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.

than in non-severe cases (66% *vs* 36%). Although these data are from few studies and few cases with short-term follow-up, taken together, data seem to indicate that prevalence of impaired DLCO decreases over time, as shown by Wu and colleagues. The systematic review[6] also found restrictive spirometry patterns in 15% patients and obstructive spirometry patterns in 7% patients.

Wu and colleagues focussed on respiratory manifestations of patients without comorbidities or more advanced disease, half of whom were older than 60 years and were admitted to hospital in the first quarter of 2020. The findings on lung function and how these are reflected in functional tests therefore apply to a selected population at the beginning of the pandemic and both presenting characteristics and case management have evolved since. We also do not know whether the findings are specific to COVID-19 or possibly shared by other infections with similar acute manifestations.

When reading isolated papers, we should remind ourselves that we are looking at a snapshot of one feature in a certain population, context, and timepoint while the details of complications after acute COVID-19 are still unfolding. Each piece of information increases knowledge but we need to agree on common methodologies, generate robust data, and improve our capacity to share, absorb, and process high volumes of research output more efficiently and quickly to be able to describe the novel syndrome. These steps will enable us to distinguish between transient and permanent patterns, differentiate real heterogeneity from bias and, importantly, to identify practical approaches to prevent, minimise and manage long-term COVID-19 complications.

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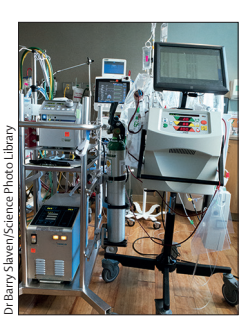
Cytokine adsorption during ECMO for COVID-19-related ARDS



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A syndrome of dysregulated systemic immune overactivation has been described in patients with COVID-19. Initially a cytokine storm paradigm[1] was proposed, however subsequently, it has been shown that systemic concentrations of inflammatory cytokines, although elevated in patients with severe COVID-19, are not as high as has been reported in patients with other causes of the acute respiratory distress syndrome (ARDS).[2] Despite this, data to support the use of immunomodulatory therapies, such as corticosteroids[3] and interleukin-6 (IL-6) receptor antagonists,[4] in patients critically ill with COVID-19 have emerged. With this in mind, it might seem plausible that the direct removal of circulating inflammatory mediators could offer a way to reset the cytokine milieu and provide clinical benefit.

In an important test of this hypothesis, in *The Lancet Respiratory Medicine*, Alexander Supady and colleagues[5] examined the efficiency of extracorporeal cytokine adsorption for the removal of IL-6. In their single-centre, pilot trial, the authors randomly allocated patients with COVID-19-related ARDS receiving venovenous extracorporeal membrane oxygenation (ECMO) to cytokine adsorption (n=17) for 72 h. Those not undergoing cytokine adsorption on ECMO served as controls (n=17) and the serum IL-6 concentrations were compared at 72 h. Mediator removal is concentration dependent and cytokine adsorption removes not only proinflammatory and anti-inflammatory mediators but many other biological substances (up to 55 kDa) as well.

There was no difference in the primary outcome (serum IL-6 concentrations measured at 72 h) between

groups. By day 30, 13 (76%) of 17 patients in the intervention group and three of (18%) 17 in the control group had died—a marked difference in mortality favouring the control group. The authors did several exploratory post-hoc analyses in light of this finding, yet they could not establish specific causative mechanisms implicating harm from the intervention itself. Pending further evidence, as Supady and colleagues note, the use of cytokine adsorption in patients receiving ECMO for COVID-19-related ARDS should be confined to research studies. Even before this trial, the Extracorporeal Life Support Organization's COVID-19 guidelines did not recommend extracorporeal cytokine adsorption outside the context of a clinical trial.[6] The authors have stopped recruitment for their multicentre version of this trial (CYCOV-II; NCT04385771) and it might be challenging to establish equipoise for future trials in a similar setting.

Why would such a plausible intervention turn out not only to be inefficient but also potentially harmful? First, the inability to remove IL-6 is unexpected, although smaller studies in the past have reported similar findings.[7] There were no reported technical issues that might have led to reduced IL-6 clearance. Second, the median IL-6 concentration at baseline was 357·0 pg/mL, which is substantially lower when compared with studies that reported better IL-6 clearance[8] and concentration dependent clearance might be at play. Notwithstanding this, both groups had reductions in IL-6 concentrations at 72 h (median, baseline [72 h], 357·0 pg/mL [98·6 pg/mL] *vs* 289·0 pg/mL [112·0 pg/mL]). It is unclear whether the reductions are due to the effects of ventilation strategies during ECMO, treatment effects of other therapies, or potential cytokine sequestration in the ECMO circuit. It might also simply be related to improvements seen over time, as reported previously.[9] Third, timing of treatment initiation and patient inclusion criteria in this trial might be pertinent. It might be too late to see a benefit from cytokine adsorption when initiated in patients already receiving ECMO. In contrast, IL-6 receptor antagonists were shown to be more effective when critically ill patients were treated early[4] (within 24 h after commencing organ support in the intensive care unit). Fourth, the patients in this study exhibited highly variable IL-6 concentrations at baseline and it is difficult to ascertain whether outcomes would be different if the trial had been enriched with patients having higher IL-6 concentrations, for instance greater than 1000 pg/mL. This highlights the need to develop point of care assays for cytokines such as IL-6, which is being tested in the ongoing point-of-care assay to identify phenotypes in the ARDS (PHIND) trial (NCT04009330). Fifth, systemic cytokine concentrations might be less relevant, and it is possible that local pulmonary inflammation could be a more useful indicator of which patients will benefit from cytokine adsorption. Lastly, initiation of cytokine adsorption might have unknown interactions with other immunomodulatory therapies, such as corticosteroids and IL-6 receptor antagonists. The effect of cytokine adsorption on the concentrations of these vital disease modifying drugs is unclear and there are reports of suboptimal antimicrobial concentrations during cytokine adsorption.[10]

In the end, the cause of the apparent harm of the intervention is unknown. It is important to reiterate that, no matter how compelling the mechanisms supporting a proposed intervention, the intervention must still be subjected to a well designed clinical trial. The authors should be commended for doing precisely that. The study by Supady and colleagues, clearly highlights the potential risks of cytokine adsorption in patients receiving ECMO for COVID-19-related ARDS and the importance of minimising iatrogenic harm by testing promising interventions in clinical trials.

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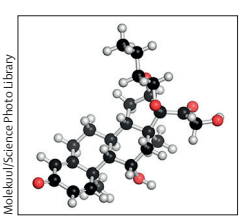
Early treatment with inhaled budesonide to prevent clinical deterioration in patients with COVID-19



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In most individuals, infection with SARS-CoV-2 is either asymptomatic or produces mild illness (COVID-19) that resolves spontaneously; yet, a small proportion of patients with COVID-19 develop severe disease, require hospitalisation (often in a critical-care setting), and die.[1] A dysregulated type I interferon response to SARS-CoV-2 with overproduction of proinflammatory cytokines seems to be a key pathogenic mechanism underlying progression to severe COVID-19 and death.[1] Thus, controlling this excessive inflammatory response might potentially prevent disease progression.

Inhaled corticosteroids have been used for more than 30 years in the treatment of several inflammatory respiratory conditions, such as asthma and chronic obstructive pulmonary disease (COPD), to control dysregulated airway inflammation, with a good efficacy and safety track record.[2,3] In the context of the current pandemic, it was noted that patients with asthma and COPD appear to be under-represented among COVID-19-infected individuals seeking emergency care, and it was hypothesised that the chronic use of inhaled corticosteroids might have controlled the excessive inflammatory response induced by SARS-CoV-2 in these individuals.[4] Yet, a later observational study did not support this possibility.[5]

In *The Lancet Respiratory Medicine*, Sanjay Ramakrishnan and colleagues[6] explored this hypothesis in a prospective, randomised, open-label, phase 2 trial that compared treatment with 1600 µg (two puffs of 400 µg to be taken twice per day) of inhaled budesonide, a widely used inhaled corticosteroid, versus usual care in 146 adults within 7 days of the onset of mild COVID-19 symptoms.[6] The primary outcome of the trial was urgent care visit, emergency department assessment, or hospitalisation.[6] Results showed that, in the per-protocol analysis, this primary outcome occurred in ten (14%) participants in the usual care group and one (1%) participant in the budesonide group (difference in proportions 0·131, 95% CI 0·043–0·218; p=0·004), indicating a relative risk reduction of 91% for budesonide; importantly, the number needed to treat with budesonide to reduce COVID-19 deterioration was eight patients.[6] Secondary outcome results showed that clinical recovery was also significantly reduced in the budesonide group.[6] Based on these observations, the authors concluded that early administration of inhaled budesonide in patients infected with SARS-CoV-2 reduced the likelihood of needing urgent medical care and enhanced clinical recovery.[6]

Ramakrishnan and colleagues' study is important because it is the first to show that an easily accessible therapeutic intervention is effective to prevent COVID-19 clinical deterioration. However, the study has a potentially important limitation that needs careful consideration: it was terminated early due to "the impact of the national pandemic control measures and national prioritisation rules for clinical research trials in the UK"[6] and, as a result, the number of randomised patients (n=146) was much lower than that estimated originally (n=398).[6] Although