

Blood Purification





RESEARCH

Blood Purification

Introduction

Blood Purif 2022;51(suppl 3):1 DOI: 10.1159/000528705 Received: December 7, 2022 Accepted: December 14, 2022 Published online: February 13, 2023

Workshop Purification Therapies – From Research to Clinical Evidence

The Aferetica team and the Scientific Committee, together with all the partners and collaborators, are very glad to present the scientific contributions of *The Workshop Purification Therapies – From Research to Clinical Evidence*, held in Milan on September 30 and October 1, 2022.

This edition of the workshop is a part of a long journey, started with the first edition in 2017, or even further back in time, with the foundation of Aferetica in 2013, involving an interdisciplinary community of clinicians, researchers and industry partners in an innovation-oriented Collaborative Research cooperation, a concept on the basis and the origins of the greatest medical breakthrough.

The transformation of ideas into concrete therapeutic solutions and the establishment of both their widespread application and the clinical evidence in some of the most challenging fields of medicine – organ transplantation and overwhelming inflammatory disorders – were the main topics addressed during the workshop.

The event involved 450 participants from all over Europe to discuss and share experiences about the crucial issues in the field of organ transplantation, with the main focus on the therapeutic solutions for organ ex vivo man-

agement, and overwhelming inflammatory disorders diagnosis and purification therapies in order to move forward in their solid clinical applications and more exhaustive knowledge.

The scientific contributions included in this supplement are the result of everyday confrontation and clinical practice. They are divided into categories, according to the major clinical fields and applications, in order to facilitate the comprehension and the comparison of all the presented results.

We would like to thank all the members of the Scientific Committee, all the faculty and the participants for bringing their expertise and experience, engaging in such fruitful, constructive and open exchanges throughout the event, allowing to take a step forward in the knowledge of pathologies, therapies, their development and their clinical use.

Mauro Atti

Conflict of Interest Statement

Dr. Mauro Atti is one of the founders and CEO of Aferetica srl.

karger@karger.com www.karger.com/bpu © 2023 S. Karger AG, Basel



TRANSPLANTATION

A01

A single-center, pilot, clinical study of hypothermic oxygenated machine perfusion with or without adsorption in histologically evaluated kidneys from marginal donors

F. Tomatis¹, C. Carrara¹, G. Remuzzi² and P. Ruggenenti^{1,2}

¹Unit of Nephrology and Dialysis, Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy

²Clinical Research Center for Rare Diseases "Aldo e Cele Daccò", Istituto di Ricerche Farmacologiche Mario Negri, IRCCS, Bergamo, Italy

Background/aims: The use of kidneys from marginal donors (i.e., older donors or donors with hypertension, diabetes and/or non- nephrotic proteinuria) increased donors pool and transplant activity, but also the risk of delayed graft function (DGF)and premature graft failure. Pre-transplant machine perfusion (MP) has been found to reduce the incidence of DGF and improve short-term graft survival, as compared to cold storage. The aim of our study is to investigate whether pre-transplant hypothermic oxygenated machine perfusion (HOPE) - with or without concomitant adsorption - of histologically evaluated kidneys from marginal donors modifies biochemical and molecular markers that may mediate ischemia-reperfusion damage to the graft and adversely affect short- and long-term graft outcomes.

Methods: Patients eligible to single or dual transplantation with histologically evaluated kidneys from marginal donors will be allocated to either HOPE with adsorption or HOPE without adsorption in a 1:1 ratio. MP will be delivered by PerLife[®] - PerKidney[®] system (Aferetica) with the use of CytoSorb cartridge, when needed. Physical perfusion parameters and perfusate samples will be collected throughout the entire perfusion period. Biochemical and molecular markers of kidney function, acute kidney injury, inflammation and ischemia/reperfusion damage will be evaluated.

Results: On the basis of the available experience, we expect that pre-transplant treatment of kidneys from marginal donors with HOPE with concomitant adsorption will reduce the burden of inflammation, acute kidney injury and ischemia/reperfusion damage to the graft as compared to HOPE without adsorption.

Conclusion: The study findings are expected to show that adsorption associated with HOPE will ameliorate markers of ischemia/reperfusion damage of grafts from marginal donors as compared to HOPE without adsorption. The benefitsof HOPE-associated adsorption are expected to translate into improved short- and long-term outcomes of transplants of histologically evaluated kidneys from marginal donors. Whether this will apply more in general to kidneys from expanded criteria donors will be worth investigating.

First experience of a new ex-situ perfusion device in donors after circulatory death (DCD) pig livers

C. Martinelli¹, F. Melandro¹, F. Torri¹, D. Patrono², Q. Lai³, R. De Carlis⁴, S. Camagni⁵, A. Gambella⁶, F. Ruberto⁷, P. De Simone¹ and D. Ghinolfi¹

¹Hepatobiliary Surgery and Liver Transplantation, University of Pisa Medical School Hospital, Pisa, Italy.

²General Surgery and Liver Transplantation, University of Turin Medical School Hospital, Turin, Italy.

³Department of General Surgery and Organ Transplantation, Sapienza University of Rome, Rome, Italy.

⁴General Surgery and Transplantation, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy.

⁵Division of Liver Transplantation, AO Papa Giovanni XXIII, Bergamo, Italy.

⁶Pathology Unit, Department of Medical Sciences, A.O.U. Città Della Salute e Della Scienza di Torino, University of Torino, Torino, Italy.

⁷Department of Anesthesiology, Critical Care Medicine and Pain Therapy, Sapienza University of Rome, Rome, Italy.

Background/Aims: The use of ex-situ hypothermic (HMP) and normothermic machine perfusion (NMP) represent a growing strategy to mitigate liver damage before transplantation. In this study, we evaluated a new ex situ machine perfusion device: PerLife system (Aferetica, Bologna, Italy) using model of donors after circulatory death (DCD) liver grafts from slaughterhouse pigs.

Methods: Fourteen pig liver grafts, perfused for 2 hours, were divided in two groups and perfusion data analyzed. 6 grafts were perfused under hypothermic conditions and 8 under normothermic conditions. We analyzed the perfusate and bile samples to assess liver metabolism. We also tested an integrated adsorption device: Cytosorb[®] (CS), based on polymer technology, on 3 livers perfused by NMP. Perfusion parameters (pressure, flow, vascular resistance, temperature) were continuously monitored, while perfusate samples were collected at the start of perfusion and after 10, 30, 60, 90 and 120 minutes. Additional perfusate samples were collected to evaluate Interleukin 6 (IL-6) release ratio.

Results: Temperature was 8,5 (7,8-9,6 °C) during HMP and 36,9 (36,2-37,4) C° during NMP and remain stable through all procedures. During all MP a progressive reduction of vascular resistances was observed which determined and an increase of portal vein and hepatic artery flow was observed. Perfusate ALT concentration progressively increased during treatments and was statistically higher during NMP with no differences between NMP vs NMP+CS, whereas lactate levels were statistically lower in NMP+CS compared to NMP group (p=0.032). IL-6 release ratio was similar between NMP and NMP+CS. In the period t 90- t 120 CS removed a median of 493,106 pg of IL-6. All NMP grafts produced bile. Bile pH was higher in the NMP+CS group 7,21 (7,11- 7,21) vs 7,35 (7,07-7,63) at 120 minutes and characterized by higher glucose and bicarbonate concentration.

Conclusions: This is a preliminary and limited experience. However, on the basis of these data, we could affirm that this new ex situ machine perfusion represents a new efficient and safe device, in addition Cytosorb[®] would be an effective therapeutic tool to improve grafts quality before transplantation by the absorption cytokines and inflammatory mediators.

Hypothermic Oxygenated Machine Perfusion for Liver Transplantation: An Initial Experience with a new device

C. Martinelli¹, F. Melandro¹, F. Torri¹, G. Catalano¹, G. Tincani¹, E. Balzano¹, J. Bronzoni¹, S. Palladino¹, M. Franzini², V. De Tata², M. Masini², P. De Simone¹ and D. Ghinolfi¹

^{1.} Hepatobiliary Surgery and Liver Transplantation, University of Pisa Medical School Hospital, Pisa, Italy.

² Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy.

Background/Aims: Hypothermic oxygenated machine perfusions could reduce ischemia-reperfusion injury after liver transplant and recent studies shows an important role of cytokines in regulation of this processes. We tested a new ex situ machine perfusion (MP) device, PerLife system (Aferetica, Bologna, Italy), in hypothermic setting, with an integrated cytokine filter (CytoSorb[®]) to assess the benefits in terms of inflammatory modulation and postoperative outcomes.

Methods: In this pilot study, 6 liver grafts were perfused at 10 °C and then transplanted. 3 cases with CytoSorb[®] (filter group) were compared with 3 cases without (control group). Perfusate samples were collected at MP start, after the first 30 min and hourly. Thereafter, interleukin 1beta, 6, 10, TNF alpha perfusate concentration were evaluated.

Results: Median donor age was 85 years (82-89) in filter group vs 81 years (81-82) in control group, (P 0,09). The grafts were perfused for a median of 133 minutes (125-158). Recipient median age was 55 (56-59) in filter group vs 54 (53-57) years in control, (P 0.66). Arterial flow in the filter group was significantly higher at first hour of ex situ perfusion: 120 (100-144) ml/min in filter group vs 86 (80-94) ml/mi in control, (P 0,06). Median IL-6 at first hours differs between the two groups, without statistically significance: 2,1 (0,6-4,0) pg/ml in filter group vs 5,4 (2,0-14,4) pg/ml in control group, (P 0,26). Not statistically significant difference of median serum AST and ALT levels in the two groups were observed in the first postoperative week: 260 (232-452) U/L and 133 (110-218) U/L in filter group versus 220 (203-285) U/L and 137 (129-178) U/L in controls respectively (P 0,85; 0,47). No PRS, EAD or vascular complications were reported and at 6 months no anastomotic stricture and no ischemic cholangiopathy in both groups. Complications at discharge, based on the Comprehensive Complication Index, were similar in both groups: s 20,9 (0-20,90) in filter group vs 20,9 (0-33,50) in control, (P 0,40).

Conclusion: This new device with cytokine filter seems to guarantee a better liver arterial flow under hypothermic perfusion and a reduction of cytokines in the perfusate. Further work is obviously needed due the small number of cases.

Perfusate cytokines concentrations during liver grafts ex-situ normothermic perfusion

F. Torri¹, F. Melandro¹, C. Martinelli¹, J. Bronzoni¹, M. Franzini², E. Balzano¹, G. Catalano¹, S. Palladino¹, G. Tincani¹, M.L. Bindi³, G. Biancofiore³, P. De Simone¹, A. Paolicchi², D. Ghinolfi¹

¹ Hepatobiliary Surgery and Liver Transplantation, University of Pisa Medical School Hospital, Pisa, Italy.

² Department of Surgical, Medical, Biochemical Pathology, University of Pisa Medical School Hospital, Pisa, Italy.

³ Intensive Care, University of Pisa Medical School Hospital, Pisa, Italy.

Background: The potentialities of ex-situ normothermic machine perfusion as a preservation method before liver transplantation are under investigation. The perfusion at normothermic conditions exposes the liver grafts to ischemia reperfusion injury, induces oxidative stress and the release of several inflammatory cytokines that may exacerbate the damage.

Methods: In the period from April 2016 to May 2022, we collected the perfusate of liver grafts preserved under normothermic conditions at commencing and hourly during ex-situ perfusion. All grafts were considered eligible to liver transplant and were eventually transplanted. pH, vascular flows, lactate, transaminases, glucose and cytokines (IL-6, IL-10 and TNF-alpha) perfusate concentrations, absolute value and release ratio were analyzed and correlated to clinical endpoints (graft and patients' survival, post-reperfusion syndrome, post-liver transplant renal failure and transaminases peak, early allograft disfunction, post-operative vasopressors requirement, hospitalization length).

Results: Twenty-six liver grafts (16 DBD, 10 DCD) were evaluated. Preliminarily, cytokine curve during NMP was built and the potential influence of confounding factors (donor type, age, gender and comorbidities, ischemic times, preprocurement lab data) was assessed. Median donor age was 77 years (IQR: 27-87), median duration of ex-situ perfusion was 250 minutes (IQR 200-302). IL-6, IL-10 and TNF-alpha showed a peak at the third hour of perfusion and decreased thereafter. IL-6 release ratio was higher in older donor (p=0.012), IL-10 release ratio was higher in DCD donor type (p=0.041), while TNF-alpha release ratio increased when donors required high dose of vasopressors (p<0.001). At univariate analysis, a higher IL-10 release ratio was associated to a more severe risk of developing acute kidney injury (AKI) after liver transplantation.

Conclusion: Cytokines inflammatory response stabilize 3-hours after commencing normothermic machine perfusion. Higher IL-10 release ratio correlates to the development of kidney injury after liver transplantation. In viable liver grafts, cytokines (IL-6, IL-10 and TNF-alpha) release ratio and absolute concentrations do not correlate to graft or patient survival.

The use of cytokines hemadsorption filter during ex-situ normothermic machine perfusion in liver transplantation: preliminary experience of a pilot randomized study

F. Torri¹, F. Melandro¹, C. Martinelli¹, J. Bronzoni¹, M. Franzini², E. Balzano¹, G. Catalano¹, S. Palladino¹, G. Tincani¹, M.L. Bindi³, G. Biancofiore³, P. De Simone¹, A. Paolicchi², D. Ghinolfi¹

¹ Hepatobiliary Surgery and Liver Transplantation, University of Pisa Medical School Hospital, Pisa, Italy

² Department of Surgical, Medical, Biochemical Pathology, University of Pisa Medical School Hospital, Pisa, Italy

³ Intensive Care, University of Pisa Medical School Hospital, Pisa, Italy

Background/Aims: Several studies correlated cytokines release and ischemia/reperfusion injury to postoperative outcomes in liver transplantation. We assessed the safety and the potential benefits of a cytokines hemadsorption device (Cytosorb[®]) integrated in a new perfusion device (PerLife[®], Aferetica, Bologna, Italy) during ex-situ normothermic perfusion.

Methods: We compared postoperative outcomes in terms of intensive care unit (ICU) stay, hospital stay, complications, early allograft dysfunction (EAD), graft survival in two groups of patients: those receiving a liver graft preserved with exsitu normothermic machine perfusion and those with ex-situ machine perfusion with a Cytosorb[®] integrated in the circuit. Perfusate samples were collected at commencing perfusion and hourly thereafter. IL-1, IL-6, IL-10 and TNF-alpha perfusate concentrations were evaluated together with perfusion parameters and post-operative laboratory and clinical data.

Results: Four liver grafts were perfused ex-situ with PerLife® machine at 37°C and eventually transplanted. Two cases were randomized to the Cytosorb® group (CS-group). Median donor age was 84 years in CS-group vs 80 years in control group. The grafts were perfused for a median of 258 minutes (241- 307). Recipient median age was 52 in CS-group vs 61 years in the controls. Median IL-1, IL-6, IL-10, TNF-alpha at 4 hours did not differs in the two groups. Median ICU stay was 6 days in CS-group and 17 in control group (p=0.50). In the control group one case of primary non function was observed. One case of EAD was reported in the CS-group. No biliary or vascular complications were reported. Median Comprehensive Complication Index was 10.45 (8.7-12.2) in CS-group vs 40.95 (47.3-34.6) in control group (p=0.04).

Conclusion: Cytosorb[®] use during NMP is safe and feasible, but its capacity to minimize cytokines perfusate concentration and clinical outcomes should be verified in large multicentric trials.

HOPE with Cytokine filtration in Liver Transplantation

S. Camagni¹, A. Amaduzzi¹, F. Neri¹, D. Pinelli¹, M. Guizzetti¹, E. Panetta², F. Ganzerli², A. Kurevija², M. Colledan¹

¹Department of Organ Failure and Transplantation, ASST Papa Giovanni XXIII, Bergamo, Italy

²Aferetica srl, Bologna, Italy

Background: Livers from extended criteria donors are particularly susceptible to ischemia-reperfusion injury (IRI) and at higher risk of post-reperfusion syndrome (PRS), early allograft dysfunction (EAD) and graft failure. The pathogenesis of IRI is a complex downstream inflammation process. It has become evident that end-ischemic ex-vivo hypothermic oxygenated perfusion (HOPE) protects against IRI. In the setting of liver transplantation with high-risk grafts, cytokine filtration during HOPE may potentiate the beneficial effects of HOPE itself, further mitigating IRI and, consequently, further reducing the incidence of PRS and EAD. We present an ongoing trial aiming at verifying the feasibility and safety of cytokine filtration during HOPE of high-risk livers.

Methods: This is a monocentric, pilot, randomized controlled study. Each enrolled patient is transplanted with a liver from an extended criteria brain-dead donor, preserved with end-ischemic, pressure-controlled dual HOPE. Randomization is about the use (experimental arm, 10 patients), or not (control arm, 10 patients), of the cytokine adsorber CytoSorb during HOPE. Scheduled samples of the perfusate and patient serum are stored for the subsequent analysis of TNF-alfa, IL-6, IL-8, and ET-1 levels. The primary endpoint is the incidence of PRS, the secondary endpoints are the incidence of EAD and the extent of IRI.

Results: So far, 4 patients have been enrolled: Two were randomly assigned to the experimental arm, and 2 to the control arm. The HOPE procedures were uncomplicated. There were no differences in HOPE hydrodynamics between the two groups. The median portal and arterial flows were 286 ml/min and 172 ml/min, respectively. The median increase in portal and arterial flows throughout the procedures was of 9,85% and 82,1%, respectively. No PRS occurred. One high-urgency patient in the experimental arm developed EAD. One patient in the control arm was retransplanted due to primary nonfunction. Histology for IRI and cytokine levels have not been analyzed, yet.

Conclusion: In this very preliminary experience, cytokine filtration during HOPE of high-risk livers appeared to be feasible and safe. The case of EAD observed in the experimental arm was an expected outcome in a very high-risk patient. A midterm, comprehensive interim analysis is planned.

Feasibility Evaluation of Sequential DHOPE-COR-NMP with PerLife

S. Camagni¹, F. Neri¹, M. Franchini², F. Ganzerli², E. Panetta², M. Colledan¹

¹Department of Organ Failure and Transplantation, ASST Papa Giovanni XXIII, Bergamo, Italy

²Aferetica srl, Bologna, Italy

Background: Ex vivo liver perfusion (MP) can be performed according to many different protocols, depending on the goals of perfusion: ischemia-reperfusion injury (IRI) reduction/limitation, prolongation of the preservation time, improve of the organ conditions and functions and viability assessment prior to transplantation. Hypothermic MP (HMP, 4–10°C) helps organ preservation with reduced IRI thanks to ATP recharging. In contrast, normothermic MP (NMP, 37°C) aims to provide an approximately near physiological environment for organs, facilitating functional assessment. Controlled oxygenated rewarming (COR) is a halfway approach to rescue cold-stored marginal grafts by gentle oxygenated warming up, which may also have an IRI reducing effect. The aim of this study is to evaluate the feasibility of a combined protocol HMP-COR -NMP performed with PerLife MP system, using grafts procured from DCD slaughterhouse pigs.

Methods: Sequential use of HMP-COR -NMP was performed with PerLife MP in PerLiver operational mode according to the following protocol:

- 2h HMP;
- 1h COR with 15 minutes full liquid exchange (from HMP to Colloidal solution and Red Blood Cells (RBC) addition);
- 1.5h NMP with RBC-based solution.

Temperature settings (Figure 1-A) were manually changed, adjusting consequently also the arterial and venous pressures' targets (Figure 1-B). Gas supply was adapted to perfusion conditions.

Results: HMP started at 4°C temperature set. At 90 min, COR started and the temperature set was changed to 18°C, keeping 100% O2 2L/min supply as in HMP. At 18°C, HMP liquid discharge and colloid-based additive-free liquid infusion started, with no prefusion interruption. At 22°C, RBCs were added and 33%O2/67% N2 at 2L/min was supplied. After RBCs addition, temperature was set at 37°C and the NMP treatment started once it was reached.

Conclusion: Sequential DHOPE-COR-NMP using PerLife was feasible. The possibility of performing HMP-COR-NMP with no perfusion interruption is an interesting feature which should furtherly explored in terms of temperature and other perfusion target settings.



Figure 1: A - HM P-COR-NMP temperature settings and B - Perfusion Parameters

Impact of Hypothermic and Normothermic Machine Perfusion on renal resistance, vascular flow and graft

inflammatory state in an experimental model of DCD

R. Franzin¹, A. Stasi¹, M. Fiorentino¹, I. Scalera², A. Deleonardis¹, F. Sallustio^{1,3}, P. Pontrelli¹, G. Castellano⁴, S.

Simone¹, L. Gesualdo¹

¹Nefrology, dialysis and transplant, DETO, University of Bari, Bari, Italy

²Hepatobiliary and Liver Transplant Unit, Department of Emergency and Organ Transplantation, University Hospital Policlinic of Bari, Bari, Italy

³ Interdisciplinary Department of Medicine, University of Bari, Policlinic, Bari, Italy

⁴ Department of Nephrology, Dialysis and Transplantation, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Italy

Background: Kidney transplantation is currently the standard treatment for patients with end-stage renal disease, unfortunately, the shortage of available donor kidneys represents an important limitation that forced to accept marginal, higher-risk organs from circulatory death (DCD) donors and expanded criteria donors. Recently, the use of hypothermic (HMP) and normothermic (NMP) perfusion machines is an important strategy to improve graft quality, thereby to increase renal function and survival.

Methods: In an experimental model of donation in cardiac death (DCD), after 60 minutes of warm ischemia, porcine kidneys were retrieved in anatomical blocks in a certified and standardized slaughter facility (UNI-En ISO 9001) and subjected to Standard Cold Storage overnight (SCS). The oxygenated hypothermic and normothermic renal perfusion were carried out using the innovative PerLife system (PerKidney, Aferetica) with a pressure of 75 mmHg, oxygenation 1100 ml/min and a duration of 4h. Gradual increase of temperaturewas possible in normothermic treatment ranging from 8 °C to 32 °C. The perfused organs biopsies were compared to organs stored on ice (SCS). In vitro analysis, endothelial cells exposed to H₂O₂, C5a were analyzed by cell proliferation assay, qPCR, Western blot and FACS analysis.

Results: Compared with the beginning of treatment (T0), resistances and flows improved in both HMP and NMP perfused kidneys groups. ELISA data on perfusates show a significant reduction of levels of MCP-1, TNF α , ICAM, VCAM and the renal injury markers ASAT and LDH compared to T0 (p<0,05), the reduction was observed both HMP and NMP treatments. In the SCS group, by histological staining (eosin and hematoxylin and PAS stainings) the tubules appear dilated, the interstitium with infiltrate, the floccule detached from the Bowman capsule. HMP and NMP treatment reduced tubular necrosis compared to SCS, particularly NMP treatment appeared more efficient compared to HMP (p<0,05). Endothelial cells after H₂O₂ and C5a exposition and tissues from SCS organs showed increased IL-6 and Endothelin-1 gene expression, indicating the acquirement of a pro-inflammatory state and vasoconstriction.

Conclusion: HMP and NMP treatments induced a reduction in the gene expression of IL-6 and Endothelin-1 compared toSCS renal tissue. The use of HMP and NMP could counteract tissue damage, and inflammation induced by the ischemia-reperfusion and increase the possibility of using marginal organs.

Cytokine filter connected with machine perfusion for marginal dcd liver grafts from pigs

I. Scalera¹, R. Franzin², A. Stasi², A. Castellaneta³, E. Fischetti¹, G. Morelli¹, M. Raele¹, L. Gesualdo²

¹ Hepatobiliary and Liver Transplant Unit, Department of Emergency and Organ Transplantation, University Hospital Policlinic of Bari, Bari, Italy

²Department of Emergency and Organ Transplantation, Nephrology, Dialysis and Transplantation Unit, University of Bari Aldo Moro, Bari, Italy

³ Gastroenterology and Digestive Endoscopy Unit, University of Bari Aldo Moro, Bari, Italy

Background: Several inflammatory cytokines (CK) are continuously released by the grafts in the circulating fluid during the treatment in the machine perfusion (MP), because of the ischemia- reperfusion-injury (IRI). Aim of the study is to analyze the role of MP connected to a sorbent cartridge (PerSorb [®]) and used for DCD pigs' livers.

Methods: Six grafts were procured from 6 pigs from a slaughterhouse. All grafts had at least 60min of dWIT and 24hours of Standard Cold Storage (SCS) to make them very marginal grafts: 2 grafts were perfused in hypothermic MP (HMP) with PerSorb (Cyt), other 2 grafts in HMP without the cartridge (NoCyt) and the rest 2 livers were stored in the ice box (noTreat). The CK were measured before the HMP cycle(T0) and at the end (Tend) and analyzed per H&E, PAS and Sirius red. Biopsies were taken at T0 and Tend.

Results: All 4 grafts treated with HMP had a negative lactate trend after 3 hours of treatment: the lowest lactate value for Cyt group was 4.7mmol/l, for noCyt was 4 mmol/l and for noTreat was stable at 15 mmol/l. ELISA analysis showed a reduction of MCP-1, TNF α and IL-1 β for noCyt group at Tend and a complete clearing of the same CK in Cyt livers already after 2 hours of treatment. At Tend, the arterial resistances in Cyt group were lower of 0.30mmHg/ml/min compared with T0 value, 0.03 in noCyt group. Similarly, a better arterial flow was measured in Cyt (50ml/min), compared with noCyt (10ml/min). Biopsied showed a reduction of the perisinusoidal edema for the Cyt grafts, versus the noCyt.

Conclusion: These observational data suggest a potential protective role of the treatment with MP and a sorbent cartridge of marginal DCD grafts in reducing the inflammatory response after the ischemic damage.

Hypothermic machine perfusion after static cold storage to improve renal function of Expanded Criteria Donors: first experience from Nephrology Unit of Bari, Italy

S. Simone ¹, R. Franzin ¹, I. Scalera ², A. Stasi ¹, C. Musajo Somma ³, R. Guido ³, A. Casanova¹, A. Montinaro¹, M. Rossini¹, V. Pronzo¹, M. Matera⁴, P. Ditonno⁴, M. Battaglia⁴, L. Gesualdo ¹

¹ Nephrology, dialysis and transplant, DETO, University Hospital Policlinic of Bari, Bari, Bari;

² Hepatobiliary and Liver Transplant Unit, Department of Emergency and Organ Transplantation, University Hospital Policlinic of Bari, Bari, Italy

³ Centre of Reference of the Apulia Region for Organ Transplantations – University Hospital of Bari, Bari, Italy

⁴ Department of Emergency and Organ Transplantation, Urology, Andrology and Kidney Transplantation Unit, University of Bari, Bari, Italy

Background: Hypothermic machine perfusion (HMP) is a novel clinical approach to overcome the limitations of traditional static cold storage (SCS) preservation. HMP can be used to assess and reconditionExpanded Criteria Donors by improving quality and outcome of kidneys for transplantation. In this study, we reported our first experience with HMP in our Unit of Nephrology by using the system PerKidney (PerLife, Aferetica) device.

Methods: Kidneys from three marginal donors (age 69, 82, 70 with diabetes and hypertension) were retrieved after 20 \pm 15 min of in situ warm ischaemia. Then, kidneys were preserved by 4±2.5 h of SCS, followed by 4h±3.5 of HMP with oxygenated preservation solution (Pump Protect[®], Osmolality of 300 mOsm/kg, pH 7.4 potassium 25 mmol/l sodium 100 mmol/l), pressure 35 mmHg and average flow of oxygenation of 1100 ml/min. Renal biopsies and perfusates were collected before and after HMP treatment, the latter immediately before than reperfusion in the recipient. Four kidneys were transplanted by Dual Kidney transplantation (DKT), two kidneys were declared unsuitable for transplant based on Karpinsky score (Sx 7, Dx 6, 82 years donor).

Results: Intrarenal resistance was significantly reduced during the HMP treatment (Vascular Renal Resistance: mmHg/ml/min: T0:1.58±0.52, T2: 0.546 ± 0.32, TEND: 0.320 ± 0.236, p<0.05), in accordance with improved renal flow (ml/min: T0: 35 ± 15 ; T2: 47 ±22; TEND: 65 ± 23 , p<0.05). Compared to T0, by histological and PAS staining we found a reduced tubular necrosis, dilatation and flattening, reduced PBMCs infiltration and lower detachment of floccule from Bowman capsule after HMP treatments. Donor serum creatinine were respectively 1.1 mg/dL, 0.93 mg/dL and 0.86 mg/dL, BUN 44 mg/Dl, 51 mg/dL and 41 mg/dL, with absence of protein at urine exam. Urine output were respectively 5000ml/24h (400 ml/h), 2990 ml/24h (200 ml/2h) and4550 ml/24h. Serum creatinine in recipients at hospital discharge were 1.24 mg/dL and 1.79 mg/dL and werelower than after SCS as retrospectively compared by similar ECD donors with same age, sex, time of warm and cold ischemia and comorbidities. The two recipients never needed dialysis. Furthermore, by ELISA assay,the detected IL-6 and MCP-1 levels in perfusates were significantly reduced from T0 to TEND (for IL-6: T0: 55,86 ± 25, 78 pg/ml, TEND: 8, 85 ± 5.6 pg/ml, p<0.05).

Conclusion: HMP treatment resulted in an improved vascular resistance and renal blood flow using kidneys from expanded criteria donors, with reduced histological damage and cytokines levels in the perfusates. Using machine perfusion is safe; no adverse surgical events occurred during the procedure and lower creatinine at hospital discharge was observed.

Proof of concept of a new option to preserve and evaluate kidney grafts from cadaveric donors: en-bloc dual kidney specimen hypothermic oxygenated machine perfusion model from an animal DCD

E. F. Kauffmann¹, N. Napoli¹, A. Salamone¹, A. Ripolli¹, G. Taddei¹, C. Cacace¹, M. Ginesini¹, U. Boggi¹, F. Vistoli¹

¹ Division of General Surgery and Transplantation - University of Pisa, Pisa, Italy

Introduction: Increasing use of donors after cardiac death (DCD) lead to a new interest in the organ perfusion. Sometimes in case of unavailability of multiple systems for organ perfusion or in case of contemporary multiple donors some organ could be statically cold stored instead than perfused possibly determining impaired function. Here we present a hypothermic oxygenated machine perfusion applied to an en-bloc dual kidney retrieved from an animal (pig) DCD model.

Method: After the pig was dead, the abdominal organs bloc was retrieved. After the separation of the liver and pancreas, the bloc, composed by kidneys, aorta and inferior vena cava was prepared at the back-table and perfused with perfusion solution (Celsior 1I) added with heparine (10.000UI). The back-table surgery consisted in the accurate ligation of collateral branches from aorta and inferior vena cava, ligation of perirenal fat, proximal aortic stump ligation and distal aortic stump cannulation (Fig 1a). The perfusion was performed with PerKidney machine perfusion (PerLife, Aferetica s.r.l, Bologna, Italy). During the hypothermic oxygenated perfusion was set a target pressure (P) of 50 mmHg and a target flow (F) of 100ml/min. Normothermic perfusion, intended as a simulation of transplant, was performed setting a target P of 75 mmHg and a target F of 500ml/min.

Results: The no-flow period lasted 35min. The back-table surgery lasted 27.5 \pm 3.5 min. The hypothermic perfusion lasted 110 min: the mean temperature (T) during perfusion was 6.8 \pm 1.4 °C,the mean F was 120.4 \pm 58.7 ml/min, the mean P was 40.3 \pm 11.2 mmHg and the mean resistance (R)was 0.37 \pm 0.26. R started at 1.07 constantly dropped down and concluded after 55min at 0.06. Thetrend of parameters during hypothermic perfusion are reported in figure2a. The normothermic perfusion lasted 49 min: the mean T was 35.3 \pm 1.5 °C, the mean F was 495 \pm 11 ml/min, the mean Pwas 18 \pm 8 mmHg and the mean R was 0.031 \pm 0.016. R started at 0.05 stably dropped down after 10min at 0.01. During the perfusion kidneys gradually changed in color (Fig 1b-1c). The trends of parameters during normothermic perfusion are reported in figure2b.

Conclusion: In this preliminary proof of concept on a large animal model the dual kidney en-bloc perfusion appears feasible. The decreasing of R, the maintenance of F and P, changing in color and urine production are favorable characteristics supporting this option, potentially useful in case of lack of devices and contemporary donations. Larger experience is needed for precise setting of parameters during the perfusion, surgical preparation and setting of a standardized method to evaluate single parameters of each kidney of the en-bloc dual specimen.



Figure for Abstract A11

Preliminary experience with PerLife system for ex-situ liver perfusion and purification

I. Vella¹, R. De Carlis¹, A. Lauterio^{1,2}, R. Cerchione¹, M. Migliorini¹, L. Centonze¹, L. De Carlis^{1,2}

¹ Department of General Surgery and Transplantation, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy. ² Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy.

Background: Liver transplantation is a life-saving treatment. The extended criteria donors (ECD) could increase the number of livers available for transplantation, but these organs are at a higher risk of post- transplant complications. Machine perfusion is a strategy aiming at the recovery of ECD organs. In this report, we show our preliminary experience of ex-situ ECD liver perfusion with PerLife, according to dual hypothermic oxygenated perfusion (DHOPE) and normothermic (NMP) protocols.

Methods: Two grafts were recovered from ECD (case 1: 55-year-old male died from head trauma, with hemodynamic instability; case 2: 70-year-old female died from anoxia, macrosteatosis 45%). To get acquainted with the system, a first 90-minute DHOPE treatment was performed. Then, the second liver underwent NMP with the integration of PerSorb cartridge to remove inflammatory mediators from the perfusate. A 2L/min gas mixture oxygenation was supplied and adjusted with electrolytes and pH on blood- gas evaluation when needed. Perfusion parameters (pressure, flow, resistance, temperature) were continuously monitored, while perfusate samples were collected at the beginning of the procedure and every30 min.

Results: There was a progressive increase of the arterial and the venous flows: in DHOPE, arterial flow increased from 60 to 80mL/min and venous from 190 to 250mL/min, while, in NMP, arterial and portal flowsincreased from 70 to 170mL/min and from 250 to 860mL/min, respectively. In NMP, a decrease by 89.9% was observed in perfusate lactate levels after 220min of treatment. Perfusate IL-6 peaked at 602 and decreased to 371pg/mL at the end of perfusion. Both grafts were transplanted after the treatment (case 1: 66-year-old men with HCV and HCC, MELD-Na 13; case 2: 43-year-old male with NASH and HCC, MELD-Na 18). The transaminase peak was 930IU/L and 787IU/L for case 1 and case 2, respectively. The postoperative course was uneventful and both recipients did well after an overall follow-up of 5 and 4 months.

Conclusions: Both DHOPE and NMP ex-situ organ perfusion with PerLife were safe and feasible. The combination of NMP and PerSorb resulted in optimal organ perfusion. This is a preliminary experience: further evaluations are needed to explore the potential role of inflammatory mediators' adsorption in ex-situ treatments.



Figure 1: Lactates during NMP+PerSorb.

Protective effect of ex-vivo reconditioning with PerSorb on renal tubularmitochondrial dysfunction induced by ischemia-reperfusion injury

V. Cantaluppi¹, C. Grange², A. Colombatto¹, C. Riganti³, R. Cassatella⁴, C.Porta⁴, G. Marchioro⁵, A. Volpe⁵, B. Bussolati³

¹Nephrology and Kidney Transplantation Unit, Piemonte Orientale University (UPO), AOU Maggiore della Carità, Novara, Italy

²Department of Medical Sciences, University of Turin, Turin, Italy

³Molecular Biotechnology Center (MBC), University of Turin, Turin, Italy

⁴Vascular Surgery Unit, AOU Maggiore della Carità, Novara, Italy

⁵Urology Unit, Università del Piemonte Orientale (UPO), AOU Maggiore della Carità, Novara, Italy

Background/Aims: In kidney transplant, ischemia-reperfusion injury (IRI) is the main cause of delayed graft function (DGF). Mitochondrial dysfunction (MD) represents an important mechanism of acute kidney injury, accelerating the processes of fibrosis and cellular senescence, leading to an early graft dysfunction. In this study, mitochondrial metabolic activities (MMA) were assessed in ex vivo perfusion of pig kidneys, with/without PerSorb integration.

Materials and Methods: 3 en-block kidneys animal donors were procured: from each block, one kidney was perfused for 2 or 4 hours with PerLife system (Aferetica SRL, Bologna, Italy), with/without PerSorb, and the other one was used as a control. The following data were collected: temperature, arterial flow, arterial pressure (with initial target set at60 mmHg), vascular resistance. Biochemical analyses were performed on proteins extracted from bioptic samples collected hourly, frozen, sonicated and processed by extraction of the mitochondrial component. In particular, MMA evaluation was done on enzymes of the Krebs cycle, of the electron transport chain and on the efficiency of ATP synthesis. MD parameters (oxidation and loss of membrane potential) were also evaluated.

Results: Ex-vivo perfusion with Perlife system, independently with or without PerSorb, has given excellent results in terms of basic perfusion parameters with optimal arterial temperatures and pressures, as well as a significant reduction in vascular resistance (T0: 0.942 mmHg/ml/min; T2: 0.292 mmHg/ml/min; T4: 0.138 mmHg/ml/min). To better characterize the effect on IRI-induced renal tubular damage, we focused on MMA. The perfusion system was able to improve the activity of the relevant enzymes of the Krebs cycle (citrate synthase, alpha- ketoglutarate, succinate and malate dehydrogenase) and oxidative phosphorylation, suggesting an improvement in mitochondrial function particularly evident after 4 hours of perfusion. Consistently, ex-vivo treatment increased the activity of enzymes of the electron transport chain, along with increased intracellular ATP level. In addition, MD (free radicals, mitochondrial reagents of thiobarbituric acid and loss of membrane potential) appeared significantly reduced in perfused kidneys vs. controls, with further enhanced with Persorb.

Conclusions: The overall results of this study suggest that kidney perfused with PerLife and PerSorb significantly restored the homeostasis of MA with a possible limitation of IRI, promoting the tubular regeneration.

Cytokine mass balance levels in donation after circulatory death donors using hemoadsorption: case series report

S. Baroni¹, A. Marudi¹, S. Rinaldi¹. S. Ghedini², P. Magistri³, G. P. Guerrini³, T. Olivieri³, C. Dallai¹, M. Talamonti¹, J. Maccieri², F. Di Benedetto³, E. Bertellini¹

¹Department of Anaesthesia and Intensive Care, Azienda Ospedaliero Universitaria Policlinico, Modena, Italy ²Department of Anaesthesia and Intensive Care, Azienda Ospedaliero Universitaria Policlinico, Bologna, Italy ³Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, University of Modena adReggio Emilia, Modena, Italy

Background: The shortage of organs available for transplantation has encouraged the expansion of the donorpool by including donation after circulatory death (DCD). In Italy, the "no-touch interval" lasts for 20 minutes, that prolongs Warm Ischemia Time (WIT). WIT is considered to start when systolic blood pressure falls below50 mmHg and continues until the beginning of the extracorporeal normothermic regional perfusion (NRP), necessary for organ recovery performed with Extracorporeal membrane oxygenator (ECMO). The reperfusion phase leads to a reperfusion syndrome developing a high presence of cytokines and free radicals. This paper describes a case series of inflammatory cytokine levels before and after hemoadsorption during NRP in DCD donors of liver and kidneys.

Methods: We describe a case series of inflammatory cytokine levels before and after hemoadsorption duringNRP in DCD donors of liver and kidneys. All DCD donor subjects, mean age of 58.1 ± 6.2 years without evidentcritical conditions, no liver or kidney dysfunction known, presented with poor neurological outcomes. After the declaration of cardiac death, we performed NRP through cannulation of the femoral artery and vein. Later, we placed a Fogarty catheter into the contralateral femoral artery, followed by heparin administrationand occlusion of the supra celiac aorta to exclude the supradiaphragmatic circle. NRP has been performed in combination with the CytoSorb® cartridge. We measured cytokine mass balance (MB) as well as total removalratio (RR). MB represents the difference between pre and post adsorption cartridges median IL-6/IL-8/IL- 10/TNF- α values multiplied by median NRP flow and median perfusion time. Total RR is the difference between pre and post adsorption cartridges median IL-6/IL-8/IL- 10/TNF- α values.

Results: We observed in our patients a reduction of IL-10 and TNF- α levels during the main phases of NRP, accompanied by a blood lactates reduction. We transplanted all livers and kidneys. Receiving patients spentless than three days in the intensive care unit. Nobody had primary non-function or required renal replacement therapy during the hospitalization period. No apparent device-related adverse events occurredduring NRP perfusion.

Conclusions: Finding strategies to implement organ quality is necessary to implement several organs available for donation and reduce the waiting list. Our model shows encouraging data for a possible positive effect of hemoadsorption to implement organ quality.



A new system for organ transport: PerTravel

F. G. Besso¹, M. Mansouri¹, M. Brunelli¹, A. Amoroso¹, G. Guglieri², M. Chiaberge², G. Quaglia²

¹ Department of Medical Sciences, University of Torino and Immunogenetics and Transplant Biology Service, University Hospital "Città della Salute e della Scienza di Torino" and Regional Transplant Centre of Piemonte, Turin, Italy

² Department of Mechanical and Aerospace Engineering, Politecnico di Torino, Turin, Italy

Background: Up to day, in static cold storage (SCS), the organ is flushed through with a preservation solution, andkept in this solution in plastic bags, with organ direct exposure to ice temperature, without direct monitoring of temperature near the organ, the need of ice recharging for long transport duration and bringing about risk of freezing the organ if ice is too cold. The aim of the PerTravel project is therealization of an innovative medical device for the transport of biological material, specifically organs, cells and tissues, aimed at ensuring the safety of the organ.

Methods: The PerTravel should be designed to transport kidneys, pancreas, liver, heart and biological samples. The primary container of an already existing system for organ ex vivo preservation, the PerLife system, will be used as the primary organ container. By this way it will be possible to have a device directly compatible with an organ perfusion system. Then, the primary container will be placed inside the isothermal compartment. The maintenance of the temperature will be guaranteed through PCM that will allow a temperature-controlled transport between 2 and6 C°. The container dedicated to biological samples and documents will be a separate solution to the organ compartment, here the test tubes will be placed, and fixed by means of a foam rubber device. Pertravel's cloud will be needed to provide a state-of-the-art tracking and monitoring system. It is useful for the acquisition and visualization of the most decisive parameters in the process of transport of biological material, as internal, external temperature and inertial sensor, that warn users in case of any impact that could damage the organ. Here a database will be created with all the reports of the missions carried out, enabling the complete traceability of the process that could be consulted by all the institutions involved in the transplant management.

Results: Up to day, an initial prototype has been produced to assess the feasibility and maintenanceof isothermal conditions using the chosen solution. Development of the first device and thededicated disposable system is in progress.

Conclusion: PerTravel proposes to guarantee better quality and safety in the transport of organs through improved management, logistics and real-time control of the fundamental parameters for the well-being of the organ and the consequent success of the transplant.

Using Drones For Organ Transportation: INDOOR project

F. G. Besso¹, M. Mansouri¹, M. Brunelli¹, A. Amoroso¹, C. Bosso¹, G. Guglieri², M. Chiaberge², G. Quaglia²

¹ Department of Medical Sciences, University of Torino and Immunogenetics and Transplant Biology Service, University Hospital "Città della Salute e della Scienza di Torino" and Regional Transplant Centre of Piemonte, Turin, Italy

² Department of Mechanical and Aerospace Engineering, Politecnico di Torino, Turin, Italy

Background/aims: Nowadays, the recurring need to simplify and speed up the transport operations of biological material matches the demand for the reduction of its transport time between two geographic points that are not toofar from each other. Moreover, the promotion of innovation and automation of critical clinical processes, and the development of a very high technology device can be considered as competitive tasks. It must be considered that the transport conditions (mechanical stresses, temperature) can influence the outcome of clinical operations. Today's technology provides tested, controlled and safe devices – the drones – for multiple applications, which can be extended to the medical field, too.

Methods: Two maximum parameters of two types of drones – a multi-rotor (MR) and a fixed-wing (FW) drone – were considered: the cruising speed (MR: 60 km/h, FW 100 km/h) and battery autonomy (MR: 45 mins, FW: 2 hours). However, generally fixed-wing drones can lift higher loads than the others. By Italian Civil Aviation Authority (ENAC) regulations a drone flight requires authorizations and granted after an adequate risk assessment. Therefore, two parallel studies were carried out: the first one aimed to design the box for biological material (biological samples and kidneys – the other organs require the presence of the surgical transplant team, so they can't be transported by drone), to detect and process vibrations signals aboard thedrone and to their replication by a test machine – shaker –, by stressing biological samples and studying theirbiochemical response. The second one, aimed to the flight of a drone within an urban environment in the absence of biological material on board. The purpose of the project is the integration of these two branchesto validate the flight of biological material, first in Visual Line of Sight (VLOS) and then in Beyond Visual Line Of Sight (BVLOS) conditions.

Results: The biological samples were solicited in a selected frequency range (0–150 Hz) and the appropriate documentation was drawn up. The risk analysis made it possible to identify the security level, acceptable to ENAC to confirm its interest in the operation.



Figure 1 The figure shows the configuration of the primary container and of the foam rubber (shock-absorbing) platforms: in the case of biological samples, the tube holder is necessary; in the case of kidney, a support to the base and to the wall of the box is needed.

Conclusion: The technology of a drone is almost consolidated: this study is going to prove the feasibility of integrating smartly aeronautical specifications to the transplant clinical needs.

Critical points in randomized research on DCD donor in-situ perfusion (NRP): the interim DONARE Study clinical evaluation

L. Masiero^{*}, F. Procaccio^{*}, F. Vespasiano^{*}, F. Puoti^{*}, G. Bedeschi^{*}, M. Prugnoli¹, M. V. Antonini¹, S. Peverelli², A. Lombardo², S. Baroni³, P. Fassini⁴, G. Lanzillotti⁴, F. De Min⁵, M.A Donato⁵, M. Sacchi⁶, E. Masturzo⁶, S. Vesconi^{*}, A. Troni^{*}, A. Montemurro^{*} and M. Cardillo^{*} on behalf of the DONARE Study Working Group

* Italian National Transplant Centre (CNT). National Health Institute, Rome, Italy

¹Cesena; ²Como; ³Modena-Baggiovara; ⁴Legnano; ⁵Varese; ⁶ Milano-Niguarda

° Transplantation Foundation Onlus, Milan, Italy

Background/aims: Controlled DCD organ donation (cDCD) is a strategic target for the Italian transplantation network. Italian peculiarities in cDCD donation make published results questionable and raise concern over organ ischemic damage. Consequently, normothermic regional perfusion (NRP) has been strongly recommended in potential cDCD donors. In 2019 the randomized multicenter DONARE study was designed to describe ischemic-reperfusion and inflammatory biomarkers during NRP and to test the potential benefit of apheresis by an adsorbent filter (*CytoSorb®*) included in the NRP circuit. The aim of this report is to describe the modulation of the clinical characteristics and of the NRP in the DONARE study enrolled cases.

Methods: The study protocol was defined by the DCD national working group and proposed to all the Italian DCD donation centers. The coordinating center (CNT) has monitored the evolving cDCD activity to preserve the study capacity of representing the Italian scenario. Samples have been blindly centralized to an independent laboratory for cytokines profiling. The outcomes of transplanted organs have been recorded in the national quality database.

Results: From September 2020 to June 2022, 27 out of the 40 planned cases have been enrolled insix centers: 4 in 2020, 12 in 2021 and 11 within June 2022. Approval is still pending in other centers. Main causes of exclusion among potential cDCD donors were: age above 65 (in 2020), e-CPR prior- to-death, shortage in personnel and COVID-19 restrictions. The age limit for enrolment (<65yrs) was abolished by amendment due to the national trend: meanage of enrolled cases increased from 57±6 in 2020 to 67±6 years in 2022. Mean NRP duration decreased from 223,3±39,2 in 2020 to 168,9±42,6 minutes in 2022; serial samples (4/2 with/without *Cytosorb®*, from T0 to T4) from different points of the NRP circuit havebeen completed throughout the procedure in all the cases. All the enrolled cases became utilized donors. No study-related adverse event has been reported.

Conclusions: Coordination of multicenter studies in the rapidly evolving scenario of controlled DCDdonation should take advantage of continuous monitoring of real-life procedures and auditing of adherence to operational recommendations. The interim evaluation confirms the feasibility and safety of the study.

Combining normothermic machine perfusion with novel therapeutic procedures to improve the function of marginal donor livers

A. Körtge^{1*}, H. Krüsemann¹, S. Aldarwish², S. Hinz², S. Mitzner³

¹Fraunhofer Institute for Cell Therapy and Immunology IZI, Department of Extracorporeal Therapy Systems, Rostock, Germany

²University Medicine Rostock, Clinic and Polyclinic for General, Visceral, Thoracic, Vascular and Transplant Surgery, Rostock, Germany

³University Medicine Rostock, Centre for Internal Medicine, Division of Nephrology, Rostock, Germany

*Correspondence: andreas.koertge@izi.fraunhofer.de

Background/Aims: Marginal organs are increasingly used to expand the donor pool and to address organ shortage. In this light, normothermic machine perfusion (NMP) has become increasingly important in recent years as it enables extended preservation times which can be used for an objective viability testing. Our aim is to use a modified NMP with extended preservation time to apply therapeutic blood purification methods on discarded organs to make them suitable for transplantation again.

Methods: In the course of a large animal study with pigs, an NMP lab demonstrator is developed, which is capable of perfusing livers under physiologic conditions with regard to temperature, flow rates, pressures, and oxygenation. Laboratory roller pumps are used for perfusing the hepatic artery and the portal vein. The perfusate (RBC concentrate, albumin solution, further supplements) is oxygenated using a pediatric oxygenator. A rapid control prototyping platform is usedfor controlling purposes. Livers are damaged by applying cold ischemia times between 6 to 12 hours. The condition of the livers is evaluated using a broad range of assays. Modifications regarding the standard NMP procedure will be implemented, including blood purification approaches and modifications of the perfusate.

Results: The basic hardware and software framework for the automatic normothermic perfusion of pig livers, perfusion, and surgical protocols were established inorder to enable a standardized, comparable perfusion of the damaged organs. Implementation of a control concept for the perfusion at physiologic pressures/flow rates is in progress. NMP modifications are expected be added at the end of 2022.

Conclusion: In the future, the organ shortage is expected to worsen as a result of increasing prevalence of metabolic syndrome and the aging society. NMP is a potential key technology that enables the application of therapeutic procedures to organ grafts that were not applicable in this way until now, potentially contributing to a significant increase in the donor pool.

Quantification of dissolved oxygen: state of the art and potential application to organ ex-vivo machineperfusion

V. Marassi^{1,2}, A. Kurevija³, A. Lembo¹, S. Giordani¹, E. Panetta³, B. Roda^{1,2}, P. Reschiglian^{1,2}, M. Atti³, A. Zattoni^{1,2}

¹Department of Chemistry, University of Bologna, Bologna, Italy

² byFlow srl, Bologna, Italy

³ Aferetica srl, Bologna, Italy

Background: Oxygen is the key molecule in organ metabolism: alterations in O2 levels can reflect many pathophysiological states, making it one of the target molecules in diagnostic and therapeutic approaches. A peculiar and rapidly evolving field exploring the role of oxygen is organ preservation for transplantation. In recent years, oxygenated ex-situ perfusion (O-MP) of grafts is becoming an alternative for static cold storage (SCS), with the aim of increasing the number of suitable organs and improving their quality. O-MP depends on the goal of perfusion: ischemia-reperfusion injury limitation, prolongation of preservation time, improvement of organ conditions and functions and viability assessment prior to transplantation. Protocols differ in the temperature modes and the perfusate solution used. A reliable measurement of perfusate oxygenation ensures a high-quality process, while the amount of oxygenconsumption could be a useful tool for organ quality evaluation. It is crucial to provide a high-accuracy, real-time method for its quantification. This study aims at presenting and discussing the main oxygen detection and quantification methods, with a focus on the technical needs for their translation to the clinical practice.

Methods: Through systematic bibliographic research, we summarized the available oxygen sensing techniques, in terms of mechanisms and fields of application. For all methods, the analysis of compatibility with the use in O-MP was conducted considering two main factors: oxygen solubility and diffusivity in different types of conditions(temperature and types of perfusate). A method comparison study was conducted simulating O-MP conditions and environment, in the most critical settings for the techniques identified.



Results: Three classes of methods were identified: titration, electrochemical analysis (Blood gas analyzer - BGA, the most widely used in clinics), and photochemical analysis (fluorescence sensors). Titration was validated as a reference method and the comparison between Titration and BGA and titration and fluorescence were explored.

Conclusions: This study represents an assessment of current oxygen sensing methods and their applicability to clinical settings. It is a starting point for further validation of oxygen sensing technologies in order to establish a goldstandard for oxygen consumption quantification in O-MP.

Outcomes of kidney transplantation from uncontrolled donors after circulatory death vs expanded-criteria or standard-criteria donors after brain death at an Italian Academic Centre: a prospective observational study

R. Campi¹⁻², A. Pecoraro¹, M. L. Gallo¹, F. Sessa¹, D. Facchiano¹, G. Vignolini¹, L. Caroti³, C. Lazzeri⁴, A. Peris⁴, S. Serni^{1,2}, V. Li Marzi¹

¹Unit of Urological Robotic Surgery and Renal Transplantation, University of Florence, Careggi Hospital, Florence, Italy;

²Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy;

³Nephrology, Dialysis and Transplant Unit, Careggi University Hospital, Florence, Italy;

⁴Intensive Care Unit and Regional, ECMO Referral Centre, Azienda Ospedaliero- Universitaria Careggi, Florence, Italy.

Background/Aims: The use of kidneys from "expanded criteria" donors after brain death (ECD) and uncontrolled donors after circulatory death (uDCD) has been warranted to increase the pool of donors for kidney transplantation (KT). However, there is lack of evidence on the feasibility and safety of KT from such donors in the Italian setting.

Methods: We queried our prospectively KT database to select patients undergoing KT from uDCDs, ECDs, andstandardcriteria donors [SCD] from January 2017 to December 2020. All grafts from uDCDs were perfused with hypothermic machine perfusion (HMP) before KT (Figure 1). The feasibility of KT from uDCD was established considering the resistance during HMP (≤0.3 mmHg/ml/min). We compared the perioperative and mid-term functional outcomes among different donor types.

Results: Overall, 172 KTs were included (20% from uDCDs; 37% from ECDs, and 43% from SCDs). The donor'sprofile was different among the study groups, while recipients' characteristics did not significantly differ expect for median age and median Charlson comorbidity index. Median warm ischemia time for uDCDs was149 min (IQR 143-160). uDCDs and ECDs grafts had longer median cold ischemia times as compared to SCDsgrafts. Among uDCD, the median perfusion time was 10 hours (IQR 8-15), with a median minimal resistance of 0.18 mmHg/ml/min (IQR 0.13-0.26). The proportion of patients experiencing DGF, the median LOH, the overall and major complications rate, were significantly higher among recipients from uDCDs. The proportion of patients needing dialysis at last follow-up was significantly higher among recipients from uDCDs (33.3% vs8.5% vs 5.4%, p<0.001). However, the median eGFR was lower for recipients from ECDs compared to those from uDCDs and SCDs, respectively (45.2 vs 56.6 vs 59.0 ml/min, p<0.001).

Conclusion: While "marginal" donors represent a relevant source of organs, KTs from uDCDs carry higher risks of surgical complications, DGF, and graft nephrectomy as compared to KT from both ECDs and SCDs. Yet, recipients of uDCDs with no early postoperative adverse events showed functional outcomes at a mid- term follow-up that are better than those from ECDs. Further research is needed to establish the impact of HMP on organs from ECDs and uDCDs in the Italian scenario.



Celector®, a new quality control platform for the standardization of regenerative medicine products

S. Zia¹, P. Marrazzo², V. Pizzuti², F. Alviano², L. Bonsi², A. Zattoni^{1,3}, B. Roda^{1,3}, P. Reschiglian^{1,3}

¹Stem Sel srl, Bologna, Italy

²Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy

³Department of chemistry "G. Ciamician", University of Bologna, Bologna, Italy

Background: Cell therapy represents an innovative medical approach in many clinical fields such as osteoarticular reconstructive surgery, tissue engineering, and cancer therapy. Advanced therapy medicinal products (ATMPs) are cells and tissue products that are considered new types of drugs. Mesenchymal stromal stem cells (MSCs) are the most promising candidates in current clinical trials. Besides their regenerative properties, MSCs have shown also high immunomodulatory potential. In fact, cellular therapy with MSC has recently emerged as a promising strategy, allowing immunosuppressive drug minimization and tolerance induction in transplants. The ATMP products should follow requirements including sterility, identity, purity, viability, potency, and reproducibility. New approaches for the standardization of cell-based protocols may allow for the development of new high-efficiency drug systems. Nonetheless, the effectiveness of the existing techniques to isolate, qualify, and quantify cell-based ATMPs is still insufficient.

Methods: In this work, we present Celector[®], a new technology able to select, without extra manipulation, the most potent cell components from heterogeneous stem cell populations of different origins. The separation is obtained in a short time (around 15 minutes) in a capillary device, through to the combined action of gravity, acting perpendicularly to the flow, and opposing lift forces that depend on the morphological features of thesample. A micro-camera is connected as a detector and tailored software was designed for image acquisition, post-processing, and data analysis to fingerprint the biological sample.



Results: Celector[®] highlights physical differences that can be correlated to cell viability and regenerative potential. Cells eluted at a specific time show homogeneous physical properties, providing more homogenous cell populations with characteristic features. The methodology allows enrichment of the mesenchymal component with higher expression of mesenchymal markers and depletion of debris. In addition, cells with stable and reproducible doubling time analysis can be collected and used.

Conclusions: Celector[®] can be then used to obtain homogeneous and "good" cell-based ATMPs even from very heterogeneous cell samples to improve the success rate of ATMP applications. Cellular therapy with MSC hasrecently emerged as a promising strategy, allowing immunosuppressive drug minimization and tolerance induction in transplants. The potential of Celector[®] in select precise type f MSC could improve specific therapies during organ regeneration and transplant.

LIVER FAILURE

A22

The use of CytoSorb extracorporeal hemadsorption in liver failure: a retrospective single-centerregistry study

M. Valsecchi¹, M. Zaniboni¹, S. Gianni¹, R. De Carlis², A. Lauterio^{2,3}, G. Monti¹, L. De Carlis^{2,3,4}, R. Fumagalli^{1,3} ¹Department of Anesthesiology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

²Department of Transplantation. Division of General Surgery and Transplantation, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

³Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

⁴International Center for Digestive Health, University of Milano-Bicocca, Milan, Italy

Background: Little is known of the use of CytoSorb^{*} to provide biochemical control of liver impairment in patients withsepsis, acute on chronic liver failure (ACLF) or primary non function (PNF) after liver transplantation (LT).

Methods: This retrospective single-center study was conducted to elucidate beneficial and side effects of CytoSorb^{*} in 17 consecutive patients treated during the period January 2020 to February 2022: 3 (18%) with liver failure during septic shock, 8 (47%) with PNF, and 6 (35%) with ACLF. All patients had received primary continuousrenal replacement therapy prior to combination with CytoSorb^{*}. The CytoSorb^{*} effect was quantified comparing the following laboratory parameters pre-therapy and after 12-hour treatment periods: SOFA score, MELD score, CLIF-C ACLF, the need for inotropic drugs, mean arterial pressure, cardiac index, PaO2/FiO2, lactate, pH, procalcitonin levels, bilirubin, creatinine, BUN, platelet count, INR/PTT, transaminases, and IL- 6.

Results: Mean/median bilirubin, blood urea, procalcitonin, proinflammatory cytokines and IL-6 levels fell significantly following treatment (Table 1). In contrast, no significant improvement was observed in hemodynamics, coagulation profile, and respiratory function. In-hospital ICU mortality of CytoSorb[®]-treated patients was 47%.

Conclusions: As a limited, non-granular, self-reported study, the only accurate outcome to demonstrate CytoSorb^{*} efficacywas considered to be in-hospital mortality. The mortality reported for this series (47%) was on average lower than expected in light of the extremely poor patient scores at the time the decision was taken to start CytoSorb^{*} treatment: 87.7% for SOFA score > 14; 52.6% for MELD \geq 39; 100% at 3-7 days for CLIF-C ACLF > 65. Although only registry data, our experience nonetheless shows a clear association between hemadsorption and lower predicted mortality. Extracorporeal hemadsorption therapy should therefore always be considered an adjuvant along with standardtreatment in high mortality-risk patients. In addition, it would seem a promising therapy to buy time to transplantation in patients with ACLF. A randomized controlled trial is needed to further evaluate the efficacy and indications for hemadsorption in this uncommon clinical setting.

BILIVER study: observational study on hepatic toxins kinetic and evaluation of organ damage in acute on chronic liver failure (ACLF) patients

A. Siniscalchi¹, S. Faenza², C. Laici¹, E. Cerutti³, M. Valsecchi⁴, R. Fumagalli⁴, G. Biancofiore⁵, A. Ottobrelli⁶, T. Bove⁷, P. Navalesi⁸, P. Feltracco⁸, I. Riva⁹, F. Fabretti⁹

¹Anaesthesiology Intensive Care and Transplantation Unit, St. Orsola-Malpighi Hospital, Bologna, Italy.

² Department of Specialist, Diagnostic and Experimental Medicine, University of Bologna, Italy.

³ Anesthesia and Transplant Surgical Intensive Care Unit, Ospedali Riuniti, Ancona, Italy

⁴ Department of Anesthesia and Intensive Care Medicine, Niguarda Ca' Granda Hospital, Milan, Italy

⁵ Unit of Transplant Anesthesia and Critical Care, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy

⁶ Gastrohepatology Unit, AOU Città della Salute e della Scienza di Torino, University of Turin, Turin, Italy.

⁷ Department of Anesthesia and Intensive Care, Academic Hospital of Udine, Udine, Italy.

⁸ Institute of Anesthesiology and Intensive Care, Padua University Hospital, Padua, Italy

⁹ Anesthesiology Intensive Care Unit 3, ASST Papa Giovanni XXIII, Bergamo, Italy

Background: Acute on Chronic Liver Failure (ACLF) is an acute deterioration of pre-existing liver disease: an altered response of the organism to hepatic or extrahepatic stress triggers a systemic inflammatoryresponse syndrome (SIRS), then evolving into one or multi-organ failures. Currently, there is no resolution therapy for liver failure other than transplantation. Liver transplantation is the only treatment option for end-stage liver failure and acute liver failure. Therefore, many livers support extracorporeal therapies (LSET) have been developed offering an opportunity to stabilize liver function while allowing for native liver recovery or as a bridge to transplantation. Among LSET used, heamoadsorption is one of the most promising and easy to perform. In the BILIVER study, we want to assess the modulation of bilirubin and other toxic molecules and mediators by heamoadsorption and its effects on the severity of organ failure in patients with ACLF.

Methods: This is a Multicentric Perspective Observational Study. The population size is 50 patients to be enrolled. For each patient included, the demographic, anamnestic, severity score, clinical parameters and laboratory data will be collected on daily basis, from ICU admition until ICU discharge, according to the routine clinical practice. Blood samples willbe collected to assess bilirubin, ammonia, bile acids and cytokine efficacy of removal. The last Follow-up at 3 months. The primary endpoint is the assessment of the removal of major hepatic toxins. the secondary endpoint is the evaluation of effects on clinical outcomes and hepatic recovery.

Conclusion: The BILIVER study should help to deepen the knowledge about ACLF and LSET efficacy in a real-life practise, giving the possibility to further improve the management of these complex conditions by the application of hemoadsorption support therapy.

Extracorporeal blood purification therapy with CytoSorb[®] for severe hyperbilirubinemia and jaundice in druginduced liver injury

D. Diena¹, P. P. Inguaggiato¹, G. Daidola¹, G. Gigliola¹, M. R. Loi¹, L. Besso¹

¹Nephrology and Dialysis Unit, AO S. Croce e Carle – Cuneo, Cuneo, Italy

Background: Drug-induced liver injuries (DILI) are characterized by disproportionate elevation of alkaline phosphatase compared with the serum aminotransferases and elevation of serum bilirubin (1). Anabolic steroids are a known cause of DILI generally arising within 1-4 months by start of therapy (2).

Methods: A previously healthy 46 years old man, developed jaundice with mild increase in liver enzymes, marked increase of alkaline phosphatase and severe mixed hyperbilirubinemia (12.5 mg/dl). Viral, infectious and immunologic causes were excluded as well as presence of biliopancreatic pathology. CT and MR scan showed a liver with slightly increased dimension without focal lesions. A liver biopsy showed focal-sever cytoplasmic and intracanalicular cholestasis with limited focal hepatocyte necrosis, suggesting the hypothesis of a toxic hepatitis. Patient's assumption of anabolic drugs in the previous weeks for weight training and muscle bulk was ascertained. Bilirubin levels increased up to 40 mg/dl.

Results: Bilirubin rose despite forced diuresis and urine alkalinization. Extracorporeal blood purification therapy (EBPT) with regional citrate anticoagulation in association with a sorbent cartridge (CytoSorb[®]) was performed. A first cycle of 72 hours (showing 50% reduction of bilirubin) and a further cycle of treatment of 24 hours were performed, without circuits clotting or other complications. The evolution of bilirubin levels in correlation with EBPT was showed in figure 1. Six months later the patient had normal hepatic enzymes and bilirubin values normal and no jaundice.

Conclusions: Severe hyperbilirubinemia represents a potential life-threatening situation that, in the absence of acuteliver insufficiency, does not have indication to liver transplant. CytoSorb is an extracorporeal blood purification device with a large sorbent surface that adsorb a wide spectrum of molecules up to 55 kDa. It is mainly used in septic shock. Some case series demonstrated the effective removal of bilirubin by CytoSorb (3). A recent analysis on 109 patients from CytoSorb international registry treated for liver indication confirmed a significant bilirubin removal (4). The use of EBPT in patients without renal dysfunction to provide support for other organs is highly debated due to cost, potential complications and logistic problems related to intensive care needed. A multidisciplinary assessment is mandatory. In this case, EBPT was a feasible bridge therapy due to the lacking of direct liver indication (e.g. Liver transplantation) and due to the intrinsic characteristic of DILI with improvement of the liver injury following to drug discontinuation.



Figure 1: Bilirubin Levels in correlation with EBPT

Bibliography

^{1.} Lee WM. Drug-induced hepatotoxicity. N Engl J Med. 2003 Jul 31;349(5):474-85.

^{2.} LiverTox: Clinical and Research Information on DrugInduced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Androgenic Steroids. [Updated 2020 May 30].

^{3.} Tomescu D, Popescu M, David C, Sima R, Dima S. Haemoadsorption by CytoSorb® in patients with acute liver failure: A case series. Int J Artif Organs. 2021 Aug;44(8):560–4. 4. Ocskay K, Tomescu D, Faltlhauser A, Jacob D, Friesecke S, Malbrain M, et al. Hemoadsorption in "Liver Indication'-Analysis of 109 Patients" Data from the CytoSorb International Registry. J Clin Med. 2021 Nov 5;10(21):5182.

RHABDOMYOLYSIS

A25

Hemoperfusion with Cytosorb® in severe trauma: a case report.

F. Ferrari¹, N.S.M. Bianchi Bosisio², L. D'Auria², M. Manera², M. De Amici³, M. Belliato⁴

¹ International Renal Research Institute of Vicenza (IRRIV) and Department of Nephrology, Dialysis and Transplantation, San Bortolo Hospital, Vicenza, Italy

² Department of clinical-surgical, diagnostic, and paediatric sciences, Unit of Anaesthesia and Intensive care, University of Pavia, Pavia, Italy

³Immunoallergology Laboratory of Clinical Chemistry Unit - Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

⁴UOC Anestesia e Rianimazione II Cardiopolmonare, Foundation IRCCS Policlinico San Matteo, Pavia, Italy

Background/aims: Rhabdomyolysis is the breakdown of striated muscle cells, resulting in the release of potentially toxic compounds in the circulation. Following the lysis of myocytes, a large amount of salts, enzymes (aldolase, CK, LDH), and Mb, are released into the bloodstream. The incidence of Rhabdomyolysis is 1/10000 in the USA, with 8-15% of all cases of AKI, and a mortality of 5%. We hereby present a case of the use of CytoSorb® during CRRT after crush syndrome.

Methods: A young male (22 years old) was admitted to our hospital after a car accident, with prehospital parameters (GCS 13, HR 125/min, BP 90 /60 mmHg, RR 24/min, SpO2 92%). FAST exam showed right haemothorax, PNX, Morrison+++, Douglas+++, spleen-kidney space+++ with a HB 8g/dl and 4.2 mmol/L lactate values. He subsequently underwent splenectomy and liver packing in the OR. Total body angioCT was negative for brain damage and positive for polytrauma (VI, VII, VIII, IX right ribs, blushing, and contusion of both liver and kidneys). We used CytoSorb[®] for myoglobin and bilirubin levels reduction.

Results: CytoSorb[®] showed effective removal of toxic chemical agents following polytraumatic rhabdomyolysis, without bilirubin and biliary acid backflow into the bloodstream. Figure Table 1 shows vital and blood parameters ad ICU admission, on day 1, day 2, and day 3. In figure 1 is shown vital and blood parameters at ICU admission, on day 1, day 2, and day 3 and pre- and post-adsorption values of myoglobin and bilirubin.

Conclusion: Myoglobin elimination could avert permanent kidney damage by avoiding its deposition in the kidneys. Our case report suggests the potential of CytoSorb in removing toxic chemicals accumulation in the bloodstream after crush syndrome, restoring myoglobin and bilirubin to physiological range. It is fundamental for the clinicians to understand the physiochemical mechanism regulating molecular surface adsorption, the specific target molecules and the specific clinical case, in order to achieve the best results.







Figure 1: vital and blood parameters at ICU admission, on day 1, day 2, and day 3 and pre- and post-adsorption values of myoglobin and bilirubin.

Hemoadsorption treatment in polytraumatized patient with rhabdomyolysis: A case series

A. lacono¹, I. Guarrera¹, D. Burrascano¹, L. Chiarenza¹, A. Romeo¹, M. Corda¹, F. Lo Cascio¹

¹Trauma Center, AOR villa sofia – Cervello, Palermo, Italy

Background: Post-traumatic rhabdomyolysis is a syndrome characterized by a damage to skeletal muscle and consequent release of myocellular components into the blood stream (Creatin Kinase CK, LDH, myoglobin). Disseminated intravascular coagulation (DIC) and Acute kidney injury (AKI) aresevere complication of rhabdomyolysis. When rhabdomyolysis is suspected or certain, an early optimized medical therapy with hydration, urine alkalinization, forced diuresis and organ support with Continuous Renal Replacement Therapy (CRRT) should be initiated to prevent irreversible organ damage. Extracorporeal blood purification with CytoSorb represents a promising adjuvant therapy to rapidly lower high levels of myocellular components.

Materials and Methods: Between August 2020 and October 2021, 175 patients have been included due to rhabdomyolysis (CK>1000 U/L and myoglobin>5000 ng/ml) and 9 patients received CytoSorb blood purification due to high levels of myocellular components (CK>5000 U/L and myoglobin>10000 ng/ml).

Results: During the study period, 9 patients with crush-syndrome related severe rhabdomyolysis received a CytoSorb treatment in hemoperfusion or together with CRRT for 24 consecutive hours. The early use of CytoSorb allowed a rapid and efficient stabilization of myoglobin and CK levels in blood, avoiding AKI development (compared to the no-CytoSorb group in which 13% of patients developed AKI).



Conclusion: The early use of the extracorporeal blood purification adsorption cartridge CytoSorb tomodulate high levels of myoglobin and CK in the bloodstream after severe rhabdomyolysis might be potential option to prevent the development of AKI in polytraumatized patient and avoid chronic kidney disease.

A successful treatment with CytoSorb of AKI due to rhabdomyolysis, multifactorial cirrhosis and Staphylococcus Cohnii Sepsis

G. Leonardi¹, A. Flores¹, A. De Giorgi¹, P. Covella¹, B. Di Renzo¹, C. Balestra¹, P. Schiavone¹, M. Mangiulli¹, F. Capaccio¹, M. Recupero¹, A. Montanaro¹, A. De Marco¹, L. Vernaglione¹
¹Nephrology and Dialysis Unit, "A. Perrino" Hospital, Brindisi, Italy

Background: Rhabdomyolysis is a syndrome characterized by skeletal muscle necrosis resulting in the release of electrolytes, myoglobin, and other muscle proteins into the bloodstream. The cause may be traumatic or non-traumatic. Myoglobin can lead to renal damage due to a direct cytotoxic effect on the epithelial cells of the proximal tubule and subsequent oxidative stress.

Methods: We describe the case of a patient admitted to Emergency Unit with sudden onset of soporific state and accidental fall. He is affected by HCV and drug addiction history. The exams showed neutrophilic leukocytosis(WBC: 23.300 CRP: 6,2 mg/dl), an increase in transaminases (AST 1460 UI/l, ALT 295 UI/l) and ammoniemia of218 umol/l. It also showed positivity for methadone and cannabinoids and a slight worsening of renal function with creatininemia: 1.5 mg/dl was observed. The patient was admitted to the Department of Internal Medicine with a diagnosis of multifactorial cirrhosis with hyperammonemic decompensation. At the same time of clinical worsened, there were a rapid deterioration in renal function (Creatinine: 3.4 mg/dl), the appearance of faecal vomiting, decreased diuresis (<100 ml) and indices of massive rhabdomyolysis with Myoglobin: 261252 ng/ml, Troponin: 1513 ng/ml CPK: 93900 IU/l. So, the patient was transferred to the nephrology unit, where was started CVVHDF treatment with CytoSorb. This procedure was associated with antibiotic therapy with Meropenem and Linezolid.

Results: A total of 3 treatment of CytoSorb was performed with change every 24 hours. After the treatment there wasa substantial improvement in clinical conditions and blood values (table and figure 1). After 72 hours from the admission, we found positive blood cultures for *Staphylococcus Cohnii*; so, the antibiotic therapy with clindamycin was started. From the 4^{TH} day CVVHDF was stopped and intermitted dialysis of an average duration of 3 h was started. After 28 days there was a complete recovery of renal function.



Figure 1: Blood Values during CVVHDF+CytoSorb Therapy and CK and Myoglobin Trend

Conclusion: This case shows the importance of the association between haemodialysis and haemoadsorption methods and also underlines the crucial importance of starting treatment early in the case of rhabdomyolysis. Treatment with CytoSorb was effective in reducing the myoglobinemia caused by massive rhabdomyolysis and resulted in a complete recovery of renal function, together with the resolution of the septic state caused by Staphylococcus Cohnii.

Prevention of Rhabdomyolysis-Associated Acute Kidney Injury by Extracorporeal Blood Purification with CytoSorb: A Case Report

S. Rauch^{1,2}, A. Borgato¹, E. Gruber³, C. Leggieri¹, M. Bock^{1,4}, P.M.E. Seraglio¹

- ^{1.} Department of Anesthesia and Intensive Care Medicine, "F. Tappeiner" Hospital, Merano, Italy
- ^{2.} Institute of Mountain Emergency Medicine, Eurac Research, Bolzano, Italy
- ^{3.} Department of Surgery, "F. Tappeiner" Hospital, Merano, Italy
- ^{4.} Department of Anaesthesiology, Perioperative Medicine and Intensive Care Medicine, ParacelsusMedical University, Salzburg, Austria

Background: Rhabdomyolysis is a clinical syndrome caused by damage to skeletal muscle and release of its breakdown products into the circulation. Acute kidney injury (AKI) is a severe complication of rhabdomyolysis. The pathophysiology of rhabdomyolysis-associated AKI is complex, but myoglobin related damage plays a majorrole. The mainstay of prevention and treatment of rhabdomyolysis-associated AKI is the early and aggressive hydration, administration of bicarbonate and in case of refractory hyperkalemia, acidosis and/or volume overload, renal replacement therapy is indicated. Extracorporeal blood purification via modulation of high levels of myoglobin is therefore an appealing target to prevent AKI, however, attempts to remove myoglobin with standard dialysis membranes have so far been unsuccessful.

Case Presentation: Here we report the case of a 12-year-old boy with severe trauma-related rhabdomyolysis admitted to the intensive care unit after a surgical fasciotomy at the lower leg to prevent a compartment syndrome. A massive rhabdomyolysis was developed few hours after surgery with Creatinine Kinase (CK) and myoglobin values reaching a peak of >42,670 U/l and >12,000 µg/l, respectively. We decided to start continuous renal replacement therapy (CVVHDF) in combination with 2 cycles of CytoSorb to modulate CK and myoglobin levels and prevent AKI.

Results: After 24 hours of CVVHDF + CytoSorb, extracorporeal treatment was interrupted due to a continuous increase of CK and myoglobin, then a second cycle of 24 hours of CVVHDF + CytoSorb was started and successfully lead to a restoration of physiological values in the blood, as shown in the figure.



The early use and the rapid change of extracorporeal blood purification with CytoSorb allowed a rapid and efficient stabilization of myoglobin and CK levels in blood.

Conclusion: The early use of extracorporeal blood purification techniques, such as CytoSorb, to remodulate high levels of myoglobin in the bloodstream after severe rhabdomyolysis might be a potential option and should be further investigated as a tool to prevent the development of AKI.

A successful treatment of severe opioid-abuse-rhabdomyolysis with CVVHD and CytoSorb®

M. Guarneri¹, L. Calandra¹, E. Mancia¹, D. Altieri¹, C. Carollo¹, G. Mulè¹, S. Cottone¹

¹ Unity of Nephrology and Dialysis and School of Specialization in Nephrology, AOUP P. Giaccone, University of Palermo, Palermo, Italy

Background: Opioid produces rhabdomyolysis by several different mechanisms, including myotoxic effect ofnarcotics and prolonged immobilization [1]. Acute kidney injury (AKI) is the most frequent and the most severe complication of rhabdomyolysis [2]. We report a case of AKI due to opioid-abuse-rhabdomyolysis in which we used CRRT [3] plus hemadsorption, with recovery of kidney function.

Case Presentation: A 41 years-old man without history of nephropathy was admitted to hospital after a reported overdose of heroin by general discomfort.

At the admission, the patient was unconscious and anuric. Laboratory diagnostics showed: severe rhabdomyolysis (Myoglobin >2000 μ g/L and CK >2000 U/L, LDH 3099 U/L), AKI (BUN 157mg/dl, sCr 8.98 mg/dl), metabolic acidosis with hyperkalemia (pH = 7.27, HCO3 = 13.6 mmol/L, Lactate 4.3 mmol/L, K+ 8.5 mmol/l).

Despite aggressive hydration therapy anuria was persistent, therefore in order to remove myoglobin and CPKfrom the bloodstream CVVHD with CytoSorb[®] was carried on. Anticoagulation with systemic heparin was used. We performed two cycles of therapy each one for a 24-hour period.

Results: Myoglobin and CPK levels were reduced significantly (Fig. 1). Successively, four HDs were performedleading to a gradual and adequate recovery of spontaneous diuresis.

The patient was dismissed with normal diuresis and partial improvement of renal function (sCr 3.2 mg/dl at discarge).



Conclusion: Our report shows that use of CVVHD plus CytoSorb[®] is safe and effective in the treatment ofopioidabuse rhabdomyolysis AKI.

References

- 1. Richards JR. Rhabdomyolysis and drugs of abuse. J Emerg Med. 2000;19(1):51-56.
- 2. Bosch X. Rhabdomyolysis and acute kidney injury. N Engl J Med. 2009;361(1):62.
- 3. Ronco C. Extracorporeal therapies in acute rhabdomyolysis and myoglobin clearance. Crit Care 2005.

A29
Blood purification with CytoSorb for the elimination of myoglobin in a case of severe rhabdomyolysis due to polytrauma

L. Rizzi¹, L. Venitucci¹, A. Nardelli¹, A. Gisotti¹, A. Saponaro¹, N. Di Venosa¹ ¹Department of Anesthesia and Intensive Care, "L. Bonomo" Hospital, Andria, Italy

Background: Rhabdomyolysis describes the disintegration of skeletal muscles, leading to the release of muscle components into the blood. The most common cause is traumatic damage of the muscles, for example in patients after multiple traumas. In addition to electrolyte disorders caused by cell decay, there is also an accumulation of creatine kinase (CK) and myoglobin in the blood. An accumulation of large amounts of myoglobin might have nephrotoxic effects leading to AKI.

Methods: Here we describe the case of a 29-year-old boy with polytrauma-related rhabdomyolysis admitted to the intensive care unit after an urgent treatment of spinal cord decompression and stabilization of the spine. The first day creatinine was 1.11 mg/dl and CK 6241 U/L. On the following day the creatinine increased to 2.77, the CK to 7513 U/L and myoglobin was 4104 mcg/L. On day 3 there is the appearance of oliguria, despitediuretic therapy, the Creatinine and CK values reaching a peak of 3,22 mg/dl and 19902U/l respectively. Themyoglobin remains above the laboratory measurement cut-off. The Mc Mahone score for rhabdomyolysis iscalculated and found to be 9.5, so we decided to start continuous renal replacement therapy (CVVHDF) in combination with 3 cycles of CytoSorb to modulate CK and myoglobin levels and prevent AKI.

Results: After 72 hours of CVVHDF + CytoSorb, there was a restoration of physiological values in the blood as shown in the figure 1. Due to respiratory weaning difficulties, also linked to his psychical state, the patient was tracheostomized in the following days and, subjected to ad hoc treatment with antidepressant drugs, he was able to be weaned from the respiratory support and on day 32 transferred to the rehabilitation center.



Figure 1: Myoglobin, CK and Creatinine Trend

Conclusion: Blood purification with Cytosorb[®] integrated into a CRRT system may be a useful tool for the elimination of myoglobin in patients with rhabdomyolysis. In addition, myoglobin elimination could avert permanent kidney damage by avoiding its deposition in the kidney.

Creatine-phosphokinase and myoglobin adsorption with CytoSorb® in multi-operated patient: a casereport

D. Polieri¹, R. Anaclerio¹, C. Petrillo¹ ¹ P.O. Divenere, ASL Bari, Bari, Italy

Background: Rhabdomyolysis (RM) is a clinical condition associated with elevated levels of creatine-phosphokinase (CpK), myoglobin and electrolyte imbalance caused by severe trauma, muscle injuries, among other factors. In addition to preventing further muscle injuries, intensive treatment is primarily aimed at reducing these potentially nephrotoxic agents (CpK, myoglobin) and correcting metabolic acidosis. CytoSorb[®] is an adsorption device that can be used as standalone therapy or in combination with CRRT. In this case report, we describe the use of CytoSorb[®] in rapidly reducing CpK and myoglobin levels in a patient after 2 surgeries.

Case description: the patient was admitted to peripheral Emergency Unit for an acute abdomen, abdominal CT scan showed signs of intestinal occlusions. She underwent laparotomy viscerolysis, removal of the right external iliac vein, resection of the transverse colon with latero-lateral anastomosis and appendectomy. In the immediate postoperative period CT angiography was performed and arterial thrombosis was found. She was then transferred to our hospital and underwent embolectomy surgery and subsequent admission to the intensive care unit. On admission to the ward, the patient was sedated and ventilated with adequate exchanges, haemodynamics sustained by noradrenaline at 0.25 mcg/kg/min and volumetric filling was carried out (1000ml crystalloids), with slight lactacidemia at 2.48 mml/L. Indices of muscle necrosis severely increased as well as indices of sepsis. Antibiotic therapy with piperacillin tazobactam and teicoplanin is imposed. After2 days catecholamines 0.33 mcg/kg/min, diuresis always present, but with worsening renal function indices and persistently out of range muscle necrosis indices. Perform nephrological assessment and start CVVHDF with 1 treatment with CytoSorb x 12 h.

Results: After CVVHDF + CytoSorb treatment there was a reduction in haemodynamic support 0.15 mcg/kg/min, reduced muscle necrosis indexes, so CVVHDF was continued and started second cycle of CytoSorb x 12 h. After 48 hours and a third treatment with CytoSorb haemodynamic support was reduced to 0,05 mcg/kg/min. In figure 1 was shown trend of CpK, myoglobin and LDH.

Conclusion: In the present case, we successfully treated a patient suffering from severe rhabdomyolysis after surgery with CVVHDF and CytoSorb. This treatment led to improvement of sepsis indices and renal function, allowing creatinine, Cpk and LDH clereance.



Figure 1: Myoglobin, CpK and LDH trend during ICU stay

Use of Cytosorb in rhabdomyolysis treatment: a retrospective observational study

C. Maisto¹, A. Accogli¹, D.M.L. Burzo¹, A. Mudoni¹, F. Musio¹, A. Naticchia¹, M.D. Zacheo¹, F. Caccetta¹, P. Ciocchetti² and D. Gemma²

¹ Nephrology and Dialysis Unit, Ospedale Cardinale Panico, Tricase (Le), Italy

² Anaesthesia and Intensive Care Unit, Ospedale Cardinale Panico, Tricase (Le), Italy

Background: Rhabdomyolysis is a common and potentially life-threatening syndrome, characterized bymuscle necrosis, with release into the circulation of the intracellular contents, in particular of myoglobin. The release of myoglobin plays a fundamental role in the pathogenesis of Acute kidney injury (AKI). The treatment of severe forms involves the use of renal replacement therapy, however theremoval of myoglobin from the circulation is also important in order to ensure faster recovery.

Methods: We present a 3-year retrospective observational study, includes 6 patients admitted to "Cardinale G. Panico" Hospital, Tricase (LE) for rhabdomyolysis and treated with CRRT + Cytosorb as adjuvant therapy to standard supportive care. CytoSorb was applied in combination with standard CVVHD on Multifiltrate CiCa, using an AV1000S hemofilter (Fresenius Medical Care). From 2 to 6 consecutive CytoSorb cartridges was used. The adsorbers were changed every 24 h. Blood flow rates (Qb) were maintained between 100 and 150 mL/min, and dialysis doses ranged from 20 to 35 mL/kg /h accord- ing to standard care. For each patient were described different profiles: the renal profile (creatinine, azotemia and 24h diuresis); the hemodynamic profile (mean arterial pressure MAP, number of inotropes used, lactates); the acid-base profile (pH). The trend of myoglobin over time was also evaluated. All these items were recorded at time 0 (TO), before the start of Cytosorb, after 24h from the start of treatment with Cytosorb, and also at 48h, 72h and 96h.

Results: The observed survival rate was 100%. Only one patient had to continue renal replacement therapy with intermittent hemodialysis. In all patients we observed a reduction in the myoglobin levels, and an improvement in haemodynamics (increase in MAP and decrease in lactate levels and in use of inotropic drugs). We have also seen a rapid increase in diuresis.



Figure 1A: Trend of myoglobin

Figure1B: Increase in diuresis

Conclusion: Our experience, the role of myoglobin and the evidence related to an improvement in renal outcome following the removal of this toxin support the hypothesis that the adsorbent cartridge may have a fundamental role in the prognosis of these patients, inreducing the recovery and costs related to hospitalization.

Successful use of CytoSorb hemoadsorption in a patient with rhabdomyolysis with acute renal failure due to neuroleptic malignant syndrome

M. Grassi Bertazzi¹, B. Lanzafame², V. La Rosa³, G. Scrofani¹, D. Grasso¹, D. Lauretta¹, A. Spampinato¹, O. Sciuto¹, M. Gennaro¹, S. Borraccino¹

¹Department of Anaesthesia and Intensive Care, Cannizzaro Hospital, Catania, Italy

² Department of Anaesthesia and Intensive Care, Umberto I Hospital, Siracusa, Italy

³ Department of Anaesthesia and Intensive Care, Humanitas Hospital, Catania, Italy

Background: Neuroleptic malignant syndrome (NMS) represents a rare but sometimes life-threatening reaction to neuroleptic drugs which can progress to renal failure secondary to rhabdomyolysis. Although extracorporeal therapies appear capable in this setting, positive results remain sparse. Extracorporeal hemoadsorption could represent a promising treatment alternative, as it has been successfully applied in indications sharing similar features with NMS. **Case Presentation:** A 39-year-old woman was admitted to the Emergency Department following development of NMS due to the administration of multiple neuroleptics. Following development of multiple organ dysfunction including acute renal failure due to rhabdomyolysis, hemodiafiltration was started and then combined with plasmapheresis later on. Both therapies proved ineffective so the decision was made to install a CytoSorb hemoadsorption cartridge into the CVVHDF circuit in a pre-dialyzer position in order to reduce myoglobin plasma concentrations and to support standard therapy. Two consecutive CytoSorb treatments (48 hours per treatment) were run at a blood flow rate of 100 ml/min, dialysate 2000 ml/h, reinfusion 1000 ml/h, using citrate anticoagulation.

Results: The combination of continuous renal replacement therapy (CRRT) and CytoSorb resulted in a continued decrease in serum myoglobin levels from 34,236 µg/l to 8,607 µg/l after the first cycle, reaching 567 µg/l at the end of the treatment. Spontaneous diuresis recurred on day 20 with gradual increasing volumes thereafter. Respiratory gas exchange gradually improved during CytoSorb treatment as did renal function as evidenced by a gradual decrease in creatinine (3 to 1.28 mg/dl) and blood urea nitrogen (93 to 25 mg/dl) levels throughout the treatment. The hemodynamic condition also improved, followed by reduction and complete discontinuation of vasopressor support on day 23 of ICU admission. She could be extubated successfully one day later and was finally discharged to the rehabilitation ward making a full renal recovery.



Fig.1. Timeline of treatment during ICU stay

Conclusions: To our knowledge this is the first case describing the use of CytoSorb hemoadsorption in combination with hemodiafiltration and standard therapeutic measures to treat a patient with rhabdomyolysis, acute renal failure and neuroleptic malignant syndrome. Combined therapy was both safe and easy to perform. This case emphasizes the use of CytoSorb hemoadsorption in rhabdomyolysis, in which other extracorporeal treatments such as plasmapheresis may be ineffective.

Use of Cytosorb in rhabdomyolysis, heart failure and AKI aftercocaine abuse in a cardiopathic patient: a case report E.G. Porcile¹, A. Di Noto¹, G. Zucco¹, M. Speranza¹, I. Iovino¹, M. Pastorino¹, E. Costa², M. Centanaro¹, A. Gratarola³

¹ Postoperative Intensive Care Unit, Anaesthesia and ICU Operative Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

² Resident, Nephrology, University of Genoa, Genoa, Italy

³ Director of Department of Emergency, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

Background: Both rhabdomyolysis and myocardial toxicity (ischemia/infarction, heart failure)due to cocaine abuse are a known occurring condition in critically ill patients, resulting in a highrisk of acute kidney injury (AKI) and potentially permanent kidney damage. Early renal replacement therapy (RRT) might be an approach to prevent AKI, but conventional dialysis membranes may fail in eliminating high molecular weight products. The use of additional filtersin high fluxRRT has been shown to be an efficient way to eliminate proinflammatory and toxic agents.

Methods: We describe a case of a 31-year-old severe cardiopathic, former drug addict female who developed cardiogenic and septic shock, rhabdomyolysis and AKI after drug relapse. After admission at ER she rapidly developed multiorgan dysfunction with severe cardiac, hepatic and anuric renal failure, then she was admitted in our ICU where she was intubated and underwent RRT via CVVHDF with sepsis-specific filters at the beginning with Oxiris[®] (Baxter) and because of worsening of her clinical conditions we switched to Cytosorb[®] (Aferetica), with two cartridges. CRRT was discontinued after 23 days, a few intermittent dialysis sessions were then performed and then subsequent discontinuation of the method due to evidence of recovery of renal function, which returned eventually to normal values of creatinine and urea. We monitored the level of creatine phosphokinase (CPK), lactate dehydrogenase, hepatic and cardiac enzymes during ICU stay.

Results: During and immediately after CRRT performed with Cytosorb[®] a decrease of lysis enzymes, CPK and cardiac enzymes has been registered and patient's clinical conditions rapidly improved.

Conclusions: CRRT with Cytosorb[®] showed to be a safe and efficient treatment of rhabdomyolysis and AKI due to cocaine taking, leading to a reduction of high level of lysis enzymes. Moreover, we observed stability of hemodynamic values even in severe heart failure, and the patient rapidly and completely recovered renal function after discontinuation of RRT.



Fig.1 Graphic shows the trend of lysis enzymes during days of treatment. Cytosorb was used on G2 and G3. (Please note 14000 U/l is lab cap for CPK in routine exams)

COVID-19

A35

Potential role of Pancreatic Stone Protein (PSP) as early marker of bacterial infection in COVID-19 patients

D. Morri¹, A. Potalivo¹, B. Cappati¹, S. Domizi¹, A. Pazzini¹, S. Di Giandomenico¹, G. Fricassè¹, C. Vannini¹, F. Facondini¹, G. Nardi¹, J. Montomoli¹

¹Department of Anaesthesia and Intensive Care, AUSL Romagna, Infermi Hospital, Rimini, Italy

Background: Sepsis is a life-threatening condition that needs immediate diagnosis and treatment to maximize the chances of survival. Bacterial superinfection is a severe and frequent complication among COVID-19 patients and its diagnosis is challenging. Previous reports suggested that Pancreatic Stone Protein(PSP) may be a predictive biomarker for sepsis in critically ill patients. We report a case series of three COVID-19 patients admitted to our intensive care unit (ICU) with risk of sepsis.

Methods: We daily monitored PSP, procalcitonin (PCT), and C-reactive protein (CRP) levels in three COVID- 19 patients admitted to our ICU. Microbiological sampling and antibiotic treatment were performed according to the ward organization and in case of clinical suspects for infection. Positive cultures and antibiotic treatment were retrieved from clinical charts and patients were followed from ICU admission up to a maximum of 20 days.

Results: Patient 1 (male, 55 years-old, overweight, no other comorbidity) was admitted to the ICU in treatment with Ceftriaxone then interrupted on day 7. On day 2 he was intubated and piperacillin/tazobactam was started on day 12 for suspected hospital acquired pneumonia. PSP levels markedly increased on day 10 with no significant changes in CRP and PCT levels. On day 13 a positive bronchospirate for Klebsiella pneumoniae was found. Similarly, patient 2 (male, 70 years-old, mild emphysema and diabetes) was admitted to ICU without antibiotic and with a PSP level of 287 ng/ml. His conditions rapidly worsened in severe septic shock requiringintubation. CRP markedly raised 48-72 hours after PSP with only mild increase of PCT. Patient 3 (male, 78 years-old, no comorbidities) was admitted to ICU with high levels of PSP and piperacillin/tazobactam therapy was started. After 48-72 hours CRP levels increased with no significant changes of PCT. A positive bronchospirate for Ps. aeruginosa was collected on day 3.

Conclusion: Our findings suggest a potential role of PSP as early biomarker of sepsis in critically ill COVID-19 patients. Daily PSP monitoring may anticipate an appropriate treatment of COVID-19 patients with a septic complication in comparison with the actual laboratory markers. Further studies are needed to confirm our hypothesis.



Fig. 1. PSP, PCT and CRP trend

COMPARATIVE EFFECTS OF TOCILIZUMAB AND CYTOSORB® ON BLOOD CYTOKIENE LEVELS INPATIENTS WITH SARS-CoV-2 PNEUMONIA

G. Berlot¹, A. Tomasini¹, V. di Maso², F. Bianco², U. Gerini²

¹ Department of Anesthesia and Intensive Care Medicine, Cattinara University Hospital, Azienda Sanitaria Universitaria Giuliano-Isontina, Trieste, Friuli-Venezia Giulia, Italy

² Department of Nephrology, Cattinara University Hospital, Azienda Sanitaria Universitaria Giuliano-Isontina, Trieste, Friuli-Venezia Giulia, Italy

Background/aims: SARS-CoV-2 is responsible of respiratory failure and also causes a massive release of inflammatory mediators such as IL-6, IL-1, CRP etc. This hyperinflammatory condition, often indicated as Cytokine Release Syndrome (CRS), could led to life-threatening events. The clinical course resembles septic shock and the elevated values of inflammatory mediators are associated with a higher viral load and reducedsurvival. The use of techniques aiming to contrast the surge of inflammatory mediators has been advocated in the treatment of this condition.

Methods: Four patients were retrospectively admitted in Intensive Care Unit with respiratory failure caused by SARS-CoV-2 infection. Two patients were treated with Tocilizumab (TCZ) alone, the others receivedTCZ in association with hemoadsorption (HA) treatment. The HA procedure was performed with CytoSorb responsible of removing hydrophobic molecules with a molecular weight of up to approximately 60 kDa including cytokines and other inflammatory mediators involved in CRS. Each procedure lasts 24 hours.

Blood values of IL-6, C-reactive protein (CRP) and other biochemical variables were measured in two patients who received Tocilizumab (TCZ) alone and in other two in whom it was associated with hemoadsorption (TCZ-HA). All variables were measured before, during and after the treatment.

The aim of the study is to assess the variations of IL-6 in patients with SARS-CoV-2 infection treated with TCZalone or in association with hemoadsorption (HA).

Results: All patients full-filled the criteria of severe SARS-CoV-2 infection. In all patients the administration of TCZ was followed by an increasing in IL-6 values. Its values remained elevated in patients given TCZ but sharply decreased in the following days in those treated also with HA. The percentage variations of IL-6 from the baseline between the two groups was +344% and +89% in the two patients treated with TCZ alone and -56% and -15% in TCZ-HA group. Both TCZ and TCZ-HA were well tolerated.



Conclusions: The increase of the IL-6 can be ascribed to its displacement from cellular and soluble receptors, whereas its decrease is likely due to the scavenging effect exerted by the HA. Although the association TCZ- HA could be valuable in the treatment of the Cytokine Release Storm (CRS) associated with SARS-CoV-2, theHA could be more effective as it neutralizes a wider panel of inflammatory mediators. More experience is needed to identify the best candidate for TCZ or TCZ-HA.

A37 Cytokine elimination in suspected COVID-19 perymyocarditis

J. Kompatscher¹, S. Canestrini¹, M. Kaufmann¹

¹Intensive care medicine PA-ICU, Central Hospital of Bolzano, South Tyrol, Italy

Background: Only recently studies have been able to demonstrate the safety and efficacy of purification therapiesin inflammatory diseases. Here we present the management of a young (21y) male patient in severecardiogenic shock due to COVID-19 perymyocarditis admitted to the ICU at Bolzano Central Hospital.November 30th 2020 the patient developed high fever (>40 C) and diarrhea. After unsuccessfully being treated orally with a macrolide he was admitted to a peripheral hospital the 4th of December.The day after he deteriorated, required transfer to the ICU, endotracheal intubation and pharmacological cardiovascular support (Norepinephrine, Levosimendan). Antimicrobial treatmentwas started with piperacillin/tazobactam, linezolid and metronidazole. Despite multiple radiological and microbiological diagnostic attempts the origin of this severe septic shock remained unclear. December 6th the patient was transferred to Bolzano Central Hospital for VA-ECMO evaluation.

Methods: The transesophageal echocardiography revealed 15-20% of EF, lactate (5,2 mmol/l), cardiac enzymes (TropT 1400 mcg/l) and inflammatory parameters (PCT 35 ng/ml, IL-6 685 pg/ml) were elevated. We performed cardiac monitoring via Swan-Ganz catheter. The cardiac index was 1,6 l/min/m². The peak dosage for Norepinephrine reached 7,5mg/h (1,47 mcg/kg/min). At Bolzano ICUwe facilitate the pharmacological therapy with milrinone, vasopressin and low dose epinephrine. Furthermore, we impost continuous hemodiafiltration with CytoSorb[®] filter.

Results: Only hours after the start of filtration therapy the patient improved and we were able to gradually reduce catecholamine therapy, lactate values decreased. A VA-ECMO implantation was no more necessary. December 10th, we saw a stable patient without ventilatory or cardiovascular support, atechocardiography we revealed a normal EF.

Conclusion: Clinically we saw a young patient in severe septic/cardiogenic shock due to perimyocarditis. Yet diagnostic attempts (CT-scan, multiple blood/urinary/liquor cultures) remained negative. Despite multiple negative PCR tests for SARS-CoV2 infection we performed specific immunoglobulin analysisand received a positive result for IgM. We therefore conclude on a COVID-19 associated perymyocarditis. Furthermore, this case illustrates the potential benefit of cytokine filtration and elimination in COVID-19 patients with altered IL6 levels.

Extracorporeal cytokine hemadsorption in severe COVID-19 respiratory failure

M. Damiani¹, L. Gandini¹, F. Landi², G. Borleri², F. Fabretti¹, G. Gritti², I. Riva¹

¹Intensive Care Unit and ²Hematology Unit, Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy

Background: At least 20% of coronavirus disease 2019 (COVID-19) patients develop acute hypoxemicrespiratory failure requiring admission to intensive care unit in 5–32% of the cases. Hyper-inflammatory activation characterized by immune cell infiltration and elevated levels of cytokines was reported as the main mechanism leading to critical illness and severe acute respiratory distress syndrome (ARDS). CytoSorb[®] is currently used for all the conditions where elevated levels of cytokines are present. Along with the beneficial effect on systemic inflammation, CytoSorb[®] can be easily integrated with all extracorporeal circulation systems.

Case Presentation: Here, we present the laboratory and clinical outcomes of 11 patients with microbiological confirmed SARS-CoV-2 infection. These patients were treated with CytoSorb® to remove the excess of cytokine. All patients were male, overweight and only 3 (27%) were over 70 years old. Medianage was 62 years and median body mass index was 28. Best supportive care was provided according to hospital guidelines of that moment and included antibiotic therapy, antiretroviral therapy and protective ventilation.

Results: Cytokines levels were evaluated before and after treatment. A significant reduction of IL-6, IL-8, IL-10 and IL-1 β was observed. A significant drop of C-reactive protein (CRP) median levels was observed starting from 48 hours after treatment start levels. The decrease in the inflammatory status was associated with a progressive improvement in the respiratory function, with a significant increase in P/F from the first day after the endof the therapy. A similar trend was observed for procalcitonin.

Conclusion: CytoSorb therapy proved to be safe in COVID-19 patients. A clinical improvement was observed in most of the treated patients despite the severity of the disease. In this study CytoSorb was used empirically for 24– 48 hours based on previous experience in septic shock. The persistence of significant levels of IL-6 and CRP after CytoSorb® treatment may suggest that a prolonged treatment can improve the efficacy in controlling COVID-19 hyperinflammatory status.



Hemoperfusion with CytoSorb as Adjuvant Therapy in Critically III Patients with SARS-CoV2Pneumonia

T. Rampino,^a M. Gregorini,^{a,b,*} L. Perotti,^c F. Ferrari,^{c,d} E.F. Pattonieri,^a M.A. Grignano,^a M. Valente,^{a,b} A. Garrone,^{a,b} T. Islam,^{a,b} C.Libetta,^{a,b} V. Sepe,^a R. Albertini,^e R. Bruno,^{f,g} and M. Belliato^c

^aUnit of Nephrology, Dialysis and Transplantation, Fondazione I.R.C.C.S. Policlinico San Matteo, Pavia, Italy

^bDepartment of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy

^cDepartment of Anaesthesia and ICU, Fondazione I.R.C.C.S. Policlinico San Matteo, Pavia, Italy

^d International Renal Research of Vicenza (IRRIV), San Bortolo Hospital, Vicenza, Italy

^eClinical Chemistry Laboratory, Fondazione I.R.C.C.S. Policlinico San Matteo, Pavia, Italy

^fDivision of Infectious Diseases I, Fondazione I.R.C.C.S. Policlinico San Matteo, Pavia, Italy ^gDepartment of Clinical, Surgical, Diagnostic, and Pediatric Sciences, University of Pavia, Pavia, Italy

Background: Several pro- and anti-inflammatory cytokines involved in COVID-19 and it is reasonable to speculate that their removal from blood might limit organ damage. Hemoperfusion with CytoSorb is a technique developed to adsorb molecules in the middle molecular weight range (up to 55 kDa). Studies in vitro and in vivo have shown that HP is highly effective in clearing blood from a number of cytokines.

Methods: We report a case series of 9 consecutive COVID-patients admitted to our COVID Intensive Care Unit (ICU). Five of them were treated with HP using CytoSorb (T), due to the heavy emergency overload it was impossible to deliver blood purification in the other 4 patients (C), who were also considered as potentialcandidates by the attending medical team. All patients had pneumonia and respiratory failure requiring continuous positive airway pressure. Different antibacterial prophylaxes, antiviral, and anti-inflammatory therapies including steroids were delivered.

Results: Our results show a better clinical course of T compared to control patients (C), in fact all T except 1 survived, and only 2 of them were intubated, while all C required intubation and died.

CRP decreased in both groups, but to a greater extent after HP. Lymphocytopenia worsened in control patientbut not in treated patient after HP. Procalcitonin increased in 2 of the not treated patients. In all survived patients (n = 4) HP reduced pro-inflammatory cytokines, as IL-6, TNF- α , and IL-8. Notably, a striking effect was observed on IL-6 levels that at the end of the second session were decreased by a 40% than before the first treatment. Serum levels of IL-8 and TNF- α were lowered within normal range. In all patients the treatment was safe and there were no complications.

Conclusion: Our study suggests a potential efficacy of HP in an early phase of viral infection not only for improving survival in the treated patients but also by the remodeling treatment-associated cytokine levels.

A40 Hemoadsorption by CytoSorb in septic no-Covid and Covid patients: a case series

I. Calamai¹, R. Giuntini¹, I. Mori¹, L. Venturi¹, C. Tani¹, S. Peruzzi¹, L. Bichi¹, R. Spina¹, L. Bichi¹

¹Anesthesia and Intensive Care Unit, AUSL Toscana Centro, San Giuseppe Hospital, Empoli (Fi), Italy

Background: Septic shock is a life-threatening organ dysfunction caused by a dysregulated host response toinfection. The reduction of pro-inflammatory and anti-inflammatory mediators by hemoadsorption represents a new tool in the treatment of sepsis. In the present case series, we evaluated the impact of CytoSorb on adult patients with septic shock.

Methods: Patients with septic shock, admitted to Intensive Care Unit (ICU) from March 1, 2021 to February 28, 2022 who received CytoSorb therapy within 72 hours of admission were enrolled in the study. The severity of clinical conditions at admission was assessed by the SAPS II and SOFA scores; The magnitude of the inflammatory response was estimated using the plasmatic levels of C reactive protein (CRP) and interleukin-6 (IL-6). The effect of CytoSorb therapy on the inflammatory state, was evaluated measuring thepercentage reduction of IL-6 and CRP. Time elapsed from ICU admission and the start of CytoSorb therapy was also assessed. T-test was used to compare the means of the groups of Survivors and No survivors. Fisher's test was used to evaluated the difference in mortality between *Covid* and *No covid* patients.

Results: Twelve patients were evaluated. Six patients tested positive for covid-19, while the other six did not. Table 1 shows the values of age, SAPSII, SOFA, IL-6, CRP, PCT and timing between the survivors and the no survivors. Overall, there was no significant difference between the two groups in terms of SAPSII, SOFA, age, CRP. There was a significant difference in the timing of Cytosorb start and percentage of IL-6 removal: In surviving patients the timing of intervention was shorter (3,3±1,8 vs 23,5±18,9 hours) than in non- survivors. The IL-6 removal rate was significantly higher in the survivor group (70,8±15,87 vs 33,2±12,26).

Value	Survivors	No survivors	p value
Age	60,80±11,23	69,00±8,58	0,1806
SAPSII	43±16,19	45,29±13,78	0,7972
SOFA	9,40±4,45	8,00±5,13	0,6341
IL-6 Admission (pg/ml)	1913.86±1990.80	1813.20±1825.96	0,9356
IL-6 Reduction Rate (%)	70,80±15,87	33,20±12,26	0,0030
CRP (mg/dl)	14,07±12,55	15,23±10,41	0,8637
CRP reduction rate (%)	51,20±13,1	5,13±59,52	0,1213
Timing (hours)	3,30±1,86	23,43 ± 18,98	0,0420
Covid +	3	3	1,0000
No Covid	2	4	1,0000

Conclusions: In survivors the timing of CytoSorb therapy was shorter and the IL-6 removal rate was higher than in nonsurvivors. This suggest that the early applying of CytoSorb adsorber in combination with Continuous Renal Replacement Therapy (CRRT) techniques, could increase the survival rate of septic shock patients. Using CytoSorb was safe and well tolerated with no device-related adverse events during or after the treatment.

A41 A Successful Treatment of a Critically Patient with SARS-CoV2

G. Aiello¹, S. Tomasello¹, F. Timpone¹, R. Bellanca¹, P. Slavikova¹, F. Leggio¹, P Tutone¹

¹Intensive Care Unit, PO Civico Partinico, ASP Palermo, Palermo, Italy

Background: The role of inflammatory cytokines is known in the pathogenesis of organ damage and is also confirmed in the context of COVID-19 disease. The modulation of the cytokine storm seems to determine endothelial protection, which can translate into a reduction of the "capillary leak syndrome", and, consequently, in a better control of the formation of edema and pulmonary infiltrates. CytoSorb stands in this context as a cartridge capable of adsorbing cytokines and allowinga better clinical course.

Case Report: A 69 years-old woman with a history of arterial hypertension, diabetes mellitus and CKD, was admitted to ICU for SARS Cov 2 related critical illness staged with chest CT, blood gas analysis and PCR. At the admission, the patient presented with ubiquitous interstitial pneumonia, PaO2 60 mmHg with 90% Airvo2 and PCR 36.67. Therefore, in order to remove inflammatory cytokines, the patient underwent hemoperfusion treatment with the CytoSorb adsorbent cartridge.

Method: The protocol used is approved by the FDA for the treatment of covid patients and consists of the use of 4 cartridges 12h, 12h, 24h, 24h with measurement for each cycle of PCR, PaO2 and chest CT control.

Results: During the hemoperfusion whit CytoSorb, respiratory failure improved until the patient wasdischarged from the ICU on the tenth day, with oxygen support via simple facial mask. Below the progressive values of the PCR, PaO2 and the chest CT control on the twelfth day.

Filters	PCR	PaO ₂	Filters	PCR	PaO ₂
1°	10.41	60	3°	6.69	90
2°	10.19	70	4°	4.2	102



Conclusion: The hemoperfusion treatment with the CytoSorb adsorbent cartridge proved to be a valid adjuvant therapy in determining a better clinical course both in terms of the need for invasive mechanical ventilation and survival.

A42 The use of CytoSorb in a septic shock patient with ARDS due to Sars Cov-2

S. Greco¹, G. Liso¹, D. Maiorano¹

¹Rianimazione, Presidio Ospedaliero "Vittorio Emanuele II", ASL BAT, Bisceglie, Italy

Background: Septic shock is a clinical condition of sepsis aggravated by circulatory, cellular and metabolic dysregulation. Diagnostic criteria include the need for vasopressors to maintain a PAM>65 and serum lactate levels>2 under adequate fluid therapy. Early identification of critically septic patients is necessary to allow early and adequate treatment with improved prognosis. In this case report we evaluate the haemodynamic impact of CytoSorb therapy in a case of septic shock in a patient with ARDS Sars cov2.

Methods: Patient with Sars Cov-2 ARDS was admitted to our department. He was intubated and had a SOFA Score 7. On day 15 the patient presented an increase in PCT CRP and WBC levels with the need for norepinephrine infusion. Empirical antibiotic therapy was started and after 24 hours also CytoSorb Therapy.Four CytoSorb cartridge columns were used. The first two were changed every 12 h and then the next two were changed every 24 h.

Results: Two days after CytoSorb therapy there was an improvement in haemodynamic without the need of vasopressor support. There was also a reduction in inflammatory parameters and lactates. The trend of these values was shown in figure 1.



Figure 1: Noradrenaline, lactate and PCT trend; the light blue boxes denote the periods in which treatment with CytoSorb® was performed

Conclusion: In this case report we evaluated the impact of CytoSorb therapy in a case of septic shock in a patient with ARDS Sars Cov-2. The early use of hemadsorption with CytoSorb combined with re-evaluation of antibiotic therapy resulted in a marked improvement in the patient's clinical status.

Blood purification treatment and cytokine removal using Cytosorb[®] device incritically ill patients with COVID-19 infection

M.Fiorentino¹, F. Paganelli¹, P. Raimondo², S. Grasso², L. Gesualdo¹

1 Department of Emergency and Organ Transplantation, Nephrology, Dialysis and Transplantation Unit, University of Bari

² Department of Emergency and Organ Transplantation, Cardio Thoracic Intensive Care Unit, University of Bari

Introduction: Acute kidney injury (AKI) is a complication of SARS-CoV-2 disease, associated with worse clinical outcomes. Renal replacement therapy (RRT) in combination with sequential extracorporeal blood purification therapies (EBPT) might support renal function, attenuate systemicinflammation, and prevent or mitigate multiple organ dysfunctions.

Methods: We retrospectively analyzed 20 patients admitted in ICU for ARDS and who developed moderate-to-severe AKI requiring RRT. Cytokine hemadsorption with Cytosorb[®] was performed in association with CRRT. The main indication for this treatment was the worsening of hemodynamic and respiratory conditions and suspicion of cytokine storm. The protocol consisted in the use of 3-4 cartridges in total; among these, the first 2 were changed after 12 hours of treatment to maximize cytokine removal, while the others after 24 hours. We examined comorbidities, clinical and laboratory characteristics and the impact of treatment in terms ofmortality rate and changes in data before and after treatment.

Results: Nineteen patients (95%) had an AKI at any time during their ICU stay. Of these, 5 patients (25%) had AKI stage II and 14 patients (70%) had AKI stage III. All patients included in this subgroupwere mechanical ventilated and required vasopressor's use. Mean prescribed CRRT dose was 31.2

 \pm 11.7 ml/kg/h. The median time to strating RRT after ICU admission was 7 days (IQR 3.5-15 days) and the median duration was 7 days (IQR 2.5-12.5 days). Mean SOFA score at the time of RRT start was extremely high (14.5 \pm 2.8). Mortality rate was important (18 patients, 90%) in our cohort. Comparing clinical and laboratory data before and after treatment, a significant improvement of inflammatory markers was reported, with the reduction of C-reactive protein (CRP, 143 [62.1- 328.5] vs 83.5 [66.7-153.5] mg/L); however, no significant changes in IL-6, WBC and PCT values were observed. A slight increase of PaO2/FiO2 were described, although not statistically significant (PaO2/FiO2 ratio 144 [82.7-174.2] vs 183 [132-355.5] mmHg).

Conclusions: Our experience supports the need of an adequate timing for the use of Cytosorb[®] in critically ill patients with Covid-19. Although a discrete efficacy in improving inflammatory cascade, the late use of EBPT, when organ dysfunction was already ongoing, didn't impact survival.

	Main outcomes after EBPT							
	N° patients	who completed	12 (60%)					
	treatment Nr (%)		- />					
	Difference h	ospital admission/	3 (0.5 – 8)					
	admission U	TI (Days Median,						
	IQR)	Clieduciesieur / First						
	Difference in	LU admission / First	7 (3.5-15)					
	IOR)	ent (Days wedian,						
	Death (Nr; %	6)	18 (90%)					
	Lenght of IC	U Stay (Days	12 (6.5-21)					
	Median, IQR	R)						
	Lenght of St	ay from First	5 (1-10)					
	Treatment (Days						
	Median, IQR	k)						
		ICU ADMISSION	PRE-TREATMENT	POST-	p-			
				TREATMENT	value			
CRP (m	ng/L)	89.7 (59.5-144.2)	143 (62.1-328.5)	83.5 (66.7-153.5)	0.025			
MAP (mmHg)	87.8 ± 8.3	81.9 ± 15.8	73.1 ± 17.1	0.265			
PaO2/	FiO2 ratio	136 (89-232.2)	144 (82.7-174.2)	183 (132-355.5)	0.068			
(mmH	g)							
Lactate	e (mmol/L)	1.35 (1-2.1)	1.9 (1.2-4.1)	2.1 (1.6-3.4)	0.135			
WBC (10 ³ /mcg)	11.1 ± 4.4	11.5 ± 8.1	12.8 ± 5.8	0.613			
IL6 (pg	;/ml)	90.1 (28.7-317.5)	178 (43-2866.5)	194 (63.5-777.5)	0.791			
PCT (n	g/ml)	0.13 (0-0.6)	1.1 (0.59-5.04)	1.68 (0.5-5.5)	0.420			
D-dim	ers (mcg/L)	3376.5 (708.5-	5110 (2278-	5311 (4147-8766)	0.508			
		9080)	10550)					

Figure 1: Outcomes after EBPT, laboratory and clinical parameters before and after treatment

SEPSIS AND MODS

A44

In-vitro comparison of the CytoSorb[®] 300mL hemoadsorber and the Oxiris[®] hemofilter on two major proinflammatory cytokines

A. Körtge¹, A. Kribben², R. Wasserkor¹, S. Mitzner¹

¹ Fraunhofer Institute for Cell Therapy and Immunology, Department of Extracorporeal Immunomodulation, Rostock, Germany

² Department of Nephrology University Hospital Essen, University Duisburg-Essen, Essen, Germany

Introduction: We performed an analysis of two blood purification systems to determine their performance for removing the two most common pro-inflammatory cytokines from whole blood.

Methods An in-vitro full-scale benchtop recirculation model was used to compare the CytoSorb[®] 300mL (CytoSorbents Inc., Princeton, USA) and oXiris[®] (Baxter, Deerfield, IL, USA) devices. Human target molecules were added at t=0min (bolus 1), 120min (bolus 2), and 240min (bolus 3). Overall removal was compared at various timepoints (t= 0, 5, 15, 30, 60, 120, 121, 125, 135, 150, 180, 240, 241, 245, 255, 270, 300 and 360 mins). A total of three runs were completed. Purified recombinant human interleukins (IL)-1 beta and IL-6 were used. The removal rate r was defined as follows:

$$r[\%] = \&1 - \frac{c_{bolus_{iend}}}{c_{bolus_{sta(t)}}} * 100\%; (i = 1, 2, 3)$$

Equation: $c_{bolus_i}end$ and $c_{bolus_i}sta(t)$ is the target molecule concentration measured at the beginning and the end of each bolus time interval, respectively. All measurements were in accordance to DIN EN ISO 8637:2014-03 for testing of hemodialyzers.

Results: Both devices showed effective removal of the tested targets. IL-1b (-42.8%, 25/75%-CI: -52.6 — -18.9; p<0.01) and IL-6 (-33.3%, 25/75%-CI: -35.1 — -27.5; p<0.01) were removed more quickly and to a higher extent by the CytoSorb[®] device. Figure #1 exemplifies the overall removal of IL-1b and IL-6 at the three different timepoints. As expected, the overall removal decreased over time after adding another bolus suggesting a stepwise saturation of both devices. This trend was more pronounced in the Oxiris[®] filter group.

Conclusions: Both devices were capable of removing cytokines from blood in this benchtop model. The CytoSorb[®] device was significantly more efficient in removing both tested substances. These findings might have an impact on the decision-making process in patients with pronounced cytokine storm.



Figure 1

Effects of the timing and intensity of treatment on septic shock patients treated with CytoSorb[®]: Clinical experience G. Berlot¹, V. Samola¹, I. Barbaresco¹, A. Tomasini¹, V. Di Maso², F. Bianco² and U. Gerini²

¹ Department of Anesthesia and Intensive Care Medicine, Cattinara University Hospital, Azienda Sanitaria Universitaria Giuliano-Isontina, Trieste, Friuli-Venezia Giulia, Italy

² Department of Nephrology, Cattinara University Hospital, Azienda Sanitaria Universitaria Giuliano-Isontina, Trieste, Friuli-Venezia Giulia, Italy

Introduction

In the last three decades a number of devices have been developed to neutralize the pathogen or damage-associated molecular patterns (PAMPs and DAMPs) responsible for the multiple-organ dysfunction syndrome (MODS) observed in septic shock and in other conditions characterized by a cytokine release.

The hemoadsorption (HA) with the CytoSorb[®] (Cytosorbents Corporation, New Jersey, USA) have been extensively used in septic shock patients. This technique uses a biocompatible resin capable of absorbing hydrophobic substances from whole blood with a molecular weight <60 kD.

Case presentation

In the present study we assessed the role of the intensity of treatment, the pre-treatment interval and its duration in a group of septic shock patients treated with CytoSorb[®] since 1.1.2018 to 31.12.2020.

The cartridge was located downstream a filter used for a Continuous Veno-Venous Hemodiafiltration (CVVHD) using an initial Qb of 150–200 mL/min. Each patients received two HA sessions which were to last 24 h but the effective duration of a session was influenced also by other factors, including the clotting of the circuit, the occurrence of hemodynamic instability etc.

Results

51 patients were treated with the CytoSorb[®]; 26 patients (51%) survived (S) and 25 (NS) (49%) died in the ICU; age and frailties did not differ among S and NS. At the end of treatment, the MAP increased in both groups but in NS this variation was associated with the increase of both CI and PCAI. The pre-treatment interval was shorter in S than in NS; the volume of blood processed was higher and the duration of the procedure was longer in S than in NS.

Conclusions

CytoSorb should be used on an individual basis taking into account the cause of septic shock and coexisting disease, that the pre-treatment interval should be reduced as much as possible and, finally, that its intensity should be frequently adjusted by evaluating both clinical and biochemical indicators, including changes in vasopressor needs and changes in blood levels of septic mediators.

Variable	All	Survivors	Non-survivors	p*
Age(years)	68(59–76)	65(56–72)	71(63–79)	n.s.
Charlson comorbidity index	4 (1–5)	3 (1–5)	4 (2–7)	n.s.
SAPS II	56 (51–62)	53 (49–59)	62 (56–65)	<0.05
SOFA pre	11 (9–13)	9 (8–12)	13 (11–15)	0.002
SOFA after	11 (9–13)	9 (8–12)	12 (11–15)	<0.05
MAP (mmHg) pre	58 (51–63)	60 (58–63)	53 (50–60)	<0.05
MAP (mmHg)after	67 (61–77)	77 (68–80)	62 (50–60)	<0.05
Cl pre	106 (74–133)	95 (73–119)	98 (76–138)	n.s
Cl after	69 (13–112)	19 (7–29)	108 (38–171)	<0.05
PCAI pre	1.90 (1.27–2.25)	1.90 (1.2–3.0)	1.70 (1.3–2.1)	n.s
PCAI after	1.21 (0.17–1.84)	0.26 (0.1–0.4)	1.67 (0.56–3.5)	<0.05
Pre-treatment time (h)	30 (8–36)	15 (7–24)	25 (10–52)	<0.05
Duration of treatment (h)	47(27–70)	53(46–70)	28(13–60)	0.007
Volume prcessed (I)	567(331–838)	645(561–848)	342(162–722)	0.007

Renal and hepatic support in severe septic shock from leptospirosis: a "CaseSeries" and the adoption of a new dialysis protocol

P. Lentini^{1 2}, C. Benedetti¹, G. Laudadio¹, S. Andrighetto¹, V. Fuso¹, F. Vienna¹, G. Berlingò¹, A. Previti²

¹ Department of nephrology and dialysis, "Ospedale San Bassiano" Aulss7, Bassano del Grappa (Vi), Italy

² Department of nephrology and dialysis, Ospedale Alto Vicentino, AULSS7, Santorso (VI), Italy

Background: Leptospirosis is a zoonosis caused by a gram-negative bacterium of the Spirochetales family (leptospiraceae) associated with high mortality if not treated in time. The infection is contracted through direct exposure with the urine of carrier animals [1]. Clinical manifestations can range from pauci-symptomatic flu-like pictures, to manifestations with renal tubular damage (25-40%), to extremely severe conditions with potentially fatal multi-organ involvement (10-15%) known as Weil's disease [2]. The aim of this work is to analyze the benefit in applying our treatment protocol in patients with septic shock with AKI and ALF in the ICU, in terms of dose reduction of vasopressors and improvement of blood chemistry parameters.

Methods: The patients were all subjected to mechanical ventilation and the circulation supported by inotropes. All had severe AKI (Stage 3) and ALF (MELD Score> 16 or Bilirubin> 20 mg/dL). Patients underwent a combined treatment of CVVH (Amplya Medtronic ©) together with the use of CytoSorb ©. The CVVH was performed with Qb 150 ml/min, with a dialysis dose of at least 40 ml/kg/h (70% in pre-dilution). In two patients citrate was used as anticoagulant in the third patient the treatment was performed with a high pre-dilution (80%). The cartridge was replaced every 24 hours for three consecutive cycles. Antibiotic therapy was adequate considering an estimated removal of 40-50% of the recommended effective dose. Blood samples were taken to determine the rate of reduction of bilirubin, creatinine, WBC and PCR for each session.

Results: Three patients, all male, mean age 57 years, were enrolled following the diagnosis of leptospira-related septic shock. The starting conditions appeared homogeneous (Saps II 78 \pm 6, SOFA 15 \pm 5, Apache II 34 \pm 6) with high total bilirubin values (> 20 mg/dl) and high inflammation indices (WBC, PCR, ESR). In all patients there was a progressive improvement in vital parameters with a reduction in the dose of vasopressors, ventilatory performance and in blood chemistry parameters (Total Bilirubin, RRS = 37.4%). All 3 patients survived after a prolonged stay in the ICU (LOS 31 +/- 3 dd).

Conclusions: Supportive treatment of hepatic and renal function in AKI and ALF performed with CVVH and Cytosorb was be safe and effective.

References

- 1. Levett PN. Leptospirosis. Clin Microbiol Rev. 2001;14(2):296.
- 2. Yang C-W, Wu M-S, Pan M-J. Leptospirosis renal disease. Nephrol Dial Transplant. 2001;16(Suppl. 5):73–77.

CYTOSORB HEMOADSORPTION IMPROVES HAEMODYNAMICS AND SOFA SCORE IN SEPTIC SHOCK

F. Aucella¹, A. M. Pellegrino¹, G. Ferrara¹, G. Gatta¹, P. Vaira P², A. Del Gaudio³

¹Department of Nephrology, IRCCS Casa Sollievo della Sofferenza Hospital, SanGiovanni Rotondo (FG), Italy ^{2,3}Intensive Care Units, IRCCS Casa Sollievo della Sofferenza Hospital, SanGiovanni Rotondo (FG), Italy

BACKGROUND: Sepsis is the most common cause of death in medical intensive care units (ICU). If sepsis progresses to refractory septic shock, mortality may reach 90–100% despite optimum current therapy. Cytokine reduction using hemoadsorption represents a new concept for blood purification, developed to attenuate the systemic levels of pro-inflammatory and anti-inflammatory mediators released in the early phase of sepsis.

METHODS: We retrospectively evaluated the impact of CytoSorb, used as adjunctive therapy, on hemodynamics and clinically relevant outcome parameters in 38 critically ill patients with septic shock and in need of renal replacement therapy (RRT) in Intensive Care Unit. Mean levels of MAP, procalcitonin, noradrenalin need and SOFA score were evaluated. RRT of acute renal failure was performed either as continuous venovenous hemofiltration (CVVH) or continuous venovenous haemodialysis (CVVHD) at the discretion of the attending physician. Hemoperfusion was started after refractory shock was diagnosed. The adsorber CytoSorb was connected in a prae-filter position into the CRRT circuit. The first exchange was performed within 24 h without interruption. Further adsorber exchanges were at the discretion of the physicians, mean cartridge number was 2.8/patient, mean time between admission and hemoperfusion treatment start was 44±9 hours.

RESULTS: Demography is showed in **Table n. 1 - A**. After CytoSorb treatment procalcitonin, C-reactive protein and white cells count, all decreased vs basal levels; these features were associated with hemodynamic stabilization and reduction of noradrenaline infusion (**Table n. 1 - B**). Moreover, urine output showed a relevant increase. SOFA score improved in 22 (57%) patients, and overall, in hospital mortality was 43% despite a 65% SOFA predicted score. Treatment using the CytoSorb device was safe and well-tolerated with no device-related adverse events during or after the treatment sessions.

Table n. 1

	-
A)	Demography

AGE	M/F	SEPSIS ORIGIN	SURGICAL	COMORBIDITY (n.)	
59±15	21/17	24 (63%) abdominal	22/38 (57%)	2.5±1.8	

	PCR	РСТ	WC (x 1000)	NOR-µg/kg/min	MAP	SOFA	URINE OUTPUT
BASELINE	35±12	42±11	23±7	0.88±2.3	69±15	12.8±2.7	450±125 ml
AFTER 1	31±9	34±15	19±6	0.9±1.5	68±12	/	425±110 ml
CARTRIDGE							
END OF	12±6	9±9	15±8	0.4±2.1	88±25	6.3±3.4	680±190 ml
TREATMENT							

B) Outcome parameters

CONCLUSION: In severe septic shock unresponsive to standard treatment, haemodynamic stabilization and inflammatory parameters improved using cytokine adsorption therapy. These effects seem to be more pronounced in patients in whom therapy started within 24 h of sepsis diagnosis, whereas a delay in thestart of therapy was associated with a poor response to therapy in terms of reduction of catecholamine demand and survival.

Hemoadsorption with CytoSorb in critically-ill pediatric patients: potential clinical applications and practical use G. Bottari¹

¹Pediatric Emergency Department, Pediatric Intensive Care Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

Background: In recent years, several extracorporeal techniques for the treatment of critically-ill patients have been introduced in the clinical practice. Blood purification via adsorption seems to be a promising adjuvant therapy in critical patients characterized by overwhelming inflammation and elevated levels of toxic molecules in the bloodstream. Hemoperfusion with CytoSorb is a safe and well-tolerated therapy in critically-ill patients, including children, and seems to play a fundamental role in the modulation of peak concentration with consequent hemodynamic and metabolic stabilization. The large adsorbent surface area allows an efficient modulation of the target molecules, also in relation to the amount of blood purified and especially in children, characterized by a lower blood volume.

Methods: Latest clinical evidences suggest a potential application of blood purification techniques in different clinical contexts, such as sepsis and septic shock, liver failure, rhabdomyolysis, critically-ill conditions requiring ECMO support, cardiogenic shock, ARDS, HLH syndrome, Severe Multisystem Inflammatory Syndrome (MIS-C), Cytokine Release Syndrome, drug removal. The versatility of CytoSorb allows its use in several configurations: hemoperfusion, together with CKRT, during CPB and ECMO support. According to the IFU, the adsorbent cartridge can be inserted in the CKRT circuit in series with the haemofilter, in a pre- or post-filter position, depending on the type of machine, and in the CPB/ECMO circuit in parallel position. Regardless of the chosen configuration, CytoSorb is flushed by gravity with saline solutions and, if necessary, primed with 120 ml of albumin or blood at discretion of the attending physicians, in order to reduce the possible haemodilution. It is normally suggested to change the absorber every 24 hours or, according to the latest FDA indications, every 12 hours in the first day and every 24 hours for two more days, followed by a clinical assessment after 72 hours to evaluate the clinical benefit for continuation of therapy.

Conclusions: Blood purification with CytoSorb is a useful adjuvant therapy in severe critically-ill patients. Potential efficacy has been shown in different promising clinical pictures characterized by overwhelming inflammation and elevated levels of toxic molecules (septic shock, CRS after CAR-T cells, MIS-C, HLH...). Its early use – within 24h from shock onset – is suggested and supported by literature evidences. The amount of blood purified – exacerbated in pediatric patients – seems to be directly linked to the efficacy and clinical benefits. Preliminary results on drug monitoring seem to be promising, but need to be more investigated in order to achieve quality standard protocols. International Multicentric Investigations, such as registries and study protocols of precision and individualized medicine, are required to collect more clinical evidences.

References:

- 1. Bottari G, Merli P, Guzzo I, et al. Multimodal Therapeutic Approach of Cytokine Release Syndrome Developing in a Child Given Chimeric Antigen Receptor-Modified T Cell Infusion. Crit Care Explor. 2020 Jan 29;2(1):e0071.
- 2. Bottari G, Lorenzetti G, Severini F, et al. Role of Hemoperfusion With CytoSorb Associated With Continuous Kidney Replacement Therapy on Renal Outcome in Critically III Children With Septic Shock. Front Pediatr. 2021 Aug 24;9:718049.
- 3. Bottari G, Confalone V, Cotugno N, et al. Efficacy of CytoSorb in a Pediatric Case of Severe Multisystem Infammatory Syndrome (MIS-C): A Clinical Case Report. Front Pediatr. 2021 Jun 11;9:676298.
- 4. Bottari G, et al. Hemoperfusion with CytoSorb to Manage Multiorgan Dysfunction in the Spectrum of Hemophagocytic Lymphohistiocytosis Syndrome in Critically III Children. Blood Purif. 2021 Aug 3:1-8.
- 5. Rauch S, Borgato A, Gruber E, et al. Case Report: Prevention of Rhabdomyolysis-Associated Acute Kidney Injury by Extracorporeal Blood Purification With Cytosorb[®]. Front Pediatr. 2022 Jan 24;9:801807.

Preliminary results of antibiotics pharmacokinetics in critically ill children with septic shock treated with CKRT and Cytosorb hemoperfusion

G. Bottari¹, C. Maccarrone², A. Cappoli³, M. Marano¹, S. Cairoli⁴, V. Ventura⁴, A. T. Mazzeo², B. Goffredo⁴, I. Guzzo³, C. Cecchetti¹

¹Pediatric Intensive Care, Emergency Department, Children Hospital Bambino Gesù (IRCSS), Rome, Italy ²Anesthesia and Intensive Care. Department of Human Pathology. University of Messina, Messina, Italy ³Dialysis Unit, Pediatric Department, Children Hospital Bambino Gesù, (IRCSS), Rome, Italy ⁴ Division of Metabolic Diseases and Drug Biology. Children Hospital Bambino Gesù (IRCSS), Rome, Italy

Background/Aim: Extracorporeal hemadsorption (HA) techniques are increasingly used as adjuvant therapeutic strategies in septic shock with severe hyperinflammatory response. Although treatment seems to be most effective to remove pro-inflammatory mediators, its influence on antimicrobials pharmacokinetic should not neglect with potentially clinical impact. In addition, critically ill children and newborn have different drugs pharmacokinetics than adults, due to different volume distribution and body composition, furthermore using cartridge with high priming volume can expose pediatric patients to unsuccessfully therapies. In this preliminary report we report preliminary results the impact of Cytosorb pharmacokinetics of different antibacterial agents commonly used in pediatric patients.

Methods: We performed therapeutic drug monitoring in 5 critically ill children with septic shock. treated with CKRT and Cytosorb located in post-hemofilter position. Three molecules (**Meropenem, Levofloxacin, Ceftazidime**) with a time dependent mechanism of action were tested at trough for 3 consecutive days by the start of the hemoperfusion and 1 molecule (**Amikacine**) with concentration dependent mechanism of action was tested at peak and trough for 2 consecutive days by the start of the hemoperfusion. Drugs concentrations were monitored in 4 sites: pre-hemofilter (P_{PRE}), post-hemofilter (P_{POST}), post-cartridge (P_{CY}) and in the waste bag (P_{EFF}). We calculated the removal ratio (Rr)% of the extracorporeal platforms (Rr%CKRT; Rr%CS; Rr%Total =Rr%CKRT + Rr%CS).

Results: In Figure 1 are reported median concentration of the antibiotics monitored in the four sites of the circuits. Median removal ratio percentage of the extracorporeal platform were: **Meropenem** RrCKRT 16,03% Rr%Cs -0,99% Rr%total 18,98%; **Ceftazidime** RrCKRT 23,69% RrCs 6,19% Rrtotal 29,86%; **Levofloxacine** RrCKRT 22,06% Rr%Cs 22,40% Rrtotal 44,46%; **Amikacine** RrCKRT 41% (peak) and trough 11% Rr%Cs 0 Rr%total peak 41% and trough 11%.

Conclusion: Authors considered a percentage of removal minimal or negligible < 30%, moderate between 30-60% and high >60% (1): by our preliminary reports we have observed a minimal impact of Cytosorb removal ration for four of the most common used antibiotics in clinical practice. To the best of our knowledge this is the first report about pharmacokinetics dynamic in critically il children treated with CKRT and Cytosorb for septic shock.

Reference:

(1) Scheier J. et al. Critical Care Explor. 2022; 4(5): 1-9









Figure 1 for Abstract A49

The use of CytoSorb in septic shock patients with MOF due to inveterate stercoraceous peritonitis from perforated diverticulitis

F. Pennacchiotti¹; E. Erminio²; L. Morrone³

¹ Department of Nephrology and Dialysis, Presidio Ospedaliero Orientale, Manduria, Taranto, Italy

² Department of Anaesthesia and Intensive Care, Presidio Ospedaliero Orientale, Manduria, Taranto, Italy

³ Department of Nephrology and Dialysis, Ospedale Santissima Annunziata, Taranto, Italy

Background: Sepsis and septic shock are characterized by complex organ dysfunction caused by a misdirected host response to infection with persistent high morbidity and mortality. An important determinant of multi-organ dysfunction is the excessive release of pro and anti-inflammatory cytokines. Hemoadsorption using CytoSorb® offers a new therapeutic approach. In this case we report the use of Cytosorb in a septic shock patient with MOF.

Methods: We present a case of 62-years-old woman admitted to Emergency Unit for abdominal pain with asthenia and hypotension. In the history she presented chronic renal failure, bowel diverticulosis and ischaemic cardiomyopathy. CT scan with contrast diagnosed acute abdomen from probable diverticular intestinal perforation. Resection of the sigma according to Hartman, with left colonstomy, was performed for a picture of inveterate diverticular perforation of the colon with associated stercoraceous peritonitis. Postoperatively, haemodynamic was supported with noradrenaline 0.2 μ g/kg/min, she needed for haemodialysis, depurative and ultrafiltrate treatment for hyperpotassaemia. Elevated sepsis markers showed the presence of septic shock with MOF, so within 12 hours after surgery, haemadsorption with CytoSorb was started with CRRT in CVVHD mode.

Results: After 24 hours of CytoSorb with CVVHD there was an improvement in haemodynamic and support with noradrenaline was discontinued. Respiratory parameters also improved with weaning from mechanical ventilation 24 hours after surgery. Inflammation indices remained constant (PCR from 422 mg/L to 391 mg/L) indicating, however, a clear control of the hyperinflammatory situation post-treatment. Sepsis markers showed a return to normal (PCT - procalcitonin from 41.36 to 0.06, WBC from 12.000 to 10.120 mm³, myoglobinemia from 943 to 358 μ g/l) and there was also a clear improvement in NTproBNP from 16,078 to 2,000 pg/ml). In figure 1 is show PCT and NTproBNP trend.



Figure 1: PCT and NTproBNP pre and post CytoSorb

Conclusion: In this case the use of CytoSorb shows to be effective to stabilisation of haemodynamics, resolution of metabolic acidosis, control of hyperinflammatory response and sepsis. CytoSorb therapy was found well tolerated and safe, without adverse reaction.

Usefulness of adiuvant haemoadsorption (CytoSorb) in the early phase of sepsis: a retrospective observational study

D. Gemma¹, P. Ciocchetti¹, F. Caccetta², A. Naticchia², G. Ferraro³, C. Maisto²

¹ Intensive Care Unit, Azienda Ospedaliera Pia Fondazione Panico, Tricase, Italy

² Dialysis and Nephrology Unit, Azienda Ospedaliera Pia Fondazione Panico, Tricase, Italy

³ Pharmacy Unit, Azienda Ospedaliera Pia Fondazione Panico, Tricase, Italy

INTRODUCTION: Sepsis is a clinical syndrome defined by a systemic response to infection. With progression to sepsisassociated organ failure or hypotension (septic shock) morbidity and mortality increase. Despite all medicaladvances, it continues to be a substantial problem, as to date therapeutic approaches have failed to prove efficacy. In recent years, hemoadsorption (CytoSorb) has been used more frequently to treat septic shock, especially in refractory conditions, in which standard therapy did not seem to be sufficient enough.

METHODS: Here we present a 3-years retrospective observational study of 18 patients, that were reported to "Cardinale G. Panico" Hospital, Tricase (LE) from January 2019, to April 2021, affected from sepsis/septicshock of various origins and treated with CRRT plus CytoSorb as adjuvant therapy to standard medical approach. Patients had a sepsis approach initiated within 3 hours after arrival in the emergency departmentor after the triggering cause in inpatient or surgical wards. Every patient was submitted to CRRT (Ci-Ca CVVHDF, Multifilter) with pre-dyalizer CytoSorb adsorber (from a minimum of 1 to max 4 cartridges). The treatment was started within 6 hours (for a group of patients), no later than 12 hours (for another group, according with our internal sepsis management protocol) and later than 12 hours (against our internal protocol, for a group of patients in which the delay of CytoSorb administration was due to logistical problems). Of each patient we dosed different items recording each value at time zero, 24, 48 and 72 hoursafter the cartridge's administration. Each adsorber was changed every 12 hours.

RESULTS: The results are show in table 1 and figure 1. We demonstrated that an early use of CRRT CytoSorb (< 12 hours) according by a DSS score > 6, was associated, compared with patients with a delayed CytoSorb administration (> 12 hours) and with the control group with CRRT use only, with an improvement in hemodynamic indices at 24, 48 and 72 hours (decreasing in use of vasoactive amines, improvement of MAP and reduction of lactate) and in inflammatory items (PCR, PCT and SOFA score). Finally, we recorded a decreasing in mortality in ICU compared with control groups. This improvement is also detectable in patients with an initial compromised clinical situation (APACHE II score > 30).

CONCLUSION: We recommend an early as possible use of CytoSorb in patients with diagnosis of sepsis (NEWS score > 5 and an increasing of SOFA score > 2 point than the baseline). This action-time is preferable to be < 12 hours, although best results are obtained if the cartridge is administered within 6 hours. We also note the uselessness but the harmfulness of this treatment in terms of delay in administration of new therapies or new adsorbers when number of CytoSorb cartridges is > 3.



	Cy	/toSorb sta	rt within 12	h	CytoSorb start after 12 h			
	т0	T24	T48	T72	Т0	T24	T48	T72
Nr.Patients	11				7			
PCT (ng/ml)	34,91	23,04	16,32	12,43	24,75	12,97	9,2	7,08
CRP (mg/dl)	20,84	26,5	23,2	19,11	29,36	24,48	19,2	12,85
Lac (mmol/L)	9,41	7,03	3,67	3,95	11,39	10,86	4,13	6,23
Inotropes	1,55	1,18	0,91	0,27	1,29	1,14	1	1
Sofa	17,91	12,8	8,9	5,1	18	20,43	16	19
Nr. Cartridge	2,64				2,14			

Table 1: T_0 (at time zero), T_{12} (after 12 hours of treatment), T_{24} (after 24 hours of treatment), T_{48} (after 48 hours of treatment *LAC* (lactate). In green: patients in which a positive outcome was recorded (Transferred to ward). In yellow: patients unresponsive/dead.

Hemodynamic assessment with CytoSorb® treatment in Lemierre's syndrome

A. Barile², A. Recchia¹, L. Mirabella², G. Cinnella², A. Del Gaudio¹

¹Anesthesia and Intensive Care Unit 2, IRCCS "Casa Sollievo della Sofferenza ", San Giovanni Rotondo, Italy ²Department of Anesthesia and Intensive Care, University of Foggia, Foggia, Italy

Background: Lemierre's syndrome is a septic condition with frequent evolution to septic shock due to Fusobacteriun necrophorum. A multimodal approach with proper diagnosis, early source control, antibiotics administration and hemodynamic support is mandatory for a better prognosis. Purification therapies are helpful to reduce the inflammatory syndrome improving the hemodynamic assessment.

Methods: A 20 years old man was admitted to ICU for septic shock and Lemierre's syndrome. Continuous Renal Replacement (CRRT) with CytoSorb® cartridge begun from day 3 to day 7. Daily values of sepsis markers were collected. Hemodynamic assessment was performed with norepinephrine and argipressin synergic administration and continuous hemodynamic noninvasive monitoring methods. The bedside measurement of the Power Doppler ultrasound assessment of the Resistance Index in different bilateral arterial districts -Renal Artery (ARE), Radial Artery (AR), Central Retinal Artery (ACR), Superior Mesenteric Artery (AMS)- was performed with linear and convex probes at the beginning of the administration of Norepinephrine (0.1 mcg/Kg/min) and Argipressin (0.3 IU/min) (T0), at 1h (T1), at 24h (T2) and 48h (T3)

Results: Laboratory values improvement before and after CytoSorb[®] treatment (T0 and T5). T0: Procalcitonin (29.47 ng/ml); Total Bilirubin (8.2 mg/dl); Interleukin 6 (168.3 pg/ml); Platelets (86000/mmc). T5: Procalcitonin (3.5 ng/ml); Total bilirubin (5.8 mg/dl); Interleukin 6 (23.4 pg/ml); Platelets (294000/mmc). Reduction of the Resistance Index measured in different arterial districts at Day 0 (T0) and at Day 3 (T3): T0: ACR DX 0.92; ACR SN 0.90; AR SN 1.14; ARE DX 0.66; ARE SN 0.71; AMS 0.69 T3: ACR DX 0.82; ACR SN 0.83; AR SN 1.04; ARE DX 0.65; ARE SIN 0.67; AMS 0.65.

Conclusion: In Lemierre's syndrome the hemadsorption CytoSorb[®] in combination with CRRT is effective to reduce pro inflammatory cytokines and total bilirubin values improving hemodynamic as assessed by monitoring Arterial Resistance Index in different districts.

A53 CytoSorb® on the Septic Shock

X. Grabocka¹, S. Di Stante¹, V. Bertuzzi¹, M. Martello¹, S. Belcastro¹, H. Kulurianu¹, F. Pizzolante¹, A. Cardillo¹, O. Paci Della Costanza¹, C. Silvestri C¹, M. Di Luca¹

¹Department of Nephrology and Dialysis, Azienda Ospedaliera Ospedali Riuniti Marche Nord, Pesaro, Italy

Background: Septic shock, defined as organ dysfunction caused by a dysregulated host response to infection, is a condition associated with high morbidity and mortality. One of the hallmarks of sepsis is the excessive release of cytokines and other inflammatory mediators that cause septic shock and multi-organ failure (MOF). New adsorbents are now available as adjuvant therapy aimed at modulating the cytokine "storm" in sepsis. They are thought to be useful if adopted early (within 8-24 hours of the diagnosis of septic shock) in patients who are unresponsive to standard therapy. Here we report our experience with CytoSorb[®].

Methods: From January 2021 to May 2022, 46 patients with septic shock were treated with continuous renal replacement therapy (CRRT) associated with hemoadsorption with CytoSorb[®]. All cases presented organ failure including AKI. Surgical patients (n = 13) were treated with surgery, COVID patients (n = 15) and medical patients (n = 16) with medical therapy; all surgery cases were operated on before starting the haemadsorption and in some cases reoperation with the need to suspend the adsorption. The mean age was 69 ± 17 years (SD). On admission the mean SAPSII score was 50 ± 11 (SD). CRRT as hemodiafiltration (CVVHDF) was performed. All patients received at least one CytoSorb[®] treatment and additional treatments (up to 21 filters in a Covid patient) according to our indication.

The CytoSorb cartridge was installed in series to the high cut-off filter; blood flow rates were maintained between 120 and 150 mL/min while dialysis doses from 18 to 45 mL/kg/hour. CytoSorb was renewed every 24 hours. We evaluated the impact of CytoSorb on 30-day survival, haemodynamics and relevant outcomes.

Results: The 30-day survival was 30%. During treatment with CytoSorb[®], patients had a hemodynamic stabilization with a significant improvement in MAP, a reduction in amines and a decrease in PCR and PCT (Figure 1). Mortality at 30 days among medical patients was almost comparable to that of COVID patients and higher than that of surgical patients (70%, 69% and 61%, respectively). It should be noted that almost half of the deceased patients arrived late in the hospital, thus leading to a late start of treatment.

Conclusions: We confirm the efficacy and usefulness of the CytoSorb[®] if adopted early in patients who do not respond to standard therapy. CytoSorb[®] treatment was safe and well tolerated with no device-related adverse events during or after treatment sessions.



Figure 1: Parameters before and after CytoSorb treatment

Blood purification with CytoSorb® in septic shock with intravascular disseminated coagulation: case report

F. Massaro¹, V. Delmonte¹, A. Caracciolo¹

¹Anestesthesia and Intensive Care Unit, "Miulli Hospital", Acquaviva delle Fonti (Ba), Italy

BACKGROUND: Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is defined as sepsis with persisting hypotension requiring vasopressors to maintain MAP \geq 65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. Early identification and appropriate management in the initial hours after the development of sepsis improve outcomes. Disseminated intravascular coagulation (DIC; also called consumption coagulopathy and defibrination syndrome) is a systemic process with the potential for causing thrombosis and hemorrhage. It can present as an acute, life-threatening emergencyor a chronic, subclinical process. It can occur in sepsis and septic shock conditions. Identifying DIC and the underlying condition responsible for it are critical to propermanagement.

METHODS: We present the case of a 47-years-old female patient, without relevant comorbidities, with acute and severe septic shock and DIC originated from a urinary infection sustained by E.Coli. In this case report we evaluate the impact of the CytoSorb blood purification therapy on multiple organ dysfunction syndrome causedby septic shock. She underwent CytoSorb treatment with the following protocol: 2 cartridges on the second day from admission in ICU (12 hours of treatment each CytoSorb), 1 cartridge for 24 hours on the third day and 1 cartridge for 24 hours on the fourth day.

RESULTS: The results are shown in figure 1. Improvement of hemodynamics and cardiac function (together with a Levosimendam treatment), reduction until stop of vasopressors support, gradual improvement of the P/F ratio (two failures of weaning with intubation), improvement of platelet count, renal function until resumption of spontaneous diuresis, liver function. Progressive reduction of inflammation indices and lactates.



Figure 1: Clinical and inflammatory parameters trend during CytoSorb Therapy (light blue box) and ICU stay

CONCLUSIONS: The early use of hemadsorption with CytoSorb therapy together with appropriate antibiotic therapy and an early intervention strategy for septic shock and its complications seems to have improved the clinical status and the organ function, determining the good outcome of this patient.

A55 Use of CytoSorb in childhood onset systemic lupus erythematosus (c-SLE) septic shock

L. Milella¹, M. T. Ficarella¹, G. Calabrese¹, M. Sisto¹, F. Lenoci¹, F. Cito Fabiana¹, P. Moliterni¹, M. L. Lasorella¹

¹ Anaesthesia and Intensive Care Unit, Children's Hospital "Giovanni XXIII", Bari, Italy

Background: The c-SLE is a rare connective tissue disorder, median age at diagnosis is 11-12 years. The cause ofc-SLE death is usually the multi-organ dysfunction syndrome (MODS)sepsis-related. Here is a case report of 16 years old girl affected by cutaneous lupus Erytematosus (CLE) inappropriately treated at home and evolved in c-SLE.

Methods: On admission she presented malnutrition, saporous status, acute renal failure and dyspnea until acute respiratory failure requiring emergency intubation and inotropic support. Total body CT scanwas performed with evidence of a massive ascitic effusion, altered renal cortical density and pleural effusion. Blood test showed leukopenia= 2730 ul and platelet 47000 uL, PCR= 100 mg/dl, PCT > 1.5 pgr /ml,LDH > 400mg/dl, altered ferritin and triglyceride values compatible with initial macrophage- histocytic activation process (MAS). Broad-spectrum and targeted therapy was initiated on the basis of the antibiogram and the results of the cultures.

In order to control the MODS linked to the septic state, rescue therapy of three cycles of CytoSorb Absorber on Prismaflex (Baxter) in post CVVHDF filter was performed over the following 3 days. Each cycle lasted 24 h, with heparinization and blood flow rate of 200 ml/min.

Results: Rescue therapy with cytokine apheresis with CytoSorb absorber, instituted early at the onset of MODS allowed reduction of organ dysfunction: rapid respiratory weaning at 48 hours, discontinuation of inotropic support at 24h after CytoSorb treatment. There was no recovery of renal function following stabilization of renal organ damage with AKI KIDNO SCORE 2. Initially APACHE II score calculated was 27 with 55% estimated non-operative mortality. A clear reductionin the risk of death was observed with a calculated APACHE II of 2 with estimated non-operative mortality < 4% ten days later at discharge.

Conclusion: CytoSorb immunoapheresis has proven effective in our case in the treatment of MODS even in presence of acute and amplified dysregulation of innate and acquired immunity and insufficient immunological regulation of systemic inflammation as in c-SLE.

Efficacy of hemadsorption combined with CRRT in the treatment of irreversible septic shock. Review of the case studies of the last two years in the Intensive Care of Trieste

V. Votrico¹, B. Perencin¹, A. Yazbek¹, F. Ianche¹, L. Cipriani¹, U. Gerini¹, G. Berlot², F. Bianco¹ ¹SC Nephrology and Dialysis, Giuliano Isontina University Hospital – ASUGI – Trieste Hospital, Trieste, Italy ²SC Anesthesia Resuscitation Pain therapy Unit, Giuliano Isontina University Hospital – ASUGI – Trieste Hospital, Trieste, Italy

Introduction: Septic shock is a complexevolution of sepsis characterized by vasoplegia, multi-organ hypoperfusion, and acute renal failure (S-AKI) secondary to cytokine storm, often resistant to support with vasopressor drugs. A rapid and sustained reduction of cytokine burden and thus attenuation of excess immune response by the use of inflammatory mediators adsorbtion with Cytosorb[®] is often reported as an adjunctive therapy aimed at circulatory stabilization and thereby increasing the chance of recovery. In this study, we evaluated the impact of CRRT + Cytosorb[®] treatment in the patient hospitalized for S-AKI in the ICU on hemodynamic stability, inflammation and survival.

Methods: This is a retrospective study on adult patients with S-AKI treated with CRRT in ICU between January 2020 and April 2022. For each patient, data on blood pressure values (PAS, PAD, PAM), phlogosis indices (PCR, PCT), vasopressor therapy with noradrenaline (gamma / kg / min) and vital status at discharge were collected. The treatment time was used as a measure of the intensity of the treatment. The variation in clinical-laboratory parameters between the start and end of the observation (Δ = final value - initial value) was used to define the clinical, hemodynamic and infectious impact of the method. Non-parametric statistical tests were used to compare the clinical and blood chemistry variables of interest between the groups.

Results: Overall, 59 patients with S-AKI (36 m, 23 f), age 64 (IQR 54-76) were selected; 26 were discharged from TI (S), 33 died (NS) (Table 1). Patients S and those with greater treatment intensity (duration \geq 72 h) had better control of hemodynamics and the trend of inflammation indices (Table 1).

Conclusions: Our data confirm the efficacy of CRRT + Cytosorb[®] therapy in the management of patients with S-AKI, optimizing hemodynamic and inflammatory control and improving the outcome in TI.

Tabella 1. Confronto tra sopravvissuti e non sopravvissuti per le variabili cliniche ed ematochimiche di interesse

	Totale	Sopravvissuti	Non Sopravvissuti	P *
	No 59	No 26	No 33	
PAS pre, mmHg, mediana [IQR]	100.0 [90.0, 110.0]	100.0 [90.0, 105.0]	100.0 [90.0, 110.0]	0.763
PAS post, mmHg, mediana [IQR]	105.0 [80.0, 120.0]	120.0 [111.3, 130.0]	90.0 [80.0, 110.0]	< 0.001
ΔPAS, mmHg, mediana [IQR]	5.0 [-20.0, 30.0]	25.0 [10.0, 33.8]	-15.0 [-30.0, 5.0]	<0.001
PAD pre, mmHg, mediana [IQR]	50.0 [40.0, 60.0]	50.0 [40.0, 57.5]	50.0 [40.0, 60.0]	0.447
PAD post, mmHg, mediana [IQR]	50.0 [40.0, 57.5]	60.0 [50.0, 70.0]	40.0 [30.0, 50.0]	<0.001
ΔPAD, mmHg, mediana [IQR]	0.0 [-17.5, 10.0]	10.0 [0.0, 13.8]	-10.0 [-20.0, 0.0]	<0.001
PAM pre, mmHg, mediana [IQR]	66.7 [59.2, 73.3]	64.2 [58.8, 71.3]	66.7 [60.0, 75.0]	0.453
PAM post, mmHg, mediana [IQR]	66.7 [55.0, 80.0]	80.0 [68.8, 92.5]	60.0 [46.7, 65.0]	<0.001
ΔPAM, mmHg, mediana [IQR]	3.3 [-16.7, 16.5]	15.0 [8.8, 24.6]	-10.0 [-25.0, 3.3]	<0.001
PCT pre, ng/mL, mediana [IQR]	9.3 [2.2, 69.1]	24.0 [2.7, 77.7]	8.8 [2.2, 47.6]	0.567
PCT post, ng/mL, mediana [IQR]	3.2 [2.2, 10.5]	3.0 [0.4, 9.3]	3.2 [2.4, 14.4]	0.187
ΔPCT, ng/mL, mediana [IQR]	-7.0 [-41.4, -0.7]	-22.0 [-63.4, -1.4]	-4.0 [-27.9, 0.3]	0.148
PCR pre, mg/L, mediana [IQR]	236.9 [131.8, 285.9]	246.0 [174.2, 285.2]	204.0 [94.6, 285.9]	0.352
PCR post, mg/L, mediana [IQR]	88.7 [40.4, 131.8]	70.0 [32.0, 104.2]	107.3 [47.8, 196.3]	0.039
ΔPCR, mg/L, mediana [IQR]	-108.5 [-190.3, -16.1]	-170.2 [-223.6, -94.5]	-32.5 [-114.9, 6.7]	<0.001
Lat pre, mmol/L, mediana [IQR]	20.1 [12.6, 41.3]	20.9 [14.9, 42.5]	18.8 [9.5, 40.7]	0.455
Lat post, mmol/L, mediana [IQR]	12.3 [6.2, 26.7]	7.9 [4.8, 12.3]	20.0 [11.2, 93.0]	0.001
ΔLat, mmol/L, mediana [IQR]	-3.8 [-14.1, 7.1]	-11.7 [-28.7, -7.5]	4.3 [-2.2, 31.3]	<0.001
Nora pre, gamma/Kg/min, mediana [IQR]	0.6 [0.4, 0.9]	0.5 [0.4, 0.8]	0.6 [0.4, 1.0]	0.277
Nora post, gamma/Kg/min, mediana [IQR]	0.5 [0.1, 1.0]	0.0 [0.0, 0.1]	0.9 [0.5, 1.2]	<0.001
ΔNora, gamma/Kg/min, mediana [IQR]	-0.1 [-0.6, 0.3]	-0.5 [-0.7, -0.1]	0.1 [-0.1, 0.7]	<0.001
Durata CRRT-Cyt, ore, mediana [IQR]	72.0 [24.0, 132.0]	72.0 [72.0, 162.0]	48.0 [24.0, 96.0]	0.048

PAS, pressione arteriosa sistolica; PAD, pressione arteriosa diastolica; PAM, pressione arteriosa media; PCT, procalcitonina; PCR, proteina C-reattiva; Lat, lattati; Nora, noradrenalina; Δ , valore post – valore pre; Cyt, Cytosorbe; * test Mann-Whitney

Pancreatic Stone Protein (PSP) as a predictive biomarker of multiple organ failure and clinical outcome

V. Losappio¹, F. Sangregorio¹, A. Maiorano¹, B. Infante¹, A. Stasi¹, G. S. Netti¹, F. Spadaccino¹, E. Ranieri¹, G. Stallone¹, G. Castellano²

¹Department of Nephrology, Dialysis and Transplantation, Azienda Ospedaliero Universitaria di Foggia, Foggia, Italy ²Department of Nephrology, Dialysis and Transplantation, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

Background: COVID-19 syndrome is associated with high morbidity and mortality in haemodialyzed patients. Pancreatic Stone Protein (PSP) is an early biomarker of sepsis and a prognostic biomarker of disease severity in critically-ill patients and can be rapidly measured at the patient's bedside with a point-of-care-test from a small drop of whole blood. The aim of our pilot was to investigate PSP in patients requiring haemodialysis with SARS-CoV-2 infection, at different severities of COVID-19 disease.

Methods: Between February and July 2021, 23 patients (6 severe COVID-19 with Acute Kidney Injury, 6 moderate COVID-19 haemodialyzed, 2 haemodialyzed without COVID-19 and 3 healthy controls) were recruited at the University Hospital of Foggia for PSP evaluation. Biomarker's measurements were performed within 48 hours after admission or upon arrival for haemodialysis (pre-treatment). PSP was measured at the patient's bedside with "abioSCOPE", a point-of-care test capable of evaluating PSP levels in five minutes from a small drop (50µl) of whole blood or serum.

Results: The preliminary results of this pilot study showed a trend for PSP to increase along with the severity of disease. In fact, serum PSP levels were significantly higher in Intensive Care Unit subjects than in COVID-19 negative haemodialysis subjects and controls (ANOVA p=0.032). Furthermore, PSP levels were significantly higher in subjects who died (p<0.017). Whether this increase is due to the kidney injury or COVID-19 disease remains unknown, and more research is needed to understand the relationship.



Fig. 1. Trend of Pancreatic Stone Protein at different stages of disease severity

Conclusion: Several clinical studies published in literature have shown the predictive value of PSP in the early identification of sepsis and severity of the clinical outcome. In our experience we have seen a trend for PSP to increase with disease severity also in COVID-19 patients. These results are preliminary, but PSP was significantly higher in patients who died, in accordance with the literature. This experience also has demonstrated the feasibility of a point of care system to be easily implemented in the unit and adopted by personnel and its design enables fast results and immediate decisions to be taken, especially in urgent situations.

Pancreatic Stone Protein (PSP): implementation of a point-of-care test for the early identification and monitoring of sepsis in critically-ill patients

F. Anniciello^{1,2}, D. Fruttini³ and A. Giacomucci¹

¹Intensive Care Unit, Azienda Ospedaliera di Perugia, Perugia, Italy,

²Department of Medicine and Surgery Anaesthesia, Analgesia and Intensive Care Unit, Università degli Studi di Perugia, Perugia, Italy

³Department of Medicine and Surgery Section of Internal Medicine and Endocrine and Metabolic Sciences, Università degli Studi di Perugia, Perugia, Italy

Background: Sepsis is currently one of the leading causes of death in Intensive Care Unit (ICU) and represents one of the major challenges for clinicians due to its difficult identification and consequent late treatments could have a negative impact on prognosis. The clinical criteria used for the diagnosis of sepsis and early administration of antibiotic therapy are still not consolidated and the need is to validate a biomarker able to early recognize and treat sepsis. Pancreatic stone protein (PSP) is a promising biomarkerwhose sensitivity and specificity has been shown to be predictive for the early diagnosis of sepsis.

Methods: We daily monitored PSP levels with the point-of-care test abioSCOPE in twenty critically-ill patients at risk of sepsis admitted to our ICU. Microbiological sampling and treatments were performed in case of clinical suspects for infection and according to the clinical picture.

Results: PSP levels were shown to be statistically significant in distinguishing septic patients from those without sepsis (p=0.041). Furthermore, we shown that PSP levels were significantly higher in patients who developed sepsis before its clinical diagnosis according to Sepsis-3 criteria (p=0.0265).



Fig. 1. PSP levels in patients with/without sepsis before its diagnosis according to Sepsis-3 definition

Conclusion: Our findings suggest that PSP is an early predictor of sepsis, with a positive predictive value for mortality in septic patients and a negative predictive value in those with a systemic inflammatory response. Further studies are needed to assess the role of PSP in patient management, enabling decisions at the bedside, and early treatment especially for the de-escalation of the antibiotic therapy. The implementation of a point-of-care test that allows biomarkers measurements in five minutes from a drop of blood could also have an impact on the clinical outcome and survival of septic patients.

A59 Pancreatic Stone Protein (PSP) as a sepsis biomarker in patients admitted to intensive care

G. Zani¹, G. Felloni¹, F. Di Antonio¹, E. Graziani¹, M. Valbonetti¹, D. Fiducioso¹, F. Menchise¹, E. Dal Checco¹, C. Gecele¹, S. Valenti², M. Fusari¹

¹ Department of Anaesthesia and Intensive Care, AUSL Romagna, Santa Maria delle Croci Hospital, Ravenna, Italy ² Department of Pathology, Transfusion and Laboratory Medicine, AUSL Romagna, Santa Maria delle Croci Hospital, Ravenna, Italy

Background: Sepsis is a life-threatening and time-dependent syndrome whose clinical outcome is strictly related to its rapid detection and clinical management. Although sepsis mechanisms have been largely investigated over the years there are still many unsolved questions and sepsis early recognition remains complex due to its heterogeneity. In this clinical picture the timely measurement of early biomarkers could provide a unique window of opportunity for the timely initiation of adequate treatments.

Methods: This was a monocentric prospective observational pilot study including adult ICU patients at risk of nosocomial sepsis, with the aim to investigate the use of PSP in the daily management of these critically-ill patients. Together with PSP, procalcitonin (PCT) and c-reactive protein (CRP) were analyzed at specifictiming: ICU admission, onset of a septic trigger, five days after antibiotic start, two days after antibiotic suspension. PSP was measured in five minutes at the bedside with the POCT abioSCOPE® from a single drop of whole blood.

Results: 63 patients were enrolled, 40 finally included in the analysis of whom 26 developed sepsis and 14 remained non-septic. PSP was significantly higher in patients with sepsis compared to those without sepsis both at T0 (ICU admission) and T1 (onset of septic trigger) [PSP (p<0.05), PCT (NS), CRP (NS)]. Furthermore, PSP reached peak values at T2 (five days after antibiotic start) and then decreased, as expected, at T3 (two days after antibiotic suspension).



Fig. 1. Mean PSP (ng/ml), CRP (mg/L) and PCT (ng/ml) levels in the two group of patients (septic and non-septic) over the time. *p<0.05 **Conclusion:** Our study suggests a potential role of PSP as diagnostic biomarker of sepsis in critical ICU patients. Daily PSP monitoring may anticipate an appropriate treatment and avoid worsening of the clinical picture, improving standard of care and outcome, but further studies are needed to confirm our hypothesis.

References:

- 1. Evans L, Rhodes A, Alhazzani W et al. Intensive Care Med. 2021 Nov;47(11):1181-1247.
- 2. Llewelyn MJ, Berger M, Gregory M et al. Crit Care. 2013 Mar 26;17(2):R60.
- 3. Pugin J, Daix T, Pagani JL et al. Crit Care. 2021 Apr 20;25(1):151.

INTOXICATIONS

A60

The use of CytoSorb in a patient with acute quetiapine intoxication: a case report

F. Pennacchiotti¹, E. Erminio², P. Marangiolo², M. Spennati², E. Ricchiuti²

- ¹ Department for Nephrology and Dialysis, Presidio Ospedaliero Orientale, Manduria, Taranto, Italy
- ² Department for Anaesthesia and Intensive care, Presidio Ospedaliero Orientale, Manduria, Taranto, Italy

Background: Quetiapine is an atypical antipsychotic medication used for the treatment of schizophrenia, bipolar disorder, and major depressive disorder. In an overdose, it is potentially fatal. The management of quetiapine intoxication is principally supportive, there is no specific antidote available. In this case CytoSorb was used as an adjuvant therapy for drug removal.

Case presentation: A 49-years-old woman with a medical history of personality disorder was admitted to the emergency department after ingestion of 400 mg of quetiapine in a suicide attempt. At the admission she was intubated, sedated and transferred to our ICU department. Despite continuous infusion of benzodiazepines, episodes of epileptic-like facial muscle clonias lasting a few seconds have been reported. Serious ECG for initial long QT from quetiapine intoxication were performed. Due to unstable haemodynamics, she was supported with 4 ampoules in 50 cc of physiological saline at 2 ml/h for the first 12 hours. We decided to perform hemoperfusion in order to rapidly reduce plasma quetiapine concentrations, so we performed 3 CytoSorb treatment in combination with a continuous renal replacement therapy (CRRT- PRISMAFLEX ST 150 - BAXTER) for a total of 72 h.

Results: After supportive therapy with CytoSorb she was successful extubate; there was haemodynamic stabilisation, absence of epileptogenic colonias and normalization of QTc values (figure 1). After few days she was discharged from the hospital.



Figure 1: QTc trend during ICU stay

Conclusion: In this case the use of CytoSorb resulted in a rapid improvement in clinical, neurological and cardiological condition due to the effective removal of the severe quetiapine overdose. The patient emerged from the condition of toxicity and returned to the status quo ante of chronicity.
Use of CytoSorb in a potential mushroom's intoxication due to Amanita Proxima

F. Pennacchiotti¹, V. Nosella¹, S. Andrioli¹

¹Department for Nephrology and Dialysis, Presidio Ospedaliero Orientale, Manduria, Taranto, Italy

Background: Mushroom intoxication is an environmental health problem caused by the ingestion of some poisoning mushrooms, such as those of the genus Amanita. In particular, Amanita Proxima is a well-known cause of nephrotoxicity due to the norleucine toxin, an allenic and non-protein thermostable amino acid, potentially able to determine a severe clinical syndrome.

Case presentation: Here, we describe the case of a 53-year-old female patient who was admitted to our hospital in with vomiting, diarrhoea and altered mental state, in severe hypotension and anuric. The patient had, unknowingly, ingested poisonous mushrooms belonging to the genus Amanita Proxima. Our hypothesis was then confirmed by the Poison Control Centre, which we had promptly contacted. After an initial fluid replacement therapy to rebalance the metabolic acidosis, no further clinical improvement occurred. Due to the persistence of anuria and Acute Renal Failure, we started a Continuous Renal Replacement Therapy (CRRT) in combination with 2 cycles of 24 hours each of CytoSorb blood purification therapy. The adsorption cartridge was used post-haemofilter in combination with CRRT (PRISMAFLEX ST 150 - BAXTER) in CVVHD mode with a blood flow rate of 100 ml/min, dialysate flow rate of 1000 ml/min, no ultrafiltration and a standard anticoagulation with citrate.

Results: After 48 hours of CVVHD in combination with 2 consecutive cycles of blood purification with CytoSorb we achieved a stabilization of the clinical picture with a normalization of most of the metabolic and hemodynamic parameters. Due to AKI persistence, we decided to continue with three other sessions of CVVHD, followed by a complete resolution of kidney failure.



Conclusions: The combination of CVVHD and CytoSorb therapy in a case of mushrooms intoxication was associated to a marked stabilization of many metabolic parameters. Although the direct adsorption of the toxin responsible for the norleucine syndrome is not so clear and could not be demonstrated, the use of CytoSorb in combination to the CRRT is a potential adjuvant therapy to rapidly stabilize the clinical picture and avoid chronic consequences.

Use of the CytoSorb® filter in metformin intoxication in a hemodynamically unstable patient, a case report

I. Barbaresco ^{1,2}, A. Marangone¹, V. Sagnelli¹, D. Tomasello¹, T. Pellis¹

¹ Intensive Care Unit, S. Maria degli Angeli Hospital, Azienda Sanitaria Friuli Occidentale, Pordenone, Italy

² Department of Anesthesia, Resuscitation and Analgesic therapy, Azienda sanitaria Universitaria Giuliano Isontina, Trieste, Italy

Background/Aims: Metformin is a hypoglycemic agent used in type 2 diabetes. In case of overdose, it induces lactic acidosis (LA), that occurs especially in case of chronic or acute kidney injury. To date, there is no antidote available, thus therapy is based on the support of vital functions, possibly associated with intermittent hemodialysis (IHD). Here we discuss a case of severe metformin-related metabolic acidosis in a patient with pre-renal acute kidney injury (AKI).

Clinical case: A 66 years old man with history of type 2 diabetes treated with metformin, hypertension, hypercholesterolemia, overweight, chronic cerebral vasculopathy, medullary sponge kidney associated with recurrent renal colic, was admitted to our ICU. He presented with polypnea (RR 32), hypotension (BP 70/43 mmHg) and tachycardia (HR 108 bmp), oliguric not responding to furosemide, pulmonary edema. SAPS II score was 55 and SOFA

score 7.Blood gas analysis (BGA) showed pH 6.95, PaO2 146 mmHg, PaCO2 37 mmHg, HCO3⁻ 8.2 mmol/L, base excess

(BE) -22.8, lactate (Lac) 20.64 mmol/L, Anion Gap (AG) 53.18, serum creatinine (SCr) 14.5 mg/dl, K⁺ 6.3 mmol/L.

The patient underwent prompt sedation, mechanical ventilation and norepinephrineinfusion as well as administration

of a bolus of HCO3⁻ 8.4% 250ml, followed by continuous infusion. He underwent 2 hours of IHD till hemodynamic instability became unmanageable. Thus, we startedCRRT with CytoSorb; the treatment lasted 24 hours. The first BGA

showed: pH 7.7, PaCO2 14.6 mmHg, HCO3⁻ 4.2 mmol/L, BE -24, Lac 13.08 mmol/L, AG 40. At the end of the treatment

BGA was pH 7.41, PaCO2 38.1 mmHg, HCO3⁻ 23.8 mmol/L, BE -0.6, Lac 1.59 mmol/L, AG 15.6, RR and BP had normalized. On day 2, the patient was extubated, hemodynamically stable and his urinary output normalized. He had no relapse of LA as can be seen from the pH and lactate trend reported in figure 1.

Conclusion: The use of CRRT together with CytoSorb appears to be a valid treatment for patients with metformin intoxication. CRRT + CytoSorb lead to rapid pH and lac normalization with hemodynamic stability and decreased norepinephrine support. We used CytoSorb because it is very effective in adsorbing low-medium molecular weight molecules, especially when present in high concentrations like in acute intoxication.



Figure 1 - variation of the main parameters over time. The yellow line indicates the start of the CRRT + CytoSorb® therapy

Use of CytoSorb in MALA treatment: a retrospective observational study

C. Maisto¹, A. Accogli¹, D.M.L. Burzo¹, A. Mudoni¹, F. Musio¹, A. Naticchia¹, M.D. Zacheo¹, F. Caccetta¹, P. Ciocchetti² and D. Gemma²

¹ Nephrology and Dialysis unit, Ospedale Cardinale Panico, Tricase (Le), Italy

² Anesthesia and resuscitation unit, Ospedale Cardinale Panico, Tricase (Le), Italy

Background: Metformin-associated lactic acidosis (MALA) is a rare complication of diabetes mellitustype 2 therapy. MALA is a life-threatening condition, with a mortality rate of 30-50%. The management of MALA is controversial. The use of intermittent hemodialysis or continuous renal replacement therapy has been reported in some case reports, while there are very few data available on the use of hemoadsorption.

Methods: Over a 3-years period, we retrospectively identified 3 patients admitted to "Cardinale

G. Panico" Hospital, Tricase (LE) for MALA and treated with CRRT + CytoSorb as adjuvant therapy tostandard supportive care. CRRT was performed in continuous veno-venous hemodialysis (CVVHD) using a Multifiltrate CiCa (Fresenius Medical Care) and an AV1000S hemofilter (Fresenius Medical Care) with predyalizer CytoSorb. Blood flow rates (Qb) were maintained between 100 and 150 mL/min, while dialysis doses ranged from 20 to 35mL/kg/h according to standard care. All patients received 2 CytoSorb cartridges changed every 24h.

For each patient were described: duration of CRRT treatment, CytoSorb start date, number of filtersused and duration of CytoSorb treatment. Different profiles have been studied: the renal profile (creatinine, azotemia and 24h diuresis); the hemodynamic profile (mean arterial pressure MAP, number of inotropes used, lactates); the acid-base profile (pH). All these items were recorded at time 0 (TO), before the start of CytoSorb, after 24h from the start of treatment with CytoSorb, and also at 48h, 72h and 96h.

Results: The observed survival rate was 100%. In all patients we observed a reduction in the demand for inotropic drugs and an improvement in haemodynamics (increase in MAP and decrease in lactate levels). We have also seen an improvement in pH values and a resumption of diuresis.



Conclusion: The CytoSorb cartridge is able to adsorb and remove several drugs, including metformin. This rapid drug removal allows a rapid resolution of the resulting severe metabolic acidosis. In our study, 100% of treated patients survived and showed a rapid improvement in pH, hemodynamics (MAP increase and lactate reduction) and consequently in diuresis. This is a noteworthy result since very few cases of its use in this context are reported in the literature. The cartridge, in fact, would adsorb not only the drug but also lactates, helping to reduce and resolve severe metabolic acidosis.

CARDIAC SURGERY

A64

Targeting shock and hyperinflammation with Cytosorb in patients supported with VA ECMO forrefractory outof-hospital cardiac arrest: a case-control study

M. A. Bonizzoni¹, M. Pieri¹, V. Bianchessi¹, S. Delrio¹, M. G. Calabrò¹, E. Fominskiy¹, A. M. Scandroglio¹ ¹ Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy

Background/Aims: In patients resuscitated from refractory cardiac arrest, dysregulated iperacute inflammatory response a deleterious clinical phenomenon which may be elicited from different clinical triggers, above all ischemia-reperfusion injury, contact with foreign surfaces during extracorporeal treatments, prolonged hemodynamic instability. Hemadsorption with CytoSorb (CytoSorbents Corporation, Monmouth Junction, NJ, USA) has given promising results in several clinical contexts. Its role in cardiac arrest patients, on the contrary, is debated and evidence contradictory. The aim of our study was to compare shock/inflammation laboratory parameters and outcomes of patients supported with extracorporeal cardiopulmonary resuscitation due to refractory (>60 min) out-of-hospital cardiac arrest treated with CytoSorb with a similar group of patients who didn't receive purification with CytoSorb.

Methods: Observational studies on all adult patients treated with VA ECMO for refractory cardiac arrest >48hours at our institution from 4/2015 to 8/2020. CytoSorb was started after VA ECMO cannulation according to our institutional protocol whenever possible.

Results: One-hundred ten patients received VA ECMO >48 hours due to refractory cardiac arrest during the study period: 74 patients received CytoSorb treatment while 36 didn't receive CytoSorb. CytoSorb treatment duration was 46(24-63) hours. Shock and inflammatory parameters (baseline and peak values) for both groups are shown in table 1. All patients were on mechanical ventilation and extremely ill. Although patients in the CytoSorb group presented higher laboratory parameters of shock at baseline compared to patients not treated with CytoSorb (table 1), peak values of C reactiveprotein, total and direct bilirubin were not statistically different between the two groups (p=0.7, p=0.4 and p=0.8, respectively)

Intensive care unit survival was 34/74(46%) in CytoSorb group and 20/36(56%) in no-CytoSorb patients (p=0.3); hospital survival was 34/74(46%) and 17/36(47%) in the same groups, respectively (p=0.9). No CytoSorb related adverse event was recorded.

Conclusion: We provided preliminary evidence that CytoSorb treatment is safe and effective in dumping blood circulation of molecules associated with shock and inflammation after cardiac arrest. Our data challenge existing data of possible increase mortality in patients treated with CytoSorb after cardiacarrest and highlights opportunities for further analysis in this setting.

Table 1. Laboratory parameters at baseline and peak values during intensive care unit stay.

Parameter	CytoSorb group (n=73)	No CytoSorb	P value	
		group (n=36)		
Baseline				
Inotropic score	15 (8-27)	12 (6-20)	0.3	
Lactate dehydrogenase, U/L	934 (405 - 1660)	444 (368 – 656)	0.001	
Troponin, ng/L	3040 (384 - 19294)	470 (191-2065)	0.002	
Creatin phosphokinase U/L	2587 (401 - 7068)	343 (185-1448)	< 0.001	
C Reactive protein, mg/L	16 (2-73)	1 (1-4)	0.001	
Total bilirubin, mg/dl	0.6 (0.3 - 1.15)	0.3 (0.2-0.5)	< 0.001	
Direct bilirubin, mg/dl	0.3 (0.12 - 0.54)	0.1 (0.1 – 0.2)	< 0.001	
D-dimers, microgr/ml	19 (8-20)	9 (4-12)	0.01	
Lactates, mmol/L	12 (8-18)	9 (7-11)	0.3	
Peak				
Inotropic score	20 (14-32)	16 (10-30)	0.5	
Lactate dehydrogenase, U/L	1462 (840 – 2252)	895 (634 – 1235)	0.02	
Troponin, ng/L	12657 (2136 – 25790)	4295 (2622 – 11713)	<0.001	
Creatin phosphokinase, U/L	6395 (2673 – 12445)	4159 (1258 – 7598)	0.04	
C Reactive protein, mg/L	227 (141 – 310)	229 (139 – 272)	0.7	
Total bilirubin, mg/dl	1.6 (0.9-2.3)	1.3 (0.7 – 2.8)	0.4	
Direct bilirubin, mg/dl	0.8 (0.5-1.6)	0.7 (0.4 – 2)	0.8	
D-dimers, microgr/ml	19 (10-20)	14 (10 – 18)	0.9	
Lactates, mmol/L	11 (8-15)	9 (8-11)	0.07	

Data are reported as mean (interquartile range)

Evaluation of a system for cytokines adsorption in a population of critically ill patients: a single center experience

J. Rama¹, M. Ceola Graziadei¹, L. Corubolo ¹, A. Russo¹, A. De Vigili¹, A. Vignola¹, E. Falcioni¹, K. Donadello¹, E. Polati¹, L. Gottin¹

¹Unit of CardioThoracic Anesthesiology and Intensive Care, Department of Surgery, Dentistry, Gynecology and Pediatrics, AOU University Hospital Integrated Trust of Verona, University of Verona, Verona, Italy

Introduction: The use of extracorporeal blood purification methods for immunomodulation under acute inflammatory conditions following infectious and noninfectious origins has evolved in recent years. Hemadsorption via the cytokine-adsorber CytoSorb has successfully been used as an adjunctive method in adults, mainly for the purpose of immunomodulation under acute inflammatory conditions such as sepsis and cardiac surgery.

Methods: Here we described a retrospective observational analysis of a mixed population of critically ill patients treated with CytoSorb. Our Primary Endpoint was the evaluation of the efficacy in terms of outcome's improvement laboratory parameters dosage, catecholamines dosage, SOFA. The Secondary Endpoint was to evaluate the impact on general variables of outcome (LOS, mortality, days on mechanical ventilation). We collected the laboratory parameters before the treatment, at days 1, 2, 3, 4.

Results: We enrolled 40 patients (34 male, 6 female) received CytoSorb therapy for sepsis (25 patients), hyperbilirubinemia (11 patients), rhabdomyolysis (3 patients) and multi organ failure (1 patient). 11 patients out of 40 required Extracorporeal Membrane Oxygenation (ECMO). In these patients, the mean number of cartridges was of 2,82 \pm 1,72. As shown in figure 1A and 1B a significant reduction of inflammatory biomarkers (PCT, CRP, Leukocytes) and vasopressors dosage was observed. There was also an improvement in bilirubin (from a mean of 9 mg/dl to 7,3 mg/dl), creatinine (from a mean of 210 µmol/l to 120 µmol/l) and CPK (from a mean of 2900 U/l to 2500 U/l).





Conclusions: Cytokines adsorption results as a method with a good efficacy in improving many laboratory parameters and hemodynamic stability in a selected category of patients. Indications for a wide clinical use must be further confirmed by studies on population with an adequate sample dimension.

Combined treatment with IGM enriched immunoglobulin and CytoSorb ininfective endocarditis: case series

G. Paternoster¹, A. Covino¹, M. Vitiello¹; R. Vignale¹; F. Gallicchio¹; M. T. Tucciariello¹ and G. Pittella¹

¹ Department of Cardiovascular Anesthesia and Intensive Care, San Carlo Hospital, Potenza, Italy

Introduction: Infective endocarditis is a serious disease condition. Depending on the causative microorganism and clinical symptoms, cardiac surgery and valve replacement may be needed, posing additional risks to patients who may simultaneously suffer from septic shock. The combination of surgery bacterial spread out and artificial cardiopulmonary bypass (CPB) surfaces results in a release of key inflammatory mediators leading to an overshooting systemic hyperinflammatory state frequently associated with compromised hemodynamic and organ function. Combined use of hemoadsorption and IgM enriched Immunoglobulin might represent a potential approach to control the hyperinflammatory systemic reaction associated with the procedure itself and subsequent clinical conditions by reducing a broad range of immuno-regulatory mediators and endotoxemia.

Methods: We describe retrospectively 8 cardiac surgery patients with proven acute infective endocarditis obtaining valve replacement with CPB surgery in combination with intra e postoperative CytoSorb hemoadsorption and intravenous administration of IgM enriched Immunoglobulin (Pentaglobin[®]) 5 ml/kg die. for three consecutive days

Results: Combined treatment of hemoadsorption and IgM enriched Immunoglobulin was associated with a mitigated postoperative response of key cytokines with a significative reduction of IL-6 and Endotoxemia an increase of IL10; an improvement of clinical metabolic parameters (WBC and SOFA score). Moreover, patients showed hemodynamic stability which possibly could be attributed to the additional combined treatment. Intraoperative hemoperfusion and Pentaglobin administration were well tolerated and safe without the occurrence of any related adverse event. **Conclusions:** This approach may open up potentially promising therapeutic options for infective endocarditis, with pro and anti-inflammatory modulation, improved hemodynamic stability and organ function as seen in our experience.

A67 Apixaban blood levels reduced by the use of Cytosorb added to cardio-pulmonary bypass

M.Nardi¹, I. Damato¹, A. Caso¹, F. Distaso¹, F. Aucella¹, E. Grandone¹, F. Greco¹

¹ Complex Unit of Cardiac Anesthesia and Intensive Care, IRCCS Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy

Background: Nowadays the new direct oral anti-coagulant (DOAC) Apixaban is largerly used for its safety and effectiveness. However, it exposes the patient who require urgent surgery to an higher risk of bleeding. This report aims to describe the effects of the CytoSorb[®] device added to cardio- pulmonary bypass (CBP) in an urgent atrial myxoma resection in a patient anti- coagulated withApixaban.

Methods: We report a case of a 65-year-old woman treated with Apixaban underwent cardiac myxomaresection followed by patch application. The patient stopped the treatment with Apixaban 48hours before surgery and then Antifactor Xa levels were measured.

Anti-factor Xa peri-operatively levels were 34,6 ng/ml and this was considered not exposing thepatient to higher risk of bleeding by our expert of hemostasis and thrombosis. Nevertheless, a thromboelastographic control performed with Quantra[®] device showed abnormalities in the coagulation (CT 207 s) due to the presence of some anti-coagulant still in blood circulation.

A CytoSorb[®] cartridge was added to the CPB in order to reduce the cytokine and IL-6 blood levelswhich increase during the mobilization of the myxoma and with the aim to increase Apixaban clearance. The duration of CBP was 95 minutes during which the patient was anti-coagulated as usual with non-fractioned heparin reaching an Activted Clotting Time (ACT) of 480 seconds. AfterCPB weaning the heparin was antagonizes by the protamine until a regular ACT (145 s).

Results: The last thromboelastographic Quantra[®] control showed a normalization of coagulation (CT 119 s). The contextual Anti-factor Xa levels dosage was 18 ng/ml.

Conclusion: This case report confirms that the addition of CytoSorb[®] to CPB for a duration of 95 minutes allows a reduction in Apixaban blood levels which do not interfere with the coagulation and allowa regular hemostasis with minimal postoperative bleeding, without needing for transfusions of blood products. For all these reasons it may represent an intraoperative treatment strategy in Apixaban-treated patients undergoing emergent cardiothoracic surgery.

A68 CytoSorb application in a case of severe Rivaroxaban associated bleeding: a potential lifesaving therapy

A. De Pascalis¹, S. Barbarini¹, P. Ria¹, A. Zito¹, M. Napoli¹

¹ Department of Nephrology, Dialysis and Transplant, Vito Fazzi Hospital, Lecce, Italy

Background: Rivaroxaban is an oral X Factor inhibitor that is used to prevent blood clotting. We present a severe bleeding complication due to use of Rivaroxaban and we discuss the indication to early treatment with CytoSorb.

Case Presentation: A 68-year-old female patient, on anticoagulant therapy because of previous MI, was admitted to the emergency department with hemodynamically hypotensive cardiogenic shock state, with reduced urine output and acute renal failure. The general condition of the patient was poor; therefore, she was intubated, subsequently, after finding of severe anemia (Hb 5.1 g/dL), the patient was transfused until the hemodynamics stabilized. Contrast abdominal computed tomography (CT) was performed which showed large areas of haemorrhage-hematoma were present in the right psoas ileus and right kidney.

Results: 48 hours post admission, Rivaroxaban specific antiXa activity resulted still altered and after three successive embolization, spontaneous bleeding was still present.

Conclusions: Treatment with CytoSorb allowed stabilization of the clinical picture, normalization of antiXA activity and patient survival.

Use of Cytosorb in a patient with septic and cardiogenic shock by fulminant autoimmune myocarditis.

P. Lisi¹, A. Teutonico¹, M. Pezzuto², V. Del Monte², V. Montinaro¹

¹Division of Nephrology and Dialysis, Ente Ecclesiastico Ospedale Generale Regionale "Miulli" Acquaviva delle Fonti (Ba), Italy

²Intensive Care Unit, Ente Ecclesiastico Ospedale Generale Regionale "Miulli" Acquaviva delle Fonti (Ba), Italy

BACKGROUND: Sepsis is defined as a dysregulated host immune response to microbial invasion leading to end organ dysfunctionand shock. Acute kidney injury (AKI) is a frequent complication, often requiring renal replacement therapy. Also, hemoadsorption using CytoSorb® has gained attention as a potential immunotherapy to control systemic inflammation and sepsis. We report a case of a young patient affected by adult-onset Still's disease with a severeand cardiogenic septic shock and AKI, that was successfully early treated by a combination of Sustained Low Efficiency dialysis (SLED) and hemoadsoption with CytoSorb®.

METHODS: A 27-year-old man was admitted to hospital for fever, after being treated at home with antibiotic and antipyretictherapy, without clinical improvement. His medical history included arthralgias and skin manifestations. On admission he presented with hypotension, renal failure, liver failure, leukocytosis and elevated plasma levels of inflammatory markers; he was transferred to the intensive care unit.

In the following hours the patient clinical conditions deteriorated, and he manifested acute respiratory failure, anuric AKI, elevated lactate, SOFA SCORE 19, cardiac dysfunction; the patient underwent coronarography (whichshowed no coronary disease), and a myocardic biopsy. An intra-aortic balloon pump (IABP) was placed, and the patient received life support and renal support dialysisin combination with hemoadsorption using CytoSorb[®]. Three CytoSorb[®] plus SLED sessions of 24 hours were performed in the first three days, followed by three dialysis session of 12 hours with SLED alone and another CytoSorb[®] and SLED session of 24 hours.

Blood culture demonstrated MRSA infection, then antibiotic treatment was started, and histological examination of the myocardium showed autoimmune myocarditis, for which hydrocortisone therapy was started.

RESULTS: The three first and consecutive sessions of hemoadsorption resulted in an improvement of the hemodynamic: increase blood pressure (BP), reduction of lactate, tapering of vasopressor dosage (norepinephrine, epinephrine and vasopressin) and partial recovery of the renal function. After three dialysis sessions, procalcitonin (PCT) increased, then another CytoSorb[®] and SLED session of 24 hours was performed, with complete recovery of renal function.

CONCLUSIONS: Early dialysis treatment with SLED in combination with hemoadsorption (CytoSorb[®]) could help to improve the hemodynamic conditions and renal recovery in patients with septic and cardiogenic shock and AKI.

The use of CytoSorb in patients with cardiogenic shock treated with VA-ECMO support

M. Berardi¹, E. Ramoni¹, R. Ceresa¹, J. L. Zulueta², G. P. Mazzanti², F. Perrucci³, S. Sutera Sardo³, Mauro Lamarra¹

¹ Cardiac Surgery Unit, Villa Torri Hospital, GVM Care & Research, Bologna, Italy

² Anaesthesiology & Intensive Care Unit, Villa Torri Hospital, GVM Care & Research, Bologna, Italy

³ Cardiovascular Perfusionist Unit, Villa Torri Hospital, GVM Care & Research, Bologna, Italy

Background: Venoarterial Extracorporeal Membrane Oxygenation (VA-ECMO) is increasingly used for treating cardiogenic shock, protected interventions and life support including resuscitation. Most patients on VA-ECMO are affected by a systemic inflammatory response with cytokine release caused by the underlying disease as well as the VA-ECMO support itself, which contributes to tissue hypoperfusion, multi-organ failure and death. In this context, extracorporeal hemoadsorption by CytoSorb has emerged as a promising novel therapeutic principle. Here we described 2 patients treated with CytoSorb during VA-ECMO support (EcmoLife) and CRRT (Fresenius Medical Care).

Methods: Patient 1 (male, 79 years) suffered from postcardiotomy cardiogenic shock after elective coronary artery bypass graft surgery. He had severely increased inflammatory parameters and was treated with VA-ECMO and hemadsorption (72 hrs). Patient 2 (male, 56 years) suffered from post-MI cardiogenic shock. He underwent emergent coronary artery bypass graft surgery, VA-ECMO and consecutive hemadsorption (total 72 hrs). The CytoSorb adsorber cartridges were integrated in CRRT-CVVHDF with heparin as regional anticoagulation.

Results: In patient 1 VA-ECMO was started on postoperative day 2. After 17 days of VA-ECMO, due to worsening clinical conditions, it was decided to start hemadsorption therapy with CytoSorb. After 3 days, there was worsening of the clinical condition leading to the patient's death. In the second patient, VA-ECMO was started on postoperative day 1 and CytoSorb treatment was institute after 3 days, with an improvement of blood parameters. The SVO₂, tissue perfusion index, reduced in patient 1 but increased considerably in patient 2. The indexes of organ dysfunction increased in patient 1 despite CytoSorb treatment: CPK-MB 11 to 89 UI/L, GOT-AST 156 to 430 U/L, GPT-ALT 54 to 77 U/L, Amylase 117 to 404 U/L. In the patient 2, these values improved: CPK-MB 207 to 36 UI/L, GOT-AST 500 to 65 U/L, GPT-ALT 329 to 88 U/L, Amylase stable around 180 U/L. Blood values of both patients are shown in figure 1.



Figure 1: Trend of blood and hemodynamic values of both patients.

Conclusion: Hemadsorption may offer a potentially promising therapeutic option for critically ill patients undergoing extracorporeal life support therapy, with cytokine reduction and a consecutively mitigated inflammatory response. These two cases confirm the importance of early treatment with CytoSorb.

Early use of CytoSorb during CPB in patient undergoing surgery for bacterial endocarditis

N. Tenga¹, C. Mariscano¹, A. Mastroianni¹, F. Ruotolo¹, T.L. Di Gennaro¹

¹Department of Emergency, Cardio-Anesthesia and ICU, Sant'Anna and San Sebastiano Hospital, Caserta, Italy

Introduction: Infective endocarditis is a disease caused by microorganisms that enter the bloodstream and settle on the endocardium, heart valve, or intracardiac device. This disease is associated with high mortality and morbidity. Depending on the causative microorganism and symptoms, cardiac surgery may be needed, with an additional risk in these patients. Cardiopulmonary bypass (CPB) can cause a systemic inflammatory response. These conditions result in a release of key inflammatory mediators leading to an overshooting systemic hyperinflammatory state frequently associated with compromised hemodynamic and organ function. The early use of CytoSorb® during CPB in these patients might represent a potential approach to control the hyperinflammatory systemic reaction associated with the procedure itself and subsequent clinical conditions by reducing immune-regulatory mediators.

Methods: We describe 17 surgery patients with acute infective endocarditis undergoing valve replacement. During CPB we use CytoSorb hemadsorption in 8 patients. 9 patients didn't receive the adsorbing cartridge. We tested laboratory parameters of inflammation (IL-6, WBC, PCR, procalcitonin, $TNF\alpha$), hemodynamics parameters (vasopressor dose and MAP), metabolic variables (serum lactates), pre and after 24-, 48-, and 72-hours post-treatment. We made another treatment with CytoSorb in ICU for 24 hours.

Results: CytoSorb treatment was associated with a mitigate response of key cytokine and clinical and metabolic parameters. Patients showed hemodynamic stability during and after the operation with a reduction of catecholamines. In the CytoSorb group, we had 7 survivors and 1 non-survivor. In the non-CytoSorb[®] we had 8 survivors and 1 non-survivor. The time of CytoSorb[®] treatment was from 80 to 650 minutes duration (median 156 minutes). All patients showed an increase in inflammatory mediators at the end of surgery. This was followed by a decrease in levels of IL-6 and IL-8 after 24 hours and a return to baseline levels after 72 hours post-surgery. We observed stabilization of hemodynamic parameters, with concomitant reduction of catecholamine need. Intraoperative hemoperfusion treatment was well tolerated and safe.

Conclusion: The early use of CytoSorb may open up promising therapeutic options for critically ill patients with acute infective endocarditis during and after surgery, with cytokine reduction, improved hemodynamic stability, and organ function.



Figure 1

Hemoadsorption with Cytosorb and mechanical circulatory support in apediatric patient after congenital heart surgery: a clinical case report

M. Agulli¹, S. Giovannini¹, D. Milanesi¹, S. Schirru¹, M.S. Ravaglia¹, A. Castelli¹

¹Anesthesiology and Intensive Care, Cardiothoracic and Vascular Department, IRCCS Azienda Ospedaliero-universitaria di Bologna, Bologna, Italy

Background: CytoSorb[®] is an hemoadsorptiondevice capable of removing molecules weighing between 10 and 55 kDa including troponin (TnI), myoglobin (Mb), creatine kinase (CK) and inflammatory cytokines. Itcan be used alongside CRRT (continuous renal replacement therapy) or other hemofiltration techniques. The use of CytoSorb[®] is labelled in patients weighing more than 10 Kg but is not contraindicated in children under that weight.

Case Report: We report a case of an 8-months-old child weighing 7Kg with Di George syndrome and ToF that underwent surgical correction. The operation was performed without any surgical or anesthesiologic complication and the patient was extubated after the surgical procedure with minimal inotropic support. The day after surgery the patient presented severe tachyarrhythmias with hemodynamic instability and lab tests consistent with massive rhabdomyolysis leading to heart and renal failure. After few noninvasive trials, central venous and arterial cannulas was placed and VA-ECMO started; alongside with ECMO, CRRT was started for renal failure and anuria. After 48 hours the clinical state of the patient was severe with high ECMO support and rising CK (108473 U/L), Mb (>38620 ng/ml) and TnI (>265480 ng/L). Because of the extreme severity of the case, we decided to try the use of CytoSorb[®] even if the weight of the patient was under 10Kg.

Results: After 12 hours of CytoSorb[®]-CRRT we reported a significant drop of the rhabdomyolysis indices, report in Table 1. The treatment was discontinued after 12 hours following a worsening of already existing thrombocytopenia (Table.1) without any major bleeding. Despite the interruption of the treatment the beneficial effect of the therapy was stable 12 and 24 hours after (Table.1). VA-ECMO was discontinued after 7 days and CRRT after 20 days with a good heart and renal function. The patient was transferred in the semi-intensive care unit 25 days after the surgery. No cause of rhabdomyolysis was identified even with genetical

and metabolic research.

Conclusion: In this case we highlight the persistent efficacy of CytoSorb[®] in clearing rhabdomyolysis products that could lead to an improvement of organ function in a child under 10 Kg. We also recommend caution since the important impact on the coagulative state of the patient.

Lab Value	Pre CytoSorb®	12h	12h stop	24h stop
Platelets (*10 ⁹)	62	6	50	39
PT-INR	1,74	2,25	1,41	1,23
PT ratio	1,7	2,18	1,39	1,2
PTT ratio	1,4	8,08	2,37	2,01
Myoglobin (ng/ml)	>3862	4510	4613	4528
Troponin I	>265480	24184	69478	76493
Creatin Kinase	108473	82889	74621	63815

Table 1: 12h: 12 hours after the beginning of the treatment; 12h stop: 12 hours after discontinuing CytoSorb®;24hstop: hours after discontinuing CytoSorb®

Pancreatic stone protein (PSP) as outcome predictor in patients with cardiogenic shock requiring mechanical circulatory support: a pilot observational study

A. Belletti¹, M. Pieri¹, P. Osenberg¹, N. Maimeri¹, R. Sofia¹, M. Di Piazza¹, G. Landoni^{1,2}, A. M. Scandroglio¹

¹ Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy

² School of Medicine, Vita-Salute San Raffaele University, Milan, Italy

Background: Pancreatic Stone Protein (PSP) has been recently suggested as a promisingbiomarker for early detection of sepsis. Several studies investigated levels and prognostic value of PSP in general ICU patients. However, no study evaluated PSP in the setting of early severe cardiogenic shock(CS) requiring mechanical circulatory support (MCS). Aim of this pilot observational study was to identify level and potential prognostic value of PSP in this specific setting.

Methods: Adult patients with CS requiring MCS were enrolled in this observational study. Patients receiving extracorporeal membrane oxygenation for refractory cardiac arrest or MCS for sepsis-related cardiovascular failure were excluded. PSP level was measured at time of MCS implantation (T0) and then daily for five days (T1-T5) or until death or ICU discharge, whichever came first. Blood samples were analyzed with point-of-care abioSCOPE[®] device. Outcome data included occurrence of sepsis, length of ICU and hospital stay, and mortality.

Results: a total of 15 patients (median age 70 [65-74]) were enrolled. The majority of patients hadpost-cardiotomy shock (7 [46%]) and the most frequently used MCS device was intra-aortic balloon pump (10 patients [66.7%]) (Table 1). Daily median PSP levels are presented in Table 1. Median peak PSP level was 556 (257 – 601) ng/mL. A total of 12 patients (80%) had at least one measurement > 250mg/mL (representing high risk of sepsis). Six patients (40%) developed sepsis, while in-hospital mortality was 20%. We found no significant peak PSP level > median had significantly higher risk of sepsis, longer ICU and hospital stay, and a trend towards higher need for upgrade of MCS, despite no difference in peak C-reactive protein, lactate or inotropic score (Table 1).

Conclusion: Patients with CS requiring MCS display high values of PSP during the early phase of shock. Higher PSP cutoff may be necessary to predict risk of sepsis in this setting. PSP may be a useful marker of disease severity. Future studies exploring the role of PSP in patients with CS are warranted.

Table 1. Baseline characteristics and outcome

Variable	Overall	Peak PSP < median	Peak PSP > median	p-
	(N=15)	(N= 8)	(N=7)	value
Age, years – median (IQR)	70 (65-74)	70 (60 – 73)	69 (66 - 74)	0.99
Female sex – no. (%)	3 (20%)	2 (25%)	1 (14.3%)	0.55
Cardiogenic shock cause – no. (%)				0.42
Post-cardiotomy	7 (46.7%)	5 (62.5%)	2 (28.6%)	
Arrhythmia	2 (13.3%)	1 (12.5%)	1 (14.3%)	
AMI/ischemia	2 (13.3%)	0 (0%)	2 (28.6%)	
Mechanical complications of AMI	4 (26.7%)	2 (25%)	2 (28.6%)	
MCS at inclusion – no. (%)				0.45
➢ IABP	10 (66.7%)	6 (75%)	4 (57.1%)	
VA-ECMO+IABP	3 (20%)	2 (25%)	1 (14.3%)	
Impella	2 (13.3%)	0 (0%)	2 (28.6%)	
SOFA at ICU admission – median (IQR)	7 (6-7)	6 (6 – 7)	7 (6 – 7)	0.70
APACHE II at ICU admission – median (IQR)	13 (9-14)	13 (9 – 14)	12 (10 – 13)	0.85
PSP, T0, ng/mL – median (IQR)	141 (62.5 – 222)	97.5 (38 – 175)	390 (179 – 601)	0.09
PSP, T1, ng/mL – median (IQR)	206 (142 – 456)	144 (82 – 216)	251 (161 – 500)	0.06
PSP, T2, ng/mL – median (IQR)	280 (154 – 601)	154 (93 – 257)	601 (335 - 601)	0.005
PSP, T3, ng/mL – median (IQR)	326 (218 – 601)	218 (157 – 257)	545 (409 – 601)	0.009
PSP, T4, ng/mL – median (IQR)	441 (221 – 544)	210 (199 – 225)	532 (659 – 301)	0.02
PSP, T5, ng/mL – median (IQR)	458 (240 – 583)	310 8171 – 371)	601 (565 – 601)	0.02
PSP > 250 ng/mL at any time – no. (%)	12 (80%)	5 (62.5%)	7 (100%)	0.12
Peak PSP, ng/mL – median (IQR)	556 (257 – 601)	308 (195 – 390)	601 (601 - 601)	< 0.001
Peak CRP, mg/L– median (IQR)	188.3 (137.6 – 267.2)	168.6 (117.6 – 219.4)	223.8 (173.0 - 310.0)	0.24
Peak VIS – median (IQR)	18 (16 – 23)	20 (16 – 40)	17.5 (15 – 23)	0.51
Peak lactate, mmol/L– median (IQR)	6.7 (2.8 – 8.0)	6.9 (5.5 – 9.0)	6.5 (1.9 – 8)	0.40
Clinical outcomes				
Upgrade MCS – no. (%)	3 (20%)	0 (0%)	3 (42.8%)	0.07
Weaning from MCS – no. (%)	13 (86.7%)	7 (87.5%)	6 (85.7%)	0.73
Sepsis at any time – no. (%)	6 (40%)	1 (12.5%)	5 (71.4%)	0.035
In-hospital mortality – no. (%)	3 (20%)	1 (12.5%)	2 (28.6%)	0.44
ICU stay, days – median (IQR)	13 (7-22)	7.5 (3 – 12)	22 (15 – 25)	0.007
o In survivors	14 (7.5-21)	8 (3 - 13)	22 (20 -24)	0.005
Hospital stay, days – median (IQR)	27 (9-37)	11 (6 – 21)	30 (28 – 49)	0.015
o In survivors	24.5 (11-33.5)	13 (6 – 27)	30 (28 – 37)	0.061

AMI: acute myocardial infarction; CRP: C-reactive protein; IABP: intra-aortic balloon pump; ICU: intensive care unit; IQR: interquartile range; MCS: mechanical circulatory support; PSP: pancreatic stone protein; VA-ECMO: venoarterial extracorporeal membrane oxygenation; VIS: vasoactive-inotropic score

The role of Pancreatic Stone Protein as an early biomarker of sepsis in Cardiac Surgery and Heart Transplantation

P. Raimondo¹, F. De Palma¹, M. Fiorentino², G. Rubino¹, S. Lenoci¹, A. Stripoli¹, A. Armenise¹, M. A. Villani¹, G. Colantuono¹, G. Fiore¹, L. Gesualdo², S. Grasso¹

¹ Department of Emergency and Organ Transplantation, Cardiothoracic Surgery ICU, University of Bari "Aldo Moro", Bari, Italy

² Department of Emergency and Organ Transplantation, Nephrology, Dialysis and Transplantation Unit, University of Bari "Aldo Moro", Bari, Italy

Background and Aim: Cardiac surgery and heart transplantation are conditions able to stimulate the inflammatory cascade, affecting patients' status and outcome. Early identification and appropriate management after the development of this inflammatory response improve outcomes. In recent years, several biomarkers have been studied to early identify sepsis and discriminate inflammatory conditions. We want to evaluate if Pancreatic Stone Protein (PSP) - a protein producedduring early stages of the development of sepsis - can predict perioperative infection in cardiac surgery.

Methods: This is a monocentric experimental study conducted in our adult cardiothoracic surgery Intensive Care Unit (ICU) at the Teaching Hospital "Policlinico di Bari" in first part of 2022. After theadmission, all patients undergoing cardiac surgery were approached by a resident anesthesiologist, their compliance with inclusion criteria [ASA < 4; age > 18] and exclusion criteria (inability or unwillingness to give informed consent, ASA > 5) was checked and the Informed Consent was obtained from all patients or their relatives. In perioperative period, baseline blood samples were taken for analysis of PSP, CRP, WBC and other routine parameters. All other data were collected in a dedicated database and evaluated using R Studio.

Results: For this brief case series, we enrolled 18 patients: 3 patients who received heart transplantation, 6 patients scheduled for myocardial revascularization, 4 patients with endocarditis, 2 patients with aortic dissection and 3 patients scheduled for valve replacement. Median age of participants was 63 years (IQR 53-72), with a predominance of male patients (15/18). All laboratorydata was evaluated in the study population in Figure 1.

Conclusions: In our brief case series, PSP early confirms the postoperative inflammatory reaction asFig 1 shows in the comparison with WBC. The PSP confirms the trend of the other validated biomarkers but using an easily bed side point-of-care test. High level (> 200 ng/ml) were developedduring important inflammatory response after cardiac surgery or for risk factor (es. back in ICU or end-stage renal disease undergoing dialysis). Further research is needed about sensibility, specify and timing, but PSP can become an early marker for postoperative sepsis.





MEAN	WBC	PCR	РСТ	PRESEPSIN	IL6	PSP
PREOP	7,7744	12,8389	0,275	286	33,4	118,07
DAY1	12,2983	85,45	9,3043	1129,1	226,98	209,29
DAY4	10,2553	157,51	3,345	1202,5	25,5	264,1
DAY7	10,2911	94,6	4,33	5388,8	13,6	235,2
DAY10	9,652	273,56	1,063	2111,7		87
DIM	9,7083	66,73	0,075			108

Pancreatic Stone Protein (PSP) predictive perioperative SEPSIS in critically ill patients undergoing cardiac surgery

M. Fiorentino^{*1}, P. Raimondo^{*2}, F. De Palma², S. Carparelli¹, A. Stasi¹, R. Franzin¹, A. Schirinzi³, F. Di Serio³, T. Bottio², A. D. Milano², S. Grasso², L. Gesualdo¹

¹Department of Emergency and Organ Transplantation, Nephrology, Dialysis and TransplantationUnit, University of Bari "Aldo Moro", Bari, Italy

²Department of Emergency and Organ Transplantation, Cardiothoracic Surgery ICU, University ofBari "Aldo Moro", Bari, Italy

³Clinic Pathology Unit, University Hospital of Bari, Bari

* These authors contributed equally to this work

Introduction: Sepsis represents a life-threatening organ dysfunction caused by a dysregulated host response to infection. Pancreatic Stone Protein (PSP) is a protein produced during early stages of sepsis, so it may improve early identification and management of sepsis in criticallypatients. Here, we analyze the use of PSP in predicting the onset of sepsis in patients undergoing cardiac surgery.

Methods: This case series included 18 patients undergoing cardiac surgery between February and May 2022. Blood samples atadmission were taken for analysis of PSP and the results were compared to other inflammatory markers at several time points (the day after and 4 days after the surgical procedure). The primary goal is to assess trends in inflammatory markers, as well as the ability of PSP in predicting mortality and the development of organ dysfunction.

Results: We included 3 patients who received heart transplantation, 6 patients scheduled for myocardial revascularization, 4 patients with endocarditis, 2 patients with aortic dissection and 3 patients scheduled for valve replacement. PSP, CRP and WBC were evaluated and in **Figure 1** data were reported for each case. PSP was able to early detect patients at high risk for developing postoperative sepsis. PSP showed elevated levels (> 200 ng/ml) before cardiac surgery in only 2 patients, both were characterized by organ dysfunction withthe need of CRRT (one patient was on chronic hemodialysis, while the other was on CRRT before kidney transplantation); however, they had a persistence of high PSP at the two determinations after surgery, indeed they were readmitted in ICU due to sepsis complication after cardiac surgery. A third patient with elevated PSP presented sepsis and severe neurological complications. Conversely, in the other patients PSP were not significant: they presented stable values in the postoperative period and didn't present sepsis complications and ICU readmission. Both CRP and WBC were able to discriminate these 2 patients; CRP values increased later compared to PSP (in the fourth postoperative day), while WBCs count showed unspecific trend during the study period.

Conclusion: In this case series, we reported the application of PSP in predicting the onset of postoperative sepsis, as well as organ dysfunction and prolonged ICU length of stay and/or readmission.

Figure 1. Trends of PSP concentration (ng/ml) in the study cohort, compared to C-reactiveprotein (CRP) and White Blood Cells (WBCs)



AUTOIMMUNE DISORDERS

A76

Cascade Filtration in Stiff Person Syndrome: case report

A. Ostuni¹, M. Colonna¹, C. Battista¹, A. Tullo¹, C. Citarella¹
¹UO Medicina Trasfusionale, AOU Consorziale Policlinico di Bari, Bari, Italy

Background: Stiff-person syndrome (SPS) is a rare acquired, autoimmune neurological disorder characterized by fluctuating muscle rigidity as well as increased sensitivity to noise, touch and emotional distress which can result in muscle spasms. Autoantibodies reactive to 65 kDa glutamic acid decarboxylase (GAD65), the enzyme responsible for the synthesis of γ -aminobutyric acid (GABA) in the brain and pancreatic islet cells, are present in the serum in up to 90% of patients withSPS. These antibodies block GABA synthesis. The paraneoplastic form of the syndrome is associated with autoantibodies to the 128 kDa synaptic protein amphiphysin.

Treatment consists of immune therapies, anti-anxiety medications, muscle relaxants, anticonvulsants and pain relievers. Therapeutic Plasma Exchange (TPE) can deplete normal immunoglobulins. TPE may be considered, in addition to standard drug therapy, if the patient is unresponsive to conventional therapy. Cascade Filtration (CF) is a technique used for the selective removal of specific molecules from the plasma. CF consists of a first separation of the plasma from the blood through a cell-separator, then the plasma is conveyed through a special equipment into a fractionator filter, which remove the target molecules. Small molecular weight components such as albumin, return to the patient.

Methods: We present the case of 55-year-old female patient with SPS. The patient was treated with47 standard plasma exchange procedures from 2019 to 2021; then, he had 6 CF procedures, using the Evaflux 2A20 filter; with the aim of removing from the blood the anti-GAD antibodies that are excessively produced due to the pathology.

Results: Blood therapy sessions were conducted every 21 days and she was treated of at least one blood volume (approximately 3.5L). The anti-GAD antibody titer (90-115 U/ml) remained constant during treatment with standard procedures, it showed a slight reduction (79 U/ml) after the 6 procedures with CF. All procedures performed were safe and had no adverse effects on the patient. The patient's outcome was positive.

Conclusion: The CF treatment seems to reduce the concentration of anti-GAD antibodies from the blood, was simple and safe, allowing an improvement in the patient's quality of life and a benefit on the costs of the procedures as it does not use albumin.

Cascade Filtration as a rescue therapy for Autoimmune hemolytic Anemia: A Case Report

L. Abbruzzese¹, M. Caputo¹, G. Greco², R. Vitali¹, G. Circhetta¹, V. Pavone² ¹Transfusion Medicine Service, Card. G. Panico" Hospital, Tricase, Italy

²Hematology Unit, Card. G. Panico" Hospital, Tricase, Italy

Background: Anemia is a condition in which haemoglobin (Hb) concentration and red blood cell (RBC) numbers in the blood are lower than normal and insufficient to provide adequate oxygenation to the body's tissues. Autoimmune haemolytic anemia (AIHA) is an acquired autoimmune disorder characterized by the development of antibodies directed against antigens on autologous erythrocytes.

Case Presentation: We present the case of a 63-year-old man with AIHA (positive direct Coombs test: IgG antibody), dyserythropoiesis and piastrinopenia with a blood count of 8.6 g/d Hb, 8530/mmc RBC and 18000/mmc platelets. Steroid therapy was started, but with poor tolerability; so, the patient underwent splenectomy with subsequent recovery of platelet count, but no response in increasing Hb. Then cyclosporine and erythropoietin therapy were started, but he underwent a new hospitalization for worsening anaemia with 4,8 g/d Hb and 19920/mmc RBC. He was treated with immunoglobulin infusion and weekly rituximab therapy. Following rituximab therapy, a slight improvement in blood crashes was noted. Afterwards worsening of anaemia, he was treated with Urbason; then following no therapeutic effect, with Endoxan and cyclosporine. He was also subjected to Intravenous immunoglobulin (IVIg). Subsequently the lack of response to all pharmacological treatments and the consequent worsening of the clinical picture (Hb 4.1 g/d, RBC 16700 /mmc), it was decided to perform therapeutic plasmapheresis cycles, as a rescue therapy, for a total of 5 cycle of Cascade Filtration (CF) with the fractionator filter Evaflux 3A20.

Results: In the first week was performed 2 treatments of CF, 1 volume of plasma was processed in each one. Subsequently, one procedure per week was performed. A final maintenance session was done more than one month later. After the last cycle of plasmapheresis an improvement in blood crasis values was found with 14,3 g/d Hb and 14150 mmc RBC (Figure 1).

Conclusion: CF can be effective in immune-mediated diseases by clearing circulating immune complexes and other disease mediators. In this case CF was the only therapy shown to be effective in recovering haemoglobin values and consequently discharging the patient, improving the quality of life.



Figure 1: HB trend

Cascade Filtration: a successful treatment of Thrombotic Thrombocytopenic Purpura

L. Abbruzzese¹, M. Caputo¹, A. Mele², R. Vitali¹, F. Carbone¹, V. Pavone² ¹Transfusion Medicine Service, Card. G. Panico" Hospital, Tricase, Italy ²Hematology Unit, Card. G. Panico" Hospital, Tricase, Italy

Background: Thrombotic thrombocytopenic purpura (TTP) is a rare, often fatal blood disorder characterized by thrombocytopenia and microangiopathic haemolytic anaemia. Most patients have immune mediated TTP, that is associated with a deficiency of plasma ADAMTS13 enzyme activity. The mainstay of treatment is therapeutic plasma exchange (TPE) to remove the causative antibody.

Case Presentation: We describe a case of a 60-year-old male presented to our hospital for stroke suspicion associated to dysesthesia and strength deficits. The encephalic CT scan revealed a small area of hypodensity in the cortico-subcortical area of the right middle frontal gyrus, followed by an MRI scan with a positive result for small ischemic lesions in the acute phase. On the basis of hematochemical results and morphological examination of the peripheral venous blood smear showing the presence of schistocytes, TTP was suspected and confirmed by severe enzymatic deficiency of ADAMTS 13 (3%). Treatment with daily TPE in combination with steroids was started, with improvement of blood crashes and regression of neurological symptoms.

Results: A total of 8 sessions of plasmapheresis were performed and the patient was discharged. Two days after he returned to emergency room following strength deficit with paraesthesia and disturbance in speech production. 3 sessions of TPE were performed, but in the fourth session he developed an allergic reaction, which was thought to be due to caplacizumab, so a fifth session of TPE was done with a new allergic reaction. So, it was decided to continue therapy with Cascade Filtration (CF) directly connected with cell-separator system. Plasma obtained by centrifugation is conveyed into a fractionator filter, Evaflux 3A20, which allows a semi-selective plasma purification and removes autoantibodies responsible for the pathophysiology. After purification the plasma returns to the patient, avoiding plasma donor infusion and consequent possible adverse reactions. A total of 8 sessions of CF were performed with no adverse reactions. Treatment with CF continued on an outpatient basis for another 4 sessions.



PLT Trend

Figure 1: PLT Trend

Conclusions: CF has proven to be effective as TPE, then we conclude that it can be considered as a safe and valid alternative therapy to TPE for the treatment of TTP.

Effects of Rheopheresis on haemodialyzed patients with Peripheral Artery Disease (PAD)

M. Martone¹, D. Berbecar¹, E. Boer¹, M. Bosco¹, P. Mattei¹, N. Milutinovic¹ ¹Complex Operative Unit of Nephrology and Dialysis, Presidio Ospedaliero di Gorizia-Monfalcone, Italy

Background: Peripheral Artery Disease (PAD) is a clinical condition characterised by obstructive lesions of thearteries with hypoperfusion of the lower limbs. The aetiology is mostly atherosclerotic, the worldwide prevalence varies from 4 to 12% and is higher in haemodialyzed patients with major clinical complications. This clinical condition often leads to skin ulcers occurrence and consequent lower-extremity amputations. Unfortunately, current therapeutic strategies do not always provide real effectiveness in the treatment and care of PAD. Double Filtration Plasmapheresis (DFPP) is an alternative extracorporeal treatment aimed to improve microcirculatory disorders thanks to the elimination from blood of specific macromolecules responsible for the higher plasma viscosity.

Methods: We evaluated the effect of DFPP in five haemodialyzed patients affected by severe PAD (Fontainestage IV) with involvement of micro or macrocirculation, non-responder to the standard care and surgical revascularization. DFPP was carried out using the automatic system Plasmapher/Apherlungs: plasma obtained with a plasmafilter is conveyed into the fractionator filter Evaflux 5A20, which allows a semi- selective plasma purification from high molecular weight proteins (such as LDL-cholesterol, fibrinogen, a2- macroglobulin and fibronectin), resulting in a lowered blood plasma viscosity and an improvement of the microcirculation. Treatments were performed twice a week for the first two weeks and once a week for the consecutive eight weeks, for a total of 12 DFPP treatments per patient. One plasma volume was treated in the first four sessions, then one and a half for the last eight sessions.

Results: In most of the treated patients we observed a stabilization of laboratory parameters associated to a persistence of low values of inflammation and blood plasma viscosity. It has not been possible to measure the decrease of fibrinogen and a2-macroglobulin. Nevertheless, three to five patients referred an improvement of clinical symptoms at the end of the cycle. Furthermore, we observed a higher clinical benefitin patients with disorders of the microcirculation instead of the principal arteries.

Conclusion: We showed that DFPP is an effective and safe treatment for patients with microcirculatory disorders caused by high molecular weight proteins accumulation, who show inadequate response to the pharmacological and surgical therapies.

A80 Leukocytapheresis in patient affected Ulcerative Colitis refractory to pharmacotherapy

E. R. Testa¹, A. Masotti¹, P. Valeri¹, L. Bet ¹, K. Piccinin¹, M. Simonella¹, P. Pupulin¹, V. Brunetta¹, A. Bontadini¹ ¹Blood Transfusion Department, Santa Maria degli Angeli Hospital, ASFO, Pordenone (PN), Italy

Background/Aims: Leukocytoapheresis in patients suffering from Chronic Inflammatory Bowel Diseases (IBD): Crohn's disease (CD) and Ulcerative Colitis (UC), are chronic inflammatory disorders, impairing quality of life. IBD inflammation induced by activation of inflammatory markers, increased leukocytes levels, into the inflammatory cascade. Pharmacotherapy is based on steroids-immunosoppressive, with inadequate response or intolerance to conventional therapy. The topic of these case reports is to present experiences to develop possible evidence and support the indications of Leukocytoapheresis therapy. In addition, to support existing studies about the combination of Leukocyteapheresis and Vedolizumab in patients affected from Ulcerative Colitis, refractory to medical therapy.

Methods: We report a patient of a 53-year-old woman affected steroid-dependent Ulcerative Colitis (UC), diagnosed in 2009, in clinical exacerbation phase. Between 2010 and 2011, treatments with Azathioprine, Ciclosporin and Infliximab were unsuccessful. The gastroenterologist proposal Vedolizumab, but the patient would prefer to first repeat cycles of Leukocyteapheresis, performed in 2011 with success clinical response. In 2021 Leukocyteapheresis five procedures are planned to be performed weekly at our Departement, carriedout with a hydrophilic polysulfone sorbent cartridge (Leukocyte Adsorber, Leucapher). The possible protocol will evaluate a maintenance treatment, with a monthly interval procedure for 6-12 months, based on the clinical response. 1800 ml of blood were processed. ACD 160 ml was used as the anticoagulant and after to continue with heparin sodium 9000 UI. None immediate adverse events.

Results: Blood chemicals tests pre-Leukocyteapheresis: hemoglobin 14 g/dL, platelets normal count. PCR 0.12. Iron, Transferrin, Ferritin normal. After the third procedure: relief of symptoms (reduction in the number of 5 to 2 stools/day, abdominal pain and rectal bleeding, Mayo score 2), VES negative, WBC 10.56 10* 3/mcL, fecal calprotectin 108mg. Control colonoscopy, after Leukocyteapheresis cycle completed, shows a picture of the intestinal mucosa in remission, it appears regular. Symptoms restart and she continues Vedolizumab (Entyvio) 300 mg at 2-4-8 weeks to stabilize.

Conclusion: We suggest a possible adjuvant role of Leukocyteapheresis in combination therapy with vedolizumab. The adjunct of apheresis to biologics could represent an opportunity in patients with UC no responder to biologics, for to try to reduce the need of colectomy.

Efficacy and safety of leukocytapheresis adsorber device LA25: experience with 10 patients

A. Ferronato¹, M. Rigno², K. I. Rodriguez-Castro¹, L. Brozzi¹, G. Errigo², M. Castelli², M. Franchini³, G.Baldassarre¹

¹ Digestive Endoscopy Unit, PO Alto Vicentino, AULSS 7 Pedemontana, Santorso (VI), Italy

² Therapeutic Apheresis Unit, Ospedale San Bortolo, AULSS 8 Berica, Vicenza (VI), Italy

³ Aferetica s.r.l., San Giovanni in Persiceto (BO), Italy

Background/Aims: Inflammatory Bowel Diseases (IBD), i.e. Crohn's disease (CD) and Ulcerative Colitis (UC), are chronic inflammatory disorders, impairing both digestive function and patient quality of life. Increased leukocytes levels are typical, since, once migrated from the peripheral blood to the intestinal wall, they participate into the inflammatory cascade and cause bowel damage. Therapeutic strategies are essentially based on immunosuppressive and anti-inflammatory drugs. In recent years, selective depletion of myeloid lineage leucocytes by adsorptive leukocytapheresis have been applied as a non-pharmacologic treatment strategy. LA25 aphaeresis (Leukocyte Adsorber 25) is an effective and safe method for IBD patients who showed inadequate response or intolerance to conventional therapy.

Methods: Between August 2015 and January 2021, 17 patients (10 female and 7 male, 2 CD and 15 UC, average age 48,5 years) have been treated with LA25 leukocytapheresis. 7 additional patients were excluded due to contraindication for the aphaeretic treatment. The indication for leukocytapheresis were: bridge therapy (1) active disease (9), refractory disease (5) and oncological comorbidities (2). Overall, 8 patients hadsome contraindication to conventional IBD therapies.

All patients received 5 weekly apheresis session using LA25, each one at 30 mL/min flow rate for 60 min, witha final volume of 1.8 L of peripheral venous blood processed per session. 10 patients received 1 monthly maintenance apheresis. Concurrent therapies included mesalamine (9) and steroids (7), while 2 patients were in thiopurines. We evaluated patients at the beginning of therapy, then after 3 and 12 months.

Results: After apheresis treatment, clinical disease activity indexes, for UC (Mayo partial score – MPS) decreased from moderate to mild (MPS from 4,9 to 2,5). 10 patients started maintenance protocol with monthly apheresis. After 3 months, average Blood parameters levels (leukocyte, hemoglobin, MCV, platelets, ERS and CRP) did not changed, while fecal calprotectin (FC) reduced from median 527 to 320 in responders, and 3 patients needed to start therapy with biologics. After 12 month, 8 patients (1 CD, 7 UC, 5 in the maintenance protocol) maintained clinical remission, 7 patients achieved an improvement of endoscopic activity, all patients withdrew steroids, with median FC 117. There were no adverse side effects documented with these extracorporeal circulation procedures. **Conclusion:** Leukocytapheresis using LA25 is safe and effective in terms of clinical and endoscopic response in IBD patients, also in the maintenance protocols. Due to its safety profile, it can be indicated in patients with high risk of complications using standard therapy or biologics.

Possible therapies in patients with Ulcerative Colitis refractory to anti-TNFα: Leukocytapheresis and new biologics drug

A. Ferronato¹, M. Rigno², K. I. Rodriguez-Castro¹, L. Brozzi¹, G. Errigo², M. Castelli², M. Franchini³, G.Baldassarre¹

¹ Digestive Endoscopy Unit, PO Alto Vicentino, AULSS 7 Pedemontana, Santorso (VI), Italy

² Theraeutic Apheresis Unit, Ospedale San Bortolo, AULSS 8 Berica, Vicenza (VI), Italy

³ Aferetica s.r.l., Bologna, Italy

Background: Various therapeutic advances have led to a paradigm shift in the clinical management of patients with inflammatory bowel diseases (IBD). Recently the $\alpha 4\beta 7$ integrin blocker - vedolizumab and interleukin IL-12 and IL-23 blocker - ustekinumab have been introduced for clinical IBD therapy as a second choice to anti TNF- α . Recently guidelines have included these new biologics as a therapeutic choice in all patients in whom an anti-TNF-alpha cannot be used. Moreover, also blood purification therapy, like Leukocytapheresis, is a potential option for the treatment for the IBD patients. The aim of this study is to assess leukocytapheresis and if it can still have a use in selected ulcerative colitis (UC) patient also comparingit with new biologics therapies.

Methods: From February 2019 to November 2021 15 patients with UC were evaluated: 8 patients treated with leukocytapheresis (group 1) and 7 with new biological drug: Vedolizumab (group 2). All patients had contraindications to anti-TNF-alpha use. We evaluated patients by clinical disease activity indexes and blood parameters levels at the beginning of therapy, then after 3 and 12 months.

Results: In the first group after 12 months of follow up (FU) 5 patients achieved clinical remission with 3 patients who received maintenance therapy (12 session for patient). Instead, 3 patients during the FU have started biological therapy (2 adalimumab and 1 vedolizumab). In the second group after 12 months of FU 3 patients achieved clinical remission. In table 1 is shown the clinical disease activity for each patient and in the figure 1 is shows the trend of Mayo partial score (MPS). As shown in figure 1, the development of the average blood parameters is almost the same in the two groups. In the first group after 12 months average blood parameters levels slightly reduced: leukocyte from 6,1 to 5,8 10³/mm³; erythrocyte sedimentation rate(ESR) from 21,1 to 15,6 mm/h; platelets (PLT) from 286,6 to 269,5 10³/mm³. While fecal calprotectin (FC) reduced from median 579,1 to 208,5 mg/kg. In the second group after 12 months average blood parameters:leukocyte from 8,7 to 7,7 10³/mm³; erythrocyte sedimentation rate (ESR) from 2,2 to 45,5 mm/h; platelets(PLT) from 320,8 to 266,3 10³/mm³. While faecal calprotectin (FC) reduced from median 586,2 to 257,2 mg/kg.

Conclusion: From this first clinical experience apheresis appears to be effective as second-choice biological drugs. This type of therapy should not be abandoned, but should be investigated further with othercomparative study. Could also be evaluated a synergistic approach between these two therapies.

a)		Clinical disease activity				Clinical disease activity		
	Patient	T0 FU 3		FU 12	Patient	то	FU 3	FU 12
	1	mild	remission	remission	9	severe	moderate	moderate
	2	mild	remission	remission	12	moderate	remission	remission
	3	moderate	mild	remission	13	moderate	remission	remission
	4	moderate	moderate	Vedolizumab	14	moderate	mild	mild
	5	mild	remission	remission	15	mild	remission	mild
	6	moderate	mild	adalimumab	16	moderate	mild	moderate
	7	mild	mild	adalimumab	19	mild	remission	remission
	8	moderate	remission	remission				



Figure 1: a) Clinical disease activity, in red patient who received leukocytoapheresis, in yellow who received maintenance therapy and in blue who have biological therapy. B) trend of average MPS and blood values.