INVITED ARTICLE

Extracorporeal Therapy in Sepsis

Deepak Govil[1], Praveen Kumar G[2]

Keywords: Cytokines, Endotoxin, Extracorporeal therapy, Sepsis.
Indian Journal of Critical Care Medicine (2020): 10.5005/jp-journals-10071-23382

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by dysregulated host response to infection. Sepsis continues to be a global health concern, with rising incidence and high mortality, ranging between 20% and 50%, despite advances in diagnosis and management.[1] Apart from adequate source control and appropriate antibiotics, no specific therapy exists for treatment of sepsis. Increasing resistance to antibiotics and high mortality necessitate urgent targeted therapies for improving outcomes, and blood purification by extracorporeal techniques may be proposed for treating sepsis.

Immune Response and Potential Role of Blood Purification in Sepsis

The first response to any invading pathogen is recognition of the pathogen by the host immune system. Every pathogen (virus, bacteria, fungus, and parasite) expresses certain molecular patterns or endotoxins called as pathogen-associated molecular patterns (PAMPs) and these are recognized by toll-like receptors and other pattern recognition receptors which are predominantly expressed by the neutrophils. This leads to activation of innate immunity and leukocytes, leading to increase in release of cytokines, both proinflammatory and anti-inflammatory, which includes interleukins 1 (IL-1), 6, 8, and 10 and tumor necrosis factor.[2,3] This profound release of cytokines, often referred to as cytokine storm, is responsible for dysregulated host response to infection and contributes to organ failures. The initial response to infection and release of cytokines damages the host cells and the injured host cells express alarmins and other proteins called as damage-associated molecular patterns (DAMPs). Alarmins and DAMPs can be recognized by pattern recognition receptors and cause further activation of leukocytes, aggravating the dysregulated response.[4] After the initial florid response, follows a phase of immunoparalysis, which contributes to reactivation of viral infections and new onset hospital-acquired infections.

Novel treatment strategies in sepsis and septic shock include early and adequate fluid resuscitation, vasopressors and inotropic support when indicated, early use of broad-spectrum antibiotics with source control, with close monitoring and organ support, if indicated. Other therapies such as immune-modulation and blood purification have been tried to improve outcomes in patients with sepsis and septic shock. Immunomodulation and blood purification techniques aim at restoring the balance of the immune response to infection, by removing the triggers for the response and the cytokines produced and thereby achieve immune homeostasis. Blood purification techniques can potentially disrupt the immune response at various stages, by removing endotoxins, PAMPs, DAMPs, activated leukocytes, cytokines, and direct removal of pathogens from blood.[5] In this review, we would address the mechanism behind the various therapies and the current evidence pertaining to their use in sepsis and septic shock.

[1,2]Institute of Critical Care and Anesthesiology, Medanta - The Medicity, Gurugram, Haryana, India

Corresponding Author: Deepak Govil, Institute of Critical Care and Anesthesiology, Medanta - The Medicity, Gurugram, Haryana, India, Phone: +91 9818056688, e-mail: drdeepak_govil@yahoo.co.in

How to cite this article: Govil D, Kumar GP. Extracorporeal Therapy in Sepsis. Indian J Crit Care Med 2020;24(Suppl 3):S117–S121.

Source of support: Nil

Conflict of interest: None

The various hypothesis or theories supporting the role of blood purification include the peak concentration theory, the cytokinetic or threshold immunomodulation concept, the iceberg theory, mediator delivery hypothesis, among others. The iceberg theory was proposed by Cavaillon et al., and it suggests that the cytokines present in blood are because of the saturation at the tissue level, and the presence of mediator does not necessarily parallel the same amount of activity.[6] The peak concentration theory is cutting or disrupting the peak concentration of soluble inflammatory mediators and was proposed by Ronco et al.[7] The authors postulated that by disrupting the peaks of soluble inflammatory mediators and by constantly reducing high levels of the mediators, the inflammatory cascade could be curtailed or stopped and thereby preventing organ injury. The cytokinetic theory postulates that removal of inflammatory mediators from the plasma creates a gradient between tissue and plasma and cause the migration of mediators from tissue into blood compartment.[8] Various blood purification modalities, which have been tried include high-volume hemofiltration (HVHF), polymyxin B hemoperfusion, cytokine hemoadsorption, coupled plasma filtration adsorption (CPFA), plasma exchange, among others (Flowchart 1).

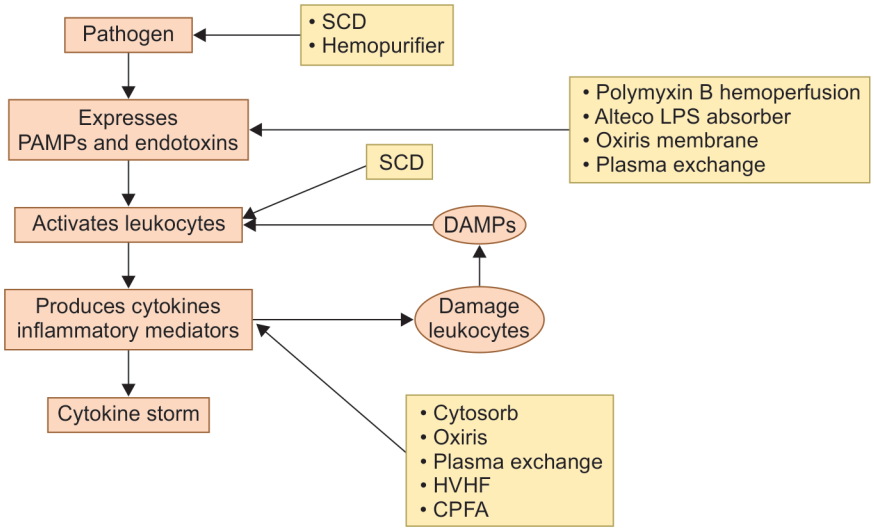
Cytokine Removal in Sepsis

Inflammatory mediators and cytokines can be removed by HVHF, CytoSorb hemoadsorption cartridge, and CPFA.

High-volume Hemofiltration

Standard renal dose hemofiltration is defined as effluent rates up to 25 mL/kg/hour and any dose above 35 mL/kg/hour is considered as HVHF. The consensus conference defined HVHF as continuous hemofiltration with effluent volumes between 50 and 70 mL/kg/hour for 24 hours or 100 to 120 mL/kg/hour for 4 to 8 hours intermittently followed by renal dose hemofiltration,[9] using a high-flux dialyzer. Most of the inflammatory mediators in the plasma are water soluble and has a molecular weight of less than 60 kDa

Flowchart 1: Immune response to sepsis and extracorporeal therapies



SCD, selective cytopheretic device; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patters; HVHF, high-volume hemofiltration; CPFA, coupled plasma filtration adsorption

and, thus, can be easily cleared from plasma by convection. Also, many currently used membranes such as AN69 membranes, have adsorptive properties and improve solute and middle molecular clearance. With hemofiltration dosing higher than conventional volumes, a significant amount of mediators can be cleared from the plasma.[10]

Initial animal and human studies, predominantly observational or case series, showed significant improvement in hemodynamic variables after HVHF, though data on mortality were lacking. The initial human studies were of small patient numbers and heterogeneous, using different doses of hemofiltration. The only large randomized trial, IVOIRE study, compared filtration doses of 35 mL/kg/hour with 70 mL/kg/hour.[11] In a total of 137 patients, who were analyzed, no difference was observed in mortality and any of the secondary end points such as hemodynamic variables, duration of mechanical ventilation or organ function scores. The study was prematurely terminated because of slow recruitment and the necessitated number of patients to achieve a power of 85% could not be achieved. A Cochrane review of four randomized trails, involving 200 patients, showed a pooled risk ratio of mortality at 0.89 with HVHF.[12] The Cochrane review and similar meta-analysis in the past have failed to show any mortality benefit with HVHF.

The main demerits with HVHF is the large volume exchanges. Along with inflammatory mediators, antibiotics, vitamins, and essential elements, nutrients and albumin are also lost in the effluent. Also HVHF is likely to cause massive electrolyte shifts, thus offsetting the potential benefits. These drawbacks can be overcome by use of cascade hemofiltration, though not popularly used.

CytoSorb® Hemoadsorption

CytoSorb® hemoadsorption device (CytoSorbents, New Jersey, USA) is a cytokine adsorption cartridge made of polystyrene divinylbenzene copolymer beads. The device has a surface area of 45000 m^2 with a molecular cutoff size of 60 kDa, thereby adsorbing both pro- and anti-inflammatory mediators, but not endotoxins. Apart from inflammatory mediators, it has also been shown to adsorb myoglobin, bilirubin, bile acids, PAMPs, and DAMPs.[5] It can be used as a stand-alone therapy with standard blood pumps or can be connected in series with hemodialysis or continuous renal replacement therapy (CRRT).

Multiple case series have shown improved hemodynamics, reduction in vasopressor dose, and reduced observed mortality in patients with sepsis, when compared to predicted mortality, without significant adverse effects.[13,14] Two randomized control trials using CytoSorb® have been conducted by the same group of investigators. In the initial trial involving 43 patients with septic shock and acute lung injury, the use of Cytosorb® for 6 hours a day for 7 days was associated with significant reductions in cytokines IL-6, IL-8, and monocyte chemotactic proteins. The intervention did not translate into any survival benefit.[15] The same group of investigators followed up with larger intervention involving 97 patients of septic shock with acute respiratory distress syndrome and used CytoSorb® for similar duration with or without renal replacement therapy. Primary outcome of the intervention was to analyze reduction in plasma IL-6 concentrations. The study showed a significant elimination of IL-6 per pass of blood through the cartridge (5 to 18% per pass), but IL-6 levels were comparable in both groups at the end of therapy. No improvement was observed in other secondary parameters such as ventilation days, vasopressor index, and oxygenation and a higher 60-day mortality was observed in the intervention group.[16] Albeit, the study was not powered to assess mortality, and the number of patients requiring renal replacement therapy was higher in the intervention group (31.9 vs 16.3%), suggesting sicker patients in the study arm.

Although initial duration of therapy was recommended as 24 hours per session, potential concern exists over saturation of adsorption beyond 8 hours of therapy as noted by rebound increase in vasopressor levels after 8 hours of therapy, which reversed after the cartridge was changed.[8] Multiple theories exist for the failure of therapy. Most appropriate is the cytokinetic theory, as discussed previously.[8] Cytokine release is a continuous process and thereby a continuous therapy could prove beneficial when compared to intermittent treatment, especially when initiated early in the treatment of septic shock. This was recently evaluated in a pilot study and showed significant reduction in norepinephrine levels and in procalcitonin and big-endothelin 1 concentrations in the treatment group.[17]

With limited evidence and heterogeneous trial interventions, routine use of CytoSorb® cannot be recommended, and further studies are needed, taking into consideration the pitfalls of previous studies like desired dose and duration of therapy.

Coupled Plasma Filtration Adsorption

The circuit of CPFA contains a plasma filter, a resin sorbent cartridge, and a high-flux dialyzer for convection (Fig. 1). The CPFA technique separates plasma from blood. The cytokines in the plasma component is then adsorbed through a sorbent cartridge and the plasma free of cytokines is redirected to the dialyzer for renal replacement therapy. The potential advantages of CPFA include improved biocompatibility and less hemolysis, as there is no direct contact between blood cells and sorbent, improved cytokine clearance as lower plasma flow allows longer duration of contact with the resin cartridge, and combined cytokine removal with renal replacement therapy by convection.[18] The suggested duration of therapy is a 10-hour session, for 5 consecutive days, with a plasma filtration fraction ranging between 10 and 18%.[19] Beyond 10 hours, the sorbent cartridge shows signs of saturation.

Multiple small observational studies showed improved hemodynamics without survival benefits. In a large multicenter trial involving 192 patients, the use of CPFA did not result in any survival benefit. No difference was observed in any of the secondary outcome parameters such as new organ function scores and intensive care unit length of stay.[20] Although the study was adequately powered for assessing mortality, it had multiple limitations. Close to 48.4% of the patients in the intervention group did not receive the desired dose of CPFA, and clotting of the circuit was the single most common factor for treatment interruption. This is despite the fact that heparin was used for anticoagulation. The study was also stopped prematurely due to futility.[20] The perceived benefits of CPFA are offset by multiple factors, complexity of the circuit needing trained staff, increased need for anticoagulation, and filter cost. A large randomized control trial, COMPACT 2, is ongoing (Clinicaltrials.gov NCT01639664) and would bring new insights in the role of CPFA for cytokine removal in sepsis.

Endotoxin Removal in Sepsis

Polymyxin B Hemoperfusion (PMX; Toraymyxin)

The technique of hemoperfusion brings the blood in direct contact with adsorbents. Various methods by which a sorbent attracts a solute or endotoxin include hydrophobic interaction, hydrogen bonding, van der Waals forces, and ionic bonding. The cartridge also has high absorption potential, thereby can adsorb large molecule solutes beyond the capacity of high cutoff membranes. Polymyxin B hemoperfusion (Toraymyxin: Toray industries, Inc., Japan) and Alteco® LPS adsorber (Alteco Medical AB; Sweden) are the two devices widely used for endotoxin removal.

Polymyxin B hemoperfusion has been extensively investigated for endotoxin removal. The EUPHAS trial investigated 64 patients with intra-abdominal sepsis with septic shock. Patients were enrolled after adequate source control by laparotomy and were treated with two sessions of polymyxin B hemoperfusion. The treatment arm showed improved hemodynamics and organ function scores and overall improved the 28-day mortality.[21] The results of EUPHAS were not replicated in subsequent studies. The ABDOMIX trial group investigated similar set of patients and found no improvement either in hemodynamics or in organ function scores and also reported a slightly increased trend toward mortality in the intervention group.[22] The trial had a lot of limitations, the therapy was completed in only 69.8% of patients and higher incidence of filter clotting was reported. Albeit, both the trials involved surgical patients with intra-abdominal sepsis, post laparotomy, the results were contradictory. The EUPHRATES multicenter trial included 449 patients with septic shock, with endotoxin assay of more than 0.60. The intervention group received two sessions of polymyxin B hemoperfusion of 90 to 120 minutes each. Unlike the previous studies, the trial also included patients with extra abdominal source of infection and also patients with gram-positive sepsis. A total of 295 patients had a multiple organ dysfunction syndrome (MODS) score of more than 9. Although the trial included patients with high endotoxin assay, it did not translate into any improvement in mortality, either in overall population or in patients with MODS score of more than 9. Slight, nonsignificant increase in worsening of sepsis was observed in the treatment group.[23]

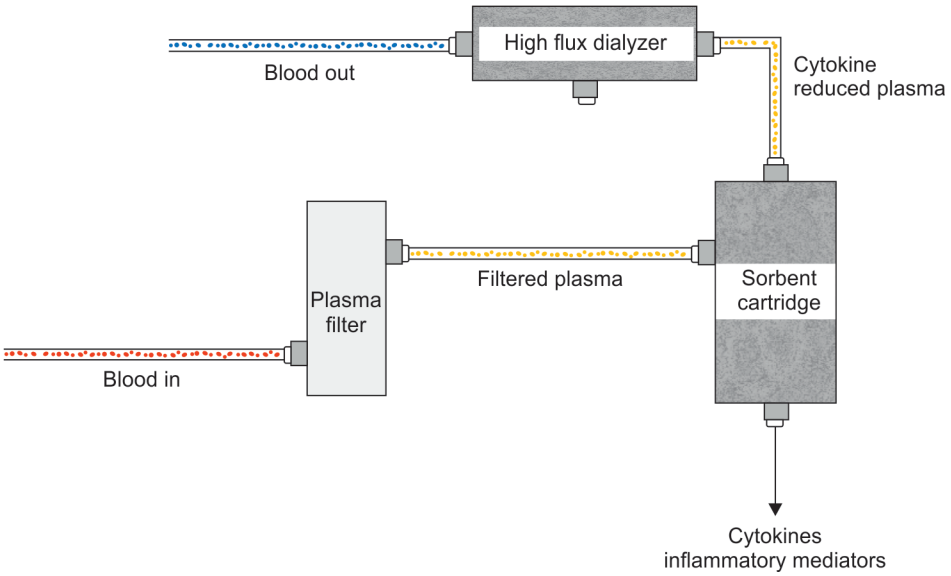


Fig. 1: Coupled plasma filtration adsorption

The *post hoc* analysis of EUPHRATES trial showed an improved 28-day mortality in patients with endotoxin assay of 0.6 to 0.9. Treatment with polymyxin B hemoperfusion also showed improved secondary outcome variables such as ventilator-free days and hemodynamics. A recent systematic review and meta-analysis included 857 patients from six trials showed no improvement in survival with polymyxin B hemoperfusion when compared to the standard therapy.[24]

Potential reasons for the failure of benefit in the trials include baseline high endotoxin activity, effectiveness of assessing endotoxin load by endotoxin assay, dose, duration, and timing of therapy. Although multiple questions need to be addressed, there is at present insufficient evidence to recommend routine use of polymyxin B hemoperfusion in treatment of severe sepsis or septic shock.

Combined Endotoxin and Cytokine Removal

oXiris® Membrane (Baxter, Meyzieu, France)

oXiris® membrane can be used for both cytokine adsorption and endotoxin removal, along with CRRT, all by single-membrane filter. The AN69 membrane is composed of polymers containing sulfonate groups and contains a microporous structure that helps in adsorption of cytokines by cationic residues and hygroscopic adsorption. oXiris® is a modification of AN69-ST (surface-treated) membrane. The modifications include improvement in surface treatment of polyethyleneimine (PEI). The PEI is highly positively charged and, thus, improves the adsorption of endotoxins. Second modification is the pregrafting of the membrane with 4500 international units/m^2 of heparin, thereby improving the antithrombotic properties. Thus, oXiris® membrane has the ability to remove both cytokines and endotoxins.[5]

In an *in vitro* analysis, comparing oXiris®, Toraymyxin, and Cytosorb®, oXiris® showed comparable reductions in endotoxins with Toraymyxin and similar clearance of cytokines in comparison with CytoSorb®.[25] Albeit, the potential advantages of the membrane and comparable endotoxin and cytokine clearance, no large randomized trial exists. Multiple small case series have shown favorable outcomes with the use of oXiris®.[5] One crossover trial comparing oXiris® and standard ST-150 membrane (NCT 02600312), and another randomized trial comparing oXiris® with Toraymyxin for endotoxin removal (ENDoX study; NCT 01948778) have been recently completed, and the results show new insights in the use of oXiris® membrane in sepsis and septic shock.

Multimodal Approach

Plasma Exchange in Sepsis

Plasma exchange can be a novel therapeutic strategy in sepsis, because it can remove the pathogens and toxins produced by them, PAMPs, DAMPs, cytokines, and other inflammatory mediators and activated leukocytes. Moreover, based on the replacement fluid used, it can replenish proteins, protective blood factors like angiopoietin 1 and vascular endothelial growth factor, and blood component cells and thus reduce inflammation and improve outcomes.[26,27]

Plasma filtration or exchange has shown improved outcomes in pediatric patients with sepsis.[28] Few studies exist in adult literature regarding the use of plasma exchange for septic patients. In a trial involving 22 adult patients, the use of plasma exchange of up to five plasma volumes did not result in improved survival. Patients in the intervention group had reduced acute phase reactants, but no change in IL-6 levels at the end of trial intervention.[29] The largest randomized control trial included 106 patients. The patients in the intervention group were treated with one session of plasma exchange with volumes up to 40 mL/kg. Another session was repeated if there was no clinical improvement after the first session. The authors noted 20.5% absolute risk reduction of mortality in plasma exchange group. No significant side effects were noted with plasma exchange.[30] In a meta-analysis of four clinical trials involving both adult and pediatric patients, plasma exchange did not result in any difference in all-cause mortality. Analysis of two studies, which included adult patients, showed a relative risk of 0.63 for all-cause mortality. The trials included in the meta-analysis were heterogeneous and had used different treatment dosages and replacement fluids.[31] In a recently concluded pilot study, early use of plasma exchange at the dose of 1.2 plasma volumes, when initiated within 12 hours of shock, showed significant improvement in hemodynamics and reduced IL-6, IL-1b, and angiopoietin 2. The levels of angiopoietin 1, which is a protective antipermeability factor, did not change at the end of treatment.[26]

Initial results with plasma exchange have been encouraging, but there is a potential risk of dilution of mediators and thereby attenuating the host response to infection. Further trials should investigate the role of plasma exchange in sepsis, by factoring parameters such as timing, dose of therapy, duration of therapy, and replacement fluids.

Newer Therapeutic Approach

Treatment strategies directly targeting the pathogen and activated leukocytes have been tested in experimental studies and in animal population. Selective cytopheretic device (SCD) is a cartridge, which sequesters activated leukocytes connected to the CRRT device. Interestingly, SCD with regional citrate anticoagulation has been shown to change the activity of the bound leukocytes, probably due to the inhibition of neutrophils by ionized hypocalcemia in the filter. The SCD has been evaluated in clinical trials of patients with sepsis and acute kidney injury and a randomized trial of 134 patients, wherein the use of SCD was not found to be superior to CRRT alone. But the subset of patients in whom post filter ionized hypocalcemia of 0.4 mmol/L was maintained, a significant reduction was observed in the 60-day mortality.[32]

Adsorption and removal of various pathogens is a potential treatment strategy to improve outcomes in sepsis patients. Multiple cartridges are under various stages of trials. The Seraph® 100 Microbind® Affinity Blood Filter (ExThera Medical, California, USA) can bind both bacteria and viruses. The Hemopurifier® (Aethlon Medical, California, USA) and FcMBL (Opsonix, USA) are predominantly virus-binding cartridges and opens a new horizon in the management of sepsis.

Pitfalls of Extracorporeal Therapies

Although theoretically compelling, multiple pitfalls exist with extracorporeal blood purification in septic patients. First and the biggest demerit of any extracorporeal therapy is the use of central catheters, risk of thrombosis, blood stream infections, and hypothermia. Second, all therapies need anticoagulation to prevent circuit thrombosis, thus increasing the risk of bleeding. Third, there is a potential risk of loss of antibiotics with treatment, thereby increasing the risk of underdosing and treatment failure.

Fourth, fluid shifts, electrolyte imbalances, and nutritional loss have been reported with certain modalities. Fifth, all therapies incur a high cost on the patient. Finally, no therapy exists till date which can conquer all stages of inflammation and reduce the dysregulated host response to infection.

Conclusion

Significant progress has been made in the arena of sepsis treatment and blood purification, but till date no conclusive evidence has emerged to support a routine use of any of these modalities as an adjunct to standard sepsis care. With limited evidence, the therapy should be individualized to patient-specific needs and resources available, and further research should be directed at unanswered questions of previous trials.

References

1. Manuscript A, Trials R. NIH public access. 2014;41(9):2209–2220.
2. Angus DC, Van Der Poll T. Severe sepsis and septic shock. N Engl J Med 2013;369(9):840–851. DOI: 10.1056/NEJMra1208623.
3. Prince LR, Whyte MK, Sabroe I, Parker LC. The role of TLRs in neutrophil activation. Curr Opin Pharmacol 2011;11(4):397–403. DOI: 10.1016/j.coph.2011.06.007.
4. Chan JK, Roth J, Oppenheim JJ, Tracey KJ, Vogl T, Feldmann M, et al. Science in medicine alarmins: awaiting a clinical response. J Clin Invest 2012;122(8):2711–2719. DOI: 10.1172/JCI62423.
5. Monard C, Rimmelé T, Ronco C. Extracorporeal blood purification therapies for sepsis. Blood Purif 2019;47(Suppl 3):2–15. DOI: 10.1159/000499520.
6. Cavaillon JM, Munoz C, Fitting C, Misset B, Carlet J. Circulating cytokines: the tip of the iceberg? Circ Shock 1992;38(2):145–152.
7. Ronco C, Tetta C, Mariano F, Wratten ML, Bonello M, Bordoni V, et al. Interpreting the mechanisms of continuous renal replacement therapy in sepsis: the peak concentration hypothesis. Artif Organs 2003;27(9):792–801. DOI: 10.1046/j.1525-1594.2003.07289.x.
8. Honore PM, Hoste E, Molnár Z, Jacobs R, Joannes-Boyau O, Malbrain MLNG, et al. Cytokine removal in human septic shock: where are we and where are we going? Ann Intensive Care 2019;9(1):56. DOI: 10.1186/s13613-019-0530-y.
9. Honoré PM, Jacobs R, Boer W, Joannes-Boyau O, De Regt J, De Waele E, et al. New insights regarding rationale, therapeutic target and dose of hemofiltration and hybrid therapies in septic acute kidney injury. Blood Purif 2012;33:(1-3):44–51. DOI: 10.1159/000333837.
10. De Vriese AS, Vanholder RC, Pascual M, Lameire NH, Colardyn FA. Can inflammatory cytokines be removed efficiently by continuous renal replacement therapies? Intensive Care Med 1999;25:(9):903–910. DOI: 10.1007/s001340050981.
11. Joannes-Boyau O, Honoré PM, Perez P, Bagshaw SM, Grand H, Canivet JL, et al. High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. Intensive Care Med 2013;39(9):1535–1546. DOI: 10.1007/s00134-013-2967-z.
12. Borthwick EMJ, Hill CJ, Rabindranath KS, Maxwell AP, McAuley DF, Blackwood B. High-volume haemofiltration for sepsis in adults (review) summary of findings for the main comparison. Cochrane Database Syst Rev 2017; 2017(1):CD008075.
13. Friesecke S, Stecher SS, Gross S, Felix SB, Nierhaus A. Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study. J Artif Organs 2017;20(3):252–259. DOI: 10.1007/s10047-017-0967-4.
14. Kogelmann K, Jarczak D, Scheller M, Drüner M. Hemoadsorption by CytoSorb in septic patients: a case series. Crit Care 2017;21(1):1–10. DOI: 10.1186/s13054-017-1662-9.
15. Schädler D, Porzelius C, Jörres A, Marx G, Meier-Hellmann A, Putensen C, et al. A multicenter randomized controlled study of an extracorporeal cytokine hemoadsorption device in septic patients. Crit Care 2013;17(S2):P62. DOI: 10.1186/cc12000.
16. Schädler D, Pausch C, Heise D, Meier-Hellmann A, Brederlau J, Weiler N, et al. The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: a randomized controlled trial. PLoS ONE 2017;12(10):1–19. DOI: 10.1371/journal.pone.0187015.
17. Hawchar F, László I, Öveges N, Trásy D, Ondrik Z, Molnar Z. Extracorporeal cytokine adsorption in septic shock: a proof of concept randomized, controlled pilot study. J Crit Care 2019;49:172–178. DOI: 10.1016/j.jcrc.2018.11.003.
18. Formica M, Inguaggiato P, Bainotti S, Lou. WM. Coupled plasma filtration adsorption. Contrib Nephrol 2007;156:405–410. DOI: 10.1159/000102131.
19. Ronco C, Brendolan A, D'Intini V, Ricci Z, Lou WM, Bellomo R. Coupled plasma filtration adsorption: rationale, technical development and early clinical experience. Blood Purif 2003;21(6):409–416. DOI: 10.1159/000073444.
20. Livigni S, Bertolini G, Rossi C, Ferrari F, Giardino M, Pozzato M, et al. Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: a multicenter randomised controlled clinical trial. BMJ Open 2014;4(1):1–10. DOI: 10.1136/bmjopen-2013-003536.
21. Cruz DN, Antonelli M, Fumagalli R, Foltran F, Brienza N, Donati A, et al. Early use of Polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. J Am Med Assoc 2009;301(23):2445–2452. DOI: 10.1001/jama.2009.856.
22. Payen DM, Guilhot J, Launey Y, Lukaszewicz AC, Kaaki M, Veber B, et al. Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial. Intensive Care Med 2015;41(6):975–984. DOI: 10.1007/s00134-015-3751-z.
23. Dellinger RP, Bagshaw SM, Antonelli M, Foster DM, Klein DJ, Marshall JC, et al. Effect of targeted polymyxin B hemoperfusion on 28-day mortality in patients with septic shock and elevated endotoxin level: the EUPHRATES randomized clinical trial. J Am Med Assoc 2018;320(14):1455–1463. DOI: 10.1001/jama.2018.14618.
24. Fujii T, Ganeko R, Kataoka Y, Furukawa TA, Featherstone R, Doi K, et al. Polymyxin B-immobilized hemoperfusion and mortality in critically ill adult patients with sepsis/septic shock: a systematic review with meta-analysis and trial sequential analysis. Intensive Care Med 2018;44(2):167–178. DOI: 10.1007/s00134-017-5004-9.
25. Malard B, Lambert C, Kellum JA. In vitro comparison of the adsorption of inflammatory mediators by blood purification devices. Intensive Care Med Exp 2018;6(1). DOI: 10.1186/s40635-018-0177-2.
26. Knaup H, Stahl K, Schmidt BMW, Idowu TO, Busch M, Wiesner O, et al. Early therapeutic plasma exchange in septic shock: a prospective open-label nonrandomized pilot study focusing on safety, hemodynamics, vascular barrier function, and biologic markers. Crit Care 2018;22(1):1–11. DOI: 10.1186/s13054-018-2220-9.
27. Sanford K. Extracorporeal photopheresis: clinical use so far. J Clin Apher 2013;28:349–355.
28. Long EJ, Taylor A, Delzoppo C, Shann F, Pearson G, Buckley D, et al. A randomised controlled trial of plasma filtration in severe paediatric sepsis. Crit Care Resusc 2013;15(3):198–204.
29. Reeves JH, Butt WW, Shann F, Layton JE, Stewart A, Waring PM, et al. Continuous plasmafiltration in sepsis syndrome. Crit Care Med 1999;27(10):2096–2104. DOI: 10.1097/00003246-199910000-00003.
30. Busund R, Koukline V, Utrobin U, Nedashkovsky E. Plasmapheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial. Intensive Care Med 2002;28(10):1434–1439. DOI: 10.1007/s00134-002-1410-7.
31. Rimmer E, Houston BL, Kumar A, Abou-Setta AM, Friesen C, Marshall JC, et al. The efficacy and safety of plasma exchange in patients with sepsis and septic shock: a systematic review and meta-analysis. Crit Care 2014;18(1):1–8. DOI: 10.1186/s13054-014-0699-2.
32. Tumlin JA, Galphin CM, Tolwani AJ, Chan MR, Vijayan A, Finkel K, et al. A multi-center, randomized, controlled, pivotal study to assess the safety and efficacy of a selective cytopheretic device in patients with acute kidney injury. PLoS ONE 2015;10(8):e0132482. DOI: 10.1371/journal.pone.0132482.