

COVID-19 Action Newsletter

UT Southwestern Department of Internal Medicine
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The Situation: U.S. Confirmed COVID Cases Top 1.8 Million

In the world as of June 5, 2020, 6,664,908 cases of Covid-19 have been confirmed, including 820,409 with onset in the past 7 days, and 391,686 deaths. In the United States, there have been 1,872,660 cases, the most in the world followed in order by Brazil, Russia, the United Kingdom, Spain, Italy, India, France, Germany, Peru, Turkey, Iran, Chile, Mexico, Canada, Saudi Arabia, Pakistan and China.¹ Deaths in the U.S. through June 5 are estimated at 108,496.²

From March 10 through June 4, there have been 11,243 confirmed cases of Covid-19 reported from Dallas County with 250 confirmed deaths, over one-third of these from long-term care facilities.³ Of hospitalized cases in Dallas County, two-thirds have been under 65 years of age. Diabetes mellitus has been 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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1. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (Updated 6/5/20)
2. Worldometer. Coronavirus update 6/5/20
3. Dallas County Health and Human Services. Acute Communicable Disease Epidemiology Division 6/5/20

Feature Article

Acute Kidney Injury (AKI) in Covid-19

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Initial reports from Wuhan, China, suggested incidence of AKI to be 5% in patients with Covid-19,¹ but more recent studies from North America suggested a higher incidence, reported to be 37% in 13 hospitals in New York (N=5,449 patients).² Independent risk factors associated with AKI included older age, the presence of hypertension, diabetes and cardiovascular disease, and requirement for vasopressors or ventilation. The study also showed that AKI was associated with a poor prognosis, corroborated in 701 patients from Wuhan, with a dose-dependent relationship between more severe AKI stages and death.^{1,2} Potential mechanisms for AKI are multifactorial, with usual suspects being ischemia-induced acute tubular necrosis and nephrotoxin-associated acute interstitial nephritis. Virus-induced cardiomyopathy may result in cardiorenal syndrome. Proinflammatory and proapoptotic sequelae of the cytokine release syndrome from SARS-CoV can result in medullary hypoxia and rhabdomyolysis. Hypercoagulability can induce endothelial damage, microthrombi, and renal infarction.³ Postmortem renal histopathology of 26 patients with Covid-19 from China revealed pathologic evidence of acute kidney tubular injury in all cases. Fibrin thrombi and coronavirus-like particles were found in podocytes and the glomerular basement membrane on electron microscopy. There was indirect immunofluorescent staining with anti-SARS-CoV nucleoprotein antibody.⁴

SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2), of which expression is abundant in the kidney, as a cell entry receptor, raising concern that ACE inhibitors (ACEI) and angiotensin-receptor blockers (ARB) may be harmful in this clinical context. In addition, Covid-19 may disproportionately affect people with cardiovascular disease, a higher proportion of which are treated with ACEI/ARB. Available data provisionally support guidelines put forth by the American Heart Association, American College of Cardiology, and the International Society of Hypertension that patients receiving ACEI/ARB who contract Covid-19 should continue treatment with these agents unless there is an indication for discontinuation, such as hyperkalemia or hypotension.

Performing renal replacement therapy in those with COVID-19 and AKI poses challenges such as limiting exposure of staff, preservation of PPE, coagulopathy, and hypoxemia due to Acute Respiratory Distress Syndrome. Continuous Renal Replacement Therapy (CRRT) is the preferred modality, with sustained low-efficiency dialysis also an option as both can be managed without 1:1 hemodialysis nursing support.³ Placing the CRRT machine outside of the patient's room in the hallway minimizes the need for repeated entry to troubleshoot the machine and reduces PPE use (**photo**). No special provisions for disposal are necessary, since the presence of SARS-CoV-2 has not been demonstrated in the dialysis effluent.



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2. Hirsch J, et al. *Kidney Int*, 2020, published online May 16. doi.org/10.1016/j.kint.2020.05.006
3. Ronco C, et al. *Lancet Respir Med*, 2020; published online May 14. doi.org/10.1016/S2213-2600(20)30229-0
4. Su H, et al. *Kidney Int*, 2020. DOI: 10.1016/j.kint.2020.04.003

Feature Article

End Stage Renal Disease in Covid-19

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Transplant and glomerulonephritis patients require chronic immunosuppression and appear to be at high risk of severe infection with Covid-19 and can have more rapid clinical progression.^{1,2} Mortality in transplant patients has been reported as high as 28%.¹ As no effective treatment is available for renal patients, initial management includes decrease in antimetabolite therapy and other immunosuppression.

Dialysis patients are also at higher risk of exposure and mortality due to underlying comorbidities of diabetes, hypertension and cardiac disease. Mortality in dialysis patients with Covid-19 has been reported to range from 10-30%.^{3,4} Uremia is associated with impaired immune response and leads an increased incidence of microbial infections.⁵ If infected, in-center dialysis patients cannot be quarantined at home due to their need to return for dialysis. Screening of dialysis patients for Covid-19 can also be challenging since many do not develop typical clinical features of fever, cough and shortness of breath.³

To date, there are no clear guidelines on treatment of dialysis patients with Covid-19. Remdesivir has been shown to decrease the time to recovery in hospitalized patients, but formal drug studies have excluded

patients with impaired renal function or need for dialysis.⁶ For now, the only treatment option for advanced kidney disease patients seems to be convalescent plasma.

In the absence of a vaccine and treatment options for dialysis patients with Covid-19, preventing epidemic spread of infection is the highest priority. The Centers for Disease Control and Prevention (CDC) and the American Society of Nephrology (ASN) have recently published guidelines for infection prevention and control of Covid-19 in outpatient dialysis units.^{7,8} Universal screening and face masks for patients and dialysis staff were implemented in the first week of March and are being performed now at UT Southwestern-affiliated dialysis facilities. If Covid-19 testing is positive on a repeat test and the patient does not require inpatient admission, then dialysis is arranged in a dedicated Covid-19 dialysis facility for at least 14 days. No clear association has been described between length of illness and post recovery of the virus in dialysis patients, but recent data suggest replication-competent (infective) virus shedding approaches zero by 10 days of illness in the general population.⁹ Transition of patients back to their native dialysis center can be done after 2 negative tests >24 hours apart and being symptom free, or if testing is not available, then being symptom- and fever-free without any antipyretics for at least 72 hours and >14 days since symptoms first appeared.¹⁰

Since Covid-19 is associated with coagulopathy, these patients require close monitoring of dialysis access and adjustment of anticoagulation dose on dialysis. In areas where dedicated outpatient dialysis access centers for Covid-19 patients are not available, the only choice of access procedures has been in hospital settings. Anemia management can also be challenging in Covid-19 dialysis patients. Anemia of ESKD is usually treated with intravenous iron and erythropoiesis-stimulating agents. With active infection, IV Iron is stopped due to active infection and high ferritin levels. There is no published data on use of erythropoiesis-stimulating agents in dialysis patients with Covid-19 and risk of thrombotic events.

During the Covid-19 pandemic, home dialysis is a better option for ESKD patients and includes home hemodialysis and peritoneal dialysis. Managing these patients remotely limits their exposure to other patients and health care workers.

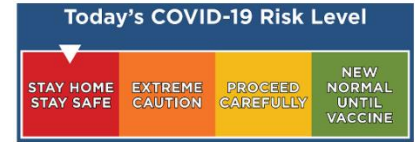
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10. *Considerations for Providing Hemodialysis to Patients with Suspected or Confirmed COVID-19 in Acute Care Settings*. Apr 24, 2020. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/dialysis/dialysis-in-acute-care.html>.

Epi Corner

How Do We Know If the Epidemic is Going Away or Getting Worse?

A cornerstone of the effort to control the Covid-19 epidemic in Dallas County is the newly developed system that alerts the public to the present level of risk of acquiring the infection. Each day the risk level is displayed by the color chart at the right. At the recommendation of the County

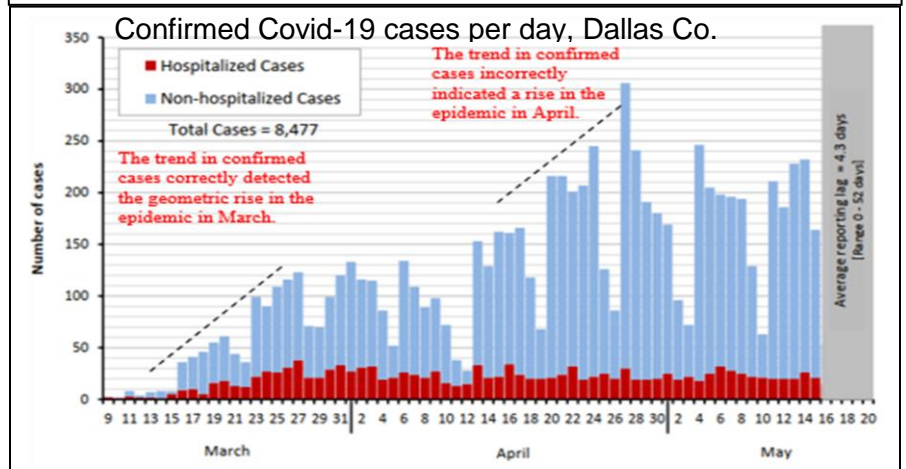
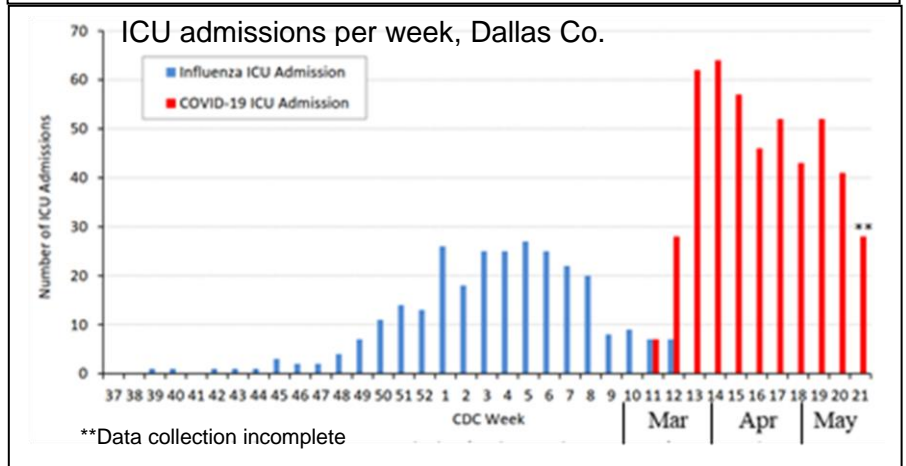
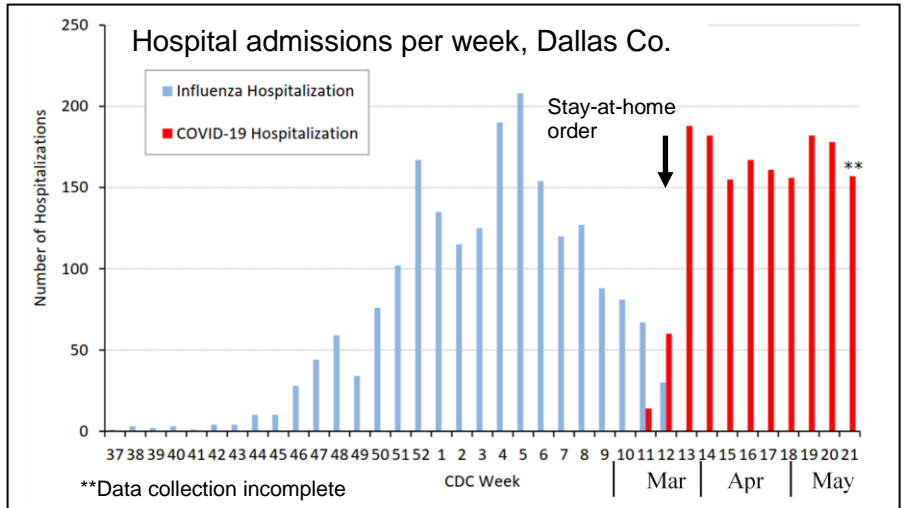


Judge's Public Health Committee, the risk level was initially set at **Level Red** (Stay at Home, Stay Safe). The risk level will be downgraded by one level after 2 consecutive weeks of consistent decline in the numbers of hospital admissions and ICU admissions in hospitals in the county (top and middle graphs).

These visuals, along with detailed guidance for the public on safe behaviors to avoid infection, are found on the County Health Department's website (below).

A frequently asked question is why the committee chose to use the trends in hospital and ICU admissions rather than the number of new Covid-19 cases confirmed each day (bottom graph). The reason is that the trend in the number of new cases is heavily influenced by the amount of Covid-19 testing that is done; whereas, people are admitted to the hospital or the ICU basically because they can't breathe, unrelated to testing capacity in the community.

Notice that the geometric explosion in admissions in March was correctly identified by the daily case count, but a steep increase in cases in mid-to-late April suggested an upsurge in the epidemic not confirmed by admissions. There was a rapid increase in testing capacity during that time.



DCHHS website: <https://www.dallascounty.org/departments/dchhs/2019-novel-coronavirus.php>

News Updates

Influential Study Showing Hydroxychloroquine Harm Retracted Second Study Showing Safety of ACEi and ARBs in Covid-19 Under Scrutiny

Late last week a group of over 100 influential scientists, including clinical researchers, epidemiologists, statisticians, and ethicists, submitted a letter to the editor of *The Lancet* questioning the veracity of the article, published online by the journal a week earlier,¹ showing that chloroquine (CQ) or hydroxychloroquine (HCQ) increases the risk of ventricular arrhythmias and death.

The large observational study compared 15,000 Covid-19 patients who had received one of the drugs with or without azithromycin with 81,000 Covid-19 patients who did not receive any of the drugs, collected from 671 hospitals on 6 continents. The large clinical database was collected by a previously unknown data analytics company named *Surgisphere*, whose CEO co-authored the paper. The results showed >30% increase in death in the cases receiving the drugs and a 2- to 5-fold increase in ventricular arrhythmias (see last week's *Covid-19 Action Newsletter* for details). The large size and broad geographic representation of the study immediately generated intense worldwide media coverage announcing the demise of the drugs and stimulated the immediate suspension of many of the over 200 clinical trials of HCQ in progress worldwide, including the large multinational collaborative trial sponsored by the World Health Organization.

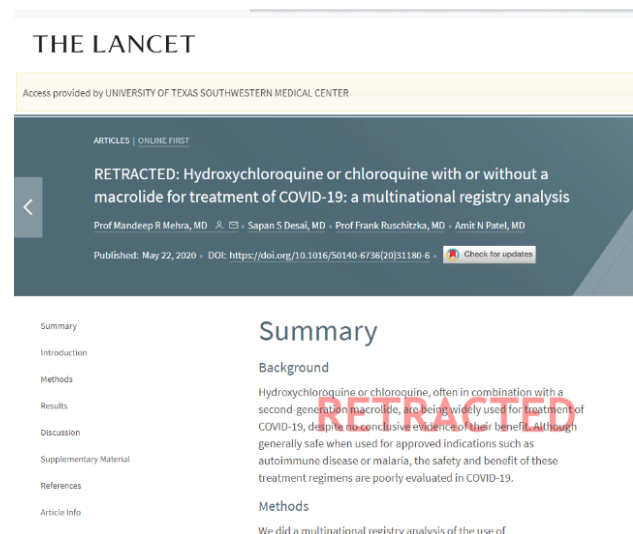
The 10 concerns listed in the letter included implausible numbers of Covid-19 cases and ability to detect ventricular arrhythmias in some of the regions contributing data, case counts incompatible with government reports from some countries, unusually small reported variances in important variables, implausible ratios of CQ to HCQ in some continents, lack of adjustment for important and measured confounders, failure to disclose and acknowledge all the countries and hospitals that contributed data, and lack of an ethics review.

Upon receiving the letter, the *Lancet* editor immediately called for the authors to obtain an independent review of the database and the analysis. This week, however, the 3 academic authors, from Harvard Medical School, University Hospital of Zurich, and University of Utah Department of Bioengineering and HCA Research Institute, reported that they were unable to obtain the data from *Surgisphere* and therefore had decided to retract the paper. Upon news of retraction, the WHO as well as an unknown number of other sites announced that their clinical trials would resume.

Reasoning that the problems with the *Lancet* paper would likely affect other papers published from the *Surgisphere* database, the 100+ authors sent a similar letter to the editor of the *New England Journal of Medicine* registering their concerns about a second paper by the same authors,² supporting the safety of ACEi and ARBs in Covid-19 patients, that the journal had published near the same time as the *Lancet* paper came out. The *NEJM* editor asked the authors to provide evidence of the validity of their paper, but when they were again unable to make the data available to a third party for validation, they retracted this article as well.

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From the Editors

The editors thank Drs. Susan Hedayati and Nilum Rajora for their feature articles on renal disease in 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.