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.

diminished. Any gain in earlier discharge would therefore not exceed 24 h.

The SIMPLE trial illustrated several bigger issues in the management of patients with MPE. First, the trial highlighted the absence of any robust comparator as the BTS recommendation is not based on data—part of the evidence-free reality clinicians face when carrying out pleurodesis. How often the BTS recommendation is followed in real-world practice is unknown.

Second, clinicians long for a reliable way to predict pleurodesis success. The SIMPLE study focused on evaluating length of hospital stay with ultrasonography versus the BTS volume cutoff approach; the trial did not directly compare the accuracy of either method. Of the 200 patients evaluable at 3 months, 61 had pleurodesis failure (27 [29·7%] of 91 in the ultrasonography group; 34 [31·2%] of 109 in the standard care group); neither approach seemed to be ideal. Separating how many patients fulfilled the criteria and later relapsed (method failure) from those who never reached the cutoff (intrinsic pleurodesis failure) would provide important insights. Ultrasonography has limitations: it can only assess gliding of the parietal (but not mediastinal or fissural) pleura, is operator-dependent and position-dependent, and gliding can be absent in conditions (eg, chronic obstructive pulmonary disease or bullous disease) other than pleurodesis. If method failure rates were high, novel approaches (beyond ultrasonography or fluid cutoff) should be the next goal. Better ways to enhance pleurodesis success and patient selection are warranted if intrinsic pleurodesis failure predominates.

Third, the SIMPLE trial showed that patients undergoing talc pleurodesis endured several days of hospital admission and invasive procedures; yet one-third had pleurodesis failure within 3 months, requiring further drainages, presumably including the 55 (18%) of 313 patients with trapped lung. If reducing length of hospital stay is important, the data from this trial lend further support to the use of an indwelling pleural catheter (with or without talc instillation via the catheter) and ambulatory fluid drainage—an approach shown to save lifetime hospitalisation days[10] irrespective of trapped lung.

Since Norman Bethune published on the use of talc poudrage in 1935, talc pleurodesis has been and continues to be carried out worldwide, but with minimal knowledge about how best to deliver it. More efforts like the SIMPLE trial are desperately needed.

I have led clinical trials for which Rocket Med has provided free drainage kits for patients. I am an Australian Medical Research Future Fund Practitioner Fellow.

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Intravenous immunoglobulin therapy for COVID-19 ARDS

Published **Online**
November 11, 2021
https://doi.org/10.1016/S2213-2600(21)00450-1

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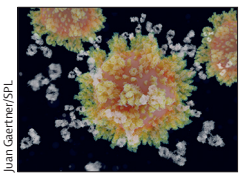
To date, the SARS-CoV-2 virus and COVID-19 has killed more than 4 million individuals worldwide. Morbidity and mortality arise from direct viral-induced injury to multiple organ systems, a dysregulated systemic immune response, and thrombosis.[1] Pharmacological immunomodulation has decreased mortality in severe COVID-19. Dexamethasone was the first drug to significantly reduce the risk of death in patients hospitalised with COVID-19 requiring supplemental oxygen.[2] Since then, IL-6 antagonists[3] and the Janus kinase inhibitor, baracitinib,[4] have been shown to reduce COVID-19-related mortality.[5]


Juan Gaertner/SPL

In the *Lancet Respiratory Medicine*, Aurélien Mazeraud and colleagues[6] report the results of a multicentre, double-blind, placebo-controlled, phase 3 trial of 146 patients with moderate-to-severe COVID-19-associated acute respiratory distress syndrome (ARDS) who received either intravenous immunoglobulin (IVIG; 69 [47%] patients) or placebo (77 [53%] patients).[6] IVIG is an attractive adjuvant for the management of severe COVID-19-associated ARDS because of its ability to simultaneously modulate multiple immune compartments. IVIG can neutralise autoantibodies, inhibit activation of the complement cascade, impair the costimulatory and antigen presenting capabilities of dendritic cells, inhibit T helper 17 cell proliferation, and expand regulatory T cell populations.[7] Because dendritic cell, B cell, and T cell dysregulation is associated with severe COVID-19,[8] the multimodal effects of IVIG make it a good therapeutic candidate for patients hospitalised with COVID-19.

The patients included in the study reflected the wider population of critically ill patients with COVID-19-associated ARDS. 103 (71%) patients were male, and 87 (60%) patients were 65 years old or older. The mean body-mass index in both groups was more than 30 kg/m^2. Patients were intubated at a median of 8 days after symptom onset, randomly assigned within 72 h of initiating invasive mechanical ventilation, and met the moderate-to-severe hypoxaemia categories of the Berlin definition of ARDS. The exclusion criteria were acute renal failure, pregnancy, allergy to IVIG, or immunoglobulin A deficiency. 121 (83%) patients received antibiotics, and 104 (71%) patients received corticosteroids, which is expected given the enrolment period. Baseline demographics, severity of illness, and indices of respiratory failure were similar between the placebo group and the IVIG group. Neither the primary outcome of ventilator-free days over 28 days nor 90-day mortality were different between the two groups. Of note, the number of deaths in the placebo group at day 28 (20 [26%] patients) was much lower than the predicted 28-day mortality rate of 50%, but the observed mortality was similar to the 29% mortality reported in the dexamethasone group of the RECOVERY trial.[2] Numerically, both 28-day mortality and median time to extubation both favoured the placebo group, although the confidence intervals were wide.

There was a trend towards increased serious adverse events in the IVIG group, but the difference was not significant. Three-times as many patients in the IVIG group (ten [15%] patients) compared with the placebo (three [4%] patients) developed deep venous thrombosis or pulmonary embolism. IVIG is associated with an increased risk of thromboembolism, potentially due to infusion-related transient hyperviscosity syndrome. Reduction of infusion rates, coadministration of hydration, and therapeutic enoxaparin can ameliorate these risks.[9] This trial infused IVIG slowly over 8 h, but therapeutic anticoagulation and hydration were not part of the trial protocol, which was reasonable in this patient population. However, the hypercoagulable state of COVID-19 probably increased the risk of IVIG associated thrombosis. Additionally, IVIG induced immune haemolytic anaemia was reported in two (3%) patients. Although the risk of thrombosis and haemolytic anaemia were not statistically significant, their presence raises the question of harm without a perceived potential benefit.

Patients in the IVIG group had increased IL-13 concentration at day 7 and an increased proportion of CD4 T regulatory and memory cells at day 28, but interpretation of these findings is challenging. IL-13 has been reported to both improve lung injury[10] and worsen pulmonary fibrosis.[11] Most deaths in the trial occurred before day 28; as a result, interpretation of the CD4 T regulatory and memory cell findings is limited by survivor bias.

The question of whether a subgroup of patients with severe COVID-19 might benefit from IVIG remains. Mazeraud and colleagues[6] postulate that IVIG might prevent progression of severe COVID-19 to ARDS or be beneficial in the recovery phase, but replacement doses of IVIG might benefit patients with hypogammaglobulinaemia due to either a primary immunodeficiency or secondary hypogammaglobulinaemia due to B cell depleting drugs, such as rituximab. Hypogammaglobulinaemia is associated with an increased risk of encapsulated bacterial organisms, and hypogammaglobulinaemic patients with septic shock are at increased risk of death.[12] Although plausible that replacement doses of IVIG could benefit critically ill patients with hypogammaglobulinaemia, additional studies are required.

In conclusion, IVIG did not significantly improve outcomes in moderate-to-severe COVID-19-associated ARDS and was associated with an increase in

thromboembolic adverse events. Future work might identify subgroups of patients with acute COVID-19 who would benefit from IVIG, but the current evidence does not support use of IVIG in COVID-19-associated ARDS.

EMW reports support from the National Institutes of Health (NIH); and reports research funding and consulting fees from Boehringer-Ingelheim, outside of the submitted work. MAM reports funding from the NIH, outside the submitted work; and consulting fees from Citrus Pharmaceuticals, outside the submitted work.

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Vaccine efficacy and immune interference: co-administering COVID-19 and influenza vaccines

As we head towards the second anniversary of the COVID-19 pandemic, attention widens to encompass the array of unforeseen health-care consequences of these unprecedented times and measures. In this context, efforts have been made to analyse data and predict how the winter months will look in terms of the interplay between infections by SARS-CoV-2 and other common respiratory viruses, influenza, and respiratory syncytial virus. To an extent, there is still no consensus in the scientific and medical communities as to the risk and impact of concomitant respiratory infections: on the one hand, lockdown and other mitigations that have limited the spread of COVID-19 would be predicted to have limited influenza and respiratory syncytial virus too.[1,2] On the other hand, children especially might have heightened vulnerability, having now missed out on nearly 2 years of the normal interactions that prime immunity, and adults will have seen their immunity wane.[3,4] Certainly, a paucity of data exist on which to base any accurate predictions about which influenza strains are most likely to circulate this coming winter. One must also consider the rather uncharted territory of the interactive effects of respiratory pathogens: not much is known about the consequences of co-infection by these pathogens, but since each is associated with somewhat differently nuanced lung inflammatory pathology, serious additive effects might be anticipated. At a time when many countries have national programmes for COVID-19 vaccination, this uncertainty has raised the logistical question of what might be the nature of the influenza vaccine plus SARS-CoV-2 vaccine co-administration programmes. In some respects, no better time has occurred to roll out such respiratory vaccination programmes. Public confidence in vaccines is high, having largely overcome a considerable degree of hesitancy in many countries, and national logistics for vaccine programme delivery have been impressive.

The NVX-CoV2373 (ie, Novavax) vaccine is an adjuvanted recombinant protein vaccine, which has performed rather well in terms of safety, immunogenicity, and efficacy in clinical trials.[5] So what happens if you co-administer a seasonal influenza vaccine in one arm and a COVID-19 vaccine in the other arm? To answer this question in *The Lancet Respiratory*


Jim West/Science Photo Library

Published **Online**
November 17, 2021
https://doi.org/10.1016/S2213-2600(21)00438-0

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