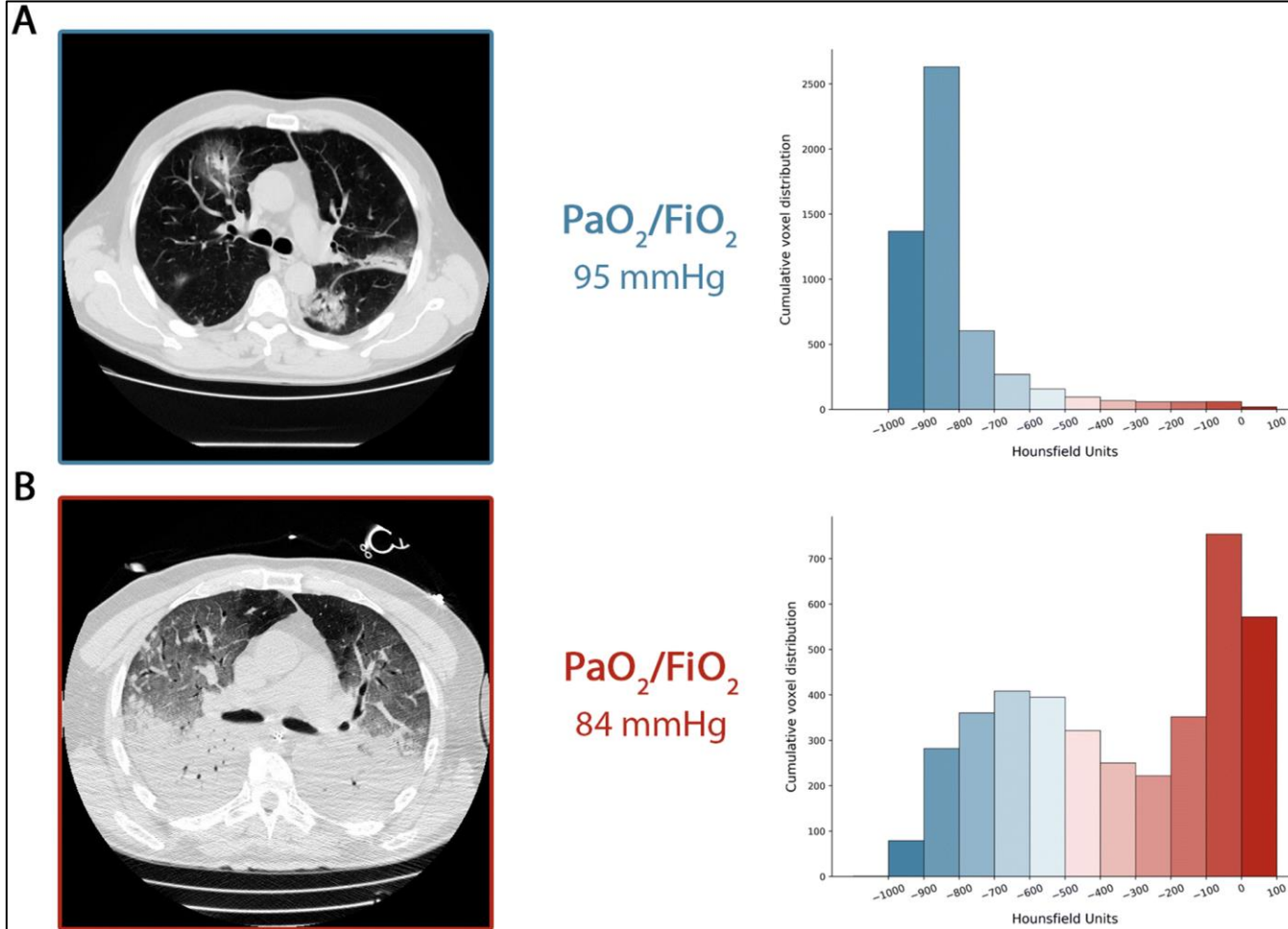
## *Intubation*

- Preparation
  - Goals of care discussion\*
  - Airborne isolation if possible
  - Proper PPE and equipment
- Procedure
  - Limit personnel in room
  - Pre-oxygenation
  - RSI with video-laryngoscopy
  - Connect directly to ventilator



# Respiratory Failure

## *The search for the silver bullet*



Editorial | [Open Access](#) | Published: 14 April 2020

# COVID-19 pneumonia: different respiratory treatments for different phenotypes?

[Luciano Gattinoni](#) ✉, [Davide Chiumello](#), [Pietro Caironi](#), [Mattia Busana](#), [Federica Romitti](#), [Luca Brazzi](#) & [Luigi Camporota](#)

*Intensive Care Medicine* **46**, 1099–1102(2020) | [Cite this article](#)

**117k** Accesses | **166** Citations | **644** Altmetric | [Metrics](#)



## The perils of premature phenotyping in COVID-19: a call for caution

Lieuwe D.J. Bos, Pratik Sinha, Robert P. Dickson

European Respiratory Journal 2020 56: 2001768; DOI: 10.1183/13993003.01768-2020

[Eur Respir J.](#) 2020 Aug; 56(2): 2002195.

Published online 2020 Aug 27. doi: [10.1183/13993003.02195-2020](https://doi.org/10.1183/13993003.02195-2020)

PMCID: PMC7331647

PMID: [32616591](#)

## COVID-19 phenotypes: leading or misleading?

[Luciano Gattinoni](#),<sup>1</sup> [Luigi Camporota](#),<sup>2</sup> and [John J. Marini](#)<sup>3</sup>

[Eur Respir J.](#) 2020 Aug; 56(2): 2002756.

Published online 2020 Aug 27. doi: [10.1183/13993003.02756-2020](https://doi.org/10.1183/13993003.02756-2020)

PMCID: PMC7397944

PMID: [32747393](#)

## Response to COVID-19 phenotyping correspondence

[Lieuwe D.J. Bos](#),<sup>1,2</sup> [Pratik Sinha](#),<sup>3,4</sup> and [Robert P. Dickson](#)<sup>5,6,7</sup>

Authors	PMID	Specimen type	No. of cases	Main findings	DAD	Thrombi
Xu et al. [38]	32,085,846	Post-mortem biopsies of lung, liver, and heart	1	DAD	Yes	None mentioned
Tian et al. [39]	32,114,094	Lobectomies	2	DAD and mononuclear inflammatory cells	Yes (early DAD pattern in 1 of 2)	None mentioned
Barton et al. [40]	32,275,742	Complete autopsies	2	DAD and chronic airway inflammation	Yes (1 case)	Few (lung, case 1)
Karami et al. [41]	32,283,217	Autopsy of the lungs	1	Hyaline membranes and viral cytopathic effect	Yes (hyaline membrane noted)	None mentioned
Tian et al. [42]	32,291,399	Post-mortem biopsies of lung, liver, and heart	4	DAD	Yes	None mentioned
Magro et al. [43]	32,299,776	Limited autopsies (2) and skin biopsies (3)	5	"Hemorrhagic pneumonitis" (lung), and "thrombogenic vasculopathy" (skin)	Yes (hyaline membranes in 1 of 2 cases in which lungs were examined)	Yes (skin)
Barnes et al. [44]	32,302,401	Autopsies (brief mention)	3	"Neutrophil extracellular traps"	Not mentioned	None mentioned
Varga et al. [45]	32,325,026	Autopsies (2) and small intestine resection (1)	3	"Endothelitis, DAD, and viral inclusions in the endothelial cells of kidney"	Yes	"Only scattered fibrin thrombi"
Konopka et al. [46]	32,360,729	Autopsy	1	"Fibrinous pneumonia"	Yes	"Rare fibrin thrombi were also identified within small vessels and a small muscular pulmonary artery"
Menter et al. [27]	32,364,264	Autopsy	21	DAD (exudative in 16, proliferative in 8); superimposed bronchopneumonia in 10/21	Yes	Pulmonary embolism in 4/21; microthrombi of alveolar capillaries in 5/11
Wichmann et al. [47]	32,374,815	Complete autopsies	12	DAD (8/12; "focal bronchopneumonia" (no DAD) in 4/12)	Yes	"Massive pulmonary embolism" (4/12); deep vein thrombosis in 3; fresh thrombosis in prostatic venous plexus (6/9 men)
Lax et al. [48]	32,422,076	Autopsies	11	DAD (11/11); bronchopneumonia (6/11); Fibrous adhesions (7/11)	Yes	Thrombosis of small and mid-sized pulmonary arteries (11/11)
Yan et al. [49]	32,422,081	Complete autopsy	1	DAD	Yes	Pulmonary infarction
Buja et al. [50]	32,434,133	Complete autopsies	3	DAD	Yes	Pulmonary embolism in 1/3
Martinez et al. [51]	32,437,316	Complete autopsies	8	DAD	Yes	Fibrinous thrombi in 1/8
Schaller et al. [52]	32,437,497	Complete autopsies	10	DAD	Yes	—
Duarte-Neto et al. [53]	32,443,177	Post-mortem "biopsies"	10	DAD	Yes	Fibrinous thrombi in 8/10; small thrombi in kidneys (glomeruli) and other organs
Sekulic et al. [54]	32,451,533	Complete (1) and partial(1) autopsy	2	DAD	Yes	—
Aguiar et al. [55]	32,458,044	Complete autopsy	1	DAD, superimposed pneumonia	Yes	—
Schaefer et al. [56]	32,561,849	Autopsies	7	Acute DAD (5/7), organizing DAD (5/7)	Yes	Pulmonary thromboembolism (5/7)
Beigmohammadi et al. [57]	32,552,178	Post-mortem biopsies from Lung, Heart and Liver	7	DAD (5/7), Acute pneumonia (2/7)	Yes	None mentioned
Konopka et al. [58]	32,542,743	Limited autopsies	8	DAD (8/8)	Yes	Fibrin thrombi (5/8)
Escher et al. [59]	32,529,795	Endomyocardial biopsy	5	Myocardial necrosis, small arterial obliteration	Not applicable	None mentioned

# Respiratory Failure

## *Mechanical Ventilation*



### Mechanically Ventilated Adults

#### General Considerations

##### *Recommendations*

For mechanically ventilated adults with COVID-19 and ARDS:

- The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) ([A1](#)).
- The Panel recommends targeting plateau pressures of <30 cm H<sub>2</sub>O ([A1a](#)).
- The Panel recommends using a conservative fluid strategy over a liberal fluid strategy ([B1a](#)).
- The Panel **recommends against** the routine use of inhaled nitric oxide ([A1a](#)).

##### *Rationale*

There is no evidence that the ventilator management of patients with hypoxemic respiratory failure due to COVID-19 should differ from the ventilator management of patients with hypoxemic respiratory failure due to other causes.

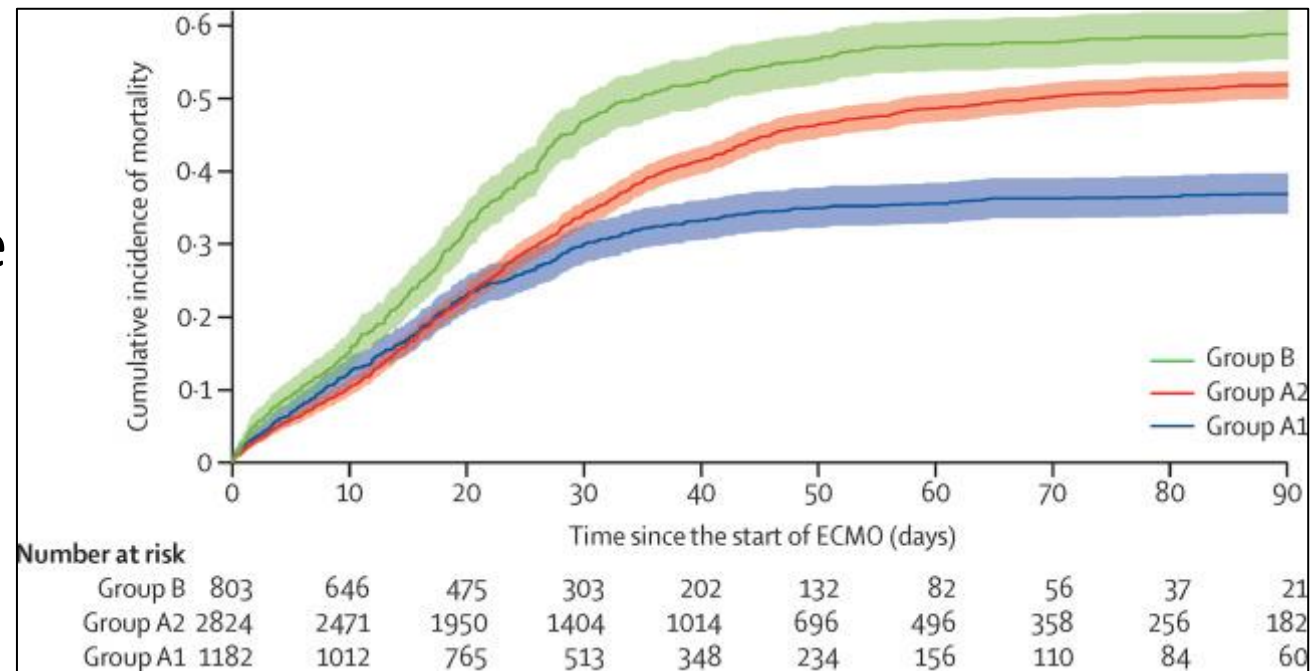
# Respiratory Failure

## *Refractory Hypoxemia - ECMO*

### Contraindications

- Age (>65)
- Multiorgan failure (excluding cardiopulmonary)
- Active, uncontrollable hemorrhage
- Prolonged mechanical ventilation (7-10 days)
- Irreversible neurologic injury or unknown neurologic status
- Significant baseline comorbidities

### Outcomes



# Respiratory Failure

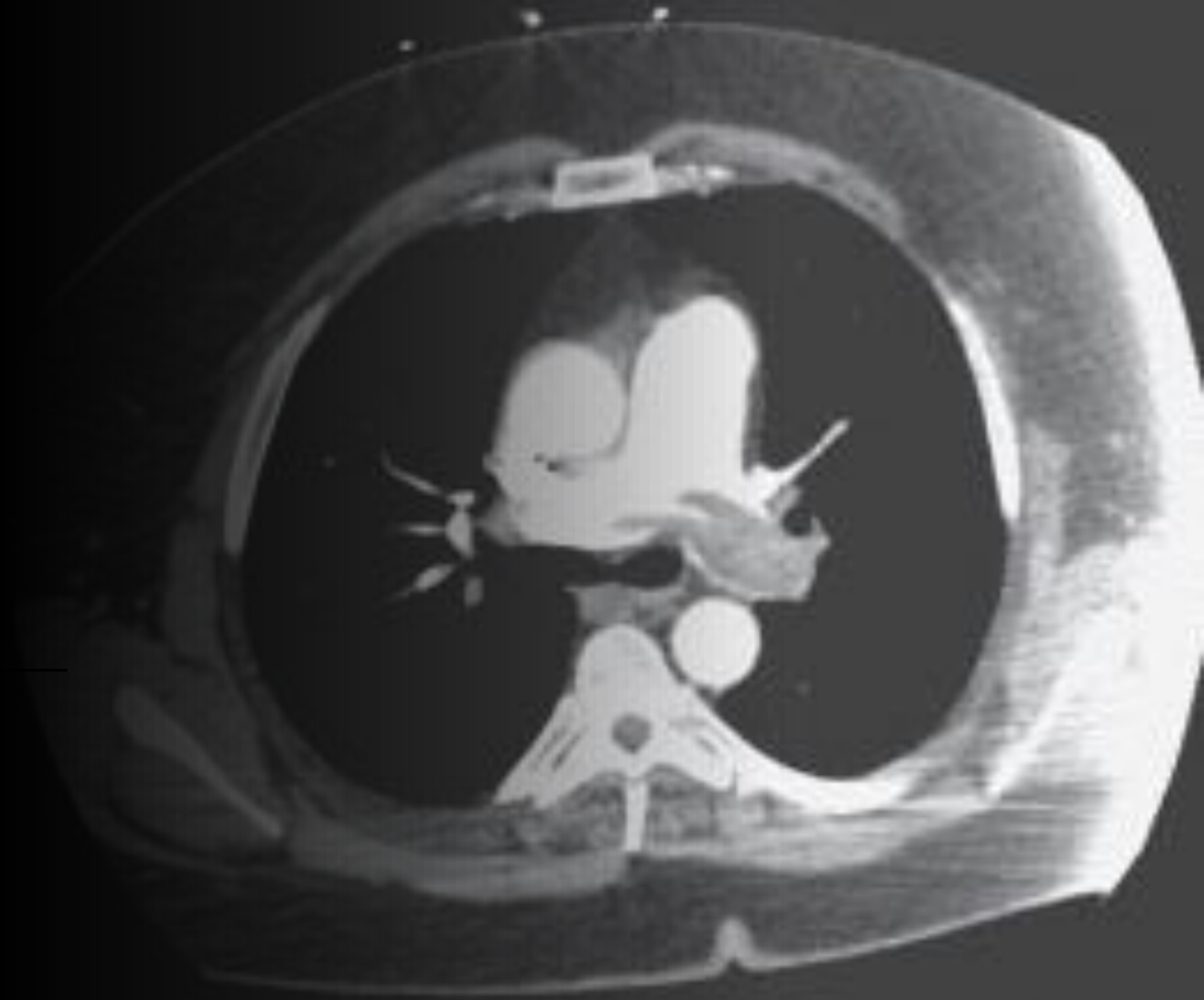
## *Ventilator Weaning, Extubation and Tracheostomy*

- Weaning as per usual protocol with daily SAT/ST when appropriate
- Extubation
  - Ensure appropriate PPE
  - Limit personnel in room
  - If possible, limit entry into room for 45-60 minutes after procedure
- Tracheostomy
  - Goals of care
    - In general ICU population, 60% 1-year mortality for those ventilator dependent at discharge
  - Guidelines evolving
  - Previous guidance suggested until waiting until day 21 or COVID PCR negative
  - Attempt to limit healthcare worker exposure as much as practical
    - PPE
    - Limited/essential staff
    - Paralysis
    - Mouth packing





Thrombosis





# Thrombosis

A 52 year old male, non-obese patient with a history of hypertension is admitted to the ICU for COVID-19 pneumonia. He has no other chronic or acute indications for anticoagulation. He should:

- a) Be placed on therapeutic anticoagulation with a heparin drip
- b) Be placed on therapeutic anticoagulation with a bivalirudin drip
- c) Be placed on intermediate dose anticoagulation (i.e., higher than standard prophylactic dosing but not “therapeutic”)
- d) Be placed on standard prophylactic dose anticoagulation

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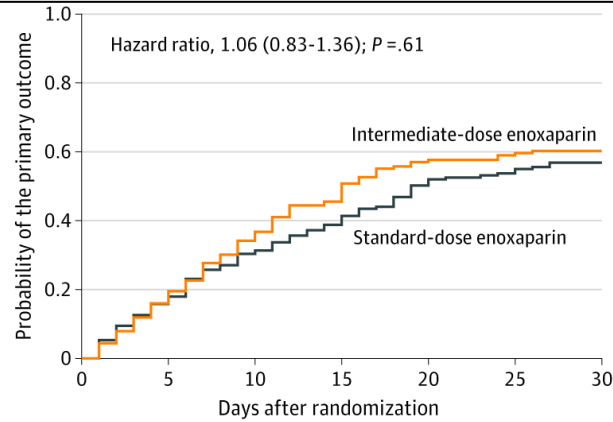
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# Thrombosis

Studies of therapeutic and intermediate anticoagulation have had mixed results but in general:

- 1) They do NOT support increased intensity of anticoagulation for **CRITICALLY ILL** COVID-19 patients
- 2) They MAY support increased intensity of anticoagulation for severe but **NON-CRITICALLY ILL** COVID-19 patients

# Thrombosis



No. of patients at risk							
Intermediate dose							
Total	276	235	196	175	156	154	150
Primary outcome	0	41	39	21	19	2	4
All-cause mortality	0	37	41 <sup>a</sup>	20	16	2	2
VTE	0	4	1	1	2	0	0
Ischemic stroke	0	0	0	0	1	0	0
Standard dose							
Total	286	244	211	194	173	167	160
Primary outcome	0	42	33	17	21	6	7
All-cause mortality	0	38	29	17 <sup>a</sup>	21 <sup>a</sup>	6	6
VTE	0	3	4	1	2 <sup>b</sup>	0	1
Ischemic stroke	0	1	0	0	0	0	0

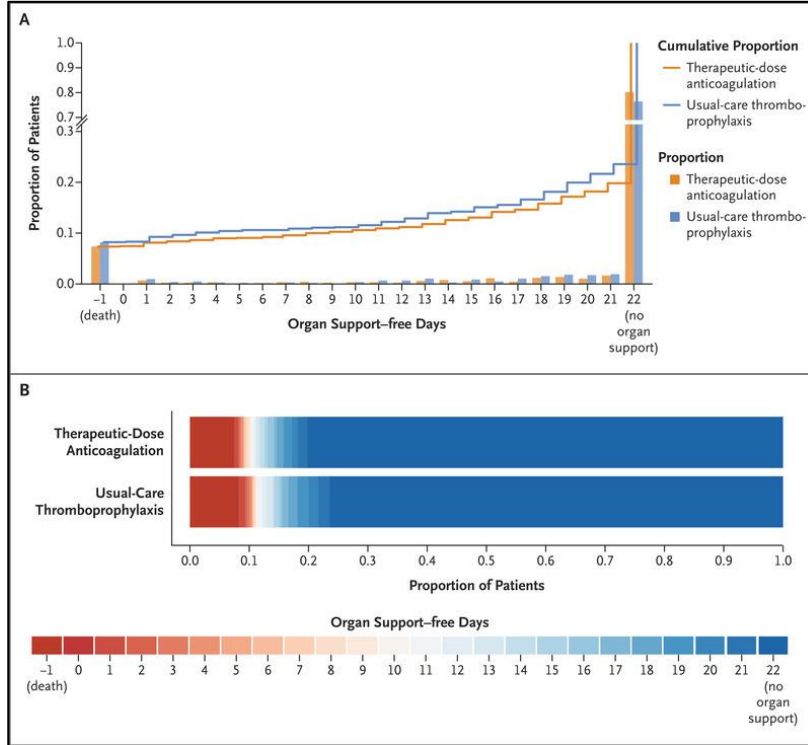
## INSPIRATION, JAMA, 2021

**Intervention:** Intermediate vs. standard dose enoxaparin

**Patient population:** Unselected ICU population

**Outcome:** Composite thrombosis, ECMO, mortality

**Result:** No benefit



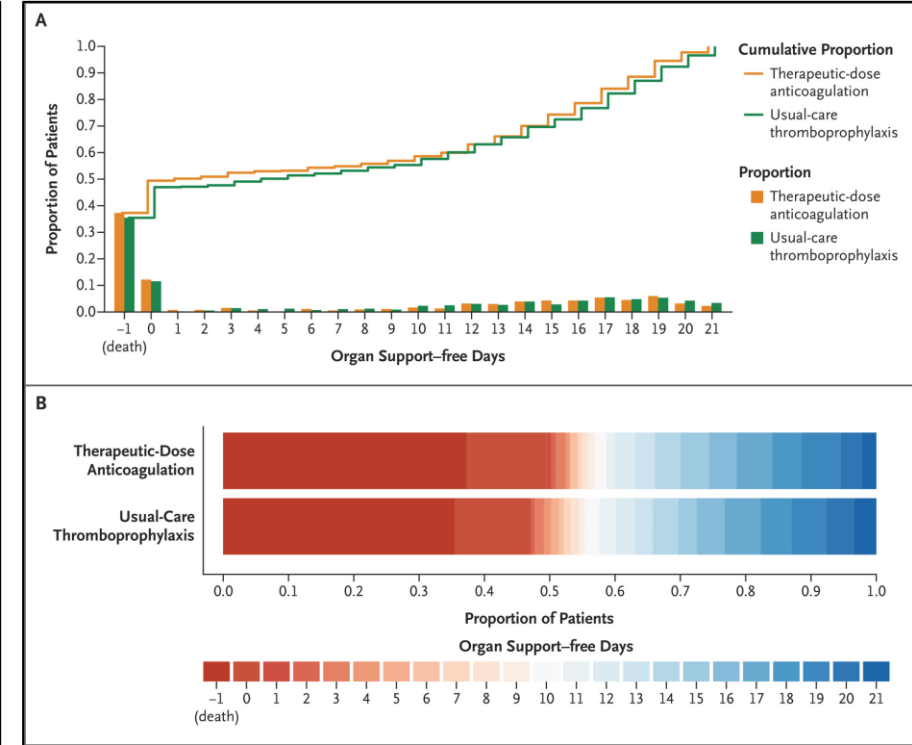
## Critically Ill REMAP-CAP, ACTIV-4a, and ATTACC, NEJM, 2021

**Intervention:** Therapeutic vs. standard dose enoxaparin

**Patient population:** Patients requiring ICU level support

**Outcome:** Organ support-free days

**Result:** No benefit



## Non-Critically Ill REMAP-CAP, ACTIV-4a, and ATTACC, NEJM, 2021

**Intervention:** Therapeutic vs. standard dose enoxaparin

**Patient population:** Hospitalized but non-critically ill

**Outcome:** Organ support-free days

**Result:** Probability of increased organ support free days = 98% (OR 1.27)

# COVID Directed Therapy

Histogram of on

- **There are no FDA-approved therapeutics for COVID-19**

- Remdesivir:

- May improve time to recovery
- Especially in severe disease

- Consider clinical trial if available:

- Convalescent plasma
- Ravulizumab
- Sarilumab

- If not available, then consider:

- Tocilizumab
- Anakinra

## COVID Specific Therapy

2020



### Disease Severity Scale:

- 1, not hospitalized, no limitations
- 2, not hospitalized, limitations
- 3, hospitalized, not requiring
- 4, hospitalized, not requiring
- 5, hospitalized, requiring
- 6, hospitalized, requiring

# COVID Specific Therapy

You are called to evaluate a 62 year old female patient with a history of hyperlipidemia and osteoporosis on the general medical floor. She was admitted with COVID-19 pneumonia 12 hours ago and her oxygen requirement has increased from 2 LPM by nasal cannula in the emergency department to 15 LPM by non-rebreather mask. She has received her first doses of dexamethasone and remdesivir, and you elect to transfer her to the ICU for oxygen administration by high flow nasal cannula. The best additional intervention at this time is:

- A) Administer high titer convalescent plasma
- B) Administer baricitinib
- C) Increase the dexamethasone dose to 12mg daily
- D) Administer inhaled epoprostonol via the high flow nasal cannula

# COVID Specific Therapy

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# COVID Specific Therapy

## *Hospitalized Patients*

Disease Severity	Recommended Therapy	Specific Clinical Situation
Requires oxygen	Remdesivir	Those with minimal oxygen requirements
	Dexamethasone + remdesivir	Most patients
	Dexamethasone alone	When combination with remdesivir cannot be used
	Dexamethasone +/- remdesivir + baricitinib or tocilizumab	Consider if rapid increase in oxygen requirement*
Requires NIV or HFNC	Dexamethasone + baricitinib or tocilizumab +/- remdesivir	Any NIV or HFNC
Requires mechanical ventilation or ECMO	Dexamethasone	Any mechanical ventilation or ECMO
	Dexamethasone + baricitinib or tocilizumab**	Within 24 hours of admission to the ICU**

### Notes:

\* Inconclusive evidence

\*\* Abatacept, infliximab or sarilumab may be considered alternatives to baricitinib or tocilizumab

\*\*\* Conflicting recommendations. The eligibility window can likely be extended at least through the first 4 days of the ICU course.

### Additional Notes:

- If a patient has been started on remdesivir and progresses, then complete the full course of remdesivir
- Immunomodulatory medications other than dexamethasone (tocilizumab, baricitinib, tofacitinib, sarilumab) should NOT be used in combination with each other.
- Some institutions recommend baricitinib be substituted for dexamethasone in the very rare instance that there is an absolute contraindication to steroids.
- If baricitinib and tocilizumab are not available or not feasible, *tofacitinib can be used instead of baricitinib* and *sarilumab can be used instead of tocilizumab*.

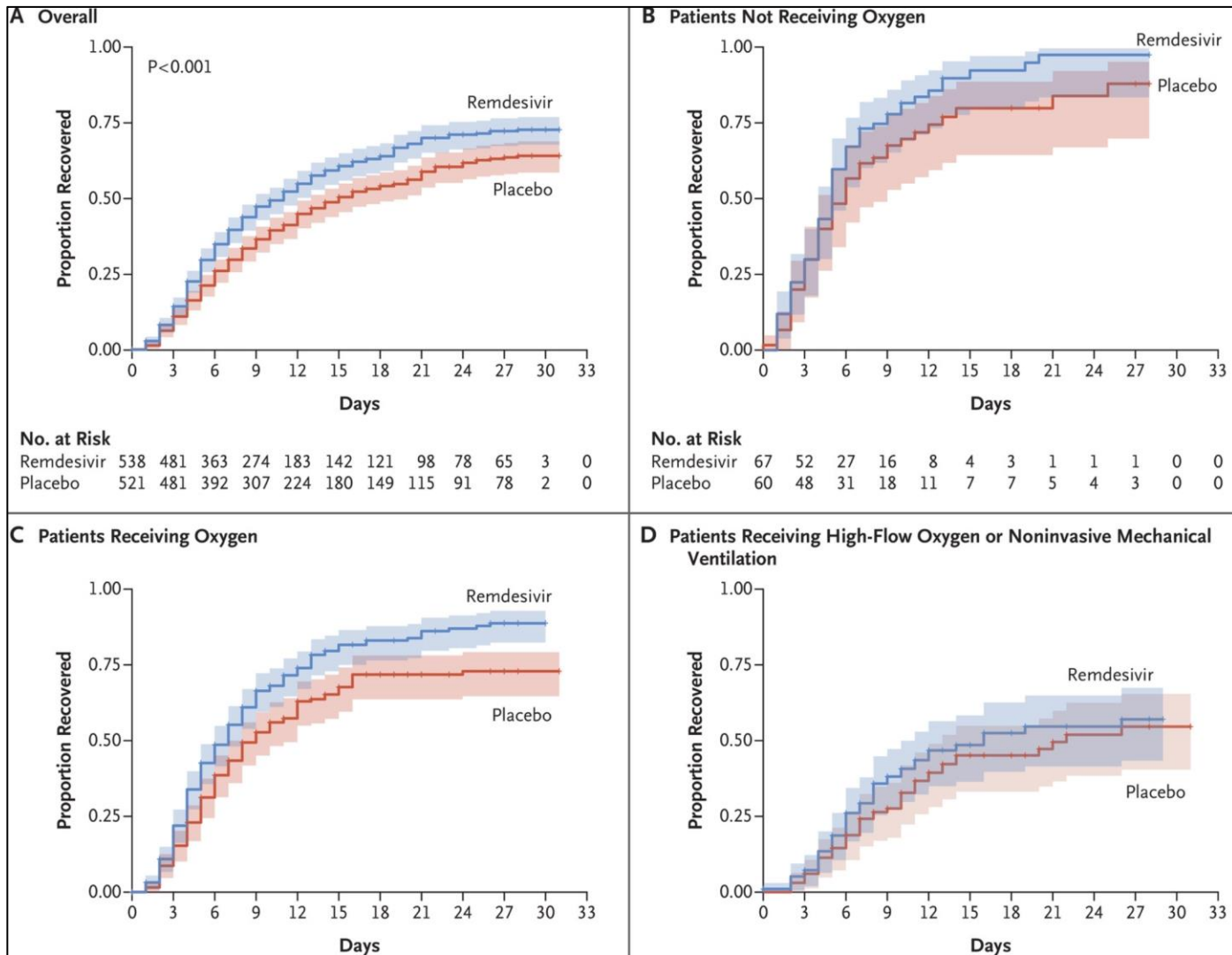
<https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/>

<https://opencriticalcare.org/covid-dashboard/>



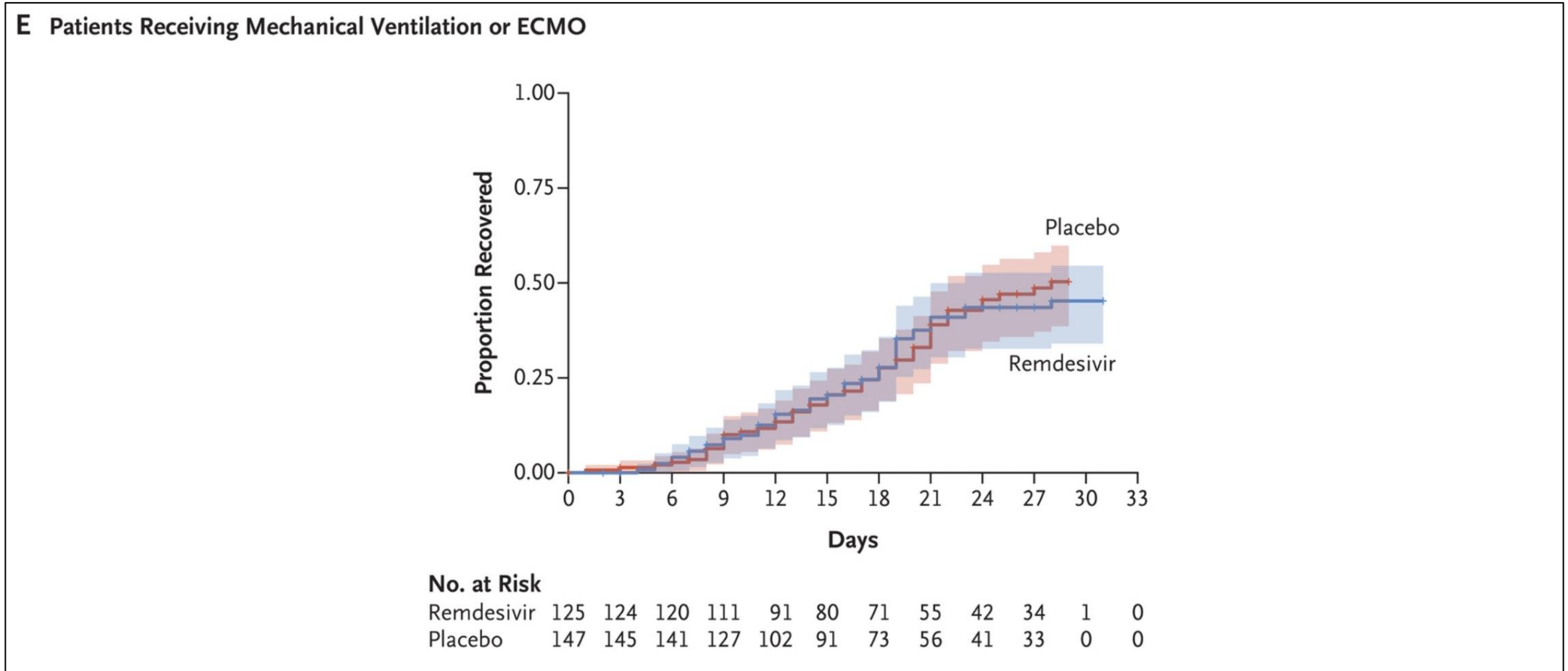
# COVID Specific Therapy

## *Remdesivir*



# COVID Specific Therapy

## *Remdesivir*



# COVID Specific Therapy

## Steroids

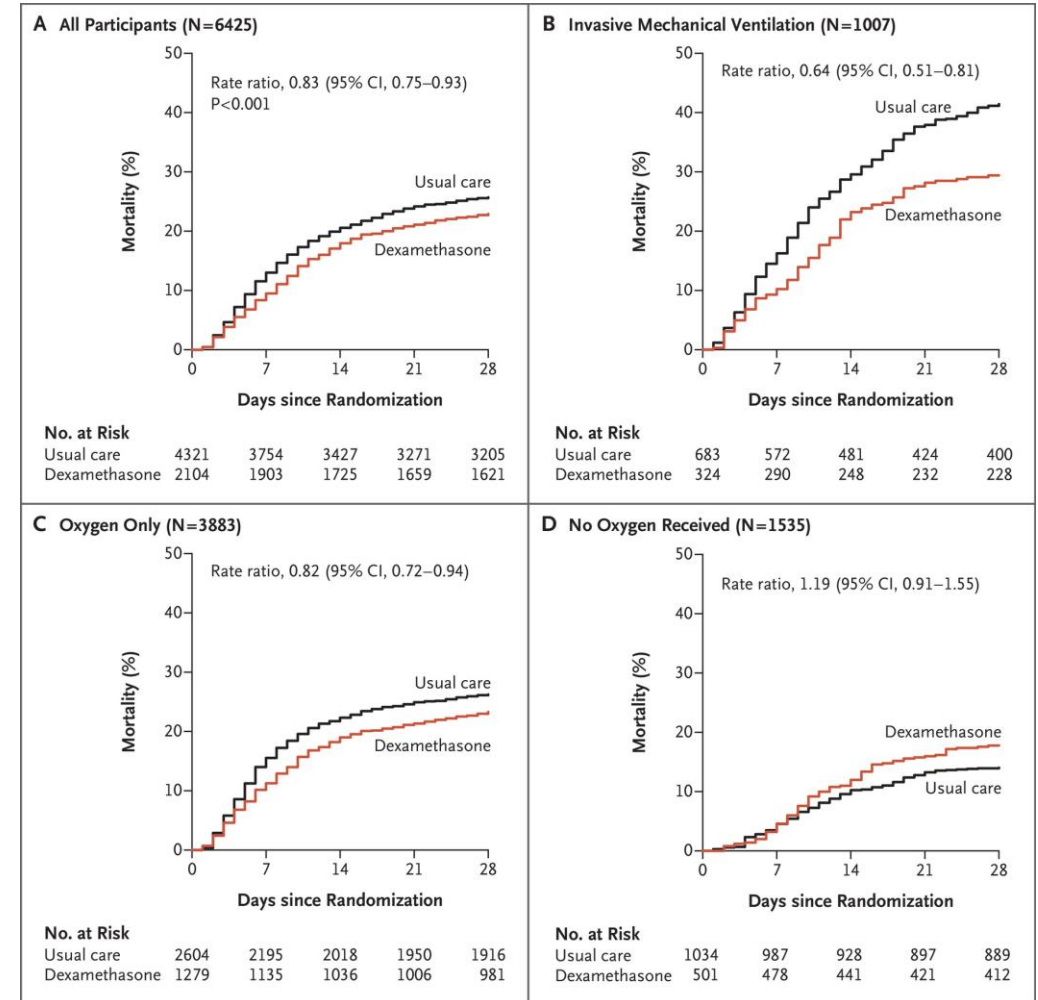
- Dexamethasone preferred
- 6mg daily x 10 days\*
  - \*possibly until hospital discharge

**Table 2.** Primary and Secondary Outcomes.

Outcome	Dexamethasone (N = 2104)	Usual Care (N = 4321)	Rate or Risk Ratio (95% CI)*
<i>no./total no. of patients (%)</i>			
<b>Primary outcome</b>			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
<b>Secondary outcomes</b>			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

\* Rate ratios have been adjusted for age with respect to the outcomes of 28-day mortality and hospital discharge. Risk ratios have been adjusted for age with respect to the outcome of receipt of invasive mechanical ventilation or death and its subcomponents.

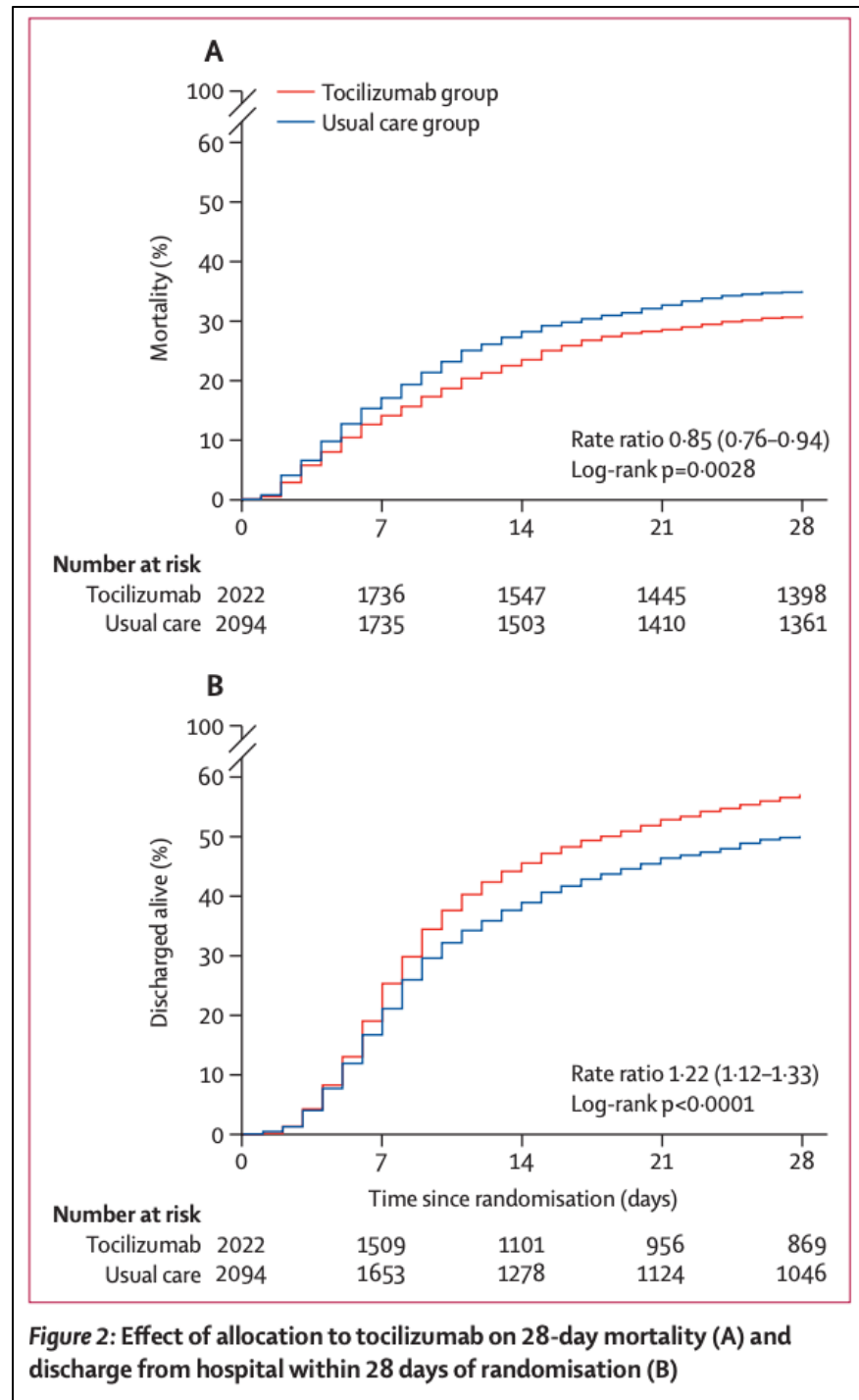
† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.



# COVID Specific Therapy

## *Tocilizumab*

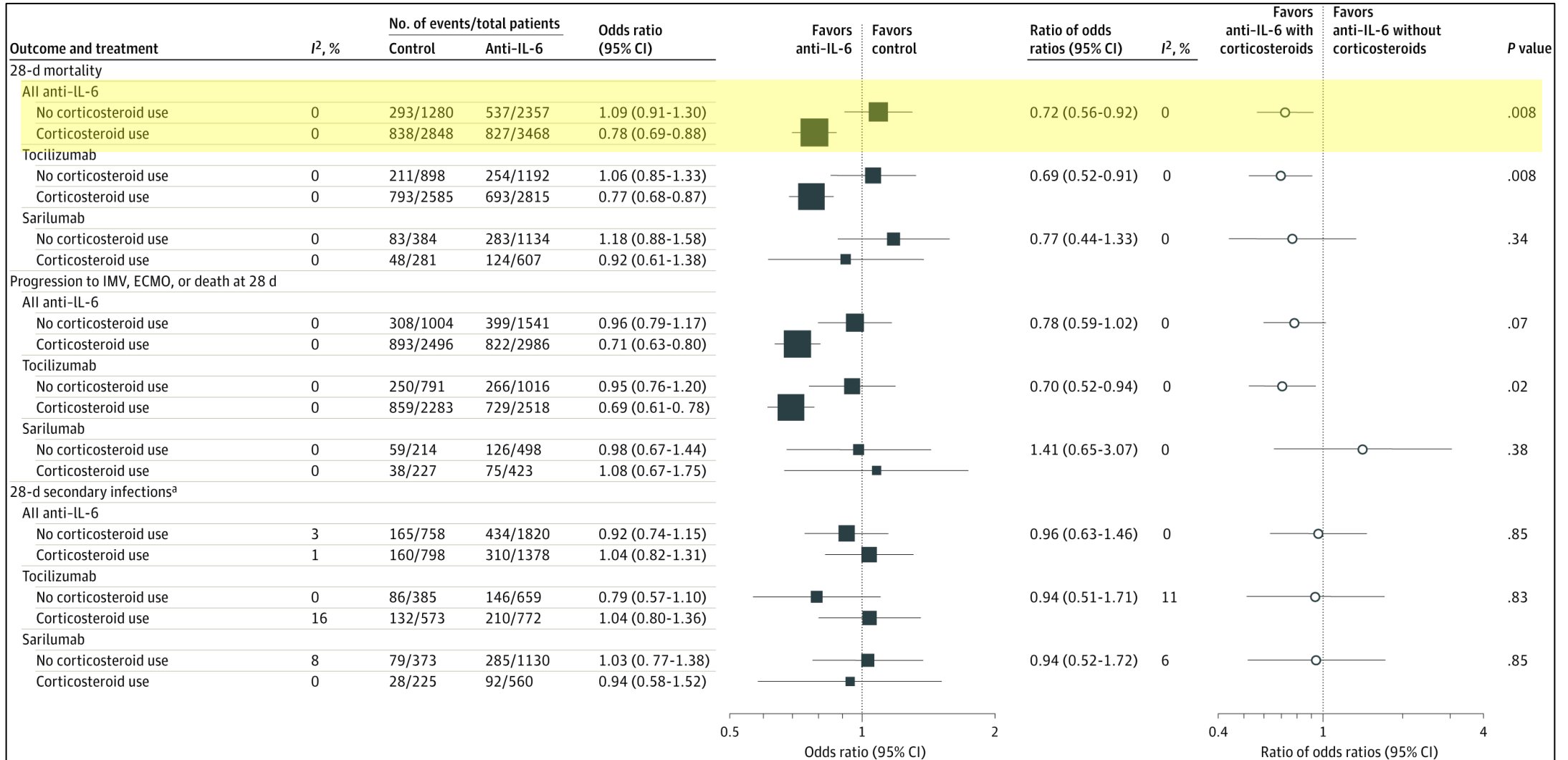
- Interleukin 6 Inhibitor
- 8mg/kg up to 800mg once
- Likely most beneficial early in disease course or in those who are most “inflamed”



**Figure 2: Effect of allocation to tocilizumab on 28-day mortality (A) and discharge from hospital within 28 days of randomisation (B)**

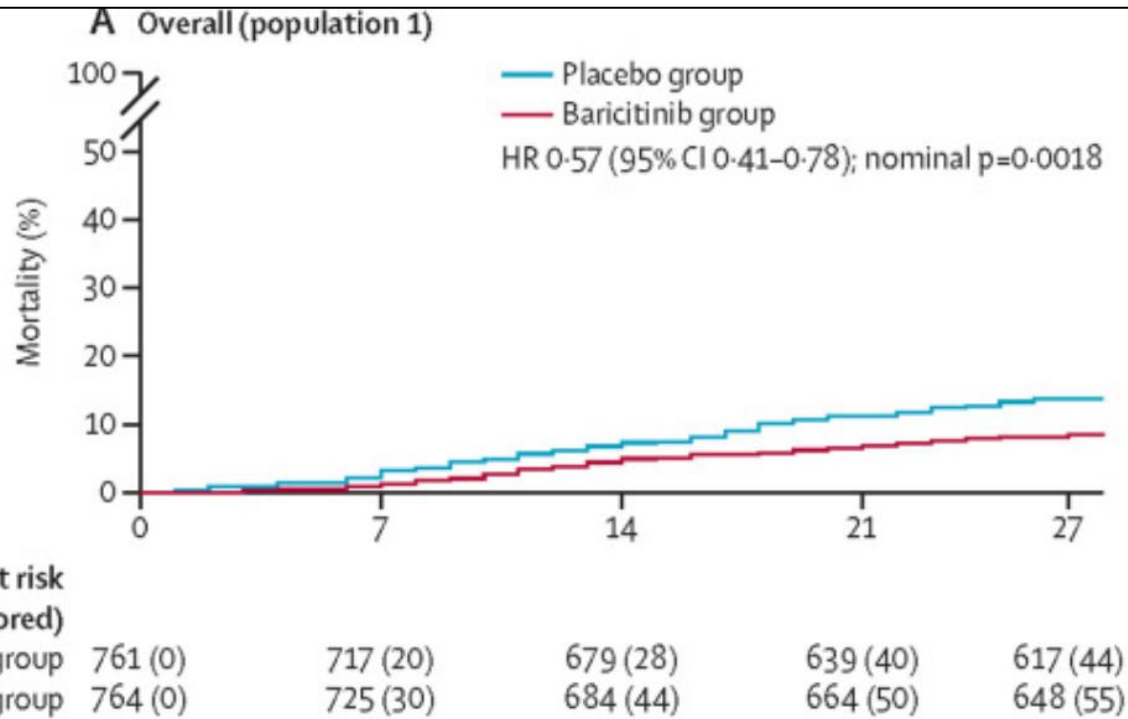
# COVID Specific Therapy

## Anti-IL-6

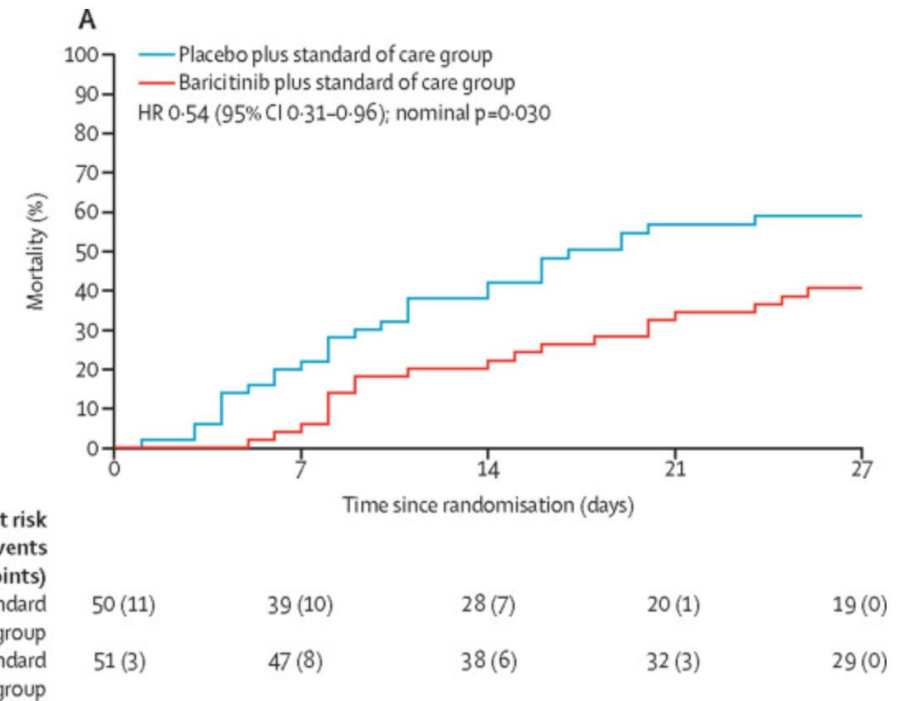


# COVID Specific Therapy

## *Baricitinib*



**Hospitalized Adults**  
(No mechanical ventilation or ECMO)

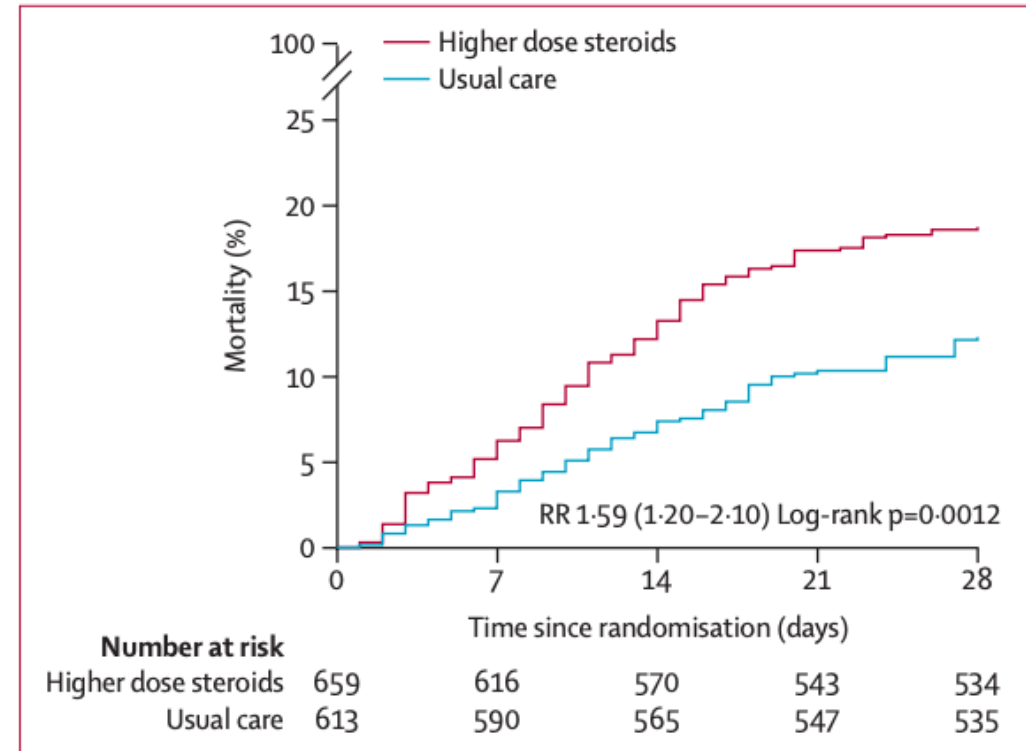


**Mechanical Ventilation or ECMO**

# COVID Specific Therapy

## *Steroid Dosing*

- Patients with hypoxia requiring simple oxygen only
- May 2021 - May 2022
- Dexamethasone 6mg daily vs Dexamethasone 20mg x 5 days and then 10mg x 5 days



**Figure 2: Effect of allocation to higher dose corticosteroids or usual care (lower dose corticosteroids) on 28-day mortality in patients receiving no oxygen or simple oxygen only**  
RR=rate ratio.

# Summary/MOC Reflective Statements

- The key tenets of the critical care of patients with COVID-19 are the same as those for the care of all critically ill patients and departures from general standards of care should be based only on specific evidence
- The primary driver of adverse outcomes is respiratory failure, and the proper management of ARDS is critical for the care of critically ill COVID-19 patients
- Current evidence does not support the routine use of intermediate or therapeutic anticoagulation in critically ill COVID-19 patients
- Multiple COVID specific therapies are available, and their selection is based on the severity of disease





LAST UPDATED MAY 15, 2022

BY COLLABORATORS FROM:

## COVID-19 Guidelines Dashboard



# No longer updated

# as of April 2023

## COVIDProtocols v2.0

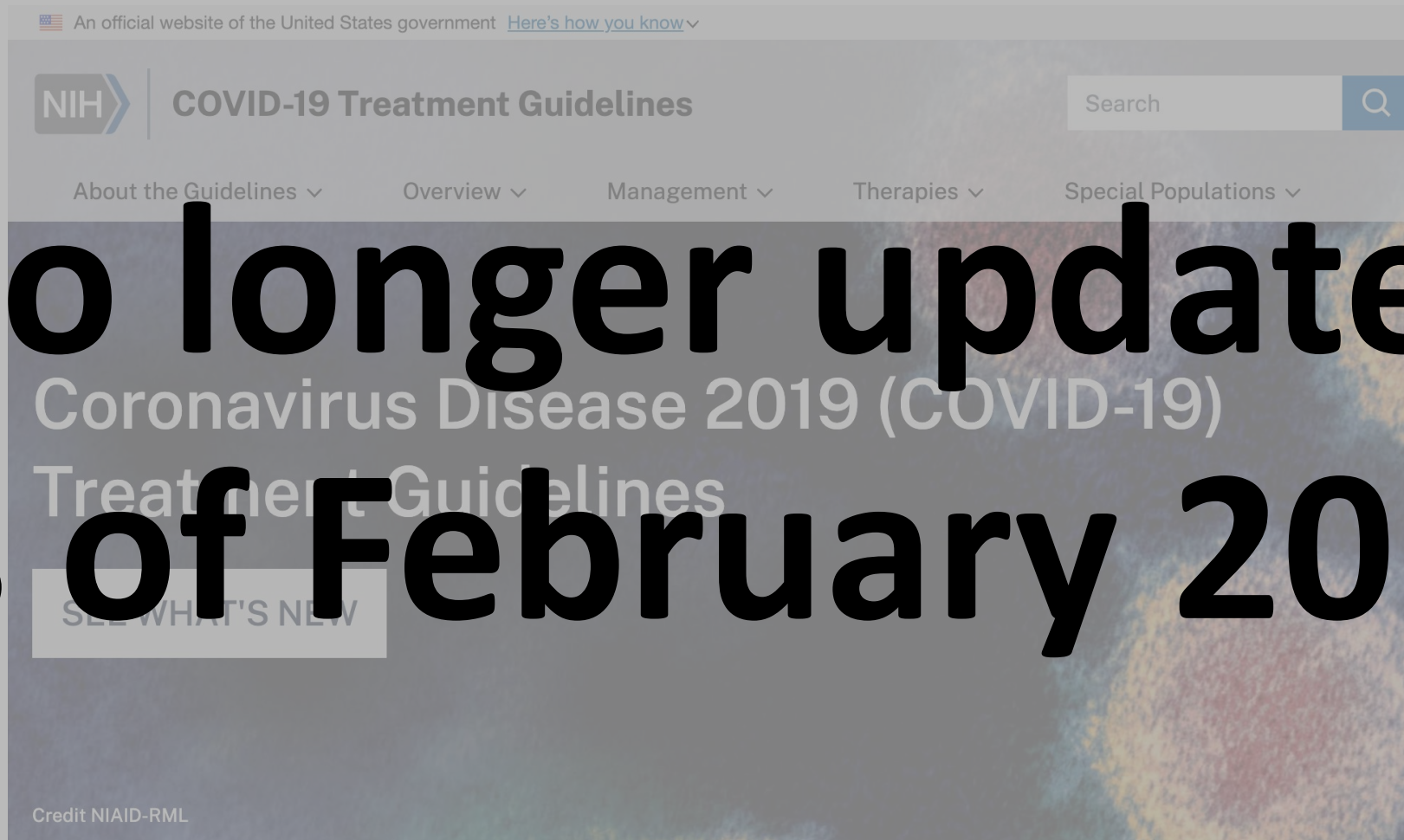
Search protocols



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as of February 2024**



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