

# COVID-19 Management

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Infectious Disease

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## JSH COVID-19 Treatment Recommendations for Adult Inpatients

### COVID-19 Severity Classification

Severity	Criteria
<b>Mild</b>	<ul style="list-style-type: none"><li>- Symptoms compatible with COVID-19<sup>a</sup></li></ul> <p><b><u>AND</u></b></p> <ul style="list-style-type: none"><li>- SpO2 &gt; 94% at room air</li><li>- No radiographic evidence of pneumonia</li></ul>
<b>Moderate</b>	<ul style="list-style-type: none"><li>- Symptoms compatible with COVID-19<sup>a</sup> AND oxygen requirement via NC</li></ul> <p><b><u>OR</u></b></p> <ul style="list-style-type: none"><li>- Patients with co-morbidities<sup>b</sup> and symptoms compatible with COVID-19<sup>a</sup> with radiographic evidence of pneumonia (irrespective of O2 requirement)</li></ul>
<b>Severe</b>	<ul style="list-style-type: none"><li>- Symptomatic<sup>a</sup> AND one or more of the following:<ul style="list-style-type: none"><li>a. Radiographic evidence of pneumonia</li><li>b. SpO2 &lt; 94% at RA needing higher level of oxygen supplementation (NRB, NIV, mechanical ventilation)</li></ul></li></ul>
<b>Critical</b>	<ul style="list-style-type: none"><li>- Severe criteria</li></ul> <p><b><u>AND</u></b></p> <ul style="list-style-type: none"><li>- Multi-organ failure OR ARDS</li></ul>

<sup>a</sup>Symptoms may include fever, anosmia, respiratory symptoms (ie cough, shortness of breath, sore throat, rhinorrhea, etc.), or diarrhea

<sup>b</sup>Co-morbidities: e.g. hypertension, HIV, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, cancer, immunosuppressed

# Initial Assessment

- Vital signs, including oxygen saturation and respiratory rate at presentation on room air
- Co-morbid conditions (DM, HTN, CKD, obesity) that would make the patient more likely to develop severe disease
- Duration of symptoms
- Home environment
  - How many residents in the home, ability to self-isolate when discharged
  - Criteria for self-isolation: patient spends all their time in their own room, with their own bathroom and own kitchen

# Comorbid conditions

- Increasing age
  - Fatality highest in persons > 85 (10 – 27%) vs. aged 65 – 85 (3 - 11%) vs aged 55 – 64 (1 – 3%)<sup>1</sup>
- Greater number of comorbid conditions increases the risk of death<sup>2</sup>...
  - HTN (increase risk of death by x 2.4)
  - Respiratory system disease (x 2.46)
  - Cardiovascular disease (x 3.42)
  - DM (x 2.07) – not statistically significant
- ...And increases the risk of severe disease or ICU admission
  - Current smokers<sup>3</sup>
  - Obesity<sup>4</sup> more than doubled risk

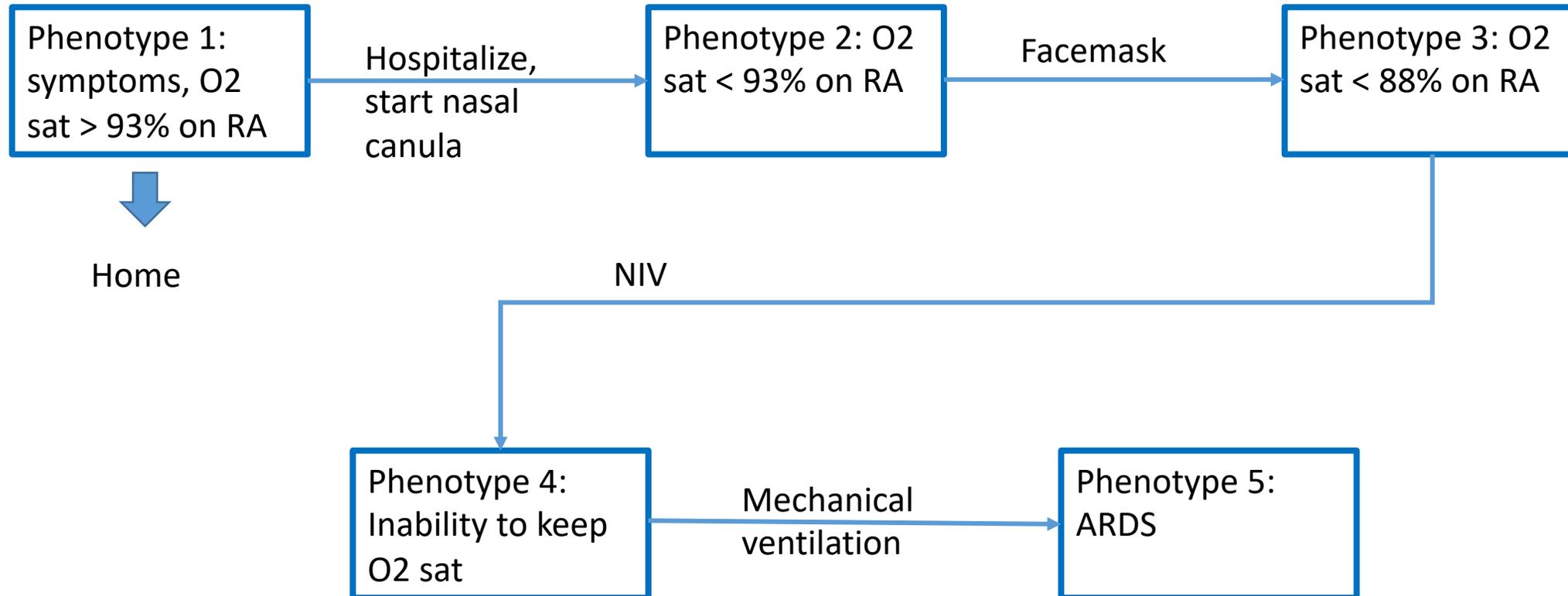
1. MMWR Early Release. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) – United States, February 12 – March 16, 2020

2. Yang, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis May 2020

3. Guan, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. NEJM 2020 Apr 30.

4. Lighter, et al. Obesity in Patients Younger Than 60 Years is a Risk Factor for Covid-19 Hospital Admission. Clin Infect Dis. 2020 Apr 9.

# Severity-dependent protocol to manage COVID-19



# Severity-dependent protocol to manage COVID-19

- Phenotype 1 (mild): Fever, mild respiratory symptoms, SpO<sub>2</sub> > 93% on room air, no CXR changes
- Disposition: Self-isolation at home
- Treatment: Symptomatic treatment only

# Severity-dependent protocol to manage COVID-19

- Phenotype 2 (moderate): SpO<sub>2</sub> < 93% or with CXR opacities
- Disposition: Hospitalization
- Support: symptomatic treatment, oxygen through nasal cannula
- Evidence: effective at maintaining SpO<sub>2</sub> > 93%



# Severity-dependent protocol to manage COVID-19

- Phenotype 3 (pre-critical): severe hypoxia (O<sub>2</sub> sat < 88%) on room air, but responsive to high flow O<sub>2</sub> (SpO<sub>2</sub> > 93% with O<sub>2</sub> 10 – 15L/min)
- Disposition: Hospitalization in a sub-intensive care unit
- Treatment: Oxygenation through high flow nasal cannula, face mask to keep SpO<sub>2</sub> > 93%, prone positioning
- If target not reached in 30 minutes, progress to Phenotype 4



# Severity-dependent protocol to manage COVID-19

- Phenotype 4 (Critical illness): high probability of ARDS evolution, non-invasive ventilation to keep acceptable SpO<sub>2</sub> Levels
- Disposition: Intensive care unit
- Treatment: CPAP or other non-invasive ventilation with target O<sub>2</sub> sat > 93%, prone positioning
- If target not reached after 2 hours, progress to Phenotype 5



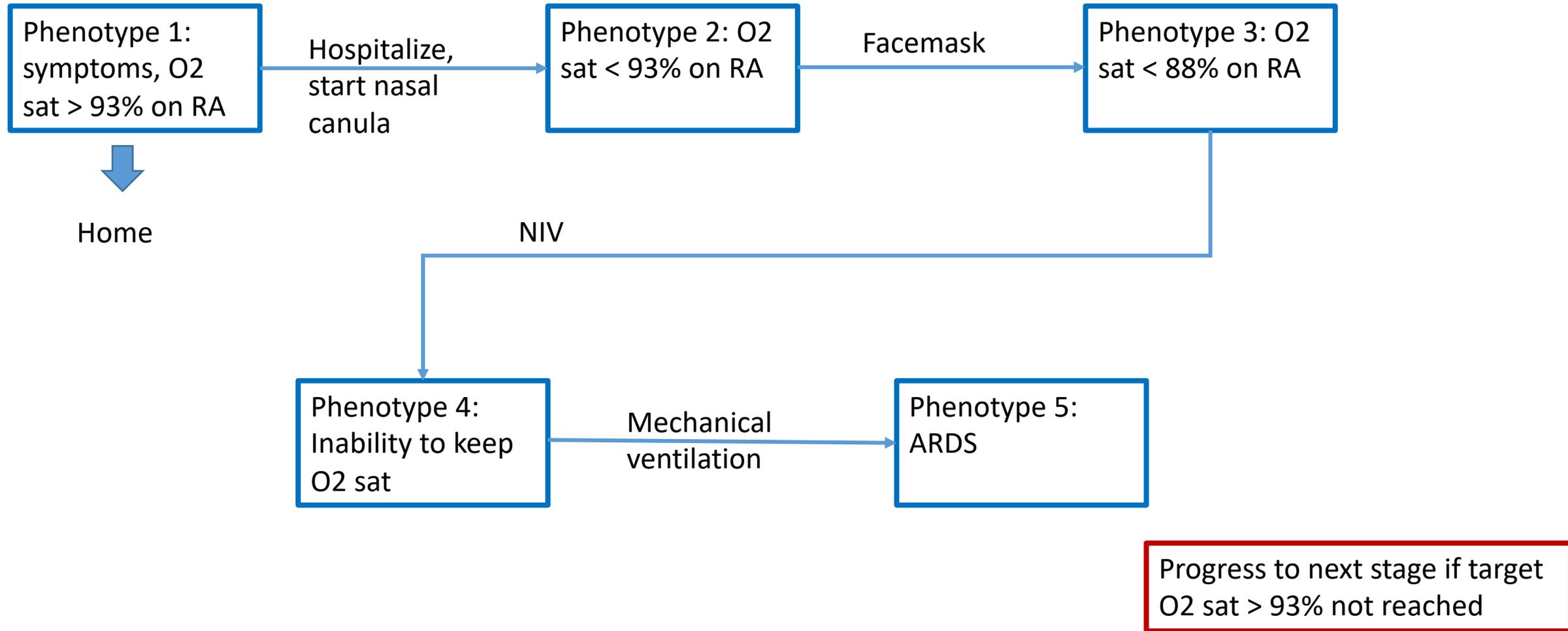
# Severity-dependent protocol to manage COVID-19

- Phenotype 5 (critical): ARDS
- Disposition: Intensive care unit
- Treatment: endotracheal intubation, mechanical ventilator with high PEEP values and frequent repeat positioning with proning if possible
- Titrate FiO<sub>2</sub> to maintain O<sub>2</sub> sat > 93%

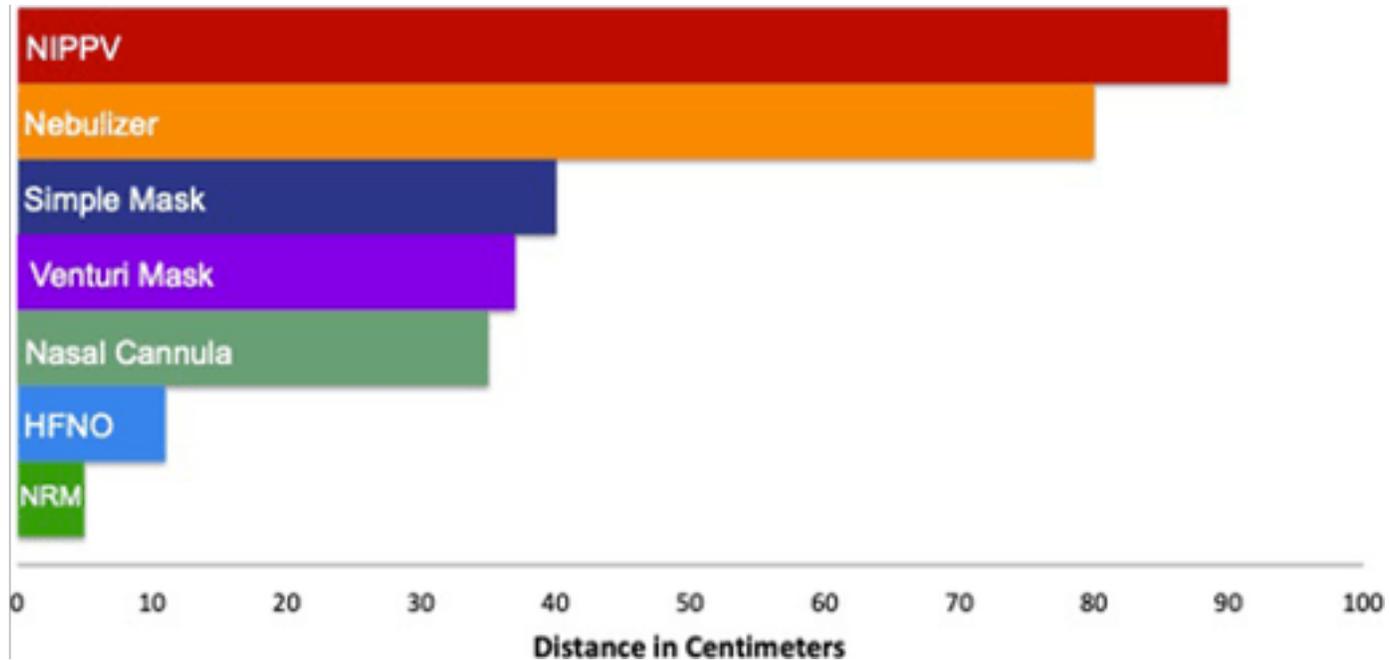


Source: Pascarella, et al. COVID-19 diagnosis and management: a comprehensive review. J Intern Med 2020 May 13.

# Severity-dependent protocol to manage COVID-19



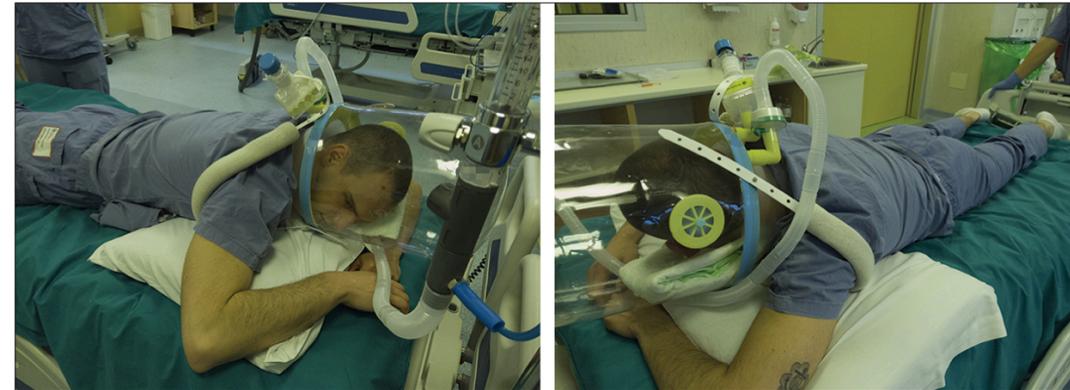
# Dispersion distance with different oxygen modalities



The greater the dispersion distance, the greater the aerosolization risk  
The higher the aerosolization, the greater need for staff protection with **N95 masks**

# Prone positioning

- 56 patients were placed into a prone position for 3 hours on day one of enrollment, then had the option to continue periods of proning the rest of the hospitalization, or at discretion of treating physician
- Proning was feasible in 47 patients (83.9%)
- Prone positioning rapidly increased oxygenation parameters
- Improved oxygenation was maintained in 50% after resupination



**Figure 1: Prone positioning with a helmet interface to enable continuous positive airway pressure**  
Example demonstrated by volunteer.

Coppo, 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 19 June 2020

# Co-administration of antibiotics

- Bacterial and fungal co-infection at presentation is rare
- In a review of 1007 abstracts, 18 texts described bacterial or fungal co-infection<sup>1</sup>
  - 50% reported COVID-19 28% SARS-1 6% MERS 17% other coronaviruses
- For COVID-19, 62/806 (8%) of patients were reported as experiencing bacterial or fungal coinfection during hospital admission
  - 72% of patients received broad-spectrum antimicrobials
- At our institution, we routinely do not prescribe antibiotics in a person with COVID-19 pneumonia
  - Unless ventilator associated pneumonia strongly suspected

1. Rawson, et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis 2020 May 2.

# Hydroxychloroquine

- Hydroxychloroquine and chloroquine have shown to inhibit viral replication *in vitro*
- Several small studies showed more rapid viral clearance (time to negative PCR) in patients treated with HCQ with or without azithromycin compared to supportive care, without clinical data
- FDA approved hydroxychloroquine under emergency use authorization on 28 March, 2020
- Later, other studies showed increased risk of death and arrhythmia without clinical benefit
  - Large study in Brazil was discontinued early
- Retrospective Lancet study of > 9600 patients (later retracted) treated in multiple countries did not show a benefit, showed higher mortality in treatment group
- WHO discontinued HCQ trial, FDA discontinued EUA 15 June 2020

# Hydroxychloroquine

- Fallen out of favor, no evidence of benefit and potential for increased harm
- No randomized, placebo controlled trial
- Possible role for ambulatory patients being addressed in randomized controlled trials

# Remdesivir for the Treatment of Covid-19 — Preliminary Report

John H. Beigel, M.D., Kay M. Tomashek, M.D., M.P.H., Lori E. Dodd, Ph.D., Aneesh K. Mehta, M.D., Barry S. Zingman, M.D., Andre C. Kalil, M.D., M.P.H., Elizabeth Hohmann, M.D., Helen Y. Chu, M.D., M.P.H., Annie Luetkemeyer, M.D., Susan Kline, M.D., M.P.H., Diego Lopez de Castilla, M.D., M.P.H., Robert W. Finberg, M.D., Kerry Dierberg, M.D., M.P.H., Victor Tanson, M.D., Lanny Hsieh, M.D., Thomas F. Patterson, M.D., Roger Paredes, M.D., Ph.D., Daniel A. Sweeney, M.D., William R. Short, M.D., M.P.H., Giota Touloumi, Ph.D., David Chien Lye, M.B., B.S., Norio Ohmagari, M.D., Ph.D., Myoung-don Oh, M.D., Guillermo M. Ruiz-Palacios, M.D., Thomas Benfield, M.D., Gerd Fätkenheuer, M.D., Mark G. Kortepeter, M.D., Robert L. Atmar, M.D., C. Buddy Creech, M.D., M.P.H., Jens Lundgren, M.D., Abdel G. Babiker, Ph.D., Sarah Pett, Ph.D., James D. Neaton, Ph.D., Timothy H. Burgess, M.D., M.P.H., Tyler Bonnett, M.S., Michelle Green, M.P.H., M.B.A., Mat Makowski, Ph.D., Anu Osinusi, M.D., M.P.H., Seema Nayak, M.D., and H. Clifford Lane, M.D. for the ACTT-1 Study Group Members\*

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[Article](#)[Figures/Media](#)[Metrics](#)

May 22, 2020

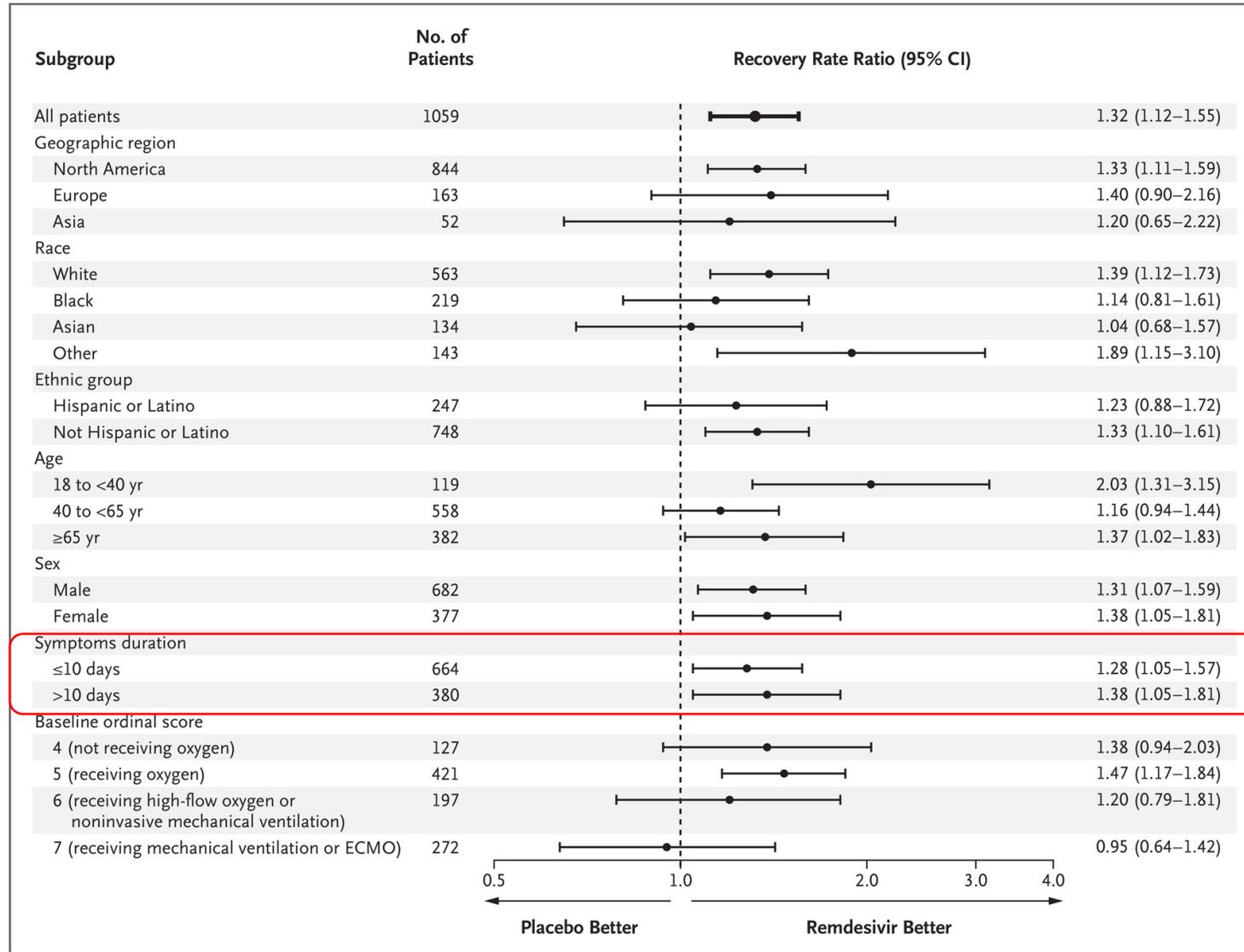
DOI: 10.1056/NEJMoa2007764

- Double-blind, Randomized, placebo controlled
- 60 trial sites, 45 in the United States
- All patients received standard of care
- Primary endpoint: time to improvement in symptoms
- Inclusion criteria: COVID-19 and need for supplemental oxygen or radiographic evidence of pneumonia
- Exclusion criteria: AST or ALT > 5x normal, CrCl < 50 mL/min

# Primary outcome

- RDV group had shorter time to recovery than placebo group (11 versus 15 days): rate ratio for recovery 1.32 (95% CI, 1.12 to 1.55,  $P < 0.001$ ) in 1059 patients analyzed
- Mortality at day 15 was numerically lower in RDV, but not statistically significant (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04)

# Recovery by subgroup analysis



# Potential conclusions

- RDV does not appear to provide any more harm than placebo
- RDV appears to have a positive effect with respect to recovery time in those requiring oxygen, but perhaps less of an effect on those requiring invasive mechanical ventilation or ECMO at randomization

These preliminary findings support the use of remdesivir for patients who are hospitalized with Covid-19 and require supplemental oxygen therapy. However, given high mortality despite the use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient. Future strategies should evaluate antiviral agents in combination with other therapeutic approaches or combinations of antiviral agents to continue to improve patient outcomes in Covid-19.

# Colchicine

- Since acute lung injury and ARDS are thought to be driven by intense an inflammatory response, colchicine has been hypothesized to be beneficial
- Prospective, open-label, randomized trial comparing optimal medical treatment to colchicine across 16 hospitals in Greece
  - Patients in both groups did received hydroxychloroquine and/or azithromycin
  - 50 patients in control group vs 55 patients in colchicine group
- Loading dose of colchicine 1.5 mg orally followed by 0.5 mg 60 minutes later
- End point was time to clinical deterioration and elevation of inflammatory markers

Deftereos, et al. Effect of Colchicine vs Standard of Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019. JAMA. 2020 June 24

# Colchicine

- Primary endpoint occurred in 7 patients in the control group (14%) compared to 1 patient in colchicine group (1.8%)
- No difference in elevation of inflammatory markers, including troponin and CRP
- No difference in adverse events in both groups (except for diarrhea in the colchicine group)
- Study was greatly underpowered, needed approximately 180 patients

Deftereos, et al. Effect of Colchicine vs Standard of Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019. JAMA. 2020 June 24

# Dexamethasone

- Part of RECOVERY (Randomised Evaluation of COVID-19 thERapY) trial out of Oxford, England
- Total of 2104 patients randomized to receive dexamethasone 6mg once per day (PO or IV) for ten days compared to 4321 who received standard of care
- Dexamethasone reduced deaths by one-third in the ventilated patients (RR 0.65,  $p=0.0003$ ) and by one-fifth in patients receiving oxygen only (RR 0.80,  $p=0.0021$ )
- There was no benefit among those patients who did not require respiratory support (RR 1.22,  $p = 0.14$ )
- Number needed to treat: 1 death prevented for every 8 ventilated patients treated or for every 25 patients on oxygen

# Dexamethasone

- Dexamethasone is the first drug found to improve mortality in patients with severe COVID-19
- Cheap, easily accessible drug worldwide
- Clear indication: those who require oxygen
- Unclear if more steroids leads to greater improvement
- Unclear if can extrapolate this data to other steroids

# Dexamethasone

- Dexamethasone 6 mg is equivalent to:
  - Methylprednisolone 32 mg (total daily dose)
  - Prednisone 40 mg
  - Hydrocortisone 160 mg (total daily dose)
  - Cortisone 200 mg (total daily dose)

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### JSH COVID-19 Therapeutic and Diagnostic Recommendations

<b>*Remdesivir EUA – restricted to infectious diseases</b>	
<b>Indication</b>	<b>A. Severe disease defined as one off the following:</b>  <ol style="list-style-type: none"><li>1. Oxygen saturation (SpO<sub>2</sub>) ≤ 94% on room air</li><li>2. Supplemental O<sub>2</sub></li><li>3. On mechanical ventilation</li></ol>
<b>Dose</b>	IV Remdesivir 200 mg single dose on day 1, then 100 mg daily (for 5 days)
<b>Baseline diagnostics or monitoring</b>	On Day 1, obtain EKG, CBC and CMP.  On Day 3, 5 obtain CBC and CMP.
<b>Side Effects</b>	GI: nausea, vomiting, elevated transaminases GU: reversible kidney injury
<b>Contraindications</b>	GFR < 30ml/min LFT's > 5x ULN
<b>Drug-drug Interactions</b>	Rifamycins Inotropes
<p>*The name and pager number of the infectious diseases attending who approved Remdesivir is required when placing the order</p>	

# Conclusions

- Initial assessment includes vital signs and co-morbidities that make patient at risk for severe complications
- Treatment is largely supportive, with increasing oxygen modalities to keep oxygen saturation > 93%
- Prone positioning improves oxygenation and may delay time to intubation
- Antibiotics are not necessary
- Hydroxychloroquine and colchicine are potentially helpful, but further trials are needed and the risks of the treatment don't seem to outweigh the benefits
- Remdesivir improves time to recovery, no mortality benefit
- Dexamethasone is the first widely available drug to have clear benefits, especially in those with critical illness



Thank you!