*Week in Review: 20-24 April 2020*

# ***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 no trial has shown convincing evidence either drug should be used for covid-19 despite widespread adoption around the country. A new study in *JAMA Network Open* this week 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 CQ. 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 on 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. **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. 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% 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. 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. *Abbreviated from Brief19 for 24 April 2020. –Joshua Niforatos, MD Research Section Editor.*

**What happens to children diagnosed with covid-19?** A hot off the press systematic review published on April 22 in *JAMA Pediatrics* assessed the known literature (at the time of submission) of pediatric cases of SARS-CoV-2 infection. The authors found 18 studies with 1,065 patients (444 patients younger than 10 years, 553 were aged 10 - 19) with confirmed SARS-CoV-2 infection. Notably, all of the included studies came from China except for one case report from Singapore. Most children in the study had mild symptoms, including fever, dry cough, and fatigue. Many were entirely symptom-free. Interestingly, imaging (x-rays, CT scans, etc.) found mildly symptomatic and asymptomatic children to be similar. No deaths were reported in children aged 0-9, and one death was reported in a person 10-19 years old. However, since these data were submitted, we know that a small number of children have died here in the United States. This study confirms prior observations that children tend not to have severe covid-

19. However, these results reflect "publication bias." The true case fatality rate, while likely extraordinarily low in children, remains unknown. *22 April 2020.*

*–Joshua Niforatos, MD Research Section Editor.*

**Early New York Hospital data emerges.** In a correspondence to the *New England Journal of Medicine,* physicians at two affiliated New York City hospitals describe their early experience with covid-19. In some ways the description of patients matches previous observations from cohorts in Wuhan city and Hubei province in China. Pre-existing medical conditions such as high blood pressure and diabetes were common. While thus far 10.2 percent of the hospitalized patients have died, the researchers note that testing was quite limited during the time that these first 393 patients were evaluated and treated. Male sex (61%) and obesity (36%) were common. As in other patients around the world, a low number of white blood cells was often observed. Mechanical ventilation (intubation) was required in 33.1 percent of patients. However, one third of those patients are now "extubated," meaning they are breathing on their own without the aid of machines. This is a far higher rate of success than many other studies. The reasons for this are unclear, but may reflect differences in patient populations. *20 April 2020.*

*–Jeremy Samuel Faust MD MS*

**Confirmed ways to decontaminate and reuse N95 masks.**
With PPE shortages occurring in coronavirus hot spots, effective methods for decontamination and reuse of limited resources has become an area of high interest. The National Institutes of Health (NIH) has released a preprint comparing different techniques. The study compared ultraviolet radiation at 260-285 nanometers, 70° Celsius heat, 70 percent ethanol, and vaporized hydrogen peroxide (VHP) in their ability to reduce contamination. They also assessed whether these processes damage the N95 mask material over several cleanings. Masks were subjected to two hours of continuous wear followed by a cleaning cycle for a total of three cycles. They were evaluated based on inactivation rates of the virus on mask material compared to stainless steel. Tests were also done to determine how many viral particles violate recycled masks. The ethanol and VHP methods most rapidly inactivated the virus on N95 masks, while UV light and heat had similar rates of inactivation. After the initial round of wear and decontamination there were no significant differences between mask integrity, but after subsequent rounds, sharp drops in the effectiveness of the alcohol and heat-treated masks were seen. The UV and VHP-treated masks maintained acceptable function through the entire phase of testing. Overall, the study shows superiority of VHP treatment for both speed of decontamination and retained function and supports up to three cycles of cleaning for equipment reuse. *The National Institutes of Health. 21 April 2020.*

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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.