Use of extracorporeal blood purification therapy (ECBPT) as an adjuvant to high-dose corticosteroids in a severely ill COVID-19 patient with concomitant bacterial infection

Min Xian Lim,[1] Kean Khang Fong,[1] Tat Boon Yeap [2]

[1]Department of Anaesthesiology and Intensive Care, Hospital Queen Elizabeth, Kota Kinabalu, Sabah, Malaysia
[2]Department of Anaesthesiology and Intensive Care, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia

Correspondence to
Dr Tat Boon Yeap;
boontat@ums.edu.my

Accepted 28 September 2021

To cite: Lim MX, Fong KK, Yeap TB. *BMJ Case Rep* 2021;**14**:e245639. doi:10.1136/bcr-2021-245639

SUMMARY

COVID-19 presents with a spectrum of severity, ranging from asymptomatic or mild symptoms to those with acute respiratory distress syndrome. Corticosteroids are widely used for their efficacy in reducing inflammatory responses. However, its use may be limited to patients with immunosuppression. An adjunct therapy for cytokine storm in COVID-19 is extracorporeal blood purification therapies using high adsorptive filters, such as oXiris, to remove cytokines. We share our experience in using continuous renal replacement therapy with oXiris haemofilter as a temporising measure to high-dose corticosteroids in managing cytokine storm in a deteriorating COVID-19 patient with concomitant bacterial infection.

BACKGROUND

COVID-19, which was caused by SARS-CoV-2, is one of the most overwhelming pandemics that mankind has ever had. The pathophysiology of COVID-19 describes a rise in cytokines such as C reactive protein (CRP) and interleukin-6 (IL-6), which heralds progression of the disease and increased severity.[1] An adjunct therapy that has been described in literatures is the usage of continuous renal replacement therapy (CRRT) using high-throughput membranes with high adsorptive oXiris filter. This manuscript describes our success in using CRRT with oXiris filter as an adjuvant to high-dose corticosteroids in a severely ill COVID-19 patient with bacterial coinfection.

CASE PRESENTATION

A healthy 54-year-old man (weight=62 kg, height=1.72 m) presented with a 5-day history of fever, cough and pleuritic chest pain. He had contact with his son who was tested positive for COVID-19 a few days earlier. On presentation, our patient was tachypnoeic with a respiratory rate of 30 breaths per minute, blood pressure of 109/72 mm Hg, heart rate of 112 beats per minute, oxygen saturation (SaO2) of 92% under room air and afebrile. He required high-flow nasal cannula (HFNC) fraction of inspired oxygen (FiO2) 0.8 with 60 L/min flow to maintain SaO2 of >95%. On physical examination, there were reduced breath sounds on both lungs with coarse crackles at the left lower zone. Other examinations were unremarkable.

INVESTIGATIONS

- His haemoglobin was 153 g/L (normal values: 120–155 g/L), total white cell count was 12.4×10^9 /L (normal values: 7–11 $\times10^9$ /L) dan platelet at 246×10^9 (normal values: 150–400 $\times$ 10^9 /L).
- The electrolytes, liver and renal function were within normal range.
- Serum ferritin was severely elevated at 2537 ng/mL (normal values: <1000 ng/mL).
- CRP was increased at 16 mg/L (normal values: <10 mg/L).
- Serum procalcitonin (PCT) level was initially not raised at 0.13 ng/mL on admission (bacterial infection unlikely 0.1–0.25).
- His arterial blood gases showed type 1 respiratory failure on HFNC FiO2 0.8 with 60 L/min flow.
- Serum lactate dehydrogenase was raised at 630 U/L (normal values: 140–300 U/L).
- Chest radiograph showed consolidation over the left lower zone which eventually worsened to bilateral infiltrates over the course of his admission in Intensive care unit (ICU) (figure 1).
- A high-resolution CT scan of the lungs showed presence of organising pneumonia with basal atelectasis and no evidence of pulmonary embolism (figure 2).
- His nasopharyngeal swab for real time reverse transcription—PCR assay for the detection of SARS-coV-2 was positive on admission.
- Blood and sputum cultured did not reveal any micro-organisms.

DIFFERENTIAL DIAGNOSIS

The provisional diagnosis was severe COVID-19 pneumonia with concomitant bacterial infection.

TREATMENT

Our patient was admitted to the ICU for critical care management. He was put on HFNC FiO2 0.9 with 60 L/min flow and started on intravenous methylprednisolone 1 mg/kg two times per day. He initially showed improvement in his oxygenation with partial pressure of oxygen to FiO2 (P/F ratio) of 132 and we were able to wean down the FiO2 to 0.6.

However, on his fifth day of ICU admission, he deteriorated and required increased HFNC FiO2 to

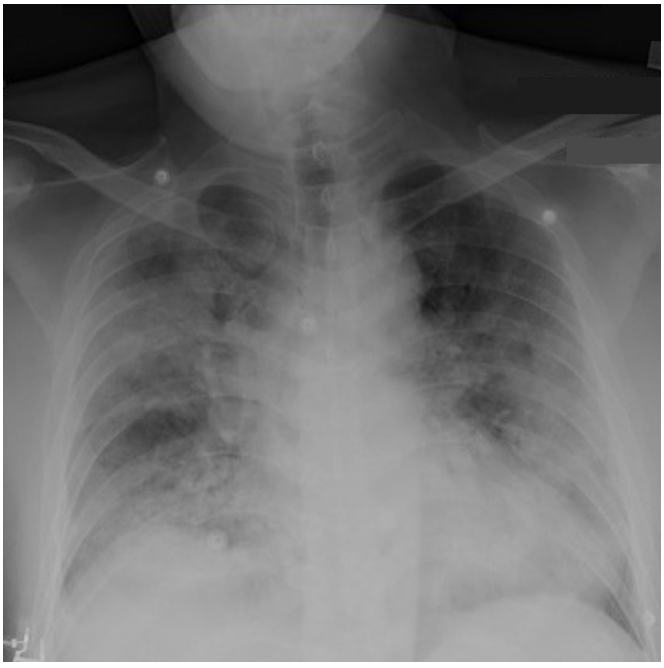

Figure 1 Chest X-ray of the patient during admission which showed generalised bilateral haziness of both lungs.

0.9 with worsening oxygenation (P/F ratio of 113). He developed high grade fever of 38.5°C, with a significant increase in his CRP to 70.2 mg/L and an elevated PCT of 0.33 ng/mL, signifying a concomitant bacterial infection. Intravenous Tazocin (piperacillin and tazobactam) was initiated for bacterial pneumonia. We attributed his deterioration to cytokine release syndrome (CRS) with superimposed bacterial infection. In view of this, we decided not to start pulsed methylprednisolone to avoid further immunosuppression.

As the patient further deteriorated, we commenced continuous venovenous haemodiafiltration (CVVHDF) with a newer generation high adsorptive filter (oXiris) on the seventh day of his ICU admission. As he did not have any renal impairment at that time and was producing adequate amount of urine at

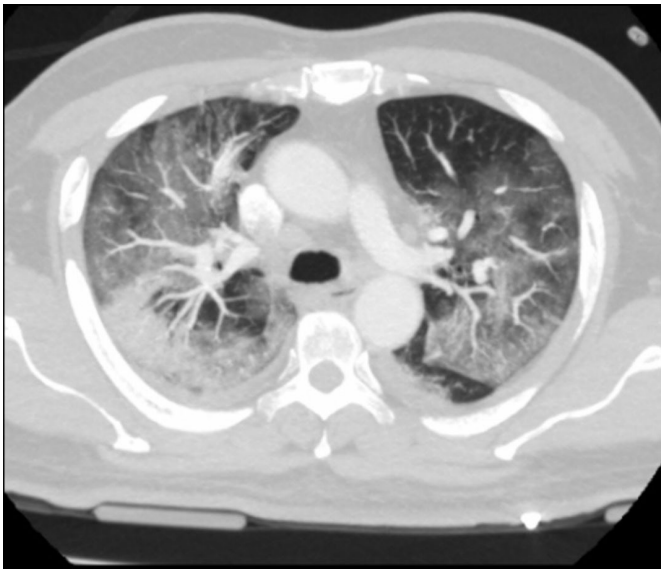

Figure 2 HRCT of the lungs which showed organising pneumonia of left lung. HRCT, high-resolution CT.

0.5–0.8 mL/kg/hour, the CRRT was started for blood purification and reduction of the cytokine and endotoxin load. Our aim was to allow time for the antibiotic therapy to treat the bacterial infection and to monitor the CRP and PCT levels prior to recommencement of the pulsed methylprednisolone therapy. The CRRT prescription was as table 1.

He underwent 30 hours of CRRT in the ICU. We progressively discontinued the CVVHDF when his CRP and PCT levels started to decrease (figure 3) along with good clinical improvement and a higher P/F ratio. His haemodynamics were stable throughout the process without the usage of vasopressors. After that, we commenced pulsed methylprednisolone for 3 days to treat the organising pneumonia. We were able to gradually wean down his HFNC settings as well.

OUTCOME AND FOLLOW-UP

The patient was weaned off HFNC in the following days and was transferred out to the general ward on day 22 of hospital admission. He was discharged home safely after 31 days of hospitalisation.

DISCUSSION

One of the major features of COVID-19 pathophysiology is the inflammatory response, which contributes to the severity of the illness. A rise in cytokines released, also known as cytokine release storm or CRS, is associated with severe illness and often leads to increased morbidity and mortality.[1] Certain parameters are especially useful to monitor this increased inflammatory response. Two commonly used parameters include CRP and PCT. The former is an acute-phase reactant that is a sensitive inflammatory marker and studies have shown that patients with high CRP levels are often associated with severe COVID-19 disease. On the other hand, PCT is a glycoprotein with normally undetectable levels in serum and remains low during viral infections. PCT is raised in bacterial infections and can be used clinically to detect a superimposed bacterial infection with COVID-19.[2]

Corticosteroids have been widely administered in COVID-19 with the aim of reducing the inflammatory response and hence, disease severity. Studies have demonstrated the efficacy of corticosteroids, with the Randomized Evaluation of Covid-19 Therapy (RECOVERY) Trial being one of the most prominent, showing a reduction of 28-day mortality in COVID-19 patients with a dose of intravenous dexamethasone 6 mg daily for up to 10 days.[3] The use of intravenous methylprednisolone as an adjunct to treat COVID-19, particularly in patients with an increase in CRP and IL-6, has been explored in other studies. It has been demonstrated that pulsed methylprednisolone therapy in the early stages of the illness reduced the severity, mortality rate and rise of inflammatory markers.[4] Another trial demonstrated reduced mortality in patients above the age of 60, who also had elevated CRP levels.[5] A limiting factor in corticosteroid therapy, particularly the use of high dose of methylprednisolone or pulse therapy, is concomitant bacterial infections. Corticosteroid therapy also increases the incidence of bacterial and fungal infections in COVID-19 patients due to the immunosuppression. Ultimately, this could lead to more severe outcomes and increased mortality.[6]

Our patient deteriorated and required increased oxygen therapy during his ICU stay. His deterioration was accompanied by a significant increase in CRP levels, which was in line with CRS. However, he also demonstrated features of a concomitant bacterial infection, with high-grade fever and increased PCT levels. Pulsed methylprednisolone therapy was considered to

Table 1 CRRT prescription for the patient in the ICU

Mode	Anticoagulation	Effluent dose (mL/kg/hour)	Renal impairment	Time commenced	Total duration of treatment	Filters used
CVVHDF	Heparin 500 µ/hour	40	Nil	Day 7 of ICU admission	30 hours	4

CRRT, continuous renal replacement therapy; CVVHDF, continuous venovenous haemodiafiltration; ICU, intensive care unit.

reduce the exaggerated inflammatory response associated with CRS. However, with evidence of a likely superimposed bacterial pneumonia, pulsed methylprednisolone therapy could worsen the patient's condition. Therefore, we decided to use blood purification therapy via CVVHDF to adsorb the cytokines and endotoxins to reduce the inflammatory response as a temporising measure.

The use of extracorporeal blood purification therapies to reduce cytokine levels has been explored in COVID-19. The basis of its usage was derived from previous experience with SARS and Middle East respiratory syndrome. The advent of newer high-throughput membranes with high adsorption levels based on the AN69 membrane, such as the oXiris filter, has made CRRT more effective in removing cytokines and inflammatory mediators. The oXiris filter was constructed with a higher number of positively charged free amino groups, allowing it to adsorb large negatively charged molecules such as cytokines. It also consists of three layers, which serves multiple functions—renal support, cytokine and endotoxin clearance as well as local anticoagulant properties. A recent case series showed improvement in COVID-19 patients' haemodynamics and organ function following CRRT with oXiris filter.[7] Another study also demonstrated the safety of CRRT with oXiris filter in COVID-19 patients with reduction in CRP, IL-6 and PCT levels. However, there is still insufficient evidence on the optimum timing and indication for initiation of CRRT with oXiris filter in order to achieve the best outcome.[8] Furthermore, the high cost of CRRT with such filters and its limited availability may limit its usage. In addition, the need for insertion of haemodialysis catheters into central veins prior to commencement of CRRT, carry the risks of pneumothorax, bleeding and catheter-related sepsis.[9] In such circumstances, it may not be feasible to administer CRRT for all COVID-19 patients with CRS, especially in resource-limited health facilities.

A clinical situation where CRRT for blood purification may be warranted is the occurrence of bacterial infection with concomitant CRS, despite the absence of renal impairment. Immunosuppression caused by high dose of corticosteroids may worsen the patient's outcome and lead to increased mortality. It can also lead to an increased incidence of bacterial and fungal infections. The commencement of blood purification therapies can help reduce cytokine load and prevent progression of the inflammatory changes in COVID-19 pneumonia while allowing time for empirical antimicrobial therapy to work and reduce systemic bacterial load. Subsequently, high-dose corticosteroids such as pulsed methylprednisolone can be initiated. Based on our experience in this patient, there was significant improvements in his CRP, PCT and clinical condition approximately 30 hours after commencement of CVVHDF. Most importantly, our patient avoided intubation, which may progress to prolonged ventilation and death, with the early implementation of CVVHDF using the oXiris haemofilter.

In summary, CRRT for blood purification can be initiated early in severe COVID-19 disease patients with concomitant bacterial infection, despite the absence of renal impairment. Its use had been demonstrated to reduce the risks of irreversible end organ damage and mortality. However, it may not be readily available in resource-limited facilities. Thus, thorough selection of COVID-19 patients with excellent prognosis is needed to ensure treatment success.

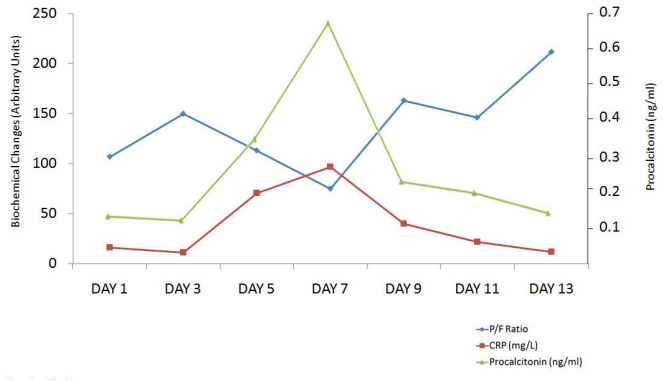

Figure 3 Biochemical trends of procalcitonin, CRP and P/F ratio. CRP, C reactive protein, P/F, partial pressure of oxygen to fraction of inspired oxygen.

Acknowledgements We would like to thank the Director General of the Malaysian Ministry of Health for his permission for us to publish this article.

Contributors KKF and MXL comanaged the patient in the ICU. MXL and TBY coauthored this manuscript with the supervision of KKF.

Patient's perspective

I am thankful to the wonderful team of doctors in the ICU for saving my life. Having a severe near-death condition of COVID-19 was an awful and unforgettable experience for me. I hope the people out there will always observe personal hygiene and take the COVID-19 vaccine to protect yourself and those around you.

Learning points

- Cytokine release syndrome in COVID-19 is often associated with worsening disease severity and poor prognosis.
- Corticosteroids have been shown to be useful in reducing inflammatory process but their uses may not be ideal in immunosuppressed patients with superimposed bacterial infection.
- Severely ill COVID-19 patients with concomitant bacterial infections should be considered for extracorporeal blood purification therapies (ECBPT) with oXiris as a temporising measure to high dose of corticosteroids.
- The cost inefficiency of ECBPT may limit its usage to only a small group of patients.
- More qualitative clinical trials are needed to demonstrate the efficacy and timing for ECBPT in patients with severe COVID-19.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Tat Boon Yeap http://orcid.org/0000-0002-2517-597X

REFERENCES

1 Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
2 Liu F, Li L, Xu M, *et al*. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *J Clin Virol* 2020;127:104370.
3 RECOVERY Collaborative Group, Horby P, Lim WS, *et al*. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021;384:693–704.
4 Jeronimo CMP, Farias MEL, Val FFA, *et al*. Methylprednisolone as adjunctive therapy for patients hospitalized with coronavirus disease 2019 (COVID-19; Metcovid): a randomized, double-blind, phase IIb, placebo-controlled trial. *Clin Infect Dis* 2021;72:e373–81.
5 Edalatifard M, Akhtari M, Salehi M, *et al*. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. *Eur Respir J* 2020;56. doi:10.1183/13993003.02808-2020. [Epub ahead of print: 24 12 2020].
6 Yang Z, Liu J, Zhou Y, *et al*. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. *J Infect* 2020;81:e13–20.
7 Zhang H, Zhu G, Yan L, *et al*. The absorbing filter oxiris in severe coronavirus disease 2019 patients: a case series. *Artif Organs* 2020;44:1296–302.
8 Rosalia RA, Ugurov P, Neziri D, *et al*. Extracorporeal blood purification in moderate and severe COVID-19 patients: a prospective cohort study. *Blood Purif* 2021:1–10.
9 Teah MK, Chan GK, Wong MTF, *et al*. Treatment of benzodiazepine withdrawal syndrome in a severe traumatic brain injury patient. *BMJ Case Rep* 2021;14:e238318.