COVID-19 Action Newsletter
UT Southwestern Department of Internal Medicine
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The Situation: Confirmed U.S. Deaths Pass 250,000

In the world as of November 20, 2020, 57,110,286 cases and 1,364,073 deaths have been confirmed. In the United States, there have been 11,740,229 cases, the most in the world followed in order by India, Brazil, France and Russia. China is now 65th in the world with 91,965 cases. Deaths in the U.S. through November 20 have been estimated at 252,838.[1]

From March 10 through November 19, there have been 113,764 confirmed cases of Covid-19 reported from Dallas County with 1,164 deaths, about 24% of these from long-term care facilities.[2] Sixty-eight percent of hospitalized cases in Dallas County have been under 65 years of age. Diabetes mellitus has been seen in about one-third of all hospitalized patients. More men (63%) than women (37%) have died, and 47% of the hospitalized cases have occurred in the Hispanic population. As of 11/17, 1,147 deaths have been analyzed by race with 25% occurring in Whites (actual White population 29%), Hispanics 47% (population 41%), Blacks 24% (population 24%), and Asians 3% (population 7%). Specimens submitted for diagnosis of respiratory viruses show continuing positivity for SARS-CoV-2 with the latest result on 11/7 being 15.3%, down from a peak value of 30.5% obtained during the week ending 7/4/20. Influenza A and B antigen tests in specimens from the respiratory tract from 8/1 through 11/7/20 have been negative except for two positive tests (0.6%) collected during the week ending 10/24/20.

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<u>Feature Article</u>

Update on the Pharmacologic Treatments for Covid-19

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As the number of global cases of coronavirus 2019 disease (Covid-19) continue to surge, the need for effective pharmacologic treatments remains urgent. The pace of clinical research and the preliminary nature of much of the data introduces challenges for frontline clinicians to keep up and to apply evidence-based approaches to this rapidly changing therapeutic landscape. Reliance on unbiased resources for evidence summaries[1] and national guidelines[2] provide useful tools to track evidence, but clinicians should strive to adopt what has been termed a "sensible medicine" approach,[3] which "encourages supportive restraint and heightened therapeutic humility" while relying on the highest quality evidence available.

Although many approaches exist to categorize Covid-19 therapeutics, one useful framework focuses on the broad mechanism of action coupled with a recognition of what disease severity (mild/moderate vs. severe/critical) and what phase of the illness (early viral phase vs. later inflammatory phase) the therapy is likely to be most effective in. The following is a summary update of select proposed or studied treatments in 4 broad categories: antivirals, immune system mimics, immunomodulators, and other treatments.

Antivirals

The first category of treatments includes agents that directly target the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These antivirals likely work best in the early viral phase, generally considered to be the first 7-10 days of illness. The primary example of this is the nucleoside analogue prodrug **remdesivir (RDV),** which interferes with the viral RNA-dependent RNA polymerase. In the NIH-sponsored randomized-controlled ACTT-1 trial, a 10 day course of intravenous RDV was shown to significantly reduce the median time to recovery by 5 days compared to placebo (10 vs. 15 days, RR 1.29, p <0.001).[4] Overall, this study did not show a mortality benefit although it may have been underpowered for this outcome; in subgroup analysis, patients who were on low-flow oxygen appeared to have the greatest benefit whereas patients on high-flow oxygen, non-invasive ventilation or mechanical ventilation did not appear to benefit substantially from this therapy. Importantly, virologic outcomes are yet to be published from this study.

Subsequent trials sponsored by the pharmaceutical company Gilead have demonstrated non-inferiority when comparing 5 vs. 10 days of RDV therapy, although there were no patients on mechanical ventilation in this study.[5]

Contrary to the results of the ACTT-1 study, an earlier randomized clinical trial in China failed to show a clinical or virologic benefit from RDV compared to placebo, although this study was underpowered.[6]

Finally, the pragmatic open-label platform SOLIDARITY trial sponsored by the World Health Organization (WHO) has reported in pre-print form that no mortality benefit was seen when RDV was compared to standard of care in over 7,500 patients, with the final data pending peer-review and publication.[7]

On the basis of the ACTT-1 data, the NIH guidelines have endorsed the use of remdesivir, particularly for those on supplemental low-flow or high-flow oxygen (**Figure 1**),[2] and it became the first FDA-approved treatment for Covid-19 on October 22, 2020. International guidelines from the WHO, however, have been more reticent to endorse its routine use outside of clinical trials, given its lack of a proven mortality benefit, limited availability in many countries outside the United States, and requirement for intravenous administration at significant cost.[8] Ongoing trials are evaluating the use of inhaled RDV or shorter intravenous courses in outpatients with milder Covid-19.

There remains a significant need for efficacious and cost-effective oral antivirals that can be given to outpatients with milder disease or those in the early stages of their hospitalization. Unfortunately, most of the proposed early treatments such as the repurposed antimalarials (hydroxychloroquine/chloroquine) or antiretrovirals (lopinavir-ritonavir) have failed to show any meaningful clinical benefits when studied in rigorous clinical trials.[7,9] So, the search for highly effective antivirals against SARS-CoV-2 continues, although it is likely that increased understanding of its virology will eventually yield targeted therapies that are more effective than the current repurposed therapies.

Immune System Mimics

The second category of treatments includes agents that mimic the host's own immune response to SARS-CoV-2. These agents likely work best when given early prior to the body's own immune response or when given as post-exposure prophylaxis. The first example of this is **convalescent plasma (CP)**, where plasma from a patient who has recovered from Covid-19 is given to another patient with active disease. Early in the pandemic, a nationwide program for expanded access to CP was created through the Mayo Clinic, which as of the end of October had treated over 100,000 patients in the US with this therapy. While the early data from the first 20,000 patients treated suggested a low rate of serious adverse events (<1% deemed related to CP), the lack of a control or placebo arm precludes any meaningful assessment of efficacy from this data.[10] Despite the FDA grant of emergency use authorization (EUA) status for CP on 8/23/20, the available randomized clinical trial evidence has failed to demonstrate clinical efficacy from this therapy,[11] and concerns remain about potential risks in this unproven therapy.[12]

The more promising category of immune mimics are the **monoclonal antibodies** against the SARS-CoV-2 spike protein. Two monoclonal antibody preparations—Eli Lilly's LY-CoV555 or bamlanivimab and Regeneron's REGN-CoV2 cocktail—are in late phase 3 trials for use in outpatients with mild-to-moderate disease. An interim

analysis of the former therapy from the BLAZE-1 trial demonstrated a significant reduction in hospitalization or ED visits with the monoclonal antibody therapy, although the primary virologic outcome was positive in only one of the three doses studied.[13] Based on this preliminary data, the FDA granted and emergency use authorization (EUA) for bamlanivimab on 11/9/20 for its use in non-hospitalized Covid-19 patients with mild-to-moderate Covid-19 and at high risk for progression to severe disease.[14] The REGN-CoV2 product is currently being evaluated for EUA based on unpublished data showing both a reduction in medical visits and a faster decrease in viral load compared to placebo in non-hospitalized patients, with the greatest benefit seen in patients with high viral loads and baseline seronegativity.[15]

Despite these encouraging preliminary results, larger data sets from the fully powered trials are needed to better understand which patients are likely to benefit most from these therapies. Moreover, their current limited availability, requirement for monitored infusion in a protected environment, anticipated costs, and limited efficacy and safety data will significantly limit their use and preclude their incorporation into routine standard of care for Covid-19 outpatients for the foreseeable future. Trials for both monoclonal antibodies in hospitalized patients have been stopped due to futility, again emphasizing the early, narrow window during which they are likely to benefit patients.

Immunomodulators
The third category of treatments includes agents that modulate or dampen the host immune response to SARS-CoV-2. These drugs likely work best during the later inflammatory phase of the disease or possibly when given in combination with antiviral drugs. The most prominent example is **corticosteroids**, which remain the only treatment with a proven mortality benefit in severe or critically ill Covid-19 patients. The landmark adaptive platform trial RECOVERY, conducted in 176 sites in the UK, demonstrated a 17% relative risk reduction in 28 day mortality for those receiving dexamethasone 6 mg daily for up to 10 days compared to usual care in a trial of over 6,400 patients.[16] The benefit was strongest in patients on mechanical ventilation at entry into the study (36% relative risk reduction and 12% absolute risk reduction in mortality), but dexamethasone also showed a benefit in those on only supplemental oxygen therapy. A subsequent meta-analysis including 6 additional trials confirmed a benefit with steroids in critically ill Covid-19 patients with an odds ratio for all-cause mortality of 0.66 (95% CI, 0.52-0.82) in the steroid arms.[17] While this appears to be a class effect for at least dexamethasone and hydrocortisone, data on the optimal dosing and timing of steroid initiation remain uncertain.

A number of clinical trials are investigating various **cytokine inhibitors** to target the so-called "cytokine storm", including anti-IL-6, anti-IL-1, and anti-GM-CSF agents. The existing published data primarily with the anti-IL-6 inhibitor tocilizumab, however, have failed to show a consistent benefit on mortality or other hard clinical outcomes in the more rigorous, randomized clinical trials.[18]

Finally, oral inhibitors of Janus kinase 1 (**JAK inhibitors**) were suggested to work based on early observational data, and the FDA on November 19, 2020, granted EUA status for the combination of remdesivir and **baricitinib** based on the NIH ACTT-2 trial, which demonstrated a 1 day faster median time to clinical recovery and lower odds of progression to death or mechanical ventilation compared to remdesivir alone.[19] Since this clinical trial has yet to be published in a peer-reviewed journal, however, a more complete analysis is required to understand the efficacy, safety and appropriate role in treatment for this drug combination.

Other Treatments
The final category of treatments includes agents that may play a supportive role or work in specific populations, such as those with Covid-19-related ARDS. Vitamin and mineral supplements such as vitamin C, vitamin D and zinc have been proposed to work at early stages of disease or as preventive measures. While randomized trial data showing efficacy for these therapies is lacking, they have been widely adopted due to their low cost and well-established safety profile when taken at standard dosages.

Clinical trials are also ongoing with various inhaled pulmonary vasodilators such as epoprostenol or inhaled nitric oxide, primarily as rescue therapy in those who are critically ill on mechanical ventilation.

Finally, prophylactic and therapeutic anticoagulation in Covid-19 patients is a major topic that is beyond the scope of this review. It is currently being investigated in several large randomized trials sponsored by the NIH.[20]

NIH Covid-19 treatment guidelines[2] summarize the current recommended therapies (**Figure**). They will undoubtedly continue to evolve as emerging clinical trial data appear. At present, besides dexamethasone for severe and critical Covid-19 patients and possibly remdesivir for those requiring supplemental oxygen but not yet on mechanical ventilation, enrollment in ongoing randomized clinical trials appears vital to strengthening our management of this global disease of pandemic proportions.

NIH Treatment Recommendations (as of 11/9/2020)[2]

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
	(Recommendations are listed in order of preference in each category below; however, all options are considered acceptable.)
Not Hospitalized *or* **Hospitalized but Does Not Require Supplemental Oxygen**	No specific antiviral or immunomodulatory therapy recommended The Panel **recommends against** the use of **dexamethasone (AI)** See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.[a]
Hospitalized and Requires Supplemental Oxygen **(but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)**	**Remdesivir** 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first **(AI)[b,c,d]** *or* **Remdesivir** (dose and duration as above) plus **dexamethasone[e]** 6 mg IV or PO for up to 10 days or until hospital discharge, whichever comes first **(BIII)[f]** If **remdesivir** cannot be used, **dexamethasone[e]** may be used instead **(BIII)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	**Dexamethasone[d]** plus **remdesivir** at the doses and durations discussed above **(AIII)[f]** *or* **Dexamethasone[d,e]** at the dose and duration discussed above **(AI)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone[d,e]** at the dose and duration discussed above **(AI)** *or* **Dexamethasone[e]** plus **remdesivir** for patients who have recently been intubated at the doses and durations discussed above **(CIII)[f]**

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

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Epi Corner
Big Data Modeling Implicates "Superspreader" Locations

Last week a team of computer scientists, epidemiologists and sociologists from Stanford and Northwestern Universities published a paper in *Nature* analyzing a novel combination of mobility and Covid-19 infection rate data to compare the contribution of crowding in different types of gathering places to infection risk.[1,2] They obtained the anonymized cell phone location data from **98 million people** residing in 10 of the largest U.S. metropolitan areas, including the Dallas-Ft. Worth area, and mapped the hourly movements of every individual from their residential census blocks to various venues, or "points of interest" (POIs), such as work places, stores, gas stations, bars, restaurants and churches.

They combined these data with publicly available daily Covid-19 case counts for each metro area from *The New York Times'* database and applied a relatively simple SEIR model to identify patterns in the mobility data that best fit the observed changes in the cases. [An SEIR model tracks individuals as they progress through the stages of Susceptible (S), Exposed (E), Infectious (I), and Recovered (R), and has been widely used to predict how a contagious disease spreads, its contagiousness (Reproduction number R_0), and the effectiveness of control measures or vaccines.] By testing alternative mobility models representing different hypotheses and comparing how well they fit the infection data, they could draw inferences about the relative contributions of different venues to transmission of infection.

In this model, they tracked the number of people visiting each venue, how long they stayed, and how these parameters changed over time to estimate how Covid-19 transmission varied with how long people stayed in venues more densely occupied. These mobility parameters allowed their models to predict the changes in infection rates better than models of traditional epidemiologic approaches lacking mobility data. The results led to three conclusions.

First, they concluded that a small minority of settings account for a large majority of infections. Specifically, the venues that, upon reopening, would increase infections per 100,000 population the most are restaurants, fitness centers, cafes and snack bars, hotels and motels, and religious organizations (churches, synagogues, etc) (**Figure, next page**).

Second, the modeling demonstrated that limiting occupancy at each of these "superspreading" venues would be more effective in reducing Covid-19 transmission in a community than generalized measures, such as closing all nonessential businesses, barring outdoor activities, etc., that uniformly reduce mobility.

Third, the models accurately predicted higher infection rates among disadvantaged racial and socioeconomic groups but then explained this disproportionate risk from their mobility characteristics. Specifically, because these groups are more often employed in essential occupations, they are unable to reduce their

mobility as much as more advantaged groups who can work from home do, and the venues they visit tend to be more crowded, putting them at higher risk.

The authors suggested that disease-control policies might be more efficiently directed squarely at restricting occupancy at the "superspreading" venues and work situations that are accounting for most transmission.

The findings also support our current understanding that most transmission of SARS-CoV-2 is from asymptomatic individuals in the 2 days before onset of symptoms; from those who are infected but will never manifest symptoms; or from symptomatic individuals who fail to isolate themselves and expose others in the week after symptom onset.

These findings appear compatible with a similar modeling study from the University of Texas at Austin Covid-19 Modeling Consortium that found disproportionate risk in construction workers exposed on the job in indoor jobs when working without masking.[3] From March through mid-July, the Austin health department identified over 40 clusters of Covid-19 infection in construction workers, and the relative risk for hospitalization from Covid-19 in construction workers in Austin was 4.9 (95% CI 3.8-6.2) compared with other occupational categories in the same age group. Computer modeling suggested that the unrestricted construction work would have increased the Covid-19 hospitalization rate of the entire community from 0.38 to 1.5 hospitalizations per 1,000 residents. The models further suggested that an increase of even 50% in worksite precautions including masking would have fully mitigated the increased community risk. The authors also advocated that more construction companies provide paid sick leave for Covid-19 illness to prevent construction workers from frequently coming to work ill.
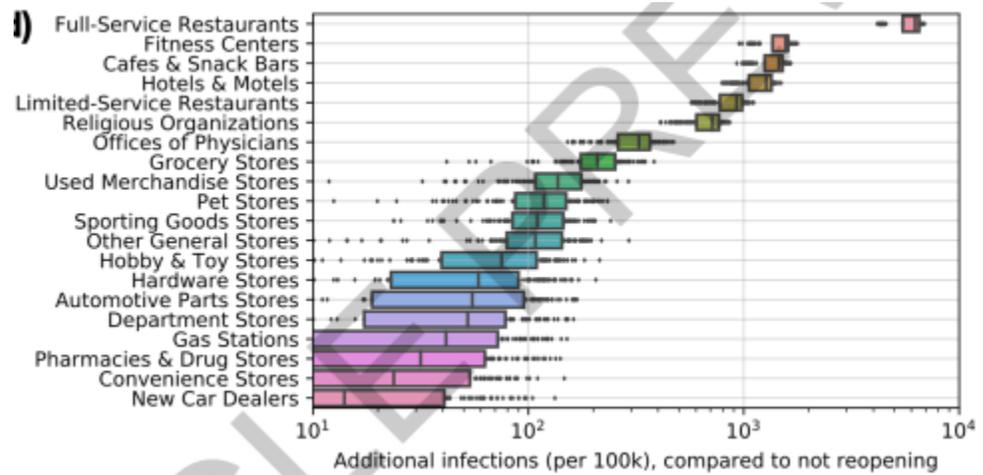
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From the Editors

The editors thank Dr. Cutrell for his/her feature article on pharmacologic treatments for Covid-19.

The aim of this weekly newsletter is to serve as a source of information for the UT Southwestern community which can lead to better understanding and control of a new disease (Covid-19) caused by the pandemic spread of an emerging viral pathogen (SARS-CoV-2). We welcome questions, comments, and suggestions for topics and authors.