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.

The scale, design, and use of a placebo control in this trial[8] mitigates this finding being an aberrant result and, consequently, there appears to be no future for subcutaneous interferon beta therapy in hospitalised patients with COVID-19. However, consideration of the trial context and the specifics of drug delivery could be valuable to inform future studies. The standard of care for COVID-19 has evolved rapidly and currently includes the use of systemic steroids following data from the RECOVERY study in June, 2020. The use of systemic steroids is an important consideration in the context of interferon beta treatment because corticosteroids directly affect IFN signalling, not only by reducing transcription of key factors including STAT1 and IRF9,[9] but also by their direct effects on the IFNβ receptor.[10] Therefore, corticosteroids, which were used as standard supportive care, could have abrogated the potential antiviral effects of interferon beta-1a in this trial.[8] Additional considerations are the subcutaneous route of drug delivery. The bioavailability of the drug at key sites of viral replication, especially in the respiratory epithelium, might not have been optimal compared with alternative routes, such as inhalation.[7] This factor could be particularly relevant in the context of pulmonary microvascular pathology leading to perfusion defects, which has been observed in patients with severe disease. These factors combined could have diluted or annulled any potential for beneficial effects of treatment in the study.[8]

The urgent need to develop better therapies for COVID-19 remains, and learnings from negative trials such as this[8] are important. Questioning current treatment strategies and the standards of care included when trials are designed will be key not only to identify efficacious therapies but also to ultimately define an optimised treatment plan for a disease that might continue to be prevalent for years to come.

TW reports being a founder and director of, and a shareholder in, my mhealth, outside of the submitted work; receiving research grants for trials of interferon beta and other COVID-19 treatments from AstraZeneca, GlaxoSmithKline, Synairgen, Bergenbio, UCB, NIHR, UKRI, and my mhealth within the submitted work; receiving consultancy fees from AstraZeneca, Synairgen, my mhealth, Valneva, OM Pharma, Boehringer Ingelheim, and Roche within the submitted work; receiving fees for attending lectures and meetings from Boehringer Ingelheim, AstraZeneca, Chiesi, Teva, and GlaxoSmithKline outside the submitted work; receiving travel support for attending conferences and meetings from Nutricia, AstraZeneca, Chiesi, Boehringer Ingelheim, and GlaxoSmithKline outside the submitted work; applying for patents for bacterial vaccines with GlaxoSmithKline and my mhealth, outside of the submitted work; being a member of a specialist chronic obstructive pulmonary disease advisory group within the submitted work; and being a member of the independent data monitoring committee of a vaccine study sponsored by Valneva and Synairgen within the submitted work.

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COVID-19-related ARDS: one disease, two trajectories, and several unanswered questions

Since the early days of medicine, doctors have described the natural history of disease and its different forms, primarily based on personal interpretation or intuition, in contrast to modern evidence-based medicine. For example, leptospirosis has been described with icterohaemorrhagic or pulmonary subtypes, but the existence of these phenotypes has been confirmed only relatively recently.[1] Recent improvements in analysis and comprehension have been made possible using modern statistical analysis. For example, a previous

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study showed that two distinct phenotypes of acute respiratory distress syndrome (ARDS) co-exist, but also—and more importantly for clinicians—that those phenotypes differed by their response to different treatment strategies.[2] Unfortunately, these strategies have not been validated in prospective randomised trials.

This modern side of critical care has received increased publicity during the COVID-19 pandemic. In the early phase of the pandemic, a strong debate between experts focused on the possible existence of two phenotypes and, more importantly, on modifications of mechanical ventilation settings according to each phenotype. Previous studies found different numbers of phenotypes,[3] but these had several problems, including a retrospective nature, taking place at a single centre only, or absence of external validation.

In *The Lancet Respiratory Medicine*, Lieuwe Bos and colleagues[4] reported that advanced statistical analyses cannot identify different phenotypes of COVID-19-related ARDS at the time of invasive mechanical ventilation initiation, in contrast to the results of previous studies.[3] Furthermore, COVID-19 appeared to have two distinct phenotypes in the early course of mechanical ventilation. Mechanical power and ventilatory ratio can help to identify these two phenotypes, supporting the results of a previous study.[5] Bos and colleagues should be congratulated for doing such studies in the difficult context of the COVID-19 pandemic. Although an increasing number of papers are dedicated to machine learning, few have as many quality criteria, and even fewer are informative for clinicians. However, I would like to raise several points in relation to the study.

First, COVID-19-related ARDS is a homogenous syndrome at initiation of mechanical ventilation, but it evolved during the early phase of ventilation into two distinct phenotypes. However, these phenotypes could be related to treatment heterogeneity in intensive care units, as acknowledged by the authors.

Second, the study[4] highlights the importance of measuring several respiratory parameters multiple times, including static respiratory measures (PaO_2/FiO_2, plateau pressure, driving pressure, and static compliance) and dynamic measures (mechanical power and ventilatory ratio). For example, concerning the high respiratory drive of patients with COVID-19, spontaneous breathing with a high respiratory rate will substantially influence mechanical power and could potentially artificially induce a more severe phenotype. A large proportion of guidelines advocate a neuromuscular blockade or prone session according to the level of PaO_2/FiO_2.[6] However, superiority of one measure over another has not been proven, leading clinicians to try to integrate them into each patient scenario.[2]

Third, unfortunately, the authors were unable to study biomarkers. Biomarkers are the main determinant of ARDS phenotypes that have previously been studied,[7] and have value regradless of physician ability to perform bedside measures (ie, static and dynamic ventilation indicators).

Finally, although multiple randomised trials have been dedicated to antiviral or immunomodulation treatments, the results of this study highlight that large randomised trials can be done to better define the best way to deliver ventilation to patients with ARDS, and to define the best settings for positive end-expiratory pressure for patients with ARDS (related or unrelated to COVID-19), despite a moderate level of evidence in ARDS guidelines[6] and COVID-19 panel opinion.[8] The same can be said for prone positioning—despite a mean PaO_2/FiO_2 ratio of 148 mm Hg (SD 75), only 30% of patients received prone positioning during the first day of mechanical ventilation.[4]

In conclusion, such promising results must be replicated in randomised trials. Currently, randomised trials only support the use of higher anticoagulation doses for patients with COVID-19 in hospital wards, in contrast to patients managed in critical care. However, such trials were not stratified for phenotypes. Identification of these phenotypes might be difficult at the bedside. Previously validated tools (including machine learning) could help to simplify this aspect of modern critical care research[9] and guidelines are available to develop such an approach in other areas of critical care.[10] Tailoring treatment to phenotypes could be a good balance between evidence-based medicine, which requires many patients, and clinical personalised medicine.

I declare no competing interests.

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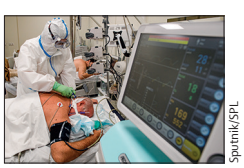
Awake prone positioning in COVID-19: is tummy time ready for prime time?

Prone positioning reduces mortality in moderate to severe acute respiratory distress syndrome requiring invasive mechanical ventilation.[1,2] Before COVID-19, evidence supporting prone positioning for awake non-intubated patients with hypoxaemic respiratory failure was limited to small case series.[3] Early in the COVID-19 pandemic, use of awake prone positioning (or so-called tummy time) to avoid intubation quickly gained traction in the media.[4] Several observational studies reported that prone positioning improved oxygenation in awake non-intubated patients with COVID-19.[5,6] Globally, many health-care jurisdictions adopted awake prone positioning for COVID-19, despite no high quality evidence from randomised controlled trials of improved clinically meaningful outcomes, including invasive mechanical ventilation or mortality. Of note, the Surviving Sepsis Campaign Guidelines highlighted this equipoise, stating that there was insufficient evidence to recommend awake prone positioning for COVID-19.[7]

In the *Lancet Respiratory Medicine*, Stephan Ehrmann and colleagues[8] report a meta-trial on awake prone positioning to reduce intubation or death in patients with COVID-19. The meta-trial pooled individual patient-level data from six independent randomised controlled trials with harmonised eligibility criteria, randomisation procedures, and outcomes. 1126 patients with COVID-19 and hypoxaemic respiratory failure from six countries were randomly assigned to either awake prone positioning or standard care. The composite primary outcome was treatment failure (either intubation or death within 28 days). Composite outcomes generally are controversial, with misplaced belief that combining events will increase power, and such outcomes ignore additional problems that treatment effects across components might be unequal in magnitude and importance. However, Ehrmann and colleagues' two outcomes are reasonable and clinically meaningful: awake prone positioning reduced treatment failure (relative risk 0·86, 95% CI 0·75–0·98), primarily driven by a reduction in intubation (Hazard ratio [HR] 0·75, 95% CI 0·62–0·91), compared with usual care, with strong overlap between the components (almost three quarters of deaths were preceded by intubation).

This novel meta-trial study design has several notable strengths. It is more efficient, cheaper, and quicker to initiate than a single multinational trial.[9] These advantages are particularly important during a pandemic, and the authors deserve praise for their innovation and organisation to rapidly answer this important clinical question. However, the study was necessarily open (unblinded). Therefore, to minimise potential bias in primary outcome assessment, they used a composite of all-cause mortality (which was completely objective) and need for intubation (by standardising the potentially subjective criteria for intubation). The study used a group sequential design, using a Kim-DeMets alpha spending function to reduce the chance of a false positive treatment effect with multiple interim analyses, scheduling four of them and permitting early stopping. The study did indeed terminate for benefit at the third scheduled interim analysis, planned for 600 participants with complete



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