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BRIEF19

A daily review of covid-19 research and policy

RESEARCH BRIEFING

Colchicine trial comes up empty for covid-19. RECOVERY trial again delivers answers.

Of the half-baked ideas cooked up by scientists, pundits, and other blundering washouts hoping to stumble upon a game-changing covid-19 treatment from amongst our existing arsenal of drugs previously approved for other medical conditions, colchicine has had both the most promising data and the fewest number of wacky proponents.

Colchicine is a potent anti-inflammatory medication and disordered inflammation is thought to play a role in the development of severe covid-19. But theories are not enough. Clinical data are always needed. Almost a year ago, *Brief19* covered a small randomized study that showed promise—albeit we were skeptical that the findings would hold up. Since then, more studies of varying quality have appeared, which have either been less encouraging or so methodologically flawed that the results were essentially impossible to interpret.

Once again, the RECOVERY trial, a large conglomerate of researchers in the United Kingdom has provided much-needed and compelling answers, in a manuscript posted yesterday on the preprint server *medRxiv.* The report of the study's findings has not yet undergone peer review by a medical journal.

In this randomized trial that included over 11,300 patients (children and pregnant patients were excluded because colchicine has some substantial toxicities associated with it) admitted to a hospital for the treatment of covid-19, there was no difference in mortality regardless of whether patients were randomly selected to receive colchicine for 10 days (or until well enough to be released from the hospital), or not. Either way, the average length of the hospitalization was 10 days. Either way, 70 percent of the patients were alive 28 days later. Either way, around 25 percent of the patients who were not already on mechanical ventilators at the time of enrolling in trial ended up such a ventilator or dying. While the study enrolled patients with both suspected and confirmed SARS-CoV-2, a sub-analysis of patients later found to indeed have been positive demonstrated the same findings.

Those who believe that colchicine works, despite this evidence, will probably complain that the medication was given too late. Around half the patients were enrolled in the study between 6 and 12 days after their symptoms began. There were no differences in outcomes among people who were enrolled 6 days or less after symptoms began and those enrolled a week or more after.

The question that you may be asking is "why do large studies keep contradicting the findings from small ones?" There are many explanations for this common phenomenon, ranging from bias among researchers that is harder to tease out in small studies to the fact that some small pilot trials change their outcomes midway through, and usually do so in order to paint the study drug in a more favorable light. But one thing is for sure: large, well-randomized studies carry more weight than small ones. To that point, the RECOVERY trial authors state that the entire number of patients in all three of the small previous randomized trials that they were aware of totaled to only 285 individuals, among whom just seven deaths occurred. The RECOVERY trial, on the other hand, had far more patients (over 11,300), and far more deaths (over 2,300). That implies both great statistical power and that the cohort of patients was a markedly sicker population than those included in the previous studies.

Is colchicine another failure? For hospitalized patients, the answer, unfortunately, is yes. Might colchicine help patients not yet sick enough to be admitted to a hospital? It's possible. The

"nearly positive" COLCORONA trial hinted at a small benefit in preventing disease progression, but failed to enroll the pre-planned number of patients that the researchers believed would be necessary to find a statistically stable finding. Therefore, we do not know. At least one other important trial is underway now which may provide answers.

—Jeremy Samuel Faust, MD MS

POLICY BRIEFING

Paying for long-hauler care among covid-19 survivors.

For almost the entire duration of the covid-19 pandemic, there have been reports among some survivors of covid-19 experiencing weeks and months of residual symptoms. Called "long-haulers," our understanding of the cause, mechanism, and progression of this syndrome has continued to evolve. One problem, from a policy perspective, has been how to include the long-term care of patients who beat the infection's acute effects among national policies stating that all covid-19-related care should be covered by all insurance carriers.

But as early as October, advocates for health expenditure protection were sounding alarms that bills aimed at mitigating out-of-pocket costs for acute infections did nothing to address these chronic symptoms and the ongoing expenses incurred.

To address this, lawmakers at multiple levels of government have created survivors' registries, modeling the efforts on those generated after the 9/11 attacks to better track these individuals.

There are still many limitations to the effort: the opt-in nature of such databases may lead to exclusion from already underserved and vulnerable populations, and a large amount of data needs to be collected to analyze and develop qualification standards for protection. Further complication comes from inclusion in a national registry versus local ones, and what this will mean for data portability and interoperability. The related end-user trust, or lack thereof, of the government at any level in maintaining sensitive patient information may also be a formidable disincentive for enrolling. But with an estimated ten percent of survivors suffering from a persistent constellation of symptoms, every effort must be made to understand it and treat this syndrome. *Various*.

—Brief19 Policy Team

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