*25 November 2020*

# ***BRIEF19***

*A daily review of covid-19 research and policy*

## ***RESEARCH BRIEFING***

**Hydroxychloroquine *still* doesn't work for covid-19 prevention.**

Hydroxychloroquine (HCQ) for patients with covid-19 has been repeatedly shown to lack efficacy. HCQ has no proven success among patients with covid-19 in either the outpatient or inpatient settings. Nor does HCQ *prevent* covid-19 infection among healthcare workers. However, something we did not yet know is whether HCQ somehow prevents covid-19 infection in the community setting among individuals exposed to persons known to have covid-19.

Now we do. Spoiler: it doesn't. A randomized clinical trial published yesterday in *The England Journal of Medicine* puts another nail in the HCQ coffin. The study was an open-label, phase 3, cluster-randomized trial conducted in Catalonia, Spain between March and April. Study subjects were asymptomatic, 18 and older, and had a recent close-contact exposure to a PCR-confirmed patient with covid-19. Test subjects were randomly assigned in clusters of contacts to either HCQ (800 mg once, followed by 400 mg daily for 6 days) or to usual care (no therapy). The primary outcome was symptomatic covid-19 within 14 days. Adverse events were assessed for up to 28 days.

Nearly 2,500 individuals were included in the trial, and the average age was 48 years. Nearly 75 percent were female and less than one-third reported frequent mask use. The rate of PCR-confirmed, symptomatic covid-19 was 5.7 percent and 6.2 percent in the HCQ and usual care group, respectively, which was not statistically significant. HCQ use did *not* result in decreased transmission. Finally, there were *significantly more* side effects in the HCQ group (56.1 percent) compared to usual care (5.9 percent).

In summary, HCQ does not prevent covid-19 infection in the community setting among those exposed to another person with covid-19. The flogging of this dead horse continues,

*—Joshua Niforatos, MD, MTS*

**Trial of convalescent plasma for covid-19 falls flat, another setback for hyped treatment,**

Is convalescent plasma the miracle treatment we were promised? The answer in the latest published clinical trial appears to be no. This is more worrisome news for a proposed treatment that has been bandied about and for which the US Food and Drug Administration granted emergency use authorization, despite the absence of compelling trial data to support its use (for more, see our prior coverage in March and August).

Released yesterday, November 24, in *The New England Journal of Medicine* is a multicenter randomized, double-blind, placebo-controlled clinical trial (RCT) of 228 patients hospitalized with severe covid-19 who received either standard-of-care and convalescent plasma therapy or standard-of-care plus placebo. The primary outcome the researchers tracked was "clinical status" during follow-up at day 30.

The average age of participants was 62 years, and the majority were identified as male. Over one-fourth of patients were in intensive care units. Importantly, 93 percent of patients were on steroids, such as dexamethasone—meaning that they were already receiving the one treatment that has been shown to improve mortality rates in covid-19 patients with severe illness.

Interestingly, 68.6 percent and 61.8 percent of patients given placebo and convalescent plasma, respectively, were discharged home in good condition, though that difference was not statistically significant. Unfortunately, by day 30 there were no significant differences noted between the convalescent plasma group and the placebo group with regard to clinical outcomes

or mortality. Adverse events were similar in both groups. Previous retrospective studies have found that convalescent plasma can cause serious harms, despite the general talking point that "plasma is safe." But in a trial with just 228 patients, it is unlikely that many adverse events would occur.

The idea behind convalescent plasma makes sense: when fighting an infection, our bodies manufacture specific antibodies in bulk to combat an invading pathogen. After the infection, the body maintains a stock of "memory cells," meaning that in the event of a future infection by the same virus, bacteria, or other infectious disease, our response can be both rapid and specific. Some antiviral antibodies circulate in the blood, almost like molecular surveillance drones. If an infection re-appears those antibodies spring into action.

By mid-August it was announced that over 60,000 people had already received convalescent plasma therapy for covid-19, despite any high quality evidence of its ability to improve morbidity or mortality. Since that time, likely tens of thousands of additional patients have been given this medical therapy, largely owing to the FDA's emergency use authorization. This new study adds to a growing list of randomized trials that have failed to show a benefit for this treatment. So far, only retrospective studies have been "positive." When retrospective studies and randomized trials conflict, the trials should be seen as more definitive.

More trials are ongoing. While that is good, it is important to remember that if enough trials are conducted, one or two may find a marginal benefit, just as a result of statistical chance. Any positive findings would have to be weighed against the totality of the other existing evidence. At this time, we continue to believe that most patients should not be receiving convalescent plasma therapy outside of formal clinical trials. *—Joshua Niforatos, MD, MTS*

## ***POLICY BRIEFING***

**Highest risk factors with incarceration.**

Last week *Brief19* covered a new report from the National Academies of Sciences, Engineering, and Medicine (NASEM) with new recommendations for decarceration and steps the healthcare community can take to facilitate inmate reentry into society. Yesterday, *The New England Journal of Medicine* published a new analysis of the greatest risk factors for inmates in the state correctional system using results from symptom-based and mass testing of incarcerated persons in Connecticut.

In addition to the results of the tests, participants were followed for fourteen days to assess clinical status. The greatest risk factors for developing covid-19 were found to be dormitory-style living, Hispanic/Latino ethnicity, and older age. The study also identified heart disease, dormitory living, and older age as predictors of hospitalization; heart disease, older age and immune compromise were also risk factors for admission to intensive care units. The only risk factor for death was older age.

Dormitory style housing was the strongest overall risk factor for developing covid-19, which is consistent with prior data supporting the importance of physical distancing which emphasizes the difficulty associated with limiting the spread of infection among incarcerated individuals. *The New England Journal of Medicine.*

*—Joshua Lesko, MD*

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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 and public policy.*