

# The successful use of therapeutic plasma exchange for severe COVID-19 acute respiratory distress syndrome with multiple organ failure

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## Abstract

The COVID-19 pandemic has brought about an urgent need for effective treatment, while conserving vital resources such as intensive care unit beds and ventilators. Antivirals, convalescent plasma, and biologics have been used with mixed results. The profound “cytokine storm” induced endotheliopathy and microthrombotic disease in patients with COVID-19 may lead to acute respiratory distress syndrome, sepsis, and multi-organ failure. We present a case of SARS-COV2 pneumonia with septic shock and multi-organ failure that demonstrated significant clinical improvement after therapeutic plasma exchange. A 65-year-old female with multiple comorbidities presented with progressive dyspnea and dry cough. She was found to be COVID-19 positive with pneumonia, and developed progressive hypoxemia and shock requiring vasopressors, cardioversion, and non-invasive positive pressure ventilation. Given her worsening sepsis with multi-organ failure, she underwent therapeutic plasma exchange with rapid clinical improvement. Her case supports the theory that plasma exchange may help abate the “cytokine storm” induced endotheliopathy and microthrombosis associated with COVID-19. Further studies are needed to identify markers of this pathway and the potential role of plasma exchange in these critically ill patients.

## Keywords

COVID, therapeutic plasma exchange, multiple organ failure, acute respiratory distress syndrome, septic shock, coronavirus

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## Introduction

The COVID-19 pandemic has brought about an urgent need for effective treatment of the critically ill, while conserving vital resources such as intensive care unit (ICU) beds and ventilators. The search for effective treatment is underway worldwide. Antivirals, convalescent plasma, and biologics are all promising, but might not be sufficient treatment of more critically ill patients with acute respiratory distress syndrome (ARDS) and/or multiple organ failure (MOF).

During the SARS epidemic of 2012, researchers noted that late-term disease progression was unrelated to the initial viremia, but secondary to the host’s immunopathologic response.<sup>1</sup> The profound “cytokine storm” being described in patients with COVID-19 mimics this process.<sup>2</sup> Targeted therapy against this cytokine storm and inflammatory

response is currently being investigated, and these therapies may prove to help in select cases. However, the effect of cytokines is not limited to inflammation, but also endothelial activation and diffuse microcirculatory thrombosis.<sup>3–5</sup> It is this pathway that leads to tissue hypoxemia, organ failure, and death. Clinically, this may present as ARDS and/or sepsis with shock and MOF.<sup>6</sup> Therapeutic plasma exchange

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**Table 1.** Objective outcomes.

	Pre-TPE	Post-TPE
SOFA score	7	3
Norepi dose (mcg/min)	8	0
Midodrine dose (mg)	10 TID	10 TID <sup>a</sup>
BP	74/26	110/54
P/F ratio	158	n/a
Time on NIPPV (h)	22 h	6 h
Heart rate	158	99
NT-pro	1106	n/a
Echo findings	25%–30%, severe global hypokinesis	40%–45%, mild global hypokinesis <sup>b</sup>

TPE: therapeutic plasma exchange; SOFA: Sequential Organ Failure Assessment; NIPPV: non-invasive positive pressure ventilation.

<sup>a</sup>Discontinued 48 h post-TPE without taper.

<sup>b</sup>Echo repeated 9 days after TPE.

(TPE) is a unique treatment that works at multiple levels of the cascade.

## Case

We present a case of COVID-19 pneumonia with septic shock and MOF that demonstrated significant clinical improvement after TPE. Written informed consent was obtained from the patient for their anonymized information to be published, and the case report received exemption from the LMC IRB. A 65-year-old female with a history of congestive heart failure (CHF) and ejection fraction (EF) of 45%, paroxysmal atrial fibrillation (afib), obstructive sleep apnea, hypertension, obesity, and insulin-dependent diabetes mellitus presented with 3 days of progressive dyspnea, dry cough, rhinorrhea, fever, and malaise. On presentation, she was hypoxemic and febrile but hemodynamically stable. Chest x-ray revealed bilateral pneumonia, and chest computed tomography showed diffuse ground-glass opacities in all lung fields bilaterally. Basic metabolic panel was normal with no acidosis or renal failure. White blood cell count was 6.4 with 8% lymphocytes and no bands. Procalcitonin was undetectable. Rapid flu and a commercially available polymerase chain reaction (PCR) test for common respiratory pathogens were negative. She was admitted to an airborne-isolation unit as a suspected case of COVID-19 and was treated empirically for possible bacterial pneumonia. During the first 24 h, her COVID returned positive and she remained relatively stable. On day 2, she became febrile to 102°F and tachycardic to the 150s, with telemetry showing afib. She developed hypotension requiring increasing doses of norepinephrine and midodrine. By day 3, her respiratory status worsened with increasing oxygen requirements and single word conversational dyspnea. She required continuous non-invasive positive pressure ventilation (NIPPV) for her hypoxemia and work of breathing. Despite amiodarone with magnesium and potassium replacement, her tachycardia, hypotension, and vasopressor needs persisted. Repeat

echocardiogram revealed an EF of 25%. She was urgently cardioverted due to her hemodynamic instability but remained hypotensive and hypoxemic even after brief conversion to sinus rhythm. Given her continued decline with refractory shock and MOF, she underwent 4.5-L TPE using fresh frozen plasma (FFP) as replacement fluid. She showed rapid improvement and was weaned off vasopressors within 24 h. She had improved respiratory status and was able to alternate between NIPPV and high-flow nasal cannula. She reverted back to afib with rapid ventricular response (RVR), which proved quite difficult to control, but ultimately converted back to normal sinus rhythm (NSR) with amiodarone, digoxin, and home sotalol. Her hypoxemia improved daily, and she was slowly weaned to room air. A repeat echocardiogram on day 9 showed return of her EF to baseline. She was discharged home on hospital day 13. See Table 1 for clinical summary.

## Discussion

Our patient showed clinical improvement with adjunct TPE after declining clinically, prior to treatment. While the improvement cannot absolutely be attributed to TPE, the temporal relationship to the treatment is certain.

A growing body of evidence demonstrates safety, feasibility, and clinical improvement with TPE for select cases of sepsis with MOF,<sup>7–9</sup> and based on currently available data, the American Society for Apheresis (ASFA) offers a Category III, 2B recommendation in this setting, allowing for use on a case-to-case basis.<sup>10</sup> The clinician's challenge remains to identify those patients most likely to benefit from this adjunct therapy without specific laboratory markers. Our group has developed institutional guidelines for TPE consideration in sepsis with multiple organ dysfunction syndrome (MODS) (from any pathogen), and recently completed a retrospective review of our single-center experience in this setting.<sup>11</sup> Details are available online, and a revised version of the article will be submitted for publication. In our study, nearly half the patients

presented with pneumonia as the primary source of infection (39/80). Compared to sepsis related to another process, a subgroup analysis of these patients showed the greatest mortality benefit with TPE (47.8% mortality vs 81.3% mortality,  $p=0.05$ ). Even with the limitations inherent to the study design, the results, combined with the other referenced studies, are encouraging and are pronounced enough to consider TPE in COVID-19-related sepsis with MOF and ARDS.

COVID-19 appears unusual in that it leads to severe respiratory failure, with the effects often limited to the lungs, at least early in the disease course. Patients often succumb to hypoxemia rather than MOF that is common with other causes of ARDS and sepsis. Chang has described the “two activation theory of the endothelium” in multiple publications as unified, manifesting various clinical phenotypes depending on the organ(s) involved,<sup>5,8</sup> and our recently published editorial summarizes this process as it may apply to COVID.<sup>12</sup> Delaying treatment until historical markers of shock and MOF are present with COVID may limit efficacy. Viral cardiomyopathy appears to be present frequently,<sup>13</sup> and we suggest that evidence of cardiac dysfunction may need to be considered evidence of shock. A newly reduced EF, new or poorly controlled tachyarrhythmia, or markedly abnormal cardiac enzymes/brain natriuretic peptide not due to acute coronary syndrome or CHF, may serve as evidence of shock and organ failure. Other organ failure, as defined in various scoring systems (Acute Physiology, Age, and Chronic Health Evaluation (APACHE); Sequential Organ Failure Assessment (SOFA)), may need to serve as evidence of shock in the absence of vasopressors, in order to identify critically ill patients with COVID-19. Our patient showed a rapid clinical decline, evident by her hemodynamic compromise, worsening heart failure, progressive hypoxemia/ARDS, thrombocytopenia, and elevated SOFA score. Our decision to implement TPE, in early March 2020, was based on extrapolated data not specific to COVID. Since then, retrospective has correlated elevated C-reactive protein, ferritin, d-dimer, and lactate dehydrogenase levels with decreased survival in severe COVID infection.<sup>13,14</sup> While previously not routinely measured clinically, these values may reflect the “cytokine storm” and endotheliopathy common to this pathologic pathway and may prove valuable in patient identification and response to therapy.

The cost and resources of TPE are substantial and must also be considered. TPE is currently an option for patients with sepsis and MOF, and should only be considered in this context. The net effect on resources—ventilators, vasopressors, ICU beds, and so on—needs further study, as well.

## Conclusion

Our patient’s rapid clinical improvement after TPE suggests a potential role in severe COVID infection with MOF. Further studies to investigate the clinical efficacy, optimal

use of resources, and cost-effectiveness of TPE in critically ill COVID-19 patients are needed.

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## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethics approval

The planning, conduct, and reporting of this publication are in accordance with the Helsinki Declaration, as revised in 2013. Our institution does not require approval for reporting individual cases or case series, and we received a waiver from the Institutional Review Board for reporting of this case report.


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## Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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