

COVID-19 Action Newsletter

UT Southwestern Department of Internal Medicine
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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.

The Situation

In the world as of April 23, 2020, 2,658,387 confirmed cases of COVID-19, including 576,418 with onset in the past 7 days, and 185,421 deaths. In the United States, there have been 843,937 cases, the most in the world followed in order by Spain, Italy, France, Germany, the United Kingdom, Turkey, Iran, China and Russia.¹ Deaths in the U.S. have been estimated at 47,684.² The total number of hospitalizations in the U.S. has been reported as 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 23 there have been 2,683 cases of COVID-19 reported from Dallas County with 65 deaths.³ Of 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.

References:

1. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (Updated 4/23/20)
2. Worldometer. Coronavirus update 4/23/20
3. Dallas County Health and Human Services. Acute Communicable Disease Epidemiology Division 4/23/20

Feature Article

COVID-19 and the Cardiovascular System

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In the current worldwide pandemic, there are now over 2.6 million cases of COVID-19, an illness caused by the SARS-Coronavirus-2. Most people are familiar with its “typical” presentation of fever, cough, and pneumonia with the potential to develop life-threatening ARDS. Increasingly, there is recognition that other organs besides the lungs are involved in COVID-19. Here, I will review three issues which involve the cardiovascular system.

First, SARS-Cov-2 binds, via its spike protein, to the ACE2 receptor to gain entry into the pneumocyte. ACE2 more commonly is known for its counter-regulatory role to ACE signaling in the renin-angiotensin system. There have been concerns that ACE-inhibitors and angiotensin receptor blockers may increase ACE2 levels and thereby potentiate the ability of SARS-Cov-2 to enter its target cells and worsen the clinical course of patients with COVID-19. However, the current data do not support this concern. First, it is unclear if ACE-inhibitors or ARBs actually increase ACE2 levels or activity in humans. Second, ACE2 has been shown to have benefit in animal models of acute lung injury; thus, even if these medications did increase ACE2 levels, it is unclear whether that would be favorable or detrimental in COVID-19. Finally, discontinuation of ACE-inhibitors in systolic heart failure has been shown to lead to a withdrawal syndrome and clinical deterioration. In total, the evidence supports *not* stopping ACE-inhibitors or ARBs in an attempt to improve outcomes in COVID-19. This recommendation aligns with that by major medical societies including the Heart Failure Society of America, the American College of Cardiology, and the American Heart Association.

The second question related to the cardiovascular system in COVID-19 is whether hydroxychloroquine, a potential but unproven therapy for this illness, may have a proarrhythmic effect via lengthening of the QT interval. Increases in the QT interval can lead to Torsade de Pointes, a form of ventricular tachycardia, and sudden cardiac death. There are numerous reports of prolonged QT interval in patients with intentional overdose of hydroxychloroquine, and even some case reports with chronic use at standard doses. The concern for QT lengthening is increased because in COVID-19 hydroxychloroquine is often combined with azithromycin, a medication that also can lengthen the QT interval. Currently, the true risk of QT prolongation leading to Torsades with monotherapy with hydroxychloroquine is uncertain and further study is needed. One approach advocated by investigators from Mayo Clinic is to identify individuals that may have a very prolonged QT interval (≥ 500 msec) at baseline and modify or avoid the use of hydroxychloroquine in that group. Consideration should also be given to avoid co-administration of medications that also can prolong the QT, avoid electrolyte disturbances like hypokalemia or hypomagnesemia, and screen for cardiomyopathy or family history of sudden death.

Third, an emerging area of considerable interest is involvement of the cardiovascular system as part of COVID-19. A number of clinical presentations are now apparent including acute coronary syndromes, acute myocardial injury with troponin release in the absence of obstructive coronary artery disease, arrhythmias, decompensated heart failure, cardiogenic shock, pulmonary emboli, pericardial effusions, and even possibly cardiac tamponade. This spectrum of cardiovascular involvement has recently been termed the “Acute COVID-19 Cardiovascular Syndrome” in a paper by Dr. Nicholas Hendren (UTSW cardiology fellow), myself, and other investigators (Hendren et al, *Circulation*, 2020, in press).

It is worth focusing on the superimposed acute myocardial injury, characterized by troponin elevation on hospital admission in a sizable minority (e.g., up to 20%) of patients with an otherwise typical COVID-19 presentation, as it is now an accepted adverse prognostic marker in this illness. Further, in a segment of patients, the troponin levels rise dramatically later during the hospital stay, an ominous finding that has been reported to precede death presumably related to development of cardiogenic shock. The mechanism of the superimposed acute myocardial injury is uncertain with the two leading hypotheses currently being viral myocarditis versus a cytokine storm. Other key unanswered questions related to this acute myocardial injury in COVID-19 are: 1) What is the best therapeutic approach; 2)

What are its long-term consequences; and 3) What is different about the minority of patients who develop it? I anticipate that the rapidly occurring advances in our understanding of the cardiac complications of COVID-19 will soon provide answers to many of these questions.

Epidemiologic Concepts

What is the Reproduction Number (R_0)?

The reproduction number, also called the basic reproduction number or the reproductive number and abbreviated R_0 (pronounced R-naught), expresses the contagiousness or transmissibility of an infectious disease in a population where everyone is susceptible.¹ It is useful in predicting the course of an epidemic. In simple terms it represents the average number of secondary cases generated by transmission from each primary case (Fig. 1).² Since R_0 cannot be directly measured, it is estimated by mathematical modeling of measurable parameters. The most fundamental parameters are: how long an infected person remains infectious; the probability that a contact of a susceptible person with a case will result in an infection; and the rate of such contacts per unit time in the population. Additional parameters that may be included in the calculation capture special influences known to affect transmission in a given epidemic.

The distribution of R_0 ranges from 0 to $+\infty$. When $R_0 = 1$ the incidence rate of the epidemic is expected to remain stable; values of $R_0 > 1$ predict the epidemic will grow, and the further above 1, the faster it will grow; and conversely, values of $R_0 < 1$ predict the epidemic will die out. The following are R_0 values for selected epidemic diseases: measles 15, chickenpox 10-12, rubella 7, smallpox 7, polio 5-7, mumps 5.5, pertussis 5.5, HIV/AIDS 2-5, SARS 3.5, SARS-CoV-2 3.5, common cold 2-3, diphtheria 1.7-4.3, influenza (1918 pandemic) 1.4-2.8, Ebola 1.5-2.5, influenza (2009 pandemic) 1.4-1.6, seasonal influenza 0.9-2.1, and MERS 0.3-0.8.

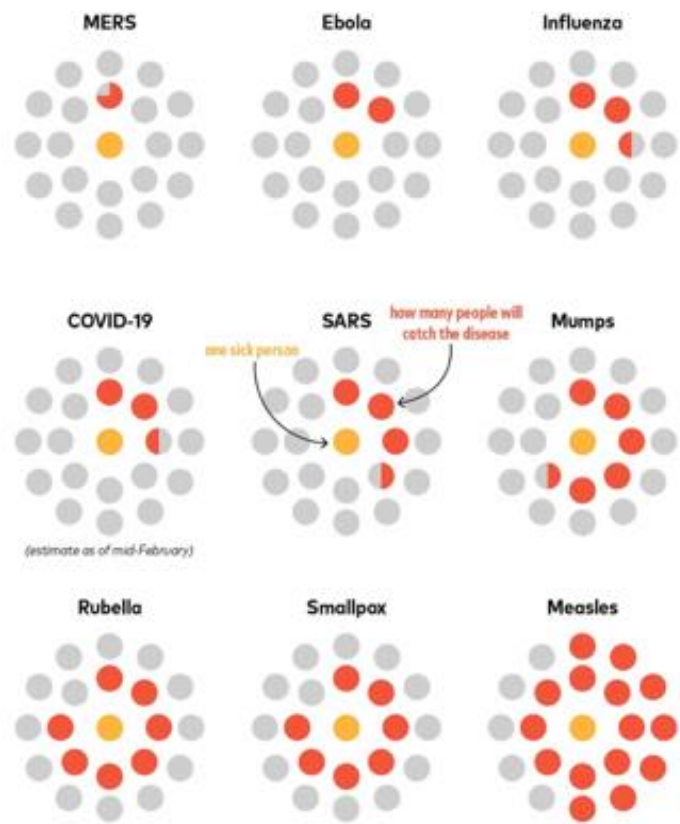
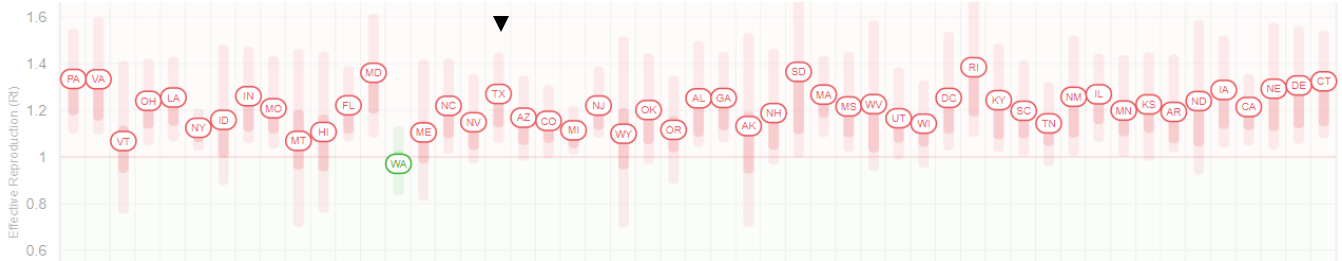


Fig. 1. R_0 values of well-known diseases. The number of contacts infected (red dots) by one case (yellow dot). Figure by Sara Chodosh.²

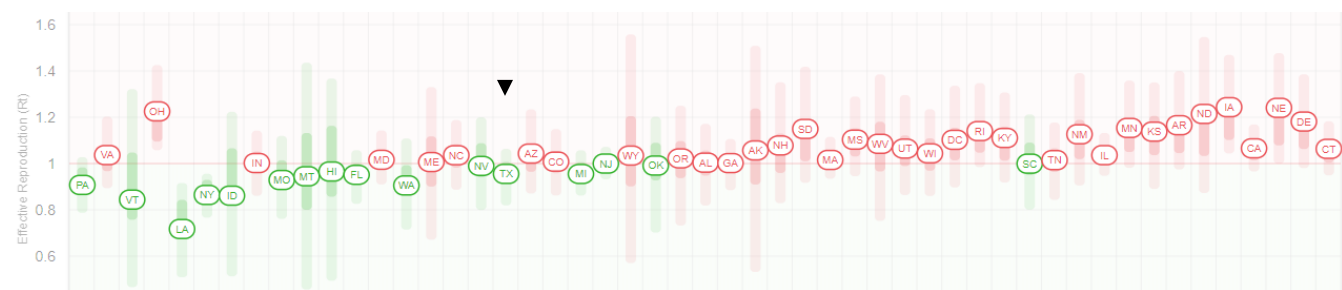
The R_0 of a given epidemic may change over time and is influenced by changes in factors that affect any of the component parameters of the calculation. For example, in the present COVID-19 epidemic the length of time a person is infectious would be reduced by a drug that inhibited the virus; the probability that a given contact will cause an infection is reduced by wearing masks and washing hands often; and the rate of such contacts is reduced by social distancing, shelter-in-place orders, and contact tracing with self-isolation and safe-quarantine of those exposed.

Useful variations of R_0 are the “effective reproduction number (R)” and the variation of R over time t (R_t). Whereas R_0 estimates the number of contacts infected by a given case *in a population where everyone is susceptible*, R is the similar estimate but with no assumption about the susceptibility of the population. Notice that an effective vaccination program would not affect R_0 because it only reduces the number of susceptible people; whereas, it would reduce R which is calculated in all people regardless of susceptibility. To see interesting state-specific plots of R_t over the period of the COVID-19 epidemic, see the website *Rt: Effective Reproduction Number* (search *rt.live*). Here is a sample (Fig. 2):

4 weeks ago



2 weeks ago



Now

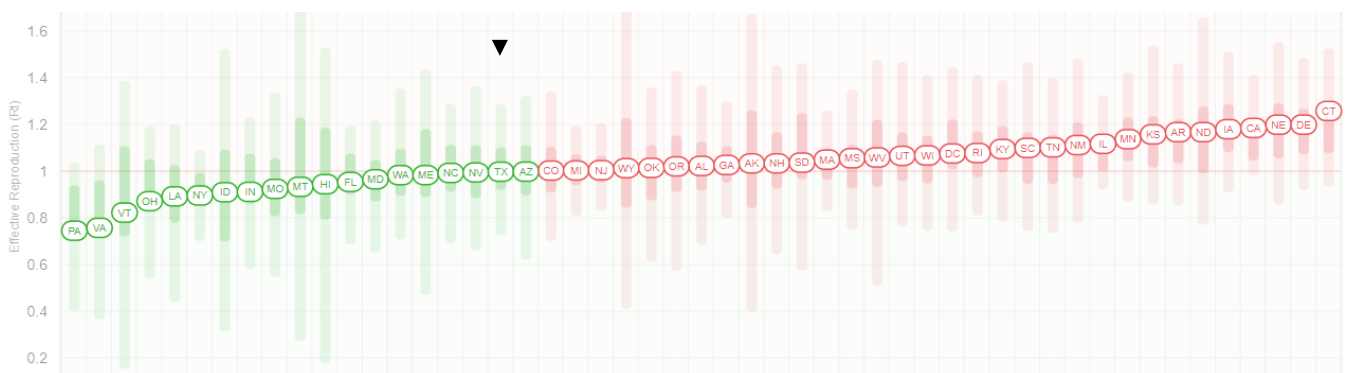


Fig. 2. Change in the effective reproduction number (R_t) over the past month by state. The black arrow marks Texas.

References

1. Delamater PL, Street EJ, Leslie TF, Yang Y, Jacobsen KH. Complexity of the Basic Reproduction Number (R_0). *Emerg Infect Dis.* 2019;25(1):1-4.
2. Francis MR. Just how contagious is COVID-19? *Popular Science.* 2020;February 20.