COVID Therapeutics
UCSF Mini-Medical School

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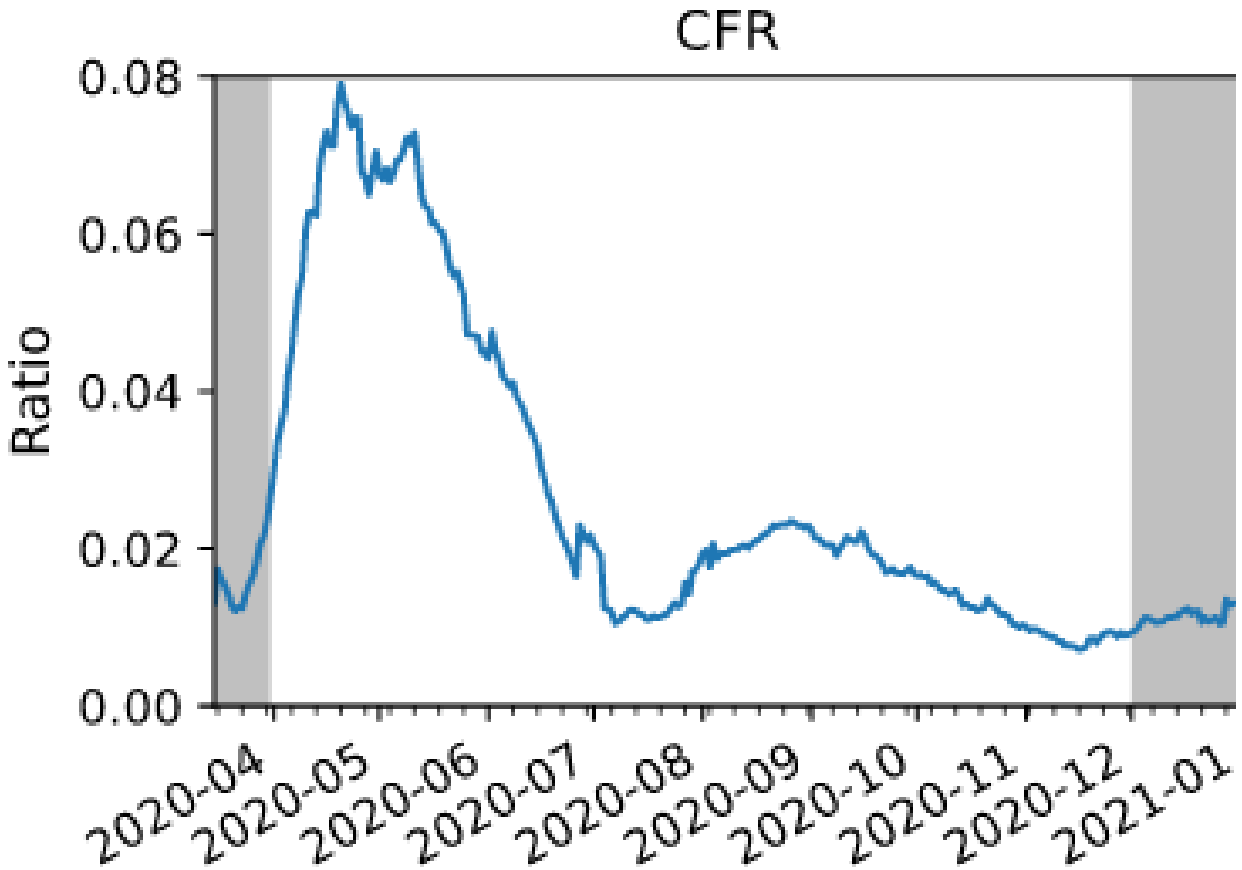
5/18/2021

Disclosures: Research grant support to UCSF related to COVID from Astra Zeneca, Gilead, Lilly and NIH

Improving outcomes for COVID patients

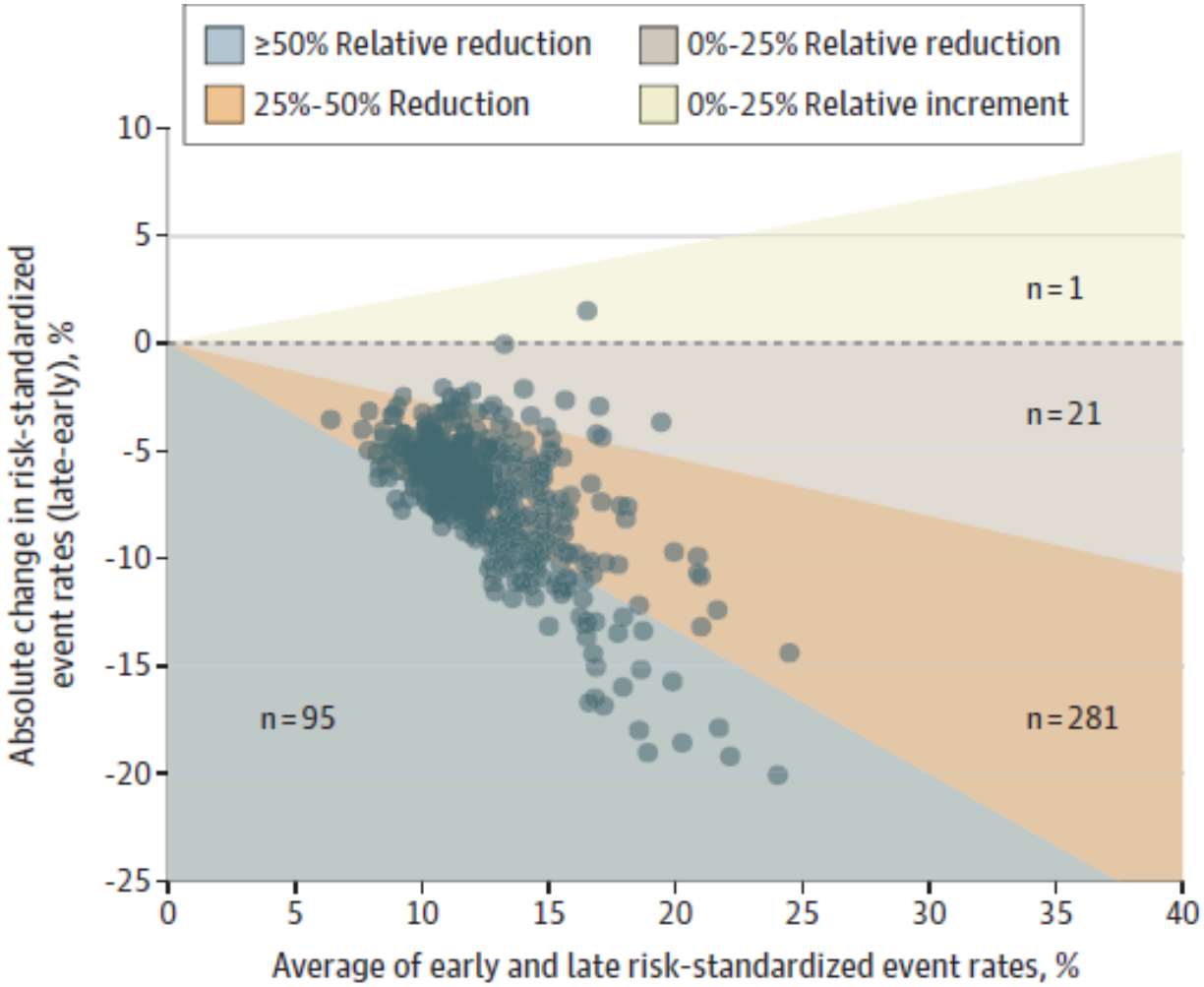
Overall Case Fatality Rate

April 2020- January 2021

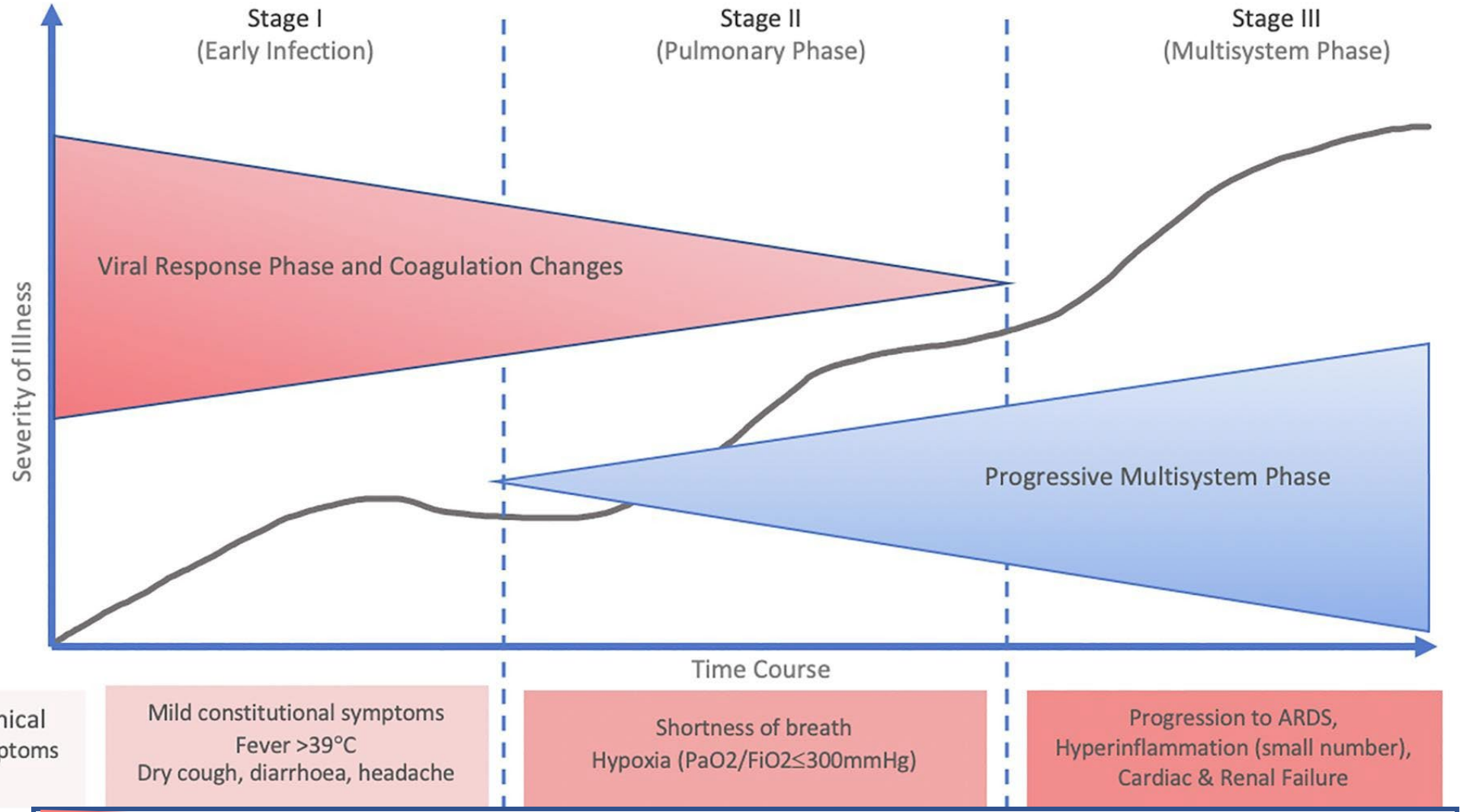


Reduction of inpatient deaths

Jan 2020 - June 2021



COVID disease stage informs treatment



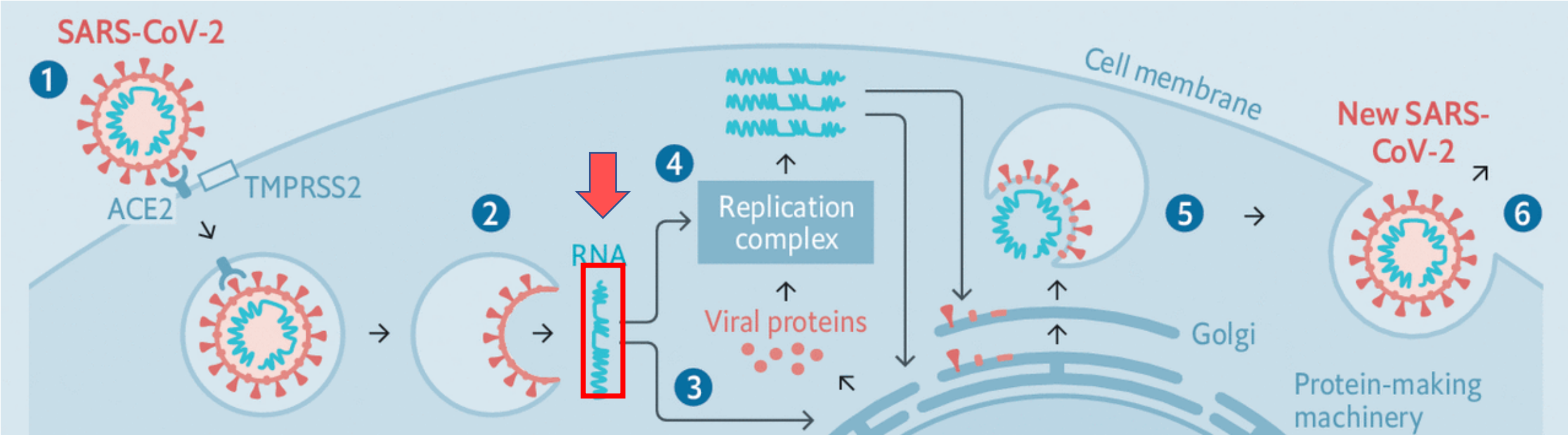
Antivirals

Anti-inflammatories

Anticoagulation (prophylactic, intermediate, full dose?)

Modified from Gan 2020
https://doi.org/10.1016/j.mehy.2020.110024

Remdesivir



- Broad activity against RNA viruses
- Initially developed for use as an Ebola drug
- Blocks viral reproduction inside the cell (nucleoside analogue of adenosine)
- Has to be given intravenously (IV) – no oral option

ACTT-1 study

IV remdesivir vs. placebo

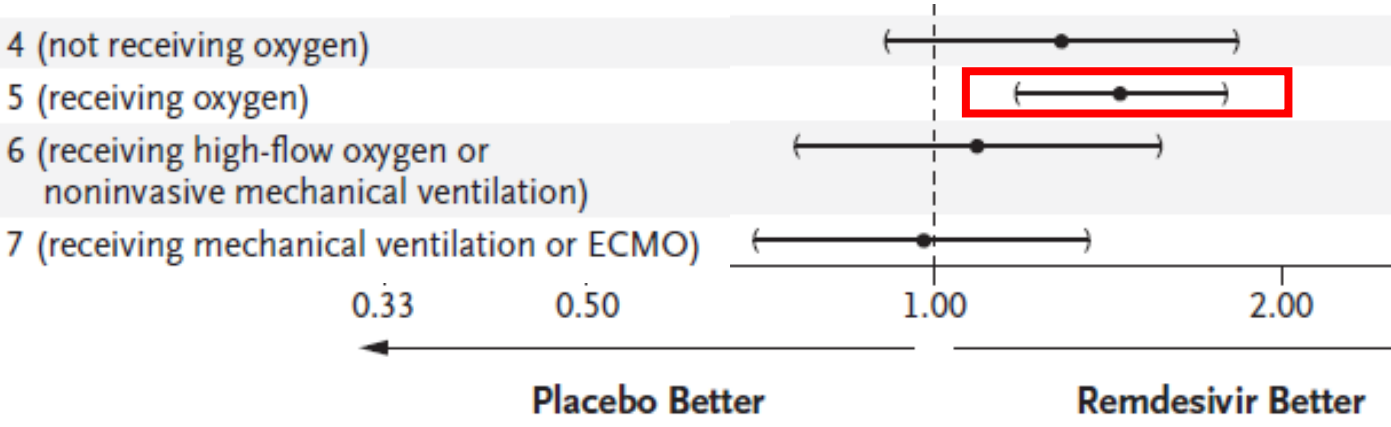
- 50% faster time to clinical improvement: 15->10 days
- 8 less days receiving oxygen
- Lower progression to ventilation
- 70% reduction in death in those on low flow 02
- Generally safe: less adverse events than placebo
- Better response if given within 10 day of symptom onset

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Final Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

Beigel et al, NEJM 10/2020



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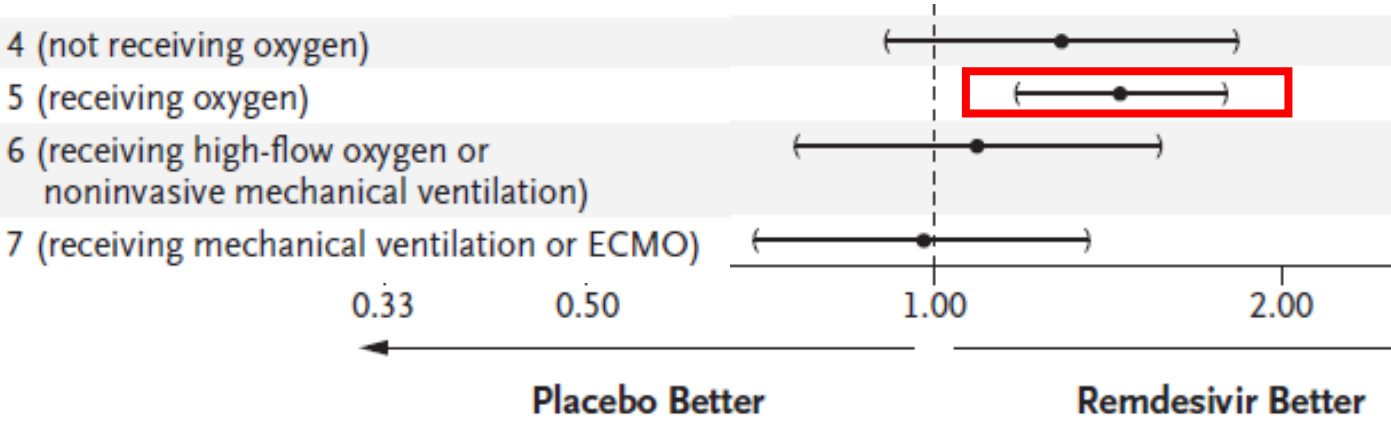


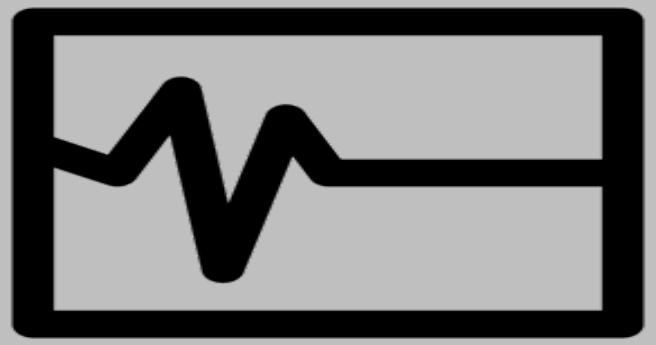
Remdesivir: a good start but more progress needed

- ACTT-1 Initial report May 2020
- Overall mortality **11%** in RDV arm
- **19-21%** in those in ICU

What was known about steroids in viral disease and acute respiratory distress (ARDS) before June 2020?

CONS

Prolonged shedding MERS, SARS



↑Mortality in flu

↑AEs

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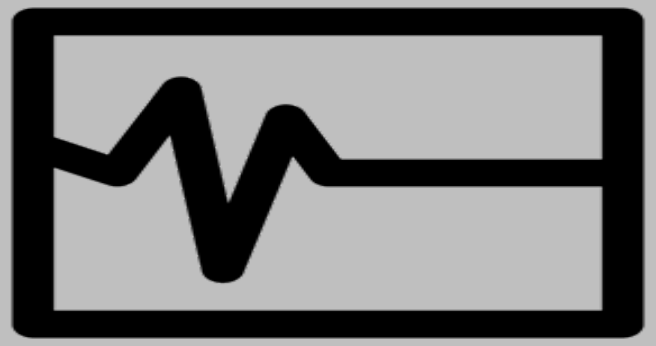

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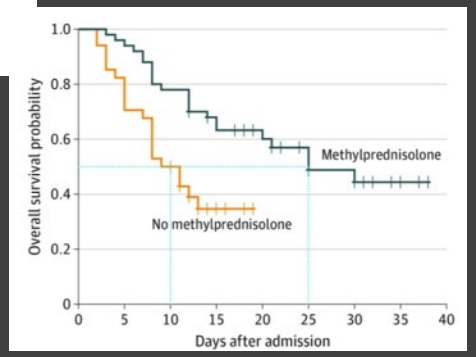
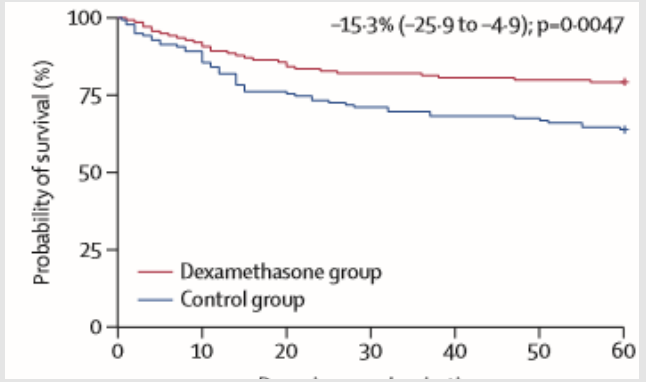


Observational data



Dex in early ARDS

SCCM/ESICM→use for early ARDS

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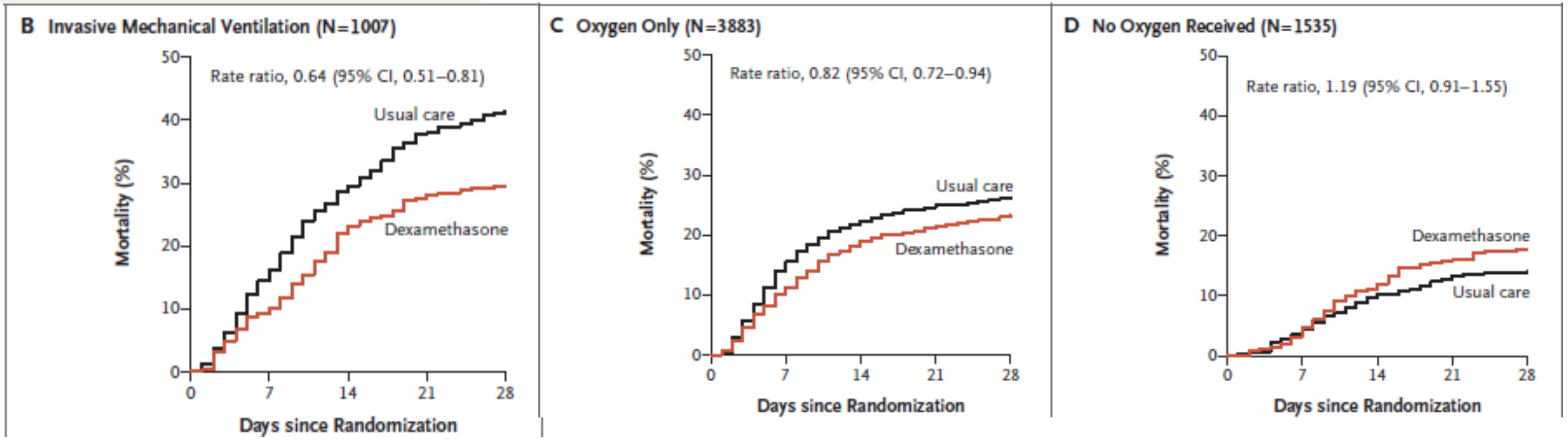
Dexamethasone

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Figure 2. Mortality at 28 Days



ICU: DEX 29.3% vs No DEX 41.4%

Hypoxic: DEX 23.3% vs no DEX 26.2%

No O2: DEX 17.8% vs No DEX 14%

Clarifications & Caveats

- RECOVERY: No details on impact of Dex by level of oxygen support outside ICU
  No data on adverse events attributed to steroid use
- WHO meta-analysis & several RCTs generally support benefit in critically ill patients

Horby RECOVERY *NEJM* 7/2020, 2/2021, WHO meta-analysis *JAMA* 9/2020 , Prescott *JAMA* 9/2020

Dexamethasone has been shown to improve mortality in intubated patients and should be used for all intubated patients unless there are contraindications for steroids. We recommend dexamethasone for most patients on HFNC, and it can be considered with at least 4L oxygen requirement and worsening clinical status.

Anticoagulation

- COVID associated with increased risk of clotting
- 3 multicenter studies examined prophylactic vs. full dose anticoagulation in hospitalized patients

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ATTACC, REMAP-CAP, and ACTIV IV-4a mpRCT

Primary outcome

State & D-dimer Strata	Proportional Odds Ratio Median (95% CrI)	Trial Statistical Conclusion
Moderate state, low D-dimer	1.57 (1.14 - 2.19)	**Superiority** [Probability of OR>1 = 0.997]
Moderate state, high D-dimer	1.53 (1.09 - 2.17)	**Superiority** [Probability of OR>1 = 0.991]
Moderate state, missing D-dimer	1.51 (1.06 – 2.15)	n/a[⏃]
Severe state	0.76 (0.60 – 0.97)	**Futility*** [Probability of OR>1.2 < 0.001]

* Posterior probability of **inferiority** [Probability of OR<1 = 0.985]

⏃ Not evaluated for stopping at interim

OR >1 represents benefit. A higher OR occurs when either mortality is improved and/or if those who survive have reduced requirement for organ support

BENEFICIAL in hospitalized patients outside the ICU

Potentially HARMFUL once critically ill

Release date: January 28, 2021

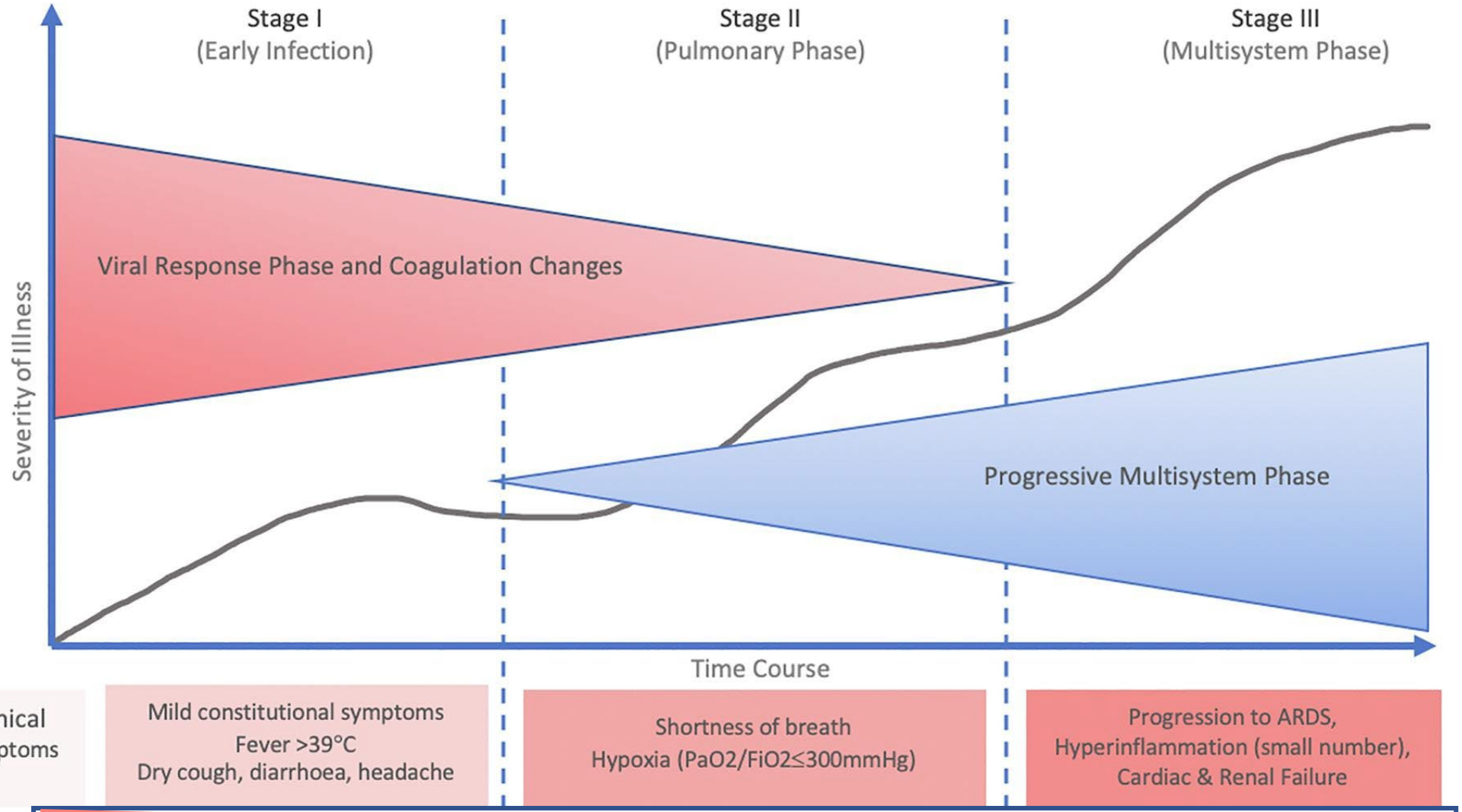
A. DVT prophylaxis is recommended in all hospitalized COVID-19 patients unless there is a contraindication.

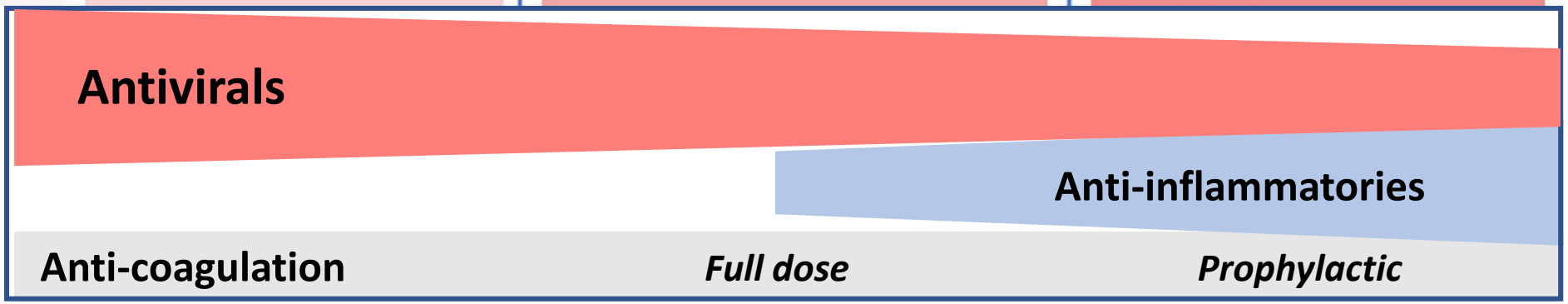
B. ICU patients and those on high flow oxygen should *not* receive therapeutic anticoagulation solely for a COVID-19 indication. Whether intermediate or standard DVT prophylaxis is preferable is an area of active research

C. Therapeutic (full-dose) anticoagulation is a consideration for the patients meeting the following criteria:

- Primary hospitalization for COVID-19 symptoms (respiratory OR GI)
- No contraindications to therapeutic anticoagulation (and are not already on DUAL-antiplatelet therapy)
- On nasal cannula oxygen therapy OR have an elevated D-dimer
- Not requiring organ support (i.e., not on HFNC, not in the ICU)

COVID disease stage informs treatment





Modified from Gan 2020
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Outpatient COVID treatment?

Goals of ideal outpatient treatment:

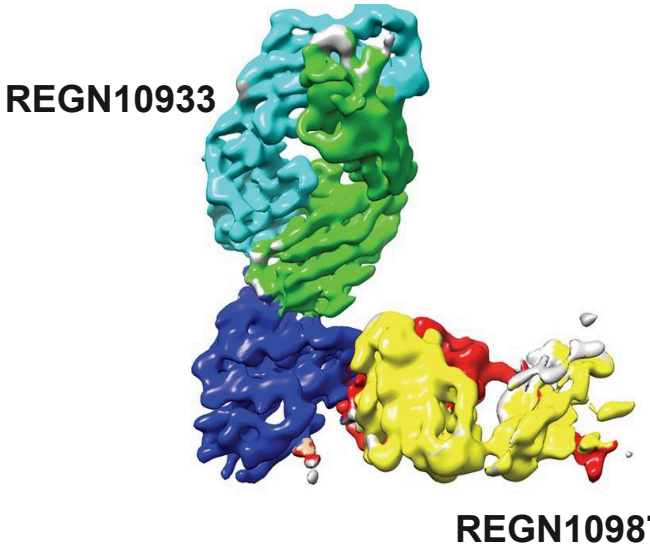
- ✓ Reduce symptom duration
- ✓ Decrease risk of severe disease & hospitalization
- ✓ Reduce infectivity
- ✓ Reduce likelihood of long-term complications
- ✓ Easily administered - oral medication ideal

"Ask your doctor if taking a pill to solve all your problems is right for you"

Limited Outpatient COVID therapies

Approved for use

- Monoclonal antibodies (IV, IM)
  - limited to those at highest risk & as prophylaxis (this indication not FDA approved)
  - Less effective against some variants



Promising but need more data:

- Inhaled corticosteroids
- Inhaled interferon
- Fluvoxamine
- Oral antivirals: polymerase inhibitor(molnupiravir) & protease inhibitor (PF-0732133)

Monk Lancet Resp Med 2021:(9)2; 196

ACTIV-2 / A5401

COVID-19 RESEARCH STUDY

won't find a treatment or cure without your help

vant to learn if study medications will prevent
talization and death in adults.

n, you must be:

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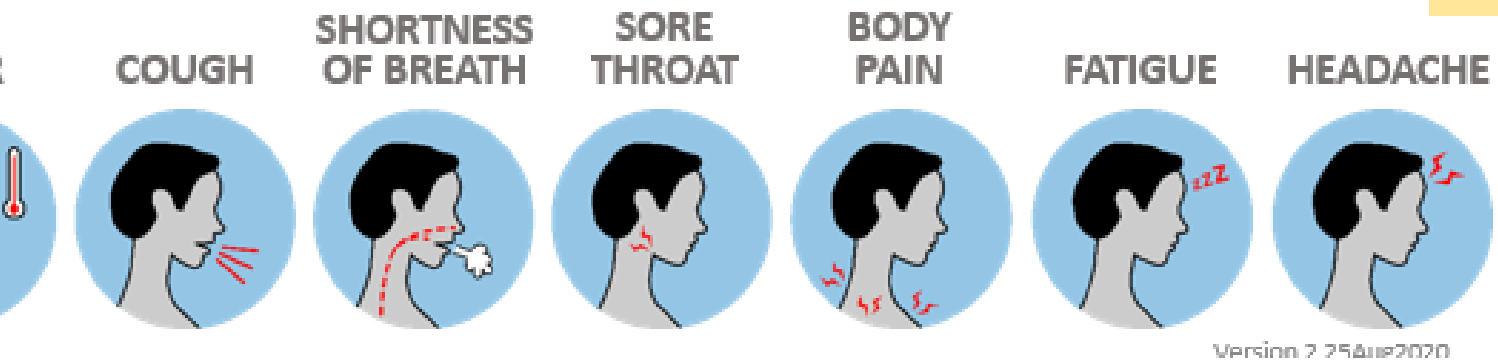

Version 2 25Aug2020

Currently evaluating:

- IV, IM and subQ Monoclonal Abs
- IV Polyclonal Bovine- derived abs
- Oral Camostat
- Inhaled IFN Beta-1a

www.riseabovecovid.com

ZSFG: (415) 806-85sdfasdf54

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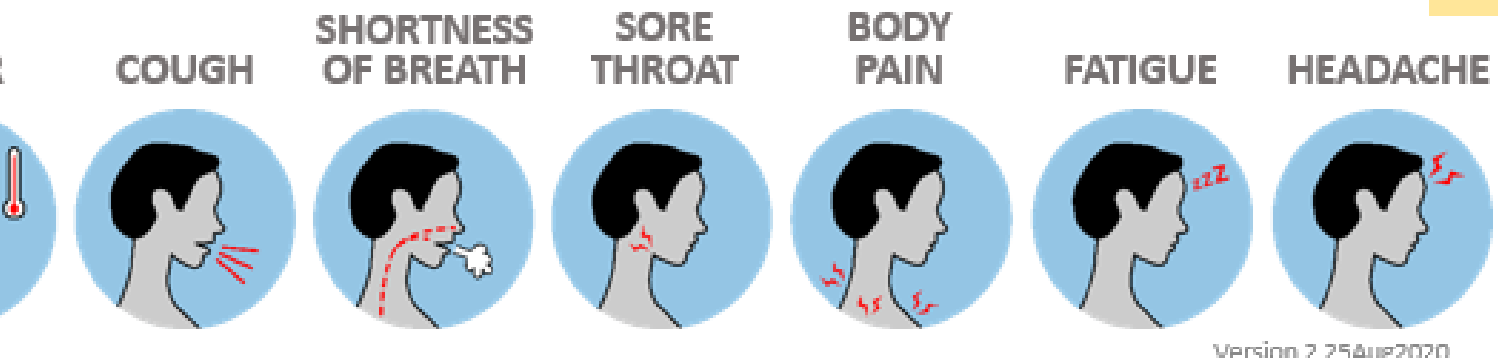

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Contactless study

- Metformin
- Ivermectin
- Fluvoxamine

covidout.umn.edu

Thank you!

a

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