[Novel Report]

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Treatment With Convalescent Plasma for Critically Ill Patients With SARS-CoV-2 Infection

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As of March 24, 2020, novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been responsible for 379,661 infection cases with 16,428 deaths globally, and the number is still increasing rapidly. Herein, we present four critically ill patients with SARS-CoV-2 infection who received supportive care and convalescent plasma. Although all four patients (including a pregnant woman) recovered from SARS-CoV-2 infection eventually, randomized trials are needed to eliminate the effect of other treatments and investigate the safety and efficacy of convalescent plasma therapy.

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KEY WORDS: convalescent plasma; critical illness; SARS-CoV-2

Since late December 2019, an outbreak of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection first appeared in Wuhan, China,[1] and rapidly spread to 171 countries. As of March 24, 2020, the virus has been responsible for 379,661 confirmed cases and 16,428 deaths worldwide. To date, no specific treatment has been recommended for SARS-CoV-2 infection except for meticulous supportive care.[2] Numerous therapeutics have been explored or developed during the outbreak. A recent trial showed lopinavir-ritonavir has no treatment benefit for severe illness caused by SARS-CoV-2.[3] Immunotherapy with virus-specific antibodies in convalescent plasma had been used as a last resort to improve the survival rate of patients with serious infectious diseases, such as severe acute respiratory syndrome, middle east respiratory syndrome coronavirus, Ebola virus disease, pandemic influenza A, and avian-origin influenza A.[4] Previous reports have shown treatment with convalescent plasma collated from recovered patients could reduce the hospital stay and mortality of patients.[5] However, the efficacy of convalescent plasma in critically ill patients with SARS-CoV-2 infection remains unclear. Herein, we report the disease course on four critically ill patients infected with SARS-CoV-2 and treated with supportive care and convalescent plasma.

ABBREVIATIONS: CDC = Center for Disease Control; CRRT = continuous renal replacement therapy; OI = oxygenation index; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

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Case Reports

Figure 1 shows the clinical course of four critically ill patients infected with SARS-CoV-2. The first case is a 69-year-old woman with a history of hypertension who presented with fever for 2 days and clear sputum for 5 days. On January 30, the patient was admitted to Dongguan Ninth People's Hospital because of positive reverse transcriptase polymerase chain reaction (RT-PCR) test of throat swab by Dongguan Center for Disease Control (CDC). A chest CT scan revealed bilateral ground-glass opacities primarily distributed along the pleura. Treatment with arbidol (200 mg three times daily), lopinavir-ritonavir (400 mg twice daily), interferon alpha inhalation (50 µg twice daily), and other supportive therapies was started. At 4 PM on February 4, the patient's Po_2 decreased to 56.5 mm Hg with an oxygenation index (OI) (Po_2/Fio_2) of 94 mm Hg. Significantly increased consolidation was observed in the right lung. The patient was transferred to the ICU of Dongguan People's Hospital (a designated center for critical illness treatment) on February 5 and received invasive mechanical ventilation. Apart from antiviral drugs (lopinavir-ritonavir, oseltamivir, and interferon alpha), human albumin, zadaxin and immunoglobulin, and antibacterial and antifungal drugs were administrated because of coinfection with bacteria and *Aspergillus*. At 6:30 PM on February 11, the patient's Po_2 was 58 mm Hg. She experienced septic shock with BP of 89/44 mm Hg 5 h later. Hypohemoglobin (92 g/L) and bloody sputum under bronchoscopy suggested

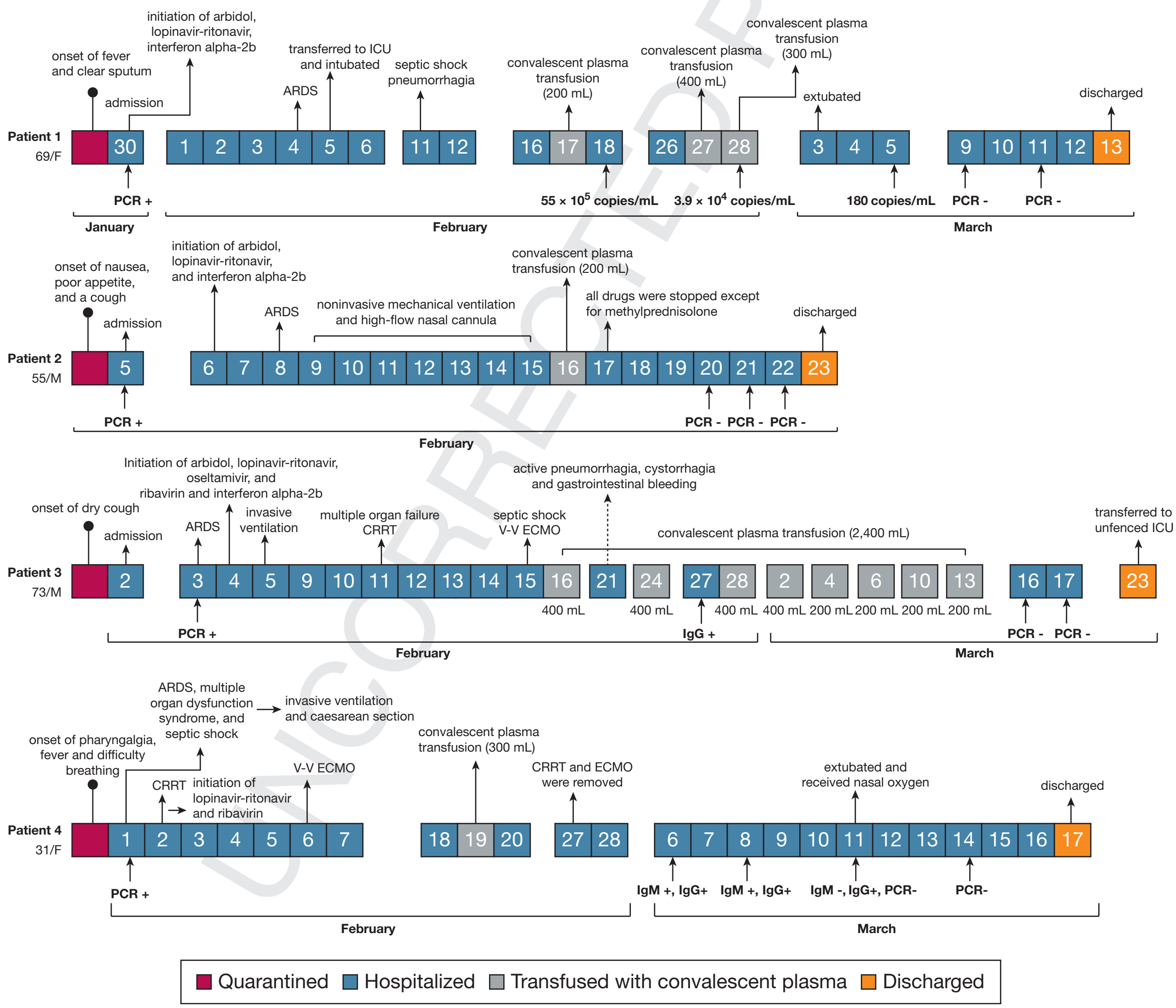

Figure 1 – *Timeline of symptom onset, reverse transcriptase polymerase chain reaction testing, antiviral therapies, severe complications, convalescent plasma transfusion, levels of virus load and antibodies after transfusion, and outcomes of the four critically ill patients with severe acute respiratory syndrome coronavirus 2 infection. CRRT = continuous renal replacement therapy; F = female; M = male; PCR = polymerase chain reaction; V-V ECMO = veno-venous extracorporeal membrane oxygenation.* Q13 Q16

pneumorrhagia. A bedside chest radiograph showed obvious progression of disease. Although the patient was successfully rescued, follow-up chest radiographs showed continuous progression of pneumonia. A total of 900 mL O-compatible convalescent plasma was transfused to the patient in three batches; the first batch was given at 8 AM on February 17 (200 mL), the second one was at 8 AM on February 27 (400 mL), and the last one was at 8 AM on February 28 (300 mL). The virus load of the patient on February 18 was 55 $\times$ 10^5 copies/mL, which significantly decreased to 3.9 $\times$ 10^4 copies/mL on February 28, and further decreased to 180 copies/mL on March 5. The patient was extubated and noninvasion ventilation was given on March 3. Chest CT scans obtained on February 27, March 6, and March 15 showed persistent absorption of consolidation. The results of two repeat RT-PCR tests of oropharyngeal swabs (with at least 1-day interval) performed on March 9 and 11 were negative. The patient was discharged on March 13.

The second case was a 55-year-old man with a history of COPD who was admitted to a fever clinic of Xiangtan Central Hospital on February 5, 2020. He had nausea, poor appetite, and cough with clear sputum for 4 days. The results of RT-PCR assay of throat swab were positive for SARS-CoV-2 infection. A chest CT scan obtained on February 6 revealed interlobular septal thickening with honeycombing change in the right upper lung. The patient started to receive antiviral treatment, including arbidol (200 mg three times daily), lopinavir-ritonavir (500 mg twice daily), and interferon alpha-2b (5 million units twice daily). After 2 days, he complained of shortness of breath and his Po_2 decreased to 50 mm Hg with an OI of 135 mm Hg. The patient was therefore diagnosed with ARDS and began to receive noninvasive mechanical ventilation and oxygen therapy through high-flow nasal cannula alternately. However, the conditions of the patient continued to deteriorate despite treatment with pulsed methylprednisolone. His Po_2 oscillated between 46 and 83 mm Hg, and symptoms were not improved. Follow-up chest CT scans obtained on February 9 to 16 showed interstitial pneumonia extended to both lungs. At 3 PM on February 16, 200 mL convalescent plasma obtained from a patient recovered from SARS-CoV-2 infection in January 2020 was transfused to the patient. No adverse reactions were observed. One day later, his Po_2 increased to 97 mm Hg with an OI of 198 mm Hg. All drugs were discontinued except for methylprednisolone. Chest images obtained on February 17 to 21 showed obvious absorption of interstitial pneumonia. Three repetitive RT-PCR test results were negative from February 20 to 22. The patient recovered and was discharged on February 23. He was asked to continue the quarantine at home for 14 days and receive home oxygen therapy.

The third case was a 73-year-old man who was admitted to Dongguan Ninth People's Hospital on February 2 because of self-reported dry cough for 4 days. He had a history of hypertension and chronic renal failure. On February 3, the patient was confirmed as being infected with SARS-CoV-2 by a virus RNA detection kit. At 11:30 PM, the patient developed acute respiratory failure with Po_2 of 53 mm Hg and OI of 124 mm Hg; high-flow oxygen through face mask was given. He was then transferred to the isolation wards of the ICU of Dongguan People's Hospital for further treatment. A chest radiograph showed bilateral infiltrative shadows. The viral load of the patient was as high as 85 $\times$ 10^5 copies/mL. The patient was treated with arbidol (200 mg three times daily), lopinavir-ritonavir (400 mg twice daily), oseltamivir (75 mg twice daily), and ribavirin and interferon alpha-2b (5 million units twice daily). On February 5, the patient was given tracheal intubation because of dyspnea and consistent decrease of oxygen saturation. On February 11, continuous renal replacement therapy (CRRT) was started on the patient. Laboratory tests obtained on February 14 showed significantly increased WBCs of 33.93 $\times$ 10^9/L and neutrophils of 31.08 $\times$ 10^9/L. He was diagnosed with multiple organ failure by clinical examination. On February 15, the patient developed septic shock and his BP decreased to 90/68 mm Hg with heart rate of 149 beat/min and respiratory rate of 30 breaths/min. A chest radiograph showed bilateral white lung. At 12:55 PM on February 15, the patient started to receive veno-venous extracorporeal membrane oxygenation, whereas the OI was unstable and symptoms were not improved. High-throughput DNA sequencing of sputum suggested *Aspergillus* infection. The patient was therefore treated with caspofungin and voriconazole. Eight transfusions of B-compatible convalescent plasma (2,400 mL) were given to the patient from February 16 to March 13. On February 21, the patient was confirmed positive for active pneumorrhagia, cystorrhagia, and GI bleeding. Antibody testing on February 27 indicated positive anti-SARS-CoV-2 IgG. The viral load was reduced (detailed values were not available). Follow-up chest radiographs showed absorbed infiltrative lesions but pneumothorax. Two repeat RT-PCR tests of sputum in deep lungs on

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March 16 and 17 (with at least 1-day interval) were negative and the serum IgM level decreased to the normal range. On March 22, the patient was transferred to the unfenced ICU for further treatment of underlying diseases and multiple organ failure.

The fourth case was a 31-year-old pregnant woman (35 weeks and 2 days) who was admitted to Xiaolan People's Hospital of Zhongshan on February 1 because of pharyngalgia for 4 days and fever (39.3°C) and difficulty breathing for half-day. The patient was confirmed as being infected with SARS-CoV-2 by Zhongshan CDC. A chest CT scan showed opacities in the lower lobe of the left lung. After admission, the patient developed severe ARDS, multiple organ dysfunction syndrome, and septic shock. Invasive ventilation and caesarean section were therefore given to the patient. Unfortunately, the newborn died of endouterine asphyxia. After the conditions turned stable, she was transferred to the Second People's Hospital of Zhongshan (a designated hospital for SARS-CoV-2 treatment) at 1:04 AM on February 2. Amounts of frothy sputum was observed under bronchofiberscope. Cardiac ultrasound suggested left ventricular enlargement with decreased systolic function. The patient received invasive ventilation and CRRT. Treatment with lopinavir-ritonavir (400 mg twice daily) and ribavirin (500 mg every 12 h) was started on February 2. Gram-positive bacteria were detected by blood culture, and imipenem and vancomycin were given to the patient. A chest radiograph showed increased consolidation and extended opacities. Oxygen saturation oscillated between 85% and 92% with an OI between 60 and 75 mm Hg. At 12 AM on February 6, the patient started to receive veno-venous extracorporeal membrane oxygenation (flow rate: 3 L/h). Her OI was significantly improved (with a maximum of 200 mm Hg). Follow-up chest radiographs showed partial absorption of opacities. Left ventricular systolic function returned to normal. At 11:30 AM on February 19, a 300-mL transfusion of convalescent plasma was given to the patient. On February 27, CRRT and Q8 ECMO were removed. On March 11, trachea cannula was removed and nasal oxygen was given to the patient. On March 6, 8, and 11, anti-SARS-CoV-2 IgM changed from positive to weakly positive to negative, whereas anti-SARS-CoV-2 IgG was persistently positive. Follow-up chest CT scan showed near-complete absorption of opacities. The results of two continual RT-PCR tests of BAL fluid on March 11 and 14 were both negative. The patient recovered from SARS-CoV-2 infection and was discharged on March 17.

Discussion

A recent retrospective review of 72,314 SARS-CoV-2-infected cases by the China CDC showed that 5% of cases were critical illness characterized by respiratory failure, septic shock, and/or multiple organ dysfunction or failure. Around 48% of patients infected with SARS-CoV-2 had comorbid conditions, commonly cardiovascular diseases and diabetes.[9] Older adults with underlying diseases were more likely to have a higher Sequential Organ Failure Assessment score and higher risk of death. The treatment of SARS-CoV-2 infection faces compelling challenges. To date, no therapeutics have yet been proven effective for the treatment of the critical illness except for supportive care, including treatment with antiviral drugs, corticosteroids, immunoglobulins, and noninvasive or invasive mechanical ventilation. The most critically ill patients infected with SARS-CoV-2 have elevated levels of infection-related biomarkers and inflammatory cytokines, indicating potential bacterial coinfection caused by a dysregulated immune system.[10] Antibacterial drugs are therefore given to these patients. Management of critical SARS-CoV-2 infection is not different from management of most viral pneumonia causing respiratory failure. The principal feature of patients with the critical illness is the development of ARDS. ECMO is recommended by World Health Organization interim guidelines to support eligible patients with ARDS, while the use of which is restricted to specialized centers globally and technology challenges.[11] In this study, two patients were treated with ECMO, but the efficacy was mixed. Apart from ARDS, other life-threatening conditions including septic shock and multiple organ dysfunction or failure may occur in a substantial proportion of patients with SARS-CoV-2-related critical illness, the management of which is according to current evidence-based guidelines.[12] In China, if the current therapeutic strategies are not satisfactory for critically ill patients, physicians might turn to convalescent plasma transfusion based on the Pneumonitis Diagnosis and Treatment Program for SARS-CoV-2 infection (Trial Version 7). Convalescent plasma has been used as a last resort to improve the survival rate of patients with severe acute respiratory syndrome infection. Previous evidence has proven that

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convalescent plasma treatment can significantly reduce the relative risk of mortality of patients,[13] which may be because antibodies from convalescent plasma might suppress viremia. The level of SARS-CoV-2 neutralizing antibodies in donor plasma could be important for the effectiveness of intervention. However, the level of neutralizing antibodies in donor plasma before transfusion cannot be determined. In this study, three patients were tested for either virus load or antibodies IgM and IgG. In the first case, SARS-CoV-2 virus load after convalescent plasma transfusion significantly dropped (from 55×10^5 to 3.9×10^4 to 180 copies/mL). Among the four patients, the time from transfusion to negative RT-PCR test results ranged from 3 to 22 days. The third and fourth cases produced anti-SARS-CoV-2 IgG approximately 14 days after convalescent plasma transfusion. Patients who survive critical illness might mount higher antibody responses, which can persist for longer periods compared with those with nonsevere disease.[14] The antibody levels, however, are confounded by other treatments, such as antiviral drugs, steroids, and IV immunoglobulin.[15] A recent animal model indicated that antibodies produced from SARS-CoV-2 infection could protect from subsequent exposures.[16]

Conclusions

Our results indicate convalescent plasma might be a potential therapy for critically ill patients infected with SARS-CoV-2. We observed no serious adverse reactions associated with the transfusion of convalescent plasma. However, the relative contributions of supportive care, investigational therapies, and patient's immune response on survival could not be determined. Whether convalescent plasma and/or supportive care provide any clinical benefit is unknown. The safety and efficacy of convalescent plasma transfusion in patients infected with SARS-CoV-2 should be studied within the context of a well-designed clinical trial.

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