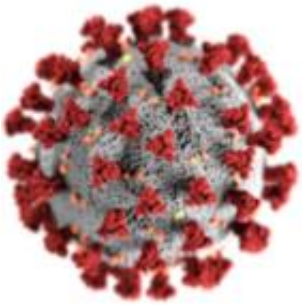

COVID-19 Action Newsletter

UT Southwestern Department of Internal Medicine
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The Situation: U.S. Confirmed Cases Exceed One Million

In the world as of May 1, 2020, 3,303,296 confirmed cases of COVID-19, including 560,043 with onset in the past 7 days, and 235,290 deaths. In the United States, there have been 1,046,428 cases, the most in the world followed in order by Spain, Italy, France, the United Kingdom, Germany, Turkey, Russia, Iran and China.[1] Deaths in the U.S. through May 1 have been estimated at 65,019.[2] The latest estimate of total number of hospitalizations in the U.S. as April 23 was 121,739 with New York, New Jersey, California, Illinois and Florida being in order the first through the fifth in number. In terms of hospitalizations, Texas ranks fifteenth in the country.

From March 10 through April 28 there have been 3,240 confirmed cases of COVID-19 reported from Dallas County with 94 confirmed deaths, 40% of these from long-term care facilities.[3] Of the 796 hospitalized cases in Dallas County the majority have been over 60 years of age or older or have had at least one known risk condition. Diabetes mellitus was seen in about one-third of all hospitalized patients. More men than women have died. Of the first cases seen in Dallas County, the distribution of cases by race/ethnicity did not differ significantly from that of the Dallas population. Differences have been seen in other cities.

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Feature Article

Pharmacologic Treatments for COVID-19

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The global pandemic of coronavirus disease 2019 (COVID-19) has created an urgency to identify effective pharmacologic treatments and prevention strategies. The rapid identification and sequencing of the causative pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has allowed screening of available approved or experimental drugs for *in vitro* activity against the virus. Previously studied therapeutics tested for SARS-CoV or MERS-CoV, two related betacoronaviruses, have also been investigated. As of April 24, 2020, over 1,000 clinical trials including more than 700 interventional clinical trials are ongoing worldwide to evaluate potential treatments.[1] **However, to date, there are no therapies whose effectiveness against this virus have been definitively established, although the treatment landscape is quickly changing.** This outline will briefly discuss current US treatment guidelines and review some of the major proposed treatments, repurposed or experimental, for COVID-19. A more comprehensive review on this topic provides additional details although this area is constantly evolving as new evidence emerges.[2]

Major treatment guidelines for COVID-19 have been recently published from both the Infectious Diseases Society of America[3] and the National Institutes of Health[4] (the latter of which Dr. Roger Bedimo,

Professor of Medicine at UT Southwestern, was a contributing member). Both guidelines conclude that "no drug has been proven to be safe and effective for treating COVID-19"[4] and, therefore, they recommend that treatments should be used in the context of a clinical trial whenever possible. Both guidelines, however, acknowledge that access to clinical trials may not be available for all patients, and so patient-centered decision making with discussions of the potential risks and benefits guided by local treatment guidelines may be required in these settings. These guidelines will be iteratively updated online as new evidence emerges from ongoing clinical trials of proposed treatments.

The first major category of proposed pharmacologic treatments targets various steps in the virus lifecycle. Drugs that potentially target viral cell entry, membrane fusion and endocytosis of the virus, processing of viral proteins, and viral RNA synthesis have been identified. A leading candidate antiviral is ***remdesivir***, which targets the RNA-dependent RNA polymerase and was previously discussed by Dr. Mamta Jain in the April 20, 2020 *COVID-19 Action Newsletter (Vol. 1, No. 1)*. This past week, the results of the first randomized, placebo-controlled trial in China including 237 patients comparing remdesivir versus standard of care found no significant difference in time to clinical improvement although the study was underpowered to detect a difference due to slow enrollment as the epidemic was controlled in China.[5] Also this week, the NIAID announced the preliminary results of a major randomized placebo-controlled trial in hospitalized COVID-19 patients sponsored by the National Institutes of Health (NCT04280705)[5] indicating that patients who received remdesivir had a 31% faster time to clinical recovery than those in the placebo arm (median of 11 days versus 15 days, p<0.001) and a non-significant trend toward lower mortality in the remdesivir arm (8.0% vs. 11.6%, p=0.059).[6] Full analysis and interpretation of these results await their publication in the peer-reviewed literature.

Other treatments proposed include ***chloroquine*** and ***hydroxychloroquine***, medications traditionally used for malaria treatment and prevention as well inflammatory conditions such as rheumatoid arthritis and systemic lupus erythematosus. These drugs are believed to act via blocking viral entry and endosomal acidification as well have immunomodulatory effects on the host.[8] Although initial reports of positive results based on small clinical trials or uncontrolled case series with these medications from China and France, either alone or in combination with azithromycin, garnered much media attention, these reports have been discredited due to lack of adequate control groups, biased results reporting, and serious methodologic and ethical concerns, particularly with the initial French study.[8] There is also increasing evidence of the potential harm related to these medication, particularly QTc prolongation and cardiac arrhythmias discussed by Dr. Mark Drazner in the April 24, 2020 *COVID-19 Action Newsletter (Vol. 1, No. 2)*. While several adequately powered clinical trials are ongoing for these medications as either treatment or prophylaxis against COVID-19, their efficacy and safety remain unproven.

A third category of drugs includes the HIV protease inhibitors, most notably ***lopinavir/ritonavir***. Based on prior data suggesting an impact in SARS-CoV, an open-label RCT comparing lopinavir/ritonavir vs. standard of care in 199 patients with COVID-19 was conducted in China, which found no evidence of clinical benefit defined as clinical improvement on a 7-category ordinal scale and no difference in viral clearance.[9] Although several trials of HIV protease inhibitors are still ongoing, enthusiasm for their use has waned based on these initial negative results. Other proposed antiviral agents such as ***favipiravir, camostat mesylate*** and ***umifenovir (Arbidol)*** are currently under investigation in clinical trials but are not available in the United States.[2]

The other major category of proposed treatments include adjunctive therapies that modulate the SARS-CoV-2 host immune response, which in a subset of patients contributes to significant organ damage due to an amplified immune response and cytokine release or "cytokine storm."[2] ***Corticosteroids*** have been proposed as a potential therapy on this basis although there are potential adverse effects and the theoretical risk of delayed viral clearance based on data with SARS-CoV and MERS-CoV[2]; current guidelines do not recommend their use outside of a clinical trial or unless a concomitant compelling indication exists (e.g., COPD exacerbation or pressor-refractory shock). ***IL-6 receptor antagonists*** (e.g. tocilizumab, sarilumab) are under investigation based on the observation that IL-6 levels are elevated in patients with "cytokine storm" and small early case series reporting clinical improvements.[2] Ongoing clinical trials will determine the efficacy of these agents as well as assess potential adverse effects such as increased secondary bacterial or fungal infections. Finally, the use of ***convalescent plasma*** donated from patients who have recovered from COVID-19 is under investigation.

Although this therapy has been used extensively in other infectious diseases including the 1918 influenza pandemic, its utility in COVID-19 remains to be determined. A national convalescent plasma expanded access program in the United States has been established through the Mayo Clinic to make this therapy more widely available, with over 2,100 participating sites including UT Southwestern and its partnering hospitals.[10]

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Flash! Testing Update

Testing Capabilities for Covid-19 in the UT Southwestern Clinical Laboratory

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PCR Testing

With the arrival of SARS-CoV-2 in early March in the DFW area, the Clinical Laboratory Services (CLS) at UTSW urgently validated, within a week, an RT-PCR assay based on CDC's newest assay. The test went live on March 15th with a limited capacity to test 60 patients per day. This test is very sensitive with a lower limit of detection (LOD) of ~65 viral copies/ml.

Because of increased demand for testing, a small new Covid lab was built in the Bio Center within 36 hours for this purpose, and two new semi-automated *M2000* PCR instruments were purchased, installed, calibrated and validated within two weeks. This currently operating RT-PCT assay has a limit of detection (LOD) of 100 viral copies/ml and increased throughput of 900 PCR tests per day. The test went live on March 28th.

The following week on April 4th, we went live with a rapid test for Covid-19 on Abbott's *ID Now* platform. This device has a point-of-care (POC) designation and gives a positive result within 5 minutes and a negative result within 15 minutes. The package insert initially stated that the preferred test material is a dry nasal swab in the POC setting, and nasopharyngeal (NP) swab in the VTM (viral transport medium) is also acceptable. To

obtain such a rapid result, *ID Now* is detecting viral RNA amplified for only 3 minutes by isothermal nucleic acid amplification in contrast to RT-PCR that amplifies it for 8 hours.

Soon, however, it was/we observed that the VTM (3 ml) was diluting the specimen and giving some false negative results. The stated LOD of this device is 125 copies/ml but when collected in the VTM, there is a significant dilution effect. In our parallel testing of samples first with *ID Now* and then on *M2000*, we observed that those patients who results were negative on *ID Now* and positive on *M2000*, had a very low viral load on their NP swab. Therefore, *ID Now* is now restricted to the Emergency Department for testing only on symptomatic patients, whose viral loads are generally far higher than those of asymptomatic patients.

If the negative result by *ID Now* does not match the clinical presentation, a PCR-based test is recommended. Since viral load is maximal at the start of the illness and declines steadily thereafter, a recent study showed that symptomatic patients tested with *ID Now* early in the course of the disease (<7 days of symptom onset) have very high probability of being positive by the more definitive RT-PCR method; whereas, after 7 days of illness, the false positive rate even by the RT-PCR method could be as high as 30-50% (1). Therefore, it is important to interpret test results in the clinical context. The false negative test result could also be due to the improper swab collection, transportation and storage at a higher temperature, etc. Currently, we are also supporting several hospitals in the DFW area for PCR testing along with the Dallas County health department and the State of Texas.

Serum Antibody Testing

The FDA has recently given Emergency Use Authorization (EAU) status to several new serological tests. Our Clinical Laboratory Service has validated an IgG antibody assay (Abbott Diagnostics) against the nucleocapsid of the SARS-CoV-2, which the package insert rates as 100% sensitive and 99.6% specific. During validation we have tested more than 200 samples from healthy blood donors from July-December 2019 and 200 samples from March-April 2020, and all tested negative, confirming high specificity in samples from our area. An additional 30 patients with known PCR positivity all tested strongly positive, confirming high sensitivity. A further study of possible cross-reactivity with known coronaviruses is underway. Currently, local guidelines on the appropriate indications for Covid-19 IgG testing are being developed. The current capability is 200 tests per day. The CLS will bring up the IgM antibody assay when available from the manufacturer.

Editor's note: This high level of accuracy distinguishes the few testing assays with FDA approval from the many being marketed without approval that have been proven inaccurate, as widely reported in the media.

Reference: doi: https://doi.org/10.1101/2020.04.05.20053355

From the Editors

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.