

NIH Treatment Guidelines

updated July 24, 2020 Remdesivir

The recommendations for using remdesivir to treat COVID-19 have been revised to account for the patient's supplemental oxygen requirements and the mode of oxygen delivery. In this revision, patients who require supplemental oxygen are divided into two groups:

- Those who require supplemental oxygen **but not** high-flow oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO); *and*
- Those who require high-flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO.

Previously, the COVID-19 Treatment Guidelines Panel recommended using remdesivir for patients who were on high-flow oxygen, mechanical ventilation, or ECMO. This recommendation has been revised due to uncertainty regarding whether starting remdesivir confers clinical benefit in these patients.

Below are the revised considering limited remdesivir doses.

- **Recommendation for Prioritizing Limited Supplies of Remdesivir**
Because remdesivir supplies are limited, the Panel recommends that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen **but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO (BI).**
- **Recommendation for Patients with COVID-19 Who Are on Supplemental Oxygen but Who Do Not Require High-Flow Oxygen, Noninvasive or Invasive Mechanical Ventilation, or ECMO**
 - The Panel recommends using **remdesivir** for 5 days or until hospital discharge, whichever comes first **(AI).**
 - If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring high-flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed.
- **Recommendation for Patients with COVID-19 Who Require High-Flow Oxygen, Noninvasive Ventilation, Mechanical Ventilation, or ECMO**
 - Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, the Panel cannot make a recommendation either for or against starting remdesivir.

Comment: This will be a significant change for some. In discussing with other PIs they all recommend sooner rather than later and recommend anyone on 2L should receive remdesivir which is consistent with the new NIH recommendation They do not recommend waiting to see if they progress first. In terms of more severe oxygen requirements, the NIH states "in a randomized clinical trial, there was no observed difference between the remdesivir and placebo groups in time to recovery or mortality rate in these subgroups. However, because the trial was not powered to detect differences in outcomes in these subgroups, there is uncertainty as to the effect of remdesivir on the course of COVID-19 in these patients."

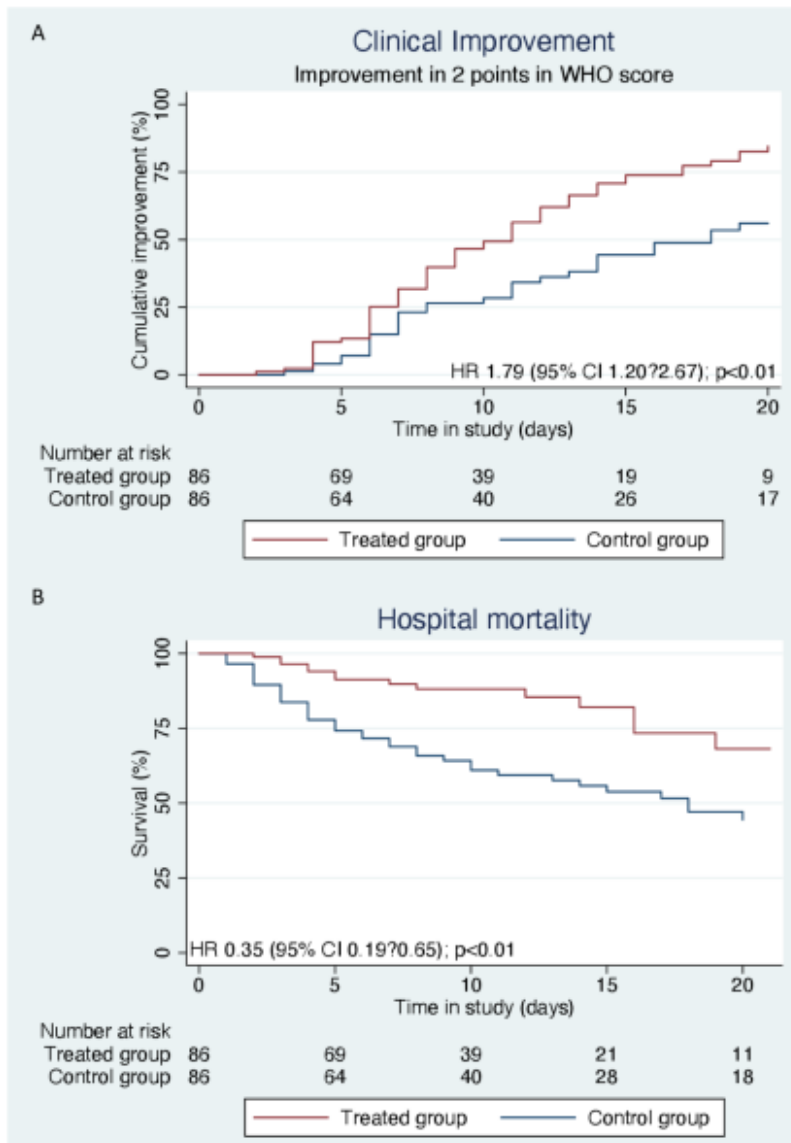
Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome (CSS): results of the CHIC study

Ann Rheum Dis published online July 24, 2020

From 1 April 2020, patients with COVID-19- associated CSS, defined as rapid respiratory deterioration plus at least two out of three biomarkers with important elevations (C-reactive protein >100 mg/L; ferritin >900 µg/L; D-dimer >1500 µg/L), received high-dose intravenous methylprednisolone for 5

consecutive days (250 mg on day 1 followed by 80 mg on days 2–5). If the respiratory condition had not improved sufficiently (in 43%), the interleukin-6 receptor blocker tocilizumab (8 mg/kg body weight, single infusion) was added on or after day 2. Control patients with COVID-19-associated CSS (same definition) were retrospectively sampled from the pool of patients (n=350) admitted between 7 March and 31 March and matched one to one to treated patients on sex and age. The primary outcome was ≥ 2 stages of improvement on a 7-item WHO-endorsed scale for trials in patients with severe influenza pneumonia, or discharge from the hospital. Secondary outcomes were hospital mortality and mechanical ventilation

At baseline all patients with COVID-19 in the treatment group (n=86) and control group (n=86) had symptoms of CSS and faced acute respiratory failure. Treated patients had 79% higher likelihood on reaching the primary outcome (HR: 1.8; 95% CI 1.2 to 2.7) (7 days earlier), 65% less mortality (HR: 0.35; 95% CI 0.19 to 0.65) and 71% less invasive mechanical ventilation (HR: 0.29; 95% CI 0.14 to 0.65). Treatment effects remained constant in confounding and sensitivity analyses. There was no difference in terms of complications.



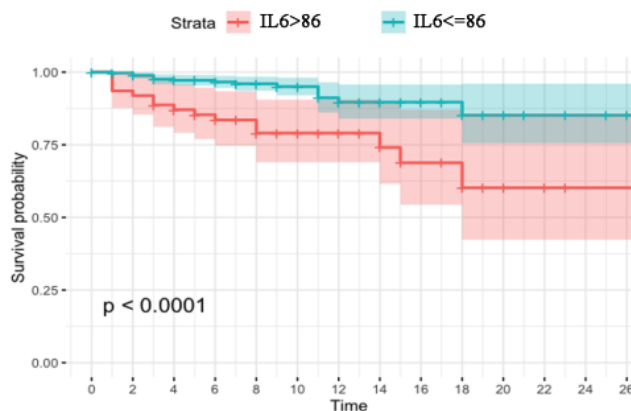
Comment: A strategy involving a course of methylprednisolone, followed by tocilizumab if needed, may be an effective strategy to optimize the use of IL-6 inhibitors. The NIH has been reviewing IL-6 inhibitors and report some observation trial with promising results. They also address the issue of sides effects. “The primary laboratory abnormalities reported with tocilizumab treatment are elevated liver enzyme levels that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. Additional AEs, such as risk for serious infections (e.g., TB, other bacterial pathogens), have been reported only in the context of continuous dosing of tocilizumab.” [one article from last week did note increased bacterial infections] For rheumatological disease use, GI perforation has been a rare complication. This historically controlled comparison of a strategy with steroids and IL-6 inhibitor versus a strategy with supportive care only in patients with COVID-19-associated CSS offers a potentially useful treatment. However, although this study (and other observational trials) is promising it is not a RCT. We await results from the RECOVER and NIH trials.

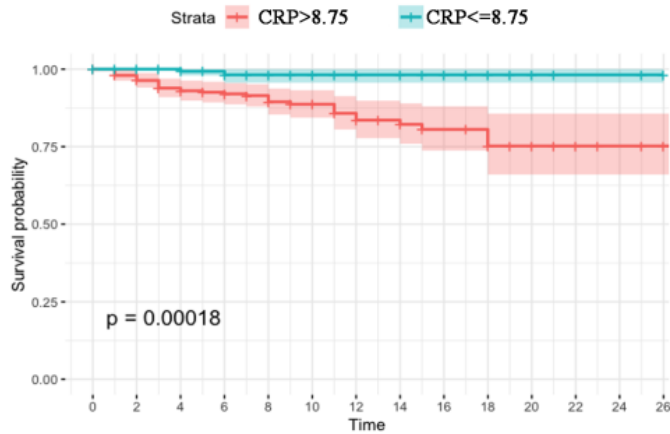
Interleukin-6-based mortality risk model for hospitalised COVID-19 patients

J Allergy and Clin Immunol published online July 24, 2020

The investigators constructed a prospective cohort with 611 adult patients diagnosed with COVID-19. They included in the analysis 501 patients who had been discharged or had died by April 20. The capacity to predict mortality of several biomarkers, measured at the beginning of hospitalization was assessed. Those biomarkers that independently contributed to improve mortality prediction were then included in a multivariable risk model.

High IL-6, CRP, LDH, ferritin, D-dimer, neutrophil count, neutrophil-to-lymphocyte (N/L) ratio, and low albumin, lymphocyte count, monocyte count and peripheral blood oxygen saturation/fraction of inspired oxygen ratio (SpO₂/FiO₂), were all predictive of mortality (AUC>0.70). A multivariable mortality risk model including SpO₂/FiO₂, N/L ratio, LDH, IL-6, and age, was developed and showed high accuracy for the prediction of fatal outcome (AUC=0.94). The optimal cut-off reliably classified patients into survivor and non-survivor, including patients with no initial respiratory distress, with 0.88 sensitivity and 0.89 specificity. IL-6 >86 pg/mL increased the likelihood of dying from 7.2% in the overall cohort to 26%. Individually, the most robust biomarkers to predict risk of mortality in this study were CRP and SpO₂/FiO₂; patients with CRP above 8.75 mg/dL(87.5 mg/L) or SpO₂/FiO₂ below 211 had 20 times more risk of dying than those below/above the threshold.





Comment: Early risk stratification of COVID-19 hospitalized patients, before the appearance of obvious signs of clinical deterioration, can be used as a tool to guide clinical decision-making including antivirals. Patients who progress to severe forms of COVID-19 are thought to have hyperactivation of the immune system with uncontrolled release of inflammatory cytokines. Signaling of the pro-inflammatory cytokine IL-6 can be blocked anti-IL-6 receptor monoclonal antibody tocilizumab. They set up the measurement of IL-6 in COVID-19 patients at their hospital, as a biomarker for inflammation, and to help guide the administration of tocilizumab together with other inflammation markers such as CRP, lymphocyte count and clinical evaluation. In their cohort, IL-6 level was increased in non-survivors. I think this reinforces the evidence that the amount of circulating IL-6 is closely linked to the severity of COVID-19, which has been further confirmed in a recent meta-analysis (J Med Virol 2020), IL-6 has also been associated with mortality risk in non- COVID-19 patients with ARDS (Crit Care 2019; 23:410) Measuring IL-6 and including it in the predictive model may not only be associated with a poor prognosis but could also improve therapeutic decision- making perhaps along with other biomarkers such as CRP. There are an increasing number of studies reporting a favorable outcome from blocking IL-6 in COVID-19 patients. (see above)

CDC Preparing K-12 School Administrators for a Safe Return to School in Fall 2020 Preparing a Safe Return to School

July 23, 2020

Highlights:

- Engage and encourage everyone in the school and the community to practice preventive behaviors. These are the most important actions that will support schools' safe reopening and will help them stay open.
- Implement multiple SARS-CoV-2 mitigation strategies (e.g., social distancing, cloth face coverings, hand hygiene, and use of cohorting).
- Communicate, educate, and reinforce appropriate hygiene and social distancing practices in ways that are developmentally appropriate for students, teachers, and staff. Integrate SARS-CoV-2 mitigation strategies into co-curricular and extracurricular activities (e.g., limiting or cancelling participation in activities where social distancing is not feasible).
- Maintain healthy environments (e.g., cleaning and disinfecting frequently touched surfaces)
- Make decisions that consider the level of community transmission. There is a section that defines levels of transmission.
- Repurpose unused or underutilized school (or community) spaces to increase classroom space and facilitate social distancing, including outside spaces, where feasible.

- Develop a proactive plan for when a student or staff member tests positive for COVID-19.
- Develop a plan with state and local health department to conduct case tracing in the event of a positive case.
- Educate parents and caregivers on the importance of monitoring for and responding to the symptoms of COVID-19 at home.
- Recommended that schools try to keep students in small groups and stay with the same teacher all day.[this is very difficult for upper grades] If a student or staff member in that cohort tests positive, all other members of that group should stay at home until they have a negative test result

There is a section on the critical role of schools:

Schools play a critical role in the wellbeing of communities.

Schools provide critical instruction and academic support

Social and emotional health of students can be enhanced through schools

Mental health of students can be fostered through school supports and services.

Continuity of other special services is important for student success

Comments: The release of this document has been politicized (what else is new concerning this pandemic) I have the original CDC document. The section on the critical role of schools was enhanced. The actual important prevention recommendations remain essentially the same: modified layout and social distancing, face coverings or masks, screening, limit class sizes, events, and gatherings, use of distance learning, modify communal spaces, enhanced cleaning and disinfections, promote hand hygiene, physical barriers especially if social distancing is difficult, posting signs everywhere promoting preventive practices, and staff training. The AAP and NAS documents have many of the same recommendations. To date, there is little guidance on when is it safe to open based on community activity.

Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020

MMWR July 24, 2020

Among 292 respondents, 94% (274) reported experiencing one or more symptoms at the time of testing; 175 (65%) reported that they had returned to their usual state of health a median of 7 days (IQR = 5–12 days) from the date of testing 35% of these symptomatic respondents reported not having returned to their usual state of health by the date of the interview (median = 16 days from testing date), including 26% among those aged 18–34 years, 32% among those aged 35–49 years, and 47% among those aged ≥50 years. Among respondents reporting cough, fatigue, or shortness of breath at the time of testing, 43%, 35%, and 29%, respectively, continued to experience these symptoms at the time of the interview. Symptoms least likely to have resolved included cough (not resolved in 43% [71 of 166]) and fatigue (not resolved in 35%[68 of 192]); among 90 who reported shortness of breath at the time of testing, this symptom had not resolved in 26 (29%) These findings indicate that COVID-19 can result in prolonged illness even among persons with milder outpatient illness, including young adults.

1 in 5 previously healthy young adults* weren't back to usual health 14-21 days after testing positive

*ages 18-34
Random sample of adult outpatients with COVID-19 from 14 U.S. academic health care systems

CDC.GOV bit.ly/MMWR72420 MMWR

To stay well and protect others...

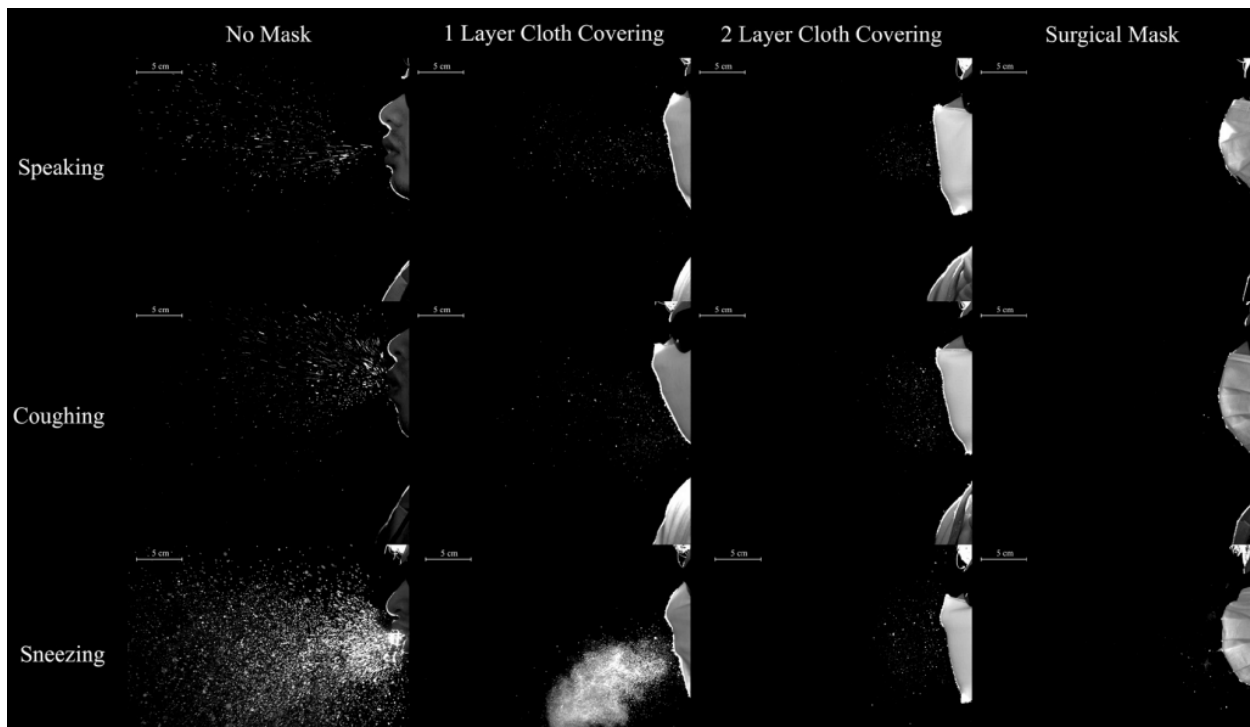
- Stay 6 feet away from others not living in your household
- Wash hands often
- Wear face coverings consistently and correctly in public

Comment: Most studies to date have focused on symptoms duration and clinical outcomes in adults hospitalized with severe COVID-19. This report indicates that even among symptomatic adults tested in outpatient settings (mild disease), it might take weeks for resolution of symptoms and return to usual health. I do not find this surprising. Since this was a telephone survey, this study relied on patient self-report and might have been subject to incomplete recall or recall bias.

Face coverings and mask to minimise droplet dispersion and aerosolisation: a video case study

Thorax published online July 24, 2020

One picture is worth 1000 words



Comment: For speaking, a single-layer cloth face covering reduced the droplet spread but a double-layer covering performed better. Even a single-layer face covering is better than no face covering. However, a double-layer cloth face covering was significantly better at reducing the droplet spread caused by coughing and sneezing. A surgical mask was the best among all the tested scenarios in preventing droplet spread from any respiratory emission. These are the 3-ply masks we all wear in our facilities. It is recommended that teachers also wear a surgical mask.