Efficacy of therapeutic plasma exchange in severe COVID-19 patients

At the end of December 2019, an outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared in Wuhan, China. After that, it became an emergency disease nationally and internationally.[1] COVID-19 can damage the respiratory system of patients, inducing symptoms of fever, cough and shortness of breath.[2] To date, there is no specific antiviral therapeutic agent or vaccine recommended for COVID-19. Although most of the patients a had good prognosis after receiving antiviral, antibiotic, and oxygen therapy, some severe patients developed acute respiratory distress syndrome, among whom several would die of multiple organ failure.[3] The deterioration, rapid aggravation, and even death might be caused by a cytokine storm (also called inflammatory storm). There is no clear evidence that any specific treatment could be useful for cytokine storm in COVID-19 patients. Here, we report the efficacy of therapeutic plasma exchange (TPE) in three severe COVID-19 patients with acute respiratory distress syndrome. The results suggested that TPE could be used as a strategy to attenuate circulating cytokines and other inflammatory mediators. This study was approved by the institutional ethics board of the first affiliated hospital of Bengbu Medical College (No. 2020KY010).

Three patients (male, aged 44, 55 and 64 years), with acute respiratory distress syndrome related to COVID-19 as confirmed by quantitative real time polymerase chain reaction (qRT-PCR) and chest computed tomography (CT), were all patients receiving TPE in the first affiliated hospital of Bengbu Medical College from January 22, 2020 to March 4, 2020. Timelines of symptom onset, qRT-PCR testing, severe complications, plasma exchange, and outcomes of the three severe patients are shown in Fig 1. The patients were admitted to the hospital with fever, dry cough, fatigue, dizziness and nausea. All three patients had received various antiviral treatments, including arbidol (200 mg three times daily) and interferon alpha-2b (atomization inhalation, 5 million units twice daily). However, despite initial antiviral treatment and other therapeutic interventions, all three patients developed respiratory distress with respiratory frequency ≥30/min, pulse oximeter oxygen saturation ≤93% at rest, or oxygenation index (PaO_2/FiO_2) ≤300 mm Hg. The lymphocyte counts of the patients were lower than the normal range in adults. In contrast the levels of C-reactive protein (CRP), neutrophil count, lactate dehydrogenase, and interleukin 6 (IL-6) were significantly higher than the normal reference ranges.

The three severe patients were transferred to the first affiliated hospital of Bengbu Medical College (a designated hospital for the treatment of severe cases of COVID-19). According to the suggestion made in the 'Diagnosis and treatment plan of novel coronavirus pneumonia (Trial version 6)' drawn up by the National Health Commission of the People's Republic of China, TPE was used as an emergency treatment for these three severe COVID-19 patients. TPE was performed with a plasma separator multi-filtration system, and about 3000 ml of normal fresh-frozen plasma was exchanged for one person. Each patient received one treatment of TPE between one and three days after being transferred to the designated hospital.

The PaO_2/FiO_2 ranged from 93 to 178 mm Hg at 2 h before plasma exchange and increased (improved) for all three patients within 24 h after TPE (range from 259 to 319 mm Hg). As shown in Table I, PaO_2/FiO_2 was significantly improved from an average of 146 to 293 ($P = 0{\cdot}0103$). One day after the treatment, the values of CRP decreased more than >70%, and the levels of IL-6 also declined to the normal reference range. After treatment, the values of the neutrophil to lymphocyte ratio (NLR) were significantly decreased. Four or five days after treatment, the patients were all changed from high-flow oxygen to receive low-flow oxygen. After one day with low-flow oxygen, all patients could breathe ambient air without requiring oxygen supplementation. About ten days after TPE, all three patients met the discharge criteria, including negative nucleic acid tests twice separated by at least one day, having a normal temperature for more than three days, showing resolved respiratory symptoms, and improved acute exudative lesions on chest CT images. The lengths of hospital stay were 14, 15, and 22 days, respectively. The time from symptom onset to recovery ranged from 18 to 25 days.

At present, the main reason for the severity and continuous progress of COVID-19 might be cytokine storm,[4] which might also be a reason to declare progression to the terminal stage of Ebola virus disease (EVD)[5] and severe acute respiratory syndrome (SARS).[6] In the clinic, anti-infective drugs, corticosteroid, nutritional support, artificial ventilation, and other non-specific combined treatment measures are often used for cytokine storm. However, clinical evidence did not support that COVID-19 could benefit from corticosteroid treatment.[7] Therapeutic plasma exchange is effective for cytokine storm and is widely used in the treatment of a variety of severe and critical patients, such as pneumonia and respiratory failure from H1N1 influenza A virus.[8] In this study, the results from

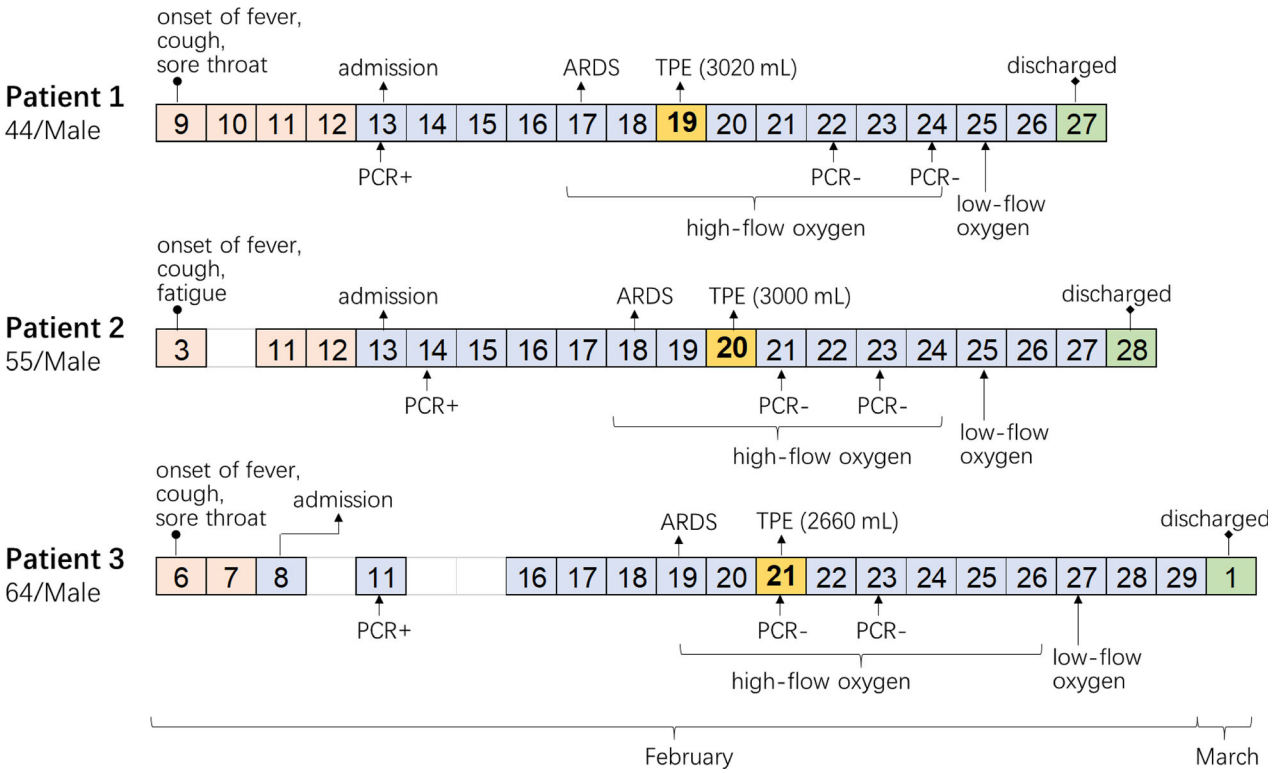

Fig 1. Timelines of symptom onset, qRT-PCR testing, severe complications, plasma exchange, and outcomes of the three severe patients. PCR, polymerase chain reaction; ARDS, acute respiratory distress syndrome; TPE, therapeutic plasma exchange.

Table I. Clinical characteristics of three severe COVID-19 patients with therapeutic plasma exchange (TPE) treatment.

	Prior to TPE			Post TPE		
	Patient 1	Patient 2	Patient 3	Patient 1	Patient 2	Patient 3
Respiratory frequency (/min)	29	22	32	23	22	26
Pulse oximeter oxygen saturation (%)*	82	93	88	98	97	98
PaO_2/FiO_2 (mm Hg)*	178	93	168	319	259	300
Lymphocyte count (10^9/l)	1·07	0·56	0·52	2·91	1·03	1·53
C-reactive protein (mg/l)*	123·1	84·8	196·3	5·2	19·4	24·4
Neutrophil count (10^9/l)*	8·49	8·00	7·96	7·09	5·15	6·17
Lactate dehydrogenase (U/l)	823	1394	433	303	325	264
IL-6 (pg/ml)	18·28	12·14	142·9	2·55	4·53	6·42
Neutrophil to lymphocyte ratio (NLR)*	7·93	14·29	15·34	2·44	5·00	4·03

*The values of these clinical characteristics were significantly increased/decreased after therapeutic plasma exchange treatment ($P < 0·05$). The average values of lactate dehydrogenase and IL-6 were reduced, but were not significant.

three severe cases suggested that TPE had an immediate effect on the treatment of the cytokine storm, which was similar to previous research results.[9] NLR was considered an inflammatory marker that could reflect a systemic inflammatory response, and the NLR values were found to increase significantly in patients with COVID-19 with severe disease.[10] In conclusion, as an efficient and rapid method to remove the abnormally elevated inflammatory factors, to supplement albumin, to improve coagulation function, and to correct immune disorder, therapeutic plasma exchange might be a rescue therapy in severe COVID-19 patients with acute respiratory distress syndrome and cytokine storm.

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Cold agglutinin autoimmune haemolytic anaemia associated with novel coronavirus (COVID-19)

Cold agglutinin syndrome (CAS), a rare disorder accounting for 25–30% of autoimmune haemolytic anaemias, has been associated with infection, autoimmune disorders and lymphoid malignancies.[1] *Mycoplasma pneumoniae*, Epstein–Barr virus, human immunodeficiency virus, rubella virus, *Legionella*, varicella zoster virus, and influenza viruses have been commonly associated with cold agglutination.[1] Described here is a case in which the patient develops acute CAS associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes coronavirus disease 2019 (COVID-19).

The pathogenesis behind secondary infectious causes of CAS remains undetermined. It is clear, however, that complement activation is associated with inflammatory states, including the up-regulation of pro-inflammatory cytokines.[2] This may indeed create the perfect storm for haemolysis, especially in such a pro-inflammatory infection as COVID-19.

A 46-year-old female with a history of immune thrombocytopenic purpura (ITP) 27 years ago during pregnancy, status post splenectomy, iron deficiency anaemia, and asthma presented with muscle aches, lethargy, and dyspnoea. Blood work performed six months prior to admission revealed normal bilirubin levels and a haemoglobin of 117 g/l, which was at the patient's baseline. Additionally, the patient had a negative rheumatologic work-up in the last several years including antinuclear antibody, rheumatoid factor and anti-citrullinated protein antibody.

On admission, patient was febrile at 38·2°C, with a heart rate of 107 beats per minute, and a respiratory rate of 29 breaths per minute. On examination, she appeared ill with generalised jaundice and increased work of breathing but did

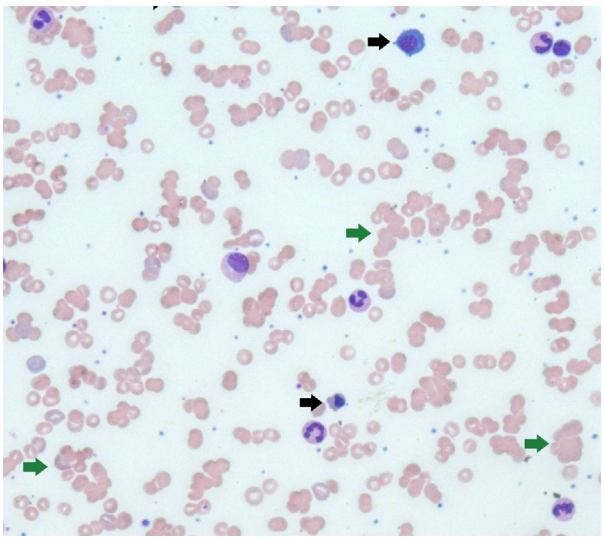

Fig 1. Black arrows represent nucleated red blood cells while green arrows represent agglutination.