Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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1 Shear MK. Complicated grief. *N Engl J Med* 2015; **372:** 153–60.
2 Davidson JE, Aslakson RA, Long AC, et al. Guidelines for family-centered care in the neonatal, pediatric, and adult ICU. *Crit Care Med* 2017; **45:** 103–28.
3 Truog RD, Campbell ML, Curtis JR, et al. Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American Academy of Critical Care Medicine. *Crit Care Med* 2008; **36:** 953–63.
4 Efstathiou N, Walker W, Metcalfe A, Vanderspank-Wright B. The state of bereavement support in adult intensive care: a systematic review and narrative synthesis. *J Crit Care* 2019; **50:** 177–87.
5 Kentish-Barnes N, Chevret S, Valade S, et al. A three-step support strategy for relatives of patients dying in the intensive care unit: a cluster randomised trial. *Lancet* 2022; published online Jan 19. https://doi.org/10.1016/S0140-6736(21)02176-0.
6 Downar J, Koo E, des Ordons AR, et al. Prevalence and predictors of severe grief reactions and desire for support following a death in the intensive care unit: a multicentre observational study. *Intensive Care Med* 2017; **44:** 521–22.
7 Vanderspank-Wright B, Efstathiou N, Vandyk AD. Critical care nurses' experiences of withdrawal of treatment: a systematic review of qualitative evidence. *Int J Nurs Stud* 2018; **77:** 15–26.
8 Crowe S, Howard AF, Vanderspank-Wright B, et al. The effect of COVID-19 pandemic on the mental health of Canadian critical care nurses providing patient care during the early phase pandemic: a mixed method study. *Intensive Crit Care Nurs* 2021; **63:** 102999.
9 Downar J, Barua R, Sinuff T. The desirability of an intensive care unit (ICU) clinician-led bereavement screening and support program for family members of ICU decedents (ICU Bereave). *J Crit Care* 2014; **29:** 311.e9–16.
10 Barnato AE, Schenker Y, Tiver G, et al. Storytelling in the early bereavement period to reduce emotional distress among surrogates involved in a decision to limit life support in the ICU: a pilot feasibility trial. *Crit Care Med* 2017; **45:** 35–46.

Another piece in the COVID-19 treatment puzzle


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A new study[1] from the RECOVERY Collaborative Group adds another piece to the puzzle of severe COVID-19 therapy. The RECOVERY trials have been pivotal in providing evidence on the efficacy of compounds within current treatment guidelines for COVID-19, such as dexamethasone, tocilizumab, and the casirivimab and imdevimab combination.[1–3] In previous randomised trials, these monoclonal antibodies[4] were effective in preventing infection and clinical progression when given in the early phase of infection.[5,6] The RECOVERY Collaborative Group should be commended for testing casirivimab and imdevimab in a large randomised trial of patients admitted to hospital, despite the fact that in this setting no virus-directed therapy had yet been proved to reduce mortality, including other monoclonal antibodies.[7,8] However, high plasma SARS-CoV-2 viraemia at admission is thought to correlate with hospital mortality as reported in the pre-print of a small trial (not yet peer reviewed),[9,10] suggesting both virological and clinical benefit of casirivimab and imdevimab combination in seronegative patients requiring low-flow oxygen.

In *The Lancet* the RECOVERY Collaborative Group report the findings of a new randomised, controlled, open-label platform trial,[1] which included 9785 patients admitted to hospital for COVID-19 and randomly assigned to casirivimab and imdevimab plus usual care versus usual care alone. Overall, 6128 (63%) patients were men, 3657 (37%) were women, and 7601 (78%) were White, with a mean age of 61·9 years (SD 14·5) and a median time since symptom onset of 9 days (IQR 6–12). Overall there were 3153 (32%) seronegative patients, 5272 (54%) seropositive patients, and 1360 (14%) patients with unknown baseline antibody status. In the 6261 patients for whom SARS-CoV-2 vaccination status was known, 5449 (87%) were unvaccinated. RECOVERY found that patients who were seronegative for SARS-CoV-2 at admission (ie, those without detectable antibodies to SARS-CoV-2 infection) receiving casirivimab and imdevimab infusion had a significant reduction in the primary outcome of 28-day all-cause mortality. In the primary efficacy population of seronegative patients, 396 (24%) of 1633 patients assigned to casirivimab and imdevimab versus 452 (30%) of 1520 patients assigned to usual care died within 28 days (rate ratio [RR] 0·79, 95% CI 0·69–0·91; p=0·0009). The proportional effect of casirivimab and imdevimab on mortality differed significantly between seropositive and seronegative patients (p value for heterogeneity=0·002). Relevantly, in seronegative patients, the estimated reduction in risk was similar regardless of the level of oxygen support needed by participants, including those receiving invasive mechanical ventilation, while the estimate of the effect of treatment was largely attenuated in an analysis that included all randomised participants (ie, regardless of baseline antibody status; RR 0·94, 95% CI 0·86–1·02; p=0·14).

This RECOVERY casirivimab and imdevimab trial[1] shows the feasibility and efficacy of use of monoclonal antibodies in patients admitted to hospital with COVID-19. Unfortunately, the weakness of monoclonal antibodies is the evolution of viral resistance with mutations of the spike glycoprotein leading to a decrease of neutralisation activity.[10] Indeed, preliminary findings in a non-peer reviewed preprint of a study suggest that casirivimab and imdevimab combination might not be effective against the B.1.1.529 (omicron) variant,[11] whereas a new monoclonal neutralising antibody sotrovimab seems to retain effectiveness (which the RECOVERY Group has started evaluating in a randomised trial).[12] Thus, there is the risk that results of trials such as the casirivimab and imdevimab RECOVERY trial[1] might become obsolete or have limited applicability in the face of a fast-evolving virus.

In general, the RECOVERY platform trials have major strengths in the large number of UK sites involved, which ensures representativeness of the sample included and large statistical power. The scientific community should be grateful to both the participants and doctors involved in RECOVERY Group trials for their crucial work and for leading to completion randomised trials in a fast-changing environment in which equipoise is often challenged by new emerging data. Nevertheless, the platform trial pragmatic approach, dictated by the pandemic and often advocated as a design strength, has limitations. Not having masked treatment assignments means that participants who receive casirivimab and imdevimab might behave differently; eg, they might be less likely to seek help initially if their symptoms worsened, or perhaps more likely to if they thought their treatment was causing side-effects. Second, although the clinical endpoint of day-28 mortality appears to be the engrained standard defined endpoint in COVID-19 trials, it has also been criticised.[13] During the course of the pandemic many deaths have occurred beyond the initial 28 days after hospital admission; although the casirivimab and imdevimab RECOVERY trial has prespecified 6-month outcomes and can provide follow-up data for up to 10 years, this analysis[1] did not use data beyond day 28 so hospital readmissions and deaths occurring after this point were not included. Additionally, although the intention-to-treat analysis is recommended in randomised trials because it guarantees that exchangeability achieved by randomisation is maintained,[14] the per-protocol analysis is equally important as it estimates the effect that would have been observed under perfect adherence to the trial protocol. To report the per-protocol analysis is also useful, for example, for future comparisons with the effect estimated in observational data.[15] In conclusion, although we acknowledge the great contribution of this study, we underline that this was a non-blinded trial, and further analyses evaluating the effectiveness of monoclonal antibodies with the newly circulating omicron variant are required.

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1 RECOVERY Collaborative Group. Casirivimab and indevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2022; **399:** 665–76.
2 RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021; **384:** 693–704.
3 RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; **397:** 1637–45.
4 Hansen J, Baum A, Pascal KE, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. *Science* 2020; **369:** 1010–14.
5 O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV antibody combination to prevent Covid-19. *N Engl J Med* 2021; **385:** 1184–95.
6 Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—final report. *N Engl J Med* 2020; **383:** 1813–26.
7 Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV antibody combination and outcomes in outpatients with Covid-19. *N Engl J Med* 2021; **385:** e81.
8 ACTIV-3/TICO LY-CoV555 Study Group. A neutralizing monoclonal antibody for hospitalized patients with Covid-19. *N Engl J Med* 2021; **384:** 905–14.
9 Rodríguez-Serrano DA, Roy-Vallejo E, Zurita Cruz ND, et al. Detection of SARS-CoV-2 RNA in serum is associated with increased mortality risk in hospitalized COVID-19 patients. *Sci Rep* 2021; **11:** 13134.
10 Somersan-Karakaya S, Mylonakis E, Menon VP, et al. REGEN-COV for treatment of hospitalized patients with Covid-19. *medRxiv* 2021; published online Nov 19. https://doi.org/10.1101/2021.11.05.21265656 (preprint).
11 Ikemura N, Hoshino A, Higuchi Y, Taminishi S, Inaba T, Matoba S. SARS-CoV-2 omicron variant escapes neutralization by vaccinated and convalescent sera and therapeutic monoclonal antibodies. *medRxiv* 2021; published online Dec 14. https://doi.org/10.1101/2021.12.13.21267761 (preprint).
12 RECOVERY news release. RECOVERY Trial to investigate sotrovimab as a possible treatment for hospitalised COVID-19 patients. Dec 23, 2021. https://www.recoverytrial.net/news/sotrovimab-to-be-investigated-by-the-recovery-trial-as-a-possible-treatment-for-patients-hospitalised-with-covid-19 (accessed Jan 4, 2022).
13 Dodd LE, Follmann D, Wang J, et al. Endpoints for randomized controlled clinical trials for COVID-19 treatments. *Clin Trials* 2020; **17:** 472–82.
14 Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. *Lancet* 2001; **356:** 373–80.
15 Lodi S, Phillips A, Lundgren J, et al. Effect estimates in randomized trials and observational studies: comparing apples with apples. *Am J Epidemiol* 2019; **188:** 1569–77.