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COVID–19
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Characterizing COVID-19 infectivity from pre-symptomatic through symptomatic infection

An understanding of the extent of pre-symptomatic transmission of SARS-CoV-2 is critical to controlling the pandemic. Researchers from Guangzhou Medical University, China and the WHO determined that an estimated 44% of cases were acquired from an infected person prior to the onset of symptoms.[1] Researchers studied the viral shedding in 94 patients and then applied findings to the evaluation of different groups of 77 infector-infectee transmission pairs. Viral load testing was measured on 414 samples from 94 patients from day of symptom onset until 32 days after symptom onset. This data showed high viral load at the time of symptom onset that decreased to the limit of detection by 21 days after symptom onset. Infectivity fell off quickly within seven days after symptom onset.

The analysis of the 77 infector-infectee pairs found a serial interval (duration between symptom onset of successive case in a transmission chain) of 5.8 days. The incubation period (time between infection and onset of symptoms) was assumed to be 5.2 days. A comparison of this data provided an estimate that 44% of transmissions occurred before symptoms were present. Further modeling suggested the peak infectious period begins 2 days before and extends to one day after symptoms begin. Other research teams suggest 48–62% of cases occurring as a result of pre-symptomatic transmission. This emphasizes the importance of social distancing and universal masking as strategies to control the spread of SARS-CoV-2. It also provides additional data to support that the average infectivity falls off quickly after symptoms begin and most patients were no longer infectious 7 days after symptom onset despite persistent PCR positivity in many patients.

Some patients recovered from COVID-19 infection had low or undetectable antibodies

It is hoped that neutralizing IgG antibodies to SARS-CoV2 would develop in most infected patients and confer immunity to subsequent infection. There are two separate questions here. First, does neutralizing IgG Abs confer immunity? This is not yet known. If these antibodies prove to be protective, it is unknown how long immunity would last. Secondly, what percentage of patients who have recovered develop neutralizing antibodies? It is this second question that the above study attempted to answer. This Chinese study looked at 175 patients with recovered mild infection and measured neutralizing antibody to the spike protein.[2] As with prior studies, most patients developed antibodies between days 10–15. Six percent of patients did not develop measurable antibody titers either at discharge or two weeks later. In general, older patients and those with a systemic inflammatory response as measured by elevated CRP levels had higher levels of antibody than younger patients with milder disease. This study raises the possibility that younger patients with asymptomatic or mild disease may not have an appreciable titer of neutralizing IgG antibodies post infection.

Further evidence on lack of COVID-19 response to hydroxychloroquine

In last week's COVID Forum dated 4-16-20, we reviewed a large well-done observational study of antimalarial therapy from France. This study did not show a beneficial effect of hydroxychloroquine (HCQ). Additionally, the first randomized (non-blinded) trial was published in abstract form from China last week.[3] In this trial 150 patients were randomized to standard of care (SOC) or HCQ plus standard of care. The HCQ patients were treated with 800 mg daily for 2–3 weeks. The primary endpoint was the 28-day negative conversion rate of SARS-CoV-2. The assessed secondary endpoints were negative conversion rate at day 4, 7, 10, 14 or 21, the improvement rate of clinical symptoms within 28 days, normalization of C-reactive protein and blood lymphocyte count within 28-days. The overall 28-day negative conversion rate was not different between SOC plus HCQ and SOC group (85% vs. 81%). Negative conversion rate at day 4, 7, 10, 14 or 21 was also similar between the two groups. No difference in 28-day symptom alleviation rate was observed between the two groups. There was a slightly faster return toward normal in the CRP level. There was a 30% rate of adverse events in the HCQ group compared to 9% in the SOC group. In summary, other than perhaps an anti-inflammatory effect as measured by a more rapid CRP decline, there were no other significant benefits to HCQ therapy.

Reduction in cardiac interventions for ST elevation myocardial infarction during the COVID-19 pandemic

There are anecdotal data on reduced utilization of acute cardiac and neurological interventions for myocardial infarction

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and stroke during the COVID-19 pandemic. A report from Spain noted a 40% reduction in acute cardiac interventions during the most intense period of infections in Spain.[4] A study was published this week[5] looking at the utilization of acute coronary interventions for STEMI from 9 high volume cardiology centers. On average, the 9 centers combined performed acute interventions at a rate of 180 per month before the COVID-19 pandemic (defined as onset March 1, 2020). Following March 1, the rate dropped to 138 per month, reflecting a 38% decline. Given the stress of social isolation and the stress of COVID-19 infection in individuals with underlying coronary disease, if anything, an increase in STEMI would be expected. Potential etiologies offered included avoidance of ER utilization due to fear of contracting infection, and misdiagnosis due to a high prevalence of severe COVID-19 infections which can cause chest pain, dyspnea, ECG abnormalities and troponin elevations. We all need to be mindful of the differential diagnoses of chest pain and dyspnea at this time and consider potential etiologies other than COVID-19 infection.

Neurologic features of COVID-19 infections

Recent case series have explored the neurologic findings associated with COVID-19 infections.

A retrospective chart review found one or more neurologic signs or symptoms in 78 (36.4%) of 214 patients hospitalized with COVID-19.[6] These included dizziness (16.8%), headache (13.1%), impaired consciousness (7.5%), impaired taste (5.6%), impaired smell (5.1%), change in vision (1.4%), and nerve pain (2.3%). Six patients developed acute cerebrovascular disease — five had ischemic stroke and one had cerebral hemorrhage. The authors highlight the finding that five of the six patients with cerebrovascular disease had severe COVID-19 infections. One patient had a seizure and one had ataxia. Signs of skeletal muscle injury developed in 10.7%, with significantly higher median creatine kinase levels (400 U/L vs. 58.5 U/L).

Neurologic features were reported from 58 patients with severe COVID-19 infections and acute respiratory distress syndrome (ARDS).[7] Agitation was common (69%) after discontinuing neuromuscular blockade. Corticospinal tract signs (clonus, hyperreflexia, and/or extensor plantar responses) were present in 67%. MRI was performed on 13 patients with encephalopathic features: leptomeningeal enhancement was present in 8; bilateral frontotemporal hypoperfusion was found in 11; two patients had imaging signs of acute ischemic stroke; one had subacute ischemic stroke. Data are lacking about the potential cause(s) of neurologic manifestations, which include critical illness-related encephalopathy, cytokine changes, medication or substance withdrawal, or a specific relationship to COVID-19 infection.

Deferring low and moderate-benefit cancer treatments during the COVID-19 pandemic

Several studies out of China suggest a two-to-threefold increased incidence of COVID-19 in patients with cancer.[8, 9] While the UK has established a national monitoring project to quantify the risks of novel coronavirus infection in patients being treated for cancer, so far high quality data on infections in U.S. cancer patients remains lacking.[10]

A recent viewpoint in JAMA has set forth a framework that many oncologists across the country have been following to balance the risks of foregoing cancer screenings or treatments against the risk of novel coronavirus infection during this pandemic. This framework proposes deferring or eliminating care whose benefit does not exceed the risk of COVID-19 disease in these generally high-risk patients. Types of care that should clearly be deferred include treatment for Gleason grade I or II prostate cancer, some low-grade thyroid tumors, and many types of third-or-later line chemotherapies for solid tumors with little chance of improving overall survival beyond a few weeks.

More personalized decisions must be made for time-sensitive therapies that bring moderate outcomes improvement, where the risk/benefit ratio will differ by geography and time.

Category	Action	Examples
Category 1: Non-time-sensitive interventions	Defer or deliver remotely	Surveillance visits in remission patients with no signs or symptoms of recurrence, evaluation of patients receiving hormonal or oral chemotherapy in low-risk patients
Category 2: Time-sensitive interventions with minimal benefit	Defer care	Screening for breast, lung, colon and prostate cancer, treatment for low-grade cancers like prostate, carcinoid or neuroendocrine tumors; third chemotherapy regimens for many solid tumors
Category 3: Time-sensitive interventions with moderate benefit	Balance risks of deferring care with risk of novel coronavirus infection	Maintenance rituximab following autologous BMT for mantle cell lymphoma
Category 4: Time-sensitive interventions with major or curative benefit	Deliver care and minimize risk of novel coronavirus infection	Treatment for new onset acute leukemia, high grade lymphoma, therapy-responsive testicular or ovarian tumors, small cell lung cancer

The primary care physician can help patients considering low-yield treatment courses balance the likely benefit of cancer treatment against their relative risk of developing COVID-19 during the treatment course. It is important that the oncology community preserve the safety of the system for patients in category 4 who absolutely must receive treatment.[11]

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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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