Week in Review: 18-22 May 2020

BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Do patients under 65 years of age have poor outcomes when infected with SARS-Cov-2? A new paper published in *The Lancet* from two New York-Presbyterian hospitals affiliated with Columbia University Irving Medical Center in Manhattan monitored patients admitted with laboratory confirmed SARS-CoV-2 from March 2 to April 1, 2020. Patients included critically ill persons with acute respiratory failure (with low blood oxygen levels) and each patient was followed for at least 28 days after the initial evaluation. During the 30-day initial period, 1,150 adults with covid-19 were admitted to these two hospitals, a staggering number. The average age of patients admitted was 62 years, and 22% were deemed to have been in critical condition. At the time of publication, 39% of the patients had died. 79% of the entire cohort required mechanical ventilation, for an average of 18 days, though typical ranges included 9 to 28 days. Over 25% of those patients were *under* the age of 50 years. Furthermore, 37% remained in the hospital at the time the paper was published; many hospitalized patients soon became sicker, with an average time to in-hospital deterioration of 3 days. This implies that patients "self-diagnosed" the severity of their illness by virtue of having presented to the hospital when they did. Using a statistical model, researchers found that the presence of chronic heart and lung disease and high levels of interleukin-6 and blood d-dimer levels (a marker of abnormal blood clotting) were independent risk factors for dying while hospitalized. **Commentary:** These data are remarkable both from the perspective of patient outcomes and hospital capacity. The number of patients treated and hospitalized by just two New York City hospitals is highly unusual if not unprecedented in modern history. It is also noteworthy that over one-fourth of all patients who died were under the age of 50 years old. *20 May 2020.* *–Joshua Niforatos MD*

Message in a bottle. Moderna's mRNA vaccine candidate makes a splash. In the past few years, the prospect of a producing vaccines that use messenger RNA instead of proteins derived from infectious pathogens including viruses and bacteria has captivated the biotechnology industry. While potential vaccines for many diseases have been synthesized, none have been approved for use anywhere in the world. Yesterday, Moderna, a company in Massachusetts, announced favorable results from a phase 1 trial testing their first vaccine candidate against SARS-CoV-2. Phase 1 trials are designed to establish doses and safety profiles for drugs and vaccines in development. Generally, phase 1 trials are small and enroll 20 or more test subjects. In addition to reporting on the safety of the vaccine—which so far appears to have caused only minimal side effects—the company announced that the vaccine, known as mRNA-1273, elicited an immune responses in the first eight volunteers who received the vaccine for whom data is currently available. This candidate vaccine is composed of genetic material (mRNA) that codes for a spike protein which extrudes from the surface of SARS-CoV-2 particles. While the theory is well-grounded, reality is what matters. It is therefore encouraging that blood later drawn from test subjects in this phase 1 study exhibited antibody levels that were similar or higher than the levels that have been detected in patients known to have recovered from SARS-CoV-2 infection. The company reports that all participants in the study "seroconverted" with respect to neutralizing antibodies, regardless of the dose given. This suggests that the subjects' immune systems recognized the vaccine appropriately though it does not necessarily mean that these

responses rendered the patients immune. But there appears to be good news on that front as well. The first eight patients were also found to have mounted "neutralizing" antibody responses 43 days after the vaccines were given. The blood from these patients were taken to labs and placed on plaques of viral particles. The plaques were observed to have been reduced in size, suggesting that the viral particles were being effectively killed. The levels of neutralizing antibodies were either similar or greater than those observed in blood from recovered covid-19 patients ("convalescent sera"). Based upon these findings, the FDA has permitted a phase 2 trial to begin on an expedited basis, which will further assess the safety of the vaccine using the dose that appears to be most promising. Hundreds of patients are to be enrolled. Generally, potential drugs and vaccines that carry serious but rare side effects are unlikely to be detected in phase 1 trials. The results of phase 2 data (as well as a phase 3 trial which would include thousands of patients and is already being planned for rollout as soon as July) will be watched closely for this reason. If the vaccine works but causes unacceptable rates of serious side effects during phase 2 or phase 3 trials, it would be back to square one. Nevertheless, the stock market rewarded this news in trading yesterday. *19 May 2020.* *–Jeremy Samuel Faust MD MS*

An update on decreased heart attacks in the US during the pandemic: Recently, *Brief19* covered research from the UK that described an possible decrease in the number of ambulance calls for patients with suspected heart attacks and strokes (the decreased number of calls did not reach "statistical significance"). Yesterday, a research letter published in *NEJM* describes the rate of newly diagnosed heart attacks throughout the entire Kaiser Permanente System in Northern California before and during the covid-19 outbreak. Kaiser Permanente consists of 21 medical centers and 255 clinics and provides comprehensive care for more than 4.4 million persons throughout Northern California. The researchers assessed whether the incidence of weekly heart attacks changed before and after the first reported death from covid-19 in Northern California, which occurred on March 4, 2020. These data were compared to weekly rates of heart attacks from the same period in 2019. These researchers found that the weekly rates of hospitalization for heart attacks decreased by up to 48% after March 4th. When compared to the similar time period in 2019, the numbers after March 4th were also lower. Also reported in the study is that patients diagnosed with heart attacks during the covid-19 period (March 4 - April 14, 2020) were healthier (i.e. had fewer pre-existing chronic medical problems) than heart attack patients who were diagnosed and treated both during the pre-covid-19 period of 2020, as well as in 2019. The authors conclude that overall there were fewer heart attacks diagnosed during the covid-19 pandemic than would be expected, even after considering typical seasonal variations. The large question is whether decreases in usual medical care for life-threatening conditions including major heart attacks have been significant contributors to the increases in the total number of deaths (from all causes combined) that have been observed to have occurred during the US outbreak. The numbers in this study suggest that this is currently unlikely. *Abbreviated from Brief19 for 21 May 2020.* *–Joshua Niforatos, MD Research Section Editor*

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Brief19 is a daily executive summary of covid-19-related medical research, news, and public policy. It was founded and created by frontline emergency medicine physicians with expertise in medical research critique, health policy, and public policy.