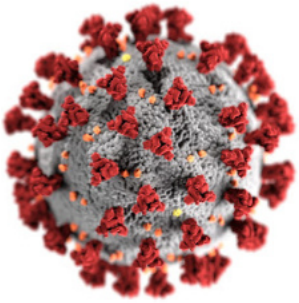

COVID-19 Action Newsletter

UT Southwestern Department of Internal Medicine
James Luby, M.D., and Robert Haley, M.D., editors

The Situation: U.S. Confirmed COVID Deaths Top 100,000

In the world as of May 29, 2020, 5,844,499 cases of Covid-19 have been confirmed, including 716,007 with onset in the past 7 days, and 361,119 deaths. In the United States, there have been 1,722,419 cases, the most in the world followed in order by Brazil, Russia, the United Kingdom, Spain, Italy, France, Germany, India, Turkey, Iran, Peru, Canada, Chile and China.[1] Deaths in the U.S. through May 29 have been estimated at 101,622.[2]

From March 10 through May 28, there have been 9,587 confirmed cases of Covid-19 reported from Dallas County with 222 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 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 5/29/20)
2. Worldometer. Coronavirus update 5/29/20
3. Dallas County Health and Human Services. Acute Communicable Disease Epidemiology Division 5/29/20

Feature Article

Endothelial Cell Dysfunction in the Pathogenesis of COVID-19

Vascular endothelial cells are distributed throughout the body, possess surface ACE2 receptors and can be sites for SARS-CoV-2 attachment to cells and subsequent internalization and replication. Two recent articles[1,2] call attention to these cells as a unifying factor in the pathogenesis of severe Covid-19 disease. After infection of these cells, ultrastructural alteration and cell death can occur. Microthrombi and inflammatory changes result. In addition, the Ackermann et al.[2] illustrate how infection can also result in angiogenesis of a particular morphologic type in the lung (termed intussusceptive angiogenesis), which may lead to the acute respiratory distress syndrome (ARDS).

Varga et al.[1] described 3 patients, the first of whom was a 71 year old man with a renal transplant, hypertension and coronary artery disease who developed Covid-19, required mechanical ventilation and died. Virus-like particles were found in the endothelial cells of the glomerular capillary loops. Inflammatory changes associated with the endothelium were also found in the lung, heart and small bowel. Their second patient was a 58 year old woman with diabetes, hypertension and obesity who developed respiratory and renal failure. Mesenteric ischemia required small bowel resection. Subsequently, she had a ST-segment-elevation myocardial infarction. Post-mortem exam showed lymphocytic endothelialitis in lung, heart, kidney and small intestine. Their third patient was a 69 year old man with hypertension who developed respiratory failure resulting from Covid-19, required mechanical ventilation and had mesenteric ischemia. Surgery showed prominent endothelialitis of the submucosal vessels of the small intestine. The authors suggested that in severe disease the

development of endotheliitis in association with the host inflammatory response may lead to microcirculatory changes resulting in tissue ischemia with clinically significant sequelae including possible extra-pulmonary disease. Recognition of this occurrence might have therapeutic implications.

In the second article appearing in the current edition of the *New England Journal*, Ackerman et al.[2] reported a study of the lungs of seven patients dying from Covid-19, seven patients with influenza A (H1N1, 2009 pandemic), and ten control patients whose lungs were obtained for transplant but were not used. The lungs were studied extensively by a variety of techniques including microCT, histopathological, and multiplexed immunohistochemical analysis, transmission and scanning electron microscopy, corrosion casting, and direct multiplexed gene-expression analysis. By conventional microscopy, patients with both Covid-19 and influenza A had ARDS with diffuse alveolar damage, edema, hemorrhage and intra-alveolar fibrin deposition. Patients with influenza A had higher lung weights reflecting more extensive alveolar damage, interstitial edema and fibrin deposition. ACE2 staining was scarce in control lungs but present in alveolar cells, endothelial cells and lymphocytes in both in both infected groups. Inflammatory related gene expression was greater in Covid-19 patients (79/249 genes measured) than influenza A patients (9/249) with 7 genes having a shared expression pattern.

Alveolar capillary microthrombi were 9 times more prevalent in patients with COVID-19 than in influenza patients. Transmission electron microscopy (TEM) showed virus in endothelial cells and ultrastructural damage. Most importantly by corrosion casting and TEM, angiogenesis of a particular morphology (intussusceptive angiogenesis) was significantly greater in Covid-19 lungs than in influenza A. The degree of angiogenesis also increased significantly with length of hospitalization for Covid-19 patients. A total of 69/323 angiogenesis-related genes were only up or down-regulated in Covid-19, 26 genes only in influenza A and 45 genes were not different between the two groups.

Editorial Note: Although virus-like particles, documenting this thesis were shown to be present in one case, further direct evidence of active viral infection needs to be pursued and documented. Experts generally agree that ARDS is heterogeneous. The authors of this paper make the point that there may be exceptions to this rule and that there are unique features of COVID-19 lung injury that could involve intussusceptive angiogenesis in severe disease. This is occurring early and is lasting throughout hospitalization. They are relating angiogenesis to the presence of the virus in endothelial cells and resulting ultrastructural abnormalities. If the virus has a unique mechanism through which it can cause ARDS, then Covid-19 might be one of the first documented examples of its occurrence and might signal the necessity of its treatment by a different management strategy.[3] Finally, note that in the two articles the key term is spelled differently– endotheliitis and endothelialitis. The former appears to have been in use longer.

References:

1. Varga Z, Flammer AJ, Steiger P et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; 395: 1417-1419.
2. Ackermann M, Verleden SE, Kuehnel M et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020. DOI: 10.1056/NEJMoa2015432.
3. Hariri L, Hardin CC. Covid-19, Angiogenesis, and ARDS Endotypes. 2020 (published online 28 May). DOI: 10.1056/NEJMe2018629.

News Update

A Cure for the Face Mask Shortage

Few problems have been as frustrating and as threatening to physicians, nurses and vital ancillary personnel caring for Covid-19 patients than the shortage of N95 masks. And if we were to experience another surge of the virus, it is not clear that there would be enough of those high efficiency filtering masks by next fall even. But did you know that a solution has been available all along?

It turns out that those black silicone masks with a transparent eye shield and magenta-capped air filters protruding out are just the thing. Known in the trade as *elastomerics*, they are widely used, and thus abundantly available. They can be reused virtually indefinitely, are readily cleaned, rapidly fitted and require little training to use. Given that they are reusable, one elastomeric replaces hundreds of N95 masks over its lifetime.

Elastomerics were recommended for pandemic response in planning over a decade ago but were never added to the Strategic National Stockpile. They are currently being used in 4 hospital systems in the U.S., including Yale Hospital and the University of Maryland, but are not on the radar screen elsewhere. Not a bad idea for the future.

Epi Corner

Studies on Hydroxychloroquine, Azythromycin and Zinc: Cutting Through the Political Smoke, Is There A Clear Signal?

In mid-March a poorly designed, non-peer-reviewed study by French researchers claiming that the combination of hydroxychloroquine (HCQ) and azithromycin (AZ) successfully treated Covid-19 surfaced on the internet. Almost immediately politicians began touting the combination as an established treatment, igniting vehement rebuttal from medical scientists that has reverberated through the news media. As rationale for HCQ's efficacy, proponents pointed to HCQ's ability to kill the virus by acidifying the endosome that holds it after it enters the host cell and preventing the cytokine storm by the well know anti-inflammatory effect for which HCQ is FDA approved for treatment of lupus and rheumatoid arthritis. Despite the widespread apparently safe use of HCQ by rheumatologists and similar safe use of AZ by all specialties, cardiologists question the safety of the combination because both drugs prolong the QT interval, possibly precipitating the torsade de pointe arrhythmia and ventricular fibrillation.

Immediately following the French release, research groups in several countries quickly undertook studies to test the claim. Barely two months later, seven studies have appeared, five published in prominent peer-reviewed journals and two released on the internet before peer review (Table below). Of these, 6 were observational studies estimating the odds ratio of morbidity or mortality in patients prescribed HCQ, AZ or both compared with those not prescribed it. Three of the observational studies found no significant difference between those taking vs those not taking the drugs, and 2 found strong evidence of harm. The release of each new study ignited furious media attention, further intensifying the political polarization over the issue.

Only one paper described a placebo-controlled clinical trial. It compared 75 hospitalized Covid-19 patients randomized to receive HCQ and 75 to placebo and found an odds ratio of 0.85, suggesting benefit,

which, with inadequate power, was not statistically significant (Table). With one clinical trial suggesting benefit and 5 observational studies suggesting no effect or harm, how should we interpret the evidence?

The elephant in the room that no one has mentioned is the possibility that the observational studies are biased toward the negative by *indication bias*. According to every paper and textbook of epidemiology that discusses bias, indication bias is about the most dramatic and predictable bias known. It occurs when the observational study design is used to evaluate the efficacy of a treatment, particularly a drug, and standard multivariable modeling does not overcome it. It is particularly severe because physicians' propensity to prescribe a drug is often proportional to the severity of the patient's condition; thus, the more severely ill a patient is, the more likely the physician is to prescribe the drug. Consequently, patients who receive the drug tend to be sicker and more likely to have bad outcomes than those not given the drug. The bias tends to be greatest in diseases that are likely to be fatal. The most often used teaching example is the initial experience in the early 1970s with giving the initial beta-blocker propranolol to patients with acute MI. When the first observational studies concluded that the drug substantially increased death in acute MI, physicians stopped using it for MI patients until randomized trials overcame the strong indication bias and proved it to be lifesaving.

In the last 10 years one of the great innovations in epidemiology has been the introduction of the propensity score, adapted from econometrics, which estimates the propensity for physicians to prescribe the drug as a function of a set of characteristics that predict prescribing. Controlling the analysis of an observational study for a propensity score, however, is only as effective in reversing indication bias as the model that develops the propensity score, and propensity scores can fail. In this case 4 of the observational studies adjusted for a propensity score; 2 of them showed no benefit, and 2 showed harm.

Only one of the 7 studies, Carlucci et al., found statistically significant evidence of benefit from an observational design, and it contained a real surprise. This was the only study in which a zinc supplement, $ZnSO_4$, was given along with HCQ and AZ. The result was a highly significant protective benefit for death or transfer to hospice (aOR 0.45, 95% CI 0.27-0.74, p=0.002, Table). The benefit was found only in mildly or moderately ill patients.

The rationale for giving zinc along with HCQ and AZ is based on the well studied ability of zinc supplementation to combat a broad array of infectious diseases by a direct antiviral effect as well as an immune-modulating effect. The combination of HCQ and zinc is thought to be important because HCQ is a zinc-ionophor, a class of compounds that accelerate the entry of zinc into cells where it can exert its effects. While this relatively strong signal is provocative, the study, which was posted on the internet before journal review, is clearly insufficient to overcome the contrary evidence.

So what should be the provisional position of careful clinicians, aware of the evidence and the potent workings of indication bias and resisting the temptation to prove meddling politicians wrong? Yes, HCQ and AZ prolong the QT interval, but the documentation of actual deaths is confined to case reports of patients who died taking HCQ but with otherwise severe illness already predisposed to arrhythmias and death, just as Covid-19 patients, particularly those with cardiac involvement, are. And yet rheumatologists prescribe HCQ frequently.

For now, equipoise appears to be the best position while waiting for the cluster of randomized clinical trials now in progress.

Published and unpublished studies evaluating the effects of hydroxychloroquine (HCQ), azithromycin (AZ) and/or zinc on Covid-19.

Study	Location	Design	Drugs tested	End point(s)	Propensity score used	Illness severity	Result (aHR or aOR, 95% CI, p value)	Conclusion
Tang[1] *BMJ*	16 Covid-19 treatment centers, China	Random-ized clinical trial	HCQ 1,200 mg qd x 3d, then 800 qd for 2 weeks in mild-mod cases or 3 weeks in severe cases vs none	Conversion to virus-negative status by 28 d	N/A	75 with mild-mod illness randomized to each group	0.85, 0.58-1.23, p=0.34	No difference
Geleris[2] *NEJM*	Manhattan	Obs	HCQ 600 x 2 on day 1, 400 qd for median of 5d vs none	Intubated or died	Yes – inverse weighting, matching, and as covariate	1,376 admissions	1.04, 0.82-1.32	No difference
Mahevas[3] *BMJ*	Paris, France	Obs	HCQ 600/d vs none	1-Tx to ICU 2-many	Yes, inverse weighting	181 admitted for O_2 need	Tx to ICU: 0.9, 0.4-2.1, NS Survival: 1.2, 0.4-3.3, NS	No difference
Mehra[4] *Lancet*	671 hospitals in 6 continents, collaborative	Obs	CQ, CQ+AZ, HCQ, or HCQ+AZ vs none	1-died 1-ventricular arrhythmia	Yes, matching	96,032	Mortality HCQ: 1.335, 1.223-1.457 HCQ+AZ: 1.368, 1.273-1.469 CQ: 1.365, 1,218-1.531 CQ+AZ: 1.368, 1.273-1.469 Ventricular arrhythmia HCQ: 2.369, 1.935-2.900 HCQ+AZ: 5.106, 4.106-5.938 CQ: 3.561, 2.760-4.569 CQ+AZ: 4.011, 3.344-4.812	Harm
Rosenberg[5] JAMA	25 hospitals in Manhattan, ransom samples of Covid pts	Obs	HCQ, AZ, or Both vs none	1-died 2-arrest or abnormal EKG (arrhythmia or prolonged QT)	No	1,438	HCQ: 1.08,0.63-1.85 AZ: 0.64, 0.27-1.56 Both: 1.35, 0.76-2.40	No difference
Magagnoli,[6] unpublished on *medRxiv*	Columbia, SC, VA	Obs	HCQ Or HCQ plus AZ vs none	1-died 2-intubated	Yes, as covariate	368 pts with positive test	HCQ: 2.61 1.10-6.17, 0.03 HCQ-AZ: 1.14 0.56-2.32, 0.72	Harm
Carlucci,[7] unpublished on *medRxiv*	New York University hospital system	Obs	HCQ 440 once, then 200 BID + AZ 500 qd with vs without $ZnSO_4$ 50 mg PO BID x 5d	1-died or Tx to hospice	No	932 pts of all severities	aOR All: 0.559, 0.385-0.811, 0.002 ICU: 1.03, 0.404-2.64, 0.95 Non-ICU: 0.449, 0.271-0.744, 0.002	Benefit

1. Tang WZ. Cao Z, Han M. et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ* 2020; **369**: m1849.
2. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. *New England Journal of Medicine* 2020 (published online).
3. Mahévas MVT, Tran M, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ* 2020; **369**: m1844.
4. Mehra MR, Desai SS, Ruschitzka F et al. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet* (published online).
5. Rosenberg ES, Dufort E., Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. *JAMA*. 2020 (published online).
6. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. *medRxiv* 2020 (published online before peer review).
7. Carlucci P, Ahuja T, Petrill CM, et al. Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients. *medRxiv* 2020 (published online before peer review).

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 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.