Blood Purification

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Blood Purification

1

Long Term Renal Outcomes and Mortality following Persistent Renal Injury among Myocardial Infarction Patients Treated by Primary Percutaneous Intervention

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Background: Limited data are present on persistent renal impairment following acute kidney injury (AKI) and long term renal outcomes among ST elevation myocardial infarction (STEMI) patients. We evaluated the incidence and prognostic implications of acute kidney disease (AKD), reduced kidney function for the duration of between 7 and 90 days after exposure to an AKI initiating event, as well as long term renal outcomes among STEMI patients undergoing primary percutaneous coronary intervention who developed AKI.

Methods: We retrospectively studied 225 consecutive STEMI patients who developed AKI. Patients were assessed for the occurrence of AKD and long term renal outcomes based on serum creatinine levels measured at 7 days/hospital discharge and within 90–180 days of renal insult. Mortality was assessed at 90 days and over a period of 1271 ± 903 days (range 2–2130) following renal insult.

Results: Progression to AKD occurred in 81/225 patients (36%) and was associated with higher 90 day and long term mortality ($p < 0.001$). Normalization of serum creatinine to a level equal/lower than hospital admission level at 90 days from renal insult occurred in 41% patients with AKD. New chronic kidney disease (CKD) was diagnosed in 24%, while 35% demonstrated progression of preexisting CKD at 90 days from renal insult. In contrast, only 7% of patients without AKD had progression of preexisting CKD, while in the rest serum creatinine remained stable.

Conclusion: Progression to AKD following an acute renal insult in STEMI is frequent and associated with adverse long term renal outcomes.

2

The Incidence Prognosis and Risk Factors of Cognitive Impairment in Maintenance Hemodialysis Patients: A Pilot Prospective Study

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Objective: To investigate the incidence and the prognosis of cognitive impairment (CI) and to find out the risk factors associated with the outcome for better understanding and preventing CI in maintenance hemodialysis (MHD) patients.

Method: Enrolled the patients who meet the criteria as below: maintenance hemodialysis patients (≥3 month) in Renji Hospital, Shanghai Jiao Tong University School of Medicine before Jul. 2014, ≥18 years old and can carry on the cognitive function score (MoCA) of voluntary cooperation. According to the score of MoCA, all enrolled patients were divided into two groups: CI (MoCA <26) and non-CI (MoCA ≥26). The follow-up period was 3 years. The incidence, demography data, medical history, hemodialysis data, laboratory examination and prognosis of CI in hemodialysis patients were prospectively compared and analyzed. Logistic regression analysis was used to investigate the risk factors of CI. Kaplan-Meier survival curve was used for survival analysis.

Results: 219 MHD patients were enrolled. The incidence of CI in MHD patients was 51.6%. The ratio of male to female was 1.46:1. Age was (60.07 ± 12.44) years old and dialysis vintage was 100.79 ± 70.23 month. Compare with non-CI group (n = 106), urine volume, post-dialysis systolic pressure, Pre-dialysis diastolic pressure, post-dialysis diastolic pressure, platelet and spKt/V were lower in CI group (n = 113). The percentage of education status (<12 years) and history of diabetes were higher in CI group than in non-CI group. Multivariate logistic regression analysis showed that education status (<12 years) [Odds Ratio (OR) = 3.428], post-dialysis diastolic pressure (<73 mm Hg) (OR = 2.234) and Kt/V (<1.72) (OR = 1.982) were independent risk factors for CI in MHD patients. During the follow-up period, a total of 20 patients died (9.13%). Among them there were 15 cases (13.2%) in CI group and 5 cases (4.72) in non-CI group ($p < 0.05$). In the CI group, the main cause of death was cardiovascular events. The Kaplan-Meier survival curve analysis showed that the survival rate of patients with CI was lower than that of non-CI group in MHD patients during 3 years follow-up ($p = 0.046$).

Conclusions: CI was one of the most common complications in MHD patients. The mortality was high in patients who suffered

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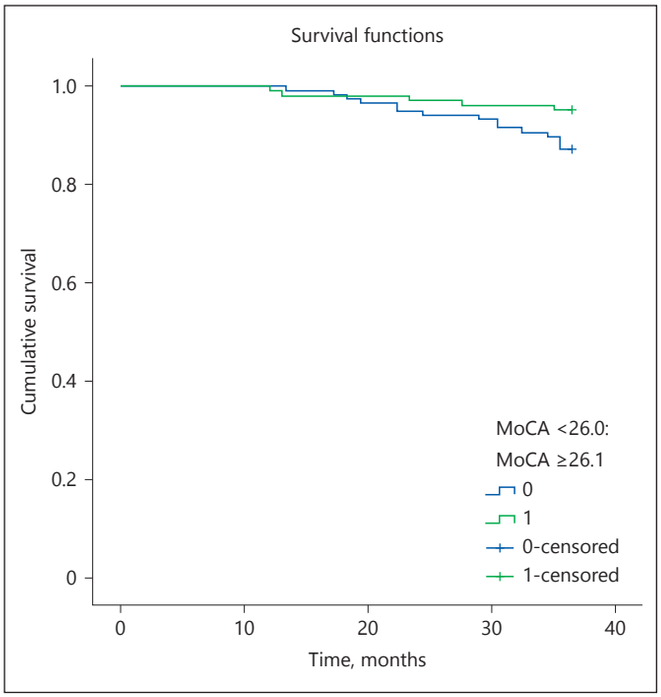

. 1. The Kaplan-Meier patient survival analysis (for Abstract no 2).

CI. Education status (<12 years), post-dialysis diastolic pressure (<73 mm Hg) and Kt/V (<1.72) were independent risk factors for CI in MHD patients.

3

Peritoneal Dialysis as an Option for Unplanned Dialysis Initiation in Patients with End-Stage Renal Disease and Diabetes Mellitus

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Aims: This study aimed to compare the short-term complications and long-term prognosis between urgent-start peritoneal dialysis (PD) and hemodialysis (HD), and explore the safety and feasibility of PD in ESRD patients with diabetes.

Methods: This retrospective study enrolled ESRD patients with diabetes who were not already receiving dialysis, and who required dialysis initiation <2 weeks after catheter placement but did not require emergent dialysis at a single center from January 2011 to December 2014. Short-term (30-day) dialysis-related complications and patient survival were compared between patients receiving PD and HD.

Results: 80 patients were included in the study, including 50 (62.5%) who underwent PD. Patients in the PD group had a significantly lower incidence of chronic heart failure, lower BNP, lower corrected serum calcium, and higher PTH, but there were no significant differences in gender, age, prevalence of primary renal diseases, and other laboratory characteristics between the groups. The incidence of dialysis-related complications (3 [6.0%] vs 8 [26.6%], p = 0.024) during the first 30 days was significantly lower in PD patients. Logistic regression identified urgent-start HD as an independent risk factor for dialysis-related complications compared with urgent-start PD (OR 4.773 [1.114–20.446], p = 0.035). The 6-, 12-, and 36-month patient survival rates in the PD and HD groups were 95.9% vs 90.9%, 85.4% vs 70.1%, and 72.5% vs 40.5%, respectively. The patient survival rate was higher in the PD group compared with the HD group according to Kaplan–Meier analysis (log-rank = 5.582, p = 0.018). Multivariate Cox modeling analysis identified urgent-start HD and serum potassium as independent risk factors for patient survival (OR 2.818 [1.082–7.337], p = 0.034).

Conclusions: PD may be acceptable, safe, and feasible for urgent-start dialysis in ESRD patients with diabetes.

4

Feasibility of Urgent-Start Peritoneal Dialysis in ESRD Patients

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Aims: Several studies have suggested that urgent-start peritoneal dialysis (PD) is a feasible alternative to hemodialysis (HD) in patients with end-stage renal disease (ESRD), but the impact of the dialysis modality on outcome, especially on short-term complications, in urgent-start dialysis has not been directly evaluated.

Methods: In this retrospective study, ESRD patients who were not already receiving dialysis, and who required dialysis initiation <2 weeks after catheter placement but did not require emergent dialysis at a single center from January 2011 to December 2014 were included. Patients were grouped according to their dialysis modality. Each patient was followed for at least 30 days after catheter insertion (until January 2016). Dialysis-related complications and patient survival were compared between the two groups.

Reults: Our study enrolled 300 patients (50.6% male), of whom 156 and 144 patients were in the PD and HD groups, respectively. Compared with HD patients, PD patients were elder, and had more diabetes, less heart failure, lower levels of BNP and higher levels of Hb. There were no significant differences in terms of gender, use of steroids, prevalence of diabetic nephropathy, prevalence of other comorbidities (hypertension, cerebrovascular diseases and malignancies) and other laboratory characteristics between the two groups. The incidence of dialysis-related complications during the first 30 days was significantly higher in HD than PD patients (25 [17.4%] vs 14 [9.0%, p = 0.031). HD patients had a significantly higher probability of bacteremia compared to PD

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patients (13 [9.0%] vs 3 [1.9%], p = 0.006). HD was an independent predictor of short-term dialysis-related complications (OR 2.131 [1.060–4.283], p = 0.034). The 3-, 6-, 12-, 24-, and 36-month survival rates of patients undergoing PD and HD were 98.1% vs. 92.9%, 96.1% vs. 92.1%, 91.2% vs. 85.7%, 86.5% vs. 74.1% and 81.9% vs. 66.8%, respectively. The patient survival rate was higher in the PD group compared with the HD group according to Kaplan–Meier analysis (p = 0.023). Multivariate Cox modeling analysis identified urgent-start HD as independent risk factors for patient survival (OR 2.220 [1.299–3.792], p = 0.004).

Conclusion: In an experienced center, PD is a safe and feasible dialysis alternative to HD for ESRD patients with an urgent need for dialysis.

5

Description of Echocardiographic Parameters in ICU Patients Undergoing CRRT

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Background: Echocardiographic parameters have been used to predict outcomes in specific ICU patient populations. However, echocardiographic parameters have not been defined in ICU patients undergoing continuous renal replacement therapy (CRRT).

Methods: Historical cohort study of consecutive adults admitted to the ICUs at two tertiary care hospitals from December 9, 2006, through November 13, 2015. Patients that underwent CRRT and had an echocardiogram (ECHO) done within 7 days of CRRT initiation (n = 1278) were included in the study. Echocardiographic parameters were defined by the American Society of Echocardiography criteria.

Results: Median patient age was 63 (IQR 53–73) and 515 (40%) were female. Decreased left ventricular ejection fraction (LVEF ≤45%) was noted in 32% and left ventricular diastolic dysfunction in 62%. Increased right ventricular systolic pressure (RVSP ≥40 mm Hg) was noted in 66% of patients. Right ventricular (RV) systolic dysfunction was observed in 39% and inferior vena cava (IVC) dilation in 71%. The most common valvular abnormality was tricuspid regurgitation (19%), followed by mitral regurgitation (8%). Cardiac ICU patients had a higher prevalence of most echocardiographic abnormalities: LVEF ≤45% (64%, P < 0.0001), inferior vena cava dilation (94%, P < 0.0001), RVSP ≥40 (80%, P = 0.0471), aortic regurgitation (5%, P < 0.0001), mitral regurgitation (25%, P < 0.0001) and tricuspid regurgitation (38%, P < 0.0001).

Patients with acute kidney injury (AKI) had lower prevalence of decreased LVEF ≤45% (31% vs. 39%, P = 0.0285), aortic stenosis (0.96% vs. 4%, p = 0.0036) and mitral stenosis (0.19% vs 2%, P = 0.0125) compared to patients with end-stage renal disease (ESRD). In contrast, AKI patients had higher prevalence of increased RVSP ≥40 mm Hg (68% vs. 57%, P = 0.01). The rest of the parameters including RV systolic dysfunction, tricuspid regurgitation, diastolic dysfunction, and IVC dilation were not statistically different between the two groups (AKI vs. ESRD).

Conclusions: In this study of ICU patients undergoing CRRT, the prevalence of RVSP ≥40 mm Hg (66%) was higher than what has been previously described in a medical ICU cohort (42%). This likely reflects the volume overload that is present in the majority of these CRRT patients. A higher prevalence of increased RVSP in AKI compared to ESRD patients may suggest that pulmonary hypertension can promote AKI through venous congestion and RV failure (cardiorenal syndrome). Future studies focused on using echocardiographic parameters to predict adverse outcomes (hypotension, mortality) in this patient population can identify modifiable risk factors and lead to improved patient care.

6

Radioisotopic Evaluation of Glomerular Filtration Rate (GFR) Before and After Kindey Donation: The Concept of Estimated Renal Functional Reserve (eRFR)

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Background: Because of the decrease of the nephron mass following nephrectomy, kidney donors (KD) develop a partial loss of renal function, defined as AKI (Acute Kidney Injury) according to KDIGO criteria (Clinical Practice Guideline, 2012). The recovery of renal function following AKI is mainly ascribed to the concept of renal reserve function (RFR), defined as the capacity of the kidney to increase glomerular filtration rate (GFR). However, there are only few studies on RFR in KD and a correlation with long term functional outcomes.

Aim of the Study: The aim of the present study is to analyze 40 KD renal function before nephrectomy, in the immediate postoperative period and 1 year after the surgical procedure, developing the concept of estimated RFR (eRFR) for the long term follow-up of renal function in KD.

Results: KD mean age at the time of donation was 54.8 years (min-max, 30–76), mean serum creatinine 0.71 mg/dL (0.5–0.96), eGFR (CKD-EPI) 99 mL/min/1.73 m^2 (69–119) and a radioisotope (^{51}Cr-EDTA) GFR 99.4 mL/min (78–129). The split function was evaluated by a concomitant scintigraphy using ^{99m}Tc-MAG: the mean percentage of renal function of right kidney was 48% (43–56) and left 52% (44–57), respectively. As expected, immediately after nephrectomy all KD worsened renal function: the mean percentage increase of serum creatinine was 75.6% (50–112.2%) within 72 hours post-surgery (we observed the peak of creatinine after 24–48 hours in the most of cases); most patients (33/40) developed AKI

stage 1, 7 donors stage 2 according to KDIGO criteria. Seven days after surgery, renal recovery was observed in all cases: the mean percentage increase of serum creatinine was 49.3%, significantly lower than the zenit of serum creatinine. These results suggest a potential gain of about 25% in comparison to the starting value of the right kidney. One year after nephrectomy (all left nephrectomies), we studied KD renal function (GFR) using a radioisotopic evaluation of renal function using ^{51}Cr-EDTA and we then compared it with the split radioisotope (^{51}Cr-EDTA) GFR of right kidney at the first scintigraphic evaluation. Mean GFR was 65.7 mL/min (50–87) vs. 47.6 mL/min (38.7–60.4) before donation with an average GFR increase of 18.1 mL/min (0.8–45.6) and a percentage increase of the right renal function up to 110% (mean 38.2%, min 1.4%).

Conclusions: The results of this study that radioisotopic evaluation is feasible and allows a precise determination of RFR at different time points after nephrectomy in KD. We observed a compensatory hypertrophy in all the 40 KD included in the study independently from age and co-morbidities such as elevated BMI and hypertension. The limitation of this study is the evaluation of RFR only after the decrease of the nephron mass due to donation: we now started a kidney stress test with a protein load to estimate RFR of KD before surgery with the aim of finding a correlation with radioisotpic GFR after nephrectomy.

7

Does AKIN Early Warning System Ensure Timely Initiation of CRRT?

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Introduction: In critically ill patients, acute renal failure is seen in 22–57% of patients, and timely continious renal replacement therapy directly affects mortality and chronicity processes. In our study, we aim to evaluate effects of the use of AKIN early warning system in the management of intensive care patients, regarding initiation of CRRT and mortality rates.

Material and Method: All patients admitted to the intensive care unit in the last 2 years were retrospectively screened using an automated clinical decision support system. Patients with known renal insufficiency were excluded from the study. The automated decision support system integrates an early AKI warning system based on the AKIN/RIFLE calssification. The CRRT decision was made by evaluating the clinical and laboratory status of patients with stage II-III AKIN warning. CRRT was performed with Prismaflex® device (Gambro Lundia AB, Branding & Market Com, Sweden) and Prismaflex M100® filters.

Results: A total of 1557 patients were admitted to the intensive care unit between January 1, 2016 and December 31, 2017. 1144 of these patients got stage I-II-III alerts according to AKIN classification. 272 patients (17.5%) underwent CRRT. 41 patients (15%) underwent before the implementation of the early warning system, with a mortality rate of 59%. In 146 patients (54%) CRRT was initiated within the first 24 hours after AKI alert and the group had a mortality of 55%. 85 patients (31%) received CRRT within the first week after AKI alert. The mortality of this group was 82%. The relationship between early versus late onset of CRRT and mortality is shown in ure 1.

Concluisons: It is known that accompanying acute renal failure in critically ill patient increases mortality rates. CRRT has minimal effect on haemodynamics, and the indications for its use are becoming diversified. We believe that timely initiation of CRRT in critically ill patients, while taking the clinical findings, creatine levels and urine output into consideration, may have positive effects on survival.

		HOURS											
	ALARM DISTANCE	>-120	-96	-72	-48	-24	0	24	48	72	96	>120	TOTAL
AKI	1	8	1		3	8	30	10	2	2	4	22	90
	EXITUS	5	1		1	6	12	5	1	2	3	21	57
AKI	2	3	1	1	1	1	18	5	1	3	4	9	47
	EXITUS	2	1	1	1		7	3	1	2	2	7	27
AKI	3	3	3	1	2	5	63	20	7	5	5	21	135
	EXITUS	1	1	1	1	3	44	9	6	4	3	18	91
	TOTAL	14	5	2	6	14	111	35	10	10	13	52	272
	TOTAL EXITUS	8	3	2	3	9	63	17	8	8	8	46	175
	MORTALITY %	57	60	100	50	64	57	49	80	80	62	88	64
		TOTAL MORTALITY					TOTAL MORTALITY		TOTAL MORTALITY				
		59%					55%		82%				

. 1. Relationship between onset of CRRT and mortality. * Alarm distance: Is the distance between the time at which the CRRT process is performed and the time at which the AKIN alarm is received (for Abstract no 7).

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8

Carbon Dioxide (CO_2) Balance in the Course of Acetate Free Biofiltration (AFB) vs On-Line Hemodiafiltration (HDFol)

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Introduction and Purpose: The aging of the dialytic population and the frequent presence of cardiorespiratory co-morbidities superimposed to the metabolic acidosis, should lead to better investigate the progression of the partial pressure of carbon dioxide (pCO2) during the hemodialysis treatment. The rapid diffusion of CO2, produced by the reaction of acetic acid with bicarbonate, from the dialysate to the blood compartment, can expose the patient to a CO2 overload that may manifest with dyspnoea, hypotension and hypercapnic respiratory acidosis.Among HDF techniques in use, the AFB, which is characterized, in contrast to other methods, due to the absence of CO2 in the dialysis bath, could guarantee a negative CO2 balance [1]. The aim of this work was to measure the mass balance of CO2 during AFB compared to that obtained in the same patients during treatment with HDFol.

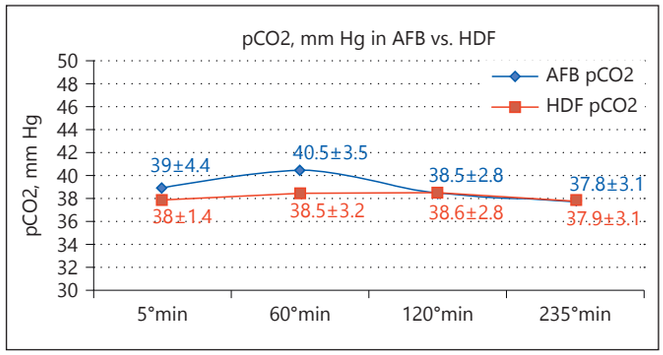
Materials and Methods: 4 stable chronic uremic patients (age = 72 ± 7, months of RDT = 89 ± 63) were subjected to 2 sessions of HDFol in post-dilution and 2 sessions of AFB (I and II HD weekly, Td = 240 min, Qb = 300 ml/min with Qinf = 37.7 ± 2.6 ml/min in AFB and 76.5 ± 8.1 ml/min in HDFol) of mass [2] the levels of pCO2 and HCO_3 were measured at the 5°, 60°, 120° and 235° min periods of dialysis, on the blood entering the filter and on the dialysis bath entering and exiting the filter. end dialysis were also recorded arterial pressure, heart rate (FC) and respiratory rate (RR).

Results and Conclusions: Both dialysis methods were equally effective in the correction of bicarbonatemia at the end of dialysis (28.3 ± 2.1 mmol/l in AFB and 26.6 ± 1.5 mmol/l in HDFol). Although not observed significant differences in pCO2 levels, the CO2 balance was overall negative during AFB (–17.6 ± 11.3 mmol/min) and positive in HDF (+30.3 ± 29.7 mmol/min) (. 1, 2).

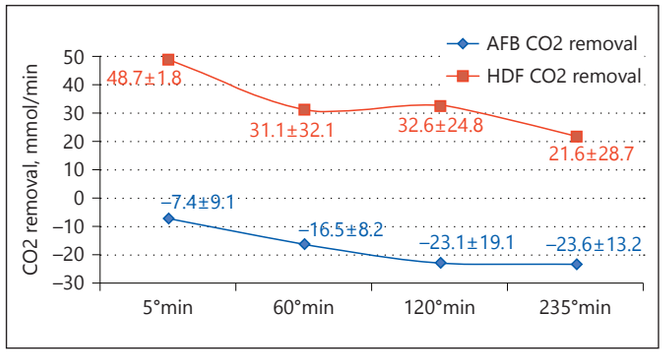
The systolic blood pressure levels at the end of dialysis were significantly lower in HDFol (108 ± 17 mm Hg) than in AFB (121 ± 17 mm Hg). During AFB there were no significant changes in CF and RR, while they were significantly higher at the end of dialysis during HDFol (FC 63 ± 4 dialysis initiation and 70 ± 6 b/min end dialysis, RR 16 ± 1 dialysis initiation and 18 ± 2 acts/min at the end of dialysis) probably indicative of a greater need for respiratory compensation the CO2 load (. 3).

Reference

1 Marano M, et al: Artificial Organs vol. 39, 960–964 (2015).
2 Thomas.



. 1. (for Abstract no 8).



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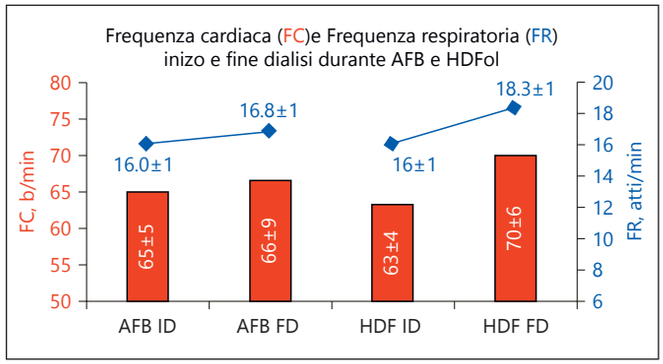

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9

Acute Rejection in Kidney Transplantation: Evaluation of Associated Polymorphisms

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Acute rejection (AR) is one of the most frequent complications after kidney transplantation, and the diagnosis is not always easy. If rejection is not correctly recognized it may lead to the loss of graft function. Evidences suggest that some single-nucleotide polymorphisms (SNPs) located in genes involved in immune response and in the metabolism of immunosuppressive drugs, may be linked to the variability in response to the immunosuppressive therapy. The aim of this study is to evaluate the SNPs associated with AR, highlighting a particular allele associated with the AR event.

We enrolled 3 groups of individuals: AR group (patients with at least one AR event after kidney transplantation), NoAR group (patients without any AR episode after kidney transplantation); Donors group.

The protocol performed for the genetic analysis is comprehensive of DNA extraction and purification, DNA quantitative and qualitative evaluation, PCR, agarose gel electrophoresis, fragments purification, Sanger sequencing reaction, purification of the sequences, capillary electrophoresis.

Heterozygosity (HET) was determined and Hardy-Weinberg equilibrium (HWE) test was performed for each SNP. Genetic associations were calculated by 'per-genotype analysis', 'per-allele analysis' and 'linear trend analysis' tests, with SAS program. Sample size was calculated by QUANTO program.

Each SNP respects HWE in the three groups. Allele frequencies of all SNPs have a homogeneous distribution in the three groups and are superimposable with those of worldwide population. Genotype frequencies determined in the three groups are similar: the most frequent polymorphism in a group is the same in the other groups. From the genetic associations no statistically significant difference is shown; no one of the studied alleles seems to be associated with AR.

In a previous analysis, AR and Donors groups were compared and allele and genotype associations of two variants of one of the studied genes were statistically significant, but in this study, the trend of previous data is not confirmed for the achievement of sample size.

However, a more in-depth study to evaluate other SNPs and a more specific data collection of immunosuppressive drugs dose, may be useful instruments to set up the anti-rejection therapy.

10

Crush Syndrome: Excellent Recovery of Renal Function by Using Hemoadsorption (Cytosorb® Adsorber) A Case Report

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Background: Crush syndrome, a traumatic rhabdomyolysis, characterized by necrosis of muscle cells and the release of intracellular contents into the blood, may induce an acute kidney injury (AKI) and it is often lethal unless treated immediately.

Case Presentation: This case study reports on a 27-year-old man who was admitted to the Emergency Room with head injury and multiple fractures after an attempted suicide by falling from the third floor of his home. He was subsequently transferred to the Intensive Care Unit where he was intubated and started ventilator support for lung failure. Computed tomographic (CT) scans revealed bilateral pleural effusion and bilateral adrenal hematomas. Arterial blood gas analysis showed respiratory acidosis (pH 7.25, pCO_2 54 mm Hg, HCO_3^- 23.7 mmol/l). He had elevated levels of white blood cells, blood urea nitrogen (280 mg/dl), serum creatinine (3.2 mg/dl), myoglobin (13898 ng/ml) and creatine kinase (3448 U/l).

Although adequate fluid administration was started right from the beginning, creatine kinase (maximum level: 7678 U/l) and myoglobin sera levels (m.l.: 23893 ng/ml) increased in combination with reduced urine excretion. So we decided to start Cytosorb® treatment in combination with CRRT (CVVHDF).

Cytosorb™ was stopped three days later (Three sessions for a total treatment time of 72 hours). Within 12 hours, myoglobin levels decreased from 18196 to 10092 ng/ml while at the end of the treatment there was a reduction of 86.3%. It has also been observed a reduction of creatinine kinase levels over 12 hours from 5705 to 4512 U/l and at the end of the treatment the reduction rate was 78.1%. During the next days, parameters of renal function, creatinine kinase and myoglobin decreased in association with an increased patient's urine output, and ventilator support was diminished. The patient's condition improved subsequently and renal function completely recovered. Finally, the patient was transferred to the hortopedics department.

Discussion and Conclusion: In the European Union, Cytosorb™ system is specifically approved as an extracorporeal cytokine filter to prevent cytokine storm and deterioration of organ function in septic shock. The effectiveness of Cytosorb™ to remove myoglobin from saline solution and blood serum, respectively, has been demonstrated in vitro by Kuntsevich V.I. et al. in 2009, whereas in vivo data are missing so far. In our case, we in vivo observed a high decrease of myoglobin and creatinine kinase levels after application of Cytosorb® cartridge followed by an improvement of renal function. Cytosorb® was easy to use and no adverse effects were observed. Thus, in our opinion Cytosorb™ should be considered in case of Crush syndrome not only for the treatment but also in the prevention of AKI.

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11

Hazard Ratio of Sepsis Patients Treated with Extracorporeal Detoxification Methods

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Introduction: Sepsis is a life-threatening and often fatal syndrome. Most of the patients with sepsis are treated in the intensive care units (ICU) and often requires use of different organ replacement therapy technologies, including mechanical lung ventilation (MLV) and continuous renal replacement therapy (CRRT). CRRT in the case of sepsis is often used as extracorporeal detoxification method and it is initiated before patients develop absolute indications. So far it is not clear, whether the use of CRRT as the method of detoxification for sepsis patients does influence the indicators of recovery.

Objective: To describe hazard ratio and potentially associated risk factors in sepsis patients treated with CRRT.

Materials and Methods: A retrospective study of 110 patients (53 males, median of age – 67.8 years) (the *interquartile* range (IQR) 57.8–75.0) who were treated at Riga East Clinical University Hospital's Clinic of Toxicology and Sepsis with diagnosis "sepsis" during the time period from 2014 to 2017 and in whom extracorporeal detoxification methods were used. SPSS software was used to analyze data, and hazard ratio (HR) as well as p-value were calculated using *Cox regression method.*

Results: 74 of all 110 treated patients that were included in this study died. Median of time spent at ICU was 6 days (IQR 2.8–11.0), median of time of hospitalization was 12 days (IQR 3.8–23.3), median of time on MLV was 3 days (IQR 1.3–7.0) and median time on CRRT was 2 days (1.0–4.0).

In unifactorial Cox regression analysis factors associated to death are as follows: male gender (HR = 1.9, p = 0.006), virus hepatitis C coinfection (HR = 2.8, p = 0.048), no surgical intervention during the treatment (HR = 2.3, p = 0.003), SOFA score (HR = 1.2, p = 0.001), use of MLV (HR = 2.5, p = 0.001) and time on MLV (HR = 0.9, p = 0.001), but not other comorbidities, patient age and sepsis origin. In multifactorial analysis only two factors were associated with death: SOFA score (HR = 1.1, p = 0.055) and use of MLV (HR = 2.0, p = 0.027).

Conclusions: The death rate among sepsis patients in whom CRRT was used is very high. Two independent predictors of adverse outcome are SOFA score and severe pulmonary insufficiency which needs use of MLV.

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Incidence, Risk Factors and Clinical Outcome of Acute Kidney Injury in Critically Ill Children: A Retrospective Cohort Study

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Introduction: Children admitted to Pediatric Intensive Care Unit (PICU) are at risk of AKI. Pediatric AKI syndrome is going to be, nowadays, a well-known disease, with a well-studied physiopathology and a specific epidemiology. However, few pediatric studies have focused on the identification of factors potentially associated with the development of this condition. The aim of our study was to assess incidence rate of AKI, identify risk factors, and evaluate clinical outcome in a large sample of critically ill children.

Methods: This retrospective observational study was conducted including patients admitted to our PICU from January 2014 to December 2016. AKI was defined according to KDIGO criteria. A comparison between patients with and without AKI was carried out. Risk factors playing a significant role in the manifestation of AKI were analyzed by univariate analysis. Multivariate analysis by stepwise regression was then performed using odds ratio (OR) with 95% confidence interval (CI).

Results: A total of 222 PICU patients out of 811 (27.4%) had AKI (stage I 39%, stage II 25%, stage III 46%). The most common PICU admission diagnoses in AKI cases were heart disease (38.6%), respiratory failure (16.8%) and postsurgical (non cardiac) patients (11%). Hypoxic-ischemic was the most frequent cause of AKI. Significant risk factors for AKI following multivariate analysis were age >2 years (OR 2.27; 95% CI 1.06–4.90; p = 0.035), inotrope exposure (OR 2.88; 95% CI 1.64–5.08 p < 0.001), multiple organ dysfunction syndrome (MODS) (OR 2.90; 95% CI 1.77–4.76; p < 0.001), coagulopathy (OR 1.57; 95% CI 0.98–2.50, p = 0.054), and thrombocytopenia (OR 2.54; 95% CI 1.34–4.79; p = 0.004). AKI was associated with a significant longer PICU stay (median LOS of 8 days, IQR 3–16, versus 4 days, IQR 2–6, in non-AKI patients; p < 0.001). The mortality rate resulted also ten-fold higher in AKI than non-AKI patients (12.6% vs. 1.3%; p < 0.001).

Conclusions: The *incidence of AKI* in *critically ill* children is *high,* with an associated increased length of stay and risk of mortality. In the PICU setting, risk factors of AKI are multiple and mainly associated with illness severity.

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Anticoagulant Related Nephropathy Induced by Dabigatran

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We describe the first case of biopsy-proven dabigatran related nephropathy in a patient without underlying IgA nephropathy. To date, dabigatran related nephropathy was seen in patients with concurrent or undiagnosed IgA nephropathy, suggesting that it may lead to a predisposition to dabigatran associated injury. However, this was not the case in our patient.

Our patient is an 81-year-old female with multiple medical comorbidities, notable for atrial fibrillation and anticoagulated with dabigatran, who presented with acute kidney injury in the setting of volume overload. Her estimated Glomerular Filtration Rate dropped from a baseline of 57 mL/min to a trough of 4 mL/min, necessitating hemodialysis. Renal ultrasound findings, fractional excretion of sodium and an active urine analysis suggested acute kidney injury with an intra-renal etiology. Serum investigations were unremarkable. Renal biopsy showed acute tubular injury, tubular red blood cell casts and an absence of active glomerulonephritis – similar to the pathological findings of warfarin related nephropathy – thus, establishing a diagnosis of anticoagulant related nephropathy secondary to dabigatran.

Therefore, our case report challenges the prevailing hypothesis that IgA nephropathy predisposes the kidneys to acquire dabigatran related damages. We propose that dabigatran, similar to warfarin, may increase tubular bleeding risks in patients irrespective of underlying kidney or glomerular disease.

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The ADVOS Device: Albumin Dialysis Based Approach for Significant and Continuous Removal of Water Soluble and Protein Bound Toxins Even at Low Blood Flows

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Introduction: ADVOS multi is a recirculating albumin-based dialysis device conceived to support kidney, liver and lung function. This extracorporeal support system is able to remove water-soluble and protein-bound substances both in vivo and in critically ill patients [1, 2]. In this work, the elimination rate and clearance for lactate and bilirubin was analyzed in vitro.

Methods: An ex vivo model using swine blood was established. Briefly, 3 x 3.3 l blood with high bilirubin (30 mg/dl) and lactate levels (>10 mmol/l) were treated with ADVOS multi for 4 hours each. This design, with 3 phases changing blood every 4 hours, allowed high concentrations of both markers in blood along 12 hours, which permitted a reliable analysis of the clearance. Bilirubin (620 mg/4 h) was added to blood always 1 hour before being treated in order to be bound to blood albumin in the same extent. Dialysate pH (7.80) and blood (100 ml/min), recirculating dialysate (1200 ml/min) and concentrate flows (160 ml/min) were not modified in the study (n = 6). The amount of albumin-bound fatty acids in the dialysate as an indirect measurement of albumin binding capacity (ABiC) was additionally investigated. A subgroup analysis for each of the 3 phases was performed.

Results: Bilirubin and lactate were efficiently removed during 12 h. Lactate removal rates were 90%, 86% and 84% for phase 1, 2 and 3 respectively, while clearance was 33, 28 and 26 ml/min in the same time frames. A reduction of clearance in Phase 2 and 3 was observed, probably due to expected dialyzers deterioration. On the other hand, bilirubin elimination rates were 66%, 62%, and 57%, respectively, resulting in a total elimination of 1150 mg in 12 h. This is 3–4 times the normal daily production of bilirubin [3]. Finally, albumin binding capacity (ABiC) was >76% at the end of the treatment indicating that the parameters used in the ADVOS system do not denaturate the albumin. A direct correlation was observed between elimination of bilirubin and ABiC.

Conclusion: ADVOS multi can continuously and efficiently eliminate water soluble and protein-bound substances. The recirculating albumin dialysate maintained an optimal detoxification

Table 1. (for Abstract no 14)

Mean ± S.D.	Lactate (mmol/l)			Bilirubin (mg/dl)		
	0–4 h	4–8 h	8–12 h	0–4 h	4–8 h	8–12 h
Cstart	9.1±2.5	10.6±3.1	11.4±3.0	31.5±3.5	31.7±2.1	31.0±1.4
Cend	0.9±0.2	1.4±0.3	1.7±0.3	10.4±2.0	12.0±1.9	13.2±2.5
Removal (%)	90.2±2.5	86.3±2.9	84.8±2.9	65.8±11.2	62.1±4.6	57.4±7.3
Clearance (ml/min)	32.6	27.9	26.4	15.2	13.3	11.7
ABiC (%)	–	–	–	85.7±3.6	82.8±3.5	76.3±5.7

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ability during the whole study duration. Extracorporeal support of kidney and liver detoxification seems feasible within a single device.

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ADVOS Reverses Metabolic Acidosis Without Elevating pCO2: Proof of Concept In Vitro

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Introduction: The Surviving Sepsis Campaign of 2012 recommends "not using sodium bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥7.15 (grade 2B)" [1]. Bicarbonate infusions might concomitantly elevate pCO_2 increasing the ventilation requirements or even resulting into respiratory acidosis. The ADVOS multi albumin recycling hemodialysis device allows a customizable dialysate pH which favors the removal of protons avoiding the mentioned negative effects. The present work shows in vitro the proof of concept for metabolic acidosis correction, which was already demonstrated in patients [2].

Methods: An ex vivo model of metabolic acidosis was prepared with either CVVHF or the ADVOS system. First of all 5 liters swine blood were dialyzed against a solution of 10 mmol/l HCO_3^- using a conventional CVVHF device. Lactic acid was infused at 140 ml/h. Once lactic acidosis was induced (i.e.: pH <7.15; pCO_2 35–45 mm Hg; HCO_3^- 12–14 mmol/l: and lactate 5–6 mmol/l), blood was treated for 1 hour with either CVVHF using a commercially available dialysate containing 35 mmol/l bicarbonate (effluent Flow: 60 ml/min postdilution) or with ADVOS multi using a dialysate pH set at 9.0. A blood flow of 200 ml/min was employed with both devices.

Results: Bicarbonate therapy during CVVHF was able to normalize HCO_3^- levels. However, due to the lack of ventilation, pCO_2 was correspondingly elevated resulting in an even lower pH after the treatment. On the other hand, ADVOS multi normalized pH and bicarbonate levels. Due to the CO_2 removal ability of the ADVOS system, even 15 ml/min of CO_2 were additionally provided during the treatment with ADVOS multi.

Conclusion: ADVOS multi can efficiently correct metabolic acidosis in vitro without elevating pCO_2 even in the absence of adequate ventilation, while treatment with bicarbonate with conventional CVVHF triggered respiratory acidosis.

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ADVOS Corrects Respiratory Acidosis Mimicking the Body's Renal Compensation: In Vitro Demonstration

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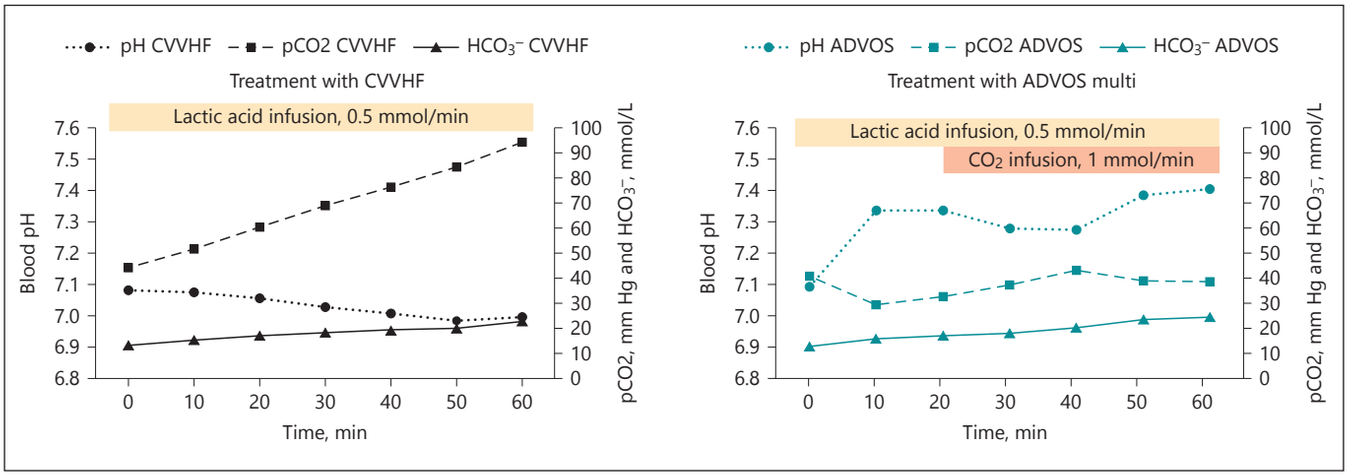
Introduction: In the renal tubular cells CO_2 is transformed to H^+, further bound to NH_3 and secreted into the urine. The remaining HCO_3^- is reabsorbed into the blood from the tubular cells. The ADVOS system is based on albumin dialysis and is able to recycle the dialysate and adjust its pH in an individualized manner. In the present work we show how this particularity might allow to correct respiratory acidosis in the absence of an oxygenator.



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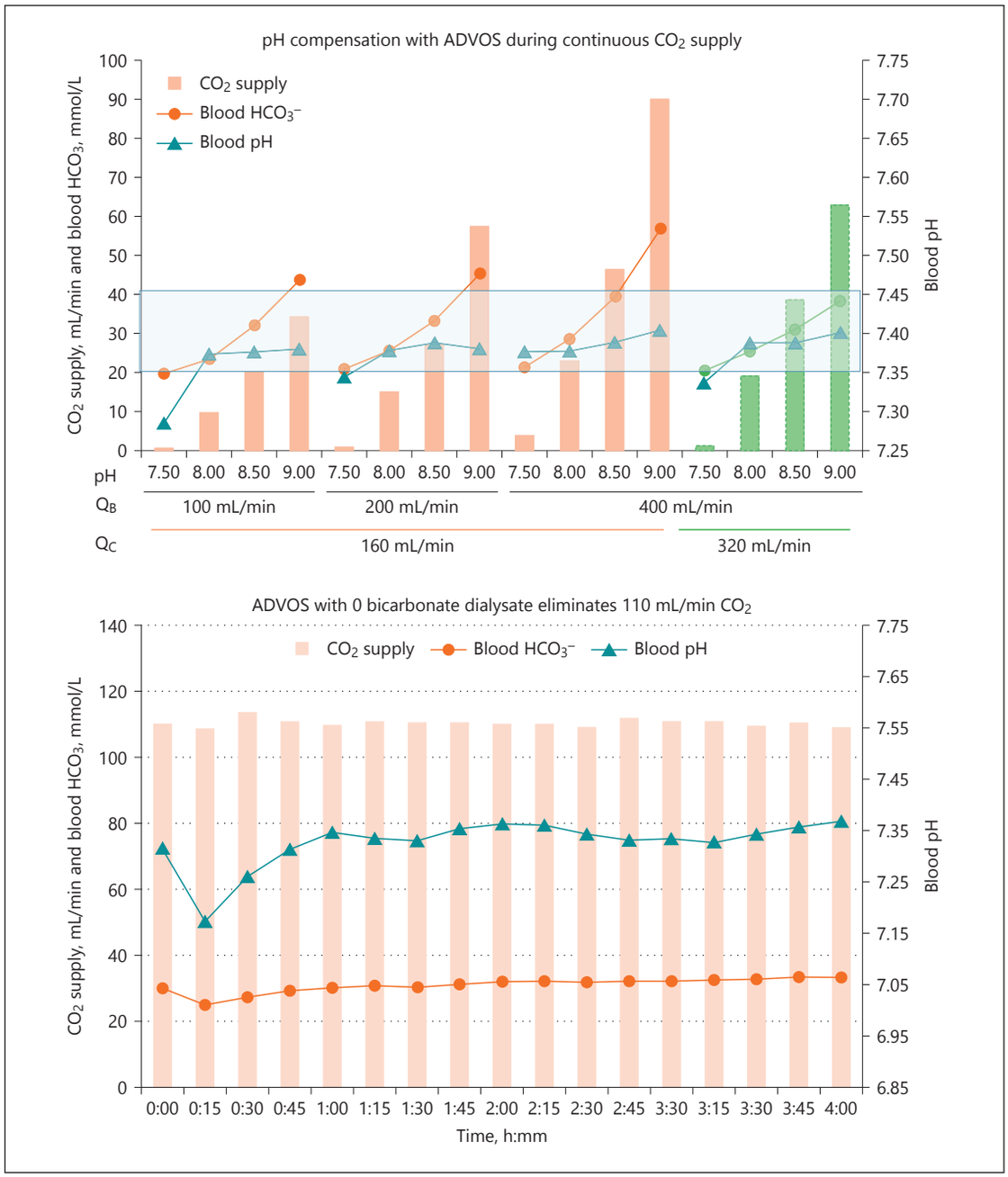

. 1. (for Abstract no 16).

Methods: The objective of the study was to determine the maximal amount of CO_2 that could be supplied (and therefore, eliminated) during ADVOS treatments using different settings. Briefly, 5 liters of swine blood were dialyzed with the ADVOS system. Different combinations of blood flows (Q_B = 100, 200 or 400 ml/min), concentrate flows (Q_C = 160 or 320 ml/min) and dialysate pH (7.5, 8.0, 8.5 or 9.0) were tested for 1 hour each. A pH probe was inserted into the blood in order to continuously control pH levels. CO_2 supply was increased accordingly as long as blood pH was maintained within physiological levels (7.35–7.45). Blood gas analysis were performed every 15 minutes. An additional experiment using a dialysate without bicarbonate was performed treating blood during 4 hours with ADVOS and supplying 110 ml/min CO_2. A Q_B of 400 ml/min, a Q_C of 320 ml/min and a dialysate pH of 10 were set.

Results: The ADVOS system was able to eliminate different amounts of CO_2 depending on the Q_B, the Q_C and the dialysate pH. Using a Q_C of 160 ml/min up to 20, 30 and 45 ml/min of CO_2 were

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eliminated with Q_B of 100, 200 and 400 ml/min without compromising HCO_3^- levels. When Q_C 320 ml/min and Q_B 400 ml/ml were employed, up to 60 ml/min of CO_2 were removed with dialysate pH 9.00. In the second experiment, using a 0 mmol/min bicarbonate dialysate up to 110 ml/min CO_2 might be eliminated. This was possible since the ADVOS system mimics the renal compensation mechanism. H^+ can directly diffuse from blood into the dialysate thanks to a concentration gradient due to a higher pH in dialysate. The albumin present in the dialysate can bind the excess of H^+ acting as a buffer. Finally, bicarbonate can be increased in case that HCO_3^- levels in blood are lower by a simple back diffusion from the dialysate.

Conclusion: ADVOS multi can efficiently eliminate CO_2 and correct respiratory acidosis in vitro thanks to its adaptable dialysate pH and the buffer capacity of albumin. It mimics therefore the renal compensatory mechanism to respiratory acidosis. To our knowledge, this is the first renal replacement device which includes this possibility.

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Acute Decompensated Heart Failure and Acute Kidney Injury: Role of Inflammation, Oxidative Stress and Tissue Damage in Cardiorenal Syndrome Type 1

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Background: Cardiorenal Syndrome Type 1 (CRS 1 type) is characterized by a rapid worsening of cardiac function leading to acute kidney injury (AKI). CRS 1 type occurs in approximately 20% to 30% of patients with acute decompensated heart failure (ADHF) and is associated with increase of mortality and in-hospital long of stay. Inflammation and oxidative stress seem to play a pivotal role in its pathophysiology.

In this *in vivo* study, we examined the putative role of inflammation and humoral markers in pathogenesis of the CRS 1 type.

Methods: We enrolled 53 patients with ADHF, 17 of them developed AKI (CRS 1 type). The cause of AKI was presumed to be related to cardiac dysfunction after having excluded other causes. We assessed plasma level of pro-inflammatory cytokines (TNF-α, IL-6, IL-18, sICAM, RANTES, GMCSF), oxidative stress marker (MPO), BNP and NGAL in ADHF and CRS 1 type patients. Statistical analysis was performed using the SPSS 15 Software package. A p-value of <0.05 was considered statistically significant.

Results: We observed significant increase of IL-6, IL-18 and MPO levels in CRS 1 type group compared to ADHF ($p < 0.001$). We found higher NGAL at-admission in CRS 1 type group compared to ADHF group ($p = 0.008$) and a positive correlation between NGAL and IL-6 (Spearman's rho = 0.45, $p = 0.003$) and between IL-6 and BNP (Spearman's rho = 0.43, $p = 0.004$). We observed lower hemoglobin in CRS 1 type patients compared to ADHF patients ($p < 0.05$) and inverse correlation between hemoglobin and cytokines (IL-6: Spearman's rho = –0.38, $p = 0.005$; IL-18 Spearman's rho = –0.32, $p = 0.02$).

Conclusion: CRS 1 type syndrome represents a diagnostic and therapeutic challenge. Patients affected by CRS 1 type present increased levels of pro-inflammatory cytokines and oxidative stress marker, increased levels of tissue damage markers and lower hemoglobin levels. All these factors may be implicated in pathophysiology of CRS 1 type syndrome. We need to recognize early at risk-patients in order to make immediately diagnosis or preventing it. We hypothesized that a combination of inflammatory, cardiac and renal damage markers in a multi-biomarkers panel as opposed to a single biomarker should be taken as "add on-value" rather than a "unique-predictive" data.

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Direct Effect of Septic Plasma in Different Human Cell Line Death

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Sepsis is a life-threatening complication to infection, characterized by a systemic inflammatory response. Despite the progress made in sepsis treatment, this complication is still a major cause of mortality and morbidity and its incidence is believed to increase, due to the growing number of elderly patients. Sepsis is often associated with high incidence of multiple organs injury and consequent failure of respiratory, renal, neurological, hepatic and cardiovascular systems. Although these macroscopic effects are evident (organ injury-dysfunction-failure-shock), little is known of how sepsis induces organ injury at the cellular and molecular levels. Several papers suggested that the immune response by itself, with the production of pro- and anti-inflammatory mediators, is crucial in determining cell death.

To better understand if inflammatory mediators alone can influence cell death, we set up an *in vitro* study where we investigated the response of renal tubular cells (RTCs), monocytes (U937) and hepatocytes (HepG2) to incubation with septic patients' plasma.

We enrolled 26 septic patients from ICU and 20 healthy controls. Plasma from patients and controls were incubated with RTCs, U937 and HepG2 for 24 hours. Cell death, caspase-3, -8, -9 and cytochrome-c levels were evaluated.

In all cell lines, we revealed a significant decrease of cell viability. However, while for RTCs and U937 cells this result was associ-

ated to higher apoptosis levels, HepG2 death was linked to necrosis increment. Next, we showed that apoptosis in RTCs and U937 cells was trigged by the intrinsic pathway, as cytochrome-c and caspase-9 levels increased and had a strong correlation, while no modulation of caspase-8 was found. Our results suggest that the direct exposure to cytotoxic agents contained in the plasma of septic patients, can rapidly enhance programmed cell death RTCs and U93, but not in HepG2. This, let us speculate that HepG2 cells could have some kind of "resistance" to inflammatory mediators' effect or that hepatocytes might require interaction and crosstalk with other cells (monocytes, macrophages, etc...) to result in cell death. To assess this point, future experiments of co-culture with HepG2 cells are needed. In addition, we showed that apoptosis in RTCs and U937 cell death is more likely due to external stimuli such as oxidative stress, than a direct response to inflammatory mediators.

Overall, the fact that septic patients' plasma contains cytotoxic agents able to induce cell apoptosis could explain why organ injury often occurs under septic conditions. In addition, our findings suggest that apoptosis inhibitors could be use as strategy to reduce the organ damages induced by sepsis.

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Induced-Fever Plasma to Understand Cytokines Response in Septic Patients

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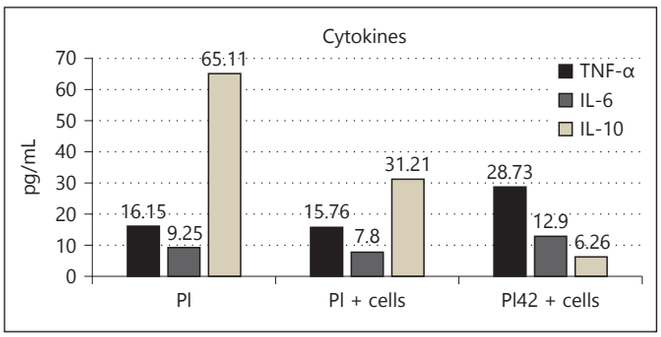
Sepsis is a global healthcare issue and continues to be the leading cause of death from infection. Cells of the immune system are activated shortly after the onset of the infection, with intense secretion of pro- and anti-inflammatory cytokines. Cytokines' targets are also the cells of immune system. The aim of this study was to value the effect of induced fever on U937 incubated with septic plasma in term of IL-6, IL-10 and TNF-α concentration.

4 frozen septic patients plasma were used for the experiment. 500 mL of septic plasma were heated at 42°C for 3 hours. 10^6 U937 were incubated for 24 hours with 500 mL of the treated plasma at 42°C (Pl42+Cells) and with 500 mL of non-treated plasma (Pl+Cells). ELISA tests for IL-6, IL-10 and TNF-α were performed on septic plasma (Pl) (negative control) and on supernatant obtained from centrifugation of Pl+Cells and Pl42+Cells.

Results are shown in the ure 1. TNF-α and IL-6 levels were similar for Pl and Pl+Cells but the levels were increased in Pl42+Cells. Otherwise, IL-10 levels decreased significantly from negative control in Pl+Cells and in Pl42+Cells.

Our findings suggest that, in induced-fever plasma of a septic patient, there is an increase of inflammatory cytokines and a decrease of anti-inflammatory cytokines.

This activation/deactivation could suggest a cellular response to septic status that could not be transferable to the real septic patient (Pl levels). This thesis could be verified by evaluating cellular viability.



. 1. Cytokines levels for septic plasma (Pl), for non-treated plasma incubated with U937 (Pl+Cells) and for treated plasma incubated with U937 (Pl42+Cells) (for Abstract no 19).

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Biocompatibility and Cytotoxic Evaluation of New Sorbent Cartridges for Blood Hemoperfusion

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Background/Aims: The use of adsorption cartridges in hemoperfusion modality during Continuous Renal Replacement Therapies is rapidly evolving. For these devices, the potential induced cytotoxicity is an important issue since they directly come in contact with blood.

The aim of this study was to investigate potential *in vitro* cytotoxic effects on U937 monocytes of sorbent cartridges HA330 and HA380 (Jafron, China), whose intended use is for critical ill patients with disease such as sepsis, pancreatitis, trauma and cardiac surgery.

Methods: Monocytes were exposed to the sorbent material in static and dynamic manners. In static test, cell medium samples were collected after 24 hrs of incubation in the cartridges. In dynamic test, hemoperfusion modality has been carried out and samples at 30, 60, 90 and 120 minutes were collected.

Results: Compared to control samples, there was no evidence of increased necrosis or apoptosis in monocytes exposed to the cartridges in the static tests, while the viability remained the same. Similarly, there was no remarkable difference in the viability, apoptosis and necrosis of monocytes between each sample of the four time points in the dynamic test and the controls (. 1).

Conclusion: Our in vitro testing suggests that HA330 and HA380 cartridges carry an optimal level of biocompatibility and their use in hemoperfusion is not associated with adverse reactions or signs of cytotoxicity.

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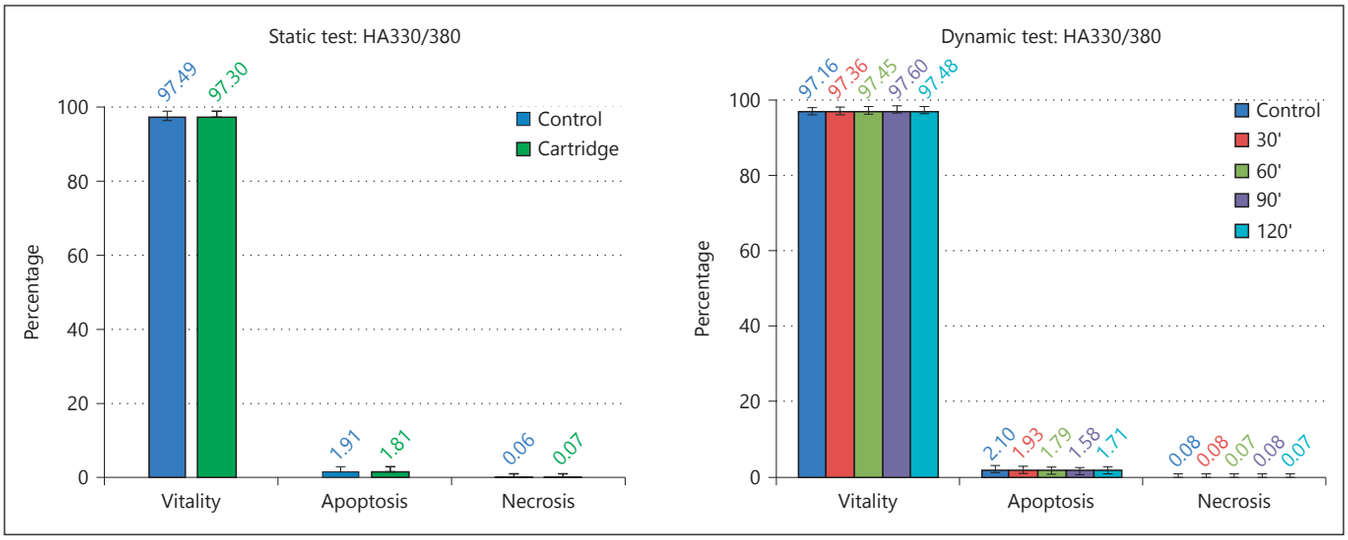

. 1. HA330/HA380 cartridges contact effects on viability, apoptosis and necrosis of U937 cell culture in static and dynamic test (for Abstract no 20).

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Clearance of Heparin-Binding Protein by Seraph Microbind-Minicartridges

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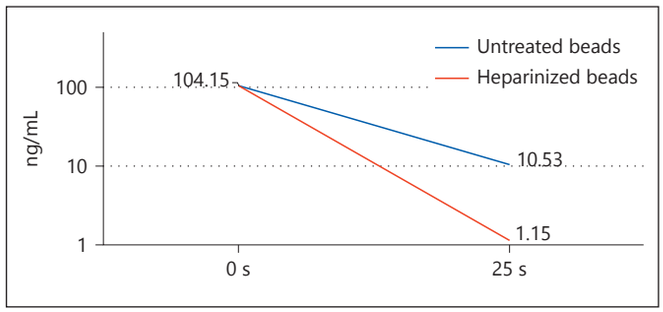
Introduction and Aims: Sepsis can be defined as a "severe endothelial dysfunction syndrome in response to intravascular and extravascular infections" (NIH/NHLBI Sepsis Panel 2010), thus causing multiple organ failure by damaging the nurturing microcirculation. One mediator with positive local but disadvantageous systemic effects is Heparin-binding protein (HBP). After contact to the endothelium HBP is released by activated neutrophils, functioning inter alia as a chemoattractant and inductor of endothelial leakage for neutrophil extravasation. However, in sepsis patients HBP is an early indicator of developing circulatory failure and death. HBP has been proposed as one of the main factors causing vascular leakage in severe sepsis. Therefore, we evaluated HBP clearance by an affinity-based blood filter.

Methods: The filter's resin (Seraph® Microbind®) and negative controls were provided in 2.5 ml minicartridges by the manufacturer (Exthera Medical, Martinez, CA, USA). The resin is made of ultrahigh molecular weight polyethylene beads with covalently end-point attached heparin. Human citrated plasma (Cat. #P9523, Sigma-Aldrich, Darmstadt, Germany) was spiked with human recombinant HBP (Cat. #C430, Novoprotein, Summit, NJ, USA) at 100 ng/ml. Next the minicartridges (3x controls with untreated beads, 3x treated beads) were primed with saline and finally 2 ml of plasma slowly passed through the cartridge. After subsequent elution of the remaining saline (and 0.5 ml plasma) the final gravity-based flow was saved and used for an HBP ELISA (#FMHBP100, Axis-Shield, Dundee, Scotland).

Results: The study is summarized in . 1. Two ml of plasma spiked with HBP (100 ng/ml, measured as 104.15 ng/ml by ELISA) were passed over treated (heparinized) respectively untreated beads and HBP concentrations pre- and post-minicartridge quantified by an ELISA. HBP was cleared at 99.99% with the treated and 89.89% with the untreated beads (shown is the mean concentration of three replicates for each group).

Conclusion: This study shows that HBP is cleared at 99.99% by Seraph Minicartridges in human plasma in vitro. Because the untreated beads have a slightly negative charge and HBP is known as cationic protein weak electrostatic, non-specific binding could account for the control group results. Considering the poor prognosis of severe sepsis – despite maximum efforts – extracorporeal elimination of pathogens and inflammatory mediators by Seraph Microbind blood filters should be trialed in vivo.



. 1. Clearance of HBP by Seraph Microbind-Minicartridges (for Abstract no 21).

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A Stroke of Genius at Light Microscopy

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A 60-year old Russian woman entered the emergency department of our hospital for abdominal pain, nausea and the impossibility to eat or drink in the last 7 days. Laboratory findings showed impaired renal function, with serum creatinine of 8 mg/dl, urea 188 mg/dl, anemia and oliguria. She was then admitted for oliguric AKI stage 3 not complicated by hyperkalemia or metabolic acidosis. In the suspect of pre – renal azotemia, intravenous fluid therapy was administered, sparing renal replacement therapy for possible worsening of the patient's conditions. Serum creatinine immediately started to decline down to 3.5 mg/dl, apparently giving sign of AKI responsive to fluid therapy. However, renal function did not further improve in the following days.

Patient's history was significant for rheumatic fever, which had caused severe stenosis of the mitral valve, replaced with mechanical prosthesis. For this reason, patient was taking oral anticoagulant medications. She was not taking drugs for any other condition. Data on her renal function before this admission were not available.

Further laboratory tests showed hypoalbuminemia (2 g/dl), markedly increased ESR (120 mm/h), negative CRP. Urinanalysis demonstrated a nephrotic range proteinuria of 10 g/24 h. Tests for autoimmunity were performed. ANA, ENA, ANCA and PLA2R antibodies were all negative, C3 and C4 levels were normal. As renal function was not further improving, a kidney biopsy was performed. Waiting for biopsy results, the patient was discharged, as her conditions were apparently stable. However, after 5 days she was admitted again with fever and severe hypotension not responsive to fluid therapy. Physical examination and routine tests did not reveal a specific localization of infection. Given her history of mitral valve prosthesis, a transesophageal echocardiography was performed, revealing vegetation on the prosthetic valve. Patient's conditions dramatically worsened. She developed a septic shock with peripheral septic embolisms. She underwent splenectomy and then cardiac surgery to remove the mitral vegetation. After surgery her renal function was compromised and continuous renal replacement therapy was started.

In the meantime, kidney biopsy results became available. At light microscopy, H&E staining revealed thirteen glomeruli out of seventeen with diffuse hyalinosis and proteinaceous casts in the tubules. PAS staining showed thickening of capillary membranes in the glomerular tufts. No specific deposits were detectable at immunofluorescence. Trichrome staining was oddly striking. Glomeruli with diffuse hyalinosis were expected to be stained in blue, which marks for sclerotic tissue in trichrome staining. They appeared instead of a light pink color. Matching this peculiar appearance with nephrotic range proteinuria, amyloidosis was suspected. To confirm the diagnosis, Congo red staining was performed. The test was conclusive, confirming amyloid deposits in the glomeruli.

The patient was not affected by monoclonal gammopathy. Therefore, other possible causes of amyloidosis were investigated. Biopsy specimens were sent to the Amyloidosis Italian Centre in Pavia and a diagnosis of AA amyloidosis was made. However, the patient was not affected by any of the most frequent causes of AA amyloidosis. Tests for tuberculosis, chronic infections of other kind, inflammatory bowel diseases and malignancies were all negative.

Over time, the patient developed a full nephrotic syndrome with severe hypoalbuminemia, dyslipidaemia and 20 g/24 h of proteinuria. Her renal function did not recover and she continued renal replacement therapy, switching to standard hemodialysis after resolution of her critical conditions .

As far as we know, the only condition that could have triggered AA amyloidosis in this patient is subacute endocarditis. If that is the case, as endocarditis was properly treated, a progressive resolution of the nephrotic syndrome and regain in renal function should be expected.

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Hepatic Regeneration with Coupled Plasmafiltration and Adsorption for Liver Extracorporeal Detoxification (Hercole Study)

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Introduction and Aims: CPFA (Coupled plasma filtration and adsorption) is currently used in the treatment of severe sepsis with the intention of removing the proinflammatory mediators from the systemic circulation. Some evidence exist about the bilirubin adsorbing ability of the neutral styrenic resin which is part of the extracorporeal circuit of CPFA. The aim of this study is to assess efficacy and safety of CPFA in extracorporeal detoxification of liver toxins in patients affected by acute or acute-on-chronic liver failure.

Methods: Twelve patients (age 23–73 years) with acute (n = 3) or acute-on-chronic (n = 9) liver failure were enrolled. A total of 31 CPFA treatments were carried out. Each CPFA treatment lasted 6 hours. Unfractionated heparin was used as anticoagulation of the extracorporeal circuit in 19 CPFA sessions; citrate anticoagulation with the concomitant infusion of calcium chloride in 12 CPFA sessions. The number of treatment for each patient was established on his/her clinical status. The reduction ratios per session of bilirubin and bile acids were considered. Haemoglobin, platelets, white blood cells, coagulation tests, urea, creatinine and electrolytes were also checked on starting CPFA and at the end of CPFA, as biocompatibility measures.

Results: All sessions were well tolerated by the patients. Alcohol was the most common aetiology of the liver injury (n = 9), 1 patient was affected by acute cholangitis and Fisher-Evans syndrome, 1 had a viral aetiology, and 1 patient had a postoperative jaundice. Median reduction rate per session for total bilirubin was

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28.8% (range 2.2–40.5); for direct bilirubin was 32.7 (range 8.3–48.9); for indirect bilirubin was 29.5% (range 6.5–65.4); for bile acids was 28.9% (16.7–59.7); for lactic acid was 30% (range -57.2%-55.6%). In 10 out of 12 patients was observed a recovery of liver function. At one year of follow-up 2 patients died during the hospitalization; 6 patients are followed like outpatients, recovered their basal liver function and 1 of them is no more in the waiting list for the transplant.

As to the remaining 4 patients who have not yet completed the one year follow-up, 2 out of 4 are still alive after a 6-month follow-up and recovered their basal liver function, 1 patient underwent a successful liver transplantation, the last patient is still alive after a 3-month follow up.

Conclusions: Although CPFA is a non-standardized technique for the liver failure, its use in patients with acute or acute-on-chronic liver failure has shown favourable effects on safety and efficacy in terms of detoxification. Thus it is considerable a "bridge technique" toward the liver transplant and the recovery of basal liver function.

24

Old and New Risk Factors for Acute Kidney Injury After Cardio-Pulmonary Bypass

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Acute Kidney Injury (AKI) is a very common complication after cardio pulmonary bypass.

We enrolled 101 consecutive adult patients, from 1st jan 2015 to 29th feb 2016, 82% males, admitted to our intensive care unit after elective on pump Coronary Artery Bypass Graft (CABG), and we analyzed retrospectively old and new risk factors for AKI after cardiac surgery. We first analyzed correlations already observed in literature, such as duration of cardio-pulmonary bypass (CPB), previous chronic renal failure, obesity and hematocrit nadir during CPB. Then, we analyzed new variables, such as chloride, base excess nadir, pre and post-operative difference in Strong Ion Gap (SIG), as indicators of metabolic distress and, last but not least, the total amount of fluids infused in operating room. We found a global AKI incidence of 28%; patients with AKI were older ($p = 0.004$) and with higher value of pre-operative creatinine ($p = 0.0007$); our data agrees with literature except for BMI, whose association with AKI was not statistically significant in our sample. We also observed that AKI group patients' stay in ICU was longer ($p = 0.01$), and this underlines the importance of early recognition of risk factors, not only for clinical reason but also for economic ones. Concerning the management of pre-CPB fluid infusions, there was a clear prevalence of blood transfusions in the AKI group patients, according to current literature ($p = 0.018$), maybe due to pre-existing renal failure and anemia, even if it cannot be ruled out that pre-CPB blood transfusion can affect renal function. During CPB the AKI group patients more frequently received non-hematic cardioplegic solution, with similar extracorporeal circulation (ECC) time and aortic closs-clamp time between the two group, with and without AKI. According to literature there is no correlation between ECC time and AKI prevalence, but we think that the non ematic cadioplegic solution, maybe in further study with a larger sample, should be related to. Finally, we observed a lower urine output and a lower hematocrit nadir during CPB in AKI group patients, but this has already been established in current literature. Regarding fluid management in the operating room, the amount of chlorides administered were not enough to influence the incidence of AKI in our sample, but this may not be true for longer surgery. Unexpectedly, the amount of chlorides administered during and after surgery was greater in the non-AKI group, with a p value close to significance; further studies are needed.

We conclude that during elective on pump CABG we cannot demonstrate the superiority of one fluidic strategy over another to prevent kidney damage. Sodium bicarbonate has been used in a non-homogeneous way, besides never in preoperative time, and it demonstrated to be ineffective to prevent AKI. Analyzing metabolic patients' profile, we observed a slightly lower pH in AKI group (always in physiological range), higher glycemia and albumin levels and significantly lower total protein levels, probably due to an underling protein losing nephropathy. Finally, by examining the parameters of anaerobic metabolism, post CPB lactates do not show significant differences between the two groups, whereas the post CPB SIG is higher in the AKI group, with a p value of 0.05; the SIG has already been correlated to metabolic distress and it could be a good early indicator for AKI risk; further studies are needed.

In conclusion, individual examination of pH and BE is not enough to classify or quantify metabolic distress; Stewart's approach to metabolic disorder and acid-base equilibrium may be more sensitive and accurate than Henderson-Hasselbalch approach or base excess analysis.

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NOV-AKI (Novara-Acute Kidney Injury) Study in Hospitalized Patients: Monocentric Analysis of AKI Impact on Outcome

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Introduction: Acute kidney injury (AKI) is a life-threatening disease that occurs in about 8–16% of hospitalized patients. This prevalence has been considerably increasing during last years due to patients' characteristics (i.e. increasing age and co-morbidities), better identification of AKI and increased rate of clinical factors associated with the decrease of renal function, in particular sepsis. AKI is known to be associated with a worse outcome, frequent re-hospitalization and increased progression toward chronic kidney disease (CKD).

Aim of the Study: To evaluate the prevalence of AKI, outcome in all hospitalized patients during 12 months at "Maggiore della Carità" University Hospital in Novara.

Methods: We performed an observational retrospective study based on data concerning all patients admitted to our hospital in 1 year. We collected data from Board Hospital Discharge (BHD) and serum creatinine from the Lab data base. We performed AKI stratification in accordance to KDIGO criteria and evaluated outcome.

Results: We observed that 17.35% of all hospital admissions showed the presence of AKI: indeed, we identified a total of 2310 AKI events further sub-classified as follows: 1355 admissions with AKI stage 1 (10.18%), 606 with AKI stage 2 (4.55%) and 349 with AKI stage 3 (2.62%) (results are expressed as number of AKI stage 1, 2 or 3 in respect to total hospital admissions).

In-hospital mortality in the non-AKI group was 3.56% in comparison to 10.63% in AKI stage 1, 20.13% in AKI stage 2 and 24.36% in AKI stage 3 group, respectively.

The mean of the maximum serum creatinine in AKI stage 1 was 1.68 mg/dl in comparison with 2.28 mg/dl for AKI group 2 and 5.13 mg/dl for group 3.

The rate for second hospitalization in AKI stage 3 was 1.15%, 2.31% for AKI stage 2 and 4.26% in AKI stage 1.

The analysis based on AKI prevalence in the different hospital departments showed that AKI stage 1 was more frequent in Cardiac Surgery, Cardiology, Coronary Unit, General Surgery, Hematology, General Medicine, ICU, Traumatology; AKI stage 2 was more frequent in Hematology, General Medicine, Traumatology, ICU, Coronary Unit, Gastroenterology; AKI stage 3 was more frequent in General Medicine, Urology, ICU, Coronary Unit, Gastroenterology.

Conclusions: AKI impacts a large part of admissions to our University Hospital with a higher prevalence for stage 1 than stage 2 and 3. As expected, we observed the highest prevalence among older people (age >70 years) even though we did not find a linear correlation between older age and more severe AKI stages. As reported in literature, mortality seems to have a significant correlation with the severity of AKI stage. The lowest rate of second hospitalizations for AKI stage 3 can be considered as an indirect measure of lethality. In conclusion, the NOV-AKI observational and retrospective study showed that AKI during hospitalization leads to a worse outcome and to the development of co-morbidities potentially associated with frequent re-hospitalization and progression toward CKD.

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Presentation, Etiology and Outcomes of Patients with Acute Kidney Injury and Multiple Myeloma

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Background: Multiple myeloma (MM) is a common encountered hematological malignancy with significant renal involvement. About 30 to 40% of patients with MM presents with acute kidney failure (AKF) or acute on chronic kidney failure (ACKF) with up to 10% of patients require dialysis.

In this study we describe the clinical presentation and outcomes in patients with MM and AKF or ACKF, and the correlation between the maximum seric creatinine and need of renal replacement therapy (RRT) with two main outcomes (death and dependence of dialysis at the time of release from hospital).

Material and Methods: A retrospective single center study, including all patients of Nephrology in-hospital consultation with a diagnosis of MM and AKF (according to KDIGO criteria) between January 2002 and December 2016, was performed, with clinical and laboratorial data collected, including need for RRT and clinical outcomes.

Results: The study included 16 patients with a mean age of 67.6 ± 13.3 years (females 8; males 8). Only 3 (12.5%) patients had a previous diagnosis of MM and 4 (25.0%) of Chronic Kidney Disease (CKD). The mean creatinine at admission was 5.2 ± 3.0 mg/dL and the mean of maximum creatinine during hospitalization was 5.8 ± 2.1 mg/dL. Eight (50%) patients required RRT, one of them continuous renal replacement therapy. The precipitating factors of AKF or ACKF identified were: hypercalcemia/light chains (50%); NSAIDs (25%); and volume depletion (18.7%); decompensated heart failure (6.2%). Of the eight patients who required dialysis, 3 (37.8%) were dialysis-independent at the time of release and had a mean of 5 sessions of hemodialysis. Three (18.7%) patients died, 2 of them were on RRT.

We verified a strong correlation between the number of sessions and dialysis dependency at the time of release ($r = 0.07$; $p < 0.001$). There was no correlation between maximum creatinine neither with the indication to do dialysis or the mortality. The need of RRT was not correlated with mortality.

Conclusions: AKF in patients with MM can be the first manifestation and may be severe, with the need of RRT in half of subjects. Over one third become dialysis dependent with the number of sessions correlated with this outcome.

27

The Influence of Arterial Hypertension, Diabetes Mellitus and Obesity on the Acute Kidney Injury (AKI) Risk in Patients with Stable Coronary Artery Disease (CAD) and 5-Year Prognosis

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Background: One of the most effective treatment strategies of stable CAD is percutaneous intervention (PCI) using contrast media (CM). Contrast-induced acute kidney injury (CI-AKI) becomes more frequent with the rise of the number of PCI procedures. As arterial hypertension, diabetes mellitus and obesity are well known risk factors of CAD and chronic kidney disease (CKD) development we decided to assess the their influence on the CI-AKI risk after PCI in patients with stable CAD and the 5-year prognosis of all groups of patients.

Methods: In a single-centre prospective observational study 561 patients aged 18–80 with stable CAD undergoing PCI were enrolled from June 2012 to October 2013. The data regarding CI-AKI risk factors and patients characteristics were collected. The 5-year prognosis including all-cause mortality, cardiovascular

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mortality, myocardial infarction (MI), stroke, gastrointestinal bleeding, decompensation of heart failure (HF) was assessed by phone calls and appointments according to the clinical situation.

Results: CI-AKI was defined as an increase of 25% or more, or an absolute increase of 0.5 mg/dl or more in serum creatinine from baseline value, at 48–72 hours following the exposure to CM.

419 (75%) were male. 435 patients (77.5%) had arterial hypertension and 219 (39%) had obesity (BMI 30 kg/m^2 and more). 88 (16%) suffered from diabetes mellitus.

During the 5-year follow up period 23 patients (4%) were lost to follow up. There were 4 (0.7%) cardiovascular deaths during this 5-year study period, 2 of them (50% of all the deaths) occurred in patients with CI-AKI – 1 male and 1 female with obesity and diabetes mellitus. All the 4 patients had arterial hypertension, 2 – diabetes mellitus and 1 was obese, 1 had anaemia. 10 (1.7%) patients needed revascularisation with coronary artery bypass grafting (CABG), 3 of them (male with arterial hypertension and no diabetes mellitus) developed CI-AKI 5 years before. 45 (8%) patients needed new PCI during the follow up period. Only 11 earlier had CI-AKI. These patients had arterial hypertension, only 3 suffered from diabetes mellitus and 3 were obese but only 1 had obesity and diabetes mellitus (a male of 51 years old). 12 cases of MI were diagnosed during the 5-year period. 1 patient (a 57-year old female with arterial hypertension and obesity) who developed CI-AKI previously had MI with numerous PCI (3 procedures) and stroke. 7 patients (1.2%) had stroke, 4 (3 females) of them with CI-AKI (3 with arterial hypertension and obesity and 1 with diabetes mellitus and obesity).

Conclusion: According to our study the most important risk factors are diabetes mellitus and arterial hypertension. There is a trend for male patients to develop MI and for female – stroke. But this information needs evaluation in bigger groups of patients. CI-AKI is associated with serious, adverse long-term outcomes (cardiovascular death, CABG and PCI).

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Development of a New Wearable Mechatronic Device for Extracorporeal Blood Ultrafiltration

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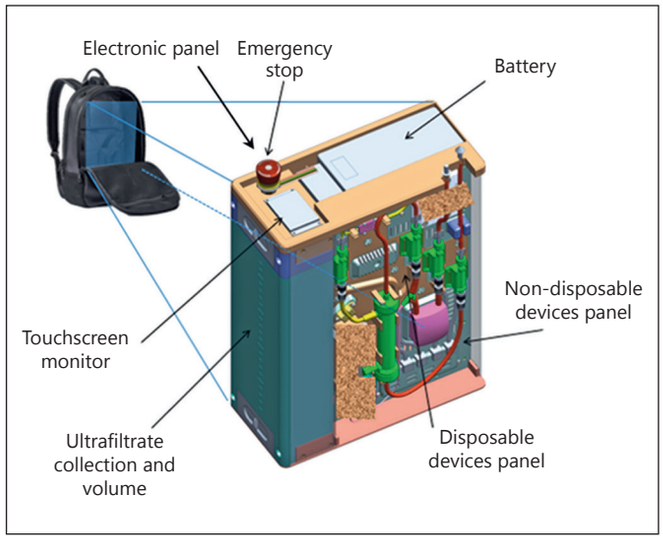
The interest in the design of portable and wearable medical devices is related to both the relevant clinical and social benefits for patients and the potential economic savings for national health services. Biomedical technologies are improving at a very fast rate and represent an extraordinary means to develop innovative portable and wearable devices which can help people live in a prosperous way, in particular reducing sorrow in case of disease.

This work presents a new wearable and portable device for extracorporeal blood ultrafiltration, named RAP, able to remove excess fluids from fluid overload patients with chronic kidney disease and/or congestive heart failure. The design requirements that a modern wearable device for extracorporeal ultrafiltration must meet have been identified thanks to a thorough literature review on previous similar proposals followed by an extensive risk analysis. Such an analysis, preliminary to the development of the system, allowed not only to identify essential components of the device, but also to propose an original approach for the RAP design, where many disposable components have been integrated. For some components, commercial (off-the-shelf) products were available, for other ones specific investigations, studies and developments were needed, leading to the design and development of customized solutions (e.g. electromechanical clamp, ultrafiltrate volume measurement and heparin infusion systems). The design of an effective, efficient, safe and reliable control architecture, based on two microcontrollers and one microcomputer, the implementation of the control logic and of a user-friendly graphical user interface have been carried out too being essential features of such a mechatronic device.



. 1. Final layout proposal for the RAP (for Abstract no 28).

A backpack/trolley design has been chosen as the layout for the device, since such a solution guarantees the best tradeoff between miniaturization and ergonomics. The design introduces an original positioning of the vast majority of components in three independent planar panels: one for disposable components, one for non-disposable devices and one for electronic boards and controllers (ure 1). This arrangement of components can drastically simplify and speed up the in-hospital operations needed before and after a therapy with the RAP.

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Air Removal in Extracorporeal Blood Purification: A Preliminary Risk Analysis Evaluation

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Background and Objectives: During extracorporeal blood purification therapies performed with continuous renal replacement therapy (CRRT) machines, the risk of embolism due to air infusion into patient circulatory systems is avoided by an air removal chamber and an air detector, both placed upstream the return vascular access.

The aim of this preliminary study is to evaluate experimentally the prevalence of the possible causes of air infusion during CRRT.

Methods: Three representative CRRTs were considered in modality of Continuous Veno-Venous Hemofiltration in post dilution. An ultrasonic air bubble detector was placed immediately upstream the air removal chamber in the return line. Digital data acquisition and processing were performed to couple the air infusion detections with the specific events happened.

Results: In each CRRT session (lasting between 11 and 24 hours), a very low volume of air was detected compared to the whole liquid volume (during treatment sessions: min 0%, max 0.021%).

Table 1 summarizes the total number of events that were associated to air detection during all the three real treatments (excluding the priming steps).

Most of the air presence during treatments was due to specific events, such as incomplete priming, procedures of bag exchange of replacement fluids or vascular access malfunctions. Half of the events causing air inflation inside pipes is due to the bag change procedures.

Conclusions: It is shown that the total volume of air bubbles circulating during a CRRT is generally low. Apart from an obvious air presence during priming sessions, air infusion seems to be confined to specific occasional events, in particular as consequence of bag change procedures. Consequently, devices like hydrophobic filters in the replacement lines may be useful to reduce or avoid half of the causes of air infusion in the main blood circuit.

Table 1. Overall prevalence of detected causes of air infusion during the treatments (for Abstract no 29)

Cause of air infusion	Number of events	% over total number of events
Incomplete priming	2	20%
BAG change	5	50%
Catheter	1	10%
Other	2	20%

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Acute Kidney Injury in Multiple Myeloma: Importance of Achieving a Complete Renal Remission. Experience in a Public Hospital

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Introduction: Acute Kidney injury (AKI) is a frequent complication in patients with multiple myeloma (MM) and is associated with a bad prognosis. MM causes fast damage, therefore it is imperative for the treatment to be as soon as possible. Its recovery could improve long time survival.

End Point: To evaluate the frequency on AKI in patients with a recent diagnostic of MM, mortality and response to treatment at the Hospital del Salvador between 2013–2016

Materials and Methods: Descriptive, retrospective study. Epidemiological and clinical characteristic were evaluated of the patients with recently diagnosis of MM with AKI between 2013–2016. AKI was defined as GFR <50 ml/min. Severe AKI was defined as plasmatic creatinine >4 mg/dl. Remission was defined according to International Mieloma Working Group (IMWG) definitions: complete response (CR) as improve of GFR or creatinine clearence from <50 ml/min to >60 ml/min. Partial response (PR) as sustained improve of GFR at creatinine clearance from <15 ml/min to 30–59 ml/min and Minimal response (MR) sustained improve GFRe from <15 ml/min to 15–29 ml/min and if it was between 15–29 ml/min at the beginning, improve to 30–59 ml/min. To calculate GFR we use MDRD-4 (according to recommendations of IMWG).

Global survival was evaluated with Kaplan-Meier and compared with log Rank.

Results: From 105 patients evaluated, 41 (39%) developed AKI, 12 patients severe AKI and 10 patients needed RRT. 16 patients had history of chronic kidney disease, all of them in stage 3. Male to Female ratio was 1:1.4. Media of age was 68 years (38–88). Media creatinine at the moment of diagnostic was 3.37 ± 0.6 mg/dl; at 1 month after diagnosed 2.1 ± 0.5 mg/dl and at the end of chemotherapy 1.6 ± 0.4 mg/dl. The classification of MM: 18 patients were Light Chain MM (43%); 15 patients IgG (37%), 8 patients IgA (20%).

Media GFR by MDRD-4 was 24 ± 4.47 ml/min. At 1 month after diagnosed 46 ± 9.6 ml/min, and at the end of chemotherapy 58 ± 10.2 ml/min.

At the end of chemotherapy, 25 patients achieved complete response, 2 patients achieved minimal response, 14 patients showed no response. 2 patients from the RRT (renal replacement therapy) group could become independent of dialysis. General survival at 1, 2, 3 years after chemotherapy was 51.8%, 47.1% and 23%, with a median survival of 16 months. Media survival of patients in with RRT vs without RRT was 5 and 31 months (p = 0.029) respectively. General survival of patients with complete response vs any other response at 1 year was 70% and 24% respectively and at 3 years 62% and 0% respectively.

Discussion: In our group of patients with MM, exist similar frequency of AKI and RRT as described in literature. As expected, majority of patients was a light chain MM. Patients who need RRT had the worst prognosis. A remarkable finding is the sig-

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nificant difference in survival in the patients that reach complete remission versus those that do not reach it, so that the renal recovery could be an attractive factor to consider in terms of prognosis.

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Detection and 3 Year Follow-Up of Acute Kidney Injury in Hospitalized Patients at De Clinical Hospital of the University of Chile. Results from a Retrospective Cohort Study

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Introduction: Acute Kidney Injury (AKI) is a sudden increase in the serum creatinine concentration and/or a decrease in urinary volume. Epidemiological studies confirm that the incidence of acute kidney injury in the general hospitalized – patient population is increasing and that in-hospital mortality is extremely high. Observational studies hace shown links between small increases in the serum creatinine concentration and a increase risk of adverse events in short-tern and long term outcomes. Observational studies have shown a that survivors from in-hospital have a strong association to out-hospital mortality and the development of chronic kidney disease (CKD) in the long term.

The objective of this study is to evaluate the incidence of in – hospital AKI using a software based detection method and adverse outcomes at short and long term.

Methods: Retrospective cohort study of adult patients admitted to the Clinical Hospital of the University of Chile between January 1º and June 30º of 2014. Patients with at least 2 serum creatinine concentration during hospitalization were included (requisite for the software based detection). CKD patients in renal replacement therapy (RRT) were excluded. The data of the patients was admitted to a software based program (AKI – HUNTER®) that diagnosed AKI with the differences between serum creatinine concentration according to KDIGO criteria. Demographical, clinical and laboratory data were collected. Moreover, we evaluated the long term outcomes (follow up until January 01º of 2018) of CKD development and mortality rates.

Results: During follow up we collected 15.547 serum creatinine concentration corresponding to 5.418 hospitalized patients. Of these, AKI – HUNTER® detected 393 (7.2%) cases of AKI (71% KDIGO stage 1; 14% KDIGO stage 2; 15% KDIGO stage 3). 14 patients were excluded because of CKD in RRT. Follow up was completed in 302 patients (80% of AKI patients) and were included in the analysis.

The mean age was 54.6 ± 11.5 years, female sex 55%, arterial hypertension 160 (51%) and diabetes 79 (25%). 69% of the patients were admitted from the emergency unit and 22% were admitted to perform elective surgery. The hospitalization units were: Critical care (43%), Surgery (31%) and Internal Medicine (26%). 26% of the patients developed in-hospital sepsis. Hospital stay averaged 18 ± 7.5 days, patients who required in hospital RRT 8%. In hospital mortality was 21.8% (66 patients). It came to our notice that 18% of the patients had nephrological evaluation and only 17% had the diagnosis of AKI in the hospital discharge data.

At the 3 year follow up of the survivors (236 patients) we found a mortality rate of 15.2%, 14.0% and 7.0% at the 1st, 2nd and 3rd year, respectively. Cumulative survival rate at 3 years was 67.7% (160 pacientes). The CKD rate at 3 years was 27.7% and 4 patients (1.8%) developed end-stage renal disease with RRT.

Conclusions: The present study shows that, even though AKI is acknowledged as an important morbidity and mortality risk factor, there is a low rate of in hospital recognition and notification in the hospital discharge data (17% of the patients with AKI). Also, it confirms the high mortality of these group of patients in the hospital setting and a high rate of mortality and development of CKD at long term follow up.

Our data suggest that an automated software based strategy for early AKI detection is effective to raise the rate of in-hospital AKI diagnosis. This could be relevant for the realization of early potencial beneficial strategies, in the short and long term, to prevent the development of adverse outcomes.

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Serial Measurement of Cell-Cycle Arrest Biomarkers [TIMP-2]·[IGFBP7] and Risk for Progression to Death, Dialysis or Severe Acute Kidney Injury in Patients with Septic Shock

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Background: Urinary tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) perform well for predicting AKI in patients with sepsis, but since most patients with sepsis present with AKI, a critical question is whether biomarkers can inform on progression to severe outcomes.

Methods: We analyzed data from 688 patients enrolled in the ProCESS trial with septic shock. We measured [TIMP-2]·[IGFBP7]

before and after a 6-hour resuscitation protocol. Our primary endpoint was the composite of severe AKI (KDIGO stage 3), renal replacement therapy or death within 7 days.

Results: A total of 113 patients (16.4%) reached the endpoint. In patients without AKI by serum creatinine or urine output over the 6 hour interval, the proportion who developed the endpoint was significantly higher when [TIMP-2] [IGFBP7] was positive (> 0.3) at hour 0 (13.7% vs 6.1%, p = 0.01); whereas no differences were found in patients with clinical AKI (32% vs 24.1%, p = 0.25). A positive [TIMP-2] [IGFBP7] following resuscitation was associated with worse outcomes in both patients with (29.1% vs 16.7%, p = 0.04) and without (16.3% vs 6.9%, p = 0.003) clinical evidence of AKI. In patients with negative [TIMP-2] [IGFBP7] at baseline, those who became positive (>0.3 units) after resuscitation had 3-times higher risk (21.8% vs 8.5%, p = 0.01; OR 3.0, 95% CI 1.31–6.87). Conversely, among patients with a positive biomarker at baseline, for those whose biomarker result became negative at hour 6, risk was reduced (9.8% vs 23.8%, p < 0.001; OR 0.35, 95% CI 0.19–0.62). Study interventions did not alter biomarker trajectories, nor did they alter outcomes in biomarker positive or negative patients. However, biomarker trajectories were associated with renal outcomes.

Conclusions: Changes in urinary [TIMP-2] [IGFBP7] following initial fluid resuscitation are associated with changes in risk of progression in septic patients with AKI.

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The Treatment of Rhabdomyolysis with EMIC2 Dialyser: Monocentric Experience

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Introduction: Rhabdomyolysis is a syndrome characterized by striated muscle injury that causes muscle necrosis and the release of intracellular consituents into the circulation; the main of these constituents is Myoglobin (MGB). High levels of MGB in peripherical blood determine tubular obstruction and acute kidney injury, often associated with oligoanuria. We observe a lot of causes of rhabdomyolyis; about 8–20 percent of these patients (PT) develop acute kidney injury due to high plasma concentration of MGB.

Aim of Study: To evaluate the removal of MGB in Continuous Renal Replacement Tehrapy (CRRT) with high cut-off membrane (EMiC2 Fresenius – cut off 40 kDa) in PT affected by rhabdomyolysis and admitted in Intensive Care Unit (ICU).

Methods: From April 2016 and February 2018 we have treated 10 PT affected by rhabdomyolysis (9 men and 1 women, age 60 ± 15 years, 9 PT needed mechanical ventilation, in 6 PT vasopressors were administrated). Three PT had preserved urinary output, 7 were oligoanuric. CRRT was performed through Citrate-anticoagulated Continous VenoVenous HemoDialysis (CiCa-CVVHD) with EMiC2 Fresenius Dialyser. Hemodyalitic parameters: Blood flow 100 ml/min, Dialysate flow 2000 ml/h. Vascular access: in 6 PT central venous catheter was placed in right internal jugular vein, in 2 PT in right subclavian vein, in 2 PT in right femoral vein. MGB, CreatinKinase (CK) and Lactate Dehydrogenase (LDH), creatinine, total protein concentration were tested at the beginning of the treatment, after 24, 48 and 72 hours (the end of the treatment).

Results: The causes of rhabdomyolysis were: post-traumatic injury (4 PT), post revascularization procedures (4 PT), cocain use disorder (1 PT), severe dermatomyositis (1 PT). Circuit Lifespan: 62 ± 13 hours. After 24 hours of treatment we observed a decrease of 41.3 percent of MGB levels, that became of 77 percent after 48 hours of treatment (MGB levels from 36687 ng/ml to 8633, p = 0.0005). PT who preserved urinary output presented significantly lower MGB levels than oligoanuric PT, but the percentage of removal was similar. Plasmatic protein and albumine levels were similar before and after CRRT.

In 6 PT we observed recovery of renal function, they were transferred to appropriate department and then discharged; 1 PT died due to complications of underlying disease; 3 PT died in ICU.

Conclusions: Acute tubular injury due to rhabdomyolysis is a common complication and can lead to prolonged hemodialysis require and long hospitalization. Our experience confirmed that CRRT with EMiC2 Fresenius allows to decrease MGB levels about 77 percent in the first 48 hours, to faster recovery of renal function and reduced hospitalization in ICU.

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Hemoadsorption by Cytosorb® in Septic Shock with Acute Kidney Injury: A Case Series

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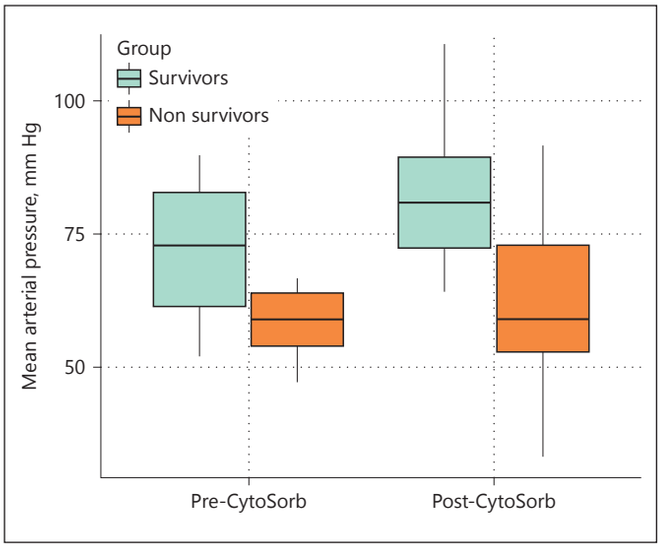
Background: Septic shock is a life-threatening disease caused by a dysregulated host response to infection; one of the main features of septic shock is the massive release of cytokines and other inflammatory mediators causing refractory hypotension, tissue damage, metabolic acidosis and ultimately multiple organ failure (MOF). All these disorders result in significant mortality, morbidity and resource usage among critically ill patients. Moreover, Acute Kidney Injury (AKI), occurring in 40–50% of septic patients, increases mortality significantly.

In this setting extracorporeal blood purification techniques have an emerging role and offer a promising adjuvant treatment; among them, we here report our experience with CytoSorb®, a recently introduced adsorbent device. In fact several animal experiments and some clinical studies have established the effectiveness of CytoSorb® for cytokine removal in sepsis.

Materials and Methods: From August 2015 to December 2017, 24 patients diagnosed with septic shock in the Intensive Care Unit (ICU) of our hospital were treated with Continuous Renal Replacement Therapy (CRRT) associated with hemoadsorption by CytoSorb®. All the cases presented organ failure including AKI. The source of infection was treated with surgery (n = 15) or with medical therapy (n = 9); all cases requiring surgery underwent operation before starting hemoadsorption.



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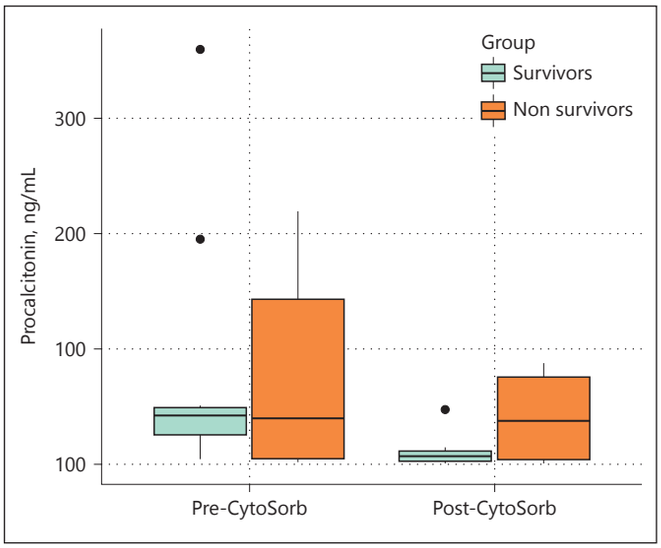

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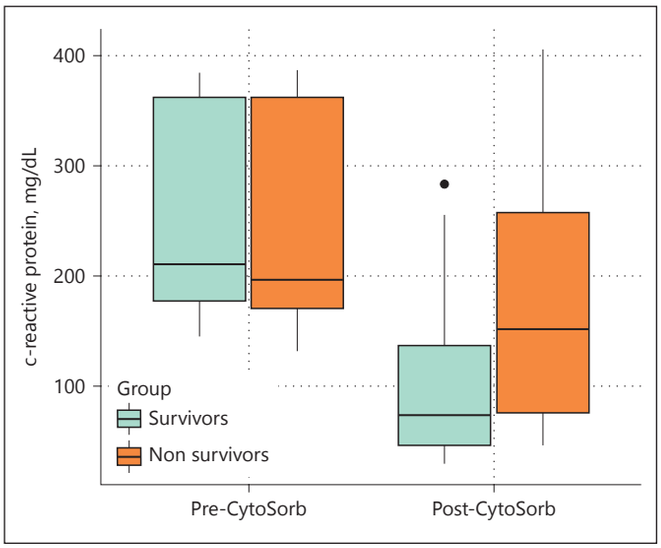

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The mean age was 67 ± 13 y (SD); 52% of the cases were male (n = 13). On admission to the ICU the mean SAPSII (Simplified Acute Physiology Score) score was 52 ± 12.9 (SD). All patients received at least one CytoSorb® treatment and additional treatments (up to five) according to the clinician's indication. The median number of CytoSorb® treatments was two. CRRT was performed as continuous veno-venous hemodialysis (CVVHD) or continuous veno-venous hemofiltration (CVVH), according to the clinical setting. The number of adsorbent filters used was variable and dependent on the general condition and the clinical response (from 1 to 5). A CytoSorb adsorber was installed pre-hemofilter to the CRRT circuit; blood flow rates were kept between 150 and 200 mL/minute while dialysis doses were in the range of 18 to 45 mL/kg/h. Adsorbers were changed every 24 h. Systemic heparin (from 500 UI/h to 1000 UI/h) was administered as anticoagulation.

Results: We observed shock reversal in 12 patients (50%). During the course of CytoSorb® treatment, patients surviving to day 30 ($n = 12$) had significant improvement of MAP (Mean Arterial Pressure) (. 1) and decreased CRP (C-Reactive Protein) and procalcitonin levels (. 2–3). Mortality at 30 days among medical patients was higher than surgical patients (56% vs 47%). Treatment using the CytoSorb® was safe and well-tolerated with no device-related adverse events during or after the treatment sessions.

Conclusions: Hemoadsorption with Cytosorb® is a promising therapeutic option in the setting of septic shock associated with AKI requiring CRRT. Our experience demonstrates that Cytosorb® is safe and easy to use; septic patients from surgically-treated source of infection had better results in terms of mortality, suggesting a potential role of Cytosorb® in these selected cases.

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CytoSorb in the Refractory Septic Shock: A Case Report

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Background: Septic shock, defined as organ dysfunction caused by a response of the dysregulated host to infection, is a condition associated with high morbidity and mortality in critically ill patients, despite progress in diagnostics, treatment and monitoring techniques and support. One of the hallmarks of sepsis is the excessive release of cytokines and other inflammatory mediators that cause refractory hypotension, tissue damage, metabolic acido-

sis, and, eventually, multi-organ failure (MOF). New adsorbents aimed at modulating the cytokine cascade are now available as adjuvant therapy in sepsis, of deemed usefulness if adopted early (within 8–24 hours from the diagnosis of septic shock) in patients not responding to standard therapy.

Methods: A male patient, 47 years old, suffering from autoimmune hepatitis in treatment with steroids and azathioprine, subjected to the previous week to a liver biopsy for persistent increase in gamma-GT, developed septic shock and MOF. Blood culture was positive for Streptococcus pneumoniae. There was a refractory septic shock, despite the resuscitation therapies and the first empiric antibiotic therapy, subsequently specific. In this patient, we evaluated the impact of a new device of haemadsorption (CytoSorb) used as adjunctive therapy, on hemodynamics and on clinically relevant outcome parameters and levels of hyperbilirubinemia. The patient was subjected to haemadsorption with Cytosorb (Qb: 150 ml/min) added in series to the high cut-off filter for a total of 2 cycles of 48 hours each. Cytosorb was replaced every 24 hours. Anticoagulation was regional with citrate.

Results: The treatment of this patient suffering from septic shock was associated with hemodynamic stabilization with progressive increase in mean arterial pressure and subsequent gradual reduction of amines until complete suspension, a reduction in the levels of sepsis dynamic markers such as C-reactive protein and procalcitonin as well as of blood lactate levels. The stabilization of hemodynamics was associated with a gradual recovery of diuresis. Bilirubin levels decreased by 25%. The patient had a >28-day survival with SAPS II (expected mortality) reduced from 84 to 70 pts and SOFA score (calculated mortality) from 19 to 13 pts. Treatment with the CytoSorb device was safe and well tolerated without adverse events related to the device during or after treatment sessions.

Conclusion: Haemadsorption with CytoSorb resulted in rapid hemodynamic stabilization and increased survival. RCTs are needed to define the potential benefits of these new treatment options.

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Coupled Plasma Filtration Absorption (CPFA) in One Case of Hepatocellular and Obstructive Jaundice

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Background: Ittrium 90 radioembolisation is a well-known therapy of metastatic hepatic lesions. This therapy is often complicated by a hepatocellular jaundice because the direct bilirubin excretion loss. Direct bilirubin is a small molecule, in prolonged jaundice almost 40% direct bilirubin is bound to plasmatic albumin with covalent strengths therefore is hardly dialyzed.

Materials and Method: A 48 years old patient with rectal adenocarcinoma was treated with rectal resection and chemotherapy. Two years after the diagnosis the patient underwent left hepatic lobectomy and pulmonary resection because metastasis spread. At month 41 a new hepatic metastasis was treated with chemotherapy and Ittrium 90 radioembolisation. Two months later the patient was hospitalized for ingravescent jaundice caused by Ittrium 90 toxicity and common bile duct stenosis, requiring extracorporeal detoxification treatment. The patient was referred to Dialysis Unit and underwent: plasma exchange (PEX) 2 treatment, 3 h each, single pass albumin dialysis (SPAD) 1 treatment of 5 hours and coupled plasma filtration absorption (CPFA) 15 treatment, 6 h each. CPFA was performed with Bellco Amplia CRRT machine, 0.45 m^2 poliethersulfone plasmafilter (Micropes®), 140 ml divinilbenzene styrenic macroporus resin (MediaSorb®) cartiridge (surface 600 m^2/g) and 1.4 m^2 polyphenylene high flux hemofilter.

Results and Discussion: PEX permitted bilirubin reduction from 32.6 to 24.09 mg/dl (–27%), with SPAD bilirubin decreased from 34.48 to 32.35 mg/dl (–7%). With CPFA we observed a bilirubin reduction of 29% (pre-treatment plasmatic bilirubin 30.47 ± 2.40 mg/dl, plasmatic bilirubin post treatment 21.89 ± 2.58 mg/dl, $p < 0.001$). We observed no complications except a heparin inducted thrombocytopenia episode resolved with anticoagulant therapy switch to fondaparinux. When patient condition was stationary ERCP was performed showing right hepatic duct stenosis treated with stenting. CPFA is a detoxification system recommended for sepsis and used as bridge in liver transplant but recently found application in acute liver failure. We used CPFA in one hepatocellular jaundice with prevalent direct bilirubin, in our experience CPFA had the highest efficiency in bilirubin removal compared with SPAD and PEX. Our result of CPFA bilirubin removal is in line with the findings of De Simone (2017) but worst compared to Muggi (2013) and Donati (2017) (respectively CPFA bilirubin removal 26.2%, 40% and 41%). CPFA bilirubin removal appears to be not inferior to the removal obtained with MARS, Gong (2008) obtained with MARS total bilirubin removal of 26.6% and Donati (2014) of 23% in a large population. In literature higher bilirubin removals than CPFA are obtained with the more complicated and expansive Prometheus technique (Evenepoel 2006).

Conclusion: To the best of our knowledge this is probably the first clinical experience comparing, in the same patient, the efficacy in direct bilirubin removal of 3 different techniques. CPFA is a valid, relatively simple and economical detoxification system in acute liver failure.

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A Rare Case of AKI Sustained by Segmental Arterial Mediolysis with Bilateral Renal Infarction

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*Socio SIN presentatore

A 45-year old man hospitalized for low back pain, fever and hematuria, associated with a rise in serum creatinine (1.75 mg/dl). Renal ultrasound showed normal findings, contrast CT showed bilateral renal infarctions. Trombophilia screen, autoimmune

markers, blood and urine cultures, trans-esophageal echocardiography and ECG-Holter, all resulted negative, hyperhomocysteinemia was found. Angio-CT showed bilateral double renal arteries with alternation of stenosis and ectasies, findings indicative for dissection. Arteriography documented dissecting aneurysm compatible with the diagnosis of segmental arterial mediolysis (SAM). A genetic screen for connective tissue pathologies was made, and cerebral MRI showed superior sagittal sinus thrombosis. Anticoagulant therapy was introduced for thrombosis, and beta-blocker was started to reduce mechanic stress on the arterial wall. At one month creatinine has returned to normal. SAM is a rare arteriopathy of medium and large vessels associated with dissecting aneurysms, thrombosis and rupture of the arterial wall. It affects average age, in 80% of cases it involves celiac artery, renal arteries are the most involved nonvisceral arteries. Clinical presentation is with flank pain. Characteristic of SAM are isolated non aorta-related peripheral arterial dissection, negative autoimmune markers and normal inflammatory indices. Therapeutic target is the maintenance of normal blood pressure to prevent vascular rupture.

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AKI in Recurrent HCV-Related Cryoglobulinemia Treated with Intermittent Renal Replacement Therapy (IRRT), Plasmapheresis and Rituximab

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A 65-year-old HBV and HCV positive woman, presented edema and palpable purpura, during AKI. We performed immunological and virological exams and kidney biopsy to investigate the hypothesis of HCV-related cryoglobulinemia. They confirmed the first hypothesis of Cryoglobulinemia IIa. As expected, the HBsAg ant HCV-Ab tests were postive, but without signs of viremia (PCR test for HBV-DNA and HCV-RNA negative). Clinical conditions, caracterized by intial fluid overload, not responder to diuretics, hyperkalemia, without electrocardiographic alterations, and hyperazotemia, without organ damage, persuaded us to start renal replacement therapy with intermittent treatment, stopped, after one week-treatment, on the basis of recovery of kidney function. We started plasmapheresis (5 sessions during the hospitalization), methylprednisolone and Rituximab. Four weeks after, our patient was admitted again, because of clinical exacerbation. Furthermore we perfomed immunological and virological exams which confirmed the hypothesis of recurrent cryoglobulinemic vasculitis. Therefore we restarted plasmapheresis and IRRT. Laboratory test showed persistent B-cell depletion, as consequence of anti-CD 20 treatment. Kidney function quicky improved after plasmapheretic treatment and IRRT.

Our case is an example of short-time recurrent HCV-related cryoglobulinemic vasculitis, despite the absence of signs of viremia, at the time of first clinical manifestation.

The negative outcome of cryoblobulinemic test, at the time of first hospital discharge, that justified the plasmapheresis's discontinuation, and the B-cell depletion, as direct consequence of anti-CD 20 therapy with Rituximab, did not exclude the possibility of recurrent form of cryoglobulinemic vasculitis, justified for the evident clinical maifestations, congruent with the first episode. RRT allowed us to stabilize clinical conditions, until recovery of kidney function, occured after plasmapheresis and Rituximab. Despite their rarity, recurrent HCV-related cryoglobulemic vasculitis, during the persistent effect of anti-CD 20 therapy, represent clinical situations that we can not understimate; they may need transitory extracorporal replacment treatment and all these issues justify a close follow-up, in order to monitor clinical conditions, even before laboratory tests.

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Human Mesenchymal Stromal Cells Improve Acute Kidney Injury in a Rat Ischemia-Reperfusion Model by Ameliorating Complement Induced Inflammatory Cascade

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Introduction: The primary rational for using mesenchymal stromal cells (MSCs) to rejuvenate damaged tissue is based on their ability to differentiate into the cells of the injured tissue. Previous studies have demonstrated beneficial effect even during the early stage, before their potential differentiation. The aim of the current study was to investigate the potential role of systemic administration of MSCs in ischemia-reperfusion (I/R) model of AKI and to gain better understanding on the potential mechanisms of action.

Methods: A rat model of I/R induced AKI was used. Rats underwent unilateral nephrectomy with simultaneous clamping of the contralateral kidney for 60 minutes, following by reperfusion. Four treatment groups received escalating dosages of human MSCs and 48 hours afterwards, rats were scarified. Blood was procured for evaluation of renal functioning and inflammatory markers. Urine was collected for creatinine clearance test (CCT) and kidneys were allocated for histopathologic examination.

Results: Renal functions were improved in U shape manner. Mean serum creatinine levels were 4.5, 2.9, 2.6, 1.7 and 4.1 mg/dL in I/R-control, I/R + 150 K cells, I/R + 250 K cells, I/R + 500 K cells and I/R with 1,000 K cells respectfully (p-values <0.05). Urine volume and CCT demonstrated consistent results with the same U shape improvement manner. The complement system that was extensively active in the kidneys of the I/R control was ameliorated in MSCs treatment groups. In addition, the increased circulating C3 was also ameliorated by MSCs. At highest doses of MSCs administration, a significant increase in renal hypoxia was notice by Hypoxyprobe staining.

Conclusions: Systemic administration of MSCs improve kidney functions early after their administration by ameliorating the complement induced inflammatory cascade. High dosage of MSCs aggravates renal hypoxia and thus the U shape dose-response curve marks the need for appropriate dose selection.