Editorial

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December 16, 2022

Long-term Follow-up After Critical COVID-19
REMAP-CAP Revisited

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JAMA. Published online December 16, 2022. doi:10.1001/jama.2022.23700

The year 2020 was a grim and uncertain time for any clinician caring for inpatients with COVID-19, especially those with critical illness. In an era of modern medicine in which the range of options for many conditions can seem limitless, this novel viral threat was a reminder of the historical norm in medicine—a struggle to find the best available treatment.

As a stark example of ambiguities and resulting divergent practices during the dark days of earl one of us was an infectious diseases consultant to medical teams caring exclusively for inpatien COVID-19.[1] On one of the teams, all of their patients received adjunctive hydroxychloroquine as part of their admission medications. A second team, doing their daily rounds on the same floor of the hospital, chose the opposite approach—none of their patients received it. Members of both teams could mobilize logical arguments in favor of their practice, while simultaneously acknowledging that they were doing so without high-quality data from randomized clinical trials.

Now, more than 3 years since the first cases of COVID-19, multiple well-conducted studies have served to greatly expand treatment options. Importantly, clinical research has also crossed many ineffective treatments off the list of potential options, including, for the record, hydroxychloroquine.[2] Research has breathing room to evolve beyond the "triage" mindset of the early years of the pandemic toward refining treatment approaches and studying more than just mortality and hospitalization. Currently, 2

evidence gaps are particularly large: understanding treatment outcomes beyond a few weeks and measuring not just survival, but also quality of life.

In this issue of *JAMA*,[3] investigators from the international Randomized Embedded Multifactorial Adaptive Platform for Community Acquired Pneumonia (REMAP-CAP) consortium make a substantial step toward closing these evidence gaps through a prespecified secondary analysis of their previously published randomized clinical trials. Using an adaptive study design,[4] the REMAP-CAP trial evaluated 6 treatment classes for 4689 patients admitted to the intensive care unit with COVID-19 from March 2020 through June 2021. Most notable among their initial trial findings was a substantial clinical benefit, including short-term 21-day survival, of the IL-6 receptor antagonists tocilizumab and sarilumab.[5] These results contributed to the inclusion of this strategy in treatment guidelines for COVID-19 among critically ill patients.[6] Anticoagulation with heparin in noncritical disease of moderate severity (but not in critical disease) also improved outcomes,[7] but none of the other tested therapies yielded favorable results.

The present analysis extends the 21-day primary outcome horizon of the previous trials to evaluate 180-day mortality (the primary outcome), 180-day quality of life measured through the 5-level EuroQol-5 Dimension (EQ-5D-5L) score, and 180-day disability using the 12-item World Health Organization Disability Assessment Schedule. The 6 pragmatic trials had varying treatment and control groups. The randomized groupings were a fixed 7-day course of intravenous hydrocortisone, a shock-dependent course, or no steroids; 1 of 2 IL-6 receptor antagonists, interferon beta-1a, or no immune modulator; lopinavir-ritonavir, hydroxychloroquine, a combination of the 2, or no proposed antiviral treatment; convalescent plasma treatment, delayed treatment, or no plasma; therapeutic-dose or thromboprophylaxis-dose heparin; and aspirin, a P2Y12 inhibitor (eg, clopidogrel), or no antiplatelet agent. Notably absent from this list of interventions is remdesivir, the only antiviral that is approved by the US Food and Drug Administration for inpatient treatment of COVID-19 to date. Such an exclusion is unlikely to invalidate these results because there is limited evidence for benefit of this drug in critical illness,[8] which contrasts with clear efficacy when given earlier and in milder stages of the disease.[9]

Several unique aspects of this analysis deserve emphasis as one considers the results. The REM trial was an ambitious and forward-looking "perpetual platform trial," initially organized in 201 with an explicit purpose to provide rapid evidence in a pandemic.[10] In the earliest days of the COVID-19 pandemic, the collaboration sprang into action and expanded to 197 international sites using this adaptable research platform. Another distinctive quality of the REMAP-CAP studies was their focus on pragmatic interventions, whose goal was to "replace random variation in treatment with randomized variation in treatment," thereby embedding trials into routine care delivery. This was coupled with a sophisticated statistical framework using bayesian methods particularly well suited to deliver meaningful, time-sensitive evidence. Finally, the authors had the foresight to prespecify quality of life outcomes in their adaptive platform, enabling the important secondary outcomes in this study. The investigators deserve the highest praise for executing an expansive, forward-thinking initiative that has produced a wealth of evidence under intense pressure.

One of the main findings is unlikely to surprise readers aware of the short-term results of the REMAP-CAP trial and the current treatment guidelines for COVID-19. For the primary outcome of 180-day mortality, IL-6 receptor antagonists (tocilizumab or sarilumab) again demonstrated a very high probability of superiority (adjusted hazard ratio, 0.74 [95% credible interval {CrI}, 0.61-0.90]; >99.9% probability of superiority vs placebo). This 180-day outcome provides reassurance that early mortality benefit from IL-6 receptor antagonists did not result in longer-term adverse outcomes, such as susceptibility to late-onset opportunistic or other infections, that would offset short-term benefits.

Somewhat surprisingly given the negative results from the 21-day analysis,[11] antiplatelet agents (aspirin or P2Y12 inhibitors) also demonstrated a high likelihood of improving 180-day mortality (adjusted hazard ratio, 0.85 [95% CrI, 0.71-1.03]; 95.0% probability of superiority). Unlike the IL-6 receptor antagonists, these agents are not currently standard of care for management of critical COVID-19. Although it may seem contradictory that the corticosteroid domain did not show improved mortality rates, this component of the trial was importantly halted sooner than planned due to early evidence of benefit from the RECOVERY trial,[12] so it was underpowered to provide additional insight. As previously shown, therapeutic anticoagulation (in severe disease), lopinavir-ritonavir, hydroxychloroquine, and convalescent plasma had minimal benefit or even possible harm. Hydroxychloroquine treatment was associated with a concerning increase in mortality (adjusted hazard ratio, 1.51 [95% CrI, 0.98-2.29]). This is a reminder of the caution that clinicians should exercise in using unproven treatments and the importance of changing practice as evidence evolves.

Results examining the secondary outcomes of quality of life and disability are both more unexpected and more nuanced. There is further reassurance that the IL-6 receptor antagonists did not lead to worse quality of life or greater disability, and likely even improved these outcomes at 180 days. The benefits were even more certain for the antiplatelet agents, with a substantial gain of 0.08 in health-related quality of life over a baseline of 0.63 in the control group (adjusted mean difference, 0.08 [95% CrI, 0.02-0.13]). This result, combined with the 180-day mortality results also suggesting benefit, constitutes some of the most favorable evidence to date for these agents,[13] especially in light of the initial trial from the REMAP-CAP group showing a 95.7% probability of futility.[11]

Conflicting results and a higher bleeding risk with antiplatelet therapy for COVID-19 in critical illness means that this new evidence is not yet enough to motivate changed practice or alter consensus guidelines. Additionally, it is important to note that quality of life and disability outcome data were missing for more than 60% of the study sample, with differences between the populations with and without missing data. Regardless, antiplatelet agents deserve further study in other trials with extended data available. Ongoing study could be particularly valuable given that one proposed explanation for long-term symptoms from COVID-19 is microvascular clotting, a plausible pathophysiologic mechanism that antiplatelet agents would target.[14]

One unavoidable limitation of the present study and its applicability to current practice is that COVID-19 as a disease has changed. Although infection with SARS-CoV-2 is still very much with us, preexisting population-level immunity, from vaccination, prior infection, or both, has made severe disease progres-

sively less common.[15] There is also laboratory evidence that the widely circulating Omicron variant exhibits decreased lung infectivity,[16] making pneumonia—the clinical entity most commonly leading to intensive care unit admission—a less likely manifestation of disease. The evidence in this study remains valuable given that COVID-19 will continue to be a common cause of critical illness globally. However, the most effective strategy to reduce mortality and critical illness will be prevention through a global effort to expand COVID-19 vaccination.

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Back to top

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Published Online: December 16, 2022. doi:10.1001/jama.2022.23700

Conflict of Interest Disclosures: Dr Barnett reported receiving personal fees from Greylock McKinnon Associates outside the submitted work and being retained as an expert witness in government litigation against opioid manufacturers and distributors. No other disclosures were reported.

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