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BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

BREAKING NEWS: Chloroquine trial halted; high doses deemed too harmful.

Hydroxychloroquine (HCQ) and its parent compound chloroquine (CQ) have been widely discussed as a potential therapy for covid-19. To-date there have been a handful of trials published describing their investigational use during the pandemic. Most of these studies have been negative, and no trial has shown convincing evidence either drug should be used for covid-19 despite widespread adoption around the country. A new study hot off the press today in *JAMA Network Open* is another setback. This study was a "phase IIb trial," which are designed to test for effectiveness and safety. In this trial, 81 patients with SARS-CoV-2 in Brazil were randomized to receive either low dose or high dose chloroquine. The test subjects were in severe or critical condition. Prior to starting, the researchers estimated approximately 440 patients would be needed to test the hypothesis that mortality would be 50% reduced in patients on high doses of CQ compared to those given low doses. The researchers planned to do interim assessments of safety and effect of the doses of CQ when 25 percent, 50 percent, and 75 percent of the total number of patients had been enrolled and were taking the drugs. The patients in this study were relatively young, with an average age of 51 years, mostly male (75 percent); 50 percent had high blood pressure. Most patients also received azithromycin, ceftriaxone, and oseltamivir empirically (meaning the treating physicians were covering their bases against other infections from bacterial pneumonia to influenza). **Results:** Regarding the safety of CQ, patients who received high dose CQ more frequently showed evidence of an abnormal and potentially dangerous toxic side effect to the heart compared to patients in the low dose CQ group. Specifically, the time it takes for the ventricles of the heart to "reset" after each beat (measured by what doctors call the "QTcF interval" on ECGs) was found to be prolonged to over 500 milliseconds. Such disturbances of the heart are known side effects of CQ. They can cause a fatal heart rhythm known as torsades de pointes (TdP). While no patients experienced TdP in this study, two patients in the high dose group did develop similar rhythms (known as ventricular tachycardia) prior to dying. Regarding mortality, 27.2 percent of the patients died in this study, a rate that mirrors major studies of severe/critical covid-19 of patients who did not receive CQ. Most alarmingly, 39 percent of patients in the high dose CQ group died versus only 15% in the low dose group. Thus the odds of dying in the high dose CQ group was *3.6 times higher* than in the low dose CQ group. In an exploratory analysis adjusting for important variables associated with increased likelihood of death from covid-19, such as older age, those receiving high dose CQ had *2.8 times higher* odds for death compared to the low dose group, though that result was not statistically significant. Because of the higher rate of death in the high dose CQ group, the data and safety monitoring board immediately halted the trial. Patients were immediately removed from high dose protocols. **Analysis:** 1. The evidence of a significant increase in mortality in the high dose CQ group remained strong even after some statistical corrections were made. 2. The average in this randomized trial was younger compared to some other studies of patients with critical covid-19 in Italy and New York. This means outcomes in those areas might have been even worse had they received high dose CQ. In sum, high dose CQ should not be given, and likely might not pass muster to even be studied going forward.

–Joshua Niforatos, MD, Research Section Editor

POLICY BRIEFING

Changes in testing policy. The Laboratory Corporation of America (Labcorp) has become the first company permitted to provide at-home test kits for the coronavirus. In a statement this week, the Food and Drug Administration (FDA) reissued the Emergency Use Authorization (EUA) to permit the personal use of Labcorp's Pixel test. The first-of-its-kind allowance was granted after the test demonstrated equality of accuracy and safety at-home to that of in-office testing. Labcorp has stated that the test will be made available in the coming weeks, initially for healthcare workers and first responders. A physician's order will be required. Collected samples will be shipped directly to Labcorp. Results will be viewable to patients through a secure portal online. Kits will not be available in Maryland, New Jersey, New York, and Rhode Island, due to state laws prohibiting such unmonitored testing. *Various.*

--*Joshua Lesko, MD*

Reimbursement for uninsured care. The US Department of Health and Human Services (HHS) has announced more details on reimbursing healthcare providers treating patients without insurance for covid-19. Citing an undisclosed portion of the $100 billion Provider Relief Fund that was established as part of the CARES Act, providers will be able to directly bill to the federal government for reimbursement at Medicare rates. Registration for the program will begin on April 27 at coviduninsuredclaim.hrsa.gov and claims may be submitted in early May, "subject to available funding." *The Department of Health and Human Services.*

--*Joshua Lesko, MD*

House passage of newest stimulus bill foreshadows fight to come. Yesterday, the US House of Representatives passed its newest piece of stimulus legislation, and the bill will now go to President Trump's desk for signature. The bill includes expected provisions such as hospital funding and replenishing available small business loans. However, in a surprising last minute maneuver, House democrats inserted a provision that stands up a committee to review the Trump administration's response to the emergence of coronavirus. Beside the review committee provision, there was also significant partisan debate about whether to extend relief funds to states and cities, and how best to distribute that funding. Representative Ocasio-Cortez (D-NY) broke ranks and voted against the stimulus package over the lack of state relief funds. So far, the stimulus legislation has been remarkably bipartisan. The debate and last-minute provision surrounding this bill however portends what will likely be a much more partisan future of relief legislation. *New York Times.*

–Kimi Chernoby, MD, JD, Policy 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.