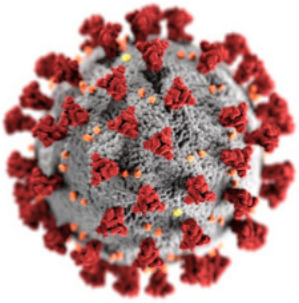

COVID-19 Action Newsletter

UT Southwestern Department of Internal Medicine
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The Situation: U.S. Confirmed Cases Exceed 1.4 Million

In the world as of May 15, 2020, 4,477,351 cases of Covid-19 have been confirmed, including 1,174,055 with onset in the past 7 days, and 303,389 deaths. In the United States, there have been 1,419,998 cases, the most in the world followed in order by Russia, the United Kingdom, Spain, Italy, Brazil, France, Germany, Turkey, Iran and China.[1] Deaths in the U.S. through May 1 have been estimated at 85,974.[2]

From March 10 through May 12, there have been 6,359 confirmed cases of Covid-19 reported from Dallas County with 148 confirmed deaths, 39% of these from long-term care facilities.[3] Of the 1,113 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 deaths 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

Covid-19 Coagulopathy

Tri Le, MD, and Ibrahim F. Ibrahim, MD

Early signals of coagulopathy associated with Covid-19 arose from the initial series of patients admitted to Jinyintan Hospital in Wuhan, China.[1] In these first 99 patients reported in early January 2020, D-dimer elevations were reported in 36% of patients, protime prolongation in 5%, and aPTT prolongation in 6%. In the ensuing months, the exponential rise of cases highlighted the distinct thromboinflammatory characteristics of Covid-19, referred to as *Covid-19-associated coagulopathy (CAC)*. Striking features of CAC include: 1) profound endothelial dysfunction causing perturbation of the natural antithrombotic state of the endothelium, 2) predilection for venous rather than arterial thrombosis, 3) early and profound elevations in fibrinogen and fibrin split products, and 4) low incidence of bleeding.

The early aberrations in coagulation parameters in Covid-19 are generally characterized by elevations in D-dimer, fibrinogen levels, factor VIII activity, and von Willebrand factor levels.[2,3] The observation of elevated D-dimers held particular significance early in the pandemic due in part to its correlation with more severe disease but also its early role in presumptive diagnostic criteria when testing was notably sparse.[4] This pattern of coagulopathy is distinct from the consumptive physiology of disseminated intravascular coagulation (DIC), in which fibrinogen and factor VIII levels are generally reduced. However, classic DIC can emerge as a later finding in Covid-19 usually after prolonged hospitalization. Among non-survivors 71% fulfilled the International Society on Thrombosis and Hemostasis (ISTH) criteria for DIC.[5] Indeed, progressive rise in D-dimer is an early harbinger of multi-organ failure and DIC among patients who did not survive.[3] Interestingly, IL-6 levels have been observed

to correlate with fibrinogen levels, highlighting a possible target for further study in the prevention of the pro-thrombotic sequalae of this disease.[6]

The presence of antiphospholipid antibodies, including anticardiolipin IgA, anti–β2-glycoprotein I IgA and IgG antibodies, and lupus anticoagulant have been reported in Covid-19 patients.[7,8] However, interpretation of this observation is evolving and does not in isolation suggest an association of antiphospholipid antibody syndrome with Covid-19. Antiphospholipid antibodies can be transiently found in acute illnesses, and the diagnosis of antiphospholipid antibody syndrome requires persistence of antibodies beyond 12 weeks at titers consistent with those outlined in the Sydney criteria.

The true incidence of thromboembolism in Covid-19 is evolving. Existing evidence is limited by short follow-up, variation in thromboprophylaxis strategies, and small sample size. In a multi-center, retrospective Dutch series of 184 critically-ill patients who all received at least standard thromboprophylaxis, cumulative incidence from ICU admission to death or discharge of a composite outcome of acute pulmonary embolism, deep vein thrombosis, ischemic stroke, myocardial infarction, or systemic embolization was 31% as of April 5th, 2020.[9] Updated analysis of this dataset with follow-up to April 22nd, 2020, unveiled an expectedly but nonetheless higher cumulative incidence of 49%.[10] Of these, 61% were segmental or more proximal pulmonary emboli, 25% were subsegmental pulmonary emboli, 4% were deep vein thromboses, and 9% were arterial thromboses. Autopsy studies from Germany also confirm the high rates of thrombosis in Covid-19 patients. In all patients, SARS-CoV-2 RNA was detected at high concentrations in the lung. Most patients were also found to exhibit viremia and high viral RNA titers in the liver, kidney, or heart.[11]

In an effort to provide guidance in the absence of randomized, controlled studies with robust sample size and follow up, the ISTH endorsed the April 20, 2020, guidelines for the management of Covid-19 and thrombotic disease based largely on expert opinion and published in the *Journal American College of Cardiology*. These were in part guided by a single-center retrospective series of 449 hospitalized Covid-19 patients in Tongji Hospital in Wuhan, China, that suggested a mortality benefit of thromboprophylaxis in Covid-19 patients with aberrant coagulation parameters.[12]

In brief, all patients hospitalized with Covid-19 without contraindication should receive prophylactic anticoagulation. Patients with mild disease in the community should be encouraged to increase mobility as the clinical benefits of outpatient prophylactic anticoagulation have yet to be demonstrated. Among patients in whom pharmacologic thromboprophylaxis is initiated, the intensity of dosing is a matter of active research. However, body weight should be taken into account in determining the prophylaxis dose as post-operative data clearly show conventional prophylaxis dosing in obese patients is inadequate with the higher dose of enoxaparin 40 mg BID being well tolerated.[13,14]

In patients in whom therapeutic anticoagulation is being considered, low-molecular weight heparin or unfractionated heparin is preferred due to the ease of parenteral administration and short half-life. In patients in whom pulmonary embolism is highly suspected but cannot be confirmed, empiric therapeutic anticoagulation should be considered barring any contraindication. DIC, in and of itself, is not a contraindication unless there is clinically significant bleeding. Additionally, clinicians should strongly consider transitioning hospitalized patients who present already on oral anticoagulation prior to a diagnosis of Covid-19 to parenteral anticoagulation. All direct oral anticoagulants (DOACs) are metabolized renally to varying degrees and may accumulate if renal dysfunction ensues. Importantly, antivirals like remdesivir, a CYP3A4 inhibitor, increase DOAC levels significantly.[15]

It is expected that these recommendations will continue to evolve as more data becomes available. In the short weeks following publication of the aforementioned guidelines, an uncontrolled, observational study of 2,773 hospitalized Covid-19 patients within the Mount Sinai Health System in NYC between March 14 and April 11, 2020, suggested that therapeutic systemic anticoagulation may provide in-hospital mortality benefit that is particularly pronounced among intubated patients without a clear increased risk of bleeding.[16] In summary, patients with Covid-19 should be monitored closely for the development of thrombosis as should coagulation indices including d-dimer and fibrinogen. While elevations in d-dimer, fibrinogen and endothelial damage appear to be hallmarks of this novel disease, therapeutic doses of anticoagulation for these findings per se are

not supported by the current data. Additionally, the role of complement activation in disease pathogenesis, and the role of viscoelastic coagulation testing need further clarification and study.

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Virology Notes

The Other Human Coronaviruses

Coronaviruses (CoV) are positively stranded RNA viruses infecting mammals and birds. Their name reflects their electron microscopic appearance showing surface projections radiating from the underlying envelope and resembling the corona of the sun. There are seven known human coronaviruses.

The first report in 1966 described a virus named *229E*, followed the next year by the discovery of *OC43*, where OC is the abbreviation for mouse "organ culture," indicating the system used to isolate this viruse. The next 2 coronaviruses isolated were *NL63* in the Netherlands and *HKU1* in Hong Kong. These 4 viruses are categorized further by structure and antigenicity as being in the *alphacoronavirus group* (229E and NL63) and the *betacoronavirus group* (OC43 and HKU1). All 4 occur in humans yearly in an endemic fashion, usually affecting mostly children, and have low case-fatality rates. They are named formally as HCoV 229E, HCoV OC43, HCoV NL63 and HCoV HKU1.

In contrast, the remaining 3—*severe acute respiratory syndrome (SARS CoV)* described first in 2002, *Mid-East respiratory syndrome (MERS CoV)* described in 2012, and *severe acute respiratory syndrome 2 (SARS CoV-2)*, first observed in 2019—occur in epidemic or pandemic fashion, affect both children and adults, and have case-fatality rates ranging from 2-35%. *SARS CoV-2* causes the disease we call *coronavirus disease 2019* or *Covid-19*.

Coronaviruses have four structural proteins: spike (S), nucleocapsid (N), envelope (E), and membrane (M). A fifth protein, hemagglutinin-esterase (HE), is seen in HCoV OC43 and HCoV HKU1. The S protein contains a receptor binding site which attaches the virus to the cellular receptor, which for HCoV NL63, SARS CoV and SARS CoV-2 is angiotensin converting enzyme 2 (ACE2). N, the nucleocapsid protein, coats the viral RNA. The E and M proteins are located on the viral envelope. Antibodies to HCoV are often directed against major proteins like S and N, and these proteins are used in serological testing in complement fixation, ELISA and neutralization reactions. These major proteins may serve as important target antigens in vaccine design and manufacture.

HCoV OC43 is the endemic coronavirus most commonly isolated from patients. It causes upper and lower respiratory infections and can produce bronchitis and pneumonia in adults. It is highly seasonal, causing mostly winter infections, when it can account for 2 – 25% of all respiratory illnesses.[1,2] It often occurs along with other viral respiratory pathogens such as influenza A or respiratory syncytial virus.

The N protein of HCoV O43 has been shown to cross-react with the N proteins of mouse hepatitis virus, bovine coronavirus and perhaps with SARS-CoV. It has been postulated that HCoV OC43 may have arisen from cross-over of bovine coronavirus into the human population during a bovine epidemic in 1890. An epidemic of HC0V OC43 infections in Canada originally was thought to be a SARS-CoV related problem until its serological cross-reaction was recognized. Young adults have been serially studied for the development of antibody to HCoV OC43. They develop antibody to the virus which wanes over a period of approximately 3 years and then are susceptible to reinfection, again causing significant disease.

HCoV NL63, only recently described, may be the most common coronavirus inducing disease after HCoV OC43. It has a relationship to the causation of croup. Its animal of origin is unknown but its human receptor is ACE2.[3,4]

HCoV 229E is an alphacoronavirus whose structure is closely related to the virus family that circulates in camels. HCoV HKU1 is a betacoronavirus and may originally have been derived from a rodent virus ancestor.[5]

Immunity to the 4 human endemic coronaviruses is usually type-specific but wanes over time, and antibody to these endemic viruses apparently does not protect against the 3 human epidemic coronaviruses. The ability to cross-react is important because it may complicate the investigation and control of epidemics like the Canadian situation mentioned above. One of the challenges of developing serological tests for antibodies to the epidemic coronaviruses is to avoid false positive results from cross-reaction with the endemic ones.

SARS appeared in 2002 with a case-fatality rate of 6%. Progressive pulmonary disease was the usual cause of death, sometimes ending in cytokine storm. Acute kidney injury occurred and complicated case management. Special problems presented by SARS included highly infectious environmental contamination with the virus and probable epidemic spread by aerosolization of virus, both of which contributed to international spread from the famous Hong Kong hotel. SARS-CoV was originally a bat virus that appears to have jumped species to the palm civet cat and then to humans.

MERS, which appeared in 2012 in Saudi Arabia, remains a problem. It too was a bat virus but jumped first to camels and then to humans. Its case-fatality rate is 35%. Healthcare-associated infections have been a particular problem, and in South Korea an extended outbreak caused 186 cases and 38 deaths.

SARS-2, the present pandemic concern, appeared in 2019. It too was originally a bat virus that appears to have jumped to pangolins and then to humans.

Since there are multiple human coronaviruses with potential transmission routes, double or triple infections with these agents appear probable and may influence the pathogenesis of disease and its complications. Concern for potentially heightened virulence of recurrent infections has been fueled by the example of dengue virus, where second infections are sometimes more severe and life-threatening than first infections. Dengue virus has 4 serotypes. Recurrent infection, which typically involves a different serotype, may result in the formation of non-neutralizing antibody which may form virus-antibody complexes that enter resident macrophages through non-specific attachment of the Fc fragment of the complex. This may ignite a

violent immunologic reaction manifested by potentially fatal hemorrhagic fever. The possibility of this happening with coronaviruses is mentioned in reviews but so far has not been recognized. The role of endemic coronavirus exposure on the subsequent behavior of SARS, MERS or SARS-2 is the focus of ongoing investigation.[6]

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Epi Corner

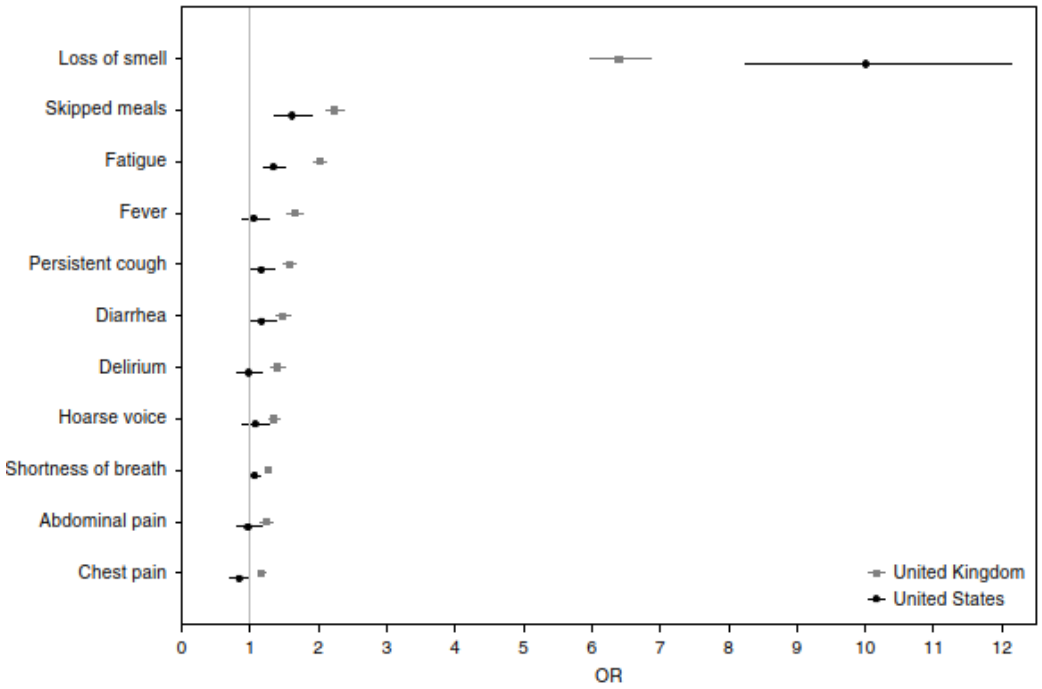
Loss of Taste and Smell: A Weapon for Controlling the Pandemic?

Up to now SARS-CoV-2 has had the upper hand, sweeping rapidly across the world, held at bay only temporarily by great economic sacrifice. But it may have made a big mistake that could shift the advantage to humans.

Researchers in the U.K. and U.S. have analyzed data from 2.5 million social media users who self-reported symptoms and Covid-19 test results into the free cell phone app *Covid Symptom Study* over 4 weeks in late March and April. In a letter to *Nature Medicine* this week,[1] the authors reported the surprising finding that the symptom that predicted a later positive PCR test by far the best was **loss of the sense of taste or smell**. From over 15,000 positive tests, the odds ratio (OR) for loss of taste or smell was 6.4 (95% CI 6.0-6.9, $P<0.0001$) in the U.K. users. The result was replicated in the U.S. user base (OR 10.0, 95% CI 8.2-12.2, $P<0.0001$). ORs for all other symptoms were <2.0 (Figure below). The main reason that loss of taste or smell was so predictive was that it is a very unusual symptom apart from Covid-19 illness, in contrast to other symptoms that commonly occur with other conditions. A prediction model from stepwise logistic regression, using age, sex, loss of taste or smell, severe cough, fatigue and skipped meals, strongly predicted a later positive test with area under the ROC curve of 0.76 (0.74-0.78) and a cross-validation value of 0.75 (0.74-0.76).

Despite several obvious sources of potential bias, such as predominantly young age of social media users, self-selection of cell phone and app use, criteria to be met for PCR testing, and influence of media reporting, the strength of the findings strongly suggest that surveillance by social media offers a powerful new weapon for rapidly predicting who out in the community is just starting to get sick. With skillful messaging, again through social media, people just noticing loss of taste or smell could self-isolate a day or two before symptoms become bothersome when studies show that virus shedding, and thus contagiousness, is at its peak. Public health agencies could mine the aggregate data in real time to identify emerging hot spots, such as nursing homes, meat packing factories or social gatherings, for interdiction.

The tide may be turning!



Association between self-reported symptoms and a later positive PCR test for SARS-CoV-2 In U.K. and U.S. users of a free social media app. Figure from Menni et al.[1]

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From the Editors

The editors thank Drs. Le and Ibrahim for contributing their article on coagulopathy 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.