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SEQUENTIAL EXTRACORPOREAL ORGAN SUPPORT IN REFRACTORY SEPTIC SHOCK: A NOVEL COMBO APPROACH WITH COMPLETE RECOVERY: A CASE REPORT AND LITERATURE REVIEW

Khaled Sewify[1], Donia Elmasry[1], Ahmad Aboutaleb[1], Ahmad Abualsaud[1], Abdelaziz Alshaer[1], Hani Hosny[2], Ahmed Sewify[3]

[1] Critical Care Department, King Fahad Military Medical Complex, Dhahran, Saudi Arabia
[2] Emergency Department, Prince Sultan Medical College, Dhahran, Saudi Arabia
[3] ARC Industrial Transformation Training Centre (ITTC) for Joint Biomechanics, Queensland University of Technology, Brisbane, Australia

Corresponding author's e-mail: drsewafie@hotmail.com

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ABSTRACT

Introduction: Refractory septic shock and multiple organ dysfunction syndrome (MODS) remain a critical challenge in intensive care because they are associated with high morbidity and mortality despite advanced care.

Case description: This case report describes the successful management of a 74-year-old female patient admitted with coronavirus disease 2019 (COVID-19) infection complicated by severe acute respiratory distress syndrome, refractory septic shock and MODS, including acute kidney injury and gastrointestinal bleeding. The patient received three sequential interventions, including continuous renal replacement therapy with the Oxiris hemofilter (Baxter International Inc, Deerfield, IL, USA) for cytokine/endotoxin removal, integrated extracorporeal CO_2 removal ($ECCO_2R$) via a single vascular access, and adjunctive IgM/IgA-enriched intravenous immunoglobulin therapy. The combined interventions resulted in a 74% reduction in C-reactive protein (325 → 85 mg/l), a 92% reduction in procalcitonin (28.3 → 2.3 ng/ml), normalization of hypercapnia (PCO_2 107 → 48 mmHg) within 24h, and successful vasopressor discontinuation within 12 days. The patient recovered completely without any sequelae.

Conclusion: This case report demonstrates how coordinated extracorporeal organ support can produce beneficial effects in patients with refractory septic shock. The combined treatment provided renal, respiratory, and immunologic support through minimal vascular access and warrants further investigation in controlled trials.

KEYWORDS

Continuous renal replacement therapy, Oxiris hemofilter, $ECCO_2R$, IgM/IgA-enriched intravenous immunoglobulin, refractory septic shock

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LEARNING POINTS

- *Oxiris hemofilter rapidly improved haemodynamics:* Initiation of Oxiris-enhanced continuous renal replacement therapy (CRRT) was associated with a 40% reduction in norepinephrine requirement within 48 hours and a marked decline in inflammatory markers (C-reactive protein, CRP 325 → 188 mg/l; procalcitonin, PCT 28.3 → 9.1 ng/ml).
- *Integrated Oxiris/ECCO$_2$R rescued severe hypercapnic failure:* During rebound crisis (PCO_2 107 mmHg; pH 7.01), integrated extracorporeal CO_2 removal (ECCO$_2$R) via the CRRT circuit enabled lung-protective ventilation and normalized PCO_2 to ~45–50 mmHg within 24 hours.
- *Adjunctive IgM/IgA-enriched immunoglobulin supported recovery:* Adding IV IgM/IgA-enriched immunoglobulin (5 ml/kg/day for 5 days) during rebound hyperinflammation was associated with further biomarker reduction (CRP 305 → 85 mg/l; PCT 15.8 → 2.3 ng/ml) and complete vasopressor discontinuation by day 12, suggesting potential synergy of sequential multi-targeted support.

INTRODUCTION

The hospital mortality rate for refractory septic shock patients with multiple organ dysfunction exceeds 40% despite adherence to evidence-based protocols[1]. The standard approach of early recognition, source control, antimicrobial therapy and conventional organ support proves insufficient for patients requiring multiple high-dose vasopressors with simultaneous renal, respiratory, and immunologic failure.

New extracorporeal treatments target specific pathophysiologic mechanisms that develop during sepsis. The Oxiris haemofilter (Baxter International Inc, Deerfield, IL, USA) uses modified AN69 membrane surfaces to deliver standard continuous renal replacement therapy (CRRT) with superior endotoxin and inflammatory mediator elimination properties[2]. Extracorporeal CO_2 removal (ECCO$_2$R) technology enables protective lung ventilation strategies and simultaneous hypercapnia management in severe acute respiratory distress syndrome cases[3].

Intravenous immunoglobulin (IVIG) provides immunomodulatory effects through neutralization of cytokines and regulation of complement[4]. IgM/IgA-enriched intravenous immunoglobulin therapy may offer enhanced bacterial binding and complement activation compared with standard immunoglobulin preparations. Case series have reported its effectiveness in modulating hyperinflammation and dysregulated immune responses, including severe refractory sepsis such as postpartum sepsis[5].

While individual case series have reported positive outcomes with these modalities separately, and Nentwich et al. (2019) demonstrated the technical feasibility of combining ECCO$_2$R with standard CRRT in chronic hypercapnic respiratory failure[6], no prior study has documented the sequential integration of Oxiris-enhanced CRRT, ECCO2R, and IgM/IgA-enriched intravenous immunoglobulin in a single patient with acute refractory septic shock and multiple organ dysfunction syndrome (MODS). The clinical significance of this case lies not in any single modality, but in demonstrating how coordinated, sequential extracorporeal and immunomodulatory support can target multiple pathophysiologic mechanisms simultaneously (cytokine storm, ventilator-induced lung injury, and immune dysregulation) through a resource-efficient approach using single vascular access for dual organ support. This is both a therapeutic paradigm and a technical innovation that warrants investigation in controlled trials.

CASE DESCRIPTION

A 74-year-old Saudi female with diabetes mellitus, hypertension, and chronic coronary syndrome presented with fatigue, headache, and decreased oral intake. Vital signs were stable, with mild bilateral lower-limb oedema. Laboratory tests showed hypovolemic hyponatremia (serum sodium 119 mmol/l), prompting admission for fluid resuscitation.

Disease progression and complications

Days 1-2: Standard supportive care maintained the patient's clinical stability.

Day 3: The patient's condition worsened, and she developed acute hypoxic respiratory failure due to coronavirus disease 2019 (COVID-19). Chest imaging showed bilateral

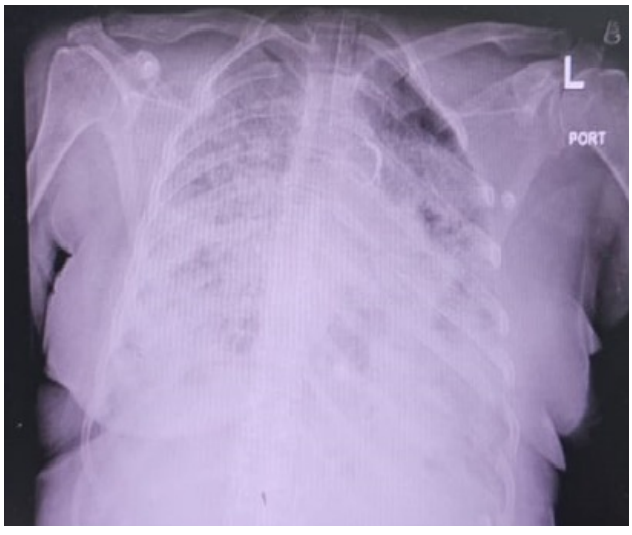


Figure 1. *Chest Imaging on day 3: Bilateral extensive infiltrates consistent with severe Coronavirus disease 2019-related acute respiratory distress syndrome.*

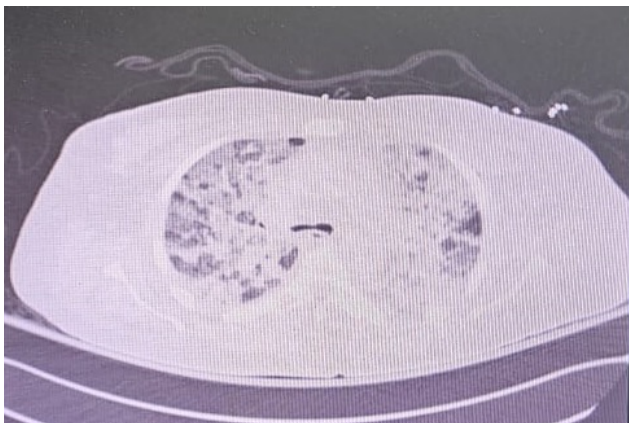


Figure 2. High-resolution computed tomography scan of the chest on day 3: extensive bilateral ground-glass opacities compatible with severe acute respiratory distress syndrome.

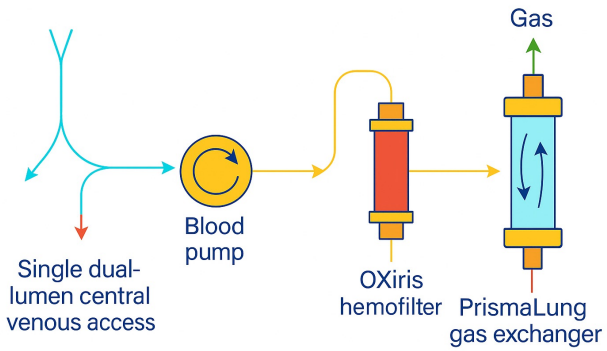


Figure 3. Integrated extracorporeal CO_2 removal-continuous renal replacement therapy circuit configuration. Schematic diagram showing the technical setup for simultaneous renal replacement and CO_2 removal through a single dual-lumen central venous access, including the blood pump, Oxiris hemofilter, and PrismaLung gas exchanger components.

extensive alveolar infiltrates consistent with moderately severe acute respiratory distress syndrome (P/F ratio <150) *(Fig. 1)*. Computed tomography showed extensive bilateral ground-glass opacities *(Fig. 2)*. The patient was intubated and managed with lung-protective ventilation (positive end-expiratory pressure 14 cmH_2O) and prone positioning. Intravenous methylprednisolone 40 mg daily was administered.

Day 3-4: The patient developed worsening hemodynamic instability despite adequate fluid resuscitation, so dual vasopressor therapy (norepinephrine 0.4 mcg/kg/min and vasopressin 0.04 U/min) was initiated. Acute kidney injury developed (serum creatinine 185 µmol/l) with prolonged oliguria (<0.5 ml/kg/h) and refractory metabolic acidosis (lactate 9 mmol/l). Ceftazidime/avibactam was started following a sputum culture positive for carbapenem-resistant Enterobacterales. Voriconazole was initiated, followed by ganciclovir due to elevated cytomegalovirus titres.

Therapeutic interventions

Phase 1: Oxiris-enhanced CRRT (days 3-4).

Continuous venovenous hemodiafiltration was initiated as CRRT because of extreme hyperinflammation to remove cytokines and endotoxins. Technical parameters included a blood flow of 150 ml/min, a dialysate flow of 1000 ml/h, and replacement fluid of 1000 ml/h under regional citrate anticoagulation. The Oxiris filter served dual functions, providing conventional renal replacement therapy and enhanced inflammatory mediator adsorption. A notable improvement became evident after 24 hours, including a 42% decrease in C-reactive protein (CRP) from 325 to 188 mg/l and a 68% decrease in procalcitonin (PCT) from 28.3 to 9.1 ng/ml. Vasopressor requirements were reduced by 40% due to a reduction in norepinephrine dose, with hemodynamic stabilization and improved cardiac output.

Phase 2: Rebound crisis and combined support (day 7).

Blood product administration for gastrointestinal bleeding resulted in transfusion-related acute lung injury (TRALI) that led to rebound hyperinflammation with rising biomarkers (CRP 305 mg/l and PCT 15.8 ng/ml), disseminated intravascular coagulation, severe hypercapnic respiratory failure (PCO_2 107 mmHg, pH 7.01), and deteriorating respiratory mechanics despite optimized ventilation.

Phase 3: Integrated $ECCO_2R$ and renewed oxiris therapy (days 7-9).

The Prisma Lung system (Löwenstein Medical, Bad Ems, Germany) was used for $ECCO_2R$ via the existing CRRT circuit through a single dual-lumen central venous catheter, following the King Fahd Military Medical Complex standardized protocol[7]. *Figure 3* illustrates the circuit configuration for delivering dual organ support from a single vascular access point. This approach optimized blood flow (350 ml/min) for enhanced CO_2 removal while maintaining renal replacement without additional invasive procedures[6]. CO_2 clearance of 45–60 ml/min enabled ultra-protective ventilation (Vt 4 mL/kg; plateau pressure <25 cmH_2O) while rapidly correcting hypercapnia. Within 12 hours of $ECCO_2R$ initiation, PCO_2 decreased from 107 → 60 mmHg and normalized to 48 mmHg within 24 hours. The pH improved from 7.01 → 7.32, with sustained respiratory improvement that facilitated subsequent weaning from mechanical ventilation.

Phase 4: Adjunctive IgM/IgA-enriched intravenous immunoglobulin therapy (days 7-12).

Immune dysregulation persisted, with elevated inflammatory markers despite extracorporeal interventions. Therefore, IV IgM/IgA-enriched immunoglobulin therapy was administered at 5 ml/kg/day for five consecutive days, based on evidence suggesting immunomodulatory effects in hyperinflammatory and immune deficiency states[5]. Following IgM/IgA-enriched immunoglobulin therapy addition to the combined regimen:

- CRP: 305 → 85 mg/l (72% additional reduction).
- PCT: 15.8 → 2.3 ng/ml (85% additional reduction).
- Progressive hemodynamic stabilization.
- Complete vasopressor discontinuation by day 12.

Clinical outcomes

The patient achieved full recovery. Inflammatory markers

decreased by total of 74% for CRP and 92% for PCT. The patient was successfully weaned from $ECCO_2R$ and liberated from mechanical ventilation on day 18. She recovered from acute kidney injury and maintained stable haemodynamics without vasopressors throughout the recovery period. No complications or adverse events related to the procedures were observed. Chest imaging at discharge showed near-complete resolution of bilateral infiltrates, consistent with clinical improvement *(Fig. 4)*.

Table 1 shows the sequential clinical and laboratory response to combined extracorporeal interventions.

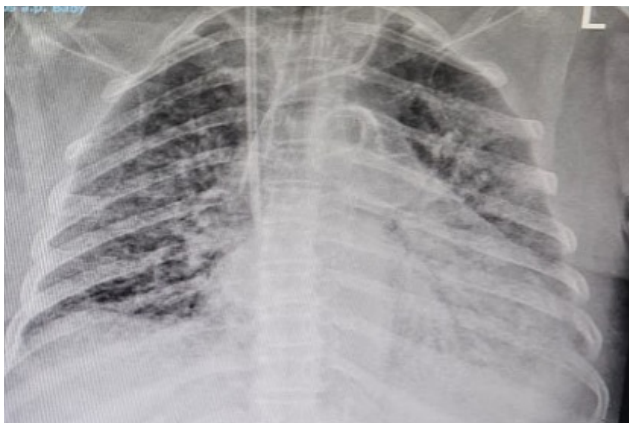


Figure 4. *Chest imaging on day 15: marked resolution following combined extracorporeal interventions with near complete radiologic recovery.*

DISCUSSION

The case highlights the first reported successful application of sequential integrated extracorporeal organ support used to treat refractory septic shock and presents three clinical innovations with potential clinical value.

The technical progress of $ECCO_2R$ integration with CRRT through single vascular access represents a major advancement. The method eliminates the requirement for extra large-bore cannulation while delivering simultaneous renal and respiratory support. CO_2 clearance of 45–60 ml/min enabled protective lung ventilation, potentially preventing further ventilator-induced lung injury while treating severe hypercapnia. The SUPERNOVA study demonstrated the feasibility and safety of $ECCO_2R$ in acute respiratory distress syndrome[3].

The clinical importance of this case extends beyond demonstrating feasibility of combining three modalities. Each intervention addressed a distinct pathophysiologic mechanism at critical timepoints:

- Oxiris-CRRT (days 3-4): Targeted the initial cytokine surge, achieving 68% PCT reduction and 40% vasopressor reduction, demonstrating the cytokine peak concentration hypothesis.
- $ECCO_2R$ (day 7): Rescued life-threatening hypercapnic respiratory failure (PCO_2 107 mmHg) while maintaining ultra-protective ventilation (Vt 4 ml/kg), preventing further ventilator-induced lung injury during the critical TRALI episode.
- IgM/IgA-enriched immunoglobulin therapy (days 7-12): Provided sustained immunomodulation during rebound

Parameter	Baseline (day 1)	Pre-Oxiris (day 3)	Post-Oxiris (day 4)	Pre-ECCO2R + IgM/IgA-enriched immunoglobulin (day 7)	Post-combined (day 9)	Full recovery (day 18)
Inflammatory markers						
CRP (mg/l)	1.9	325	188	305	85	12
Procalcitonin (ng/ml)	0.03	28.3	9.1	15.8	2.3	0.2
Organ Function						
Creatinine (µmol/l)	120	185	165	145	120	88
PCO_2 (mmHg)	35	55	48	107	48	38
P/F ratio	420	135	180	95	220	380
pH	7.38	7.28	7.32	7.01	7.32	7.4
Support requirements	–	–	–	–	–	–
Norepinephrine (µg/kg/min)	0	0.4	0.24	0.15	0.05	0
PEEP (cmH_2O)	-	14	14	14	12	-
SOFA score	2	15	11	13	6	1

Table 1. *Sequential clinical and laboratory response to combined extracorporeal interventions.*

Abbreviations: $ECCO_2R$, Extracorporeal CO_2 removal; CRP, C-reactive protein; P/F, PaO_2/FiO_2; PEEP, positive end-expiratory pressure; SOFA, sequential organ failure assessment.

Reference	Study type	Population	Intervention	Outcomes
Shum et al., 2013[11]	Prospective case series with historical controls	6 patients with septic AKI	Oxiris + CVVH	Significant reduction in SOFA scores by 37% after 48 h of therapy
Ugurov et al., 2020[12]	Single-centre case series	15 COVID-19 patients	Oxiris hemofilter	Early initiation of Oxiris was associated with stable or reducing levels of IL-6, IL-8, IL-10 and TNFα
Zhang et al., 2021[13]	Case series	5 COVID-19 patients	CRRT followed by Oxiris hemofilter therapy	Reduced levels of cytokines, hemodynamic stabilization and improvement of organ function were observed with Oxiris
Rosalia et al., 2020[14]	Prospective cohort study	44 COVID-19 cases	CVVH + Oxiris	Reduction in CRP, ferritin, fibrinogen and other inflammatory mediators were observed

Table 2. *Summary of studies on the effect of Oxiris-mediated intervention in sepsis.*

Abbreviations: AKI, acute kidney injury; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous hemofiltration; SOFA, sequential organ failure assessment.

hyperinflammation, achieving additional reductions in inflammatory markers (CRP 305 → 85 mg/l, 72%; PCT 15.8 → 2.3 ng/ml, 85%) and enabling complete vasopressor discontinuation.

The temporal relationship between each intervention and corresponding biomarker improvements *(Table 1)* suggests therapeutic effects beyond natural recovery. Moreover, the technical integration of $ECCO_2R$ with CRRT through single vascular access represents a practical advancement over standalone $ECCO_2R$ systems, eliminating additional cannulation risks while optimizing critical care resources.

While we cannot definitively attribute causation in a single case, the sequential combination addressed limitations of each modality used alone: Oxiris-CRRT lacks randomized controlled trial (RCT) mortality evidence; $ECCO_2R$ showed no mortality benefit and raised safety concerns in the REST trial[10]; and IgM/IgA-enriched immunoglobulin lacks strong evidence as monotherapy. The synergistic, coordinated approach may overcome these individual limitations, warranting systematic investigation in controlled trials for patients with MODS.

Nentwich et al. (2019) first reported the technical feasibility of combining $ECCO_2R$ with CRRT in 10 patients with chronic hypercapnic respiratory failure (chronic obstructive pulmonary disease exacerbations and obesity hypoventilation), demonstrating effective CO_2 reduction and decreased ventilation requirements[6]. Our case differs in several key aspects: the clinical context (rescue therapy in acute refractory septic shock with MODS rather than chronic stable respiratory failure), incorporation of an additional modality (IgM/IgA-enriched immunoglobulin targeting immune dysregulation), enhanced blood purification (use of the Oxiris hemofilter for cytokine/endotoxin adsorption, achieving an overall reductions of 92% in PCT and 74% in CRP), a sequential rescue strategy ($ECCO_2R$ initiated in response to an acute hypercapnic crisis [PCO_2 107 mmHg, pH 7.01] following TRALI rather than planned from the start), and complete recovery with vasopressor discontinuation and multiorgan recovery rather than improvement in ventilatory parameters alone.

While Nentwich et al. established the technical feasibility of combined $ECCO_2R$-CRRT in chronic respiratory failure[6], our case extends this concept to acute critical illness with multi-organ failure, adds a third immunomodulatory dimension, and demonstrates complete recovery in a condition with high mortality. These distinctions justify our claim of novelty in the context of refractory septic shock management.

Biological rationale: targeting multiple pathophysiologic pathways

The approach targeted three essential pathophysiologic mechanisms at the same time.

1. The 68% initial reduction in PCT after starting Oxiris therapy supports the cytokine peak concentration hypothesis, suggesting that early cytokine removal during inflammatory peaks may help halt disease progression[8]. However, the apparent effectiveness of extracorporeal adsorption filters reported in case series remains unproven for sepsis mortality reduction, as large randomized controlled trials are lacking *(Table 2)*[9].
2. Rapid correction of hypercapnia (PCO_2 107 → 48 mmHg within 24 hours) enabled ultra-protective ventilation and may have reduced ventilator-induced lung injury. The REST trial reported no mortality benefit with standalone $ECCO_2R$ and raised safety concerns, including increased bleeding risk, while facilitating lower tidal volumes; the study was not powered to detect small mortality differences[10]. In contrast, our approach integrated $ECCO_2R$ within the CRRT circuit using lower blood flow and a single access, potentially reducing cannulation burden; nonetheless, safety conclusions cannot be drawn from a single case.

3. IgM/IgA-enriched immunoglobulin therapy administered during rebound hyperinflammation provided additional immunomodulation after extracorporeal cytokine/endotoxin adsorption and was associated with an additional 85% decrease in PCT.

Clinical significance: paradigm for refractory cases

The 92% overall reduction in PCT and complete clinical recovery in this critically ill patient with multiple organ failure suggests potential for this approach in cases where conventional therapy fails. The absence of complications despite multiple extracorporeal interventions supports the safety profile when implemented by experienced teams.

Limitations and future directions

This single-case experience contains inherent limitations which prevent researchers from establishing cause-effect relationships between interventions and outcomes. The impact of standard therapies used at the same time (antimicrobials, corticosteroids) remains unaccounted for. However, the time sequence between each intervention and the corresponding biomarker improvements indicates therapeutic effects that extend beyond natural recovery.

Future research priorities:

- Controlled trials comparing sequential vs. single-modality extracorporeal support.
- Development of biomarker-guided protocols for intervention timing.
- Cost-effectiveness analysis of integrated vs. separate device approaches.
- Investigation of optimal patient selection criteria.

CONCLUSION

The sequential use of Oxiris-enhanced CRRT followed by $ECCO_2R$ and IgM/IgA-enriched immunoglobulin treatment led to a complete recovery of refractory septic shock with multiple organ dysfunction. The case demonstrates that coordinated extracorporeal organ support works effectively to treat patients who fail to respond to standard treatments.

The technical advancement of dual-organ support through single vascular access with targeted immunomodulation requires systematic multicentre controlled trials for further investigation. Research should concentrate on determining the best selection criteria for patients and timing of interventions and individual treatment effects to create evidence-based protocols for this promising method.

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