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EDUCATIONAL FORUM

Excess deaths due to COVID-19: (still) at the bottom of the class

The United States has experienced more deaths from COVID-19 than any other country and has one of the highest cumulative per capita death rates. An unanswered question is to what extent high U.S. mortality was driven by the early surge of cases prior to improvements in prevention and patient management versus a poor longer-term response. To examine this, the U.S. mortality at different time points was compared to the mortality in other countries where early COVID-19 mortality was high. In early spring, many countries saw excess mortality surge alongside COVID-19 mortality. However, since June excess mortality across developed European countries has essentially disappeared. The U.S. has the dubious distinction of being the only developed country in the world to maintain double-digit rates of excess mortality (19.4 cases per 100,000) eight months into the COVID-19 pandemic. Further, while most countries reduced their COVID-19 mortality by tenfold or more since the beginning of the pandemic, the U.S. has managed only to halve it, from ~60 COVID-19 deaths per 100,000 to ~27 per 100,000 since June.[1]

The two factors likely to be driving the overall excess mortality are persistently high risk of COVID-19 infection in most U.S. states and changes in health care access and care-seeking behavior. A second analysis reports on excess mortality by state over time, revealing a close association between excess mortality and COVID-19 surge activity at the state level. In April, excess deaths were concentrated in New York, New Jersey, Massachusetts and Illinois and Michigan. By July, they were concentrated in Texas, Florida, California and Arizona.

Nationally, only 67% of these excess deaths were due to COVID-19 infection. Addressing the issue of changes in health care access and care-seeking behaviors is important in understanding the other third of excess mortality. Non-COVID-19 mortality for heart disease peaked nationally between March 21 and April 11, following the first COVID-19 surge. Non-COVID-19 mortality for Alzheimer's disease saw two spikes: the first between March 21 and April 11 (first surge), and the second between June 6 and July 25 (summer surge in the Sunbelt). Internal OptumCare data further supports the notion of treatment delays and avoidant patients in regions where virus rates are high or increasing. We must continue to emphasize our ability to maintain safe care environments for our patients and encourage the delivery of necessary care.[2]

Immunity to SARS-CoV-2: What more do we know?

Although researchers understand more about immunity to other human coronaviruses than about immunity to SARS-CoV-2, even that knowledge is sparse. For reasons that are poorly understood, immunity to seasonal human coronaviruses tends to be short in duration, lasting from 80 days to a few years. Reinfections have been documented with all four of the seasonal human coronaviruses. These reinfections can occur as early as 6–9 months and occur frequently by one year. Reinfection, after documented infection, has been shown in patients with SARS-CoV-2, but so far has occurred only rarely. There are five well-documented cases in the face of over 38 million cases of COVID-19 worldwide. Whether such reinfection represents only transient immunity versus different strains of the same virus is unclear. In the SARS and MERS outbreaks, immunity was documented to last 2–3 years from infection but had waned by 5–6 years. Understanding the natural history of immunity to SARS-CoV-2 is critical to predicting herd immunity, the response to vaccination, and the potential need for revaccination in the future.[3]

Of the two subunits of the spike protein, the S1 subunit contains the receptor-binding domain responsible for binding to the ACE2 receptors on susceptible cells and is the main target for SARS-CoV-2 neutralizing antibodies. Recovered patients mount a significant IgM and IgG response to this and other spike protein domains, which appears to be protective. Similarly, these antibodies are seen in varying titers following immunization with the current candidate

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vaccines. However, currently available data have provided conflicting information regarding the durability of the antibody response. Several studies suggest that IgM wanes beginning around 18 days post onset of symptoms and IgG titers begin to wane about eight weeks post symptom onset. The severity of the disease seems to correlate with both increased titers and longer duration of the antibody response. Patients with mild disease were shown to have a decline in neutralizing IgG Ab within 2–4 months. Notably, in one study 13% of symptomatic individuals and 40% of asymptomatic individuals became IgG seronegative within 2–3 months following infection. On the other hand, a study from Iceland reported that 91% of 1,215 individuals who tested positive for SARS-CoV-2 by PCR remained seropositive four months following diagnosis, with no reduction in antibody titers.[4]

With respect to T-cell mediated immunity, activated T-cells specific to the spike glycoprotein were detectable in 83% of patients recovered from COVID-19. Interestingly, one study showed T-cells reactive to spike glycoprotein in 24 (35%) of 68 healthy participants who had not tested positive for COVID-19. It is unknown if this represents cross immunity from other coronaviruses. Both T4 and T8 cells appear to play important roles in immunity, although the data remain sparse on the specific roles of each.

It is thought that a balance of both vaccine-induced antibody production as well as vaccine-induced T-cell induction is important to achieve immunity and to prevent vaccine-enhanced disease. Data are available from the studies of the eight candidate vaccines which have entered phase III trials, and all appear to have this balanced effect. So far there have not been any cases of vaccine-induced disease enhancement, but the total number of vaccinated individuals remains low. The vaccine's ability to confer immunity is also critically dependent on the stability of the spike protein, and therefore there is a potential loss of vaccine efficacy should there be a significant future mutation. Although the immunological studies of the vaccines appear promising, the real-world safety, efficacy and protection rates won't be known until the publication of the large phase III trials. Lastly, to the average patient, these vaccines may all appear to be equivalent; however, they may vary considerably in terms of efficacy and side effects. It is not yet known how the various vaccines will be allocated and what degree of choice will be available.

Mother-to-newborn transmission of SARS-CoV-2 is rare, even with rooming-in and direct breastfeeding practices

Previous studies suggest that about 4% of neonates born to mothers with COVID-19 become infected,[5] but outcomes are not well-characterized. A recent retrospective study evaluated the infection rates and outcomes of 101 newborns from 100 mothers.[6] Newborns were admitted to well-baby nurseries (n=82) or neonatal intensive care units (n=19) of two affiliate hospitals in New York City, New York. Those admitted to the well-baby nursery roomed-in with their mothers who wore face masks, and direct breast-feeding (with appropriate hygiene) was encouraged.

A total of 141 SARS-CoV-2 tests were performed. Two newborns (2%) had indeterminant test results, which indicated that an infection was present but the viral copy numbers were low. Retesting was done on one of the newborns, and it was negative. Having severe/critical maternal symptoms from COVID-19 was associated with earlier delivery (approximately one week) and an increased risk of needing neonatal phototherapy, compared to mothers who had mild symptoms or were asymptomatic. Fifty-five newborns were followed up in a dedicated COVID-19 clinic between days of life 3 and 10, and all remained well.

Although there are published reports documenting symptomatic infections in neonates,[7,8] this case series suggests that substantial illness is rare, even among newborns who room in with their mothers with COVID-19 and breastfeed directly.

Remdesivir WHO (SOLIDARITY) Trial

The most recent randomized remdesivir trial was reviewed in the last edition of the COVID Forum.[9] Recall that it was a large international randomized trial of 600 patients with moderate pneumonia due to SARS-CoV-2 infection, and importantly, all patients were enrolled within four days of a positive PCR test. There were no significant differences in mortality, need for mechanical ventilation, duration of hospitalization or time to recovery. This was the third randomized trial that failed to show a reduction in mortality with remdesivir use.

Added to this body of literature, we now have the SOLIDARITY Trial which has been released "pre-peer review."[10] This is the largest trial to date, enrolling over 11,000 patients at 405 hospitals in 30 countries. The study compared the standard of care to three drug regimens: remdesivir, hydroxychloroquine, and ritonavir/lopinavir. These latter two regimens have not shown efficacy against SARS-CoV-2 infection in other trials and will not be discussed. Over 2,700 patients were randomized to receive remdesivir. Remdesivir did not reduce mortality in the overall study population or in any other subgroup of entry characteristics. The mortality rate was 301/2,743 or 10.9% in the remdesivir group versus 303/2,708 or 11.1% in the control group. Remdesivir did not reduce initiation of ventilation or hospitalization duration. The authors' trial conclusion was as follows: "For each of these four repurposed nonspecific antivirals, several thousand patients have now been randomized in various trials. The unpromising overall findings from the regimens tested suffice to refute early hopes, based on smaller or nonrandomized studies, that any will substantially reduce inpatient mortality, initiation of ventilation or hospitalization duration."

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As previously reviewed, the Institute for Clinical and Economic Review (ICER) has done a cost-effectiveness analysis of remdesivir pricing based on an assumption of a mortality reduction versus no mortality reduction.[11] In the mortality reduction scenario, the derived cost-effective price would be ~$2,650. In our current scenario, with no evidence of a significant mortality reduction, the ICER-derived cost-effective price would be $310 for a course of treatment. The current cost in the U.S. is $3,200 for a five-day course of treatment and in most of Europe, ~$2,000. Based on this study, the European countries have called for a renegotiation of the remdesivir price. Recall that remdesivir is still only approved via an EUA and not FDA-approved for use in COVID-19. Hopefully, the NIH treatment guidelines may be updated based on this most recent information to help with decision-making around the use of remdesivir.

Tocilizumab for moderate-to-severe COVID-19 pneumonia

There have been several observational trials suggesting a mortality benefit when tocilizumab, a monoclonal antibody against the IL-6 receptor, is used for moderate-to-severe COVID-19 pneumonia with clinical cytokine storm. These early data served as the motivation for multiple large trials and the results are now becoming available. Two nonblinded randomized trials and a large observational trial were published this week.[12,13,14] The observational trial showed a 10% reduction in 30-day mortality; however this was not supported by the randomized trials. The first randomized trial did not show a clinical improvement or a mortality benefit at 30 days.[12] The second trial also failed to show a mortality benefit at 30 days; however it showed a 12% absolute reduction in death or the need for mechanical ventilation at day 14.[13] This was predominantly related to a decrease in the need for mechanical ventilation. There are two other trials for which we now have preliminary data, and both of these are rigorous double blind randomized trials. Again, the data between these two trials is discordant. In the first, conducted in North America and Europe, there was no clinical improvement and no decrease in 30-day mortality.[15] Interestingly, the second trial included significant enrollment from South America and Africa. It did reveal modest clinical improvement but only a minimal 1.8% reduction in 30-day mortality.[16]

We have learned much from the COVID-19 pandemic. We have seen that observational trial results are often not supported by high quality randomized trials, and that stopping trials early can confound the conclusions and erode confidence in the results. On the other hand, we have seen that high-quality trials can be quickly conducted to provide critical information on optimal patient care. Tocilizumab therapy in COVID-19 is an example of observational trials quickly progressing to nonblinded trials, and then to randomized double blinded trials. These latter trials are providing a more precise view of its efficacy. Clearly, the clinical outcome data has not shown a large improvement in mortality. It is yet uncertain whether tocilizumab will prove to be an effective therapy, and whether subpopulations of patients may have a better response than others. These answers will hopefully be provided by the final results of the two trials for which we have preliminary data and several other similarly designed trials which are in progress.

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Kenneth Roy Cohen, MD, FACP

Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. 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 served as Chief Medical Officer from 1995 to 2020. He now serves as the Executive Director of Clinical Research for UHG R&D and Senior National Medical Director for OptumCare. 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

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

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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