Review

Extracorporeal membrane oxygenation combined with continuous renal replacement therapy for the treatment of severe burns: current status and challenges

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Abstract

Severe burns often cause various systemic complications and multiple organ dysfunction syndrome, which is the main cause of death. The lungs and kidneys are vulnerable organs in patients with multiple organ dysfunction syndrome after burns. Extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT) have been gradually applied in clinical practice and are beneficial for severe burn patients with refractory respiratory failure or renal dysfunction. However, the literature on ECMO combined with CRRT for the treatment of severe burns is limited. Here, we focus on the current status of ECMO combined with CRRT for the treatment of severe burns and the associated challenges, including the timing of treatment, nutrition support, heparinization and wound management, catheter-related infection and drug dosing in CRRT. With the advancement of medical technology, ECMO combined with CRRT will be further optimized to improve the outcomes of patients with severe burns.

Key words: Severe burns, Extracorporeal membrane oxygenation, Continuous renal replacement therapy, Multiple organ dysfunction syndrome, Acute kidney injury, Acute respiratory distress syndrome

Highlights

• This is the first review of extracorporeal membrane oxygenation combined with continuous renal replacement therapy for the treatment of severe burns, which might help to improve outcomes and reduce mortalities.
• This review is the first to focus on the current challenges of this combined therapy for the patients with severe burns, including timing of treatment, nutrition support, heparinization and wound management, catheter-related infection and drug dosing in continuous renal replacement therapy.

Background

Patients with severe burns are at a high risk of multiple organ dysfunction syndrome (MODS) due to high incidence rates of inhalation injury, shock and systemic infections. The lungs and kidneys are vulnerable organs in patients with MODS. Respiratory failure associated with acute kidney injury (AKI) is very difficult to treat and has a high mortality rate [1,2]. Extracorporeal membrane oxygenation (ECMO) originated from extracorporeal circulation technology, which provides days to weeks of life support for patients with respiratory failure and/or heart failure [3]. Early ECMO technology was mainly used as supportive care for acute respiratory
distress syndrome (ARDS) in adults and for critical neonatal conditions [4,5]. With technological advancements, ECMO has become safer and more widely applied, with applications including perioperative bridging therapy in critical cardiothoracic surgical patients, supportive care for cardiogenic shock associated with cardiac emergencies (such as fulminating myocarditis and acute myocardial infarction) and auxiliary care for cardiopulmonary resuscitation [6–8]. Based on different forms of access to patients’ vessels, the method used may be venous–venous ECMO (VV-ECMO) or venous–arterial ECMO (VA-ECMO). VV-ECMO provides only respiratory support while VA-ECMO provides both cardiac and respiratory support. In the literature, the complications of ECMO may inflict serious morbidity, which can be classified into complications related to the ECMO device (e.g. circuit clotting, pump or oxygenator malfunction, cannula issues) or physiological complications (e.g. bleeding, haemolysis, infection). The reported mortality for ECMO in severe lung failure ranges from 25% to greater than 60%, while the reported mortality of VA-ECMO remains high and within the wide range of 43–93% [9,10]. It should be noted that the quality control through a learning curve using cumulative sum analysis is essential for improving the outcome of ECMO programme. The prevalence of AKI, a common complication among severely burned patients, has been reported to be close to 25%, with an associated mortality rate of 35%. However, the reported mortality is up to 80% among those requiring renal replacement therapy [11,12]. Continuous renal replacement therapy (CRRT) refers to prolonged use of extracorporeal blood purification for continuous renal replacement to eliminate metabolites and toxins and correct fluid, electrolyte and pH imbalances [13–15]. The application of ECMO and CRRT in patients with burns has been reported in recent decades; however, the literature on ECMO combined with CRRT for the treatment of severe burns is limited. Here, we focus on the current status of ECMO combined with CRRT for the treatment of severe burns and the associated challenges.

**Review**

**ECMO combined with CRRT for MODS**

MODS is one of the systemic complications of severe burns, which is considered as the main cause of death. ARDS is one of the most serious complications of extensive burns, with an incidence of 11.8% to 17% [16,17]. If severe inhalation injury is present, the morbidity of lung replacement is substantially higher. In adult patients with burns, the prevalence of AKI is 26.6% to 53.3% [18,19]. For patients with respiratory failure and renal failure, ECMO combined with CRRT improves outcomes and reduces mortality [20,21]. Notably, AKI and fluid overload are common complications during ECMO treatment for respiratory failure and the prevalence of AKI is 70% to 85% in patients undergoing ECMO [22–24]. Some researchers believe that the presence of the ECMO circuit and catheter placement techniques contribute to ECMO-associated kidney injury, which is mainly related to the systemic inflammatory response, renal circulatory disturbances, ischaemia–reperfusion injury and oxidative stress [25–28]. Fluid overload is usually secondary to AKI or improper volume management during ECMO treatment. Research has shown that 40–60% of patients on ECMO who developed AKI were placed on CRRT [29]. Another study from the Extracorporeal Life Support Organization found that the indications for ECMO combined with CRRT include fluid overload (43%), AKI (35%), prevention of fluid overload (16%), electrolyte imbalances (4%) and other complications (2%) [30]. Nevertheless, combined therapy was associated with increased mortality compared with ECMO alone, which ranged from 39.5% to 100% [29,31,32].

**Management of ECMO combined with CRRT**

At present, three approaches can be used to combine ECMO with CRRT: connecting the CRRT machine to the ECMO circuit, connecting the filter to the ECMO circuit (Figure 1) and separate circuits (Figure 2) [20,33]. The advantages of the first approach include pressure monitoring and the ability to adjust blood flow or the ultrafiltration volume. However, this approach involves complex procedures and high costs. The advantages of the second approach include low cost and convenience, but it is rarely used in clinical practice because it does not allow pressure monitoring or adjustment of blood flow or the ultrafiltration volume. Moreover, the filter is prone to clogging. The third approach has minimal impact on ECMO but increases the risks of invasive procedures, bleeding and infection and the dosage of CRRT anticoagulants [34–37]. Different methods are available to connect the CRRT machine to the ECMO circuit: pre-pump connection of the CRRT inlet (arterial) and outlet (venous) lines (Figure 3); post-pump connection of the CRRT inlet and outlet lines (Figure 4); post-pump connection of the CRRT inlet line and pre-pump connection of the CRRT outlet line (Figure 5); and post-oxygenator connection of the CRRT inlet line and pre-oxygenator connection of the CRRT outlet line with a Luer lock (Figure 6) [38,39].

ECMO combined with CRRT is an optional regimen for critically ill patients whose condition is refractory to
conventional treatments [40,41]. The timing of CRRT in ECMO patients is generally based on kidney function and/or fluid load. Researchers believe that early use of CRRT is more beneficial [42]. Yetimakman et al. concluded that CRRT is warranted if fluid overload has reached 10% of patient weight within 24 hours [39]. Schmidt et al. showed that 42% of 172 patients received CRRT within three days after the start of ECMO and that the indications for CRRT included potassium > 6.5 mmol/L, pH < 7.2, urea > 25 mmol/L, creatinine > 300 μmol/L or organ oedema (e.g. pulmonary oedema) [43].

The application of ECMO combined with CRRT requires a multidisciplinary treatment team, including experienced burn surgeons, cardiothoracic surgeons, intensivists, nurses, nutritionists and psychotherapists [44]. During combined therapy, measures, including circuit management, haemodynamic monitoring, fluid management, anticoagulation management and respiratory monitoring, should be implemented to prevent complications such as intracranial haemorrhage, gastrointestinal haemorrhage, haemolysis, infection and limb ischaemia [45,46]. Dado et al. concluded that early integration of combined therapy with experience and expertise might contribute to improved outcomes [29].

Current status of ECMO combined with CRRT for severe burns
A few studies have investigated the effects of ECMO for burns with inhalation injury and it has been demonstrated that early implementation of ECMO is of benefit in the treatment of severe refractory ARDS [47,48]. CRRT can be used to treat AKI to alleviate fluid overload, improve renal recovery and reduce inflammation and it has been widely used in clinical practice for severe burns [49,50]. However, the literature on ECMO combined with CRRT for the treatment of burns is limited (Table 1) [51–56]. The results of these studies demonstrate encouraging survival rates in the range of 50–100% with combined therapy, indicating that this should be considered to improve outcomes in cases of worsening ARDS and AKI with unsuccessful conventional treatment.

Nevertheless, studies on the application of combined treatment in patients with burns affecting a total body surface area (TBSA) >80% have not been reported. Previously, three patients (TBSA: 85%, 91%, 95%) with refractory respiratory failure and renal insufficiency received VV-ECMO combined with CRRT in our department; two patients were successfully withdrawn from the combined treatment after recovery of respiratory and renal functions. However, we were unable to perform early debridement and skin grafting due to wound bleeding and limited device portability. All three patients died of MODS resulting from wound infection followed by severe sepsis. Some issues, especially the influence of combined
therapy on the treatment outcomes of extensive wounds, must be addressed.

Challenges of ECMO combined with CRRT for severe burns

Timing of treatment During the shock stage, patients with severe burns often have hypovolemia and hypoperfusion, which are contraindications for ECMO and CRRT as these treatments may interfere with fluid resuscitation. Therefore, ECMO combined with CRRT is usually used after the shock stage at the discretion of burn physicians [57,58]. In addition, the key to treating patients with extensive burns is early wound closure and most patients require prompt debridement and skin grafting [59,60]. ECMO and CRRT are indicated for patients with refractory ARDS and AKI before surgery. In such cases, surgery may be delayed or even cancelled for safety reasons. While ECMO combined with CRRT can replace lung and kidney functions and improve outcomes, deep, extensive wounds may still cause severe systemic infection and worsen a patient’s condition. With the advancement of medical technology and the optimization of treatment regimens, patients with extensive burns may promptly receive ECMO combined with CRRT, even during the shock stage, to improve outcomes. Likewise, they may receive combined therapy synchronized with early surgery to close the wounds to minimize sources of infection.

Nutritional support Severe burn injury leads to a hypermetabolic state, especially hypercatabolism, resulting in the consumption of more nutrients and oxygen than usual, which causes severe malnutrition, low immunity and high morbidity from infection and organ dysfunction [61–63]. Furthermore, ECMO itself causes hypercatabolism, and CRRT depletes some intravenous nutrients [64,65]. Patients with extensive burns usually require both enteral and parenteral nutrition. Lipid emulsion is an integral part of parenteral nutrition. Studies have shown that lipid emulsion infusion during ECMO causes lipid emulsion layering, aggregation and coagulation, thereby affecting haemodynamics and energy delivery [66]. To ensure the safety of ECMO, lipid emulsions are often removed from parenteral nutrition, which causes energy deficiencies in patients with severe burns. Buck et al. showed that the incidence of adverse reactions is lower if lipid emulsion is infused through a separate venous line instead of the ECMO circuit, indicating that this approach should be used when possible [67]. It is noteworthy that enteral nutrition is the primary approach for nutritional support during ECMO combined with CRRT in patients with severe burns [68]. In addition, a nasogastric or nasojejunal tube may be placed before the treatment and drugs that improve gastrointestinal motility should be administered to promote nutrient digestion and absorption. Further research is needed to explore improved regimens of sufficient nutritional support for patients with severe burns undergoing ECMO combined with CRRT.

Heparinization and wound management Anticoagulation is usually required during ECMO combined with CRRT and may cause wound bleeding or increase intraoperative blood loss [69]. Therefore, anticoagulation requirements have limited the application of ECMO in patients with severe burns. Local citrate anticoagulation is commonly used during CRRT to prevent heparin-induced bleeding [70,71]. Short-term, heparin-free ECMO may be an effective transitional treatment for patients in whom anticoagulation is contraindicated, but it requires careful monitoring and management by an experienced multidisciplinary treatment team [72,73]. For patients with extensive burns, ECMO can feasibly be administered during wound dressing and surgery as long as wound bleeding is controlled. At present, heparin is often applied via the ECMO oxygenator and monitored by the activated clotting time or anti-Xa activity [74,75]. Recently, research on anticoagulation with heparin has focused on determining the optimal heparin doses for ECMO, which will yield a more reliable and effective heparin assessment system and minimize the effect of heparinization on wound management. Lai et al. showed that fibres that release nitrogen oxide may be used on gas exchangers to reduce platelet activation and thrombosis without causing

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Table 1. Selected studies reporting treatment of ECMO combined with CRRT in burn patients

| Study               | Year | Patient No. | TBSA (%) | Type of ECMO | ECMO duration (hours) | CRRT duration (hours) |
|---------------------|------|-------------|----------|--------------|-----------------------|-----------------------|
| Askegard-Giesmann et al. [51] | 2010 | 13          | NA       | VV-ECMO      | NA                    | NA                    |
| Pu et al. [52]       | 2017 | 1           | 60       | UA-ECMO      | 224                   | 624                   |
| Hsu et al. [53]      | 2017 | 1           | 50       | VV-ECMO      | 401                   | NA                    |
| Ainsworth et al. [54] | 2018 | 9           | 1–76     | VV-ECMO      | 63–539                | NA                    |
| Szemgyorgyi et al. [55] | 2018 | 4           | 12–51    | VV-ECMO      | 264–840               | NA                    |
| Dadras et al. [56]   | 2019 | 4           | 15–75    | VV-ECMO      | 48–984                | 96–1824               |

ECMO extracorporeal membrane oxygenation, CRRT continuous renal replacement therapy, TBSA total body surface area, NA not available, VV-ECMO venous-venous extracorporeal membrane oxygenation, UA-ECMO venous-arterial extracorporeal membrane oxygenation
bleeding, which provides new insight into anticoagulation improvement during ECMO [76].

Catheter-related infection Patients receiving ECMO and CRRT are prone to catheter-related infections due to prolonged indwelling of deep venous catheters [77,78]. Catheters inserted through the burn wounds of patients with extensive burns pose a high risk of infection [79]. To prevent catheter-related infection, daily dressing changes and even the use of topical antibiotics are required. The intervals for catheter replacement should be minimized, especially when a catheter is inserted through burn wounds. Moreover, patients should be withdrawn from treatment as soon as possible after recovery of respiratory and renal functions. Likewise, to decrease the risk of infections in these patients, further study is necessary to investigate the proper timing and dosage of antibiotics during combined therapy.

Drug dosing in CRRT Most severely burned patients undergoing CRRT for AKI are treated with antimicrobials. Optimizing antimicrobial treatment in these patients can be challenging because pathophysiological changes after burns and concomitant CRRT can influence the pharmacokinetics and pharmacodynamics of antimicrobials [80,81]. Appropriate antimicrobial selection and drug dosing are essential to improve clinical outcomes, avoid overdosing-related toxicity and underdosing-related treatment failure and/or potential pathogen resistance [82–84]. Drug dosing during CRRT are recommended by literatures, including meropenem, cefepime, levofloxacin, tigecycline, polymyxin B, vancomycin, voriconazole and amphotericin B [80,82,85]. However, the antimicrobial regimen should be administered cautiously and individualized by considering factors such as the site of infection, the severity of illness, residual renal function, comorbidities, renal replacement modalities, etc. [80,86–88]. It should be noted that drug dosing adjustments with the therapeutic drug monitoring could improve the outcomes of patients with severe burns undergoing CRRT [89,90].

Conclusions

For patients with severe burns, when refractory ARDS and concomitant AKI occur, treatment using ECMO combined with CRRT may be complementary and effective, helping to improve outcomes and reduce mortality. However, various challenges remain in terms of the timing of treatment, nutritional support, anticoagulation, catheter-related infections and drug dosing in CRRT, which will be gradually addressed with the rapid development of medical technology. At present, clinical studies on ECMO combined with CRRT for severe burns are limited and multicentre clinical studies in large populations are necessary to improve the outcomes of severe burns.

Authors’ contributions

HS drafted the manuscript. ZY and YP helped in the drafting of the manuscript. GL revised the manuscript. All authors reviewed the final manuscript for important intellectual content. All authors read and approved the final manuscript.

Abbreviations

AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; MODS: multiple organ dysfunction syndrome; VA-ECMO: veno–arterial extracorporeal membrane oxygenation; VV-ECMO: venous–venous extracorporeal membrane oxygenation.

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Conflicts of interest

The authors have no conflict of interest in connection with the work submitted.

References

1. Kallinen O, Maisniemi K, Bohling T, Tukiainen E, Koljonen V. Multiple organ failure as a cause of death in patients with severe burns. J Burn Care Res. 2012;33:206–11.
2. Saffle JR, Sullivan JJ, Tuohig GM, Larson CM. Multiple organ failure in patients with thermal injury. Crit Care Med. 1993;21:1673–83.
3. White A, Fan E. What is ECMO? Am J Respir Crit Care Med. 2016;193:9–10.
4. Fletcher K, Chapman R, Keene S. An overview of medical ECMO for neonates. Semin Perinatol. 2018;42:68–79.
5. Bein T, Aubron C, Papazian L. Focus on ECMO and ECCO2R in ARDS patients. Intensive Care Med. 2017;43:1424–6.
6. Rao P, Khalpey Z, Smith R, Burkhoff D, Kociol RD. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest. J Cardiothorac Vasc Anesth. 2015;29:637–45.
7. Xie A, Phan K, Tsai YC, Yan TD, Forrest P. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest: a meta-analysis. J Cardiothorac Vasc Anesth. 2015;29:637–45.
8. Sun T, Guy A, Sidhu A, Finlayson G, Grunau B, Ding L, et al. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) for emergency cardiac support. J Crit Care. 2018;44:31–8.
9. Karagiannidis C, Brodie D, Strassmann S, Stoelben E, Philipp A, Bein T, et al. Extracorporeal membrane oxygenation: evolving epidemiology and mortality. Intensive Care Med. 2016;42:889–96.
10. Millar JE, Fanning JP, McDonald CI, McAuley DF, Fraser JF. The inflammatory response to extracorporeal membrane oxygenation (ECMO): a review of the pathophysiology. *Crit Care*. 2016;20:387. doi: 10.1186/s13054-016-1570-4.

11. Brusselaers N, Monstrey S, Colpaert K, Decruyenaere J, Blot SI, Hoste EA. Outcome of acute kidney injury in severe burns: a systematic review and meta-analysis. *Intensive Care Med*. 2010;36:915–25.

12. Chung KK, Coates EC, Smith DJ Jr, Karlnoski RA, Hickerson WL, Arnold-Ross AL, et al. High-volume hemofiltration in adult burn patients with septic shock and acute kidney injury: a multicenter randomized controlled trial. *Crit Care*. 2017;21:289. doi: 10.1186/s13054-017-1878-8.

13. Karkar A, Ronco C. Prescription of CRRT: a pathway to optimize therapy. *Ann Intensive Care*. 2020;10:32. doi: 10.1186/s13613-020-00648-y.

14. Romagnoli S, Ricci Z, Ronco C. CRRT for sepsis-induced acute kidney injury. *Curr Opin Crit Care*. 2018;24:483–92.

15. Vaara ST, Bellomo R. Extra-renal indications for continuous renal replacement therapy. *Contrib Nephrop*. 2018;194:90–8.

16. Hollingsed TC, Saffle JR, Barton RG, Craft WB, Morris SE. Etiology and consequences of respiratory failure in thermally injured patients. *Am J Surg*. 1993;166:592–6.

17. Dancey DR, Hayes J, Gomez M, Schouten D, Fish J, Peters W, et al. ARDS in patients with thermal injury. *Intensive Care Med*. 1999;25:1231–6.

18. Ricci Z, Romagnoli S, Ronco C. Renal replacement therapy. *F1000Res*. 2016;5:F1000 Faculty Rev-103. doi: 10.12688/f1000research.6935.1.

19. Helanterä I, Koljonen V, Finne P, Tukiainen E, Gissler M. The risk for end-stage renal disease is increased after burn. *Burns*. 2016;42:316–21.

20. Chen H, Yu RG, Yin NN, Zhou JX. Combination of extracorporeal membrane oxygenation and continuous renal replacement therapy in critically ill patients: a systematic review. *Crit Care*. 2014;18:675. doi: 10.1186/s13054-014-0675-x.

21. Ostermann M, Connor M Jr, Kashani K. Continuous renal replacement therapy during extracorporeal membrane oxygenation: why, when and how? *Curr Opin Crit Care*. 2018;24:493–503.

22. Askenazi DJ, Selewski DT, Paden ML, Cooper DS, Bridges BC, Zappitelli M, et al. Renal replacement therapy in critically ill patients receiving extracorporeal membrane oxygenation. *Clin J Am Soc Nephrol*. 2012;7:1328–36.

23. Cheng R, Hachamovitch R, Kittleson M, Patel J, Arabia F, Moriguchi J, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiacogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. *Ann Thorac Surg*. 2014;97:610–6.

24. Kielstein JT, Heiden AM, Beutel G, Gortlieb J, Wiesner O, Hafer C, et al. Renal function and survival in 200 patients undergoing ECMO therapy. *Nephrol Dial Transplant*. 2013;28:86–90.

25. Kilburn DJ, Shekar K, Fraser JF. The complex relationship of extracorporeal membrane oxygenation and acute kidney injury: causation or association? *Biomed Res Int*. 2016;2016:1094296. doi: 10.1155/2016/1094296.

26. Chelazzi C, Villa G, Mancinelli P, De Gaudio AR, Adembri C. Glycocalyx and sepsis-induced alterations in vascular permeability. *Crit Care*. 2015;19:26. doi: 10.1186/s13054-015-0741-2.

27. Shekar K, Fraser JF. Can timely ECMO initiation mitigate pre-ECMO risk factors for acute kidney injury? *Ann Thorac Surg*. 2014;98:1523. doi: 10.1016/j.athoracsur.2014.05.055.

28. van den Akker JP, Egal M, Groeneveld AB. Invasive mechanical ventilation as a risk factor for acute kidney injury in the critically ill: a systematic review and meta-analysis. *Crit Care*. 2013;17:R98. doi: 10.1186/cc12743.

29. Dado DN, Ainsworth CR, Thomas SB, Huang B, Piper LC, Sams VG, et al. Outcomes among patients treated with renal replacement therapy during extracorporeal membrane oxygenation: a single-center retrospective study. *Blood Purif*. 2020;49:341–7.

30. Fleming GM, Askenazi DJ, Bridges BC, Cooper DS, Paden ML, Selewski DT, et al. A multicenter international survey of renal supportive therapy during ECMO: the kidney intervention during extracorporeal membrane oxygenation (KIDMO) group. *ASAIO J*. 2012;58:407–14.

31. Gadeppalli SK, Selewski DT, Drongowski RA, Mychaliska GB. Acute kidney injury in congenital diaphragmatic hernia requiring extracorporeal life support: an insidious problem. *J Pediatr Surg*. 2011;46:630–5.

32. Smith AH, Hardison DC, Worden CR, Fleming GM, Taylor MB. Acute renal failure during extracorporeal support in the pediatric cardiac patient. *ASAIO J*. 2009;55:412–6.

33. Szczepińska B, Królkowski W, Nowak I, Jankowski M, Szuldrzyński K, Szczeklik W. Continuous renal replacement therapy during extracorporeal membrane oxygenation in patients treated in medical intensive care unit: technical considerations. *Ther Apher Dial*. 2014;18:523–34.

34. Suga N, Matsumura Y, Abe R, Hattori N, Nakada TA, Oda S. A safe procedure for connecting a continuous renal replacement therapy device into an extracorporeal membrane oxygenation circuit. *F1000Res*. 2017;20:125–31.

35. Santhanakrishnan A, Nestle T, Moore BL, Yoganathan AP, Paden ML. Design and validation of a diaphragm pump for pediatric CRRT during ECMO. *Int J Artif Organs*. 2013;36:892–9.

36. de Tymowski C, Augustin P, Houissa H, Allou N, Montravers P, Delzogne A, et al. CRRT connected to ECMO: managing high pressures. *ASAIO J*. 2017;63:48–52.

37. Rubin S, Poncer A, Wynckel A, Baehrel B. How to perform a haemodialysis using the arterial and venous lines of an extracorporeal life support. *Eur J Cardiothorac Surg*. 2010;37:967–8.

38. Ricci Z, Ronco C, Picardo S. CRRT in series with extracorporeal membrane oxygenation in pediatric patients. *Kidney Int*. 2010;77:469–70.

39. Yetimakman AF, Tanyildiz M, Kesici S, Kockuzu E, Bayrakci B. Continuous renal replacement therapy applications on extracorporeal membrane oxygenation circuit. *Indian J Crit Care Med*. 2017;21:355–8.

40. Walker PF, Buehner MF, Wood LA, Boyer NL, Driscoll IR, Lundy JB, et al. Diagnosis and management of inhalation injury: an updated review. *Crit Care*. 2015;19:351. doi: 10.1186/s13054-015-1077-4.

41. Tiruvoipati R, Moorthy T, Balasubramanian SK, Platt V, Peek GJ. Extracorporeal membrane oxygenation and extracorporeal albumin dialysis in pediatric patients with sepsis and multi-organ dysfunction syndrome. *Int J Artif Organs*. 2007;30:227–34.

42. Ostermann M, Joannidis M, Pani A, Floris M, De Rosa S, Scheinke K, et al. Impact of fluid balance on outcome of adult...
patients treated with extracorporeal membrane oxygenation. Intensive Care Med. 2014;40:1256–66.

44. Dalia AA, Ortoleva J, Fiedler A, Villavicencio M, Shelton K, Cudemus GD. Extracorporeal membrane oxygenation is a team sport: institutional survival benefits of a formalized ECMO team. J Cardiothorac Vase Anesth. 2019;33:902–7.

45. Langer T, Santini A, Bottino N, Crotti S, Batchinsky AI, Pesenti A, et al. Awake extracorporeal membrane oxygenation (ECMO): pathophysiology, technical considerations, and clinical pioneering. Crit Care. 2016;20:150. doi: 10.1186/s13054-016-1329-y.

46. Chlebowski MM, Baltagi S, Carlson M, Levy JH, Spinnell PC. Clinical controversies in anticoagulation monitoring and antithrombin supplementation for ECMO. Crit Care. 2020;24:19. doi: 10.1186/s13054-020-2726-9.

47. Kennedy JD, Thayer W, Beuno R, Kohorst K, Kumar AB. ECMO in major burn patients: feasibility and considerations when multiple modes of mechanical ventilation fail. Burns Trauma. 2017;5:20. doi: 10.1186/s13038-017-0085-9.

48. Asmussen S, Maybauer DM, Fraser JF, Jennings K, George S, Keiralla A, et al. Extracorporeal membrane oxygenation in burn and smoke inhalation injury. Burns. 2013;39:429–35.

49. Chung KK, Coates EC, Hickerson WL, Arnold-Ross AL, Caruso DM, Albrecht M, et al. Renal replacement therapy in severe burns: a multicenter observational study. J Burn Care Res. 2018;39:1017–21.

50. Peng Y, Yuan Z, Li H. Removal of inflammatory cytokines and endotoxin by veno-venous continuous renal replacement therapy for burned patients with sepsis. Burns. 2005;31:623–8.

51. Askegard-Giesmann JR, Besner GE, Fabia R, Caniano DA, Preuss CM, Carleton NM, et al. Critical care of the burn patient: the first 48 hours. Crit Care Resusc. 2010;12:230–4.

52. Jonckheer J, Spahen H, Malbrain MLNG, Oschima T, De Waele E. Energy expenditure and caloric targets during continuous renal replacement therapy under regional citrate anticoagulation. A viewpoint. Clin Nutr. 2020;39:353–7.

53. Buck ML, Ksenich RA, Wooldridge P. Effect of infusing fat emulsion into extracorporeal membrane oxygenation circuits. Pharmacotherapy. 1997;17:1292–5.

54. Buck ML, Wooldridge P, Ksenich RA. Comparison of methods for intravenous infusion of fat emulsion during extracorporeal membrane oxygenation. Pharmacotherapy. 2005;25:1536–40.

55. Wang SL. Progress of burn research in metabolism and nutrition in China. Zhonghua Shao Shang Za Zhi. 2008;24:396–9.

56. Sy E, Sklar MC, Lequier L, Fan E, Kanji HD. Anticoagulation practices and the prevalence of major bleeding, thromboembolic events, and mortality in venoarterial extracorporeal membrane oxygenation: a systematic review and meta-analysis. J Crit Care. 2017;39:87–96.

57. Morabito S, Pulewski V, Trittapepe L, Fiaccadori E. Regional citrate anticoagulation for RRTs in critically ill patients with AKI. Curr Opin Crit Care. 2014;9:2173–88.

58. Kindgen-Milles D, Brandenburger T, Dimsiti T. Regional citrate anticoagulation for continuous renal replacement therapy. Curr Opin Crit Care. 2018;24:450–4.

59. Muellenbach RM, Kredel M, Kunze E, Kranke P, Kuestermann J, Brack A, et al. Prolonged heparin-free extracorporeal membrane oxygenation in multiple injured acute respiratory distress syndrome patients with traumatic brain injury. J Trauma Acute Care Surg. 2012;72:1444–7.

60. Lee YY, Baik HJ, Lee H, Kim CH, Chung RK, Han JJ, et al. Heparin-free veno-venous extracorporeal membrane oxygenation in a multiple trauma patient: a case report. Medicine (Baltimore). 2020;99:e19070. doi: 10.1097/MD.0000000000019070.

61. Mazzeffi MA, Tanaka K, Roberts A, Rector R, Menaker J, Kon Z, et al. Bleeding, thrombosis, and transfusion with two heparin anticoagulation protocols in venoarterial ECMO patients. J Cardiothorac Vasc Anesth. 2019;33:1216–20.

62. Delmas C, Jacquemin A, Vardon-Bounes F, Georges B, Guerrero I, et al. Anticoagulation monitoring under ECMO support: a comparative study between the activated coagulation time and the anti-Xa activity assay. J Intensive Care Med. 2020;35:679–86.

63. Lai A, Demarest CT, Do-Nguyen CG, Ukita R, Skoog DJ, Carleton NM, et al. 72-hour in vivo evaluation of nitric oxide...
generating artificial lung gas exchange fibers in sheep. *Acta Biomater.* 2019;90:122–31.

77. Cheng S, Xu S, Guo J, He Q, Li A, Huang L, et al. Risk factors of central venous catheter-related bloodstream infection for continuous renal replacement therapy in kidney intensive care unit patients. *Blood Purif.* 2019;48:175–82.

78. Kim DW, Yeo HJ, Yoon SH, Lee SE, Lee SJ, Cho WH, et al. Impact of bloodstream infections on catheter colonization during extracorporeal membrane oxygenation. *J Artif Organs.* 2016;19:128–33.

79. Evans O, Gowardman J, Rabbolini D, McGrail M, Rickard CM. In situ diagnostic methods for catheter related bloodstream infection in burns patients: a pilot study. *Burns* 2016;42:434–40.

80. Hoff BM, Maker JH, Dager WE, Heintz BH. Antibiotic dosing for critically ill adult patients receiving intermittent hemodialysis, prolonged intermittent renal replacement therapy, and continuous renal replacement therapy: an update. *Ann Pharmacother.* 2020;54:43–55.

81. Roberts JA, Joynt G, Lee A, Choi G, Bellomo R, Kanji S, et al. The effect of renal replacement therapy and antibiotic dose on antibiotic concentrations in critically ill patients: data from the multinational SMARRT study. *Clin Infect Dis.* 2021;72:1369–78.

82. Pistolesi V, Morabito S, Di Mario F, Regolisti G, Cantarelli C, Fiaccadori E. A guide to understanding antimicrobial drug dosing in critically ill patients on renal replacement therapy. *Antimicrob Agents Chemother.* 2019;63:e00583–19.

83. Eyler RF, Mueller BA. Antibiotic dosing in critically ill patients with acute kidney injury. *Nat Rev Nephrol.* 2011;7:226–35.

84. Choi G, Gomersall CD, Tian Q, Joynt GM, Freebairn R, Lipman J. Principles of antibacterial dosing in continuous renal replacement therapy. *Crit Care Med.* 2009;37:2268–82.

85. Li L, Li X, Xia Y, Chu Y, Zhong H, Li J, et al. Recommendation of antimicrobial dosing optimization during continuous renal replacement therapy. *Front Pharmacol.* 2020;11:786. doi: 10.3389/fphar.2020.00786.

86. Shaw AR, Chaijamorn W, Mueller BA. We underdose antibiotics in patients on CRRT. *Semin Dial.* 2016;29:278–80.

87. Zamoner W, de Freitas FM, Garmis DS, de Oliveira MG, Balbi AL, Ponce D. Pharmacokinetics and pharmacodynamics of antibiotics in critically ill acute kidney injury patients. *Pharmacol Res Perspect.* 2016;4:e00280. doi: 10.1002/prp2.280.

88. Roberts DM, Liu X, Roberts JA, Nair P, Cole L, Roberts MS, et al. A multicenter study on the effect of continuous hemodi-filtration intensity on antibiotic pharmacokinetics. *Crit Care.* 2015;19:84. doi: 10.1186/s13054-015-0818-8.

89. Ide T, Takesue Y, Ikawa K, Morikawa N, Ueda T, Takahashi Y, et al. Population pharmacokinetics/pharmacodynamics of linezolid in sepsis patients with and without continuous renal replacement therapy. *Int J Antimicrob Agents.* 2018;51:745–51.

90. Chen W, Zhang D, Lian W, Wang X, Du W, Zhang Z, et al. Imipenem population pharmacokinetics: therapeutic drug monitoring data collected in critically ill patients with or without extracorporeal membrane oxygenation. *Antimicrob Agents Chemother.* 2020;64:e00385–20.