

Successful treatment of patients severely ill with COVID-19

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Dear Editor,

Since the outbreak of COVID-19 in December 2019 in Wuhan city, China,¹ transmission of SARS-COV-2 has been documented in over 200 countries, with 82,719 cases confirmed in China and 1,991,810 in the rest of world by 17 April 2020.² At the beginning of the outbreak, severe illness, characterised by a high rate of mortality and serious clinical manifestations, was found in 18.5% of cases.^{1,3-7} Adequate treatment protocols for severely ill patients were thus urgently needed. Rapid updates of WHO guidelines,² along with national criteria and treatment protocols⁸ were issued to improve treatment outcome.

Here, we describe a prospective observational study to better illustrate the clinical features, treatment challenges and outcomes of patients severely ill with COVID-19 presenting to Suzhou 5th Hospital, Suzhou, China, between January 8 and February 11 2020. According to the national diagnosis and treatment guidelines (7th version), severe illness was defined as the presence of at least one of the following criteria: respiratory distress (respiratory rate ≥ 30 times/min); and oxygen saturation in the resting state $\leq 93\%$; arterial oxygen partial pressure/fractional inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ≤ 300 mmHg. Antiviral treatment comprised 10 days of lopinavir/ritonavir (LPV/r) and/or arbidol.⁸ To prevent secondary bacterial infection, broad-spectrum antibiotics (fluoroquinolones [FQs], second- or third-generation cephalosporins) were empirically initiated according to the 2019 ATS/IDSA guidelines.⁹ Corticosteroid therapy (methylprednisolone 40–120 mg per day) was given as supportive care.⁸ Oxygen support was administered to patients according to the severity of hypoxaemia. All patients were assessed daily by medical examination (CT scanning, routine blood testing, etc.) throughout the course of treatment. Real-time polymerase chain reaction (RT-PCR) tests for SARS-CoV-2 were repeated every 3 days until they were negative, and then every other day to confirm viral clearance before hospital discharge or discontinuation of isolation. Outcome measures included time to viral clearance, duration of ICU stay, total length of hospital stay, adjunct therapies and procedures used, and complications. Viral clearance was defined as two consecutive negative results on RT-PCR on at least two swab specimens collected at an interval of more than 1 day. Discharge was decided by an expert panel based on viral clearance results and restored vital signs. Patients' medical records were used to prospectively collect sociodemographic, clinical and laboratory data on admission and thereafter.

Overall, 87 patients with COVID-19 were admitted to the hospital. Thirteen patients were severely ill and were included in the study. Among these, 10 were male; the median age was 51 years (range 28–70); four patients had comorbidities (two with diabetes mellitus, one with diabetes mellitus and hypertension, one with chronic obstructive pulmonary disease).

According to the Berlin definition,¹⁰ acute respiratory distress syndrome (ARDS) on admission was diagnosed to be mild in three patients, moderate in one and severe in one. Four patients with ARDS and one without ARDS were treated with non-invasive

positive pressure ventilation (NIPPV) to promote ventilation and reduce the damage from barotrauma. After treatment with NIPPV for a median of 8 days (interquartile range [IQR] 5–13), lung function recovered with a significant improvement in blood oxygen saturation and PaO₂/FiO₂. Support was subsequently changed to high-flow nasal cannula oxygen therapy (HFNC). As an example, patient #001, required 8 days of NIPPV (spontaneous/timed mode), inspiratory positive airway pressure (IPAP) of 12 cm H₂O, expiratory positive airway pressure (EPAP) of 6 cm H₂O, respirator frequency of 20 breaths/min and FiO₂ of 85%; subsequently, blood oxygen saturation gradually increased from 80% to >90%, heart rate decreased from 130 beats/min to 100 beats/min and PaO₂/FiO₂ increased from 64.3 mmHg to 215 mmHg.

Antiviral treatment was administered for a median time of 10 days (IQR 7–11). Three patients received LPV/r alone, three patients received arbidol and six patients received both drugs concomitantly. Among those who received LPV/r, only 2/9 patients had obvious gastrointestinal symptoms (diarrhea and nausea). No relevant adverse drug reactions were observed among the other patients. The median time to viral clearance was 13 days (IQR 7–15).

Empirical treatment of potential secondary bacterial infections comprised treatment with FQs alone (mainly moxifloxacin, $n = 3$), or with second- or third-generation cephalosporins in addition to FQs ($n = 10$). One case of *Klebsiella pneumoniae* on Day 3 of treatment and a case of *Acinetobacter baumannii* complex found on Day 5 were detected. During the acute stage of infection, 11 patients were treated with low-dose methylprednisolone. In five patients, liver function testing showed increased alanine aminotransferase and aspartate aminotransferase levels. One patient (#001), previously diagnosed with hypertension and diabetes, showed signs of cardiac injury. For enteral nutritional support, enteral nutritional suspension (total protein-medium chain triglycerides, 1.5 kcal/ml) was given to two patients (#001, #005) requiring flow diet of 500–1000 ml per day for 3 consecutive days.

In our study, treatment of severely ill patients with COVID-19 comprised medication with antiviral drugs, prevention of secondary bacterial infection and close monitoring of vital signs with timely support for organ function. All 13 patients recovered lung function within an average of 8 days (IQR 6–11). Repeated CT scans showed improved lesions after a median of 26 days' (IQR 18–29) treatment. One pregnant patient

(#009) successfully gave birth to a healthy baby who tested negative for COVID-19 (Figure).

Our study confirmed that NIPPV is effective in patients with mild to moderate ARDS by reducing pulmonary ventilation perfusion mismatch and the need for tracheal intubation in those with respiratory failure.^{11,12} However, the effectiveness of NIPPV in severe ARDS requires further study. At present, there is no vaccine or licensed antiviral drugs for COVID-19. If we compare previous antiviral regimens used to treat Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), which are generally used to guide COVID-19 treatment^{13,14} with the study treatment regimen, no antiviral drug has obvious advantages in viral clearance. However, the use of LPV/r causes gastrointestinal adverse reactions in some patients. Other antiviral drugs (e.g., remdesivir) that can be administered orally as well as intravenously therefore merit further assessment of their effectiveness and toleration in randomised clinical trials from different settings. A challenge is to select and properly define the standard of care for the control arm of a clinical trial.

Our observation based on 13 severely ill patients showed that short-term administration of low-dose methylprednisolone drugs as adjunctive therapy may be effective in tempering the body's inflammatory response and thereby reducing organ damage, and preventing morbidity and mortality of patients with severe community-acquired pneumonia.¹⁵ Also, in their high metabolic state, critically ill patients need reasonable nutritional support; patients were therefore given enteral nutritional suspension, which provided cells with the energy and nutrition needed for metabolism, helped to maintain the structure and function of tissue organs, and enhanced the body's immune function.

In conclusion, our results show satisfactory treatment outcomes for severely ill patients with COVID-19. Treatment included immediate respiratory support with NIPPV, as well as systematic supportive therapy using antivirals, in combination with broad spectrum antibiotics and low-dose methylprednisolone. However, standardised treatment scenarios should be studied in a randomised controlled trial to create evidence-based treatment guidance for severe respiratory viral infections.

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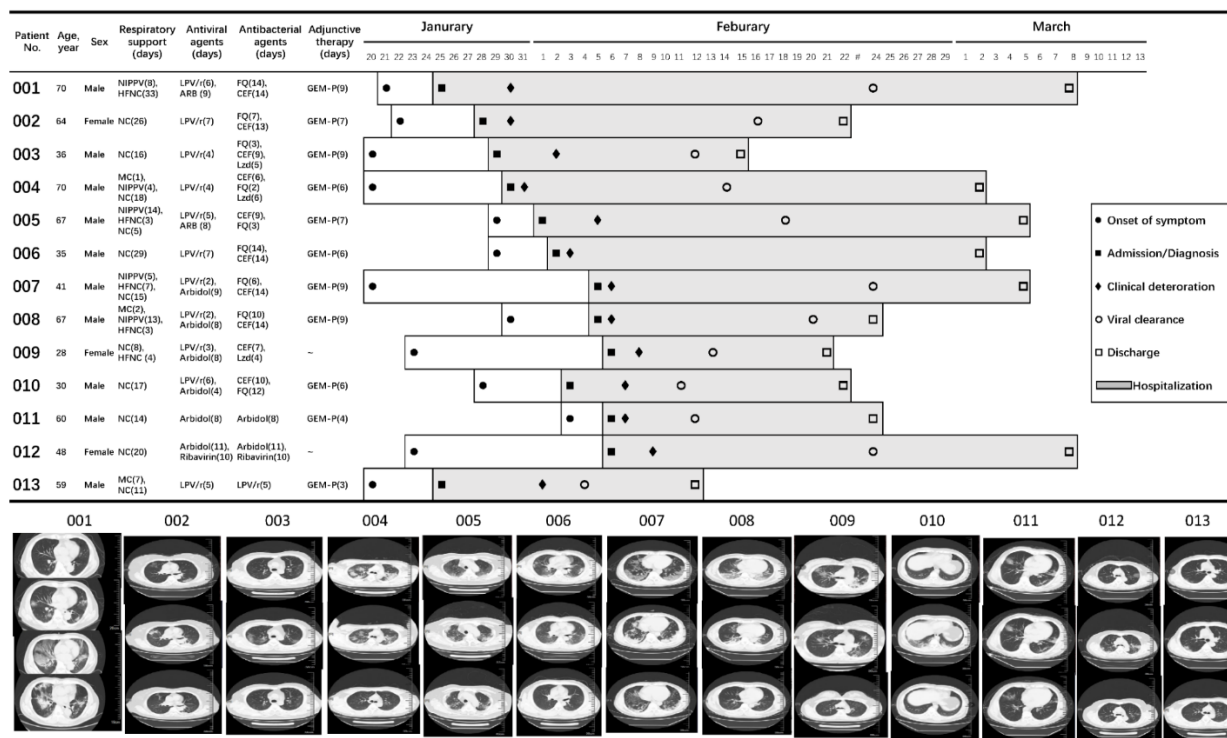


Figure Course of treatment of the 13 study patients severely ill with Coronavirus disease 2019, including medication, treatment prognosis and lesion changes on CT scan at the time of admission (top), during clinical deterioration (middle) and at the time of discharge (below). NIPPV = non-invasive positive pressure ventilation; HFNC = high-flow nasal cannula oxygen therapy; LPV/r = lopinavir/ritonavir; FQ = fluoroquinolones; CEF = cephalosporins; GEM-P = methylprednisolone.