Good morning-TGIF

Under COVID-19 News FDA has given EUA for the combination monoclonal bamlanivimab and etesevimab. The CDC has weighed in on whether vaccinated individuals who have a close contact need to quarantine.

Under Journal Reviews first is the widely publicized discussion on double masking from the CDC. Some reporting has been a little misleading. The next two articles are important updates on RDV ACP Guidance and the long-awaited RECOVERY results on tocilizumab. The last article is a small series using a single subcutaneous injection of peginterferon lambda within 7 days of symptom onset or first positive swab if asymptomatic.

I hope you enjoy these selections.

Remember Sunday is Valentine's Day.

Ed

COVID-19 News

FDA Authorizes EUA for Bamlanivimab and Etesevimab
FDA authorizes EUA for bamlanivimab and etesevimab administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age or older weighing at least 40 kilograms [about 88 pounds]) who test positive for SARS-CoV-2 and who are at high risk for progressing to severe COVID-19. The authorized use includes treatment for those who are 65 years of age or older or who have certain chronic medical conditions.

In a clinical trial of patients with COVID-19 at high risk for disease progression, a single intravenous infusion of bamlanivimab and etesevimab administered together significantly reduced COVID-19-related hospitalization and death during 29 days of follow-up compared to placebo.

Bamlanivimab and etesevimab are not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19. Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

CDC Vaccinated People and Quarantine Post Exposure
The CDC now says that people who have received either authorized COVID-19 vaccine do not need to quarantine after exposure to a person with COVID-19, provided they meet all of the following criteria:

- They've received both vaccine doses, and at least 2 weeks have passed since the second dose.
- They are within 3 months of their last dose.
- They've not developed COVID-19 symptoms since their exposure. Symptomatic COVID-19 is thought to play a greater role in the transmission of the virus than asymptomatic disease

Anyone *not* meeting all of the above should abide by current CDC guidance on quarantining.

Journal Reviews

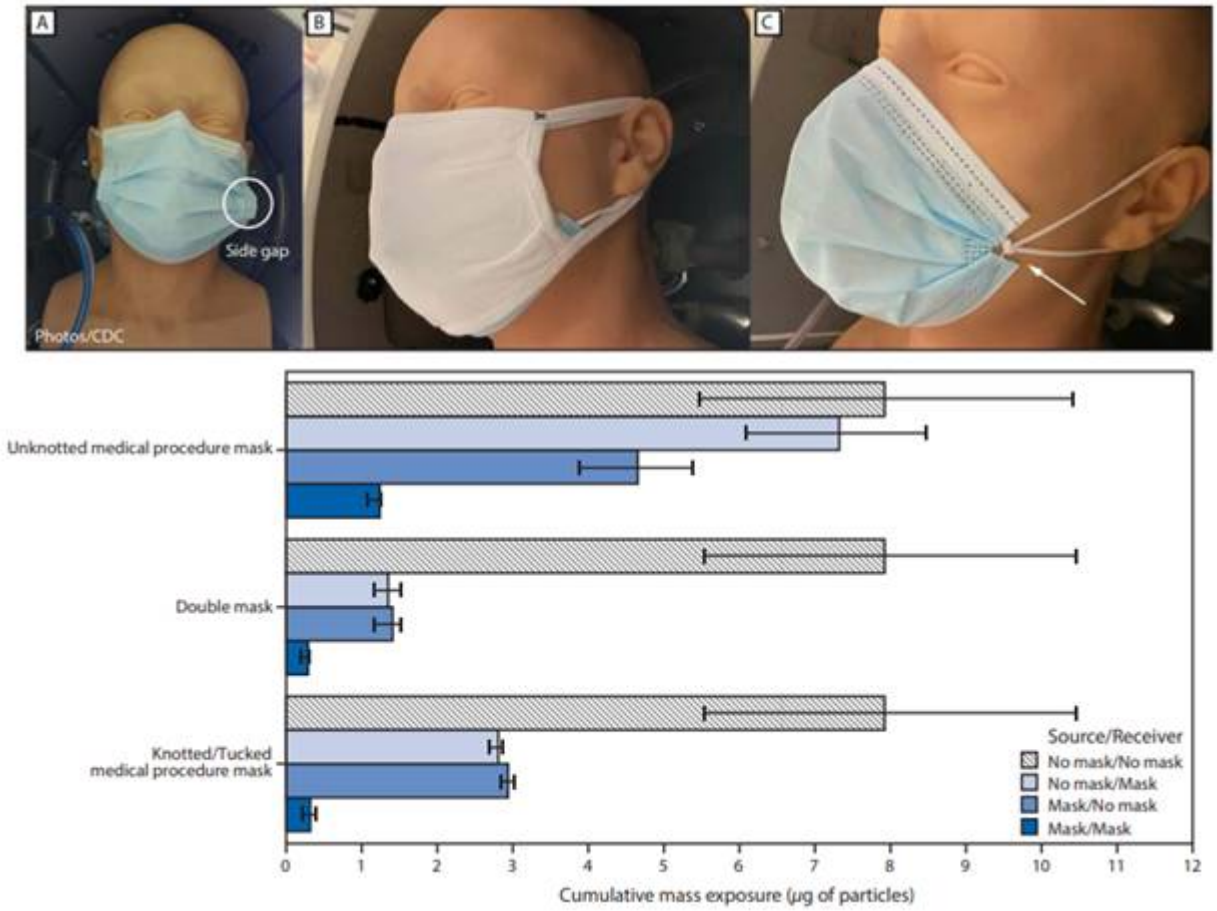
Maximizing Fit for Cloth and Medical Procedure Masks to Improve Performance and Reduce SARS-CoV-2 Transmission and Exposure, 2021

MMWR published online February 10, 2021

CDC released new data showing the fit of face masks—both cloth and surgical—can significantly reduce COVID-19 transmission, by as much as 96.5% if both infected and uninfected people wear them properly.

When exposed to aerosols that mimicked the size of COVID-19 aerosols produced by both coughing and breathing, close-fitting masks outperformed no masks or masks with gaps at the side of the face. Results from the experiment showed that the unknotted three-ply medical procedure mask alone blocked 42.0% of the particles from a simulated cough (standard deviation [SD] = 6.70), and the cloth mask alone blocked 44.3% (SD = 14.0).

The combination of the cloth mask covering the medical procedure mask (double mask) blocked 92.5% of the cough particles. Maximum protection was seen when both the "source" and "receiver" of the cough were both fitted with double masks or knotted and tucked medical masks. Then the cumulative exposure of the receiver was reduced 96.4% (SD = 0.02) and 95.9% (SD = 0.02).



Comment: The findings of these simulations should neither be generalized to the effectiveness of all medical procedure masks or cloths masks nor interpreted as being representative of the effectiveness of

these masks when worn in real-world settings. These experiments did not include any other combinations of masks, such as cloth over cloth, medical procedure mask over medical procedure mask, or medical procedure mask over cloth. The findings might not apply to children because of their smaller size or to men with beards and other facial hair, which interfere with fit. Finally, although use of double masking or knotting and tucking are two of many options that can optimize fit and enhance mask performance for source control and for wearer protection double masking might impede breathing or obstruct peripheral vision for some wearers and knotting and tucking can change the shape of the mask such that it no longer covers fully both the nose and the mouth of persons with larger faces. Bottom line, I agree an appropriate mask should fit appropriately. There are multiple simple ways to achieve better fit of masks to more effectively slow the spread of COVID-19. Also remember optimal protection occurs when both individuals wear masks.

Should Remdesivir Be Used for the Treatment of Patients With COVID-19? Rapid, Living Practice Points from the American College of Physicians (Version 2)
Ann Intern Med published online February 9, 2021
doi.org/10.7326/M20-8101
In a new recommendation, the American College of Physician now says that the antiviral drug remdesivir should not be started in hospitalized COVID-19 patients who are on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) since these patients have likely moved from the viral to the inflammatory stage of the disease. The authors also say remdesivir may be considered for 5 days in hospitalized patients not requiring ventilation or ECMO. Remdesivir may be extended to 10 days in patients who need mechanical ventilation or ECMO and have already started their 5-day course.

Comment: Current evidence suggests an overall net benefit of remdesivir in patients with COVID-19 who do not require invasive mechanical ventilation or ECMO and suggests that 5 days of treatment may be as effective as 10 days. The language of the practice point was changed from “use remdesivir” to “consider remdesivir” to highlight the importance of clinical judgment when making decisions with individual

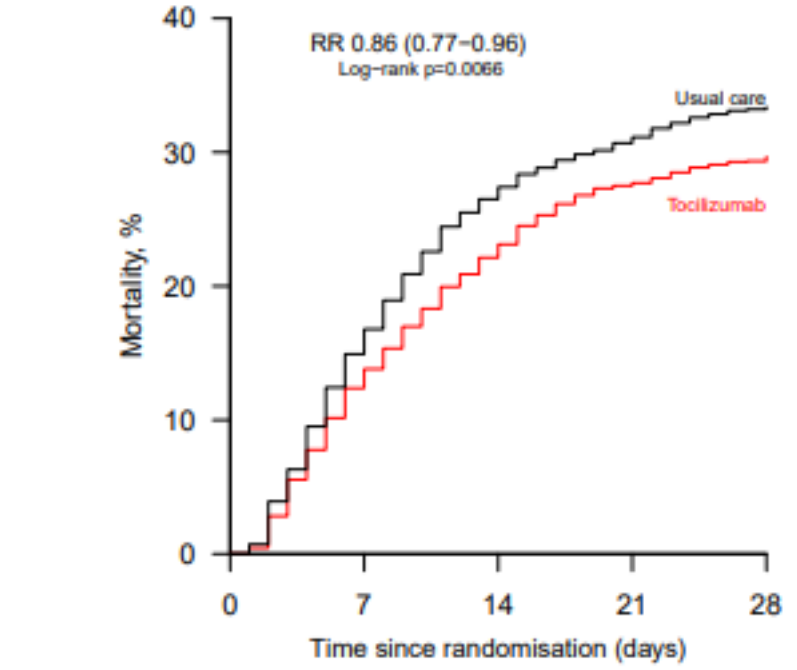
patients about whether to begin remdesivir treatment. Current understanding of COVID-19 progression is that patients who are admitted and progress to mechanical ventilation or ECMO have likely progressed beyond the viral stage of the illness to the inflammatory stage and are less likely to improve from antivirals [patients who require vapotherm are probably in this group as well]; hence, it is important to avoid any additional toxicity from remdesivir. Studies suggest that the potential harms of remdesivir may outweigh the potential benefits in patients who are receiving invasive mechanical ventilation or ECMO at baseline and cautions against initiating remdesivir treatment in these patients.

Tocilizumab in Patients Admitted to Hospital with 4 COVID-19 (RECOVERY): Preliminary Results of a 5 Randomised, Controlled, Open-Label, Platform Trial

medRvix published online February 11, 2021
doi.org/10.1101/2021.02.11.21249258

This is the long awaited Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial assigning 4,116 severely ill COVID-19 patients to receive either intravenous tocilizumab or usual care. Most (82%) of the participants also received a systemic corticosteroid such as dexamethasone. Those trial participants with hypoxia (oxygen saturation ≤92% requiring supplemental oxygen) and evidence of systemic inflammation (C-reactive protein [CRP] ≥75 mg/L-median 143mg/L) were eligible for randomization.

Of the 2,022 patients receiving tocilizumab from Apr 23, 2020, to Jan 25, 2021, 596 (29%) died within 28 days of hospitalization, versus 694 of 2,094 (33%) of patients receiving usual care (rate ratio [RR], 0.86), for a 4% absolute difference. The drug also raised the chances of being released from the hospital alive within 28 days from 47% to 54% (RR, 1.22). Patients in the tocilizumab group not receiving invasive mechanical ventilation when enrolled in the trial were also less likely to advance to needing that treatment (from 38% to 33%; RR, 0.85), and fewer went on to need dialysis (5% vs 7%). All patient subgroups saw benefits, including those who needed supplemental oxygen with a face mask and those needing mechanical ventilation in an intensive care unit. Mean participant age was 63.6 years. Among the 4,116 participants, 562 (14%) received invasive mechanical ventilation, 1,686 (41%) received noninvasive respiratory support, and 1,868 (45%) received no respiratory support except supplemental oxygen. All patients had low oxygen levels and signs of inflammation.



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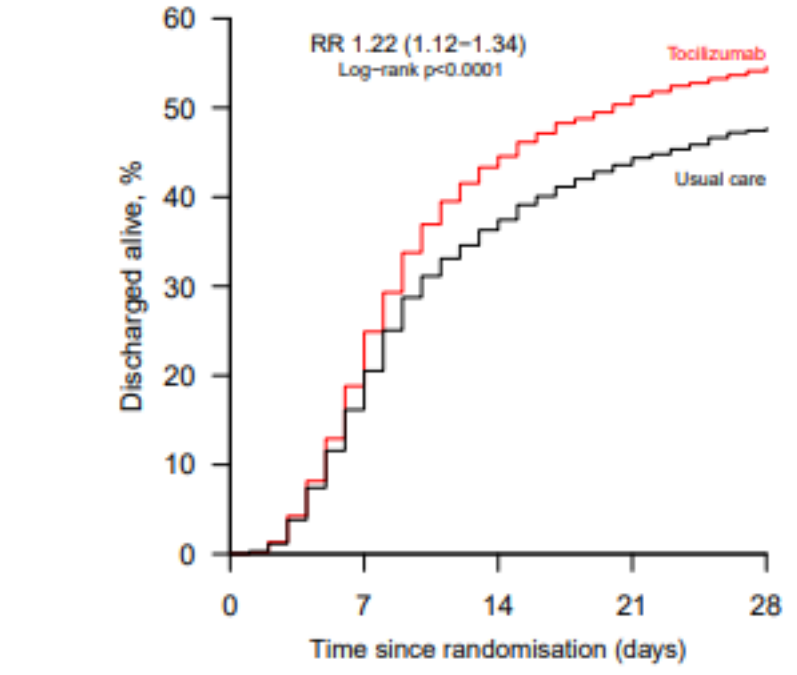
Active	2022	1741	1553	1386	1284
Control	2094	1740	1518	1372	1250



Comment: This study suggests that in COVID-19 patients who are hypoxic and have evidence of systematic inflammation, treatment with a combination of a systemic corticosteroid plus tocilizumab would be expected to reduce mortality by about one-third for patients receiving simple oxygen and nearly one-half for those receiving invasive mechanical ventilation. The interim guidance in the NHS

states that IL-6 antagonists should be considered for patients within 24 hours of starting non-invasive respiratory support or invasive mechanical ventilation. RECOVERY Trial results show that the benefits of tocilizumab extend to a broader group of patients receiving oxygen with or without other forms of respiratory support, and that those benefits include a reduction in the need for invasive mechanical ventilation and other organ support such as renal replacement therapy. Since complicating bacterial infections are infrequent in the early hospitalization period of COVID-19, this study along with the recent REMAP CAP trial suggests that tocilizumab with steroids in patients with evidence of inflammation improves outcomes. The results of RECOVERY and REMAP CAP should help clear up confusion about the potential benefits of tocilizumab for patients with COVID-19 with systemic inflammation after several recent studies with mixed results.

Peginterferon Lambda for the Treatment of Outpatients with COVID-19: A Phase 2, Placebo-Controlled Randomised Trial

Lancet Resp Med published online February 5, 2021
https://doi.org/10.1016/S2213-2600(20)30566

This is a double-blind, placebo-controlled trial. Outpatients with laboratory-confirmed COVID-19 were randomly assigned (1:1) to a single subcutaneous injection of peginterferon lambda 180 μg or placebo within 7 days of symptom onset or first positive swab if asymptomatic. The primary endpoint was the proportion of patients who were negative for SARS-CoV-2 RNA on day 7 after the injection, analyzed by a χ^2 test following an intention-to-treat principle. Prespecified analysis of the primary endpoint, adjusted for baseline viral load, using bivariate logistic regression was done.

Between May 18, and Sept 4, 2020, they recruited 30 patients per group. The decline in SARS-CoV-2 RNA was greater in those treated with peginterferon lambda than placebo from day 3 onwards, with a difference of 2·42 log copies per mL at day 7 (p=0·0041). By day 7, 24 (80%) participants in the peginterferon lambda group had an undetectable viral load, compared with 19 (63%) in the placebo group (p=0·15). After controlling for baseline viral load, patients in the peginterferon lambda group were more likely to have undetectable virus by day 7 than were those in the placebo group (odds ratio [OR] 4·12 [95% CI 1·15–16·73; p=0·029). Of those with baseline viral load above 10^6 copies per mL, 15 (79%) of 19 patients in the peginterferon lambda group had undetectable virus on day 7, compared with six (38%) of 16 in the placebo group (OR 6·25 [95% CI 1·49–31·06]; p=0·012). Most symptoms in both groups were mild to moderate, without difference in frequency or severity. While symptom improvement was generally similar over time for both groups, respiratory symptoms improved faster with peginterferon lambda, with the effect more pronounced in the high baseline viral load group (OR 5.88 (0.81-42.46; *P* = .079). Peginterferon lambda was well tolerated, and adverse events were similar between groups with mild and transient aminotransferase, concentration increases more frequently observed in the peginterferon lambda group.

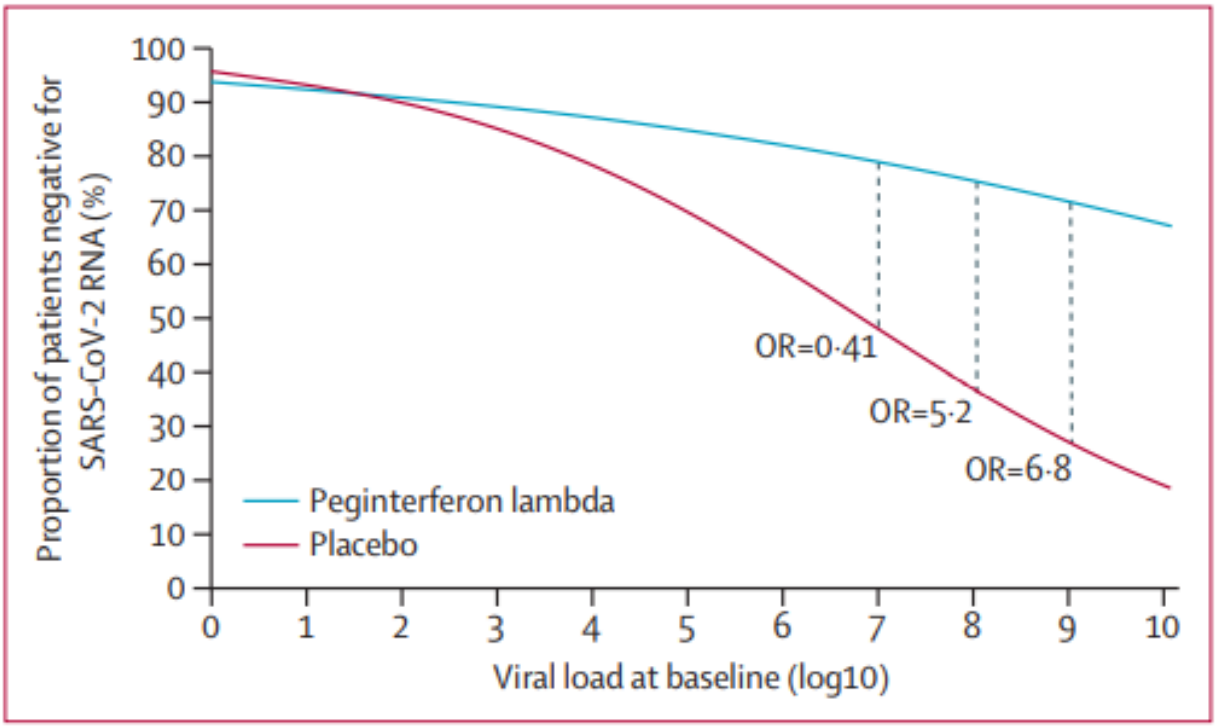


Figure 3: **Probability of SARS-CoV-2 clearance by day 7 according to baseline viral load**

Comment: Interferon lambda-1, is a type III interferon which has been shown to be involved in innate antiviral responses. Interferons drive induction of genes with antiviral, antiproliferative and immunoregulatory properties, and early treatment with interferons might halt clinical progression and shorten the duration of viral shedding with reduced onward transmission. Peginterferon lambda accelerated viral decline in outpatients with COVID-19, increasing the proportion of patients with viral clearance by day 7, particularly in those with high baseline viral load. Peginterferon lambda has potential to prevent clinical deterioration and shorten duration of viral shedding. This study showed that peginterferon lambda accelerated viral clearance, particularly in those with high baseline viral loads, highlighting the importance of quantitative viral load testing in the assessment of antiviral agents for patients with COVID-19. Treatment early in the course of disease might prevent clinical deterioration and shorten the duration of viral shedding, which might have an important public health effect by reducing transmission and reducing the duration of self-isolation. The investigators did not see a marked difference in clinical outcomes. To translate acceleration of viral clearance to clear clinical benefit, the study would need to include those at higher risk of severe disease, such as individuals older than 65 years and those with comorbidities. The study is more of a proof of concept and small. Combination monoclonals given to patients with early symptoms as outpatient also has been shown to reduce viral loads and progression.