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COVID–19
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Social distancing may have mental health consequences[1]

The COVID-19 pandemic has changed the world's social landscape. In most areas of the United States, shelter-in-place rules have restricted normal personal interactions and relegated social gatherings to phone calls and other forms of virtual exchanges. Remaining separated from others (i.e., social distancing) decreases an individual's risks of viral infection and, at the population level, slows the rate of viral transmission. Even the lay news media can adeptly describe the effects of social distancing on "flattening the curve." The authors of a recent JAMA Viewpoint highlight the other possible effects of social distancing, specifically mental health disorders. Large-scale disasters — whether traumatic (mass shootings) or natural (hurricanes) — often lead to increases in mental health disorders including depression, post-traumatic stress disorder (PTSD), and substance use disorder. With the COVID-19 pandemic the authors state: "…it appears likely that there will be substantial increases in anxiety and depression, substance use, loneliness, and domestic violence…" as well as child abuse. And they conclude that three steps can be taken to prepare for the increase in mental health disorders.

1. Plan for the inevitability of loneliness and its sequelae and develop ways to intervene. Added efforts should be made to ensure connections with elderly individuals and those who are typically marginalized including homeless persons, undocumented immigrants and people with known mental illness. Ensure that children have structured routines and the ability to connect with others remotely.
2. Implement mechanisms for surveillance, reporting and intervention. These are especially important for domestic violence and child abuse. The need for social distancing must be balanced against the availability of safe places for people at risk to live.
3. Bolster the existing mental health resources in preparation for the inevitable challenges brought on by the COVID-19 pandemic. The authors considered training of nontraditional groups to provide "psychological first aid" and to help teach the lay public to check in on one another. Additionally, "[t]elemedicine mental health visits, group visits, and delivery of care via technology platforms will be important components of stepped up care…"

The COVID-19 pandemic has affected everyone, bringing morbidity and mortality to many who have been infected by the virus and causing social and financial upheaval to the broader public, regardless of infection. A rise in mental health disorders is predictable and should be expected. The authors have proposed three steps that can be taken now to proactively prepare for the inevitable mental health consequences of this pandemic.

Empiric anticoagulation in hospitalized patients with COVID-19 infection[2]

It is well established that hypercoagulability is a cardinal feature of infection with the SARS-CoV-2 virus. The clinical manifestations include, but are not limited to, microthrombotic occlusion in the pulmonary and other vascular beds, a high frequency of DVT/PE in severely ill patients, COVID toe in younger patients, and the rare observance of large vessel strokes in otherwise healthy individuals. Additionally, elevated D-dimer levels have been observed to correlate with increased morbidity and mortality in infected patients. Clinical practice has therefore evolved to consider the role of therapeutic anticoagulation in severely ill patients with elevated D-dimer levels however, this has not been supported by rigorous clinical trial data. A study of hospitalized patients in the Mt. Sinai hospital system was recently published. It was an observational trial that looked at over 2700 patients hospitalized with confirmed COVID-19 infection and compared the 786 who received full anticoagulation with those that did not. As would be expected, those who received anticoagulation were more ill. They had higher markers of activation of the clotting cascade, and the requirement for mechanical ventilation was 30% of anticoagulated patients compared to only 8% who were not anticoagulated. Despite the much higher morbidity in the treated group, the mortality overall was the same in both groups at 23%, suggesting a benefit to anticoagulation. More importantly, when focusing on only the 395 patients who required ventilation, there was a striking difference observed. The anticoagulated group had an overall mortality of 29% with a median survival of 21 days, compared to the group that was not anticoagulated who had an overall mortality of 63% and a median survival of only nine days. Bleeding rates were low in both groups at 3% in the anticoagulated cohort compared to 1.9% in the control cohort. Absent a prospective, randomized trial, this is likely the strongest evidence we will have to apply evidence-based decision making to the use of therapeutic doses of anticoagulation in severely ill patients with COVID-19

(continued on page 2)

EDUCATIONAL FORUM

infection. Because thrombotic complications are still only rarely reported in less severely ill outpatients, we have not yet been able to define an optimal evidence based practice for this group of patients. If the microthrombosis in the pulmonary vascular bed is determined to be a major contribution to the progression of pneumonia in outpatients, there could be a future role for prophylactic or therapeutic anticoagulation in this setting.

Review of hydroxychloroquine studies — hydroxychloroquine, azithromycin, or both do not change in-hospital COVID-19 mortality[3, 4, 5, 6]

A retrospective cohort study was conducted from a random sample of all patients admitted to 25 New York hospitals with laboratory-confirmed COVID-19. Cohorts were defined by treatment with hydroxychloroquine and azithromycin, hydroxychloroquine alone, azithromycin alone, or neither drug. The random sample generated 1,438 patients. The patients who received one or both drugs were more likely than the patients who received neither drug to have diabetes, a respiratory rate greater than 22 breaths per minute, abnormal chest imaging findings, oxygen saturations lower than 90%, and aspartate aminotransferase greater than 49 U/L. The overall mortality was 20.3%. There were no significant differences in mortality between patients who did not receive either drug and those who received hydroxychloroquine and azithromycin (hazard ratio (HR), 1.35), hydroxychloroquine alone (HR, 1.08), or azithromycin alone (HR, 0.56). Additionally, patients who received hydroxychloroquine and azithromycin were more likely than those who did not receive medicine to have cardiac arrest (odds ratio, 2.13), yet there were no significant differences in abnormal electrocardiograms between groups. Overall, hydroxychloroquine and azithromycin do not change mortality when patients are hospitalized with COVID-19.

The results of this retrospective study align with several previous studies:

- French observational trial looking at 180 patients — matched to hydroxychloroquine (HQ) use vs. no HQ use. ICU transfer or death within seven days occurred in 20% of the patients in the HCQ vs. 22% in the non-HCQ group. Ten percent of patients developed either prolongation of the QT interval or new heart block.
- Chinese trial looking at 150 patients randomized to standard of care (SOC) or HQ plus SOC. On day 28 negative seroconversion rate was not different (85% vs. 81%). No difference in 28-day symptom alleviation rate.
- Brazil randomized trial compared high-dose HQ to lower-dose HQ. All patients also on azithromycin. The population was moderately severe inpatients. By day 13 of enrollment, 15% in the low-dose group had died, compared with 39% in the high-dose arm. High-dose arm cancelled.
- VA system — retrospective analysis of all veterans treated for COVID-19 infection as of April 11. Three hundred and sixty-eight patients were characterized by use of HQ alone, HQ plus azithromycin, or no HQ. Rates of death were 28% in the HQ, 22% in the HQ + azithromycin, and 11% in the no HQ group.

Tocilizumab — early information on treatment response[7]

Over the last several editions of the COVID Forum, we have been discussing that many of the trials of antiviral therapy have had only mild to moderate benefit. These trials have initiated treatment after hospitalization, often not until day 8–10 following symptom onset. We have learned that on average, viral load is rapidly diminishing by then. This declining viral load may in part account for the lack of a more robust response to antiviral therapy. Paradoxically, at a time when average viral load is diminishing, cytokine storm is ramping up and likely accounts for a major component of the morbidity and mortality seen later in the disease course. IL-6 is a major mediator of the cytokine storm. Tocilizumab (Actemra), approved for use in rheumatoid arthritis, is a monoclonal antibody which binds to IL-6 receptor and inhibits the downstream inflammatory cascade. It is also indicated for CAR-T mediated cytokine storm. There are only scant data on its use against SARS-CoV-2 infection. A recent trial from China, published in the Proceedings of the National Academy of Science, looked at its use in 21 patients. All patients were hypoxic and disease was described as severe in 18 patients and critical in three patients who required mechanical ventilation. Within 24 hours of treatment, all patients became afebrile, and CRP levels rapidly declined. Oxygenation significantly improved within three days, and lymphopenia improved within five days. Interestingly, IL-6 levels did not change with treatment, possibly related to the known blockade of the IL-6 receptor by tocilizumab. Two of three ventilated patients were weaned within five days. All patients survived to discharge with a mean hospitalization duration of 15 days. Although this is a small observational trial with no control group, both the mechanism of action of the drug and the apparent clinical response to the drug, suggest that a randomized controlled trial would be of value.

Transmission of SARS-CoV-2 in domestic cats[8]

There have been case reports of human to feline SARS-CoV-2 infection along with some data of airborne transmission of infection from cat to cat. To further study this, a group of investigators inoculated three cats with SARS-CoV-2 and then co-housed them with three non-infected cats. All three inoculated cats began to shed virus consistent with infection. By day three, all inoculated cats were shedding live virus and the duration of shedding was about five days. By day five of co-housing, all three non-inoculated cats had contracted SARS-CoV-2 infection and also shed live virus for about five days.

None of the six cats exhibited signs or symptoms of infection and remained afebrile throughout the study. So what can we learn from this study? This could be of particular importance given the potential for SARS-CoV-2 transmission between family members in households with cats while living under "shelter-in-place" orders. What is not known is whether this possible risk of transmission would be meaningfully incremental to the known high rate of human to human indoor airborne transmission. Although there has not been any documented cat to human transmission of SARS-CoV-2, cats may be a silent intermediate host of SARS-CoV-2, because infected cats may not show any appreciable symptoms that might be recognized by their owners.

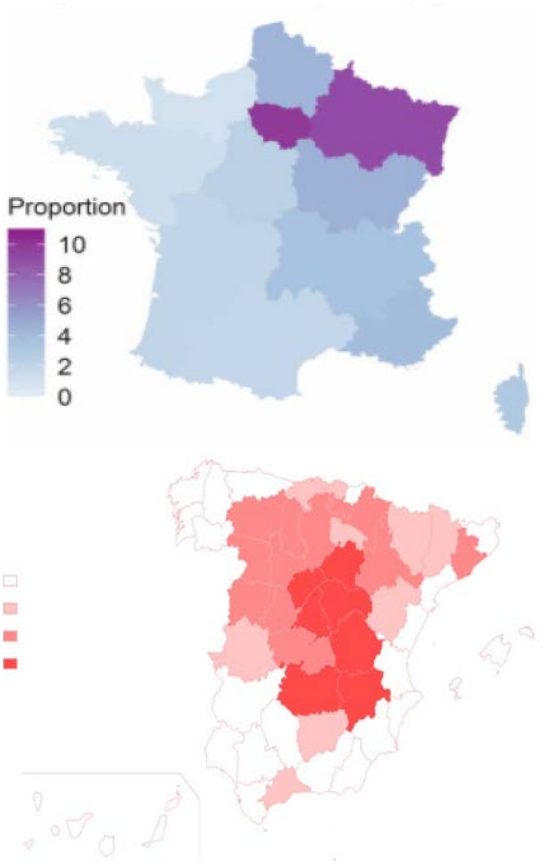
(continued on page 3)

Wide regional variation in COVID-19 disease rates and the large impact of lockdowns — affirming the value of social distancing[9, 10, 11]

A well-designed modeling study published in Science on May 13 pooled surveillance and hospital data in France to estimate the impact of its lockdown on virus transmissibility. This study calculated the novel coronavirus R_0 as 2.9 early in the epidemic, dropping to 0.67 during the lockdown — a very substantial decrease. Of note is the 10x differential in serology-confirmed positivity across the country, with higher rates up to 10% concentrated near Paris and rates as low as <1% in less populated areas of Aquitaine. This variability is similar to that observed across recent seroprevalence studies in the United States and a new paper published in Spain, which show rates of 10–13% in heavily populated major cities and as low as 0–3% in outlying rural areas.

These conclusions are reinforced by a stateside comparison of COVID-19 case rates of border counties in Illinois and Iowa. Only Illinois issued a stay-at-home order. As a result, Iowa had an observed 30% higher case rate during the 30-day period following the stay-at home order. The relationship between crowding and infection risk is now clear. What is emerging is the profound impact lockdown policies have had on transmission and how this impact may vary depending on local differences in basic human mobility and crowding.

Proportion infected - May 11th (%)



Validated clinical risk score predicts critical illness in hospitalized COIVD-19 patients

Researchers from the China Medical Treatment Expert Group for COVID-19 (CMTEG) developed a risk score applicable at hospital admission to predict which patients will develop critical illness.[12] Clinical information from a total of 1590 patients from 575 hospitals in China that were hospitalized over a two-month period was utilized to create the risk score. All patients with data submitted were included. At admission, only 24 (1.5%) of the 1590 were severe (as measured by the American Thoracic Society, CAP severity score), the remaining had mild disease. Eventually, 131 (8.2%) patients developed critical illness. Overall mortality among the 1590 patients was 3.2%.

These 10 variables:

1. CXR abnormality (OR, 3.39;95% CI,2.14-5.38;P < .001),
2. Age (OR,1.03;95%CI,1.01-1.05;P = .002),
3. Hemoptysis (OR, 4.53; 95%CI, 1.36-15.15;P = .01),
4. Dyspnea (OR, 95%CI, 1.18-3.01;P = .01),
5. Unconsciousness (OR, 4.71;95% CI, 1.39-15.98;P = .01),
6. Number of comorbidities (OR, 1.60; 95% CI, 1.27-2.00; P < .001),
7. Cancer history (OR, 4.07; 95%CI, 1.23-13.43; P = .02),
8. Neutrophil-to-lymphocyte ratio (OR, 1.06; 95% CI, 1.02-1.10; P = .003),
9. Lactate dehydrogenase (OR, 1.002; 95% CI, 1.001-1.004,P < .001), and
10. Direct bilirubin (OR, 1.15; 95%CI, 1.06-1.24; P = .001)

Researchers then validated the "COVID-GRAM" risk score in 710 patients. In the validation cohort critical illness developed in 87 (12.3%) and eight (1.1%) died. Using a bootstrap (random sampling) validation study an area under the curve (AUC) was 0.88.

This simple risk score, available on an online calculator (http://118.126.104.170/), could be useful in selecting patients at admission to target those needing more intensive observation and early intervention.

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Kenneth Roy Cohen, MD, FACP | *Chief Medical Officer*

Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. He has successfully developed and reported numerous clinical quality studies in primary care, including tobacco cessation, osteoporosis, asthma, diabetes, hypertension, and ischemic vascular disease. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of OptumCare. He has served as Chief Medical Officer since 1995. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship New West Physicians was awarded the AMGA Acclaim award in 2015 and the Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA | *Senior Medical Director*

Dr. Hitt has been a physician executive for more than 25 years. Most recently he was the CMO of Ativa Medical a medical device startup company and an independent health care consultant. Previously, he was CMO at Maricopa Integrated Health System (MIHS) and a key member of the senior leadership team having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

Dr. Hitt has over 25 years of experience in quality and performance improvement, clinical integration, academic and medical staff affairs. He served as the Chief Medical Quality Officer for Hennepin Health System, a premier Level 1 Adult and Pediatric Trauma Center. He was a physician leader for VHA (now Vizient). He was the national Medical Director for Disease Management at Caremark International and the VP of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt is a graduate of the University of Virginia where he played Division 1 soccer. He received his Medical Doctorate from the Medical College of Georgia in 1984 (AOA honors) and completed his Internal Medicine and Infectious Disease Fellowship training at the University of Minnesota Hospital and Clinics. Dr. Hitt completed his MBA at the Carlson School of Management at the University of Minnesota in 2003. He is the proud father of seven children.

Geoffrey Heyer, MD | *Senior Clinical Practice Performance Consultant*

Dr. Heyer is board certified in neurology with special certification in child neurology and in headache medicine. Prior to joining our team, Dr. Heyer was an associate professor of neurology and pediatrics at The Ohio State University and Columbia University Medical Center, specializing in autonomic disorders, headache, and pain management. He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders.

Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.

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