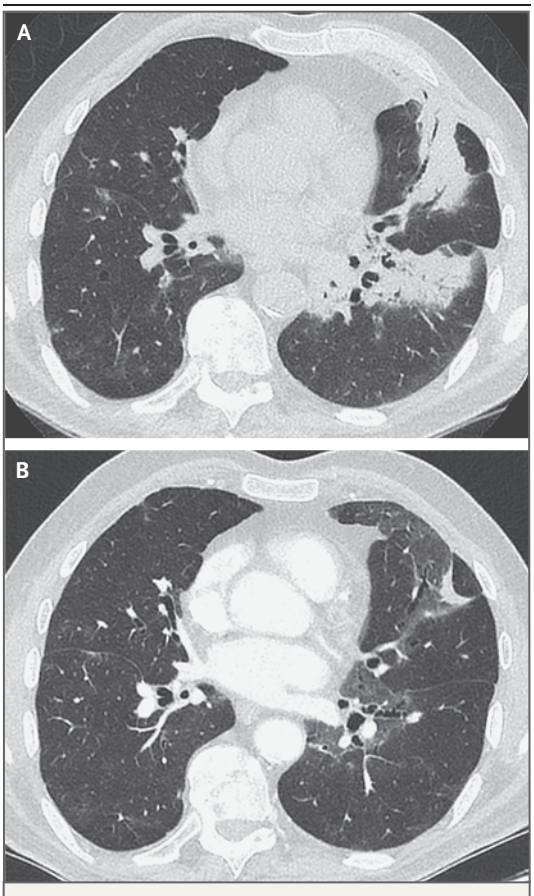

Figure 1. Radiologic Imaging before and during Treatment with Vasoactive Intestinal Peptide.

Panel A shows an axial slice image from high-resolution computed tomography (CT) performed after glucocorticoid treatment. Widespread consolidations can be seen, a finding compatible with immune checkpoint inhibitor pneumonitis. Panel B shows an axial slice image from high-resolution CT conducted approximately 90 days after initiation of treatment with inhaled vasoactive intestinal peptide, showing a marked reduction in consolidations.

and did not influence lymphocyte subtypes in peripheral blood (Table S1). Eight weeks after cessation of the treatment, the patient had systemic nonpulmonary progression of melanoma disease.

Our findings support inhaled vasoactive intestinal peptide as a local therapy to reduce the alveolar inflammation found in patients with immune checkpoint inhibitor pneumonitis. Whether this therapy has an influence on tumor progression cannot be determined on the basis of this case. However, further studies are indicated to investigate whether vasoactive intestinal peptide may be a therapeutic option for immune checkpoint inhibitor pneumonitis.

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Guillain–Barré Syndrome Associated with SARS-CoV-2

TO THE EDITOR: From February 28 through March 21, 2020, in three hospitals in northern Italy, we examined five patients who had Guillain–Barré syndrome after the onset of coronavirus disease 2019 (Covid-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). During that period, an estimated 1000 to 1200 patients with Covid-19 were admitted to these hospitals. Four of the patients in this series had a positive nasopharyngeal swab for SARS-CoV-2 at the onset of the neurologic syndrome, and one had a negative nasopharyngeal swab and negative bronchoalveolar lavage but subsequently had a positive serologic test for the virus. Detailed case reports are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.

The first symptoms of Guillain–Barré syn-

Table 1. Characteristics of Five Patients with Guillain–Barré Syndrome after the Onset of Covid-19.*

Patient No.	Onset of Neurologic Syndrome	Neurologic Signs and Symptoms	CSF Findings†	Antiganglioside Antibodies‡	MRI Results	Treatment and Outcomes at Week 4
1	7 Days after fever, cough, and ageusia	Flaccid areflexic tetraplegia evolving to facial weakness, upper-limb paresthesia (36 hr), and respiratory failure (day 6)	Day 2 (first lumbar puncture): normal protein level; no cells; negative PCR assay for SARS-CoV-2 Day 10 (second lumbar puncture): protein level, 101 mg/dl; white-cell count, 4 per mm^3; negative PCR assay for SARS-CoV-2	Negative	Head: normal Spine: enhancement of caudal nerve roots	Received 2 cycles of IVIG; had poor outcomes, including persistence of severe upper-limb weakness, dysphagia, and lower-limb paraplegia
2	10 Days after fever and pharyngitis	Facial diplegia and generalized areflexia evolving to lower-limb paresthesia with ataxia (day 2)	Day 3: protein level, 123 mg/dl; no cells; negative PCR assay for SARS-CoV-2	Not tested	Head: enhancement of facial nerve bilaterally Spine: normal	Received IVIG; had improvements, including decrease in ataxia and mild decrease in facial weakness
3	10 Days after fever and cough	Flaccid tetraparesis and facial weakness evolving to areflexia (day 2) and respiratory failure (day 5)	Day 3: protein level, 193 mg/dl; no cells; negative PCR assay for SARS-CoV-2	Negative	Head: normal Spine: enhancement of caudal nerve roots	Received 2 cycles of IVIG; had poor outcomes, including ICU admission owing to neuromuscular respiratory failure and flaccid tetraplegia
4	5 Days after cough and hyposmia	Flaccid areflexic tetraparesis and ataxia (day 4)	Day 5: normal protein level; no cells; negative PCR assay for SARS-CoV-2	Not tested	Head: normal Spine: normal	Received IVIG; had mild improvement but unable to stand 1 mo after onset
5	7 Days after cough, ageusia, and anosmia	Facial weakness, flaccid areflexic paraplegia (days 2–3), and respiratory failure (day 4)	Day 3: protein level, 40 mg/dl; white-cell count, 3 per mm^3; CSF:serum albumin ratio, 1.2%; negative PCR assay for SARS-CoV-2	Negative	Head: not performed Spine: normal	Received IVIG and plasma exchange; had bacterial pneumonia during IVIG treatment, which delayed plasma exchange

* Covid-19 denotes coronavirus disease 2019, CSF cerebrospinal fluid, ICU intensive care unit, IVIG intravenous immune globulin, MRI magnetic resonance imaging, PCR polymerase chain reaction, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

† On CSF analysis, all the patients had a normal glucose level and IgG index and a polyclonal pattern on electrophoresis. The normal range for the protein level is 15 to 45 mg per deciliter.

‡ An enzyme-linked immunosorbent assay was used to test for antibodies to GM1, GQ1b, and GD1b.

drome were lower-limb weakness and paresthesia in four patients and facial diplegia followed by ataxia and paresthesia in one patient (Table 1). Generalized, flaccid tetraparesis or tetraplegia evolved over a period of 36 hours to 4 days in four patients; three received mechanical ventilation. The interval between the onset of symptoms of Covid-19 and the first symptoms of Guillain–Barré syndrome ranged from 5 to 10 days (Table 1 and Fig. S1 in the Supplementary Appendix). None of the patients had dysautonomic features.

On analysis of the cerebrospinal fluid (CSF), two patients had a normal protein level and all the patients had a white-cell count of less than 5 per cubic millimeter. Antiganglioside antibodies were absent in the three patients who were tested. In all the patients, a real-time polymerase-chain-reaction assay of the CSF was negative for SARS-CoV-2. Results of electrophysiological studies are shown in Table S1. Compound muscle action potential amplitudes were low but could be obtained; two patients had prolonged motor distal latencies. On electromyography, fibrillation potentials were present in three patients initially; in another patient, they were absent initially but were present at 12 days. The findings were generally consistent with an axonal variant of Guillain–Barré syndrome in three patients and with a demyelinating process in two patients.[1] Magnetic resonance imaging, performed with the administration of gadolinium, showed enhancement of the caudal nerve roots in two patients, enhancement of the facial nerve in one patient, and no signal changes in nerves in two patients. Additional laboratory findings are shown in Table S2.

All the patients were treated with intravenous immune globulin (IVIG); two received a second course of IVIG and one started plasma exchange. At 4 weeks after treatment, two patients remained in the intensive care unit and were receiving mechanical ventilation, two were undergoing physical therapy because of flaccid paraplegia and had minimal upper-limb movement, and one had been discharged and was able to walk independently.

The interval of 5 to 10 days between the onset of viral illness and the first symptoms of Guillain–Barré syndrome is similar to the interval seen with Guillain–Barré syndrome that occurs during or after other infections.[2] Although many infectious agents have been associated with Guillain–Barré syndrome, there may be a propensity for preceding infection with *Campylobacter jejuni*, Epstein–Barr virus, cytomegalovirus, and Zika virus. There have been reports of an association between Guillain–Barré syndrome and coronavirus infections.[3,4]

On the basis of this observational series involving five patients, it is not possible to determine whether severe deficits and axonal involvement are typical features of Covid-19–associated Guillain–Barré syndrome. We could not determine the effect of reduced vital capacity due to neuromuscular failure from Guillain–Barré syndrome in these patients, but such an effect might be considered if findings on chest imaging are not commensurate with the severity of respiratory insufficiency. Guillain–Barré syndrome with Covid-19 should be distinguished from critical illness neuropathy and myopathy, which tend to appear later in the course of critical illness than Guillain–Barré syndrome.

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This letter is dedicated to the loving memory of Dr. Arrigo Moglia.

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Oxygen Therapy in the ICU

TO THE EDITOR: Mackle et al. (March 12 issue)[1] report that ICU-ROX (Intensive Care Unit Randomized Trial Comparing Two Approaches to Oxygen Therapy) showed that in patients undergoing mechanical ventilation, there was no significant difference in ventilator-free days between those who received conservative oxygen supplementation to avoid systemic hyperoxemia and those who received usual oxygen therapy. Although patients who had received invasive mechanical ventilation or noninvasive ventilation for 2 hours or more before enrollment were excluded, there was no mention or documentation of the fraction of inspired oxygen (F_{IO_2}) received before the trial interventions. This may be a considerable omission and possible confounder, since even short durations of hyperoxemia can affect outcomes.[2,3]

In addition, the authors chose to decrease the F_{IO_2} in the conservative-oxygen group when the oxygen saturation, as measured by pulse oximetry (S_{PO_2}), reached 97%. Pulse oximeters have an absolute accuracy of approximately 3%,[4] which means that some patients in the conservative-oxygen group could have had an oxygen saturation of up to 100% and, accordingly, a partial pressure of arterial oxygen (P_{AO_2}) higher than 150 mm Hg. The choice of an upper limit of 95% instead would have yielded a P_{AO_2} of 85 to 115 mm Hg, which would have avoided any potential hyperoxemia. These possible confounders may vitiate the clinical implications of this trial.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In the $LOCO_2$ (Liberal Oxygenation versus Conservative Oxygenation in Acute Respiratory Distress Syndrome) trial conducted by Barrot et al. (March 12 issue)[1] comparing liberal oxygen therapy with conservative oxygen therapy in patients with acute respiratory distress syndrome (ARDS), there was a signal of increased mortality in the conservative-oxygen group. This signal was part of the reason why the trial was stopped prematurely. We think the higher incidence of prone positioning during ventilation in the liberal-oxygen group than in the conservative-oxygen group (in 51.0% vs. 34.3% of the patients) should be considered as a reason for the difference in mortality between the two groups. Since we learned from the PROSEVA (Proning Severe ARDS Patients) trial[2] that prone ventilation may lead to survival benefits in patients with ARDS, it is reasonable to assume that the between-group difference of 16.7 percentage points in the use of prone positioning in the current trial may have confounded the trial results. Can the authors provide an analysis controlling for the use of prone positioning?