Blood Purification

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Abstracts

Abstract Reviewer

Claudio Ronco - Abstract Reviewer
Director, International Renal Research Institute of Vicenza IRRIV, Vicenza, Italy

Sean Bagshaw - Member of the Scientific Committee
Professor and Chair, Department of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta
Scientific Director, Alberta Health Services Critical Care Strategic Clinical Network

Rinaldo Bellomo - Member of the Scientific Committee
Professor of Intensive Care, The University of Melbourne
Professor of Medicine, Monash University
Honorary Professor of Critical Care Medicine, University of New South Wales
Honorary Fellow, Howard Florey Institute of Physiology
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Director of Data Analytics Research and Evaluation (DARE) Centre
Member of Executive, Department of Critical Care, The University of Melbourne
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Staff Specialist in Intensive Care Austin Hospital & Royal Melbourne Hospital & Warringal Private Hospital, Australia

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Medical Director, Pheresis Service, University of Cincinnati School of Medicine
Co-Director, Heart Institute Research Core, University of Cincinnati School of Medicine
Professor, UC Department of Pediatrics, University of Cincinnati School of Medicine

Hernando Gomez Danies - Member of the Scientific Committee
Associate Professor of Critical Care Medicine and Emergency Medicine, University of Pittsburgh
Director, Cardiopulmonary Research Laboratory, University of Pittsburgh
Faculty, Program for Critical Care Nephrology, University of Pittsburgh

Associate Program Director, Anesthesiology Critical Care Fellowship, University of Pittsburgh
Faculty, CRISMA Center, University of Pittsburgh

Kianoush Kashani - Member of the Scientific Committee
Consultant - Division of Nephrology & Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota
Consultant (Joint Appointment) - Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota
Assistant Professor of Medical Education - Mayo Clinic College of Medicine and Science
Professor of Medicine - Mayo Clinic College of Medicine and Science
Master's Faculty Privileges in Clinical & Translational Science - Mayo Clinic Graduate School of Biomedical Sciences, Mayo Clinic College of Medicine and Science
Section Head - Division of Nephrology & Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota
Section Head of Artificial Intelligence and Digital Health

Ravindra Mehta - Member of the Scientific Committee
Professor Emeritus of Medicine, University of California San Diego
Director, UCSD Masters in Clinical Research Program
Clinical Core PI, NIH funded UAB/UCSD O'Brien Center for AKI research
Founding member of the Acute Dialysis Quality Initiative (ADQI) and the Acute Kidney Injury network (AKIN)

Marlies Ostermann - Member of the Scientific Committee
Professor of Intensive Care and Nephrology at Guy's & St Thomas Hospital, London
Director of Research, Intensive Care Society UK

Zaccaria Ricci - Member of the Scientific Committee
Associate Professor, Director of Anesthesiology and Intensive Care Unit,
Meyer Children's Hospital Florence, Italy
Department of Health Science, University of Florence

Conflict of Interest Statement

Claudio Ronco – Advisor, consultant, speaker or member of speaker bureau for Aferetica, Asahi Kasei Medical, Astrazeneca, BioMeriéux, Baxter, B.Braun, Cytosorbents, Jafron Inc., Medtronic, Ortho Clinical Diagnostics, Estor, Fresenius Medical Care, GE Healthcare

Sean Bagshaw - Baxter (Scientific Advisory, Speaker), BioPorto (Scientific Advisory), Novartis (Scientific Advisory), bioMerieux (Scientific Advisory), Sea Star Medical (Scientific Advisory), SphingoTec (Scientific Advisory), Zorro-Flo (Shareholder)

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1

UNDERSTANDING MYOGLOBIN ADSORPTION KINETICS: AN IN VITRO MODEL

M.Marcello [a,b], *A. Lorenzin* [a,b], *M. De Cal* [a,b], *D.Marturano* [a,b], *G. Ramirez-Guerrero* [c], *C.Ronco and M. Zanella* [a,b].

[a] Department of Nephrology, Dialysis and Transplant, San Bortolo Hospital, Vicenza, Italy; [b] International Renal Research Institute Vicenza (IRRIV) Foundation, Italy; [c] Dialysis and Renal Transplant Unit, Carlos Van Buren Hospital, Valparaíso, Chile

Background: Rhabdomyolysis is a condition in which a severe injury to the muscles leads to release into the blood of various muscle cell's content including myoglobin with consequent acute renal injury. Myoglobin is a middle molecular weight uremic toxin presents a two-compartment model of distribution in the body. A possible therapeutic option is the use of High Cut-off membranes but with the risk of significant loss of albumin and other proteins. The use of adsorption can overcome these limitations. The aim of our study was to assess the myoglobin adsorption capacity of neutral microporous styrene-divinylbenzene copolymer sorbent (e.g., HA330/380, Jafron Biomedical CO, Lts, Zhuhai City, China).

Methods: Using a downscaled module of HA380 Cartridge, we set up an ex-vivo circulation experiment in which 1 liter of saline solution with high concentration of myoglobin was pumped through the cartridge. We collected samples (3 mL) at different timepoints to measure Myoglobin concentration. We calculated the removal ratio (RR) and mass adsorbed at given time points.

Results Initial myoglobin concentration was 326338 ug/L. Final myoglobin concentration after 4 hours of experiment was 2042 ug/L. Removal Ratio at 4 hour was 99.4 % with a mass adsorption of 324.35 mg of myoglobin.

Conclusion To our knowledge, this is the first experiment that assessed the adsorption capacity of polistyrene-divinylbenzene sorbent. Our study, demonstrated high adsorption capacity in the first hour of treatment, confirming the possibility to use adsorption as an effective treatment option in rhabdomyolysis and avoiding complications associated to current dialytic treatment.

2

EVALUATING THE PERFORMANCE OF CHATGPT-4 AND CLAUDE 3 OPUS IN ADDRESSING CRITICAL CARE NEPHROLOGY-RELATED QUERIES

M. Sheikh[*] [a], *C. Thongprayoon* [a], *I. Craici* [a], *F. Qureshi* [a], *K. Kashani* [a,b], *W. Cheungpasitporn* [a]

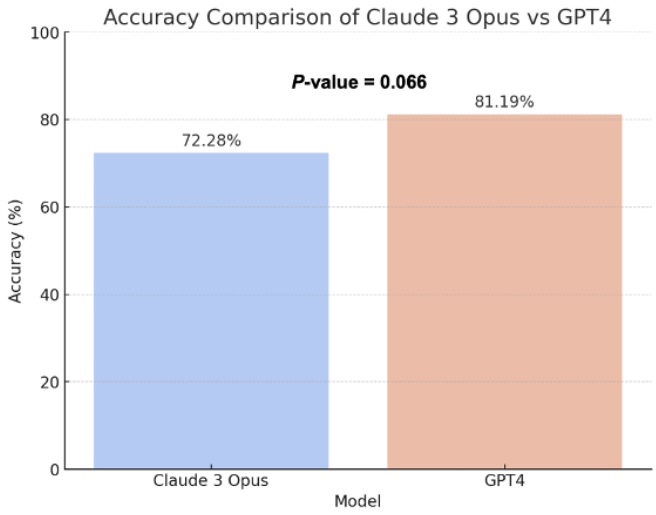
[a] Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN, USA
[b] Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic, Rochester, MN, USA

Background: The rapid advancement of large language models (LLMs) such as ChatGPT-4 and Claude 3 Opus has created novel opportunities for their potential application in clinical decision support systems. Although these models have demonstrated impressive performance across various domains, their utility in addressing nephrology-related queries has not been extensively investigated. This study aims to assess the accuracy and potential utility of these LLMs in answering questions related to acute kidney injury (AKI) and critical care nephrology, a field where accuracy and timely information is essential for optimal patient care.

Methods: We conducted a head-to-head comparison between ChatGPT-4 and Claude 3 Opus using a set of 101 multiple-choice questions specifically pertaining to AKI and critical care nephrology. These questions were sourced from the American Society of Nephrology's Self-Assessment Program (NephSAP) and Kidney Self-Assessment Program (KSAP). Data tables were reformatted into plain text for model input. Model responses were evaluated against correct answers, employing a McNemar test for accuracy differences and Cohen's kappa for inter-rater concordance.

Results: ChatGPT-4 demonstrated a higher correct response rate of 81.2% compared to Claude 3 Opus, which achieved 72.3% accuracy (P =0.066). The models agreed on 78.2% of the questions, with 86.1% of these concordant responses being correct. In cases of disagreement, ChatGPT-4 outperformed Claude 3 Opus on 14 questions, while Claude 3 Opus outperformed ChatGPT-4 on 5 questions. Both models answered three questions incorrectly with different responses. The kappa statistic of 0.71 indicated substantial agreement between the models.

Conclusion: Our findings highlight the impressive capabilities of ChatGPT-4 and Claude 3 Opus in addressing complex AKI and critical care nephrology questions, with ChatGPT-4 demonstrating an edge over its counterpart. The substantial agreement between the models suggests a consistent knowledge base, while the superior performance of ChatGPT-4 in cases of disagreement indicates potential differences in their reasoning capabilities. Despite the promising results, the occurrence of incorrect responses underscores the importance of human oversight and the need for continuous refinement of these models before their integration into clinical decision support systems.



3

ARTIFICIAL INTELLIGENCE IN NEPHROLOGY: PERCEPTIONS AND EDUCATIONAL NEEDS AMONG FELLOWS AT MAYO CLINIC MINNESOTA

M. Sheikh[*] [a], *C. Thongprayoon* [a], *I. Craici* [a], *F. Qureshi* [a], *K. Kashani* [a,b], *W. Cheungpasitporn* [a]

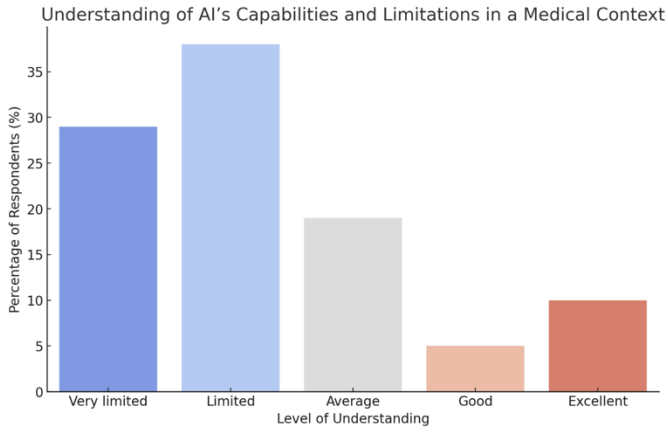
[a] Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN, USA
[b] Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic, Rochester, MN, USA

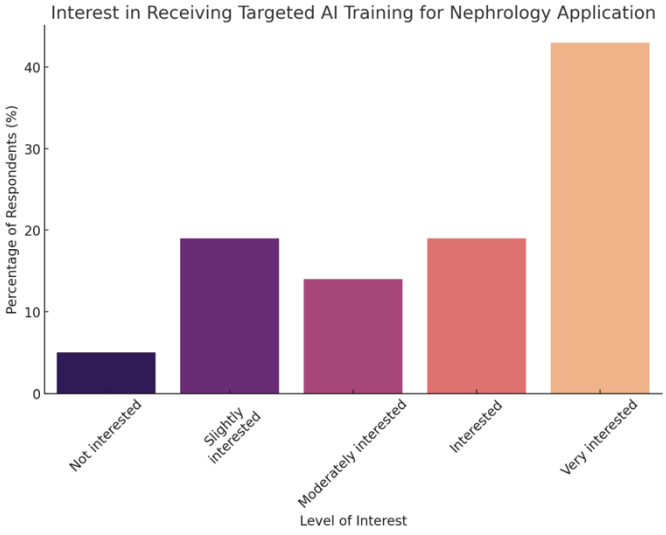
Background: Artificial intelligence (AI) has emerged as a transformative force in healthcare, offering potential benefits in clinical practice, medical education, and research. However, the adoption and integration of AI in nephrology fellowship training, including its applications in critical care nephrology, remain largely unexplored. This study aims to assess the current perceptions, utilization, and educational needs regarding AI among nephrology fellows at Mayo Clinic Minnesota.

Methods: An online survey was distributed to 14 nephrology fellows at Mayo Clinic Minnesota, including general nephrology, transplant nephrology, and onco-nephrology fellows. The survey evaluated the fellows' current usage of AI-based tools, their perceived relevance of AI in nephrology and critical care nephrology, interest in receiving AI education, preferred learning methods, and perceived barriers to AI adoption. Descriptive statistics were used to analyze the survey responses.

Results: Among the 14 fellows surveyed, 13 responded, yielding a response rate of 92.9%. The survey revealed that 69.3% of fellows had never or rarely used AI-based tools in their clinical or research activities, including in the context of critical care nephrology. None of the respondents had received formal AI education. However, 77% of the fellows rated AI's current relevance in nephrology as moderate to highly relevant, with particular interest in its applications in critical care settings, such as predicting acute kidney injury (AKI) and managing continuous renal replacement therapy (CRRT). A total 69.3% expressed moderate to high interest in receiving targeted AI training, including topics relevant to critical care nephrology. Interactive workshops were identified as the preferred method of delivering AI education by the majority of trainees. Limited knowledge was recognized as the primary barrier to AI adoption by most fellows. Optimism about AI's potential in nephrology was evident, with 76.9% and 81.0% of respondents expressing enthusiasm for its applications in predictive modeling and diagnostic imaging, respectively. However, confidence in AI for clinical decision-making, particularly in the intensive care unit (ICU) remained cautious, with 30.8% neutral and 53.9% uncertain.

Conclusion: This study highlights a significant gap between the perceived relevance of AI in nephrology and its current utilization among fellows at Mayo Clinic Minnesota. Despite the lack of formal AI education, there is a strong interest in receiving targeted AI training, particularly through interactive workshops, with an emphasis on topics relevant to critical care nephrology. The fellows' optimism about AI's potential in predictive modeling and diagnostic imaging, including in the context of AKI and CRRT management, contrasts with their cautious stance on its role in clinical decision-making in the ICU. These findings underscore the need for structured AI educational initiatives within nephrology fellowship programs to bridge the knowledge gap and facilitate the effective integration of AI technologies into the management of patients with kidney disease, including those in critical care settings.





4

A PHASE 3 STUDY OF *ravulizumab* TO PROTECT PATIENTS WITH CHRONIC KIDNEY DISEASE FROM CARDIAC SURGERY ASSOCIATED ACUTE KIDNEY INJURY AND MAJOR ADVERSE KIDNEY EVENTS: THE ARTEMIS STUDY

Marlies Ostermann[a], Pamela D. Winterberg[b], Christine M. Solinsky[b], Gerry Li[b], William T. Smith[b], Daniel Engelman[c]*

[a]Guy's and St Thomas' NHS Foundation Trust, London, UK; [b]Alexion, AstraZeneca Rare Disease, Boston, MA, USA; [c]Heart & Vascular Program, Baystate Health, University of Massachusetts Medical School - Baystate, Springfield, MA, USA

Background: In patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), pre-existing chronic kidney disease (CKD) confers a substantial risk for poor outcomes, including the development of cardiac surgery-associated acute kidney injury (CSA-AKI). CSA-AKI occurs in ≥50% of patients with CKD undergoing cardiac surgery with CPB vs ~20–25% of patients without CKD[1,2]. The risk of subsequent Major Adverse Kidney Events (MAKE; a composite of sustained kidney dysfunction, initiation of dialysis, and death) is also elevated in patients with CKD. Causes of CSA-AKI are multifactorial and complex, and may include inflammation, oxidative stress, renal congestion, and ischaemic injury (such as ischaemic-reperfusion injury [IRI]). IRI is a common cause of AKI and typically results from early hypoperfusion while on bypass, followed by kidney injury upon reperfusion. There are currently no approved therapies that reduce the risk of AKI and associated poor outcomes after cardiac surgery with CPB[3]. Preclinical and clinical studies suggest that damage and inflammation caused by IRI and CPB is amplified by complement activation[3]; early treatment with C5 inhibitors, especially before onset of ischaemia, may lower the risk of damage.

Methods: ARTEMIS (NCT05746559) is a Phase 3, randomised, double-blind, placebo-controlled, global study of ravulizumab in adults with CKD and stable cardiac disease undergoing non-emergent cardiac surgery with CPB, to reduce the risk of post-operative AKI and subsequent MAKE 90 days post-surgery. Key inclusion and exclusion criteria can be found in Figure 1. Briefly, the study consists of an up to 28-day screening period, randomisation and dosing 1–7 days prior to surgery with CPB (Day 1), a 90-day primary evaluation period post-CPB, and a survival follow-up at day 365 post-CPB. Approximately 736 participants will be randomised 1:1 to receive a single weight-based dose of ravulizumab or placebo; randomisation will be based on baseline CKD stage (3A, 3B, 4) and surgery type (mitral valve replacement or combined procedures vs other single procedures). The primary objective of this study is to assess the efficacy of ravulizumab in reducing the risk of MAKE90, defined as meeting ≥1 of the following by day 90 post-CPB: ≥25% sustained decrease from baseline in estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, based on serum Cystatin C); initiation of kidney replacement therapy; death from any cause. The safety of ravulizumab in participants with CKD undergoing non-emergent CPB will also be evaluated. Other secondary objectives include assessment of ravulizumab efficacy for reducing AKI (based on serum creatinine) and MAKE risk at earlier timepoints following CPB, alongside any effects it may have on healthcare resource utilisation and health-related quality of life in participants with CKD undergoing non-emergent CPB.

Results: The final analysis will be conducted when all participants have completed the primary evaluation period.

Conclusions: The aim of this study is to assess whether terminal complement inhibition with ravulizumab is safe and effective in reducing MAKE and improving outcomes in patients with CKD undergoing cardiac surgery with CPB.

Figure 1 - Inclusion and exclusion criteria2

Inclusion Criteria	Exclusion Criteria
• 18–90 years of age • Planned non-emergent cardiac surgery with cardiopulmonary bypass for multi-vessel coronary artery bypass graft, valve replacement/repair, or combined coronary artery bypass graft and valve surgery • Known or apparent chronic kidney disease and estimated glomerular filtration rate ≥20 to <60 mL/min/1.73m^2 (using Chronic Kidney Disease Epidemiology Collaboration equation by serum creatinine or serum cystatin C measurement, obtained by local or central laboratory during the 28 days prior to randomisation) • At risk for post-surgical kidney events as defined by a minimum Society of Thoracic Surgeons Calculator Renal Failure Risk Score of ≥2.8% assessed at time of screening	• Emergency or salvage cardiac surgery expected at screening or randomisation • Single vessel coronary artery bypass graft without valve surgery, or off-pump surgery, is planned • Any use of kidney replacement therapy or presence of acute kidney injury within 30 days prior to randomisation (except transient Stage 1 acute kidney injury after iodinated contrast exposure) • Active systemic bacterial, viral, or fungal infection within 14 days prior to randomisation; history of unexplained, recurrent infections; history of or unresolved *N. meningitidis* infection; and/or congenital immunodeficiency • Use of any complement inhibitors, plasmapheresis, or plasma exchange within the year prior to screening, or planned use during the study

5

THE FIRST LATIN AMERICAN COHORT EVALUATED NEPHROCHECK® FOR EARLY DETECTION AND PREVENTION OF ACUTE KIDNEY INJURY IN A POSTOPERATIVE CARDIOVASCULAR SURGERY PROGRAM.

*Cornu Emiliano*a Alan Boucharda Nuñez Renzoa Lanzetti Julietaa Santillan Magdalenaa Avila Rafaela*

[a] Hospital Privado Universitario de Córdoba - Argentina

Background: Acute renal failure can occur in 5-40% of patients after cardiovascular surgery, and in our center, it was observed in 23% of patients until 2022. This condition can lead to complications in other organs and increase the duration of hospital stay, intensive care, and mortality rates. While there is no specific therapy for acute renal failure, it is essential to implement a package of measures to prevent injury after cardiovascular surgery. However, it is crucial to identify the high-risk subgroup so that these measures can be applied individually and avoid incurring excessive costs.

Nephrocheck® is a marker of renal stress that can detect the condition in urine even before it develops into renal failure, according to KDIGO. It has been effective in reducing the incidence of AKI globally and in advanced stages of multicenter studies throughout Europe. However, there is no reference to using this biomarker in cardiovascular surgeries in Latin America.

Therefore, the objective of this work is to evaluate the incidence of Nephrocheck® in the postoperative period of cardiovascular surgery to determine its potential for applying the KDIGO Bundle.

Methods: Prospectively evaluated patients admitted after scheduled cardiovascular surgeries in intensive medical-surgical therapy with and without extracorporeal circulation. Nephrocheck® dosing was performed 4 hours after admission, and the KDIGO BUNDLE was applied to those with values above 0.3.

Results: A total of 105 patients were evaluated. Among them, 32 (30%) underwent revascularization surgeries, 39 (37%) had vascular replacements, 20 (19%) underwent combined surgeries, and 13 (12%) had other types of surgery. The median age of the patients was 63 (IQ 57-70). Their SOFA score was 4 (IQ 4-5), and their APACHE II score was 8 (IQ 6-11). 70% of the patients had underlying illnesses, with high blood pressure and coronary artery disease being the most common comorbidities (60% and 45%, respectively). The median extracorporeal circulation time was 105 minutes (IQ 84-133).

The incidence of positive Nephrocheck® results was 32 (30%) with a median value of 0.5 (0.31-0.85), while negative results were observed in 56 (53%) patients with a median value of 0.16 (0.1-0.85). 15 (13%) patients were not measured and excluded. After applying the KDIGO Bundle, a total of 28% of patients were diagnosed with acute renal failure, with 3% of them being in an advanced stage. The median hospital stay was four days (IQ 4-6). The compliance rate with the measures was 90%.

Conclusions: This study is the first in Latin America to use Nephrocheck® to prevent acute renal failure. Since implementing this protocol, the incidence of AKI II-III has decreased from 10.5% to 3%. The incidence of positive tests is similar to other international cohorts, revealing that revascularization surgeries and combined procedures had the highest percentage of positive tests. The study demonstrates that biomarker measurement and the application of the bundles to most patients is possible in low and middle-income countries. Selectively applied measures could help prevent kidney failure in high-risk subgroups.

6

CONTRAINDICATION OF RENAL REPLACEMENT THERAPY IN A PUBLIC HOSPITAL IN PARANÁ: AN ANALYSIS OF EPIDEMIOLOGICAL PROFILE AND LABORATORY TESTS

T. M. Pereira a, J. F. da Silva a, E. Wust Neto a, A. S. Campiolo a, J. Voltoline a, V. de S. Costa a, P. C. N. Fortes a

a State University of Western Paraná (Unioeste – Paraná - Brazil)

Introduction: Renal Replacement Therapy (RRT) is a set of techniques that restore the functions of the kidneys when necessary. Renal failure can be acute, usually reversible, or chronic, requiring permanent RRT. One of the RRT modalities is known as dialysis, which removes excess fluid, toxins, and urea from the blood, and regulates electrolytes and pH. There are two main types of dialysis: Hemodialysis and Peritoneal Dialysis. Eligibility for RRT occurs when the patient has chronic kidney disease or acute renal failure. Contraindication, in turn, occurs when patients have severe infections, hemodynamic instability, or terminal illness. In this context, the ideal choice of RRT often depends on the patient's overall health and lifestyle, and the patient's and/or family's preference. From this perspective, this study aims to analyze the epidemiological profile and laboratory data of patients with contraindication to RRT in a public hospital in Paraná, determining the main causes of contraindication.

Methodology: A retrospective study was conducted, analyzing the medical records of over 404 adult patients (over 18 years old), who underwent one or more evaluations at the nephrology service of the Hospital Regional do Sudoeste, between January 1st, 2022 and February 28th, 2023. The variables collected included age, sex, comorbidities, cause of renal failure, indication for dialysis, and reason for contraindication. In addition, laboratory tests of greatest interest were performed and analyzed for patients who were prescribed dialysis, such as arterial blood gas information and blood tests.

Results: From the 404 evaluations performed during the period, 59.88% were male and 40.11% were female. The mean age was 57.9 years, and the most prevalent age group involved those between 61 and 80 years old. The main underlying disease was chronic kidney disease (24.87%), followed by 2 or more comorbidities (23.63%) which include diseases such as hypertension, heart failure, diabetes and diseases not mentioned such as benign prostatic hyperplasia, prostate cancer and asthma, for example. The main reasons for seeking the nephrology service for dialysis included: acute renal failure caused by rhabdomyolysis, acute abdomen, mainly perforative, as well as stroke and fractures that decompensate the patient's baseline CKD. Regarding the indication for dialysis, the main causes mentioned were: acute renal failure (27.44%) and Infection and/or Sepsis (25.92%). In contraindication to dialysis, the prescription occurred mostly in male patients (65.07%) aged between 61 and 80 years (59.32%). The main cause of contraindication was hemodynamic instability (55.18%), followed by terminal illness (15.6%), palliative care (11.76%), senility (5.88%), desire of family members and other reasons (>1%). Regarding pH, most patients (66.66%) had metabolic acidosis, as the range included pHs that ranged from 6.8 to 7.3, with the normal range being 7.35 to 7.45. Regarding the analysis of PO2 (blood gas), 35.16% of the patients presented values between 101 and 221; 34.06% presented values between 27 and 29 and 30.76% presented values between 80 and 100. Regarding PCO2, 46.3% of the patients presented values between 11 and 34; 28.8% presented values between 46 and 77 and 24.7% presented values between 35 and 45. Regarding bicarbonate, it presented values between 6.4 and 25, in 71.4% of the cases. These facts may be related to compensated metabolic acidosis.

Conclusion: The study demonstrates that contraindication to dialysis in a public hospital in Paraná is mainly related to hemodynamic instability and terminal illness. Most patients are elderly males with chronic kidney disease stage V or acute renal failure and multiple comorbidities. These findings can help optimize patient selection for RRT.

7

INTERACTIONS BETWEEN THE CARDIOVASCULAR SYSTEM AND THE KIDNEYS IN THE CONTEXT OF CARDIORENAL SYNDROME: EPIDEMIOLOGY AND DIAGNOSIS

B.Bekishev [a], *A.Gaipov* [a], *A.Amanzholova* [a], *S.Nurzhanova* [a], *D.Koichubayeva* [a].

a Corporate Fund "University Medical Center"

Background: The combination of heart failure and renal failure, known as cardiorenal syndrome (CRS), is an important condition on the cardiorenal continuum and likely represents only one element of the cardiorenal-cerebral-metabolic axis. Renal dysfunction has a negative prognostic effect and is associated with increased mortality in patients with heart failure. It is important to diagnose CRS early and take it into account while managing patients suffering from heart failure.

Objective To study the prevalence and the structure of cardiorenal syndrome in cardiac patients. We studied a large cohort to describe the prevalence of different types of CRS and compare mortality, frequency of occurrence of myocardial infarction (MI), and stroke in patients with and without CRS.

Methods: The study included adult patients who were referred for diagnostic testing during the period from January 1, 2022 to January 1, 2023. Inclusion criteria for the study included patient age 18 years or older, no history of kidney or heart transplantation, and having at least one creatinine measurement within 365 days. For each patient, the mean creatinine value was calculated based on all available data for the last 365 days at the time of hospital admission and after any procedures. Baseline estimated glomerular filtration rate (eGFR) was then determined using the equation proposed by the Chronic Kidney Disease Epidemiology Collaboration.

Results Cardiorenal syndrome (CRS) was observed in 243 patients out of a total of 593 patients included in the study, which is 46%. Of these, 8 patients developed acute type 1 syndrome, 263 patients developed type 2, and 2 patients developed type 4. In addition, 17 patients with type 2 CRS developed acute kidney injury. Cardiorenal syndrome is observed more often in men (77.3%). Among cardiac diseases, the most common is arterial hypertension (81%). Heart rhythm disturbances were noted in 46.2% of patients with CRS, and coronary heart disease - in 50.9% of patients. Patients with cardiorenal syndrome have an increased risk of cardiac arrhythmias and stroke compared with patients with chronic kidney disease without cardiorenal syndrome**.** Overall, the presence of cardiac or renal dysfunction is a strong predictor of adverse contralateral organ outcome.

Conclusion Heart and kidney diseases are often associated, causing cardiorenal syndrome (CRS). This syndrome has different types, each with its own pathophysiological mechanisms. Based on the results, CRS types 2 and 4 are associated with high mortality. It is important to conduct further research to improve treatment and understanding of the relationship between the cardiovascular system and the kidneys.

Tables

Age and gender groups of patients with and without CRS.

Data	Men	Women
With CRS	211 (77.3%)	62 (22.7%)
Without CRS	208 (65.0%)	112 (35.0%)
Total	419 (70.7%)	174 (29.3%)

Incidence of diseases of the circulatory system in the structure of CRS

Disease	**With CRS**	**Without CRS**	Total
Cardiac ischemia	139 (50.9%)	205 (64.1%)	344 (58.0%)
Arterial hypertension	221 (81.0%)	259 (80.9%)	480 (80.9%)
Rhythm and conduction disturbances	126 (46.2%)	123 (38.4%)	249 (42.0%)
Stroke	40 (14.7%)	38 (11.9%)	78 (13.2%)
Diabetes	111 (40.7%)	109 (34.1%)	220 (37.1%)

	Creatinine mg,d (upon admission) Mean (SD)	**GFR ml,min (upon admission)** Mean (SD)	**Creatinine mg,dL (upon discharge)** Mean (SD)	**GFR ml,min (upon discharge)** Mean (SD)
With CRS	1.63 (2.11)	55.9 (19.8)	1.55 (0.759)	56.4 (22.4)
Without CRS	2.22 (5.64)	50.3 (23.0)	1.97 (1.57)	47.9 (24.6)
P-value	0.086	0.002	<0.001	<0.001

8

CONTRAST-ASSOCIATED NEPHROPATHY: A STUDY OF ASSOCIATED RISK FACTORS FOR RISK STRATIFICATION OF INTRA-VENOUS CONTRAST

Chang Yin Chionh[*a], *Mabel Si Hua Tan*[a]

[a] Department of Renal Medicine, Changi General Hospital, Singapore

Background: Acute kidney injury (AKI) is frequently encountered shortly after administration of iodinated contrast, termed as Contrast-Associated AKI (CA-AKI). Data on CA-AKI after intravenous (IV) contrast is limited. In a consensus statement, the risk of CA-AKI is estimated at 5% at eGFR ≥60, 10% at eGFR 45–59, 15% at eGFR 30–44, and 30% at eGFR <30 mL/min/1.73 m2. However, these estimates are very broad and do not take into account other potential risks. The aim of this study is to assess other risk factors for CA-AKI and develop a system for individualised risk assessment which can help with clinical decision making.

Methods: This is a retrospective analysis of a large, anonymized dataset from a tertiary care hospital extracted by computerized protocol from 2016–2023. The main inclusion criteria were (1) Patients who underwent a CT scan with IV contrast and (2) Serum creatinine available within 1 week after scan. Chronic dialysis patients were excluded. Logistic regression was used to model the risk of CA-AKI, and all pre-contrast factors known to be risk factors for AKI were included in the initial model. Through backward stepwise regression, factors with nonsignificant effects were deleted from the model in sequence. The odds ratio (OR) of each significant factor in the final model were determined and used to calculate a weighted score, the Contrast Risk Index (CRI). The CRI score was divided into quintiles and the probability of CA-AKI was determined for each quintile.

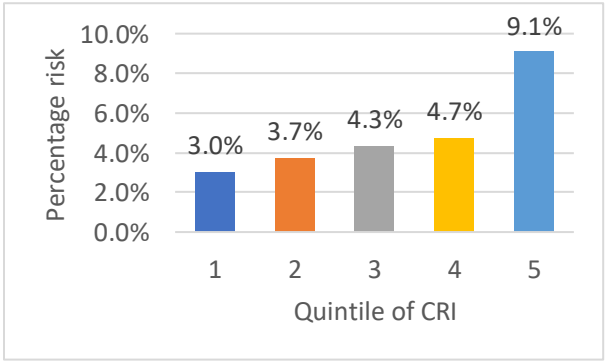
Results: Data from 24,270 patients were included. Of these patients, 55.5% were males with median age was 71 (60 - 80) years, weight 61 (51 - 72) kg, height 1.60 (1.52 - 1.67) m and body mass index 23.9 (20.8 - 27.7) kg/m^2. Baseline creatinine was 84 (64 - 110) umol/L with 4873 (20.1%) of patients with elevated creatinine at baseline. In the cohort, 6167 (25.4%) had diabetes mellitus, 10882 (44.8%) hypertensive and 7006 (28.9%) had cardiovascular diseases. The overall incidence of CA-AKI was 5.0%.

The proposed CRI includes 18 factors, each found to be independently associated with CA-AKI:

	Odds Ratio	95% CI	P		Odds Ratio	95% CI	P
Age (20 to 40 years)	0.712	0.547 – 0.928	0.012	**Diabetes mellitus**	1.206	1.048 – 1.388	0.009
Age (60 to 80 years)	1.170	1.034 – 1.324	0.013	**Hypertension**	1.147	1.002 – 1.312	0.046
Male sex	1.243	1.097 – 1.408	0.001	**Cardiovascular disease**	1.345	1.176 – 1.537	0.000
CT Trunk	0.653	0.569 – 0.75	0.000	**Hyperlactemia**	1.349	1.02 – 1.783	0.036
CT HeadNeck	0.495	0.385 – 0.637	0.000	**Anemia**	1.457	1.27 – 1.672	0.000
CT Musculoskeletal	0.172	0.054 – 0.544	0.003	**Leucocytosis**	1.250	1.097 – 1.424	0.001
Discipline – Medical	0.790	0.679 – 0.919	0.002	**NT ProBNP >300 pg/mL**	1.958	1.658 – 2.313	0.000
Admitted as inpatient	0.587	0.495 – 0.697	0.000	**Use of Diuretics**	1.629	1.302 – 2.039	0.000
Elevated Creatinine	1.882	1.64 – 2.16	0.000	**Use of SGLT2 inhibitors**	0.593	0.401 – 0.876	0.009

Factors with weak correlation in the initial model were excluded: malignancy, hypoalbuminemia, glycemic status, hyperuricemia, hyperthyroidism, polycythemia, high C-reactive protein, use of Renin-angiotension-aldosterone system inhibitors and NSAIDS.

The probability of CA-AKI for each CRI quintile are as follows:



Conclusions: This study provides a methodology for building a risk scoring system for estimating CA-AKI risk based on data from electronic medical records. With the risk calculation inbuilt into an electronic medical record, the CRI can be utilised to provide individualised risk estimates for CA-AKI. The accuracy of this estimate from a large dataset can be improved with machine learning and artificial intelligence.

9

PURIFIED GRANULOCYTES IN EXTRACORPOREAL CELL THERAPY: A MULTIFACETED APPROACH TO COMBAT SEPSIS-INDUCED IMMUNOPARALYSIS

*G. Klinkmann [a,b,d], S. Brabandt [b], M. Möller [b], JC. Schewe [b], J. Altrichter [e], S. Mitzner [c,d]

[a] International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy; [b] Department of Anaesthesiology, Intensive Care Medicine an Pain Therapy, University Medical Center, Rostock, Germany; [c] Department of Internal Medicine, Division of Nephrology, University Medical Center, Rostock, Germany; [d] Department of Extracorporeal Immunomodulation, Fraunhofer Institute for Cell Therapy and Immunology, Rostock, Germany; [e] Artcline, Rostock, Germany

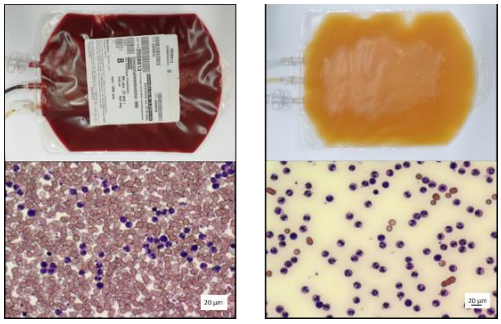
Background: Immune cell dysfunction plays a central role in sepsis-induced immunoparalysis. Targeted treatment using healthy donor immune cell transfusions, in particular granulocyte concentrates (GC) potentially induces tissue damage. Initial trials using GC in an extracorporeal immune cell perfusion system provided evidence for beneficial effects with fewer side effects, by separating patient and donor immune cell compartments. The extracorporeal immune cell therapy is a plasma treatment technology. To date, treatment duration has been empirically set at 6 hours, although no evidence exists for specific dosing concepts. Thus, this ex vivo study examines technical feasibility and cellular effects of an extended treatment interval of up to 24 hours.

Methods: Plasma is continuously filtered from the patient´s extracorporeal blood circuit and transferred into a closed-loop 'cell circuit', where the patient's plasma is brought into direct contact with therapeutically effective, human-donor immune cells. Standard GC were purified to increase the potential storage time and subsequently used in the extracorporeal immune cell perfusion system (Figure 1). The extracorporeal circuit, comprising three plasma filters (PF), operated as follows: PF BC separated patient's plasma from blood, PF CC1 housed donor immune cells for perfusion, and PF CC2 served as a redundant safety measure in the plasma backflow (Figure 2). A "10-hour setting" (33 ml/min plasma filtration) and a "24-hour setting" (13.5 ml/min) was defined, differing both in therapy duration and varying plasma filtration rates. After treatment, donor immune cells were discarded. Parameters assessed included phagocytosis activity, oxidative burst, cell viability, cytokine release, and metabolic parameters of purified GC.

Results: After a storage of 72 hours granulocytes were viable throughout the study period and exhibited preserved functionality and efficient metabolic activity. Lactate dehydrogenase activity as an indication for potential cell damage revealed no signs of impairment of the cells. The findings highlight a time-dependent nature of cytokine release by neutrophils in the extracorporeal circuit, as cytokine secretion patterns showed IL-8 peaking within 6 hours, while MCP-1, IL-6, IL-1β, and TNF-α significantly increased ($p < 0{,}001$) after 24 hours of circulation (Figure 3).

Conclusion Purified GC remain functional after 72 hours of storage and an additional 24 hours in the circulating treatment model. Cytokine secretion patterns showed a time-dependent response characterized by a significant increase, especially between 10 and 24 hours of treatment. Extending treatment time holds promise for enhancing immune response against sepsis-induced immunoparalysis. These findings provide valuable insights for optimizing therapeutic interventions targeting immune dysfunction.

Figure 1 Appearance and histology of the cell preparations



Standard GC Purified GC

Figure 2 Graphical representation of the system

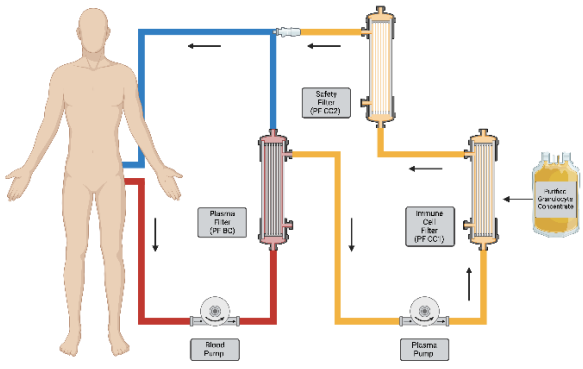
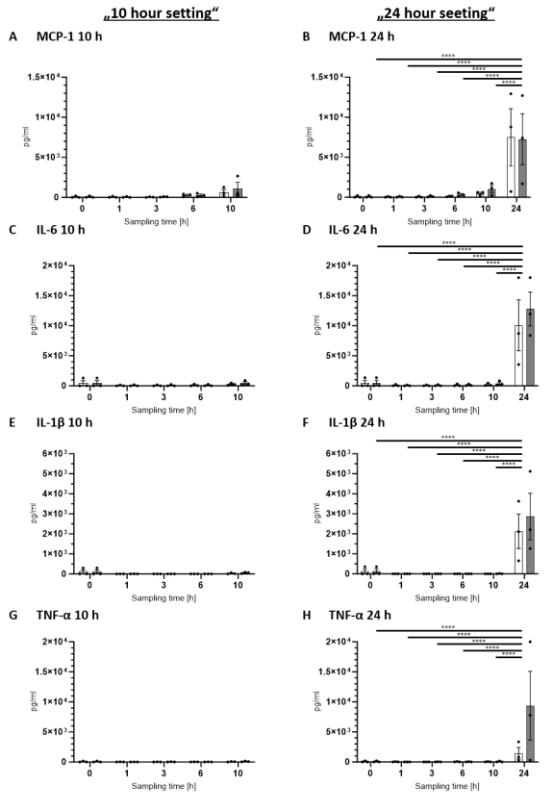


Figure Cytokine release of GC over time



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10

EFFICACY OF COMBINATION OF MAINTENANCE HEMODIALYSIS WITH HEMOADSORPTION (HA130) AND ITS EFFECT ON UREMIC COMPLICATIONS AND QUALITY OF SLEEP AND LIFE OF HAEMODIALYSIS PATIENTS: A BOSNIAN PROSPECTIVE COHORT STUDY

Bećiragić Amela[a], Čengić Roljić Badema[a], Mutevelić-Turković Alma[a], Ćorić Aida[a]

[a]Clinic for haemodialysis, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina.

Background: The aim of the study was to investigate the effect of combined therapy of hemodialysis (HD) with hemoadsorption HA130 (HA) on long-term uremic complications, sleep quality (SQ) and quality of life (QoL) - physical (PC) and mental component (MC).

Methods: The prospective cohort study included 50 HD patients divided in two groups: experimental group (N=25) received combined treatment HD+HA130 and control group (N=25) received only HD. After the follow-up period of 18 and 60-months, sociodemographic, laboratory, clinical and psychological data (measured by PSQI and SF-36) were analyzed and compared with each other.

Results: Experimental group received lower doses of erythropoietin (EPO), had lower diastolic blood pressure (DBP), higher values of ferum (Fe) and intact parathyroid hormone (iPTH) after 18-months observation in relation to control group. Higher values of Kt/V and hemoglobin (Hb) and lower values of iPTH were noticed in HD+HA130 group after 60-months in relation to 18-months observation ($p<0.05$).
We noticed better subjective sleep quality (SSQ), longer sleep duration (SD), better habitual sleep efficacy (HSE), less sleep disturbances (SDis), day dysfunction (DD), use of sleep medication (USM) and better global PSQI score after 60-months observation in HD+HA130 group ($p<0.05$).
We observed that MC was significantly better after 60-months observation in experimental group. Only bodily pain (BP) from PC was lower after 18-months observation in HD+HA group. PC of QoL and role emotional (RE) were better after 60-months in relation to 18-months observation in experimental group. On the contrary, we detected that BP, social functioning (SF) and general health (GH) were worse during the time in our control group ($p<0.05$).

Conclusion: After the 60-months observation, HD+HA130 was superior to HD, reducing the values of DBP, reducing the doses of EPO, improving the values of KT/V, Fe and Hb. We also detected better SQ and QoL in the experimental group.

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INDEXED NEUTROPHIL GELATINASE ASSOCIATED LIPOCALIN –NOVEL BIOMARKER FOR THE ASSESSMENT OF ACUTE KIDNEY INJURY

*Shir Frydman, Ophir Freund, Ariel Banai, Lior Zornitzki, Ariel Banai, Shmuel Banai, Yacov Shacham**

Department of Cardiology, Tel-Aviv Sourasky Medical Center

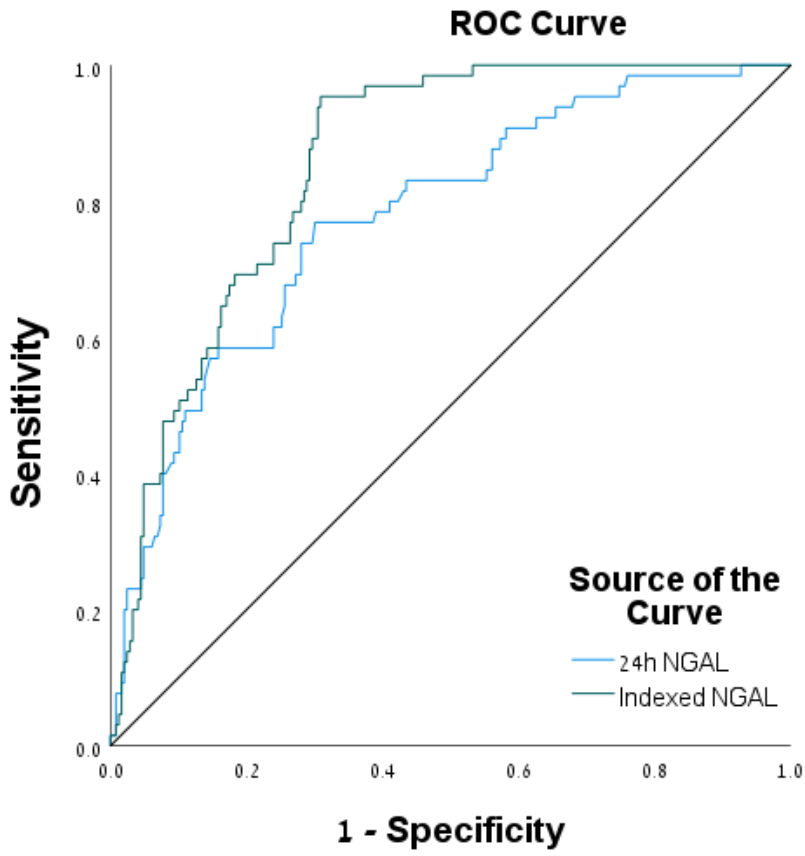
Introduction: Acute renal injury (AKI) is a significant and common complication among patients with acute coronary syndrome (ACS). Neutrophil gelatinase-associated lipocain (NGAL), secreted from different cells including renal tubules, has been widely studied as an early marker for renal injury. However, chronic kidney disease (CKD) could impact NGAL levels and alter their predictive performance. Few studies attempted to address this issue by setting different cutoff values for patients with CKD with limited success to date. Our aim was to evaluate a novel eGFR-adjusted "indexed NGAL" and its ability to predict in-hospital AKI among patients with ST elevation myocardial infarction (STEMI).

Methods: We performed a prospective, observational, single center cohort in patients admitted to the coronary intensive care unit with STEMI. Serum samples for baseline NGAL were collected within 24 h following hospital admission. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. In-hospital AKI was determined as occurring after ≥24 hours from admission. To perform an individualized adjustment, we used the result of 24h NGAL divided by the eGFR measured upon admission to the hospital (Indexed- NGAL; I-NGAL).

Results: 311 patients were included in our cohort, of them 123 (40%) had CKD, and 66 (21%) suffered in-hospital AKI. NGAL levels as well as I- NGAL levels were significantly higher in patients with AKI (136 vs. 86, $p<0.01$ and 3.13 VS. 1.06, $p<0.01$, respectively). Multivariate analysis revealed I- NGAL to be independently associated with AKI (OR 1.35 (1.12-1.59), $p<0.01$). I- NGAL had a higher predictive ability than simple NGAL results (AUC-ROC of 0.858 vs. 0.778, $p<0.001$).

Conclusions: Adjusting NGAL values according to eGFR yields a new indexed NGAL that enables better prediction for AKI regardless of baseline renal injury.

Figure 3, Receiver operating characteristic curve for prediction of in-hospital AKI.



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COMBINED BIOMARKER TESTING FOR THE ASSESSMENT OF ACUTE KIDNEY INJURY IN MYOCARDIAL INFARCTION PATIENTS

*Shir Frydman, Ophir Freund, Ariel Banai, Lior Zornitzki, Ariel Banai, Shmuel Banai, Yacov Shacham**

Department of Cardiology, Tel-Aviv Sourasky Medical Center

Introduction: The utility of different biomarkers for the prediction of acute kidney injury following ST-elevation myocardial infarction (STEMI) has been evaluated in several studies however, very few data exist on the prognostic value of combining biomarkers. Among numerous biomarkers examined, C-reactive protein (CRP) and Neutrophil gelatinase associated Lipocalin (NGAL) stand high in their utility to assess AKI risk. We aimed to assess the prognostic value of combined CRP and NGAL measurement for the assessment of the risk of AKI in reperfused STEMI patients

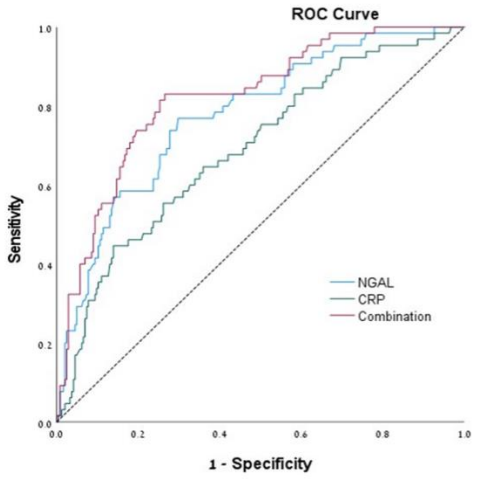
Methods: Blood samples for plasma NGAL and CRP were drawn 24 hours after admission. High NGAL and CRP were defined as values within the 4th quartile (>75percentile). Patients were stratified into 4 study groups: Low NGAL/Low CRP, LOW NGAL/high CRO, High NGAL /low CRP and high NGAL/high CRP. Patients were assessed for the occurrence of in-AKI based on the KDIGO criteria.

Results: A total of 311 patients were included (mean age 66 ± 14 years, 81% males)

According to the 4 study groups, there was a stepwise increase in the proportion of AKI (9% vs. 21% vs. 40% vs. 68% ;p,0.001). In a multivariate regression model , compared to patients having low NGAL/low CRP we observed a graded, independent increase in the risk for AKI for low NGAL/high CRP , high NGAL/low CRP and high NGAL/high CRP(OR 2.89, p=0.02 vs. OR 3.29,p<0.001 vs. OR 17.6,p<0.001 respectively). Peak concentrations showed significant areas under the curves (AUCs) for the prediction of AKI for both CRP AUC (0.692,95% CI 0.62-0.76) and NGAL (AUC 0.778,95% CI 0.72-0.84). The combination of NGAL and CRP yielded a significant increase in AUC to 0.822 (95% CI 0.77 to 0.88) (combined biomarkers vs CRP: p<0.001 and combined vs. NGAL :p=0.02;figure 1).

Conclusions: In patients with reperfused STEMI, the combined assessment of NGAL and CRP provided incremental prognostic information for the prediction AKI when compared with single-biomarker measurement.

Figure1: Receiver operating characteristic curve for AKI prediction



13

PERSISTENT RENAL DYSFUNCTION AFTER ACUTE KIDNEY INJURY IN PATIENTS UNDERGOING PRIMARY CORONARY INTERVENTION-PEVALENCE AND PREDICTORS

*Shir Frydman, Ophir Freund, Ariel Banai, Lior Zornitzki, Ariel Banai, Shmuel Banai, Yacov Shacham**

Department of Cardiology, Tel-Aviv Sourasky Medical Center

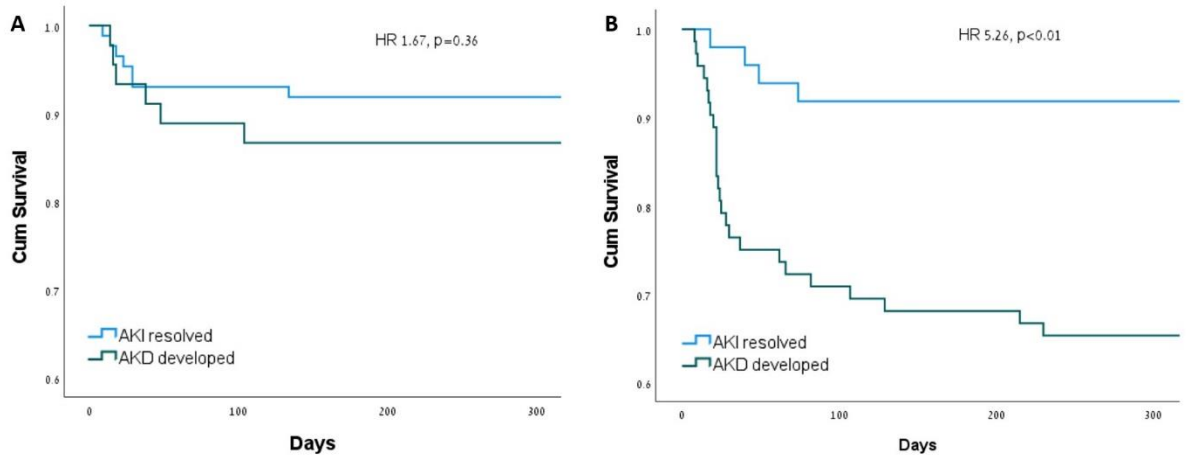
Background: One of the more common and serious complications of acute coronary syndrome is renal injury with numerous reports associating it to adverse outcomes. Common definitions for renal injury, acute kidney injury (AKI) and chronic kidney disease (CKD) are highly heterogenous leaving a wide gap between these two entities. In an effort to better understand and classify renal injuries, the term acute kidney disease (AKD) was implemented, describing prolonged renal injury, between 7 and 90 days following initial insult. We aimed to evaluate the prevalence and predictors of AKD among patients undergoing primary coronary intervention.

Methods: This retrospective observational study cohort included 2940 consecutive patients admitted with ST elevation myocardial infarction (STEMI) between the years 2008-2019. Renal function was assessed upon admission and routinely thereafter. Renal outcomes ware assessed according to KDIGO criteria while AKD was defined as persistent renal injury for more than a week and less than 3 months.

Results: 252 subjects with STEMI that suffered AKI were included, of them 117 (46%) developed AKD. Among baseline CKD patients higher rated of AKD were observed (60%). Gender, KDIGO index ≥2, reduced ejection fraction and hemodynamic instability were associated with AKD, however only higher KDIGO severity index (≥2) remained significant (OR 2.62, 1.09-6.33, p=0.027) after multivariate regression analysis. 90 days from renal insult 59% of AKD patients showed new/progressed CKD .In addition, AKD patients had higher 1-year mortality rates (HR 3.39, 95% CI 1.71-6.72, p<0.01). This trend was mainly driven by the CKD sub-population where higher mortality rates for AKD on CKD were observed (HR 5.26, 95% CI 1.83-15.1, p<0.01,figure 1).

Conclusion: AKD is common among STEMI patients with AKI. The presence of CKD and higher KDIGO stage should prompt strict monitoring for early diagnosis, treatment and prevention of renal function deterioration

Figure1: Kaplan Meier curve for survival based on the development of AKD, among patients without CKD (A) and with CKD (B).



14

A NEW FRONTIER: INTRODUCTION OF ALBUMIN BINDING CAPACITY AND ITS IMPACT ON PHARMACOKINETICS AND PHARMACODYNAMICS OF FUROSEMIDE

*G. Klinkmann [a,b,e], S. Klammt [c,e], M. Jäschke [d], S. Mitzner [c,e]

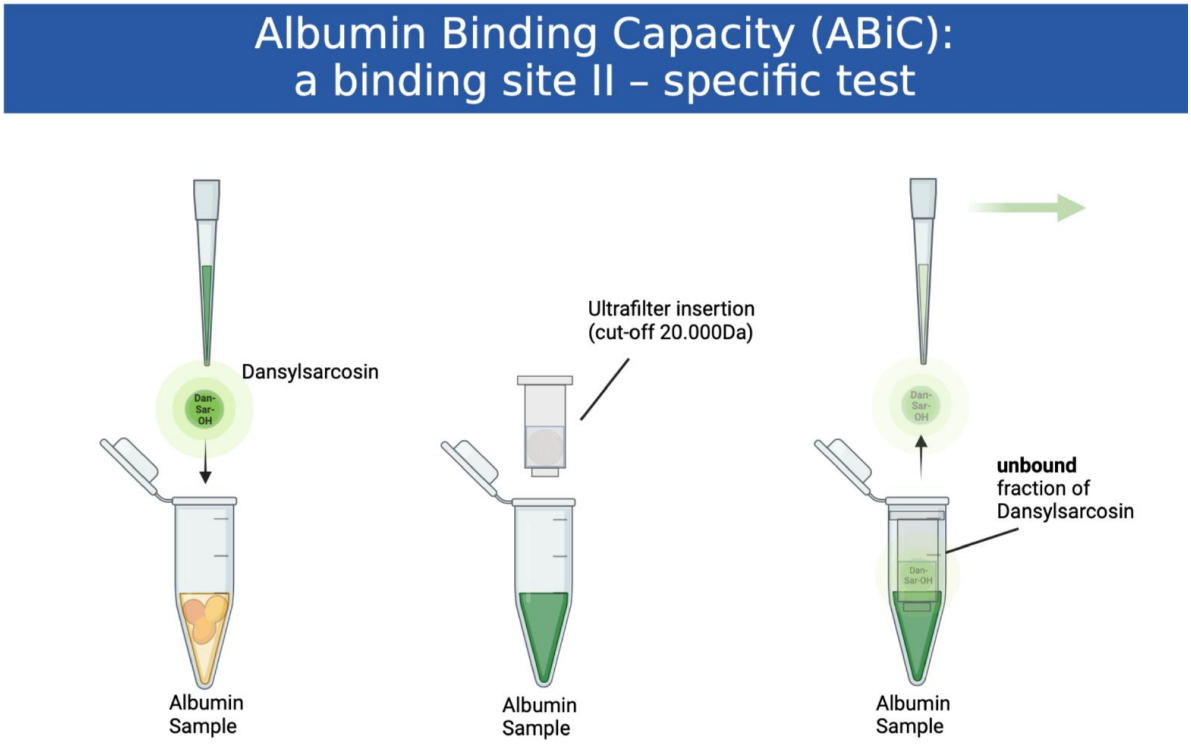
[a] International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy; [b] Department of Anaesthesiology, Intensive Care Medicine an Pain Therapy, University Medical Center Rostock, Rostock, Germany; [c] Department of Internal Medicine, Division of Nephrology, University Medical Center Rostock, Rostock, Germany; [d] Department of Internal Medicine, University Medical Center Rostock, Rostock, Germany; [e] Department of Extracorporeal Immunomodulation, Fraunhofer Institute for Cell Therapy and Immunology, Germany

Background: The binding of furosemide to albumin serves as foundation for its transportation to the kidney and subsequent tubular secretion, which is essential for its mode of action. Consequently, elevated levels of albumin should theoretically lead to increased efficacy of furosemide. However, conflicting evidence exists regarding the effectiveness of co-administering furosemide and albumin in a state of hypoalbuminemia. This study aims to provide deeper insights into this clinically relevant phenomenon by presenting novel findings on molecular mechanisms in drug-protein interactions, by introducing the concept of Albumin-Binding Capacity (ABiC) thereby enhancing our understanding of the efficacy of furosemide.

Methods: In a prospective and non-interventional clinical observational study, blood and urine samples from 50 intensive care patients receiving continuous intravenous furosemide therapy were analyzed. The determination of ABiC provided information on the binding site-specific loading status of albumin by quantifying the unbound portion of the fluorescent marker dansylsarcosine. In addition, the total concentration of furosemide in plasma and urine and the concentration of the free furosemide fraction in plasma were determined by HPLC-MS. The efficacy of furosemide was evaluated according to the ratio of urine excretion to fluid intake.

Results: ABiC values were recorded upon admission and patients were categorized based on a cutoff of 60%. In patients with an ABiC ≥ 60% free furosemide fraction was significantly lower compared to patients with a lower ABiC ($p<0.001$), urinary furosemide concentration was higher ($p=0.136$), and a significantly higher proportion of infused furosemide was excreted renally ($p=0.010$). ABiC was positively correlated ($r=0.908$, $p=0.017$) with an increase in urine excretion to fluid input ratio after initiation of furosemide therapy.

Conclusion ABiC emerges as novel marker, enabling qualitative analysis on the albumin-furosemide interaction within a clinical context. This scientific progress holds promise for understanding individual drug responses and paving the way for tailored therapeutic interventions.



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PLASMA ADSORPTION BY DPMAD AS A BRIDGE THERAPY FOR ACUTE LIVER FAILURE - A CASE REPORT

Mohssen Nassiri Toosi MD a, Mohammad Taher MD a, Samerand Fattah Ghazi MD b, Marjan Sohrabi MD c*

a Hepatologist, b Intensivists, c Infection disease specialist, Liver Transplant Research Center, Tehran University of Medical Sciences, Tehran, IRAN

Background: Fulminant hepatic failure (FHF) presents an unpredictable, swiftly progressing clinical course with high short-term mortality in acute liver failure (ALF). Apart from liver transplantation, there is no efficient treatment for FHF. Timely access to a liver organ is often unavailable. ALF frequently arises amidst a severe systemic inflammatory response. To tackle this issue, an artificial liver support system is envisioned for liver failure, aiming to eliminate toxins and provide temporary, partial liver function replacement. This system can serve as a crucial bridge during the critical wait for a liver transplant.

Case presentation: A 39-year-old lady with weakness, lethargy and mild fever followed by progressive icterus and a gradual lack of awareness (GCS 12), increased level of liver enzymes more than 15 times of upper limit of normal, total bilirubin 32 mg/dl, INR 4.4 (MELD-Na score 32), normal platelet, normal spleen, no ascites, negative viral markers, and no history of alcohol or any drugs. Besides the medical treatments for acute liver failure, the patient's level of consciousness decreased progressively, also suffered from tachycardia with very low systemic vascular resistance and polyuria with a urinary volume of 7 liters per day and acute hypernatremia (serum sodium 160 meq/l) in the setting of hepatic encephalopathy. The patient became a candidate for emergency liver transplantation. The living donor was not available. The treatment with plasmapheresis with four units of FFP was started. Due to the lack of improvement in the patient's state of consciousness, daily low-volume plasma exchange (PE) combined plasma absorption (DPMAS) with BS 330 and HA 330 type II cartridges with a CRRT device was done. This artificial liver support was done for four days. On day four, the patient underwent liver transplantation from a cadaver with the same blood group (Orthotic liver transplantation).

Result: The level of CRP, Bilirubin, ammonia and systemic vasodilatation decreased and the patient survived to reach deceased-donor liver transplantation.

Conclusion: Alternating PE with DPMAS can rapidly remove bilirubin, ammonia and cytotoxins from the blood, which could be used as an effective transitional treatment for ALF. However, more clinical trials are needed to verify the long-term efficacy in the future.

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ACUTE KIDNEY INJURY SECONDARY TO HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS SYNDROME AS A PRESENTATION OF HIV INFECTION: CASE REPORT

B-F. Paola [a], *G-V. Juan Pablo* [a], *G-T. Ricardo-Abraham* [a], *C-DG. Rolando* [b], *R-T. Lilia-M* [a] *

[a]UDEM-Hospital Christus Muguerza Alta Especialidad, Internal Medicine and Nephrology, Monterrey, Mexico. [b]IIBISMED Universidad Mayor de San Simón, School of Medicine. Division of Nephrology Hospital Obrero No 2 - CNS, Cochabamba, Bolivia.

Background: Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive immune activation, it characterizes by abnormal activation of macrophages and T cells that causes cytokine storm, with high morbidity and mortality. HLH is associated with autoimmune diseases, infections, malignancy, immunosuppression, human immunodeficiency virus (HIV) and some metabolic diseases. HLH has a high risk of progression to multi-organ disfunction syndrome (MODS) including acute kidney injury (AKI).

HLH usually presents as an acute or subacute febrile illness associated with multiple organ involvement. The diagnosis of HLH syndrome is based on a compatible clinical presentation in the setting of elevated inflammatory markers. HLH should be distinguished from other multisystem illnesses associated with fever, liver failure, and/or neurologic symptoms. HLH requires early identification since the greatest barrier to treatment and a successful outcome for individuals with HLH is a delay in diagnosis.

Methods: A 37-year-old male arrives to the ER with 3 days of abdominal pain, jaundice, nausea, and vomiting. He had a negative HIV test 6 months prior to his admission. Physical examination did not showed signs of neurological compromise; he had tachypnea and respiratory distress. He had jaundice, 38ºC of temperature, MAP of 60 mmHg, SatO2 92%, no lymphadenopathy. Abdominal examination findings were painful hepato-splenomegaly and ascites. After 48 hrs he developed neurological symptoms, and MODs (kidney, liver, lungs, and hematological involvement) became evident. We perform HIV testing by molecular biology, CD4 viral load and Epstein Barr Virus test, were positive. Antiretroviral therapy, antibiotic, and continuous renal replacement therapy (CRRT) was initiated with the following prescription: VVCHDF 30 ml/kg/hr, with no anticoagulation and oXiris® membrane. The initial response was poor with clinical deterioration. On day 4, we decided to start hemoperfusion with Cytosorb trying to improve cytokine storm and hyperbilirubinemia. A decrease in bilirubin levels shown in **Figure 1**, and a decrease of IL-6 levels from 114.20 pg/mL to 38.56 pg/mL were achieved. We performed 3 sessions of hemoperfusion (24 hours each). On day 6 the patient developed severe refractory respiratory acidosis that required IMV. HLH was suspected with no possibility to perform a bone-marrow aspiration for diagnosis confirmation due to hemodynamic instability. An H-score diagnostic criterion was applied with 88% of probability of HLH. Rituximab and corticosteroids were started. Unfortunately, patient clinical status continued to deteriorate rapidly and died the next day.

Results and Conclusion: We present the case of an atypical presentation of an acquired HIV infection, with rapid progression and clinical deterioration with the development of HLH with subsequent MODS that required extracorporeal support with IMV and CRRT plus hemoperfusion. Certain types of extracorporeal blood purification techniques can reduce the excess of inflammatory mediators and remove bilirubin. The use of hemoperfusion cartridge, which would reduce the cytokine storm and bilirubin, as shown in the present case, could improve certain patients' parameters **(Figure 2)** and serve as a bridge for the specific HLH treatment like the HLH-94 protocol but without a direct impact on survival. This case raises the possibility of MODs as initial presentation of acquired HIV.

Figure 1. Bilirrubin during hemoperfusion.

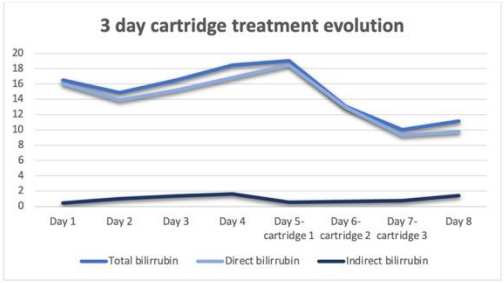
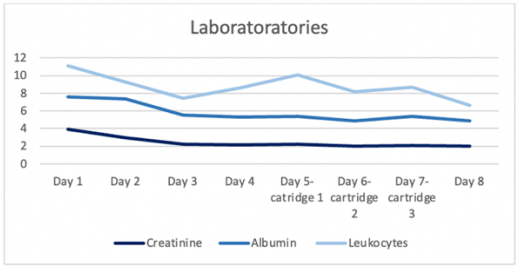


Figure 2. Other relevant parameters



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OUR CENTER'S EXPERIENCE WITH EXTRACORPOREAL BLOOD PURIFICATION IN CRITICALLY ILL PATIENTS

A. Jasarevic, M. Aleckovic Halilovic, E. Mesic, M. Pjanic, A. Altumbabic, D. Mukinovic, N. Moric, A. Klapic*

Clinic for internal diseases; Department of Nephrology, Dialysis and Transplantation ;UCC Tuzla, BiH

Background: There is mounting evidence that extracorporeal blood purification can aid in the recovery of patients with multiorgan dysfunction associated with various etiologies. Our study aimed to investigate the effects of adding extracorporeal blood purification methods to conventional treatment of critically ill patients in our center.

Methods: Our study enrolled 61 patients between 2019 and the end of 2023 who required extracorporeal blood purification due to systemic inflammatory response syndrome (SIRS), sepsis, macrophage activation syndrome (MAS), and multiorgan dysfunction syndrome (MODS), of various etiologies. Patients were primarily hospitalized in intensive care units (ICUs) of surgical and internal clinic, the COVID hospital, and our Department of Nephrology, Dialysis and Kidney Transplantation. The nephrologists indicated and managed all extracorporeal blood purification procedures, even for patients with normal kidney function.

Results: The total number of patients treated with any form of extracorporeal blood purification between 2019 and the end of 2023 was 61, and the total number of treatments was 106. The most common indication for initiating the treatment was sepsis, and the majority of patients were in intensive care units. Most often, the method of choice for initiating the treatment was hemodiafiltration, which was subsequently combined with hemoperfusion. On average, each patient received 2 treatments, each lasting between 10 to 24 hours. Approximately two-thirds of the patients survived. None of the patients with acute kidney damage or failure, among other indications for treatment, remained dependent on dialysis. In our experience, early consultation with a nephrologist and timely start of treatment were associated with positive outcomes in terms of overall survival and recovery of renal function.

Conclusion: According to our findings, extracorporeal blood purification methods should be considered the standard treatment for critically ill patients suffering from multisystem organ dysfunction and/or failure. These methods not only play an important role in purifying the blood, but also provide time to treat the underlying cause through other modalities including surgical and conservative methods.

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HEMOPERFUSION ADSORPTION DURING IN VITRO MODEL OF CA330

Yixiang Zhao a , Yilian Li a

a Guangdong Provincial Key Laboratory of Extracorporeal Circulation Adsorption and Separation Technology

Introduction: The Cytokine Adsorption cartridge CA330 is a hemoperfusion device uses cross-linked divinylbenzene/ polyvinylpyrrolidone as the adsorbent. During the hemoperfusion process, CA acts as a molecular sieve, adsorbs target substance by the pore structure, hydrophobic lipophilic effects of benzene rings, and van der Waals forces of the adsorbent. The target substance include inflammatory mediators (such as IL-6, IL-8, IL-10, IL-1β and TNF-α), bilirubin, myoglobin and drugs (such as Ticagrelor and Rivaroxaban). Though many studies demonstrating the advantage of hemoperfusion, but there is a lack of information on the performance of CA for inflammatory mediators, bilirubin, myoglobin and drugs during the hemoperfusion process, to determine the adsorption capacity of CA cartridge, in vitro experiments were conducted.

Methods: In vitro experiments, a customized cartridge was built assembling mini-module components scaled in dimension towards CA330 and filled with 16.5 ml of CA330 adsorbents (20 times scaled down the regular size cartridge), adsorption medium was bovine serum, and peristaltic pump was set at 20 ml/min. Then samples were taken at different time points (0h, 0.5h, 1h, 2h, 4h, 8h, 12h, 24h) during adsorption process to determine the concentration of target substances. Adsorption Ratio (%) = 100 × (C0- Ct) / C0. (C0 - the initial concentration of target substances, Ct - the concentration of target substance at test time points).

Results: According to the in vitro experiments, the adsorption ratio of CA330 to inflammatory mediators, bilirubin, myoglobin and drugs (Ticagrelor and Rivaroxaban) increased rapidly at 0-2 h. CA330 absorbed all the rivaroxaban within 0.5 hours, with an absorption ratio of 100%, and the adsorption ratio of IL-8 was 99% at the same time. Moreover, all the target substances adsorption ratios were all higher than 70% within 2 hours during the experiments, CA330 showed great adsorption capacity of inflammatory mediators, bilirubin, myoglobin and drugs (Ticagrelor and Rivaroxaban).

Conclusion: While further studies are needed to evaluate the potential impact of CA330 cartridge adsorption capacity on clinical outcome, CA330 is currently available as a reliable and rapid adsorption cartridge, which is recommended for patients in conditions where elevated levels of inflammatory mediators, P2Y12-Inhibitor, Factor Xa-Inhibitor, bilirubin and myoglobin.

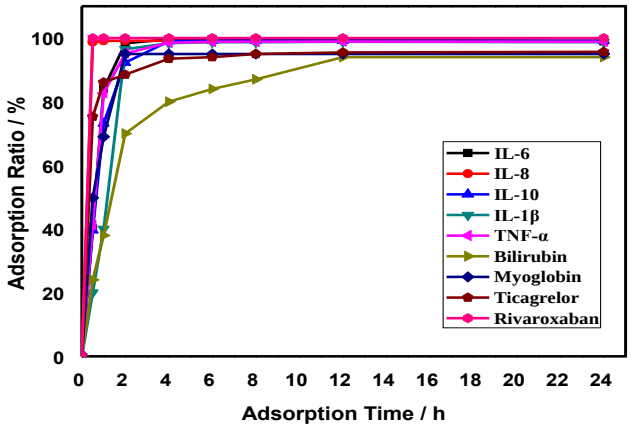

Figure 1. The adsorption curves of CA330 to inflammatory mediators (IL-6, IL-8, IL-10, IL-1β, TNF-α), bilirubin, myoglobin, Ticagrelor and Rivaroxaban

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HEMOPERFUSION ADSORPTION DURING IN VITRO MODEL OF HA380

Yilian Li a , Yixiang Zhao a

a Guangdong Provincial Key Laboratory of Extracorporeal Circulation Adsorption and Separation Technology

Background: Disposable hemoperfusion cartridge HA380 is a hemoperfusion device uses neutral macroporous resin, which possesses abundant medium to large pores and a high surface area. By utilizing the adsorption properties of the resin, HA380 can be used in extracorporeal blood circuits, it is indicated to remove endogenous and exogenous molecules including inflammatory mediators and cytokines, bilirubin, metabolic toxins, protein-bound toxins, residual drugs. Though many studies demonstrating the advantage of hemoperfusion, but there is a lack of information on the performance of HA380 for myoglobin and drugs (such as Ticagrelor and Rivaroxaban) during the hemoperfusion process, to determine the adsorption capacity of HA380 cartridge towards myoglobin, ticagrelor and rivaroxaban, in vitro experiments were conducted.

Method: In vitro dynamic adsorption experiment was conducted. In dynamic adsorption study, a customized cartridge was built assembling mini-module components scaled in dimension towards HA380 and filled with 19 ml of HA380 adsorbents (20 times scaled down the regular size cartridge), adsorption medium was bovine serum, and peristaltic pump was set at 20 ml/min. Then samples were taken at different time points (0h, 0.5h, 1h, 2h, 4h, 8h, 12h, 24h) during adsorption process to determine the concentration of target substances. Adsorption Ratio (%) = 100 × (C0- Ct)/ C0. (C0 - the initial concentration of target substances, Ct - the concentration of target substance at test time points)

Results: According to the in vitro study of HA380 cartridge, the adsorption ratio of HA380 to the target substances myoglobin, ticagrelor and rivaroxaban increased rapidly at 0-2 h. And HA380 showed great adsorption capacity to myoglobin, Ticagrelor and Rivaroxaban. HA380 absorbed all the rivaroxaban within 0.5 hours, with an absorption ratio of 100%, and all the target substances adsorption ratio were upper than 90% within 8 hours.

Conclusion: In this in vitro model, HA380 showed significant adsorption capacity toward myoglobin, ticagrelor and rivaroxaban. These preliminary results highlight that HA380 is currently available as a reliable and rapid adsorption cartridge, which can be used in extracorporeal blood circuits to remove endogenous and exogenous molecules including myoglobin and residual drugs (such as Ticagrelor and Rivaroxaban).

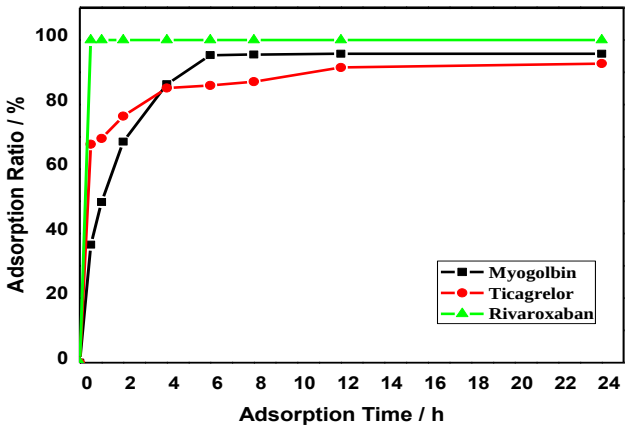

Figure 1. The adsorption curves of HA380 to myoglobin, ticagrelor and rivaroxaban

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SUCCESSFUL TREATMENT OF CANNABIS AND METHADONE OVERDOSE WITH HEMOPERFUSION – A CASE REPORT

Vishal Ramteke [a], *Ashay Shingare* [b]

a Department of Nephrology , Max Superspeciality Hospital, Nagpur; b Department of Nephrology, Jaslok Hopital and Research Centre, Nagpur

Background: Cannabis (Marijuana) is the world's most widely abused illicit substance as per the United Nations Office on Drugs and Crime (UNODC) 2017 World Drug Report with over 183.5 million people using it legally or illegally. Methadone a synthetic long-acting opioid on the contrary is not freely available. Both the drugs individually or in combination in toxic doses can cause cardio-respiratory depression, somnolence, convulsions and death. While there is no specific antidote for cannabis toxicity, acute methadone toxicity has been treated with naloxone and benzodiazepines. In the current case the mixed toxicity of cannabis and methadone led to intractable seizures for which patient was subjected to two sessions of hemoperfusion following with there was cessation of seizures and improvement in the sensorium of the patient.

Case report: A 58-year-old gentleman was brought to the emergency room by the relatives in unconscious condition of one hour duration. Upon arrival he appeared drowsy, poor verbal or motor response. Initial vital sign assessment showed pulse rate 120 beats/min, blood pressure 154/90 mmHg, shallow respiratory effort with rate of 12 breaths/min and pulse oximetry (SaO2) 92% on room air. He was warm to touch, and his blood glucose was 153 mg/dL. He had pinpoint pupils on examination and depressed deep tendon reflexes. On enquiry with the relatives there was no history of past medical and surgical illness, but history infrequent substance abuse was confirmed. A hemogram, kidney and liver function test and arterial blood gas were drawn and patient was subjected to urgent MRI brain to rule out cerebrovascular event which was normal. Patient was shifted to Medical ICU for further stabilisation.

On arrival to Medical ICU, patient had multiple generalised tonic clonic convulsions with post ictal further drop in sensorium for which he was intubated and put on positive pressure ventilation. He was given loading dose of inj Leveteracitam 1 gram and kept on fentanyl and midazolam infusion. Investigations showed blood urea 72 mg/dl, creatinine 2.1 mg/dl with normal electrolytes (sodium, potassium, calcium, magnesium). The hemogram and liver function test were normal. Arterial blood gas was suggestive of high anion gap metabolic acidosis. There was a strong suspicion of some illicit drug overdose for which the urine toxin screen was sent. Over the next 24 hours he had maintained hemodynamic with urine output of approximately 1 ml/kg/hour. But he continued to have seizures for which inj Lacosamide and intravenous propofol infusion was added but the seizures were unrelenting with intermittent atrial fibrillation.

Urine toxin screen report available after 36 hours of admission showed toxic levels of cannabis – 261 ng/ml (> = 50 ng/ml – reference level) , methadone – 719 ng/ml (> = 300ng/ml – reference level) and benzodiazepine - > 1000 ng/ml (>= 200 ng/ml- reference level) (Image 1) The positive toxic screen for benzodiazepine was attributed to the ongoing midazolam infusion for the sedation/ anticonvulsant. Thus acute intoxication of cannabis and marijuana was confirmed in this case. In view of refractory seizures with multiple anticonvulsants injections, option of extracorporeal removal of the toxins was evaluated. Cannabis and methadone both have high protein binding - about 90 % and 85 % respectively. More over both the toxins are extremely lipid soluble ruling out haemodialysis as a treatment option. Resin adsorbent based hemoperfusion was theoretically an option but no previous reported cases for management of the toxins individually or in combination. After discussion with the critical care and neurology teams and patient's family, hemoperfusion was offered as a lifesaving option. Patient was subjected to first session of hemoperfusion at 42 hours after admission. Access used was 13 fr', 16 cm right femoral double lumen haemodialysis catheter. Resin (Styrene divinylbenzene polymer) adsorbent based hemoperfusion cartridge (HA 230 – Jaffron Biomedical Co. Ltd) was connected post pump and predialyser (Fresenius – F6 polysulfone) after initial charging of cartridge with 25000 units of unfractionated heparin in 1 litre of saline. Four hours of hemoperfusion along with haemodialysis (blood flow and dialysate flow of 150 and 300 ml/min) was done on Fresenius 4008 S machine (Image 2). Patient tolerated the procedure and 12 hours post procedure there was complete cessation of the convulsions but he continued to be comatose. Second session of hemoperfusion with the similar prescription as first was done after 18 hours which was well tolerated by the patient.

Results: 24 hours after the second hemoperfusion treatment, there was gradual improvement in sensorium of the patient with eye opening, obeying of verbal commands and no convulsions suggesting significant removal of the toxins. A repeat urine toxin screen sent to confirm any presence showed non-detectable cannabis and methadone but presence of benzodiazepines which was ongoing drug (Image 3). He was gradually weaned off the ventilator and was ambulated out of bed on day 10. He confirmed consumption of the drugs at home on the day of admission. He was shifted to rooms on day 14 and was later discharged in health after mental health consultation. Patient is following up in outpatient department with no neurological residua and recovered acute kidney injury.

Conclusion: This is the first case of use of hemoperfusion for removal of cannabis and methadone in humans. There is one earlier report of use of hemoperfusion for cannabis removal in veterinary practice but drug level testing was not done.(9) In conclusions, hemoperfusion may be considered for removal of cannabis and/or methadone, especially in presence of life-threatening complications or severe neuroexcitatory symptoms.

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CLINICAL AND LABORATORY EFFICIENCY OF TREATMENT WITH HEMOADSORPTION HA330 COMBINED WITH CONTINUOUS RENAL REPLACEMENT THERAPY IN PATIENTS WITH SEPTIC SYNDROME

*Ćorić Aida [a], Bećiragić Amela [a], Dervišević Amela [b], Mašnić Fahrudin [a], Ajanović Selma [a], Bašić Adisa [a], Groša Emir [a]

a Clinic for hemodialysis, Clinical Center of the University of Sarajevo, Sarajevo, Bosnia and Herzegovina
b Department of human physiology, Faculty of medicine, University of Sarajevo, Bosnia and Herzegovina

Background: Hemoadsorption is an extracorporeal method of treatment that has been studied in detail in the last decade. HA330 is a disposable hemoperfusion cartridge (Jafron®,China) absorber that has a targeted effect on inflammatory conditions and septic shock. HA330 can be used alone or in combination with other methods of renal replacement therapy. By passing the patients' blood or plasma through specially developed absorbers, various inflammatory cytokines (molecules with a molecular weight of 10- 60 kilo-Daltons), are absorbed onto the resins inside the device and removed from the circulation. The aim was to evaluate the effect of HA330 hemoadsorption treatments on removing inflammatory parameters (CRP, leukocytes, lactates, procalcitonin), improving metabolic acidosis, renal function, and hemodynamic of patients (blood pressure, reduction dose of vasopressors, diuretic response of the patient).

Material and methods: Thirteen patients who were under suspicion of septic syndrome at the hemodialysis department or in intensive care units of the Clinical Center Sarajevo were included in this study. They received 1, 2 or 3 hemoadsorption treatments within 48 to 72 hours of Laboratory findings. The treatment mode was HA330 in addition to CVVHDF, and hemodynamic parameters, diuresis were continuously monitored before and after the hemoadsorption treatment.

Results: Monitoring of the parameters before and after treatment with HA330 showed that after hemoadsorption with HA330, CRP values (237.6 ± 81.9 mg/L vs 92.9 ± 79.7 mg/L, $p < 0.001$) and values of leukocytes (16.7 ± 5.8 x 10^3/µL vs 9.6 ± 4.1 10^3/µL, $p< 0.001$) were significantly lower. The values of lactate (2.8 mmol/L (2.5-2.95) vs 2.0 mmol/L (1.9-2.45), $p = 0.001$), procalcitonin (0.85 ng/mL (0.73-3.53) vs 0.32 ng/mL (0.23-0.55), $p = 0.002$) , D dimer (2.12 mg/L (1.55-9.93) vs 1.3 mg/L (1.00-6.73), $p = 0.001$) were also significantly lower after HA treatment.

Conclusion: The using of HA330 in septic conditions combined with CVVHDF removed the suspicion that hemoadsorption is not effective. In our study, it resulted in a decrease in the levels of inflammatory parameters, along with correction of acidosis and improvement of daily diuresis, which lead to the improvement of the patient's clinical condition and recovery of renal function.

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THE ROLE OF HEMOPERFUSION COMBINED WITH MULTIMODALITIES TREATMENT FOR MULTIPLE ORGAN DYSFUNCTION AND HEMOPHAGOCYTIC SYNDROME IN CHILDREN WITH SEVERE DENGUE SHOCK SYNDROME

Tananat Virojtriratana a , Rujipat Samransamruajkit a

a Critical Care Medicine, Department of Pediatrics, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand

Introduction: Multiple organ dysfunction (MOD) and infection-associated hemophagocytic syndrome (IAHS) are unusual dengue symptoms. IAHS can cause hemodynamic instability, organ failure and high mortality. In these cases, early hemoperfusion and multimodality treatment can reduce systemic inflammation, enhance organ functions and may prevent mortality.

Objectives: To evaluate therapeutic efficacy of combination of hemoperfusion and multimodality treatment involving IVIG, corticosteroid, plasmapheresis and/or extracorporeal organ support in children with MOD and IAHS from dengue shock syndrome (DSS).

Methods: This prospective observational study includes MOD and IAHS related DSS. All children received 4 hours of hemoperfusion with HA330 for 1 to 3 consecutive days and multimodality treatment. Improvements in ferritin, IL-6, hsCRP, organ dysfunction score and PICU mortality were assessed.

Results: Five patients were included. All patients had organ dysfunctions in more than two systems. Four of five patients received IVIG and dexamethasone, while all received hemoperfusion with CRRT and plasmapheresis. The mean PELOD-2 and vasoactiveinotropic score (VIS) decreased after intervention (9.4 vs. 6.6 and 29.4 vs. 11.0). The biomarker showed significant decreased in serum ferritin (86,453.6 vs. 47,747.8 ng/mL, p value <0.05) and serum IL-6 (8,964.3 vs. 226.9 pg/mL, p value <0.05). No additional adverse effects were noted.

Conclusion(s): Combination of hemoperfusion with HA330 and multimodality treatment were successful for reduced inflammatory biomarkers, improved hemodynamic stability and subsequently restored vital organ functions. Although, mortality outcomes must be compared across larger populations.

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EVALUATION OF THE EFFECTS OF HEMOPERFUSION PLUS HEMODIALYSIS COMPARED TO HEMODIALYSIS ALONE ON MIDDLE TO LARGE MOLECULES AND PROTEIN-BOUND UREMIC TOXINS: A RANDOMIZED CONTROLLED TRIAL

Issa Al Salmi a,b, Yaqoub Al Maimani b,c, Ahmed Atris b,d, Fady Elias b,c, Niloufar Zolfaghari e, Parisa Farzi f

a The Renal Medicine Department, The Royal Hospital, Muscat, Oman; b The Medicine Department, Oman Medical Specialty Board, Muscat, Oman; c The Renal Medicine Department, The Bousher Dialysis Center, Muscat, Oman; d The Renal Medicine Department, The Seeb Dialysis Center, Muscat, Oman; e Lung transplant Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran; f Social Determinants of Health Research Center (SDHRC), School of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran

Objective: The present study aimed to evaluate the effectiveness of the combined approach of hemodialysis(HD) and hemoperfusion(HP) on Beta-2 Microglobulin (β2-M), Parathyroid Hormone (PTH),quality of life, Sleep quality and pruritus score among hemodialysis patients.

Study design: A randomized controlled clinical trial was conducted involving 20 patients diagnosed with end-stage kidney disease recruited from 2 hemodialysis centers in Oman, comprising 70% male participants with a mean age of 46 years. Participants were randomly allocated to either the experimental or control groups. Data collection instruments included personal information forms, a blood investigation checklist, the Kidney Disease Quality of Life Short Form (KDQOL-SFTM), the Pittsburgh Sleep Quality Index (PSQI), and the 5-D Pruritus Scale. After completing the questionnaires, the control group underwent hemodialysis and the intervention group underwent hemoperfusion in addition to hemodialysis treatment. Hemoperfusion sessions were conducted weekly during the first month, followed by biweekly sessions every two weeks for a total duration of six months. Post-intervention, participants completed the questionnaires again after 24 weeks. Interventions were administered to participants at various time points: before the study commenced, monthly during the first, third, and sixth months, respectively.

The primary outcome of the study has been the evalution of the impact main result indicated a decrease in β2M and PTH levels, while secondary outcomes included enhancements in both quality of life and sleep quality, along with a decrease in patients' pruritus scores in the investigational group compared to the control group.The data were analyzed using SPSS software version 21. Independent t-test, Mann-Whitney U, Wilcoxon, Fisher, Chi-square, Kruskal-Wallis, Mochli, and one-way analysis of variance were used for this purpose.

Results: In the HD + HP group, there was a significant decrease in β2M and PTH levels after 6 months compared to the HD groups. The study demonstrated significant improvements in quality of life within the intervention group $P < 0.001$, while no statistically significant changes were observed in the control group ($p=0.014$). Significant changes in Pittsburgh Sleep Quality scores were observed in both the intervention group $P < 0.001$ and the control group ($p=0.002$).

Conclusion: Based on the study findings, Hemoperfusion, as an extracorporeal blood purification method, can impact the levels of PTH, β2 microglobulin, quality of life, sleep quality, and pruritus scores among patients. Therefore, it is recommended that hemodialysis centers consider implementing this method for the treatment of kidney disease. Further investigations involving a larger sample size of patients and an extended follow-up duration are warranted.

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THE EFFICACY OF DOUBLE PLASMA MOLECULAR ADSORPTION SYSTEM WITH SEQUENTIAL LOW-VOLUME PLASMA EXCHANGE IN HEPATITIS TYPE B & C VIRUS-RELATED ACUTE-ON-CHRONIC LIVER FAILURE: A CASE REPORT

Mohammed Alshukairi [a], *Niloufar Zolfaghari* [b], *Parisa Farzi* [c]
a Department of Intensive Care, The Armed Forces Hospital, Muscat, Oman; b Lung Transplant Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran; 3 Social Determinants of Health Research Center (SDHRC), School of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran

Background: Liver failure is one of the most deadly diseases in the world, which imposes high costs on the medical system of countries. Non-artificial liver support systems have been effective in The mortality rate of acute-on-chronic liver failure (ACLF) associated with intermediate hepatitis B virus (HBV) and HCV is high. We aimed to investigate the effect of a double molecular plasma absorption system (DPMAS) with low-volume plasma exchange (LPE) therapy in the intermediate stage of ACLF associated with HCV and HBV.

Methodology Hemoperfusion was performed for patients with liver failure through the DPMAS system. Vital signs and tests were assessed during the study before and after each treatment session.

Results: There was a statistically significant difference before and after treatment of serum levels of total bilirubin, direct bilirubin and alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase ($p < 0.05$). Improving clinical symptoms and laboratory indicators of liver patients. and SOFA score decreased after treatment.

Conclusions: Hemoperfusion through the DPMAS system greatly improves liver function in HBV- HCV-related ACLF.

TABLE 1 Changes in serum biochemistry and clotting function before and after treating Liver Failure with DPMAS.

Laboratory values	Unit	8/1/2024 12:9 pm Before Treatment	8/1/2024 6:18 am Before Treatment	8/1/2024 6:40 am Before Treatment	8/1/2024 19:48 pm **After Treatment**	9/1/2024 6;26 am **After Treatment**	9/1/2024 19:30 pm **After Treatment**	10/1/2024 morning **After Treatment**
Ammonia	**Umol/l**	79			38		58	
Bilirubin conjugated	**Umol/l**		400	401	274	302	129	164
Phosphate	**mmol/l**		1:30		0.84	1.08	0.73	1.14
Alb	**g/l**		20		27	29	33	27
ca	**mmol/l**		2.02		2.19	2.15	2.25	2.03
Ca.alb.corrected	**mmol/l**		2.42		2.45	2.37	2.39	2.29
CRP	**Mg/l**		73.6		27.5	29.1	14.2	22.5
BIL T	**Umol/lg/l**		543	538	362	410	210	244
Protein	**g/l**		71	69	62	60	55	52
Alb	**g/l**		20	20	27	29	33	27
Globulin	**g/l**		51	49	35	31	22	25
ALT	**Iu/l**		133	147	78	68	40	44
AST	**Iu/l**		316	311	185	161	93	123
ALP	**Iu/l**		319	300	226	191	146	124
Mg	**mmol/l**			0.84			0.79	
Procalcitonin	**ng/ml**		0.77		0.47		0.4	
Urea	**mmol/l**		8.8		4		3.7	5.1
Na	**mmol/l**		129		135		137	129
K	**mmol/l**		2.9		3.2		2.8	2.6
Choride	**mmol/l**		99		104		104	98
Creatinin	**Umol/l**		125		64		72	108
pt			18.1		20.3			
INR			1.62		1.83			
LDH					532	487	391	388

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THE COMBINATION OF HEMOADSORPTION WITH HEMODIALYSIS OR HEMODIAFILTRATION IN ADVANCED CHRONIC KIDNEY DISEASE IMPROVES LIFE EXPECTANCY IN A PILOT STUDY IN ECUADOR AND LATIN AMERICA

Indira Apolo [a], *Fernando Martinez* [a]

a Dialysis technical unit, Hemodialysis chronic area, Hospital Teodoro Maldonado Carbo, Guayaquil, Ecuador

Background: Among the renal replacement therapies offered in the service portfolio of the Dialysis Technical Unit of the Teodoro Maldonado Carbo Hospital are hemodialysis and hemodiafiltration, which are provided to affiliates diagnosed with stage V chronic kidney disease.

Methods: There are approximately 300 members who attend the chronic dialysis unit every three weeks on their assigned shift by georeference. The first pilot plan was carried out at the Ecuadorian Social Security level in Ecuador and Latin America, of combined techniques in patients with stage V chronic renal disease in dialysis therapies after verifying compliance with the inclusion and diagnostic criteria, 5 patients were included for the combination of hemodialysis techniques, hemodiafiltration to hemoadsorption modality with HA130 resin cartridge.

Results: After this period of application of the combination of techniques, the 5 patients were evaluated clinically and by laboratory analysis, obtaining the results of a considerable decrease in beta 2 microglobulin and parathormone values, which allowed improving the microinflammatory state and bone mineral metabolism disorders that affected the patients included.

TABLE 1 Prescribed scheme for each patient:

DURATION TIME	NUMBER OF CARTRIDGES	USED APPLICATION TIME
FIRST MONTH	3	ONE EVERY WEEK FOR 3 WEEKS/ REST 4TH WEEK
SECOND MONTH	2	ONE FIRST WEEK AND ONE 3RD WEEK
THIRD MONTH	1	ONE SECOND WEEK

TABLE 2 Results of parathormone levels:

PATIENTS	START OF STUDY: JULY 2022	END OF STUDY: SEPTEMBER 2022
1	1687	762
2	2000	265
3	1330	700
4	2000	2000
5	898	1000

TABLE 3 Results of β2 macroglobulin levels:

PATIENTS	START OF STUDY: JULY 2022	END OF STUDY: SEPTEMBER 2022
1	13.8	5.6
2	13.7	4.9
3	13.9	5.8
4	13.0	9.8
5	13.9	14.6

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SUCCESSFUL BILE ACID REMOVAL USING HEMADSORPTION IN AN INFANT

*Cs. Lodi** [a], *L. Adami* [a], *M. Bednarik* [a], *B. Legeza* [a]

[a] Pediatric Center, Semmelweis University, Budapest, Hungary

Background: 4-month-old patient (weight 4.5 kg) was admitted to our Pediatric Intensive Care Unit due to worsening cholestasis. She was born with atrial and ventricular septal defect and PDA. Four weeks before her admission, she developed a severe septic shock, as a result of which she underwent colon resection, and due to prerenal acute kidney injury she required CRRT. Upon admission surgical PDA closure and liver biopsy was performed, which showed intraductular cholestasis in addition to focal canalicular and intracellular cholestasis, assuming drug toxicity as the most likely cause (later, other conditions causing severe cholestasis were excluded). Laboratory results showed elevated liver enzymes (AST 450 U/L; ALT 349 U/L; GGT 1412 U/L), high total bile acid levels (310 µmol/L) in addition to significantly elevated bilirubin levels (total bilirubin 688 µmol/L; direct bilirubin 429 µmol/L). The retention and accumulation of hydrophobic bile acids, such as chenodeoxycholic acid and deoxycholic acid, inside hepatocytes during cholestasis have long been implicated as a major cause of liver damage. In addition, the release of toxic bile acids in the blood might lead to the damage of various organs. In order to avoid further organ damage and ensure optimal conditions for liver regeneration, we decided to start extracorporeal treatment in addition to drug therapy (cholestyramine and ursodeoxycholic acid).

Methods: We used the Prismaflex System (Baxter, IL, USA) during all treatments. CRRT required due to acute kidney injury was changed to SPAD treatment (Prismaflex ST60, Baxter, IL, USA) using 3% albumin concentration for a total of 5 days. With the improvement of kidney function, the SPAD treatment was stopped and switched to regular TPE (TPE 1000, Baxter, IL, USA) 1.5 plasma volume every 2-3 days due to repeatedly rising bilirubin and bile acid levels. Although TPE proved to be effective, we noticed a rapid rise in bile acids after the treatments. As a possibility, we decided to try adsorption hemoperfusion, which we assumed would be more effective due to the longer treatment time. Considering the low weight of our patient, we chose the smallest volume cartridge and performed the treatment with the HA60 (Jafron Biomedical Co. Ltd., Zhuhai, China) using Prismaflex HP-X Set (Baxter, IL, USA). CRRT, SPAD and TPE treatments were performed with regional citrate anticoagulation, while prostacyclin was used as an anticoagulant during hemoperfusion. The circuits were primed with 5% albumin, and if needed, a blood transfusion was given through a peripheral line at the start of treatment. Despite the baby's low weight, the treatments were not associated with hemodynamic instability.

Results: The hemadsorption treatment with HA60 cartridge lasted for 18 hours. The total bile acid level before the treatment was 212 µmol/L, at the 6th hour of the treatment 73 µmol/L, at the 12th hour 67 µmol/L, at the end of the treatment 67 µmol/L. Based on the results, adequate efficiency can be achieved with a 6-hour treatment - although the longer treatment did not cause a further decrease, but prevented the increase in bile acids. Compared to TPE, HA60 reduced bile acid levels more effectively over 6 hours - however, it should be noted that TPE treatments were shorter (about 2 hours). With SPAD treatment, we could not reduce the level of bile acids, but only a slight increase was observed in contrast to the rapid increase observed without treatment. The only complication of the treatments was the known decrease in the number of platelets, which was the largest in the case of HA60. With a shorter treatment, this complication can probably be reduced during hemadsorption. After 2.5 weeks of extracorporeal treatment, our patient's condition began to gradually improve, the bile acid and bilirubin levels began to decrease. She is currently 8 months old, her jaundice has resolved, and her mild cholestasis continues to improve with drug therapy.

Conclusion: The HA60 hemoperfusion cartridge, although designed for the treatment of septic patients, effectively reduces bile acid levels. Based on the literature data, our patient has the lowest body weight who was treated with HA60 due to liver disease. Based on our case, HA60 hemoperfusion can be used successfully in infants. During adsorption hemoperfusion in infants, prostacyclin can be effectively used as an anticoagulant. Our limitation is that we did not have the opportunity to measure the level of bile acids separately in our patient, so we have no information about the ratio of toxic and protective bile acids. The clinical benefit or harm of the bile acid adsorption needs to be evaluated in the future.

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A CASE OF FULMINATING LIVER FAILURE SECONDARY TO AUTOIMMUNE HEPATITIS

Angelares Cruz Jorge [a] , *García Peniche Carlos* [a]

a Centro de Especialidades Médicas del Sureste. Mérida Yucatán, México

Patient: CBD. 50 years old. 50-year-old woman who is admitted to our unit due to acute neurological deterioration

Pathological History: She denies chronic degenerative diseases, denies allergies to medications, and refers to social alcoholism, (less than 2 ups of wine per week), denies kidney, pulmonary, cardiac, or hepatic pathology, she refers anemia diagnosed 5 months ago in follow up and treatment by hematology with calcium and magnesium supplements and iron. she denies other pathological conditions.

Current Condition: Her relatives refers 5 days pior to her admission, started with asthenia, adynamia, hyporexia, 72 hours prior to her arrival to our unit generalized jaundice is added, it was also referred that 9 days ago she presented vomit in coffee grounds in just one occasion. Until the day of her arrival they found her with greater jaundice as well as disorientation data, being the reason why he is attracted to our unit to the emergency room.

Physical Exploration: Upon arrival, the patient was found in the following conditions: BP 80/40 mmHg HR 114 x´ RR 24 x´ Temp: 36.0ºC SpO2 92% at room air. Upon exploration, she finds herself, disoriented in time and space, little. cooperative, afebrile, integuments with generalized icteric tinge, oral mucosa dry, isochoric pupils, with palpebral edema. Rhythmic precordium, without noise aggregates. Lung exploration without rales or wheezing Pleuropulmonary syndrome is not integrated. Abdomen at the expense of a wide panicle fatty, depressible, not painful on palpation, no signs of peritoneal irritation. Integrated and functional extremities, capillary refill 4 seconds. Bedside ultrasound with bilateral pulmonary A pattern, VEXUS zero with Maximum Diameter of cava vein of 6mm, with 100% collapse, bilateral pulmonary pattern A, by heart echocardioscopy left ventricular ejection fraction preserved by MAPSE measurement. Laboratory findings: Hb: 5.0 g/dL HTO: 15%, Platelets: 129000, Leukocytes: 8820, Monocytes: 26%, Lymphocytes 9%,, Pt: 50.5s, aPTT: 60.8s, INR: 6.95, D-dimer: 2336, ng/mL. IL-6: 65.94 pg/mL, Procalcitonin: 1.10 ng/mL, Hepatitis B surface Ag: negative, AC`s anti-hepatitis C, negative, Hepatitis A antibodies IGM: negative, TB: 16.6 mg/dL, DB: 14.0 mg/dL, TGO: 145 IU/L, TGP: 49 IU/L, LDH: 373 IU/L, Albumin: 2.2 g/dL, AF: 88 IU/L, GGT: 288.8 IU/L, Huddelson: S.Typhi O. positive 1:40, S. Paratyphi A. positive 1:80, Brucella Abortus: positive, 1:40, Proteus OX-19 Positive. 1:160 Urea: 102 mg/dL, Cr: 2.6 mg/dL, Na: 130 mmol/L, K: 4.3 mmol/L, Cl: 92 mmol/L, Ca: 8.85 mmol/L, P: 5.4 mmol/L, Lipase: 57 IU/L, Amylase: 143 IU/L, CRP: 6.83 mg/L. Autoimmune disease profile: SLA/LP Positive. CEN P - A positive.

Diagnoses: Fulminant liver failure/ Probable upper gastrointestinal bleeding acute kidney injury KDIGO 3WHO grade 4 anemia, severe dehydration, hydroelectrolyte imbalance with mild hyponatremia, hypocalcemia, hyperphosphatemia. She presented torpid evolution with a requirement for extracorporeal liver support with DPMAS sessions, completing three blood purification sessions, DPMAS + PE THERAPY (Liver support HA330II and BS330 JAFFRON hemoadsorption cartridges) Total volume treated 8400 ml (2.5 volumes) 1 volume in TPE with albumin1.5 volume in DPMAS. Therapy time: 6 hours Blood flow 130 to 150 ml/min Replacement per hour: 1400 ml, as well as continuous veno-venous renal replacement therapy, presenting temporary improvement in biomarkers of liver damage, however due to the underlying diagnosis (autoimmune hepatitis) and the impossibility of finding a compatible donor for a liver transplant, evolved into irreversible multiple organ failure and death.

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OUTCOMES OF URINE DITHIONITE-GUIDED HEMOPERFUSION (HA 230) THERAPY ON EARLY PRESENTATION WITH PARAQUAT POISONING

*Ramesh Yelanati*a , Moturu Dharanindra b , Krishna Shriram Dhanasekaran c , Bala Krishna Nannappaneni d , V. Dinesh Kumar Gontla b , Maniendra Reddy e , Anita Atluri e*

a Department of Nephrology; b Department of Critical Care Medicine; c Department of Research and Publications; d Department of Pulmonology; e Department of Emergency Medicine and Clinical Cardiology

Background: Paraquat (PQ) is a highly toxic weedicide which when ingested causes multi- organ dysfunction followed by death if treatment is delayed. Interventions to reduce mortality were less beneficial in many case series and only a few studies have documented the use of urine dithionite tests (UDT) with hemoperfusion in prognosticating the outcomes. We aimed to determine the outcomes of hemoperfusion (HA 230) guided by UDT in patients with PQ poisoning in terms of presentation time.

Methods: This retrospective observational study involved 15 patients presented with paraquat ingestion. UDT was performed to confirm paraquat severity in all patients. Data on the ingested quantity, presentation time, complications developed, diagnostic results and treatment prognosis were collected and analysed.

Results: Of the 15 patients treated, hemoperfusion (HP) (with HA 230) was performed in 12 patients who tested positive for paraquat on UDT. The overall mortality rate was 40%. All patients presented early (<4h) (n=6) were successfully managed. Seventy-five percent (n=3) of late presenters succumbed to death despite HP therapy. The UDT was strongly positive (+++) in all non-survivors ($p<0.05$). Non-survivors had higher serum creatinine and bilirubin levels at post-final HP compared to survivors. Complications like respiratory dysfunction, hepatic failure and multiorgan dysfunction syndrome (MODS) were significantly higher in the non-survivors ($p<0.05$).

Conclusion: Early presentation and timely hemoperfusion (with HA 230) with diagnostic UDT guidance increases survival with fewer complications in cases with paraquat intoxication.

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STUDY ON ADSORPTION PROPERTIES OF DIFFERENT HEMOPERFUSION PRODUCTS FOR PROTEIN-BINDING TOXINS AND MIDDLE MOLECULES

Hongyan Du a , Chengcheng Shi a

a Guangdong Provincial Key Laboratory of Extracorporeal Circulation Adsorption and Separation Technology

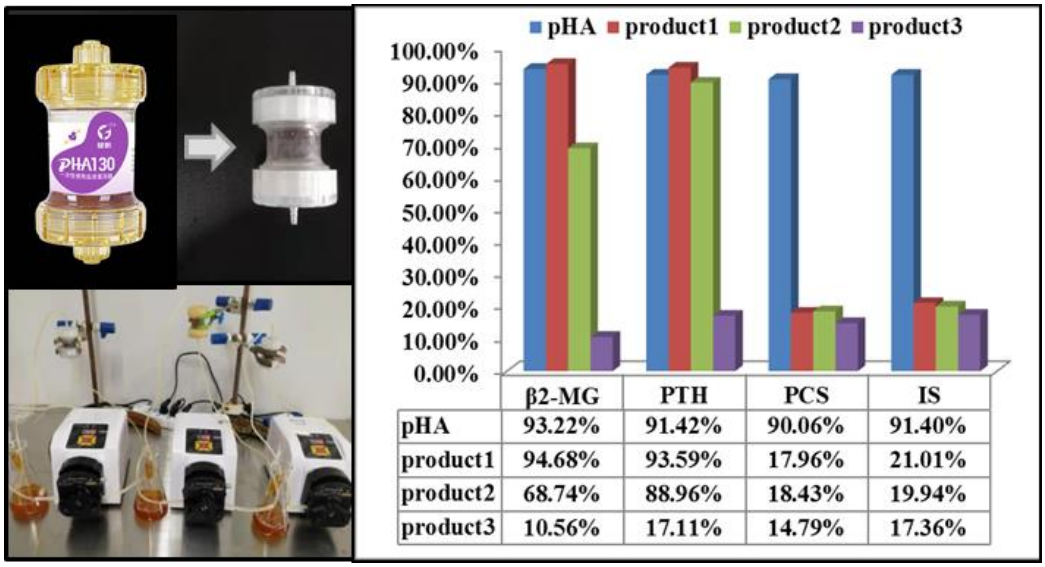
Background: In uremia patients, due to the gradual loss of renal function, various metabolic toxins accumulate in the body and cannot be excreted. Combined artificial kidney (HD+HP) has become an effective clinical treatment. At present, hemodialysis mainly solves the balance of Small water-soluble compounds and electrolyte. Hemoperfusion has advantages in the removal of middle molecules and protein-bound toxins. However, the comprehensive adsorption performance of different products for protein-binding toxins and middle molecules is still lacking.

Methods: The in vitro experiment was established by 3D printed 20 times smaller cylinder model. The pHA and other three hemoperfusion devices sold in China were precisely measured with 6.5mL wet resin, and the micro-perfusion device was connected to the circulating pump with the pipeline of the disposable infusion device to build the circulation system. Standard substances (β2-microglobulin, PTH, p-cresol sulfate, and indoxyl sulfate) were added to the plasma of healthy people. The plasma was circulated at a fringe of 10mL/min for 2h. The concentrations of p-cresol sulfate and indoxyl sulfate were determined by HPLC, and the concentrations of PTH and β2-microglobulin were determined by chemiluminescence method. The adsorption rate was calculated using the formula: [Initial concentration - Final concentration]/ Initial concentration

Results: In this study, the adsorption rates of β2 microglobulin, PTH, p-cresol sulfate and indoxyl sulfate were 93.22%, 91.42%, 90.06% and 91.40%. The adsorption rates of β2 microglobulin and PTH of product 1 were higher than 93%, but the adsorption rates of protein binding toxins were low. The adsorption rate of product 2 for PTH reached 88.96%, and the adsorption rates of rotein binding toxins were less than 20%. The adsorption rates of product 3 to the four substances were at an extremely low level.

Conclusion: The other three products only have the unilateral adsorption effect on protein binding toxins or middle molecules. pHA can efficiently remove β2 microglobulin, PTH, p-cresol sulfate and indoxyl sulfate at the same time . The results showed that pHA could bring more benefits to uremia patients with accumulation of medium hexaprotein-binding toxin in the combined HD+HP model.

Figure 1 In vitro adsorption model and adsorption rates of different products for β2 microglobulin, PTH, p-cresol sulfate and indoxyl sulfate



	β2-MG	PTH	PCS	IS
pHA	93.22%	91.42%	90.06%	91.40%
product1	94.68%	93.59%	17.96%	21.01%
product2	68.74%	88.96%	18.43%	19.94%
product3	10.56%	17.11%	14.79%	17.36%

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STUDY ON ADSORPTION PROPERTIES OF PHA TO DIFFERENT PATHWAY PROTEIN BINDING TOXINS

Hongyan Du a , Chengcheng Shi a

a Guangdong Provincial Key Laboratory of Extracorporeal Circulation Adsorption and Separation Technology

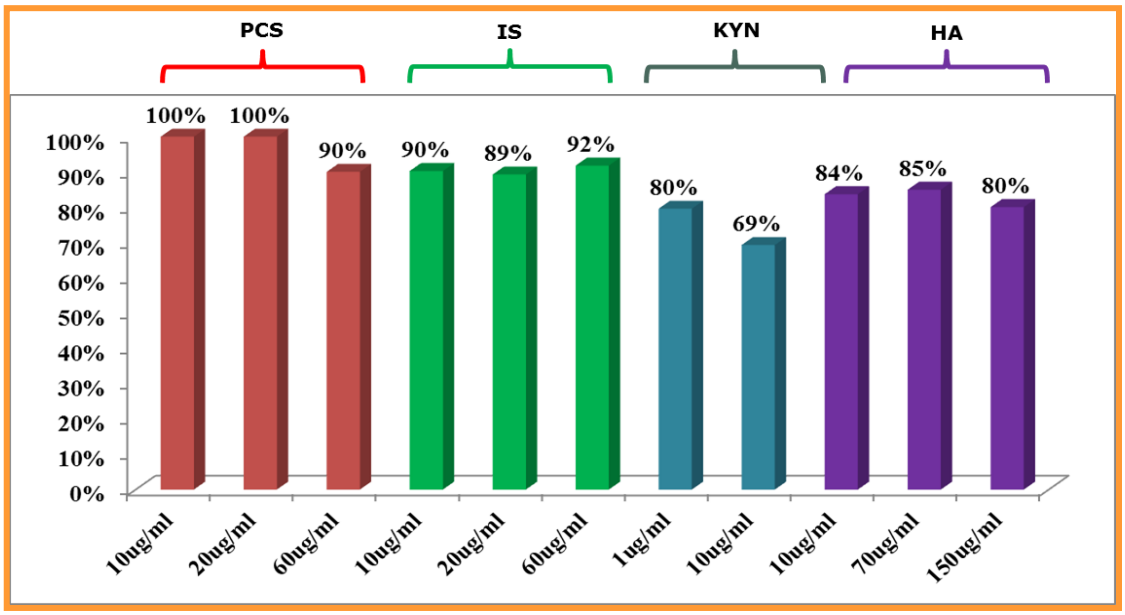
Background: More and more studies have shown that protein-bound toxins play an important role in the occurrence and development of uremia complications, and the increase of blood concentration of these toxins is closely related to the poor prognosis of patients with end-stage kidney disease. Most protein-binding toxins are enterogenic toxins, which are metabolized by bacteria in the gut from amino acids in food. At present, the clear effect of hemoperfusion products on indoxyl sulfate and cresol by sulfuric acid has been widely concerned in clinical treatment, but the clearance of other metabolic pathway proteins binding toxins is still lacking.

Methods: The adsorption properties were studied by oscillatory adsorption model in vitro: Standard substances (p-cresol sulfate, indoxyl sulfate, indole-3-acetic acid, kynurenine, kynuuric acid, o-hydroxyhippuric acid, hippuric acid) were added to the plasma of healthy people. 1mL pHA130 (Jafron Biotechnology Group Co., LTD.) was Add to 10mL simulated blood and oscillate at 140rpm/min in a 37°C thermostatic oscillator for 2h, then collect 0 or 2h of blood to determine the concentration of different protein-bound toxins by HPLC, and calculate the adsorption rate. In addition, mixed plasma containing clinically low, medium and high concentrations of p-cresol sulfate, indoxyl sulfate, hippuric acid and kynurenine was configured to determine the adsorption rate according to the same oscillation condition. The adsorption rate was calculated using the formula: [Initial concentration - Final concentration]/ Initial concentration.

Results: In this study, the adsorption rates of pHA adsorbent for indoxyl sulfate, p-cresol sulfate, indole-3-acetic acid, hippuric acid, o-hydroxyhippuric acid, kynuuric acid and kynurenine were 90.74%, 91.92%, 81.25%, 88.43%, 78.36%, 79.78% and 72.86%, respectively. We also observed that with the gradual increase of the initial concentration of the binding toxin, the adsorption performance of the pHA adsorbent did not decrease, indicating that pHA has great adsorption potential.

Conclusion: pHA adsorbents have excellent adsorption properties for proteins binding toxins of different metabolic pathways, which can still be maintained at clinical low, medium and high concentrations. The results show that pHA products have great potential and value in clinical uremic protein-binding toxin clearance.

Figure 1. Adsorption rates of pHA adsorbents for protein-binding toxins at different concentrations



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EXPANDING THE POTENTIAL THERAPEUTIC OPTIONS OF HEMODIAFILTRATION WITH JAFRON HA330 CARTRIDGES IN SEPTIC SHOCK PATIENTS: A CASE REPORT

Jesus Mier [a], *Angelica Hernandez* [a], *Ruben Merino* [a], *Amparo Mier* [a]

a Hospital Ángeles Puebla. Puebla, México

Backgrounds: Sepsis is the most common cause of patient hospitalization in the intensive care unit; this is a life-threatening organ dysfunction caused by overwhelming production of proinflammatory cytokines (1). The global recommendations for sepsis are fluid resuscitation, vasopressors and early administration of antibiotics. Growing evidence place hemoadsorption as an adjuvant treatment for sepsis. In this case report we highlight the use of JAFRON HA330 cartridge, new hemoadsorption cartridge is used in acute conditions and removes molecules weighing 10-60 KDa.

Methods: In this case report we present a 37-year-old female with a history of a 20-week gestation pregnancy and diagnosis of cervical incompetence and admitted in the intensive care unit. Upon admission, she refers chills and uterine contractions. Due to persistent signs of septic, cardiogenic and distributive shock and probable infective endocarditis, termination of pregnancy and total abdominal hysterectomy were decided. During her initial post-surgical evolution, she remained febrile, dependent on vasopressors and mechanical ventilation with a significant increase in inflammatory parameters with leukocytes blood levels of 37,000, lactate 7.7, creatinine 1.56, TP 21.1, TPT 39.4, INR 1.6, BNP 3817, DD > 10000, PCT 40 and amniotic fluid culture positive for E. coli, also the diagnosis of acute tubular necrosis and severe sepsis-induced cardiomyopathy were made, this lead to multiple organ failure (hemodynamic, respiratory, renal, and hematologic) and incipient acute kidney injury. We decided to initiate renal replacement therapy with slow hemadsorption therapy (PRISMA + JAFRON HA130 cartridge), to decrease cytokine release in severe inflammatory response, and hemoadsorption with a JAFRON HA 330 cartridge, adsorption of 50 ml/hr and the use of a diuretic if necessary, concluding 24 hours after without any eventualities. With the improvement of hemodynamic state and negative polycultures we decided to transfer her to intermediate therapy with withdrawal of amines, maintaining perfuser TAMs and an echocardiogram with a report of normal function. After 17 days of hospital stay due to adequate progress, multi-organ failure remitted and normalization of inflammatory parameters, the decision was made to discharge her from the hospital.

Results: Following the cessation of slow hemodiafiltration with PRISMA and the use of JAFRON HA330 cartridge we wait for x hours and check again the inflammatory parameters, which were reported: leukocytes 30,000, lactate 2, creatinine 0.8, TP 13.5, TPT 25.7 and INR 1.2. We also found no evidence of an infectious focus in the CT scan report.

Conclusion: We believe that Hemoadsoption with HA330 can be a prospective treatment for shocked septic patients without renal failure with the intensive care unit admission. Further investigations of hemoadsorption technology would improve the incidence of this therapy.

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HEMADSORPTION MANAGEMENT WITH SAFRON HA 330 FILTER FOR ACUTE KIDNEY INJURY SECONDARY TO SEPTIC SHOCK AFTER A WHIPPLE PROCEDURE: A CASE PRESENTATION

Mier Naylor Jesús [a] , *Morales Deborah* [a] , *Hernández Cuamani Angélica* [a] , *Vázquez Vázquez Abish Paola* [a] , *Mier Prado María Amparo* [a]

a Hospital Puebla, Puebla México

Case report: A 51 year-old male patient is presented with a clinical history of 2 months characterized by multiple nausea and vomiting episodes accompanied by hyporexia and halitosis. An endoscopic ultrasound was performed with compatible findings with a solid and cystic located around the head of the pancreas, a biopsy was taken reporting a neuroendocrine tumor. Subsequently, the symptoms worsened and started with intense abdominal pain for which he was admitted for a Whipple procedure followed by multiple abdominal surgical interventions. During the clinical evolution he presented a significant inflammatory response with subsequent increase of acute phase reactants (leukocytes 20.4, PCT 1.33, PCR 158, creatinine 2.15, BUN 69, urea 147.6) resulting in septic shock amine and vasopressor dependent and acute kidney injury AKIN II without dialytic requirement with a SOFA score of 16. Hemoadsorption was started with a SAFRON HA 330 filter. After 24 hours of ultrafiltration the patient began with a significant recovery with an important decrease of acute phase reactants and normalization of laboratory parameters (leukocytes 9.5, PCT 0.6, PCR 87.5, creatinine 0.96, BUN 41.5, urea 89) achieving a SOFA score of 3 and a good clinical evolution.

At present the patient is showing an adequate evolution, without the use of amines, with respiratory support through reservoir mask, continuing with an important decrease of the initial inflammatory response and clinical and biochemical improvement.

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DPMAS AS TREATMENT IN A SEVERE ACUTE-ON-CHRONIC LIVER FAILURE IN A PATIENT WITH AUTOIMMUNE HEPATITIS

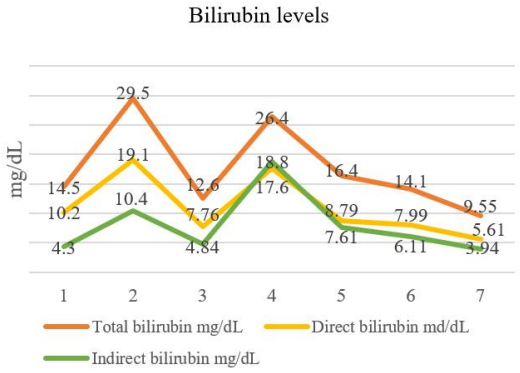
Zavala-Gómez Mariana [a], *López-Contreras Rodrigo* [a], *Alvarez-Lara Daniel* [a], *Cortez-Hernadez Ca*, *Rizo-Topete L* [a]
a Hospital Muguerza, Nuevo Leon, Mexico

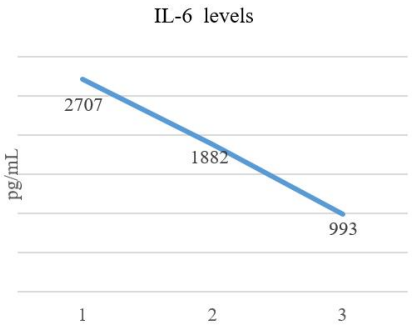
Abstract: The use of extracorporeal liver support systems (ECLS) to bridge the patient to liver transplant (LT) or recovery, has been improved in the last years. We present a case of a 55 years female with autoimmune hepatitis who presented liver failure and underwent trough 3 sessions of double plasma molecular adsorption system (DPMAS). She presented progressive improvement in clinical condition and laboratory values of bilirubin and inflammatory marker IL6.

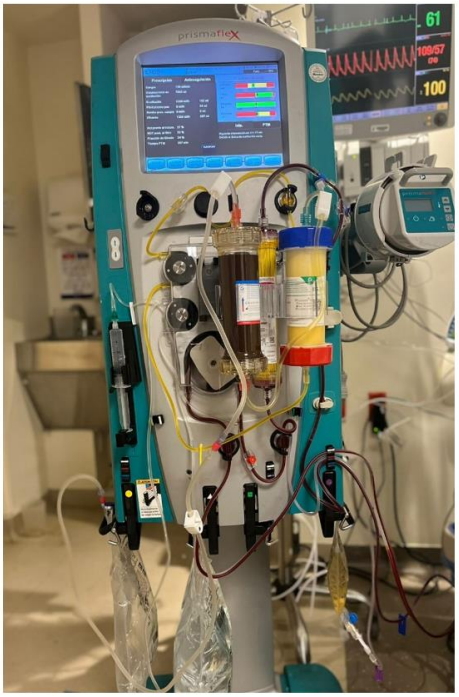
Introduction: Liver failure, acute or acute-on- chronic, is a life-threatening disease with a high mortality rate. The use of ECLS would allow support as a bridge to LT or until the patients' liver can recover or potentially provide symptom relief. ECLS aim to improve detoxification, biosynthesis, regulation, and regeneration, for improving neurological status, hemodynamics, reducing inflammation and enhancing regeneration.

Clinical Case: Female 55 years old, diagnosed with AIH for 4 years, in treatment with hydrocortisone, mycophenolic acid, and ursodeoxycholic acid. With previous exacerbations and under an incomplete liver transplant protocol. Her current condition began one week prior to admission, presenting hyporexia, asthenia, and adynamia, accompanied by diffuse colicky abdominal pain with an intensity of 5/10. Physical examination: mucocutaneous jaundice and dehydration, Grade I encephalopathy, and ascites. Edema with pitting +++ in the lower extremities. On admission, the laboratory tests were: Hb 8.9 g/dL, Hct 26%, leukocytes 5.30 per µL, platelets 54,000, PT 32.2 s, INR 2.84, aPTT 55.9 s; Cr 0.73 mg/dL; urea 72.8 mg/dL; total bilirubin 14.5 mg/dL, BD 10.2 mg/dL, BI.3 mg/dL; AST 97 U/L; ALT 60 U/L; GGT 43 UI/dL, ALP 135 U/L. MELD score of 28 points, Child-Pugh class C (13 points). On the fifth day of hospitalization, progression to Grade IV hepatic encephalopathy associated with LRA KDIGO 2 was observed, with worsening laboratory values: Cr 1.71 mg/dL, BUN 61.7 mg/dL, BT 21.9 mg/dL, BD 15.7 mg/dL. We performed 3 sessions of DPMAS, on alternate days, with TPE2000 filter cartridge HA330 II and BS 330. Each session lasted for 6 hours and with plasma volume of 1.5 for DPMAS and 1 time for TPE. With a Qb 130-150 ml/min and Qr post 1300 -1400 ml. jugular HD catheter was placed . The associated RRT technique was CVVHDF. Progressive improvement was observed in laboratory values and clinical condition after each DPMAS session.

Discussion and Conclusion: The double plasma molecular adsorption system (DPMAS) is a blood purification method that is safe and effective for reducing bilirubin levels and inflammatory markers, making it an important option for bridging to transplant or recovery. This could be observed in our patient, in whom the bilirubin and IL-6 levels decreased significantly after treatment with DPMAS, from 29.5 mg/dL and 2707 pg/mL, respectively, to 9.55 and 993 pg/mL.







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AUGMENTED RENAL CLEARANCE IN NEUROCRITICAL CARE PATIENTS: A RETROSPECTIVE COHORT STUDY

Ramírez-Guerrero G a, b, Baghetti-Hernández R a , Lucero C a , Torres-Cifuentes V a, b, Villagrán F a, b, Hauway E a, Garay O a*

a Critical Care Unit, Carlos Van Buren Hospital, Valparaíso, Chile; b Nephrology and Dialysis Unit, Carlos Van Buren Hospital, Valparaíso, Chile.

Background: The presence of augmented renal clearance (ARC) in critical patients is concerning because of its association with subtherapeutic antimicrobial drug or antiepileptic drug concentrations, increased length of stay, and higher mortality. This study aimed to describe the characteristics between ARTIC score and GFR in the neurocritical care population and, the prevalence of ARC risk defined by an ARTIC score of 6 or higher.

Methods: A retrospective cohort study was conducted in the neurocritical Care Unit. Patients admitted to the neurocritical care unit between 2016 and 2018 with a stay longer than 48 hours were retrospectively analyzed regarding the incidence, risk factors, and outcomes of ARC. The cutoff for ARC was defined as an estimated CrCl of> 130 mL/min/1.73m2. These values were obtained on the first day of admission.

Results: An ARTIC score of 6 or higher was present in 54,2% of patients, and 5% met the criteria for ARC due to eGFRCKD-EPI. Patients with a risk of ARC defined by ARTIC score ≥ 6 had a significantly higher percentage of male gender, 56,3%, compared to those without ARC, 36.2% (p = 0.002). The group with the highest ARTIC score was significantly younger, 45.6 ± 14.8 years old vs. 67.1 ± 11.5 years old. Patients on ARC risk had less presence of hypertension, 39.1% vs. 60.9% (p < 0.001), and diabetes mellitus 2, 37.1% vs. 62.9% (p = 0.026). The group with a high ARTIC score had more presence of polyuria in the next 14 days, 70.4% vs. 29.6% (P < 0.001), and had greater use of 10% hypertonic saline, 70.4% vs. 29.6% (p = 0.005). The group with the highest ARTIC score presented less acute kidney injury and less 30-day mortality, unlike the group with an ARTIC score of less than 6, 38.8% vs. 61.2% (p = 0.013) and 37.5% vs. 62.5% (p = 0.039). ARTIC score positively correlates with the glomerular filtration rate estimated by the eGFRCKD-EPI.

The incidence of AKI was 23.5%. Polyuria was observed in 50% of patients, and hyponatremia and hypernatremia were observed in 16.9% and 40.9% of patients, respectively.

Conclusion: ARC is a common phenomenon in the neurocritical care unit, especially in younger patients without cardiovascular comorbidities, and was associated with less acute kidney injury and less mortality.

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ASSESSING LINEZOLID EXTRACORPOREAL CLEARANCE DURING CVVH WITH OXIRIS: IMPLICATIONS FOR OPTIMIZING ANTIBIOTIC THERAPY IN CRITICALLY ILL PATIENTS

F. Cundari[a,b], A. Lorenzin[a], M. De Cal[a], M. Zanella[a], C. Ronco[a], N. Perin[a], L.Cattin[a], S. Lassola[a], S. De Rosa[a,b]

[a] International Renal Research Institute of Vicenza (IRRIV), San Bortolo Hospital, Vicenza, Italy
[b] Centre for Medical Sciences - CISMed, University of Trento, Trento, Italy

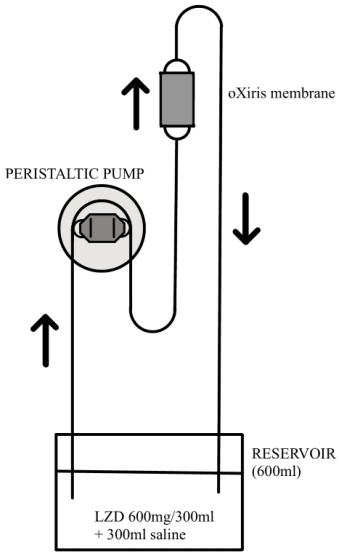
Background: Sepsis induces dysregulated inflammation, leading to organ dysfunction, necessitating antibiotic therapy for treatment. However, optimal delivery of antibiotics faces challenges due to potential loss in effluent or adsorption on sorbent surfaces. Linezolid, a common anti Gram-positive antimicrobial, may experience subtherapeutic levels during extracorporeal techniques. This study aimed to assess linezolid's in vitro interaction with the oXiris membrane.

Methods: The oXiris filter (Baxter; Deerfield, USA) features a membrane of polyacrylonitrile methalysulfonate coated with polyethyleneimine and unfractioned heparin, commonly used in septic patients. Linezolid removal via adsorption was tested by clamping the dialysate inlet and outlet and circulating a solution though the filter using a customized circuit on the Galileo platform. The circuit was primed with saline solution, and 600 mg of linezolid solution (300 ml of normal saline) mixed with 300 ml of normal saline was circulated through the filter at 120 ml/min for 120 minutes in a closed loop configuration. Samples were collected at 0, 5,10, 15, 20, 30, 60, 90 and 120 minutes from the reservoir and linezolid concentrations were measured through ARK Linezolid Assay (Figure 1).

Results: In vitro circulation showed a mild affinity of the oXiris filter to bind linezolid, with rapid antibiotic adsorption in the initial minutes. Linezolid concentration in the reservoir dropped significantly within 5 minutes, from 0.92 to 0.59 mg/ml. The removal ratio reached 36% and remained steady thereafter. Throughout the experiment, 305.6 mg of linezolid was adsorbed by the filter.

Conclusion: The present in vitro study underscores the potential risk of subtherapeutic levels of linezolid during CRRT with oXiris. Although further studies are necessary to clarify this phenomenon, linezolid level variations observed in our study should be considered to avoid antimicrobial underexposure. Several strategies are available for adjusting the dosage regimen of linezolid, but therapeutic drug monitoring is highly recommended when it is used.

Figure 1. Linezolid extracorporeal clearance during CVVH with Oxiris



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SERAPH® 100 AFFINITY BLOOD CARTRIDGE AS A POTENTIAL ADJUNCTIVE BLOOD PURIFICATION STRATEGY FOR S.AUREUS-INDUCED SEPTIC SHOCK

F. Cundari [a,b],A. Lorenzin [a],M. De Cal [a],O. Massidda[b], L.Cattin [a] ,N.Marchionna[a], M. Zanella [a], N. Perin[a], S. Lassola [a], S. De Rosa[a,b]

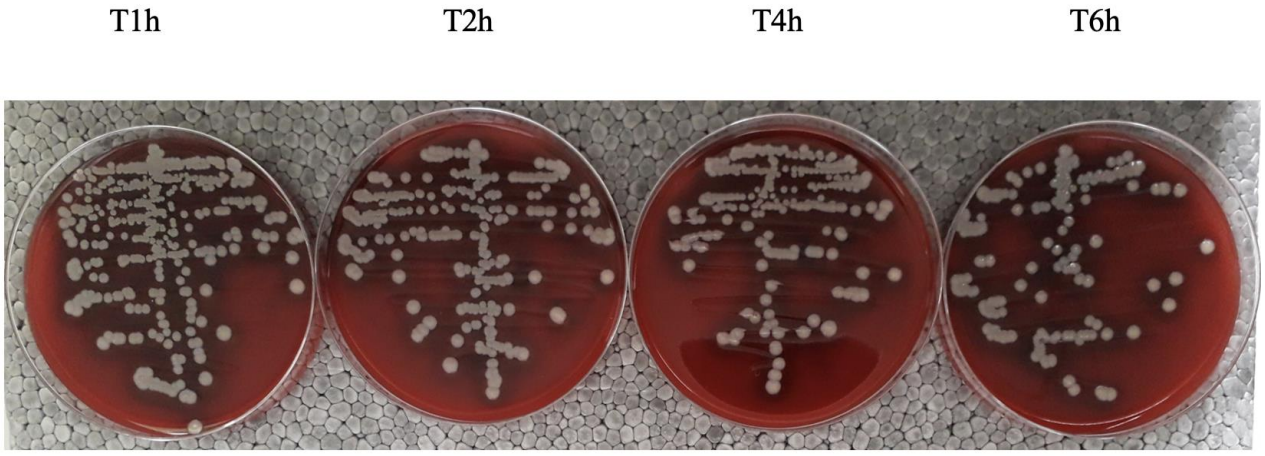
Background and Aims: S.aureus infections, particularly methicillin-resistant strains, can induce severe conditions, provoking an overwhelming immune response and contributing to systemic inflammation and organ failure. Effective antibiotic therapy and meticulous supportive care are crucial in the ICU to manage S.aureus-induced septic shock. In this context, blood purification strategies aim to target the microorganism and associated toxins, contributing to the systemic inflammatory cascade. The objective of this in-vitro study was to analyze the potential removal, through adsorption, by the Seraph100 Affinity Blood Cartridge (S100ABC) against S.aureus. Subsequently, the study assessed whether the adsorptive capabilities toward bacteria were maintained, and if so, whether the bacteria retained its bactericidal activity.

Method: The study employed an *in vitro* model of hemoadsorption to characterize the adsorption performed by the S100ABC on a circulating bacterial load inoculated in blood. A volume of 150ml of blood served as a negative control (CTR-). The remaining 650mL were enriched with a concentration of S.aureus bacteria equal to $1x10^6$ and incubated for 4h at 37°C. At 4h, the blood was divided into 2 glass bowls and stirred at 37°C: 500mL were circulated at a speed of 120mL/min via a dedicated test platform (Galileo) with Seraph100, while another 150mL was stirred and used as a positive control (CTR+). The experiment was performed twice. Samples were taken from circulating blood and the two controls for blood cultures and placement on CNA agar.

Results: This study demonstrated that the S100ABC reduces the circulating bacterial load (from $1x10^6$ at T0 to $0.25x10^6$ at T6h), leading to the adsorption of bacteria onto the cartridge. Bacteria were found adhering to the beads contained in the cartridge (Figure 1).

Conclusion: Our preliminary data show that the S100ABC effectively reduces the circulating bacterial load. The S100ABC could be an adjunct sorbent for reducing S.aureus in human blood, supporting antibiotic therapy in patients with S.aureus-induced septic shock.

Figure 1: Growth of Bacteria



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PERITONEAL INFLAMMATION IN PD-RELATED PERITONITIS INDUCES SYSTEMIC ERYPTOSIS: IN VITRO AND IN VIVO ASSESSMENTS

G.M. Virzì[a,b], *N. Morisi[c]*, *S. Milan Manani[a,b]*, *I. Tantillo[a]*, *C. Ronco[b]*, *M. Zanella[a,b]*

[a] Department of Nephrology, Dialysis and Transplant, St Bortolo Hospital, Vicenza, Italy
[b] IRRIV (International Renal Research Institute) Foundation, Vicenza, Italy
[c] Surgical, Medical and Dental Department of Morphological Sciences, Section of Nephrology, University of Modena and Reggio Emilia, Italy

Background: Erythrocytes (RBCs) have a highly specialized and organized membrane structure and undergo programmed cell death, known as eryptosis (=stress-induced RBC death mechanism). Triggers of eryptosis include oxidative stress, inflammation and several uremic toxins. Our preliminary data show a significant increase of eryptosis during peritoneal dialysis (PD)-associated peritonitis in PD patients. The aims of this study were: assessment of incrementation of eryptosis in PD patients with peritonitis, evaluation of the relationship between systemic eryptosis in peritonitis and specific peritonitis biomarkers in PD effluent (PDE), and confirmation of the induction of eryptosis by peritonitis in a vitro setting.

Methods: We enrolled 34 PD patients in stable condition (without systemic inflammation nor PD-related peritonitis in the last 3 months), 31 PD patients with acute peritonitis, and 17 healthy subjects (CTR). For PD stable patients, blood samples for eryptosis evaluation were drawn during the regular outpatient. For PD patients with peritonitis, blood samples and PDE samples were collected at the time of peritonitis diagnosis. PDE samples were used for peritoneal White Blood Cell count (pWBC), peritoneal Neutrophil Gelatinase-associated Lipocalin (pNGAL) and peritoneal cytokines levels (IL-1β and IL-6) measurements. For in vitro study, healthy RBCs were exposed to plasma of 31 PD patients with peritonitis and plasma of CTR group for 2,4 and 24 hours. Morphological markers of eryptosis (cell membrane scrambling, cell shrinkage) and eryptosis percentage (based on PS exposure at RBC surface and AnnexinV-binding) were evaluated by flow cytometric analyses in vivo and in vitro.

Results: Totally, 65 chronic PD patients were included in this study. Table 1 reports clinical data for our PD population (Table 1). The percentage of AnnexinV-binding RBCs was significantly higher in PD patients than in CTR. Eryptosis levels did not differ significantly between PD pts with and without diabetes, with and without hypertension, with and without cardiovascular disease. Eryptosis showed no significant differences between patients treated by CAPD/APD, and with Kt/Vurea values ≤ 1.7 and > 1.7. Generally, RBCs of all 65 PD patients were dramatically deranged in their morphology. In particular, RBCs from PD patients with peritonitis were characterized by dramatically deranged morphology and increased median cell volume in comparison with PD stable patients (p<0.001). The percentages of AnnexinV-binding RBCs were significantly increased in the PD-associated peritonitis group (9.6%; IQR 4.2-16.7 versus 2.7%; IQR 1.6-3.9) (p<0.0001) (Figure 1). The percentage of AnnexinV-binding RBCs was significantly higher in PD patients with peritonitis than in healthy CTR (p<0.001).We confirmed these in vivo data by in vitro results: healthy RBCs incubated with plasma from PD patients with peritonitis demonstrated a significant increase of eryptosis compared to healthy RBCs exposed to plasma from control group at all times (Figure 2).Furthermore, significant positive strong correlations were observed between eryptosis level and all analysed peritoneal biomarkers of peritonitis (Spearman's rho pWBC=0.77, p<0.001, Spearman's rho pNGAL=0.64, p=0.001, Spearman's rho IL-6 =0.61, p=0.003 and Spearman's rho IL-1β=0.64, p=0.001,) (Figure 3).

Conclusion: We investigated a potential connection between systemic eryptosis and peritoneal biomarkers of peritonitis. In particular, we theorized that the eryptosis enhancement is directly connected with peritonitis, and, based on the results, we hypothesized that the peritoneal membrane injury could be related to eryptosis. Upregulation of inflammatory markers could explain the increased rate of systemic eryptosis during PD-related peritonitis. In particular, we corroborated this point with our observations about *in vitro* induction of eryptosis by plasma from PD patients on the first day of peritonitis.

Figure 1. Eryptosis Level

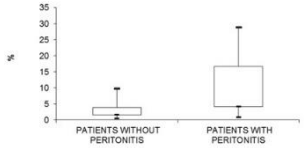


Table 1	Patients with peritonitis (n=31)	Patients without peritonitis (n=34)	p-value
Male/Female	19/12 females	27/7 females	0.11
Age, years	61.0±14.9	64.1±13.8	0.46
CVD	16/31	12/34	0.19
Diabetes	11/31	10/34	0.6
Months of dialysis	33.6, IQR 19.1-43.5	31.3, IQR 17.8-45.7	0.79
CAPD/APD	16CAPD/14APD	20CAPD/14APD	0.75
Weekly Creatinine Clearance	60.9, IQR 49.4-84.1	55.2, IQR 46.4-62.8	0.15
Weekly Kt/Vurea	1.7, IQR 1.5-1.9	1.8, IQR 1.6-2.1	0.21
CRP, mg/dL	4.4, IQR 1.0-12.6	0.4, IQR 0.3-0.9	p<0.001
IL-1β, pg/mL	36.3, IQR 3.1-58.3	1.4, IQR 0.8-2.5	p<0.001
IL-6, pg/mL	173.4, IQR 107.2-206.7	19.8, IQR 9.4-61.3	p<0.001

Figure2.In vitro Induction of eryptosis

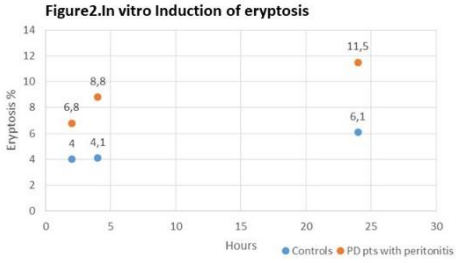
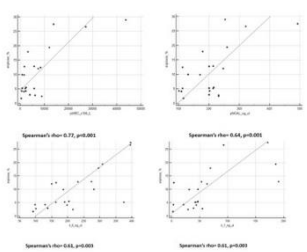


Figure 3:Correlations with PDE markers and eryptosis



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ENDOTOXIN REMOVAL BY A NEW MICROPOROUS SORBENT (XCA): IN VITRO RESULTS

*G. Klinkmann [a,c,d], A. Lorenzin [a,b], M. De Cal [a,b], N. Perin [a,b], C. Ronco [b,d]

[a] International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy; [b] Department of Nephrology, Dialysis and Kidney Transplantation, San Bortolo Hospital, Vicenza, Italy; [c] Department of Anaesthesiology, Intensive Care Medicine an Pain Therapy, University Medical Center Rostock, Rostock, Germany; [d] Department of Extracorporeal Immunomodulation, Fraunhofer Institute for Cell Therapy and Immunology, Rostock, Germany;

Background: Endotoxin, also referred to as lipopolysaccharide (LPS), is a major stimulus of the inflammatory response capable of leading to sepsis and septic shock. Patients with elevated endotoxin activity often experience a substantial degree of organ failure, which correlates with higher mortality rates. Timely and thorough removal of endotoxin can help mitigate the inflammatory cascade typical for septic shock. Hemoadsorption is a promising approach to achieve this goal. This *ex vivo* study investigates the efficacy of a XCA sorbent cartridge (Jafron® Biomedical, Zhuhai City, China) in removing endotoxin.

Methods: We studied a downscaled module of the XCA Adsorption Cartridge (Jafron® Biomedical, Zhuhai City, China) in an *ex vivo* closed-loop hemoadsorption circuit using a pool of 3000 ml heparinized blood spiked with 50 mg of LPS. The blood pool was separated into 6 units of 500 ml (5 treatment simulations; 1 control). Circulation was maintained for 2 hours at a blood flow rate of 100 mL/min with a fixed blood volume of 500 mL in each reservoir, heated to 37°C, and stirred. Circulation was conducted using the Galileo testing platform (IRRIV, Vicenza), featuring pressure sensors and peristaltic pumps. Samples were drawn at predefined time points from the blood pool, to determine Endotoxin Activity Assay (EAA) and cytokine profiles. Additionally, we measured the LPS concentration gap (ΔC) between inlet (C_{in}) and outlet (C_{out}) of the cartridge.

Results: EAA values showed a significant decrease over the course of the experiments (p = 0.002), with an initial mean concentration of 3.2 ± 0.5 and a final mean concentration of 0.7 ± 0.1 (Figure 1). LPS levels showed considerable differences of 16.2 ± 0.4 pg/ml upstream and 15.2 ± 0.3 pg/ml downstream the cartridge (p = 0.1) (Figure 2).

Conclusion Our findings represent the first evaluation of endotoxin adsorption within an *ex vivo* plasma perfusion model employing the XCA cartridge. The reduction in the EAA values over time and the LPS reduction upstream and downstream of the cartridge provide useful signals indicating its potential for endotoxin removal. The results underscore the suitability of the *ex vivo* circulation model, serving as a foundation for designing subsequent clinical investigations.

Figure 1

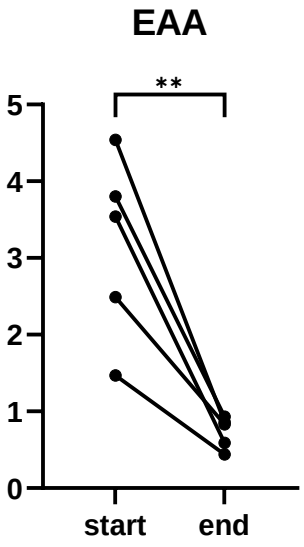
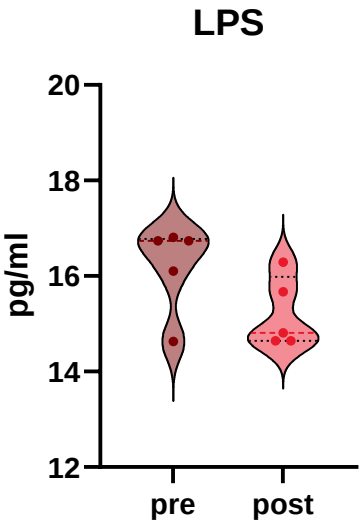


Figure 2



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EXTRACORPOREAL BLOOD PURIFICATION IN SEVERE CAR T-CELL THERAPY ASSOCIATED TOXICITY: A CASE SERIES.

Thomas Cortello [a, b], Elena Beltrametti [a, b], Valentina Zanetti [a, b], Sara Denise Vercelli [a], Novella Conti [b], Francesca Cappadona [a, b], Massimiliano Gambella [c], Annamaria Raiola [c], Monica Centanaro [d], Emanuele Angelucci [c], Francesca Viazzi [a, b], Elisa Russo [a, b], Pasquale Esposito [a, b]*

[a] Dipartimento di Medicina Interna e Specialità Mediche, Università di Genova, Italia;
[b] Clinica Nefrologica, IRCCS Ospedale Policlinico San Martino, Genova;
[c] Ematologia e terapie cellulari. IRCCS Ospedale Policlinico San Martino, Genova;
[d] Clinica Anestesiologica e terapia intensiva. IRCCS Ospedale Policlinico San Martino, Genova

Background: Chimeric antigen receptor (CAR) T-cell therapy represents a novel strategy for the treatment of haematological malignancies, such as acute lymphocyte leukaemia (ALL) or aggressive B cell lymphoma and has yielded to impressive outcomes. However serious adverse effects are reported, the most common are cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS), two conditions of immune system over activation, induced by a widespread release of cytokines, such as IL-6 and IFN-γ, following the binding of CAR-T cell with the target tumour antigens. These conditions could be life-threatening. Current management of CAR-T cell therapy toxicities consists of supportive care, corticosteroids and anti-IL-6 therapy with Tocilizumab. For severe cases, further strategies such as extracorporeal blood purification (BP) treatments are under investigation.

Methods: We performed a retrospective analysis of patients receiving CAR-T cell treatment in our centre between 2020 and 2023. We collect comprehensive baseline and longitudinal data on clinical characteristics, laboratory results, treatments, and outcomes. Individual evaluation was performed for patients who underwent BP after CAR-T cell therapy. Diagnosis and staging of acute kidney injury (AKI), cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS) were conducted according to current guidelines.

Results: We analyzed a total of 48 patients (M/F: 29/19, age 61±11 years) receiving CAR-T therapy for diffuse large B cell lymphoma (DLBL) in 40 patients and mantle cell lymphoma (MCL) in 8 cases. BP was prescribed in 4 patients (8.3%), three with DLBL and one with MCL. Detailed information on the 4 BP patients is provided in Table 1. Three out of 4 developed AKI and ICANS post-CAR-T infusion, while all experienced severe CRS.
Despite the high incidence of AKI, the primary indication for BP initiation was CRS unresponsive to steroids and anti-IL6 and anti-IL1 therapy. BP was initiated after a mean of 5.2±1.7 days post-infusion. All patients underwent Continuous Veno-Venous Hemodiafiltration using an AN69ST membrane, combined with an adsorbing cartridge (*CytoSorb®*). Following BP cycles, there was a meaningful decrease in IL-6 levels and a reduction in inotropic support, except for one patient who died just one day after BP initiation. No treatment-related complications were reported.
Overall, during hospitalization, 2 patients died due to systemic compromise, while CRS progressively resolved in the remaining two patients, one of them died for hematological disease progression about one month after BP discontinuation.

Table 1. Clinical and biochemical parameters in hematological patients undergoing BP post CAR T-cell infusion.

Pt#	Age/ Sex	AKI/ ICANS/ CRS	BP modality	BP Membrane	N° cycles	IL-6 at BP start (ng/L)	IL-6 at BP stop (ng/L)	NE at BP start (µg/kg/min)	NE at BP stop (µg/kg/min)	In-hospital death
1	69/F	✓/✓/✓	CVVHDF	modified AN69S + *CytoSorb®*	2	>5000	255	0.03	X	✓
2	47/F	✓/✓/✓	CVVHDF	AN69ST + *CytoSorb®*	4	4842	559	0.4	X	X
3	77/M	X/X/✓	CVVHDF	modified AN69S + *CytoSorb®*	5	4575	1477	0.14	0.08	✓
4	75/F	✓/✓/✓	CVVHDF	AN69ST + *CytoSorb®*	1	2452	1997	0.5	0.7	✓

Abbreviations: Chimeric Antigen Receptor T-cell (CAR T-cell) Acute Kidney Injury (AKI), Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), Cytokine Release Syndrome (CRS), Blood Purification (BP), Continuous Veno-venous Hemodiafiltration (CVVHDF) and Norepinephrine (NE)

Conclusion: BP may safely and effectively manage inflammation and improve hemodynamics in hematologic patients treated with CAR-T therapy developing early severe CRS, However, these patients remain at high mortality risk, emphasizing the importance of identifying risk factors and preventive measures for hyperinflammatory status.

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HEMOPERFUSION WITH CYTOSORB IN THE TREATMENT OF REFRACTORY CARDIOGENIC SHOCK IN A SEPTIC PEDIATRIC PATIENT: IS IT WORTH IT?

*A. Spasiano** [a], *E. Capirossi* [b], *A. De Vigili* [b], *L. Gottin* [b], *N. Pertica* [a], *G. Gambaro* [a], *P.M. Ferraro* [a]

[a] Section of Nephrology, Department of Medicine, Università degli Studi di Verona, Verona, Italy;
[b] Anesthesiology, Intensive Care and Pain Therapy Center, Department of Surgery, Università degli Studi di Verona, Verona, Italy.

Background: Refractory cardiogenic shock is one of the leading causes of death in pediatric patients worldwide. International guidelines underline the importance of an early diagnosis and a timely treatment, especially if a septic shock overlaps. Indeed, the cytokine storm plays a pivotal role in the myocardial dysfunction, in the multiorgan involvement and in the consequent cardiovascular collapse. Hence, to guarantee a full recovery, it is fundamental to turn off the underlying systemic hyperinflammation. In support of standard treatments, such as corticosteroids and immunoglobulin, a hemoperfusion treatment with CytoSorb could help in contrasting the cytokine storm. CytoSorb is a cartridge conceived for hemoadsorption composed of polystyrene divinylbenzene copolymer beads, aimed at removing molecules of medium molecular weight (up to 55 kDa), including several cytokines. It is safe and well-tolerated in children, according to available literature.

Methods: We report the case of a 5-year-old female admitted at our pediatric emergency room with fever, otalgia, latero-cervical swelling, hypotension, profuse weakness, and confusion. Her clinical history was characterized by an episode of acute pharyngitis with anaemia and neutropenia one year before, successfully treated with corticosteroids and antibiotic therapy, after exclusion of hematologic diseases through bone marrow aspiration. At physical examination, she was tachycardic and oliguric, while laboratory exams showed neutropenia, elevated inflammatory markers and NT-proBNP. The echocardiogram attested a severe biventricular dysfunction with a left ventricular ejection fraction (LVEF) of about 15%, with evidence of diffuse thickening of the pulmonary interstitium and bilateral pleural effusion at the thoracic XRay. A successive CT scan showed an extended tonsillar abscess and upper lobe pneumonia. Subsequently, a positivity for Streptococcus urinary antigen was detected. An invasive fulminant infection by Streptococcus dysgalactiae was diagnosed, rapidly evolving into a serious septic shock and a refractory cardiogenic shock, despite an adequate inotropic support and antibiotic therapy, with a Predicted Death Rate (PDR%) of 86.4%. While tracheal intubation and invasive mechanical ventilation were performed, a metabolic acidosis associated to hyperlactatemia occurred. Therefore, to contrast the cytokine storm, the patient underwent a continuous hemoperfusion with CytoSorb cartridge.

Results: Three columns were used, the first two changed every 6 h, while the last one after 12h. Moreover, she started immunomodulatory therapy with methylprednisolone and immunoglobulins. 12 hours later, we witnessed an important increase in LVEF to 38%, which improved further to 50% after 24 hours (Figure 1A). Lactate, C-reactive protein and NT-proBNP quickly returned to normal ranges. Also the Paediatric Logistic Organ Dysfunction 2 (PELOD-2) score drastically dropped, while the PDR% decreased below 20% (Figure 1B-C). In addition, inotropic agents were rapidly reduced, as demonstrated by the trend of the Vasoactive Inotropic Score (VIS) (Figure 1D), with suspension of adrenaline and dobutamine 3 and 6 days after hemoperfusion beginning, respectively.

Conclusion: The purpose of this case report is to strengthen the current data on the effectiveness of hemoperfusion with CytoSorb as adjuvant treatment of severe septic shock with multiorgan involvement, even in pediatric patients, especially if standard therapies fail in hyperinflammation control.

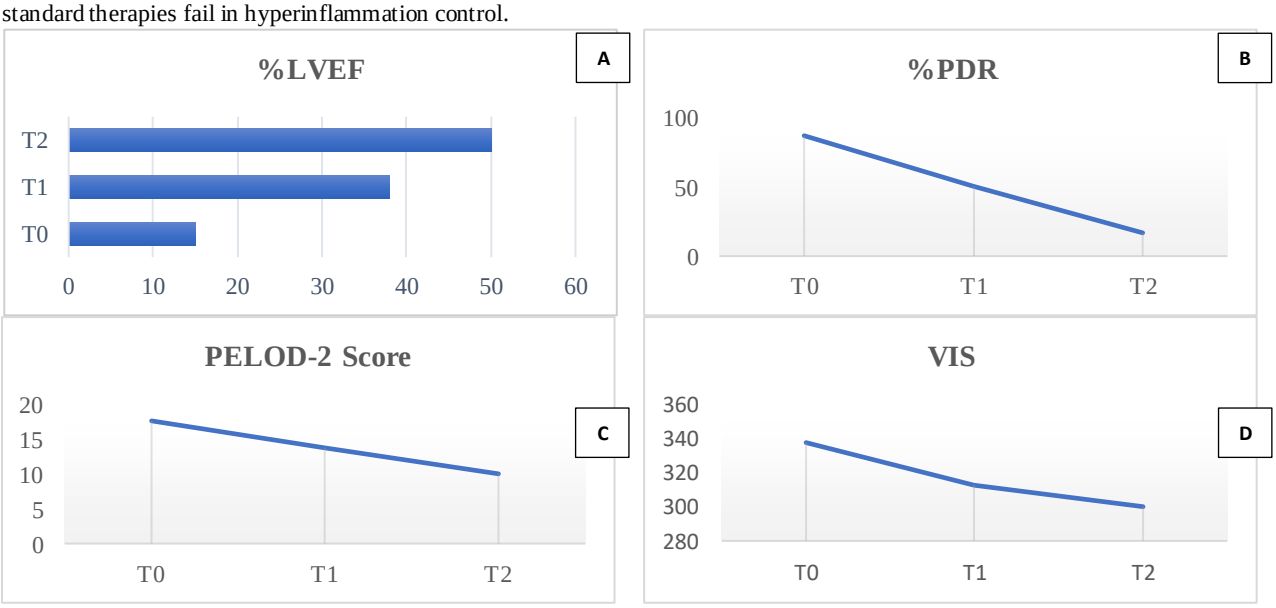

Figure 1: Trends of left ventricular ejection fraction (LVEF), Predicted Death Rate (PDR%), Paediatric Logistic Organ Dysfunction 2 (PELOD-2) Score and Vasoactive Inotropic Score (VIS) before and after the hemoperfusion with CytoSorb. T0: pre-treatment; T1:12 hours after CytoSorb; T2: 24 hours after CytoSorb

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EXPLORING THE INFLUENCE OF DIFFERING CONCENTRATIONS OF GRAM-POSITIVE AND GRAM-NEGATIVE BACTERIA ACROSS TIME ON ERIPTOSIS: AN *IN VITRO* STUDY

*G. Klinkmann [a,c,d], , M. De Cal [a,b], A. Maccà [a], C. Ronco [b,d]

[a] International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy; [b] Department of Nephrology, Dialysis and Kidney Transplantation, San Bortolo Hospital, Vicenza, Italy; [c] Department of Anaesthesiology, Intensive Care Medicine an Pain Therapy, University Medical Center Rostock, Rostock, Germany; [d] Department of Extracorporeal Immunomodulation, Fraunhofer Institute for Cell Therapy and Immunology, Rostock, Germany;

Background: Sepsis, a life-threatening condition characterized by multiple-organ dysfunction triggered by infection, stands as a prominent cause of mortality and critical illness worldwide. Its pathogenesis entails the dysregulation of various biochemical pathways, including immune response, coagulation, endothelial dysfunction, and tissue damage via cellular death or apoptosis. Recent studies have elucidated alterations in the morphology and shape of human red blood cells (RBCs) during sepsis, leading to erythrocyte death, or eryptosis. Eryptosis features cell shrinkage, membrane blebbing, and surface exposure to phosphatidylserine (PS), which serve as signals for macrophage attraction. This study aims to assess the in vitro induction of eryptosis on healthy RBCs exposed to different concentrations of gram pos. and gram neg. bacteria at different time points.

Methods: In an in vitro setting, healthy red blood cells (RBCs) were exposed to different concentrations of *Escherichia coli* (gram -) or *Staphylococcus aureus* (gram+) for up to 72 hours and compared with controls (CTR). Samples were drawn at predefined time points, to assess morphological indicators of cell death and eryptosis by flow cytometric analysis, as well as cytokine kinetics by Linked Immunosorbent Assay (ELISA).

Results: Healthy red blood cells (RBCs) exposed to varying concentrations of gram-positive and gram-negative stimuli exhibited notable morphological alterations and eryptosis when compared to those from the control cohort across all time points. A concentration-dependent rise in the proportion of AnnexinV-binding RBCs was observed over time, extending up to 72 hours. Moreover, the degree of eryptosis induced by gram-positive stimuli (Figure 1A) appeared more pronounced than that induced by gram-negative stimuli (Figure 2A). Levels of interleukin-6 (IL-6) and interleukin-1beta (IL-1β) increased progressively over time, with higher concentrations observed following bacterial stimulus compared to controls (Figure 2 & 3). Additionally, gram-positive stimulus elicited greater cytokine elevation compared to gram-negative stimulus.

Conclusion In conclusion, our study provides new insights into the influence of bacterial spectrum on the dynamics and extent of eryptosis, particularly in the comparison between *Staphylococcus aureus* and *Escherichia coli*. The findings reveal a clear correlation between bacterial concentration and eryptosis levels, suggesting that eryptosis could serve as an indicator of septic status and severity induced by elevated bacterial load. This data could be valuable in characterizing the infection status of septic patients over time, offering potential implications for clinical diagnosis and management strategies.

Staphylococcus aureus

Figure 1A S **Eryptosis**

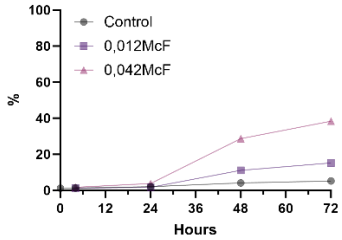


Figure 2A **IL-6**

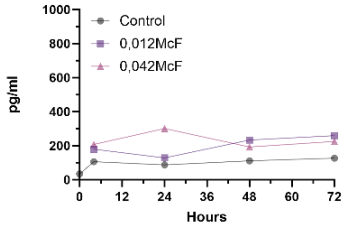
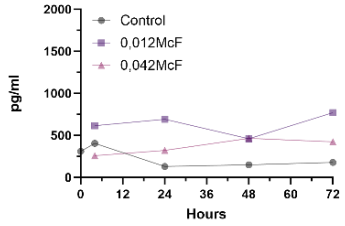


Figure 3A **IL-1β**



Escherichia coli

Figure 1B **Eryptosis**

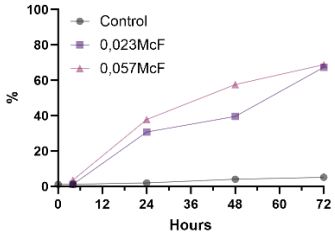


Figure 2B **IL-6**

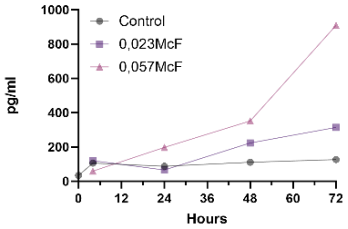
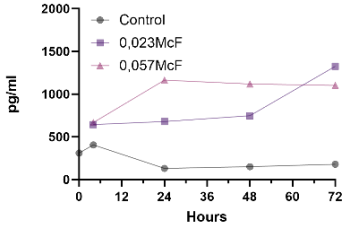


Figure 3B **IL-1β**



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PROLONGED BACTERICIDAL ACTIVITY IN EXTRACORPOREAL HEMOADSORPTION WITH VANCOMYCIN-FUNCTIONALIZED HA380 SORBENT CARTRIDGE

**G. Klinkmann a,c,d,, A. Lorenzin a,b, M. De Cal a,b, AI. Toscano a, N. Perin a,b, G. Ramírez-Guerrero a,e,f, , T. Reis a,g,h,i, M. Zanella a,b, C. Ronco a,b*

a International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy; b Department of Nephrology, Dialysis and Kidney Transplantation, San Bortolo Hospital, Vicenza, Italy; c Department of Anaesthesiology, Intensive Care Medicine an Pain Therapy, University Medical Center Rostock, Rostock, Germany; d Department of Extracorporeal Immunomodulation, Fraunhofer Institute for Cell Therapy and Immunology, Rostock, Germany; e Nephrology and Dialysis Unit, Carlos Van Buren Hospital, Valparaíso, Chile; f Department of Medicine, Universidad de Valparaíso, Chile; g From the Laboratory of Molecular Pharmacology, Faculty of Health Sciences, University of Brasília, Brasília, Brazil; h Fenix Nephrology, São Paulo, Brazil; i Hospital Sírio-Libanês, São Paulo, Brazil;

Background: Advancements in sorbent technology have propelled the evolution of adsorption-based extracorporeal therapies, expanding their applications across various medical conditions. These therapies, supported by physicochemical principles and clinical evidence, now include devices capable of removing pathogens and inflammatory mediators, complementing conventional treatments. In critical care settings, extracorporeal blood purification therapies show promise in addressing complications linked to bacteremia, a key predictor of mortality in sepsis and septic shock. Currently, the sole evidence-based causal therapy for sepsis resides in antibiotic treatment. Regrettably, this approach carries the risk of detrimental side effects stemming from potential organ toxicity. To overcome this burden and with the aim of broadening the scope of sorbent technology in sepsis management, our research group has recently proposed the utilization of surface-modified and drug-functionalized adsorption cartridges to diminish the presence of circulating bacteria. The current study investigates the in vitro efficacy of a sorbent device (mini-module with HA380 beads, Jafron Medical, Zhuhai, China) functionalized with vancomycin, evaluating its impact on circulating Staphylococcus aureus and compare it to standard of care antibiotic treatment in a simulated circulation model.

Methods: In an in vitro model, 1400 mL of heparinized blood containing bacterial load were split in two reservoirs. In Setting 1, 700 ml of blood circulated through a cartridge functionalized with vancomycin. In Setting 2, 500 mg of vancomycin were added to the blood reservoir 2 and, then, circulated through a non-functionalized cartridge. Closed-loop hemoadsorption circuits were set up using two HA380 mini-modules. Circulations were maintained at 250 mL/min for 1 hour, blood reservoirs were heated to 37°C, and stirred. Samples were drawn at predefined time points, to determine the time to positivity (TTP) for bacterial replication, vancomycin concentration and cytokine profiles. Reservoir 2 underwent Setting 2 twice consecutively.

Results: The dynamics of time to positivity (TTP) exhibited a similar trajectory in both settings after 60 minutes of hemoadsorption. However, after an additional hour of incubation, there was no change in TTP in Setting 1, while a notable decline was observed in Setting 2. Notably, the concentration of vancomycin in Reservoir 2 decreased significantly after the first cycle of hemoadsorption. Following a second dose (500 mg) of vancomycin into Reservoir 2, TTP increased significantly once more. These dynamic changes were observed again after the second cycle of hemoadsorption with the non-functionalized cartridge.

Conclusion: These findings suggest a potential treatment approach for bacteremia using antibiotic-functionalized cartridges, addressing clinical concerns related to pharmacological toxicity. The prolonged effect on extending the time to bacterial culture positivity for S. aureus after passage through a vancomycin-functionalized cartridge provides intriguing insights into its biological responses. Incorporating a functionalized cartridge as an adjunctive therapeutic measure early in the course of bacteremia could potentially expedite the resolution of bloodstream infections. However, the efficacy of this approach needs to be assessed through clinical studies.

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DEVELOPMENT OF A NEW MINIATURIZED SYSTEM FOR ULTRAFILTRATION

*A. Lorenzin[a,b], N. Perin[a,b], A. Brendolan[b], G. Ramirez-Guerrero[c], L. Sgarabotto[a,b], T. Reis[d], M. Zanella[a], C. Ronco[b]
[a]*Department of Nephrology, Dialysis and Kidney Transplantation, San Bortolo Hospital, Vicenza, Italy;*
[b]*International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy;*
[c]*Nephrology and Dialysis Unit, Carlos Van Buren Hospital, Valparaíso, Chile;*
[d]*Department of Kidney Transplantation, D'Or Institute for Research and Education (IDOR), Sao Paulo, Brazil*

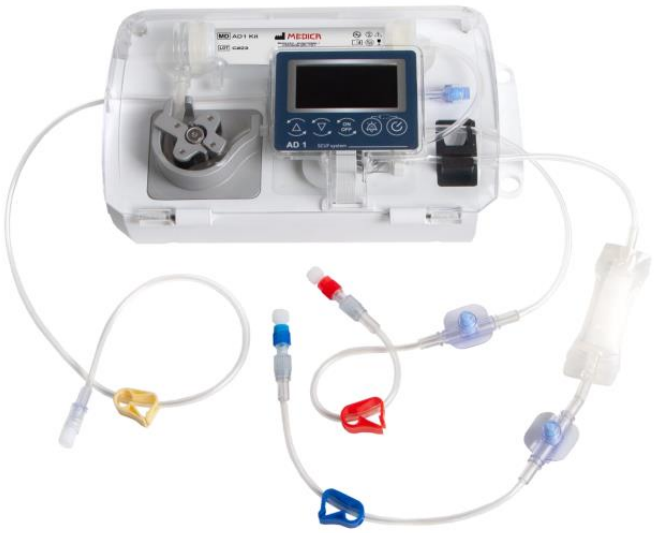
Background: Decompensated heart failure and fluid overload in acute or chronic renal failure are the most common causes of hospitalization in heart and renal failure patients and often they contribute a bad prognosis.
Initial treatment is based on high intravenous diuretics doses although there might be a percentual of refractory patients to this pharmacological approach.
Recent clinical trials, and European and North American practice guidelines suggest that ultrafiltration is indicated for patients with refractory heart failure and fluid overload not responding to medical therapy. There is an emerging demand for new extracorporeal ultrafiltration technology to provide safe and effective fluid removal with a simpler and easier modality.
Herein we describe the steps in the development of a new miniaturized wearable system for ultrafiltration, called AD1 (Artificial Diuresis), that might become available soon.

Methods: We moved from the AD1 prototype system (Figure) to perform the *in vitro* experiments to evaluate its performance in different settings. After encouraging and consistent results obtained in the *in vitro* experiment, we proceeded to animal experiments. After successful in silico simulations, *in vitro*, and *in vivo* animal experiments, exploratory human studies were planned and the study protocol was submitted to regulatory approval.

Results: The rationale for developing this kind of machine responds to several aspects.
Technical demand: current technology for ultrafiltration is represented by rather complex machines derived from the experience of hemodialysis, AD1 has proved to be easy and safe to use.
Logistic and organization: there is shortage of personnel and space in the hospital and the artificial diuresis project could respond to several unmet needs.
Ethical rationale: the commitment of the scientific community to improve patient's quality of life could be achieved using AD1, allowing ambulatory patients treatments.

Conclusion: We are confident that this new machine will represent a quantum leap in the modern approach to fluid management in congested patients. Its application may find several options in various environments including ambulatory/outpatient for long-term repeated elective treatments as a prevention of worsening heart failure with simplified or even self-administration of the procedure and also as a rescue treatment for hospitalized patients reducing the in hospital stay.

Figure:
AD1 prototype



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IN VITRO ASSESSMENT OF PROENKEPHALIN A 119-159 (PENKID) REMOVAL IN HEMOFILTRATION, HEMODIALYSIS AND HEMOADSORPTION

*N. Perin[a,b], A. Lorenzin[a,b], M. de Cal[a,b], N. Morisi[b,c], A. Brendolan[b], P.L.M. Lentini[d], M. Zanella[a], C. Ronco[b]

[a]Department of Nephrology, Dialysis, and Kidney Transplantation, St. Bortolo Hospital, Vicenza, Italy; [b]International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy; [c]Surgical, Medical and Dental Department of Morphological Sciences, Section of Nephrology, University of Modena and Reggio Emilia, Modena, Italy; [d]Department of Nephrology and Dialysis, St. Bassiano Hospital, Bassano del Grappa (VI), Italy

Background: Proenkephalin A 119-159 (penKid) is a stable surrogate marker for enkephalins (endogenous opioids regulating kidney function).
PenKid plasma concentration has been demonstrated to be correlated with measured glomerular filtration rate. Different clinical studies have shown severity-dependent increased penKid levels in patients with sepsis-associated acute kidney injury (AKI).
PenKid is used for prediction and diagnosis of AKI, and need of renal replacement therapy (RRT). The biomarker has also been used to predict the successful weaning from RRT in patients with AKI. Whether the concentration of PenKid is affected or not by RRT, is a controversial point and there are no studies describing the kinetics of the molecule in such conditions. The low molecular weight (4.5 kDa) would imply free removal by the glomerulus and the dialysis membranes. During RRT, this reduction could not be detected in clinical practice due to the complex kinetics involving either low dialytic clearance or increased production in response to impaired kidney function.
To address the issue, we planned *in vitro* experiments simulating different conditions of RRT: continuous veno-venous hemofiltration (CVVH) to determine the sieving coefficient, continuous veno-venous hemodialysis (CVVHD) to determine diffusive clearance of the penKid molecule, and hemoadsorption (HA) to define the penKid removal ratio.

Methods: Blood was spiked with lyophilized synthetic penKid to achieve target concentrations: 150 and 500 pmol/L in both CVVH and CVVHD, and 700 pmol/L in HA. For each experiment, a blood batch of 1000 mL was utilized, maintained at 37° and continuously stirred.
CVVH was performed with Q_B=150 mL/min and Q_{UF}=20 mL/min to reproduce a filtration fraction of 20%. The ultrafiltrate was reinfused in the venous line to maintain initial volume. This allowed to assess the solute sieving coefficient in pure convective mode.
CVVHD was performed with Q_B=150 mL/min and Q_D=35 mL/min (Q_{UF}=0 mL/min) to assess diffusive clearance. A polysulfone dialyzer (AV1000 Fresenius) was utilized for performing CVVH and CVVHD and samples were taken after 10, 30, 60 minutes from the initiation of circulation.
HA was performed with blood flow rate Q_B=150 mL/min using a HA380 minimodule in a closed-loop configuration. Samples were taken from the blood batch after 5, 15, 30, 60 and 120 minutes from the initiation of circulation. All the experiments were conducted in triplicate.

Results: Initial penKid concentrations in blood corresponded to the desired targets in all the experiments.
Significant removal of PenKid was observed in CVVH (sieving 1.04±0.27), in CVVHD (clearance 23.08±0.89) and in HA (removal ratio 76.1±1% after 120 minutes).
Sieving coefficients displayed values between 0.69 and 1.5 and they appear to remain stable over time. Diffusive clearance displayed values between 15.7 and 35 mL/min. Values appear to present a slight decrease over time.
The observed variability during CVVH and CVVHD can be attributed to several factors: difference in plasma protein interference in various moments of the experiments, difference in concentration of penKid in plasma water versus plasma or blood, variability in the sample measurements.
During HA, concentration of the molecule displayed a consistent reduction over time, reaching a value of 157.0±6.1 pmol/L after 120 minutes. Removal ratio at the end of the experiment reached 76.1±1%. Remarkable consistency in measured values was observed and the minimal variability observed confirming a consistent behavior of the interaction between the sorbent and the molecule.

Conclusion: Significant removal of penKid was obtained by the extracorporeal modalities tested. Further investigation is needed to assess if these findings are confirmed during *in vivo* treatments in which penKid kinetics is affected by generation, elimination and changes in distribution volume.

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IN VITRO PER- AND POLYFLUOROALKYL SUBSTANCES (PFAS) ADSORPTION ASSESSMENT THROUGH MESOPOROUS STYRENE-DIVINYLBENZENE SORBENT CARTRIDGE

*N. Perin[a,b], A. Lorenzin[a,b], M. de Cal[a,b], P. Pavan[c], L. Chiementin[c], A. Brendolan[b], N. Morisi[d], M. Zanella[a], C. Ronco[b]

[a]Department of Nephrology, Dialysis, and Kidney Transplantation, St. Bortolo Hospital, Vicenza, Italy; [b]International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy; [c]Food Hygiene and Nutrition Service (SIAN), Department of Public Health, St. Bortolo Hospital, Vicenza, Italy; [d]Surgical, Medical and Dental Department of Morphological Sciences, Section of Nephrology, University of Modena and Reggio Emilia, Modena, Italy

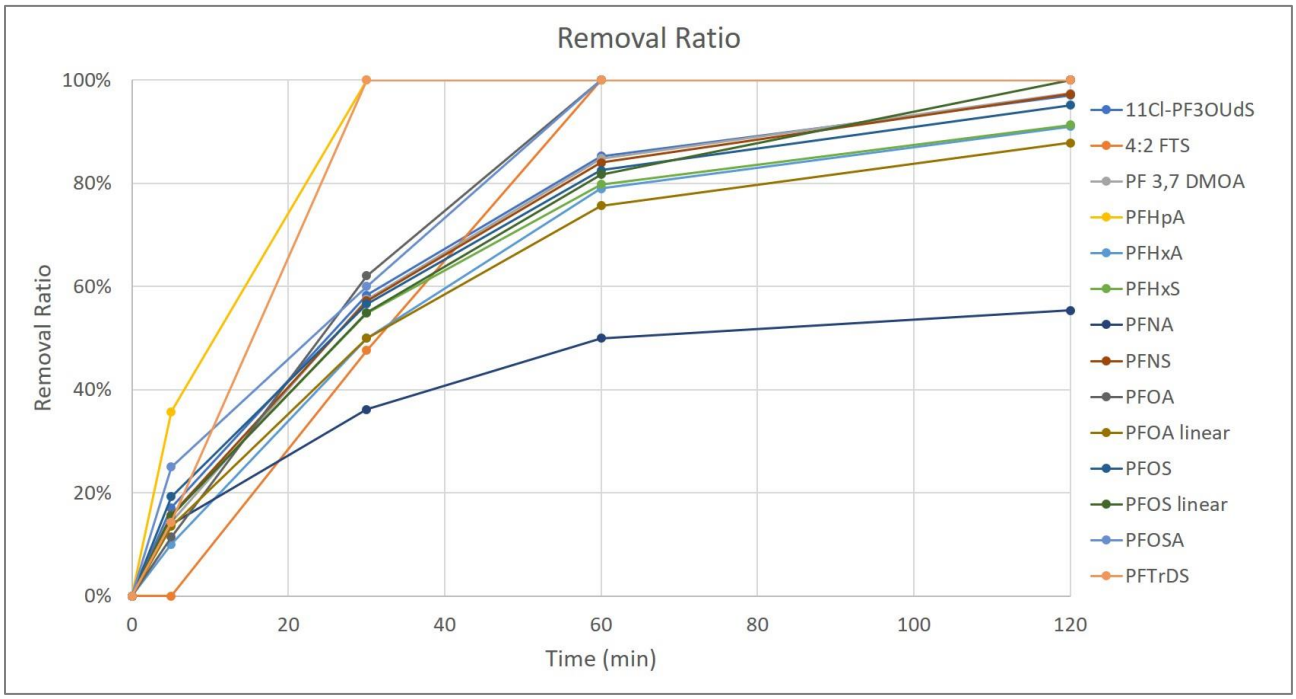
Background: Per- and polyfluoroalkyl substances (PFAS) are chemical substances used in a wide range of fields as construction materials, biocides, flame retardants etc. Due to their high stability in the environment and resistance to biodegradation, all PFAS are persistent, and many are highly mobile in global waters. High blood levels of PFAS have been associated with adverse health effects including increased risk of kidney or testicular cancer. Classic extracorporeal therapies have demonstrated limited efficiency and new approaches based on adsorption should be explored. The aim of this study was to assess the potential adsorption capacity of HA380 cartridge towards PFAS from patients with high blood levels.

Methods: We developed an *in vitro* model of hemoadsorption using GALILEO, a testing platform designed for *in vitro* extracorporeal circulation. We recirculated a highly polluted batch of water (4 liters) through a HA380 cartridge (Jafron medical, Zuhai, China) for 120 minutes at a flow rate of 150 mL/min. We collected samples after 5, 30, 60, and 120 minutes from the initiation of circulation and analyzed 39 different PFAS compounds. Removal Ratio (RR) was calculated to assess PFAS adsorption.

Results: PFAS compounds with concentrations significantly above normal showed a Removal Ratio close to 90% already within the first 60 minutes of circulation leading to almost complete elimination of all pollutants at the end of the circulation (Figure). RR is remarkably high already at the outset of the adsorption process demonstrating a high capacity of removal of HA380 cartridge. This is likely dependent on the interaction of the different solutes with the molecular structure of the sorbent.

Conclusion: The *in vitro* model of hemoadsorption suggests the possible application *in vivo* of this technique to reduce/normalize the concentrations of PFAS in patients exposed to water or environmental pollution. Hemoadsorption may therefore be considered as a new possible approach in patients with high blood levels of PFAS.

Figure: Curves of Removal Ratio values for the different studied compounds.



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A RARE CASE OF SHIGA-LIKE TOXIN PRODUCING ESCHERICHIA COLI ASSOCIATED HEMOLYTIC UREMIC SYNDROME (STEC-HUS) AND ACUTE KIDNEY INJURY IN A 34-YEAR-OLD WOMAN

*S. Polnova** a, *S.L. Starostniece* b, *A. Grigane* a, *J. Voicehovska* a

a Riga East University hospital; b Riga Stradins University

Background: Typical presentation for hemolytic uremic syndrome (HUS) is microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury (AKI) associated with Shiga toxin-producing *Escherichia coli* (STEC) infection. HUS is most found in infants and young children. In this case we present an atypical case of HUS with all associated clinical characteristics in an adult female.

Case description: On July 3rd, a 34-year-old woman was admitted to Riga East University hospital, Riga, Latvia with lower abdominal pain, bloody diarrhea every 30 minutes and tenesmus. There was no vomiting and diuresis was normal. The onset of disease was on June 29th with diarrhea up to 3 times a day, normal body temperature. It is known that the patient visited Turkey from June 11th to 18th with her son who had similar symptoms on July 2nd but no further development of an illness. On July 1st and 2nd patient had no passing of stool, so she went to the emergency department as her stomach continued to hurt, where enema was recommended, went home after that. The patient returned to the emergency department on July 3rd, where fecal PCR came back positive for Shiga-like toxin producing E. Coli (STEC) and enteroaggregative E. Coli (EAEC) alongside mild electrolyte disbalance, leukocytosis and normal kidney function. Based on clinical and biological data the patient was further admitted to Infectiology center of Latvia, gastrointestinal infections and parasitosis clinic, where symptomatic treatment was prescribed, no indications for renal replacement therapy. On July 6th diarrhea was still frequent alongside profuse vomiting and overall worsening of her physical and mental state. On the third day of hospitalization, an acute kidney injury manifested with oliguria and progressive hypervolemic symptoms overnight. Patient was transferred to the intensive care unit (ICU). Blood work shows GFR 11 ml/min and creatinine 476 mkmol/L, severe thrombocytopenia 41 10^9/L, leukocytosis, heightened CRP, severe anemia 5.5 g/dL and high D-dimers 12,32 mkg/mL, hyperbilirubinemia, high liver markers alongside anisocytosis in erythrocyte morphology testing which leads to consider AKI with HUS and sepsis as possible diagnosis, however blood microbiological testing came back negative and antimicrobial therapy was not initiated and sepsis was ruled out. Considering the patient was anuric and severely hypervolemic, continuous veno-venous high-flux dialysis (CVVHFD) was started on the fourth day of hospitalization. Due to severe anemia, multiple red blood cell transfusions were also assigned. Combined therapy of symptomatic relief and CVVHFD continued for the next 4 days, when, after a consultation with a nephrologist on day nine, plasma exchange therapy was believed necessary based on the diagnosis of STEC induced HUS with AKI. On July 15th, the patient was stable enough for a transfer to further care in Riga East University hospital, nephrology clinic. The next day her condition rapidly worsened, an X-ray showed bilateral hydrothorax therefore thoracentesis was performed and 1800ml of sanguine liquid was evacuated followed by thoracic sanation and hemostasis operation. After the operation, the patient was admitted into ICU. Patient continued to be anuric despite stimulation with diuretics and intermittent hemodialysis (IHD) was performed every other day, to lessen symptoms of hyperhydration. Starting 28th of July, the patient's dynamic was positive although her overall condition remained serious, she was transferred back to the nephrology clinic, where she continued the assigned therapy until August 9th. The patient was discharged in an overall good condition with partially restored kidney function and 500 ml diuresis, however, still had to have IHD 3 times a week for about 3 months. The patient continued to have regular follow-ups with the nephrologist and to evaluate the chronicity of the kidney injury a kidney biopsy was performed where partial glomerulosclerosis was found.

Discussion: The case presents a typical course of disease for STEC-HUS, however, because of the rarity of STEC-HUS in adults, it was not the first diagnosis that was considered despite classic clinical presentation with thrombocytopenia, anemia and acute kidney injury. Timely diagnosis following a proper therapy plan started right away could have lessened damage to internal organs, especially the kidneys. This case report shows that it is important to consider uncommon syndromes in adults given the typical clinical manifestations even if they usually occur in children to prevent further development of a chronic disease in an adult because of delayed treatment.

Conclusion: Timely diagnosis of an illness is particularly important to start adequate therapy as soon as possible thus possibly lessening further complications and have a more favorable outcome.

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POSITIVE FLUID BALANCE INCREASES THE RISK FOR RENAL REPLACEMENT THERAPY OR DEATH IN PATIENTS WITH POSITIVE CELL CYCLE ARREST BIOMARKERS ON ICU ADMISSION

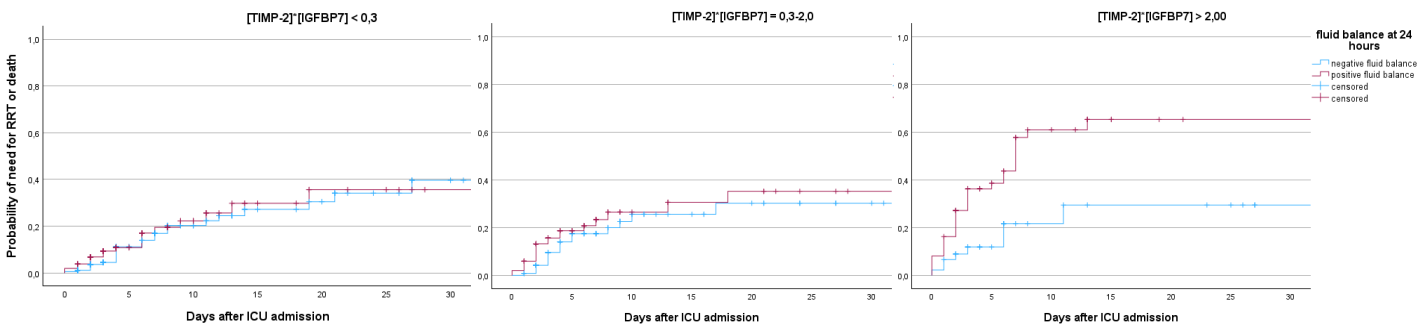
*I. Godi** [a,b], *W. Fan* [b], *C. Ronco* [b]
[a] Azienda Ospedale Università di Padova, Padova, Italy [b] International Renal Research Institute of Vicenza, Vicenza, Italy

Background: Positive fluid balance was associated with increased mortality in critically ill patients, especially those with acute kidney injury (AKI). According to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, AKI definition relies on functional markers. In line with a modern concept of AKI, together with functional markers, damage markers should be used to define AKI. Among the most promising damage biomarkers, tissue inhibitor metalloproteinase-2 /TIMP-2) and IGF-binding protein 7 (IGFBP7), also known as cell cycle arrest biomarkers, are detected in urine early after stress or damage at tubular level. Our aim is to examine the association between positive fluid balance and kidney adverse events in critically ill patients according to damage biomarkers' status.

Methods: This is a secondary analysis of a prospective observational study, including all consecutive adult patients admitted to the intensive care unit (ICU) from June 2016 to July 2017 at San Bortolo Hospital (Vicenza, Italy), regardless of their AKI risk. Urine and blood samples for measuring urinary [TIMP-2]*[IGFBP7] serum creatinine levels were obtained immediately upon admission. All other clinical data were collected from the hospital records, including fluid balance at 24 hours from admission. The aim of the present study was to explore the association of fluid balance and [TIMP-2]*[IGFBP7] with a composite endpoint of need for renal replacement therapy (RRT) or death at 30 days from admission. We defined fluid balance as negative when <0 ml/day or positive when >0 ml/day at 24 hours from ICU admission. We combined positivity of fluid balance at 24 hours with positive results of [TIMP-2]*[IGFBP7] with the cut-offs of 0,3 and 2,0. We used Cox regression to analyse the aforementioned association, adjusting for confounding factors. We examined the probability of reaching the composite endpoint according to negative or positive fluid balance, conditioned on [TIMP-2]*[IGFBP7] strata (<0,3;0,3-2,0;>2,0), by using Kaplan-Meier analysis. We assessed the predictive ability of combinations of positivity for fluid balance and/or [TIMP-2]*[IGFBP7] at cut-off of 2,0; this latter analysis was performed including AKI status within 48 hours from ICU admission, defined according KDIGO definition.

Results: Our population consisted in 642 patients: 136 patients reached the composite endpoint (32 needed renal replacement therapy and 122 died) and were more likely to be older (71 versus 62 years, p-value <0,001) and with higher Sequential Organ Failure Assessment (SOFA) scores (9 versus 6, p-value <0,001). Patients that needed RRT or died had augmented mean [TIMP-2]*[IGFBP7] levels (3,7 versus 1,9, p-value < 0,001) and higher mean fluid balance (+1520 versus +848 ml/day, p-value < 0,001) at 24 hours. Cox regression analysis showed fluid balance at 24 hours from ICU admission and urinary [TIMP-2]*[IGFBP7] levels to be both predictive of primary endpoint (unadjusted HR 1,0, 95% CI 1,0-1,0, p-value <0,001; and unadjusted HR 1,0, 95% CI 1,0-1,0, p-value 0,002, respectively). Combinations of positive fluid balance and [TIMP-2]*[IGFBP7] greater than 0,3 or 2,0 leads to an increased risk of dialysis or death at 30 days from admission, even after adjustment for age and SOFA score (aHR 1,6, 95% CI 1,2-2,1, p-value 0,002; and aHR 1,8, 95% CI 1,4-2,5, p-value < 0,001, respectively). Applying different strata of [TIMP-2]*[IGFBP7] (<0,3; 0,3-2,0; >2,0), Kaplan-Meier analysis revealed that only for [TIMP-2]*[IGFBP7] >2,0 a positive fluid balance increased the probabilty of reaching the endpoint from 23% to 40% (p-value 0,004), as highlighted in Figure 1. When assessing the predictive ability of combinations of fluid balance and [TIMP-2]*[IGFBP7] at cut-off of 2,0, there was a clear increase in the probability of reaching the endpoint when both [TIMP-2]*[IGFBP7] and fluid balance were positive (from 20% when one of them tested positive to 41% when both of them tested positive, p-value = 0,004). A final analysis revealed that AKI status further increased the probability of the composite endpoint to 53%.

Conclusion: Patients who had a positive fluid balance at 24 hours had increased risk of RRT or death at 30 days, especially when [TIMP-2]*[IGFBP7] tested positive on ICU admission with a cut-off of 2,0. The combination of positive fluid balance and cell cycle arrest biomarkers was associated with a probability of RRT or death of 40%, and this probability further increased to 53% in those patients who were classified as having AKI within 48 hours from admission.



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ACUTE KIDNEY STRESS AND *DIURETIC RESISTANCE*: ARE THEY TWO SIDES OF THE SAME COIN?

*Javier Paul-Martinez** [a], *Gonzálo Núñez-Marín* [b], *Josep Riera-Sarduni* [a], *Nestor Rodriguez-Chitiva* [a], *Jordi Soler-Majoral* [a], *Fredzzia Graterol-Torres* [a], *José Luis Górriz* [c], *Jordi Bover* [a], *Rafael de la Espriella* [b], *Gregorio Romero-González* [a,d]

a. Nephrology Department, Hospital Universitario Germans Trias I Pujol, Badalona (Spain); b. Cardiology Department, Hospital Clínico Universitario de Valencia (INCLIVA), Valencia (Spain); c. Nephrology Department, Hospital Clínico Universitario de Valencia (INCLIVA), Valencia (Spain); d. International Renal Research Institute of Vicenza, Vicenza (Italy).

Background: The emergence of congestive nephropathy concept and targeted drugs for congestion treatment has underscored the significance of tubular integrity in cardio-renal syndrome type 1. In acute heart failure (AHF) patients, tubular sodium reabsorption assumes a pivotal role in oxygen consumption and susceptibility to hypoxia, precipitating acute kidney stress (AKS). This milieu facilitates the release of two substances, tissue inhibitor of metalloproteinase 2 (TIMP2) and insulin-like growth factor-7 (IGFBP-7), commercially recognized as Nephrochek®, which correlates with AKS and has potential in predicting acute kidney injury (AKI) development. However, knowledge of these biomarkers in AHF remains limited. This study aims to assess the utility of cell cycle arrest biomarkers in AHF patients.

Methods: A prospective study was conducted in the heart failure unit of a tertiary hospital, enrolling patients with AHF and chronic heart failure necessitating intravenous diuretic therapy. Worsening kidney function (WKF) was defined as a serum creatinine increase ≥ 0.5 mg/dl, while diuretic efficiency was quantified as diuresis per milligram of furosemide received (expressed as milliliters of diuresis/40 mg of furosemide). Cell cycle arrest biomarkers were evaluated within the first 24 hours, with statistical analysis performed using STATA 17.0 software.

Results: The study included a median age of 75 ± 12 years, with 38% being female. Among them, 42% had LVEF <40%, and 42% had a history of chronic kidney disease (eGFR <60 ml/min/1.73 m²). The median Nephrochek was 0.11 (0.06 - 0.34), with 30.4% having a value >0.3. At 72 hours, 10 (8%) patients exhibited an absolute sCr increase ≥0.5 mg/dl. Patients with Nephrochek >0.3 demonstrated higher WKF rates compared to ≤ 0.3 (70% vs. 30%; p=0.005). Those with Nephrochek >0.3 received a higher cumulative furosemide dose [400 mg (220-625) vs. 370 mg (240-750); p=0.050], yet exhibited lower cumulative diuresis [5700 ml (4100 - 7885) vs. 7500 ml (5870 - 9350); p=<0.001] and diminished diuretic efficiency [1837 (1182-2535) vs. 2116 (1358 - 3255); p=0.040]. Multivariate analysis revealed an inverse relationship between Nephrochek values and low diuretic efficiency [OR: 2.04, 95% CI (1.02 - 4.07); p=0.043].

Conclusion: This study underscores the intricate interplay between acute kidney stress, worsening kidney function, and diuretic resistance. Elevated biomarker levels serve as predictive indicators for both worsening kidney function and lower diuretic efficiency. Further research is warranted to corroborate these findings.

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THE ROLE OF BIOMARKERS AS DIAGNOSTIC AND PROGNOSTIC PREDICTORS OF ACUTE KIDNEY INJURY IN DECOMPENSATED CIRRHOTIC LIVER PATIENTS

*R. Cortinhas** a, *W.S. Altran* a, *L.F. Santos* a, *L. Semionato* a, *M.B. Lima* a, *G. Cavalleiro* a, *A.A. Brom* a, *R.K. Campos* a, *N.Q. Bittencourt* a, *D.K. Mahon* a, *F.P. Jeronymo* a, *J.A. Freitas* a, *T.M. Pereira* a, *A.C. Leite* a, *D. Ponce* a

a Universidade Estadual Paulista (UNESP) – Botucatu/SP (Brazil)

Background: Acute Kidney Injury (AKI) within the context of cirrhotic patients has become increasingly frequent, being diagnosed in approximately 20% of this group. Thus, our study aimed to evaluate and compare the role of urinary indexes and the novel biomarkers NGAL, KIM-1 and IL-18 as predictor of AKI diagnostic, AKI etiology and prognostic AKI.

Methods: We conducted a prospective observational cohort study of cirrhotic patients (CHILD A, B and C) admitted to a public university hospital from December 2022 to December 2023. Patients with CKD stages 4 and 5, in palliative care, kidney transplant patients and pregnant women, and who were unable to collect urinary samples were excluded. These patients underwent serum and urine laboratory tests on admission and on subsequent days. Urine samples for biomarker dosage were collected within 24 hours of hospital admission. The diagnosis of AKI was performed according to the creatinine criteria established by KDIGO 2012. The results were presented using descriptive statistics of the study population and Chi-square, ANOVA and logistic regression tests. All the results of the hypothesis tests were discussed at the 5% significance level ($p < 0.05$).

Results: This study analyzed 100 patients with a mean age of 58 years, the main etiologies of liver cirrhosis were alcohol (41%) and NAFLD (23%). Among these patients, 56% had DM-2, 52% had hypertension and 78% had previous CKD. Infection was the main factor in decompensation of liver cirrhosis (38%). AKI occurred in 53% of the patients and the mortality rate was 20%. The main etiologies of AKI were pre-renal (49%), ischemic (22%), septic (13%), Hepatorrenal syndrome (HRS) (7%) and nephrotoxicity (7%). Univariate analysis identified the following variables as risk factor for AKI: CHILD (p: 0.001), etiology of decompensated liver cirrhosis (p: 0.03), Proteinuria (p: 0.01), Hematuria (p: 0.001), creatinine (p: 0.03), Urea (p: 0.001), Potassium (p: 0.001), Leukocytes (p: 0.002), Urinary sodium (p: 0.001) and Fractional excretion of Sodium (FENa) (p: 0.001). Univariate analysis for AKI etiology found the following statistical correlations: CHILD (p: 0.001), previous CKD (p: 0.001), Hematuria (p: 0.001), Proteinuria (p: 0.005), KDIGO (p: 0.001), MELD (p: 0.001), Baseline creatinine (p: 0.001), ATN-ISS (p: 0.001), Creatinine on admission (p: 0.001), Urea (p: 0.001), Sodium (p: 0.004), Potassium (p: 0.001), Leukocytes (p: 0.008), Urinary sodium (p: 0.014), FENa (p: 0.001) and fractional excretion of Urea (p: 0.003). Again, the biomarkers studied showed no statistical correlation with any of the etiologies evaluated in this study: NGAL (p: 0.27), KIM-1 (p: 0.35) and IL-18 (p: 0.88).

At logistic regression analysis, CHILD C (p: 0.029; OR: 1.3; 95% CI: 1.1 - 3.0), infectious as cause of decompensation of liver cirrhosis (p: 0.04; OR: 1.13; 95% CI: 1.3-2.0) and baseline creatinine (p: 0.01; OR: 2.4; 95% CI: 1.0 – 4.4) were identified as variables associated with AKI. We found no association between the development of AKI and novel biomarkers: NGAL (p: 0.9), KIM-1 (p: 0.8) and IL-18 (p: 0.4). Concerning etiology of AKI, the variables CHILD C (p: 0.04; OR: 1.13; 95% CI: 1.01 - 1.12), Hematuria (p: 0.047; OR: 1.04; 95% CI: 1.07 - 1.6), FENa >1% (p: 0.03; OR: 1.16; 95% CI: 1.16 - 1.8) and KDIGO III (p: 0.04; OR: 1.07; 95% CI: 1.05 – 1.23) were associated with acute tubular necrosis (ATN), while CHILD C (p: 0.03; OR: 1.8; 95% CI: 1.0 - 4.2), KDIGO III (p: 0.04; OR: 1.7; 95% CI: 1.1 - 3.2), Hematuria (p: 0.04; OR: 0.2; 95% CI: 0.87 - 0.98) and FENa >1% (p: 0.028; OR: 0.16; 95% CI: 0.05 - 0.89) were associated with HRS and hematuria (p: 0.048; OR: 0.78; 95% CI: 0.91 - 0.99) and FENa >1% (p: 0.028; OR: 0.16; 95% CI: 0.05 - 0.89) with transient ischemia.

Evaluating the risk of death, we found statistically significant differences in the variables CHILD (p: 0.006), KDIGO (p: 0.008), AKI Etiology (p: 0.02), Creatinine (p: 0.01), Urea (p: 0.01), C-reactive protein (p: 0.04), leukocytes (p: 0.01), Urinary sodium (p: 0.002), urinary urea (p: 0.04). IL-18 was the only novel biomarker associated with death (p: 0.02) . The others biomarkers, i.e. NGAL (p: 0.8) and KIM-1 (p: 0.058) showed no correlation with the risk of death.

Logistic regression identified as variables associated with death: Child C (p: 0.029; OR: 1.36; 95% CI: 1.0 - 4.4), baseline creatinine (p: 0.021; OR: 5.6; 95% CI: 1.29 - 24.6), KDIGO 3 (p: 0.024; OR: 11.8; 95%CI: 1.2 - 34.2), AKI of septic etiology (p: 0.026; OR: 1.06; 95% CI: 1.09 - 8.02) and IL-18 (p: 0.02; OR: 1.005; 95% CI: 1.01 - 1.9).

Conclusion: In our research, we highlight the high prevalence of AKI in patients with decompensated liver cirrhosis (53%), giving this condition greater severity and relevance, motivating us to search for diagnostic methods and therapeutic interventions to be promoted in this population, in order to prevent and reduce worst outcomes. We identified the variables CHILD C, infectious decompensation of liver cirrhosis and baseline creatinine as factors associated with AKI. CHILD C, hematuria, FENa >1% and KDIGO III were associated with the etiology of AKI. Finally, Child C, baseline creatinine, KDIGO III, AKI of septic etiology and IL-18 were associated with death outcome. We conclude this research by focusing on the still uncertain role of the biomarkers evaluated, whose further studies may bring to light new applications in clinical practice. However, we also highlight the importance of lower-cost biochemical tests, such as FENa and leukocytes, which have great applicability and relevance in predicting AKI, its etiology and severity.

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UNCOMMON ALLIANCE: A CASE REPORT OF COEXISTING METFORMIN-INDUCED LACTIC ACIDOSIS AND DIABETIC KETOACIDOSIS

*M. Dias** [a], *S. Rodrigues* [b], *V. Silva* [b], *M. Bento* [b], *P. Teixeira* [b], *I. Milet* [b]

*Presenting author; [a] ULS Almada-Seixal, Serviço de Nefrologia; [b] ULS Gaia-Espinho, Serviço de Medicina Intensiva

Background: Diabetic ketoacidosis (DKA) is a life-threatening emergency and comprises of a triad of hyperglycemia, high anion gap metabolic acidosis and ketonemia. Hyperlactemia is often noted in patients with DKA and one of its risk factors is use of metformin, a first-line therapy for the treatment of diabetes. Acute or chronic kidney injury may lead to accumulation of the drug, resulting in high anion gap metabolic acidosis, known as metformin-associated lactic acidosis (MALA), a severe complication. We report a challenging case of combined MALA and DKA. This is a rare diagnosis and there are only a few case reports and case series on this topic, most of them reporting euglycemic DKA.

Case report: This is the case of a 75-year-old female with a past medical history of: hypertension; type 2 diabetes diagnosed 20 years ago, with a prior HbA1c of 6.3%, complicated by secondary neuropathy and nephropathy (basal serum creatinine of 1.3 mg/dL and microalbuminuria); obesity; ischemic heart disease with a previous myocardial infarction and reduced left ventricular function; and peripheral artery disease. Her daily medications included bisoprolol 10 mg, candesartan+hydrochlorothiazide 16+12.5 mg, insulin glargine 30 units, metformin 3 g/day and vildagliptin 100 g/day. The patient presented to the emergency department with a 3-day history of productive cough, vomiting and diarrhea, without fever. She was prostrated and dehydrated, had cold extremities with poor peripheral perfusion, blood pressure of 90/40 mmHg, heart rate of 110/minute, tympanic temperature of 36 ºC, oxygen saturation of 100% on 4L supplemental oxygen, increased respiratory rate (40 breaths/minute) with intercostal retractions and use of accessory muscles, normal cardiopulmonary auscultation and abdominal examination, and no peripheral edema. Blood gas analysis at admission revealed pH 6.85, pO2 175 mmHg, pCO2 13.9 mmHg, bicarbonate 2.4 mmol/L, anion gap 41.7 mmol/L, sodium 137 mmol/L, potassium 6.9 mmol/L, chloride 100 mmol/L, ionized calcium 1.11 mmol/L, glycemia 296 mg/dL, and lactate 11.9 mmol/L. Ketonemia (beta-hydroxybutyrate) was measured, with a result of 7.3 mmol/L. Urinary catheterization revealed anuria. She was immediately initiated on calcium gluconate, inhaled salbutamol, fluid resuscitation, insulin infusion, 8.4% sodium bicarbonate (200 mL total) and non-invasive ventilation. Norepinephrine was required to achieve hemodynamic stability and hydrocortisone and thiamine were administered as part of the distributive shock protocol. Meanwhile, blood workup revealed: hemoglobin 12.3 g/dL, platelets 275 G/L, normal coagulation profile, leukocytes 29 G/L, neutrophils 71.8%, C-reactive protein 1 mg/dL, lactic dehydrogenase 492 U/L, urea 179 mg/dL, and creatinine 6.85 mg/dL, with no further abnormalities detected. Respiratory virus swab was negative. Chest X-ray showed bilateral interstitial and hilar reinforcement. Computed tomography demonstrated minor bronchial wall thickening in the lower lobes and discrete consolidation at the bases; no signs of obstructive uropathy; bosselated kidneys with signs of acute cortical necrosis; extensive calcification of renal arteries; and heterogeneous opacification of the pancreatic parenchyma, associated with peripancreatic fat densification. Following intubation and placement of central venous and peripheral arterial lines, the patient was admitted to the intensive care unit (ICU).
In the ICU, continuous venovenous hemodiafiltration was initiated, and insulin infusion was continued, resulting in correction of metabolic disturbances within the first 24 hours. Norepinephrine was gradually tapered (maximum dose of 0.4 ug/Kg/min). Pancreatitis was confirmed, with maximum serum lipase and amylase measurements of 575 U/L and 289 U/L, respectively, and managed conservatively. Additionally, a type 2 myocardial infarction was diagnosed on day 1, with maximum T troponin of 9473 ng/L, and echocardiography revealed no new findings. Insulin infusion was discontinued after 40 hours, and renal replacement therapy (RRT) was discontinued on day 3 due to recovery of diuresis. During the ICU stay, the patient received 6 days of empiric ceftriaxone 2 g/day (blood cultures were negative) and required blood transfusion due to worsening anemia. Extubation was performed on day 5, and the patient was transferred to an Internal Medicine ward on day 7 on 3L supplemental oxygen and with a serum creatine of 2 mg/dL and no electrolyte/metabolic abnormalities. Unfortunately, hospital stay was prolonged for 6 weeks due to complications including de novo atrial fibrillation, fever without a focus requiring multiple antibiotic regimens, and ultimately, an acute pulmonary embolism leading to the patient's death.

Conclusion: This case highlights the rarely reported and dangerous parallel occurrence of MALA and DKA, prompted by a respiratory infection and oligoanuric acute kidney injury and complicated by distributive/hypovolemic shock, pancreatitis and type 2 myocardial infarction. It was successfully managed, although other complications led to the patient's death. The main goal of therapy is resolution of hyperglycemia, ketosis and metabolic acidosis and removal of accumulated metformin through therapies such as aggressive fluid resuscitation and early initiation of RRT. Given the widespread use of metformin as a first-line treatment for diabetes, physicians must remain vigilant in promptly recognizing and managing this complication.

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ACID-BASE EQUILIBRIUM DURING CONTINUOUS VENO-VENOUS RENAL REPLACEMENT THERAPY

*Irene Sironi[a], Beatrice Brunoni[a], Francesco Zadek[a], Francesca Mulazzani[a], Riccardo Giudici[b], Thomas Langer[a,b], Roberto Fumagalli[a,b]

aDepartment of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy.
bDepartment of Anesthesia and Intensive Care Medicine, Niguarda Ca' Granda, Milano, Italy.

Introduction. About 10% of patients admitted to the intensive care unit (ICU) receive continuous renal replacement therapy (CRRT), exposing them to large exchanges of volume and electrolytes. The aim of the present study was to describe the acid-base equilibrium during Continuous Veno-Venous Hemofiltration (CVVH) and describe the kinetics of the achievement of this equilibrium.

Methods. Oligo-anuric, hemodynamically stable ICU patients with clinical indication for CRRT (PrimsmaMax, Baxter) were enrolled. CVVH modality was employed, with a blood flow rate set at 150 ml/min. Regional anticoagulation was performed with diluted citrate (Prismocitrate 18/0; Gambro, SID = 54 mEq/L) at 1500 ml/h. Phoxilium (Baxter Healthcare Spa, SID = 32 mEq/L) or Multibic 2K (Fresenius Medical Care, Germany, SID = 35 mEq/L) were administered post-dilution at 1500 mL/h as replacement solutions. Blood gas analysis and electrolytes were measured (RAPIDPoint 500 Blood Gas System, Siemens Healthcare Diagnostics) at the beginning of CVVH treatment (T0) and after 24, 48, and 72 hours. The following acid-base parameters were registered: pH, Base Excess (BE), apparent Strong Ion Difference (SIDa), effective Strong Ion Difference (SIDe), and Strong Ion Gap (SIG), a proxy of unmeasured anions. Acid-base variations were analyzed via one-way repeated measures ANOVA.

Results. Twenty-seven patients aged 62±14 years were enrolled. While SIDa remained stable over time (from 42 ± 5 to 42 ± 3 mEq/L; p=0.9), a significant increase in SIDe (from 30 ± 6 to 36 ± 3 mEq/L; p <0.001) was observed (Figure 1). As a result, SIG decreased significantly (from 12 ± 5 to 5 ± 4 mEq/L; p< 0.001) . These changes were reflected by an elevation in BE and pH (p<0.001). Acid-base and electrolyte changes are described in Table 1.

Conclusion. Our CVVH system corrected the underlying acid-base disorder through a reduction in unmeasured anions.

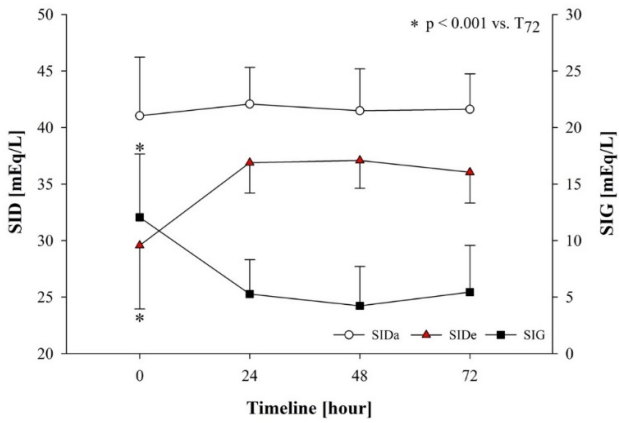

Figure 1. Main acid-base parameters change in the first 72 hours in patients undergoing CVVH. Interaction p-value of one-way ANOVA for repeated measures <0.001. * p<0.001 vs. T_{72} at post-hoc analysis. Acronyms: SIDa is Apparent Strong Ion Difference, SIDe is Effective Strong Ion Difference, SIG is Strong Ion Gap.

Variable	Baseline	24 hours	48 hours	72 hours	p
pH	7.30 ± 0.12	7.38 ± 0.06	7.39 ± 0.06	7.40 ± 0.06	<0.001
BE (mmol/L)	-3.3 ± 6.2	2.6 ± 2.9	3.5 ± 2.2	3.6 ± 2.3	<0.001
[Na^+] (mEq/L)	142 ± 7	136 ± 3	135 ± 3	135 ± 3	<0.001
[Cl^-] (mEq/L)	104 ± 6	98 ± 2	98 ± 2	98 ± 2	<0.001

Table 1. Acid-base equilibrium at CVVH start (baseline) and after 24, 48 and 72 hours of treatment. Acronyms: BE is Base Excess, [Na^+] is Sodium Concentration. [Cl^-] is Chloride Concentration.

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ACUTE KIDNEY INJURY (AKI) IN HOSPITALIZED PATIENTS: EPIDEMIOLOGICAL ANALYSIS OF INCIDENCE, OUTCOME, AND IDENTIFICATION OF BIOMARKERS OF PROGRESSION TO CHRONIC KIDNEY DISEASE (CKD)

aL. Fornara, aS. Prenna, aE.J. Fornasetti, aV. Cantaluppi

aSCDU Nefrologia e Trapianto Renale, Università del Piemonte Orientale

Introduction and aims: Acute Kidney Injury (AKI) is a frequent condition in the hospitalized population with a significant impact on mortality, dysfunction of other organs resulting in increased hospitalization rates and health care expenditures. These aspects have also been found in patients hospitalized with COVID-19, where the incidence and mortality of AKI are found to be doubled with an etiology not only related to renal hypoperfusion, but also to a direct action of the virus and the consequent stimulation of the cascades of inflammation, coagulation, and complement that can induce and perpetuate renal damage. Recent evidence underscores that certain urinary biomarkers may play an important role in identifying patients with previous AKI at increased risk of evolution to CKD, particularly NGAL and the expression of stemness markers (CD133) on the surface of urinary extracellular vesicles (uEVs).

1. RETROSPECTIVE PART: Comparative analysis of the incidence and clinical outcomes of AKI in our hospital setting during a pre-pandemic period and during the COVID-19 pandemic. 2.PROSPECTIVE PART: Establishment of an outpatient clinic for post-AKI nephrological follow-up for: A. study of the impact of AKI in the transition to CKD with urinary assay of potential biomarkers of progression (NGAL, uEVs CD133+); B. study of the impact of AKI on the dysfunction of other organs.

Methods: 1. RETROSPECTIVE PART: - PRE-COVID EPOCA: 20,854 patients who had at least one admission to our Hospital Facility in mid- to high-intensity wards within 24 months; - PANDEMIC EPOCA: i.945 patients admitted during the I wave of the SARS-CoV-2 pandemic in low- and medium-intensity wards; ii.196 patients admitted for COVID-19 in high-intensity care wards.

2. PROSPECTIVE PART: - COVID PATIENTS: i.202 patients admitted during pandemic wave I and re-evaluated at 4 and 12 months for impaired renal, pulmonary and motor function; ii.subpopulation of 31 patients from the prospective observational study, re-evaluated at 12 months by assay of biomarkers of progression to CKD (NGAL; CD133+); NON-COVID PATIENTS: 100 patients admitted during 2021 to NON-COVID wards and reassessed at 3 months for impaired renal function with assay of biomarkers of progression and distant organ cross-talk. AKI and CKD were staged according to the 2012 KDIGO guidelines. Urinary NGAL was assayed by ELISA kit; CD133+ uEVs were analyzed by Nanosight (size and concentration) and cytofluorimetric (MACSPLEX) for surface protein determination including stem cell marker CD133). Clinically, for lung function DLCO was considered normal when ≥80%, and for muscle strength assessment SPPB test with a score > 10.

Results: in the pre-pandemic era, AKI has an incidence of about 18% in hospitalized patients and is an independent risk factor for mortality (OR: 3.77); moreover, the risk increases with increasing stage of AKI. During the COVID-19 pandemic, the incidence and mortality of AKI doubled in medium- to low-intensity wards (incidence from 17.3% to 37%; mortality from 18% to 31%); in high-intensity wards, not only did the incidence of AKI double, but mortality reached 69% (despite the reduction in mean age). In patients who develop AKI-COVID, compared with COVID patients who have not developed AKI, impaired pulmonary (OR 3.78 at 4 months; OR 6.15 at 12 months) and motor capacity at 4 and 12 (OR at 4 months; OR at 12 months) months after discharge is more likely to be present. These patients also have significantly lower mean eGFR at 12 months than patients who did not develop AKI (AKI 79.16 mL/min vs. NO AKI 88.56 mL/min). NGAL was slightly higher than the physiological cut-off in a significant percentage of both AKI-COVID and no AKI-COVID patients, but was not significantly different between the two groups (64.6 vs. 57 ng/mL $p = 0.7$). CD133+ uEVs, however, were significantly lower in patients with prior AKI-COVID than in those in whom this complication did not develop (0.4% vs 3.3% $p = 0.001$).

Conclusions: overall, the totality of these data suggests that AKI in COVID-19 patients can be considered as a marker of general "frailty," identifying a patient population that is often elderly and has multiple comorbidities in which AKI markedly increases not only in-hospital mortality, but also the risk of long-term pulmonary and motor sequelae and progression to chronic kidney disease (CKD). The development of integrated follow-up models between hospital and territory and the use of urinary biomarkers for a more comprehensive assessment of renal function could also be used outside the COVID-19 issue by limiting the number of hospitalizations and post-AKI health care costs.

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QUORUM-SENSING MOLECULES GROM GRAM-NEGATIVE BACTERIA PRESENT IN PLASMA AND URINE OF SEPTIC PATIENTS CAUSE DIRECT INJURY TO HUMAN TUBULAR EPITHELIAL CELLS AND ARE EFFICIENTLY REMOVED BY POLYMYXIN B HEMOADSORPTION (PMX-HA)

aLaura Fornara, aStefania Prenna, bClaudio Medana, bFederica Dal Bello, cViviana Orlandi, dAlessandro D. Quercia, dMarita Marengo, eVito Fanelli, fClaudio Ronco, aVincenzo Cantaluppi

aSCDU Nefrologia e Trapianto Renale, Università del Piemonte Orientale
bDipartimento di Chimica, Università di Torino
cDipartimento di microbiologia, Università dell'Insubria, Varese
4dSC Nefrologia e Dialsii ASL CN1
eSC Anestesia Rianimazione U, Università di Torino
f International Renal Research Institute Vicenza (IRRIV)

Introduction and Aims: Quorum sensing (QS) are small diffusible signal molecules adopted by both Gram negative and positive bacteria for intercellular communication. QS are a system of transcriptional regulation dependent on cell density and formed by 2 elements: the signal molecule (usually an acylhomoserine lactone) able to be internalized in the cytoplasm of neighbouring cells and the transcriptional activator. Recent studies suggested that QS can interact with eukaryotic cells exerting immunomodulatory and procoagulant effects. The aim of this study was to evaluate the potential role of Gram negative QS in sepsis-associated AKI by identifying different QS families in plasma of septic patients and by studying their biological effects on human kidney tubular epithelial cells (TEC). Secondly, QS adsorption was evaluated in an ex-vivo model of Polymyxin-B hemoadsorption (PMX-HA).

Methods: HPLC-MS was used to detect and quantify different QS subtypes in critically ill patients with sepsis-associated AKI. Human TEC were isolated from kidneys of patients subjected to nephrectomy. QS from P. aeruginosa were purchased by Sigma Aldrich. In selected experiments supernatants of QS negative mutants of P. aeruginosa were used on TEC. We evaluated QS-induced: cytotoxicity (XTT), apoptosis (TUNEL, caspase-3, -8, 9 activities), alteration of cell polarity (trans-epithelial electrical resistance, TEER), ROS production, NGAL mRNA/protein expression, mitochondrial function, leukocyte adhesion and FACS or immunofluorescence analysis of molecules typical of fully differentiated TEC (ZO-1, megalin, AQP-2, E-cadherin) or involved in inflammation (ICAM-1,CD40). Minicartridges containing PMX were used to evaluate QS adsorption from LPS-activated human blood.

Results: By using HPLC-MS technology, we observed that different subtypes of QS are detectable in both blood and urine of patients with Gram-negative sepsis and AKI. In vitro, QS exerted a dose-dependent cytotoxic (XTT assay) and pro-apoptotic effect (TUNEL assay) on TEC inducing Fas and caspase activation. The percentage of tubular cell apoptosis was similar to that observed in presence of LPS. The pro-apoptotic effect of QS on tubular cells seems to be mediated by an alteration of mitochondrial membrane potential (Mytotracker analysis), increase of ROS production and NGAL release. In addition, QS induced dedifferentiation of TEC as assessed by loss of cell polarity with a significant decrease of TEER and of expression of ZO-1, megalin and AQP-2. QS also exerted a pro-inflammatory effect on TEC increasing leukocyte adhesion and surface expression of ICAM-1 and CD40. A similar pro-apoptotic effect on TEC was observed using supernatants produced from wild type P. aeruginosa, but not from QS negative mutants. The cytotoxic and pro-apoptotic effect of QS on TEC was enhanced by co-incubation with LPS. By contrast, QS-induced TEC injury was significantly decreased after adsorption in vitro with PMX-HA (Toray Industries, Tokyo, Japan).

Conclusions: Different subtypes of QS molecules are present in the peripheral blood of patients with Gram negative sepsis and may play a role in the pathogenic mechanisms of sepsis-associated AKI. QS induce different detrimental effects on TEC such as cytotoxicity, apoptosis, mitochondrial dysfunction, ROS generation, NGAL release, leukocyte adhesion and de-differentiation. QS may enhance the detrimental activity of LPS. PMX-HA may have a protective role by binding QS directly or through interaction with LPS. Preliminary in vitro data showed that PMX-HA could remove QS from blood: these results should be confirmed in patients enrolled in RCTs.

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PIPERACILLIN-TAZOBACTAM INDUCED ACUTE INTERSTITIAL NEPHRITIS: A RARE CASE OF ACUTE KIDNEY INJURY WITH A RAPID COURSE

A. Bolzon, MD[a]; I. Godi, MD[b]; I. Tiberio, MD[b]*

[a] Department of Medicine, Section of Anesthesia, Critical Care and Pain Medicine - University of Padova; [b] Department of Anesthesia and Critical Care University Hospital of Padova

Background: Acute kidney injury (AKI) is a frequent condition especially in hospitalized patients. Acute interstitial nephritis (AIN) is an important cause of AKI, characterized by interstitial primary injury resulting in decreased renal function; beta-lactams are responsible for up to 55% of antibiotic-induced AIN.

Methods: We report a case of a patient who developed AKI with interstitial involvement after receiving piperacillin-tazobactam, needing renal replacement therapy during intensive care unit stay. Renal function was tested daily using routine blood chemistry tests. Imaging assessments of kidney morphology and function were performed using abdominal ultrasound and abdominal CT. The patient provided oral consent for the case to be reported anonymously.

Results: A 52-year-old man was hospitalized with a diagnosis of pneumonia with massive pleural effusion. His medical history included arterial hypertension and a remote episode of ischemic stroke, without permanent damage.

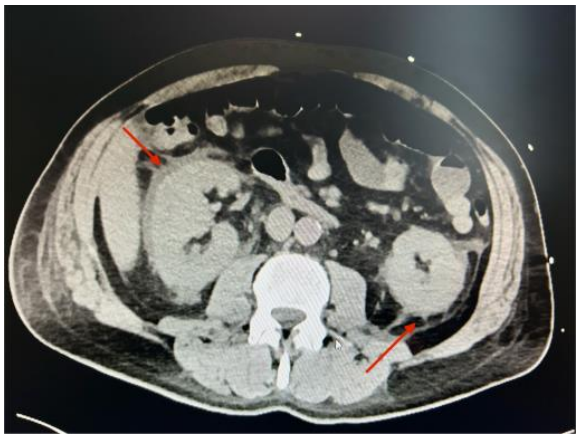
On hospital admission, his kidney function was normal (creatinine 61 µmol/L and urea 3.5 mmol/L). In the medical unit, antibiotic therapy with piperacillin/tazobactam (18 g/day) and azithromycin (500 mg/day) was initiated. The day after hospitalization, the patient was transferred to intensive care unit (ICU) due to worsening respiratory distress. In the ICU, the patient underwent the first chest computed tomography (CT) scan, which revealed empyema with adjacent pleural thickening. Evacuative surgery was scheduled and performed two days later. Meanwhile, after evidence of blood culture positivity for sensitive Staphylococcus Aureus and Epidermidis, antibiotic therapy with vancomycin (2 g/day) was administered.

On the third day of ICU stay, the patient developed oliguria despite maximal continuous intravenous furosemide therapy (1 g/day), with worsening of kidney function markers (creatinine up to 625 µmol/L and urea 28.9 mmol/L). Kidney parenchymal alterations were reported by ultrasound examination, which showed globose, increased size kidneys with compromised blood flow on Doppler evaluation and a right kidney resistive index of 0.72 (reference value < 0.70). CT revealed bilateral perirenal effusion with imbibition of the adjacent adipose tissue.

Under the suspicion of beta-lactam-induced interstitial nephritis we suspended the ongoing antibiotic therapy, replacing with combination of meropenem and linezolid, we administered a bolus of corticosteroids and started renal replacement therapy (RRT) (by continuous veno-venous hemodiafiltration with a dialytic dose 30 ml/kg/h and a regional citrate anticoagulation strategy).

RRT was suspended after 10 days and the patient was transferred to a nephrology department, meanwhile a treatment with tapering doses of corticosteroids (deltacortene initial dose of 25 mg/day) was started. Kidney function partially recovered with a serum creatinine at hospital discharge of 192 µmol/L after 31 days of hospitalization. At the follow-up visit after four weeks, diuretic therapy was discontinued owing to complete renal recovery (serum creatinine 108 µmol/L and urea 6.6 mmol/L).

Conclusion: This case is an example of early onset antibiotic nephrotoxicity with rapid organ damage and failure. Although antibiotic-induced interstitial nephropathy is rare, it is a predictable side effect of piperacillin–tazobactam use. Recognition of the condition is critical for the institution of appropriate therapy and prevention of kidney failure. The patient recovered rapidly and completely once the appropriate therapeutic strategy was initiated.



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ASSESSMENT OF THE ENDOTOXIN ADSORPTION CAPACITY OF THE OXIRIS® HEMOFILTER: IS IT POSSIBLE TO DETECT THE MEMBRANE SATURATION PHENOMENON IN VIVO?

D. Smirnova a,*c V. Liguts* a,b , *G. Freijs a, A. Skesters* d , *O. Sabelnikovs* a,c

a Pauls Stradins Clinical University Hospital, Department of Anesthesiology and Intensive Care, Riga, Latvia; b Riga Stradins Clinical University Hospital, Department of Acute Renal and Liver Replacement Therapy, Riga, Latvia; c Riga Stradins University, Department of Clinical Skills and Medical Technology, Riga, Latvia; d Riga Stradins University, Scientific Laboratory of Biochemistry, Riga, Latvia

Background: the extracorporeal removal of inflammatory mediators is a cornerstone of the hemadsorption strategy in patients with septic shock. Despite several research studies reporting beneficial effects of hemadsorption with oXiris® in these patients [1], the optimal duration of oXiris® application remains a subject of debate. Our study aims to assess in vivo preterm fouling of the oXiris® hemadsorption membrane or the membrane saturation phenomenon to ensure optimal adsorption efficacy during the hemadsorption procedure.

Methods: blood samples were collected from seven patients with septic shock undergoing CVVH with oXiris® at various time points within the first 24 hours of treatment. To ascertain the saturation limit of the oXiris® membrane, we assessed the adsorption trend by measuring the difference in endotoxin concentration (ΔC) between the inlet (Cbi, pre-filter site) and outlet (Cbo, post-filter site) lines. We defined the value of ΔC zero as indicative of a saturated membrane. Endotoxin concentration was quantified using an assay based on *Limulus amebocyte* lysate, with a detection range of 100-2500 pg/mL and a sensitivity for endotoxin concentrations ≤0.005 EU/mL.

Results: All patients admitted to the ICU had a median SOFA score of 10 [interquartile range (IQR) 8 – 11] upon admission, along with elevated levels of procalcitonin (PCT), C-reactive protein (CRP), and IL-6 (48 ng/mL [IQR 6.7-94.5], 228 mg/dL [IQR 154-318], and 18265 pg/mL [IQR 1820-35383], respectively). Norepinephrine (NE) support was required for all patients, with a median dosage of 0.41 µg/kg/min [IQR 0.11–0.61]. Gram-negative sepsis was diagnosed in all patients, with abdominal sepsis (n=4, 57%) being the most common. The median baseline endotoxin level was 0.5 EU/mL [IQR 0.19-1.35]. Hemadsorption was initiated at a median time of 3 hours [IQR 2-30] after ICU admission and 21 hours [IQR 11-129] after hospital admission. Twenty-four hours after hemadsorption initiation, there was a significant decrease in endotoxin level, NE support, PCT, CRP, IL-6, and SOFA score to 0.26 EU/mL [IQR 0.09-0.64], 0.10 µg/kg/min [IQR 0.00-0.20], 12.9 ng/mL [IQR 6.9-16.2], 310 pg/mL [IQR 133-550], and 7 [IQR 5–9] points, respectively. Regarding endotoxin concentration over time, it was observed that endotoxin levels fluctuated, with peak concentrations occurring at the initiation of hemadsorption and twelve hours later (median 0.45 EU/mL [IQR 0.25-1.62] and 0.42 EU/mL [IQR 0.09 – 1.62], respectively). Additionally, in some patients, endotoxin concentrations at the outlet were higher than at the inlet at different time points, which was not correlated with the initial endotoxin concentration load. These findings may be attributed to an unstable interaction between endotoxin and the polyethyleneimine (PEI) layer of the oXiris® membrane or to a de-adsorption phenomenon.

Conclusion: the data from this study suggest that CVVH with oXiris® effectively removes endotoxin in patients with gram-negative septic shock, resulting in favorable hemodynamic effects and reduced levels of inflammatory mediators. However, the adsorption of endotoxin to the membrane layer appears to be unstable and is influenced by various factors that warrant further investigation in subsequent studies.

References:

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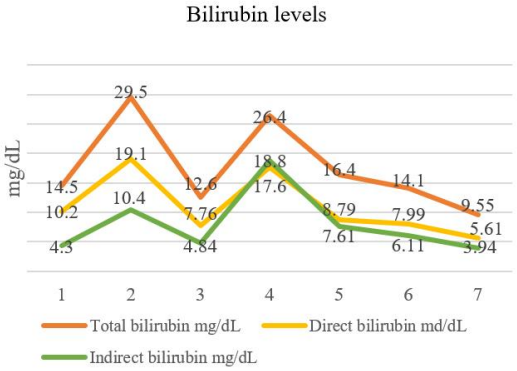
DPMAS AS TREATMENT IN A SEVERE ACUTE-ON-CHRONIC LIVER FAILURE IN A PATIENT WITH AUTOIMMUNE HEPATITIS.

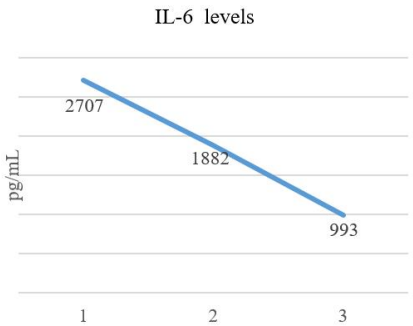
Zavala-Gómez Mariana, López-Contreras Rodrigo, Alvarez-Lara Daniel, Cortez-Hernadez Ca, Rizo-Topete L.*

Abstract: The use of extracorporeal liver support systems (ECLS) to bridge the patient to liver transplant (LT) or recovery, has been improved in the last years. We present a case of a 55 years female with autoimmune hepatitis who presented liver failure and underwent trough 3 sessions of double plasma molecular adsorption system (DPMAS). She presented progressive improvement in clinical condition and laboratory values of bilirubin and inflammatory marker IL6.

Introduction: Liver failure, acute or acute-on- chronic, is a life-threatening disease with a high mortality rate. The use of ECLS would allow support as a bridge to LT or until the patients' liver can recover or potentially provide symptom relief. ECLS aim to improve detoxification, biosynthesis, regulation, and regeneration, for improving neurological status, hemodynamics, reducing inflammation and enhancing regeneration.

Clinical Case: Female 55 years old, diagnosed with AIH for 4 years, in treatment with hydrocortisone, mycophenolic acid, and ursodeoxycholic acid. With previous exacerbations and under an incomplete liver transplant protocol. Her current condition began one week prior to admission, presenting hyporexia, asthenia, and adynamia, accompanied by diffuse colicky abdominal pain with an intensity of 5/10. Physical examination: mucocutaneous jaundice and dehydration, Grade I encephalopathy, and ascites. Edema with pitting +++ in the lower extremities. On admission, the laboratory tests were: Hb 8.9 g/dL, Hct 26%, leukocytes 5.30 per µL, platelets 54,000, PT 32.2 s, INR 2.84, aPTT 55.9 s; Cr 0.73 mg/dL; urea 72.8 mg/dL; total bilirubin 14.5 mg/dL, BD 10.2 mg/dL, BI.3 mg/dL; AST 97 U/L; ALT 60 U/L; GGT 43 UI/dL, ALP 135 U/L. MELD score of 28 points, Child-Pugh class C (13 points). On the fifth day of hospitalization, progression to Grade IV hepatic encephalopathy associated with LRA KDIGO 2 was observed, with worsening laboratory values: Cr 1.71 mg/dL, BUN 61.7 mg/dL, BT 21.9 mg/dL, BD 15.7 mg/dL. We performed 3 sessions of DPMAS, on alternate days, with TPE2000 filter cartridge HA330 II and BS 330. Each session lasted for 6 hours and with plasma volume of 1.5 for DPMAS and 1 time for TPE. With a Qb 130-150 ml/min and Qr post 1300 -1400 ml. jugular HD catheter was placed . The associated RRT technique was CVVHDF. Progressive improvement was observed in laboratory values and clinical condition after each DPMAS session.





Discussion and Conclusion: The double plasma molecular adsorption system (DPMAS) is a blood purification method that is safe and effective for reducing bilirubin levels and inflammatory markers, making it an important option for bridging to transplant or recovery. This could be observed in our patient, in whom the bilirubin and IL-6 levels decreased significantly after treatment with DPMAS, from 29.5 mg/dL and 2707 pg/mL, respectively, to 9.55 and 993 pg/mL.

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ADVANCEMENT IN PERITONITIS DIAGNOSIS: EVALUATING NGAL AS BIOMARKER

Morisi Niccolò(a), Ferrarini Marco(a), Ballestri Marco (a), Donati Gabriele (a).*
a: Surgical, Medical and Dental Department of Morphological Sciences, Section of Nephrology, University of Modena and Reggio Emilia, Modena, Italy.

Background and Aims: Neutrophil gelatinase-associated lipocalin (NGAL) is a multifunctional protein with roles beyond its traditional use as a biomarker. It actively participates in inflammation, proliferation, and migration processes. This study evaluates NGALds, a newly developed dipstick test, in comparison to the established NGALlab method for early peritonitis detection in peritoneal dialysis (PD) patients. By analysing the peritoneal fluid, researchers aim to create a rapid and effective diagnostic tool to improve peritonitis management.

Method: A retrospective analysis was conducted to validate diagnostic accuracy using parallel samples obtained from peritoneal effluents. These samples were collected from both stable peritoneal dialysis (PD) patients undergoing routine analysis and PD patients with suspected or confirmed peritonitis. The evaluation of NGALds involved a direct comparison with the established NGALlab. Peritoneal NGALlab quantification was performed using the BioPorto test, which utilizes a particle-enhanced turbidimetric immunoassay. In contrast, the NGALds is a rapid semi-quantitative assay that employs colourimetric test strips and an antibody sandwich lateral flow dipstick test. The maximum NGAL value detected by the dipstick method is 600 µg/L. Statistical analyses, including Spearman rank correlation coefficients (Rs), were carried out using SPSS Statistics 26. Additionally, ROC analysis was conducted using white cell count and the percentage of neutrophils in peritoneal fluids as the gold standard..

Results: In the analysis of 301 peritoneal effluent samples, 156 were diagnosed with suspected peritonitis using both NGALlab and ISPD criteria. Each sample underwent evaluation with both NGALlab and NGALds. As depicted in the Bland-Altman graph (Figure 1), NGALds exhibited a robust correlation with NGALlab categories (Rs = 0.876, P < 0.001), accurately identifying 96% (150 out of 156) of peritonitis cases. Discrepancies between NGALlab and NGALds were most evident when NGAL values exceeded the 600 µg/L threshold. However, these variations did not impact clinical significance, as both methods consistently diagnosed elevated NGAL values indicative of peritonitis. After ROC analysis, which yielded an AUC of 0.82 (p < 0.001) (Figure 2), the Youden Index identified a threshold value of 100 µg/L for diagnosing suspected peritonitis. Importantly, applying this threshold to NGALds demonstrated a positive predictive value of 0.64 and a negative predictive value of 0.87.

Conclusion: In conclusion, our study underscores the significant correlation between NGAL values obtained through the laboratory standard NGALlab and the novel NGALds. Notably, NGALds exhibited high efficacy, accurately identifying 96% of peritonitis cases diagnosed by NGALlab. This robust performance positions the NGAL dipstick as a valuable and accessible alternative for rapid assessment in patients exhibiting symptoms indicative of peritonitis. The user-friendly attributes of NGALds not only make it a practical diagnostic tool but also a patient-centric one. Furthermore, the high negative predictive value provides confidence in considering NGALds as a frontline diagnostic tool for suspected peritonitis. The ease of use and prompt results open a promising avenue for improving clinical workflows, offering an opportunity for expedited and efficient peritonitis diagnosis. For instance, NGALds could find utility in centres where NGAL is unavailable in the laboratory or at the patient's home.

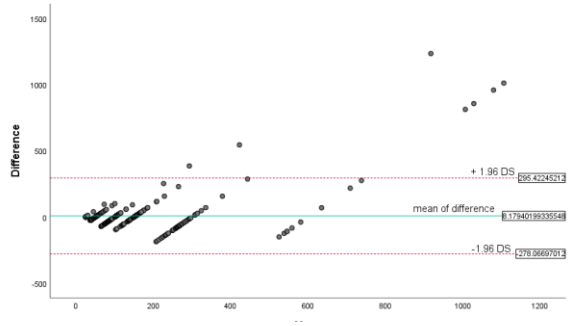

Figure1: Bland-Altman plot showing the difference between NGALlab and NGALds plotted against the average of the two methods. The mean difference is represented by the solid green line, while the dashed red lines represent the limits of agreement. The plot shows that the two methods have good agreement, with no significant bias or outliers.

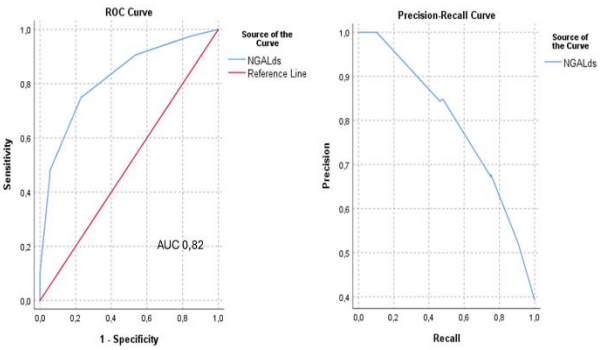

Figure2: Figure 2: On the left, a Receiver Operating Characteristic (ROC) curve in blue demonstrates a robust Area Under the Curve (AUC) of 0.82. On the right, a Precision-Recall curve provides insights into the precision and recall trade-off.

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REGIONAL CITRATE ANTICOAGULATION (RCA) VS HEPARIN SYSTEMIC ANTICOAGULATION IN CRITICALLY ILL PATIENTS RECEIVING CONTINUOUS RENAL REPLACEMENT THERAPY

M.Palmieri * [a], *F.La Fergola* [a], *S.Carparelli* [a], *Sturda E* [a], *Palaumbo C.A* [a], *M.Fiorentino* [a], *L.Gesualdo* [a]

[a] Nephrology, Dialysis and Transplantation Unit, Department of Precision and Regenerative Medicine and Ionian Area (DiMERPRE-J), University of Bari, Bari, Italy

Background: Continuous renal replacement therapies (CRRT) are essential to support critically ill patients admitted to ICUs with Acute Kidney Injury (AKI). An effective anticoagulation strategy is required to maintain the patency of the extracorporeal circuit, minimizing downtime and blood loss due to filter clotting. We aim to analyze the impact of the use of citrate anticoagulation on filter patency and personnel workload in a single center retrospective analysis.

Methods: We performed a retrospective analysis and collected data from 95 critically ill patients, who developed AKI during ICU stay and required CRRT from July 2023 to February 2024 at the several ICUs at A.O.U. Policlinico – Bari. We analyzed the overall number of treatments performed with citrate anticoagulation compared to heparin and without any anticoagulation; we compared the number of unexpected circuit coagulation (RRT discontinuation before the 72h of treatments) using Chi-square test.

Results: 95 critically ill patients were included in the present study. Mean age of study population was 63.6 ± 11.1 years, with a prevalence of male gender (73 patients, 76.8%). The majority of patients were affected by hypertension (60 patients, 63.1%) and cardiovascular disease (63 patients, 66.3%), while 48 patients (50.5%) were affected by pre-existing CKD. We reported for the first time in our hospital a higher use of citrate anticoagulation compared to other anticoagulation modalities. 522 treatments were performed, of which 112 were without the use of anticoagulant, 149 with heparin anticoagulation and 261 with citrate anticoagulation. We reported a high number of unexpected CRRT discontinuation in the no-anticoagulation group (45 circuits, 40.1%) and in the heparin group (55 circuits, 36.9%); conversely, we observed a reduced anticipated circuit coagulation in the citrate group (45 circuits, 17.2%, p>0.001) (**Table 1**).

Conclusion: Citrate anticoagulation is effective in improving circuit patency, reducing unexpected coagulation events, ensuring greater reliability of CRRT treatment, reducing downtimes, overall personnel workload and costs.

Tabel 1. Distribution of treatment interruptions according to anticoagulation modalities

	N° treatments	**N° unexpected treatment discontinuation**	**p-value**
No anticoagulation	112	45 (40,1%)	
Heparin anticoagulation	149	55 (36,9%)	
Citrate anticoagulation	261	45 (17,2%)	<0.001
	522	**147 (28,1%)**	

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PLASMA EXCHANGE VS SPAD IN ACUTE AND ACUTE ON CHRONIC LIVER FAILURE

Sergio Vazquez Olvera Emmanuel Sigfred Villalobos Arreola*

Kidney Health Institute. Querétaro Mexico

Background: Therapeutic plasma exchange (TPE) has emerged as an attractive liver support device for acute liver damage, improving survival, decreasing systemic inflammatory response and cerebral edema, changes in biochemical, physiological and SOFA score, until liver transplantation or clinical recovery. Data in patients with acute liver failure (ALF) suggest routine use of high volume TPE, while the data for such strategy is less robust for patients with acute on chronic liver failure. Single pass albumin dialysis (SPAD) is one of the albumins dialysis-based therapies available. Clinical trial has shown no difference between the efficiency of SPAD and MARS.

Methods: We present 4 cases of ACL and ACLF, with criteria for renal replacement therapy and use of standard volume plasma exchange. One of them initially on SPAD 2 sessions since it was not compatible with the available plasma. The main indication was fluid overload. The 4 patients with INR >1.5 and the causes of liver failure were sepsis and medications.

Results: The 3 patients on TPE were treated with standard volume plasma exchange (TPE 2000) in CRRT machine (PRISMAX). The received an average of 1.5 sessions, blood volume 4160 (±580), plasma volume 3232 (±754) with initial total bilirubin 20.7 (± 7.8). Treatments were performed without anticoagulation and pos filter replacement volume <1200ml/h. Patient on SPAD was the only who had a transient decrease in bilirubin, but no correction of coagulopathy. The only fatal outcome from the case series. The other 3 patients with survival until time of their las visit (>6 months on average) after hospitalization episode where they received renal replacement therapy, two of them remain dependent on renal replacement therapy.

Conclusion: Although the number of patients is not enough to provide a relevant conclusion. Even that evidence has shown that SPAD, MARS, hemo adsorption can be used in patients with acute liver failure. There are not strong recommendations in patients with severe coagulopathy. From our perspective, can be demonstrated in a prospective study, the best treatment for these patients will be plasma exchange, and may we will find the right moment to initiate this therapy for better outcomes.

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ACUTE KIDNEY INJURY REAL INCIDENCE IN HOSPITALIZED PATIENTS: A SIX YEAR OVERVIEW

Stefania Prenna a, Laura Fornara a, Riccardo Piscia a, Vincenzo Cantaluppi a*

a Nephrology and Kidney Transplantation Unit, University of Piemonte Orientale (UPO), Novara, Italy

Background: Despite its known association with mortality and progression to Chronic Kidney Disease (CKD), intra-hospital Acute Kidney Injury (AKI) is a highly underestimated disease. Particularly, AKI incidence is well known in the context of Intensive Care Units (ICU), while there is a lack of knowledge regarding the other hospital settings. The objectives of our study are mainly three: 1) To compare the incidence of intra-hospital AKI according to KDIGO guidelines with the incidence reported in Hospital Discharge Records; 2) To investigate intra-hospital AKI risk factors; 3) To explore the impact of AKI as a risk factor for poor prognosis in our cohort. Finally, we deepened the differences in intra-hospital AKI incidence both before and after COVID19 pandemic and before and after the availability of SARS-CoV2 vaccines.

Methods: We analyzed the Hospital Discharge Records of all the patients admitted to our Hospital from January 1st 2017 to December 31th 2022. We collected data regarding age, sex, duration of recovery and type of discharge (death, discharge directly to home or to other hospital facilities), type of ward (also in terms of COVID-19 ward), number of comorbidities, principal and secondary diagnoses. We also obtained laboratory findings regarding serum creatinine, serum sodium and potassium, reactive C protein (PCR), glycated hemoglobin (Hb1Ac) and hemocultures. In this way we obtained AKI diagnosis both according to Hospital Discharge Records and KDIGO 2012 Guidelines applied to serum creatinine values. The entire population and the subgroups were analyzed through variance analysis (ANOVA) and $\chi 2$ test. The statistical significance was set to a p value of 5% or lower.

Results: We analyzed data collected from 94,278 patients admitted to the AOU Maggiore della Carità in Novara from January 1, 2017, to December 31, 2022, which included 52.10% males and 47.90% females, 59.11% aged over 65 years and 40.89% aged ≤ 65 years. The incidence of AKI according to the KDIGO 2012 guidelines was found to be globally 19.41%, of which 11.60% stage 1 AKI, 4.86% Stage 2 AKI and 2.95% Stage 3 AKI, without variability between years. The incidence of AKI according to Hospital Discharge Records was significantly lower (4.28%). Considering all patients developing AKI (18,304 patients), 51,01% were men while 48.09% were women (p=0.564), and 27.1% were ≤ 65 years old while 72.9% were > 65 years old (p < 0.001). Out of all AKI patients, 21.73% were hospitalized in ICU, 18.04% in surgical wards and 60.23% in medical wards, with an association between ICU stay and the development and severity of AKI (p< 0.001). AKI, particularly Stage 3, was associated with a higher in-hospital mortality (14.6% vs 4.2%, with a Stage 3 mortality of 24.2%) (p< 0.001), together with age > 65 years (16.2% vs 10.6%) (p < 0.001). There was also an association between AKI and "not-at-home dismissions" (33.7% vs 16.8%) (p < 0.001) and between AKI and the length of hospitalization, both in ICU (22 vs 10 days, p < 0.001) and outside ICU (17 vs 8 days, p < 0.001). Furthermore, developing AKI correlated with an increased risk of hyponatremia, hypernatremia, hypokalemia and hyperkalemia (p < 0.001) and also elevated serum levels of C reactive protein (14.3 mg/dl vs 6.3 mg/dl, p < 0.001). Finally, there was a difference in AKI incidence before and after COVID19 pandemic, with an AKI incidence of 20.3% in years 2020-2022 vs 18.6% in 2017-2019 (p 0.001) and a peak in 2020 (21.2%). Particularly, there was a higher incidence of stage 2 and 3 AKI (41.3% in 2020-2022 vs 39.1% in 2017-2019, with a peak of 42.9% in 2020).

Conclusions: AKI, even Stage 3, is a highly underestimated disease that according to our study affects almost 1 of 5 hospitalized patients, with an important impact on their prognosis and a correlation with other significant medical issues, such as electrolyte disorders and inflammation. AKI is more common in ICU patients but has a high frequency also in surgical and medical wards. Particularly, only 1 of 5 AKI cases develops in ICU. The principals risk factors for AKI are age and ICU stay. Along with COVID19 pandemic, there has been an increase in AKI incidence and severity, even after the availability of SARS-CoV2 vaccines.

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DEVELOPMENT OF AN OUT-PATIENT FOLLOW-UP AFTER IN-HOSPITAL ACUTE KIDNEY INJURY: RATE OF PROGRESSION TO CHRONIC KIDNEY DISEASE AND THE PREDICTIVE ROLE OF BIOMARKERS

Stefania Prenna a, Laura Fornara a, Riccardo Piscia a, Adele Tanzi b, Benedetta Bussolati b, Nicola Giacché c, Carolina Colliva c, Francesca De Franco c, Vincenzo Cantaluppi a*

a Nephrology and Kidney Transplantation Unit, University of Piemonte Orientale (UPO), Novara, Italy; b Molecular Biotechnology Center (MBC), University of Torino; c Tes Pharma, Corciano (Perugia)

Background: Intra-hospital Acute Kidney Injury (AKI) is a highly underestimated disease and a risk factor for poor prognosis, particularly in terms of mortality – both in-hospital and out-of-hospital – and development of Chronic Kidney Disease (CKD). This emphasizes the importance of follow-up after discharge of AKI patients in order to identify CKD progressors. In this setting, biomarkers of AKI-to-CKD progression could play a role in the identification of patients requiring a specialistic follow-up. The objectives of our study are mainly two: 1) To start a follow-up after discharge of AKI patients; 2) To collect biological samples from AKI patients to create a biobank and identify biomarkers of AKI and AKI-to-CKD progression.

Methods: We recruited patients who developed AKI – diagnosed according to KDIGO 2012 Guidelines for AKI applied to serum creatinine values - during a recovery in our Hospital from June 2021 to March 2023. We recruited patients at AKI diagnosis and scheduled an out-patient follow-up at 3 and 12 months after discharge for survivors. We did not include patients with a baseline eGFR inferior to 30 ml/min. We collected data regarding age, sex, type of ward, comorbidities, chronic therapy with diuretic or RAAS-inhibitors, baseline renal function and variation during the hospitalization, principal and secondary diagnoses, development of sepsis, intravascular administration of iodinated contrast, need of Renal Replacement Therapy (RRT) and type of discharge. We also collected data regarding renal function and hospital readmissions at 3 and 12 months after discharge for survivors. Progression to CKD was identified by a decrease in eGFR at 3- and 12-months follow-up. We finally recruited hospitalized patients without AKI as a control group. We collected biological samples – blood, saliva and urine – from patients at AKI diagnosis, discharge, 3- and 12-months follow-up. Biological samples of control patients were collected at hospital discharge. We performed urinary NGAL (Neutrophil Gelatinase-Associated Lipocalin) dosing at all the timings, urinary quinolinic acid/tryptophan ratio (Qa/Trp) – marker of oxidative stress – at discharge and isolation and characterization of urinary extracellular vesicles (EVs) at discharge. Statistical analysis was performed through variance analysis (ANOVA) and $\chi 2$ test. The statistical significance was set to a p value of 5% or lower.

Results: We recruited 126 AKI patients, equally distributed in stage 1 (36), stage 2 (41) and stage 3 (49) AKI. Median age was 73 years old; 44.4% of patients were females, and 55.6% of patients were males. The median duration of hospitalization was 12.5 days. 35.1% of patients were affected by diabetes, 65.6% had a history of cardiovascular diseases, 77.1% had hypertension, 19.8% had cancer and 55.7% had pre-existing CKD with an eGFR superior to 30 ml/min. 53.2% and 55.6% of patients, respectively, took RAASi or diuretics before the hospitalization. We recruited 23 patients for the control group. 63 patients and 27 patients, respectively, were present at 3 months and 12 months follow-up appointments; loss at follow-up was in part due to out-of-hospital mortality. Median eGFR at discharge was 46 ml/min, while at 3 months follow up was 47.7 ml/min. 28 out of 63 patients (44.4%) had a reduction in eGFR at 3-months follow-up. Median urinary NGAL was 604 ng/ml at discharge and 193 ng/ml at 3 months after discharge. Urinary EVs of AKI patients at discharge showed an increased expression of HLA-DR and CD44 and a reduced expression of CD133 and CD24 in comparison with control patients. Urinary Qa/Trp was higher in AKI patients in comparison with the control group and in AKI stage 2 and 3 patients in comparison with AKI stage 1.

Conclusions: Almost half of AKI patients with a 3-months follow-up showed a reduction in eGFR, emphasizing the importance of follow up of these patients after discharge. Urinary NGAL confirms to be a marker of AKI, while it decreases both in CKD progressors and non-progressors at 3 months after discharge. Urinary EVs markers and urinary Qa/Trp could play a role as biomarkers of AKI; our group is currently exploring their possible role as biomarkers of AKI patients at risk of developing CKD.

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HEMOFILTRATE REINFUSION SUPRA: IT ROLE DURING SEPSIS-ASSOCIATED ACUTE KIDNEY INJURY IT'S BEING CONFIRMED A VALID TECHNIQUE TO TREAT INFLAMMATION AND IMPROVING PATIENTS OUTCOME

*G. Gernone** a , *M. Russo* a

a Asl Bari - Nephro Urological Department - Nephrology and Dialysis Unit Putignano (S. Maria Degli Angeli) & Monopoli (S. Giacomo) - Hospitals, Italy

Background: Sepsis is life-threatening organ dysfunction caused by dysregulated body response to an infection. Mortality rate ranging over 60% for septic shock. AKI is final common pathway of this immune dysregulation leading to systemic inflammation (SI) due to uncontrolled circulating levels of pro-inflammatory mediators and cytokine induced direct organ damage. Kidney replacement therapy (KRT) is often required in Sepsis Associated AKI (SA-AKI) and could improve SI removing pathogens and inflammatory factors. Various blood purification techniques have been used: HCO/MCO membranes, hemoperfusion, plasma filtration/adsorption and, anecdotal, Hemo Filtrate Reinfusion Supra (HFR-S): endogenous reinfusion HDF based on adsorbing resin cartridge that remove cytokines and pro-inflammatory mediators, whose full spectrum is not yet know, and myoglobin also. Aim of this study is to test HFR on outcome of SA-AKI in critically ill pts in the sorbent era.

Methods: In a retrospective observational study, we evaluated development of AKI requiring KRT in 16 consecutive SA-AKI patients (pts) admitted in the ICU of our two hospitals from December 2022. ESKD pts in chronic dialysis are excluded. SA-AKI were treated with daily IRRT: HFR-S. Given the laboratory operating standards they were daily assessed: urea, creatinine, C-reactive protein (CRP), procalcitonin (PCT), WBC, platelets (PLT), myoglobin, albumin. Mean arterial pressure (MAP), need for vasopressor, and outcome are also evaluated. The values have been reported as mean±SD or median and interquartile range (IQR). AKI was defined according to KDIGO. Statistical analyzes were performed with the Wilcoxon Signed Rank Test

Results: Among the 16 pts 10 had AKI III stage. The mean age was 73.1 ± 11.1 years, 9 were male. 90% were hypertensive, some with heart disease, 60% with CKD (70% G3-KDIGO, 30% G2) 60% were obese or with diabetes, 45% with COPD. All received mechanical ventilation and several antibiotics, 80% received amines. They underwent IRRT by HFR-S with an average of 5.5± 3.4 treatments (range 2-13 sessions); Qb= 238 ±29.6 ml/m', TT 233.2 ±45.8 m'. UF 477.9 ± 185.5ml/h. HFR-S confirm an expected reduction for urea and creatinin, significant abatement of CRP, PCT and Myoglobin. Albumin remain stable and in some cases also improved at the end of the treatment. Neutral is the effect on WBC and PLT whose progress reflects the trend of sepsis. Cardiovascular instability decreased significantly with the treatments allowing the suspension of vasoactive amines as shown by the significant increase in MAP at the end of treatment (Tab. 1) even if during the first treatments it was necessary to temporarily increase their dose, clotting of the dialysis circuit occasionally occurred. Seven patients did not survive within follow four weeks, 5 patients had renal recovery, 2 patients had chronic dialysis.

Conclusion: Our experience with HFR, in the sorbent era, may promote a new strategy to decrease SI and support renal recovery in SA-AKI pts, even in some of the not survived. The adsorbing resin is able to efficacy remove proinflammatory cytokines and many other unknow mediators, that lead to improved MAPs and lower critical illness scores, and allow to eliminate myoglobin too. Indeed there is no study on the use of HFR in SA-AKI and very few experience on his use to hypermyoglobinemia. Finally HFR-Supra is safe and is the cheapest technique for SA-AKI in comparison to the other techniques available (e.g. CRRT, HCO, Cytosorb) by excellent cost-effectiveness-sustainability ratio regarding treatment times and staff-sparing. Larger studies could confirm our evidence but, in the meantime, our cases gradually help to build a new scientific evidence.

Tab. 1- Median and interquartile range (IQR)	***Baseline***	***After***	***p value < 0,05***
CRP mg/L	222.5 (180.5 - 292)	50,1 (26.5-80.9)	*p < 0,01*
PCT ng/ml	23.7 (13.5 - 75)	2.2 (0,9 - 5)	*p < 0,01*
WBC mm^3	17.7 (6.2 - 27)	9.6 (7.8 – 17.4)	*p = 0.23*
Myoglobin ug/L	1666 (907.5 – 6749.5)	453 (219.5 - 557)	*p = 0,01*
Albumin g/dl	1.8 (1,7 – 1.9)	2,1 (2.1 - 2,3)	*p = 0,06*
MAP mmHg	70,5 (68,2 - 88,7)	87.8 (78,5 - 96,2)	*p = 0,02*

PLT mm³	198.5 (105,7-262,5)	187 (148-258.5)	*p = 0,43*

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URINE AMMONIUM CONCENTRATION AS INDICATOR OF TUBULAR FUNCTION IN PATIENTS WITH RENAL TRANSPLANTATION

**Titherington LM [a], Giglioni V [a], Mattei I [a], Ricci Z [b], Peyronel F [c], Villa G [a], Romagnoli S [a], for the Florence KING Research Group (FKRG).*

[a] Department of Anesthesia and Critical Care Azienda Ospedaliero-Universitaria Careggi, University of Florence, Florence, Italy; [b] Anesthesia and Critical Care Meyer Children's Hospital IRCCS, University of Florence, Florence, Italy; [c] Nephrology and Dialysis Unit, Meyer Children's University Hospital - IRCCS, Firenze, Italy

Background: Renal function assessment conventionally relies on serum creatinine measurement to estimate glomerular filtration rate, usually overlooking tubular function. Urine output as an indicator of renal insufficiency is limited by various clinical variables. One of the main roles of renal tubules is acid-base regulation, which is achieved through reabsorption of filtered bicarbonate (HCO_3^-), excretion of titratable acid, and synthesis and excretion of ammonium (NH_4^+), eventually regenerating HCO_3^-. NH_4^+ is mainly produced in the proximal tubule via glutamine catabolism and its net secretion into the luminal fluid is enhanced in metabolic acidosis[1]. Therefore, measuring NH_4^+ urinary concentration can provide important information on the ability of renal tubules to excrete the acid load, as a clinical indication of tubular function. However, despite its potential significance, urinary NH_4^+ concentration is not routinely measured.

Methods: This study aimed at directly measuring urinary $[NH_4^+]_u$ using the semi-continuous analyser KING® (Kidney INstant monitoring; Kures, Milan, Italy) after renal transplantation form day-1 to day-10. In addition, due to the lack of data in current literature, $[NH_4^+]_u$ measured in transplanted patients was compared with healthy volunteers as controls.

Results: Median value (interquartile range, IQR) of $[NH_4^+]_u$ at day-1 was 4.98 (4.01) mEq/L. At day-10 the values were 6.79 (13.99) mEq/L (p=0.36 vs. day-1). Controls showed a median (IQR) $[NH_4^+]_u$ of 19.15 (16.08) mEq/L (p<0.01 vs. Tx day-1 and 10) (Table 1). See Figure 1.

Conclusions: There are many limitations in using serum creatinine and eGFR as measures of renal function[2] and recent and expensive biomarkers of tubular function are not routinely measured. $[NH_4^+]_u$ could offer valuable insights into tubular acid excretory function. Our findings reveal a significant difference in $[NH_4^+]_u$ between controls and transplanted patients, highlighting the potential of $[NH_4^+]_u$ measurement. Medium and long-term follow-up will be necessary to define the potentiality of $[NH_4^+]_u$ as indicator of renal function in these categories of patients.

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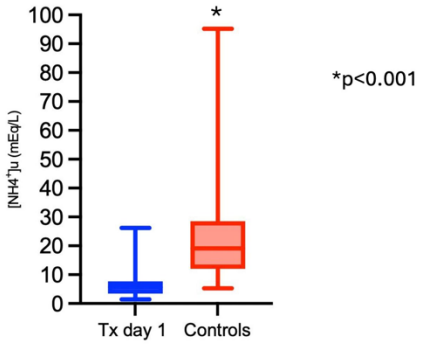
Table 1

$[NH4^+]_u$ mEq/L	Tx day 1 (n=16)	Tx day 10 (n=17)	Controls (n=34)
Median (IQR)	4.98 (4.01)	6.79 (13.99)*	19.15 (16.08)**
Min	0	1.81	5.29
Max	26.16	42.59	95.17

*p<0.01 Tx day 1 vs. controls; **p=0.36 Tx day 1 vs. Tx day 10

Abbreviations: IQR - Interquartile range; Min - minimum value; Max - maximum value; Tx, renal transplantation; $[NH4^+]_u$, urinary ammonium concentration

Figure 1. $[NH4^+]_u$ in transplanted patients in day-1 and controls. Median (IQR) and min to max.



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CAN HEMOADSORPTION WITH HA 380 BE USED AS AN ADJUVANT THERAPY IN MULTIPLE MYELOMA?

Ana Castroa,b,c, Bruno Fraga Diasa, Inês Salaa, Beatriz Gil Bragaa, José Alexandre Queirósa, Anibal Marinhod, Cristina Freitasa

a Nephrology Department, Unidade Local de Saúde de Santo António, Porto, Portugal

b UMIB - Unit for Multidisciplinary Research in Biomedicine, ICBAs - School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal

c International Renal Research Institute of Vicenza, Vicenza, Italy

d Intensive Care Department, Unidade Local de Saúde de Santo António, Porto, Portugal

Background: Multiple myeloma (MM) is a plasma cell neoplasm that results in the production of monoclonal immunoglobulin. In this setting a presumptive diagnosis of light chain cast nephropathy (LCCN) can be made in case of high free light chain (FLC) levels. Extracorporeal techniques such as high-cutoff membrane (HCO) dialysis can be used as an adjunctive therapy to chemotherapy in the management of LCCN. In the critically ill patient, hemoadsortion (HA) can represent a new option to overcome the limitations of HCO. The HA 380 cartridge (Jafron®) can remove molecules with 10-60kDa. In this case report we describe the use of HA 380 cartridge in the treatment of a LCCN in a critically ill patient.

Methods: A 76-year-old woman with previous history of hypertension and osteoporosis presented with a one-year history of weight loss, asthenia, anorexia and foamy urine. At admission she also referred dyspnea, orthopnea, paroxysmal nocturnal dyspnea and edema up to the root of the thigh. Blood analysis revealed anemia (hemoglobin of 7.9g/dl), creatinine (Cr) of 2.6mg/dL, cystatin C of 3.43 mg/L. The urine exam demonstrated albuminuria of 1980 mg/g and a Cr protein ratio of 25 g/g. On workup serum protein electrophoresis (SPEP) and FLC tests showed a lambda FLC monoclonal gammopathy – lambda FLC 1230 mg/dl. Serum immunoglobulins - IgA, IgM and IgG - were decreased (61.0 mg/dl, 320.0 mg/dl and 24.8 mg/dl, respectively). Urinary electroimmunofixation demonstrated excretion of lambda FLC. During her stay in the emergency department, she developed an atrial flutter (heart rate 170 bpm) and hemodynamic instability that progressed to shock and was, therefore, admitted to an intensive care unit (ICU). In the first 24 hours she developed progressively worsening acute kidney injury (creatinine 3.4 mg/dl), cytocholestasis and hypervolemia refractory to diuretic therapy leading to respiratory failure. The X-ray showed bilateral congestion and moderate pleural effusion on the right. The echocardiogram revealed severe TI, severe RV and LV dysfunction; the IVC was 22 mm with no respiratory variability; IV septum measuring 11 mm. She developed severe metabolic acidosis with hyperlactacidemia (pH 7.18, Bic 11.4 mmol/L; Lac 8.9). After a multidisciplinary assessment and considering the magnitude of the elevation of lambda and the cardiogenic shock it was decided to start dexamethasone, Bortezomib and continuous kidney replacement therapy (CKRT) with HA 380 cartridge.

Results: Two sessions of HA 380 cartridge combined with CKRT (patient Wt 50Kg, blood flow 150 ml/min, dialysate flow1000 ml/hr, post-filter replacement total 500 ml/hr, patient fluid removal rate 150 ml/hr, hipocoagulation with citrate) were performed. The next table describes the evolution of the reduction of lambda FLC.

	Ref. Values	Day1 t 0hr	Day 1 t 4h	Day1 t 8h	Day 2 t 4h	Day 2 t 8h	Day 3	Day 4	Day 5	Day 9
FLC (blood)										
Kappa (mg/dl)	0.33 – 1.94	0.28	0.9	0.25	0.19	0.25	0.26	0.18	0.30	1.77
Lambda (mg/dl)	0.57 - 2,63	1230.0	948.0	797.0	425.0	271.0	170.0	75.5	69.4	19.1
Rel free K/Lambda		<0.001	<0.001	<0.001	<0.001	<0.000	<0.000	<0.000	<0.000	<0.090
Removal rate (%)				35.2%		66%				
Platlets x($x10^3$/uL)		181			38		20	3	10	3

We performed sessions of 8h of HA 380 + CKRT. Before the first session Lambda FLC were 1230.0 mg/dl, after 4h 948 mg/dl and after 8h of treatment 797.0 mg/dl. After this session the first dose of Bortezomib was administered. In the second day we

decided to perform the second session of CKRT + HA 380. After this final session the concentration of Lambda FLC was 271.0 mg/dl. To calculate the removal rate (RR) (%) we considered the following formula: RR = (FLCbaseline – FLCend of session) / FLCbaseline. The RR of the first session was 35.2% and in the second session was 66%. As a possible side effect of HA in this patient, we highlight thrombocytopenia which etiological study of was not conclusive and continued to worsen even after the technique was suspended. No other possible side effects were observed. Despite all measures and support provided, the patient died 9 days after being admitted to the ICU in the context of refractory cardiogenic shock.

Conclusion: Critically ill patients present several challenges due to multiple organ involvement, complex clinical scenarios, and unmet diagnostic and therapeutic needs. This report highlights the use of HA with HA 380 cartridge + CKRT in combination with Bortezomib in reducing lambda FLC levels in a 76-year-old patient that developed renal failure secondary to LCCN. The use of HA 380 allowed a quick and effective reduction of lambda FLC before the start of action of the gold standard chemotherapy. In this case the patient's outcome was determined by cardiogenic shock due to structural cardiac pathology, unrelated to MM. Further studies using randomized control trials on the use of HA in directly reducing FLC levels, its impact on patient outcomes and possible side effects are needed.

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ATTRIBUTABLE MORTALITY OF INTENSIVE CARE UNIT-ACQUIRED ACUTE KIDNEY INJURY: A PROSPECTIVE COHORT STUDY

H. Peters-Sengers [a,b,c], *T.D.Y. Reijnders* [a], *J.M. Butler* [a], *K. Luijken* [d], *L.A. van Vught* [a,e], *O.L. Cremer* [d], *T. van der Poll* [a,b,f]

[a] Center for Experimental and Molecular Medicine, Amsterdam UMC, location Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [b] The Amsterdam Institute for Infection and Immunity, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; [c] Department of Epidemiology and Data Science, Amsterdam UMC, location VU, Amsterdam, The Netherlands; [d] Department of Intensive Care, University Medical Center Utrecht, Utrecht, the Netherlands; [e] Department of Intensive Care, Amsterdam UMC, location Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [f] Division of Infectious Diseases, Amsterdam UMC, location Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands.

Background: Background: Acquired acute kidney injury in the intensive care unit (ICU-acquired AKI; onset >48 hours after admission) is a frequent complication with sepsis as most common cause. Appropriate quantification of the impact and burden of ICU-acquired AKI are imperative to understanding its severity and the importance of additional preventive measures and timely treatment. Our objectives were to: (1) determine the case fatality rate of ICU-acquired AKI, accounting for time-dependent exposures and competing events of ICU-discharge and ICU-death, and (2) track plasma protein trajectories from day of ICU admission to the day of AKI diagnosis in the ICU.

Methods: We prospectively studied adult patients with a length of stay of at least 48h in which AKI was not present in two tertiary intensive care units in the Netherlands from 2011 to 2019. Excluded were end-stage-renal-disease patients. New onset ICU-acquired AKI was defined as stage 1 or higher by any urine or creatinine RIFLE criterion, prospectively scored. We adjusted for the evolution of disease severity and possible nephrotoxic medications until onset of ICU-acquired AKI using marginal structural modelling via inverse probability weighting, and calculated the time-dependent population-attributable fraction of ICU mortality which expresses the percentage of preventable death cases in the ICU in the absence of ICU-acquired AKI. In all ICU-acquired AKI patients and a random subset of patients without AKI, we sequentially measured 21 plasma proteins reflective of (anti-)inflammatory pathways, endothelial cell, and coagulation activation.

Results: Out of 4,228 patients with a length of stay >48h without AKI, 441 (10.4%) developed ICU-acquired AKI. Baseline risk factors for ICU-acquired AKI included older age, higher BMI, non-European ancestry, chronic renal insufficiency, and elevated APACHE acute physiology scores. Time-dependent risk factors in the ICU for AKI were cumulative exposure to colloids, inotropes, vasopressors, aminoglycoside antibiotics, and calcineurin inhibitors. After adjusting for (time-dependent) confounding, ICU-acquired AKI was associated with increased ICU mortality (adjusted hazard ratio [HR] 3.67, 95% confidence interval [CI] 2.65-5.08, p<0.001). The population attributable mortality fraction of ICU-acquired AKI was 10.2% (95% confidence interval [CI] 6.3-15.2) by day 10 and 16.3% (95%CI 12.1-24.9) by day 20. During ICU stay with maintained adequate renal clearance, patients who developed ICU-acquired AKI showed an increase in proteins linked to inflammatory and anti-inflammatory pathways, and endothelial cell activation, compared to those without AKI.

Conclusion: By accurately accounting for time-dependent exposure and confounding factors, our study demonstrates that the onset of ICU-acquired AKI substantially contributes to mortality and is linked to marked changes in inflammatory and endothelial biomarkers, highlighting the need for targeted preventive strategies.

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USE OF SERAPH® 100 MICROBIND AFFINITY BLOOD FILTER IN A PATIENT WITH A SEPTIC SHOCK: A CASE REPORT.

E. Sturdà[a], S.Rotella[a], M.Arcidiacono[a], A.Panaro[a], D.Cappiello[a], F. La Fergola[a], M. Fiorentino[a], L. Gesualdo[a]

[a]Nephrology, Dialysis and Transplantation Unit, Department of Precision and Regenerative Medicine and Ionian Area (DiMERPRE-J), University of Bari, Bari, Italy

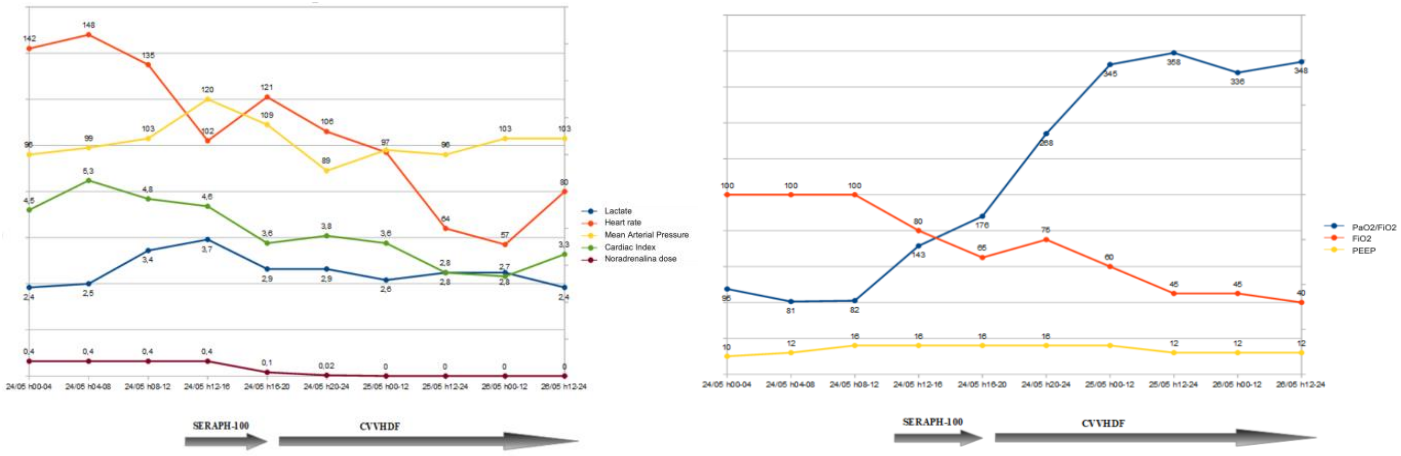
Background: The use of Seraph®100 Microbind Affinity Blood Filter has been recently proposed in several preclinical studies, as the heparin-coated microbeads of the cartridge are able to bind and remove bacterial and viral pathogens. We aim to report the potential efficacy of Seraph 100 hemoperfusion in a patient with septic shock due to Acinetobacter baumanni and Candida Albicans.

Method: We describe the case of an 18-year-old man, hospitalized at the ICU after major trauma, crush syndrome and rhabdomyolysis. The patient developed AKI stage 3 and a condition of septic shock, with the evidence of blood colture positive for C. Albicans and a CVC culture positive for multi-resistant A. Baumanni. Due to the rapid worsening of hemodynamic parameters and respiratory failure, a single hemoperfusion treatment with Seraph®100 was performed (Qb 150ml/min, duration 5 hours) followed by CRRT due to fluid overload and oliguria.

Results: Before treatment start, inflammatory indexes were elevated, and P/F ratio was 82 mmHg with FiO_2 100%; lactate levels were elevated (3.7 mmol/L) with a noradrenaline (NA) dose of 0.4 mcg/kg/min. Significant hemodynamic and respiratory improvements were reported since the first 2 hours of treatment. NA dosage was reduced during hemoperfusion and then stopped later on the same day; similarly, a slight reduction in lactate level and cardiac index were documented. We reported an impressive improvement in respiratory parameters, with P/F ratio raising to 176 mmHg and consequent reduction in FiO_2 (**Figure 1**). Serial blood cultures performed after treatment were negative, apart from one blood culture positive on the following day without clinical evidence of septic shock. CVVHDF was started after Seraph®100 hemoperfusion and discontinued after 48h of treatment for renal recovery and adequate urine output. A progressive improvement of inflammation indexes, circulatory and respiratory efficiency were reported in the following days.

Conclusion: Treatment with Seraph®100 may be effective as adjuvant therapy in septic shock management, decreasing pathogens load and the need of organ support and improving clinical outcomes in patients with septic shock.

Figure 1. Hemodynamic and respiratory improvements with Seraph®100 hemoperfusion



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ASSOCIATION OF URINARY CCL14 WITH HOST RESPONSE AND OUTCOMES IN CRITICALLY ILL SEPTIC PATIENTS WITH PERSISTENT ACUTE KIDNEY INJURY

Thei S. Steenvoorden a, Lonneke A. van Vught b, Liffert Vogt a, F.J. Bemelman a, Marcus J. Schultz b, and Tom van der Poll c,d, Hessel Peters-Sengers c,e

a Department of Nephrology, Amsterdam UMC, location University of Amsterdam, Amsterdam, The Netherlands; b Department of Intensive Care Medicine, and Laboratory of Experimental Intensive Care and Anesthesiology (L·E·I·C·A), Amsterdam UMC, location University of Amsterdam, Amsterdam, The Netherlands; c Center for Experimental and Molecular Medicine, Amsterdam UMC, location University of Amsterdam, Amsterdam, The Netherlands; d Division of Infectious Diseases, Amsterdam University Medical Centers, location University of Amsterdam, Amsterdam, The Netherlands; e Department of Clinical Epidemiology, Biostatistics and Bioinformatics, location University of Amsterdam, Amsterdam, The Netherlands.

Background: The urinary concentration of CC chemokine ligand 14 (CCL14) – a chemoattractant for T-cells and monocytes – has recently been identified as a strong predictor of persistence of severe acute kidney injury (P-AKI). The role of CCL14 in the pathogenesis of P-AKI is still unknown. With sepsis being the most frequent cause of AKI, we first wanted to externally validate whether urinary CCL14 concentration can differentiate transient-AKI (T-AKI) from P-AKI in sepsis patients admitted to the Intensive Care Unit (ICU). The second aim of the study was to compare the host response between patients with sepsis associated (SA) AKI and high CCL14 and those with low CCL14.

Methods: We used the Molecular Diagnosis and Risk Stratification of Sepsis (MARS) prospective cohort to include patients admitted to the ICU with sepsis They were categorized by the course of AKI (no-AKI, transient-AKI [T-AKI], and P-AKI, defined as lasting > 48h). Daily plasma creatinine and urine output AKI criteria were assessed prospectively, using the risk, injury, failure, loss, and end-stage kidney disease (RIFLE) classification. Within the first 24 hours of ICU admission, T-AKI and P-AKI patients fulfilled at least injury stage RIFLE criteria. CCL14 was measured in trine samples collected at ICU admission. The recently proposed cutoff of 1.3 ng/mL for the identification of patients at high risk for P-AKI was also used in this study. Levels of the following urinary biomarkers were also quantified: NGAL, TIMP-2×IGFBP7, cystatin-C, KIM-1, and L-FABP. In the same patient cohort we measured 15 plasma biomarkers reflective of: systemic inflammation and cytokine responses, endothelial cell activation, and coagulation activation. In a subset of 24 SA-AKI patients, whole-blood leukocyte genome-wide transcriptomes were determined.

Results: Urine samples taken at the day of admission were available in 158 sepsis patients enrolled in the MARS cohort. 66 patients did not have AKI, 32 had T-AKI and 66 had P-AKI. Patients with P-AKI had higher disease severity scores and more frequently had severe RIFLE AKI stages than those with T-AKI. CCL14 showed good discrimination between persistent-AKI and no-AKI (Area Under the ROC Curve [AUC], 0.86, 95%CI 0.77-0.93), and moderate discrimination between P-AKI and T-AKI (AUC 0.71, 95%CI 0.55-0.87). Other urinary biomarkers performed poorly in discriminating T-AKI from P-AKI (AUC<0.60). Of the 92 SA-AKI patients, 26 (28.3%) had high CCL14 (>1.3 ng/mL) and 66 (71.7%) had low CCL14 (<1.3 ng/mL). The majority of patients with high CCL14 had P-AKI (21 out of 26; 80.8%). High CCL14 in septic AKI was associated with more severe renal dysfunction at baseline - as reflected by higher plasma urea and creatinine concentrations – and with urinary tract, and skin infections. Plasma biomarker analysis revealed that high CCL14 in persistent SA-AKI was associated with endothelial barrier dysfunction (decreased angiopoietin-1 [p=0.009]). Gene-set-enrichment-analyses (using the Reactome pathway database) revealed a total of 168 pathways that were upregulated and 23 that were down-regulated in high CCL14 compared with low CCL14 SA-AKI. The most notable were: a heightened transcription of neutrophil degranulation pathways, a dampened response in interferon signaling pathways, and upregulated cellular stress response pathways.

Conclusion: In critically ill sepsis patients, urinary CCL14 showed good discrimination between persistent AKI and no-AKI and moderate discriminative ability for persistent and transient-AKI. Within sepsis patients with persistent AKI, high urinary

CCL14 was associated with more profound endothelial barrier dysfunction and a distinct pattern of leukocyte activation. The latter findings suggests that CCL14 might help guide future therapeutic strategies targeting specific AKI subgroups.

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NON HYPERLACTATEMIC METABOLIC ACIDOSIS IN ABDOMINAL SEPSIS. AKI OR NON-AKI? THE ROLE OF A NEW POINT-OF-CARE URINE ANALYSER: KIDNEY INSTANT MONITORING (KING®).

Valentina Giglioni[a], Lara Mary Titherington[a], Ilaria Mattei[a], Francesco Peyronel[c], Gabriele Baldini[a], Gianluca Villa[a], Zaccaria Ricci[b], Francesco Barbani[a], Lorenzo Foti[a], Giovanni Lascialfari[d], Lorenzo Ricci[d], Stefano Romagnoli[a]. For the Florence KING Research Group (FKRG).*

[a]Department of Anesthesia and Critical Care Azienda Ospedaliero-Universitaria Careggi, University of Florence, Florence, Italy. [b] Anesthesia and Critical Care Meyer Children's Hospital IRCCS Florence Italy, University of Florence, Florence, Italy [c] Nephrology and Dialysis Unit, Meyer Children's University Hospital - IRCCS, Firenze, Italy; [d] School of Medicine, University of Florence.

Background: Acid-base homeostasis is vital for cellular function, particularly in critically ill patients. Metabolic acidosis, characterized by a primary decrease in blood pH, is often encountered in intensive care settings. This study focuses on the application of the Kidney INstant monitorinG® (KING®, Kures, Milan, Italy) device, an innovative point-of-care (POC) urine analyzer, in a case of non-hyperlactatemic metabolic acidosis with increased plasma anion gap (pAG).[1]

Methods: In this case study, a 67-year-old woman underwent emergency surgery for small bowel perforation associated with abdominal sepsis. Upon blood gas analysis (BGA), she presented with elevated plasma anion gap (pAG) metabolic acidosis alongside normal lactate levels, initially indicating the possibility of sepsis-associated acute kidney injury (AKI)[2]. This condition is commonly characterized by a reduction in $NH4^+$ production and elimination (expression of tubular dysfunction)[3 4]. The use of the KING device allowed real-time analysis of the patient urine, providing crucial data for diagnostic evaluation.

Results: KING®'s measurement showed increased urine $NH4^+$ levels (see table 1), indicating normal kidney function. This was pivotal in excluding significant sepsis-associated AKI. Further investigations, focusing on alternative causes of the increased pAG metabolic acidosis[5], revealed ketones in plasma and urine, thus elucidating ketosis as the underlying aetiology of the acid-base imbalance. This case suggests the potential usefulness of a POC for urinary analysis in accurately diagnosing and managing cases of acid-base derangement.

Conclusions: The KING® device might be useful in enhancing diagnostic accuracy for metabolic acidosis in perioperative and critical care settings. By enabling rapid POC measurement of key urinary metabolites, it provides valuable insights into renal function and assists in differentiating between renal and non-renal causes of acid-base disturbances. The device's ability to redirect clinical focus in complex cases can be valuable, underscoring the need for more research into its integration into clinical practice for optimized patient outcomes.

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Table 1

BGA (during surgery)	KING® data (during surgery)	BGA during ICU stay	KING® data (during ICU stay)
pH = 7.28	pH = 5.54	pH = 7.43	pH = 5.5
$PaCO_2$ (mmHg) = 43.8	Na^+(mmol/L) = 17.44	$PaCO_2$ (mmHg) = 35.6	Na^+(mmol/L) = 158.03
HCO_3^-(mmol/L) = 19.6	K^+(mmol/L) =23.59	HCO_3^-(mmol/L) = 23.6	K^+(mmol/L) = 60.09
Na^+(mmol/L) = 137	Cl^-(mmol/L) = 30.52	Na^+(mmol/L) = 137	Cl^-(mmol/L) =158.03
Cl^-(mmol/L) = 102	$NH4^+$(mmol/L) = 43.53	Cl^-(mmol/L) = 106	$NH4^+$(mmol/L) = 56.52
sBE = -6.2		sBE= -0.8	
AG (mmol/L) = 15.4		AG (mmol/L)= 7.4	
Lac (mmol/L) = 1.1		Lac (mmol/L)= 1.2	

Abbreviations = BGA, Blood Gas, Analysis (arterial); $PaCO_2$, partial pressure of carbon dioxide; HCO_3^-, bicarbonate; Na^+, sodium; Cl^-, chloride; sBE, standard base excess; AG, anion gap; Lac, lactate; $NH4^+$, ammonium.

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EXTRACORPOREAL PURIFICATION TECHNIQUES FOR POISONING - 20 YEARS OF EXPERIENCE OF A CENTER

B. Gil Braga [a] *A. Castro*[a,] *A.Cunha* [a] *,A.Monteiro* [b,] *D. Cruz* [c] *C. Freitas* [a] ,
[a] Nephrology Department, Unidade Local de Saúde de Santo António, Porto, Portugal
[b] Internal Medicine Department, Unidade Local de Saúde de Santo António, Porto, Portugal
[c] Internal Medicine Department, Unidade Local de Saúde de Barcelos/Esposende, Barcelos, Portugal

Background:
Accidental or intentional poisoning and drug overdose are a significant source of morbidity, mortality and health care costs worldwide. Poisoning generally implies that damage results from exposure to pharmaceuticals, illicit drugs or chemicals.
The intervention of a nephrologist or intensivist is often necessary, to correct electrolyte or acid-base disturbances, manage kidney or other organ dysfunctions and evaluate the need for extracorporeal purification therapies (EPT). Extracorporeal purification techniques play a critical role in managing intoxications by enhancing the removal of toxic substances from the organism, and may improve patient's prognosis. Our aim was to review the experience of our center in EPT for poisoning in critically ill patients.

Methods: Simple descriptive and inferential statistics were used to generate results. Categorical data were described using frequency and percentage.

Results: We obtained a total of 83 intoxications. Fifty-seven (68.7%) patients were women. Mean age was 66.6± 15.4 years. The most common intoxication was metformin associated-lactic acidosis (MALA) (n=66), followed by lithium poisoning (n=4) then paracetamol (n=3) and organophosphates (n=3). Other intoxications are also presented in table 1. Regarding MALA, 58 patients were treated with Sustained Low-Efficiency Dialysis (SLED), five with CVVHDF one with both, one with CVVHDF and hemodialysis and one with hemodialysis. Fifty-four patients (81,8%) recovered, ten died (15,2%) and two lost follow up. Concerning lithium poisoning (n=4), two performed SLED and two hemodialysis, due to its clinical stability, and they all improved. In organophosphate poisoning, all three patients performed SLED and they all died. In valproate poisoning (n=2), we performed, besides SLED and hemodialysis, plasmapheresis was also performed. In the other case, mixed with other drugs, CVVHDF was done. Two of paracetamol poisonings were treated with CVVHDF, due to the concomitant liver failure and one with SLED. In one case, due to glyphosate poisoning, we performed hemocarboperfusion and the patient improved. We also had a case of iron poisoning were CVVHDF and then SLED performed after clinical improvement. The patient was submitted to successful urgent liver transplant. No patients remained on dialysis.

Table 1: Types of intoxication in our cohort; MALA- metformin associated-lactic acidosis

Type of intoxication	n
MALA	66
Lithium	4
Paracetamol	3
Glyphosate	3
Valproate	2
Barbiturates	1

Benzodiazepines	1
Paraquat	1
Antidepressants	1
Iron	1

Conclusion: In the treatment of poisoning, a quick and multidisciplinary approach is crucial. The prescription of EPT must be made on an individual basis, considering the substance to be purified and the patient's clinical status.
EPT may improve patient outcomes. The advantages of extracorporeal treatments should outweigh costs and complications of the procedure.In our center, we have good results regarding mortality concerning MALA, due to a proactive role of the nephrologist in identifying this ´life-threatening situations. SLED is the most used technique in intoxications in our hospital in the intensive care unit and our results are good.

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MORTALITY AND KIDNEY FUNCTION RECOVERY IN PATIENTS WITH SEPSIS-ASSOCIATED VS NON-SEPTIC ACUTE KIDNEY INJURY TREATED WITH CONTINUOUS RENAL REPLACEMENT THERAPY

Palumbo C.A.[a], La Fergola F. [a], Carparelli S.[a], Gesualdo L[a], Fiorentino M.[a]*

[a]Nephrology, Dialysis and Transplantation Unit, Department of Precision and Regenerative Medicine and Ionian Area (DiMePre-J), University of Bari Aldo Moro.

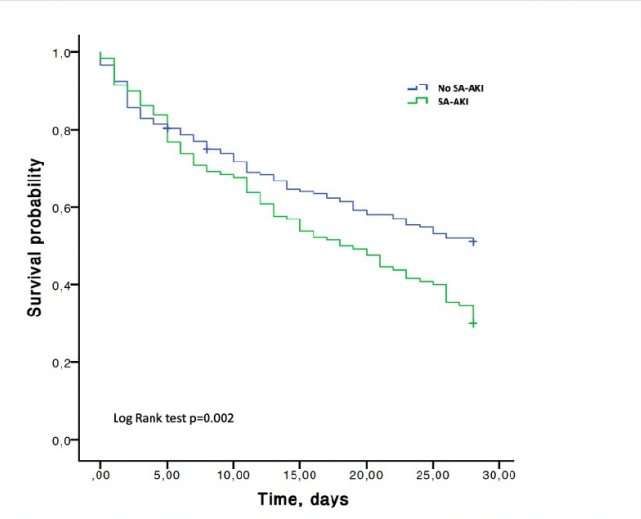
Background and Aims: It was recently suggested that sepsis-associated acute kidney injury (SA-AKI) is characterized by different pathogenesis and outcomes compared to non-Septic AKI (NS-AKI). Due to the limited data on the clinical outcomes of SA-AKI versus NS-AKI, we aim to examine risk factors and outcomes of SA-AKI vs NS-AKI among critically ill patients who developed AKI requiring renal replacement therapy (RRT).

Methods: We performed a single-center retrospective analysis, examining all patients admitted to ICU who developed AKI requiring RRT at A.O.U. Policlinico of Bari, from January 2021 to July 2023. The primary outcome was to assess mortality rate, kidney functional recovery (KFR), RRT discontinuation and ICU and hospital length of stay between SA-AKI and NS-AKI.

Results: 320 patients were included in the study; 131 patients developed SA-AKI (40.9%), while the remaining 189 were NS-AKI (59.1%). A significant percentage of patients had an history of cardiovascular disease in NS-AKI group compared to SA-AKI group (54.5% vs 29%, p<0.001). 268 patients (83.8%) developed AKI Stage 3 and 40 patients reached AKI stage 2 (12.5%) at RRT initiation. All patients were treated with continuous modalities (CRRT). There was no significant difference in CRRT duration between groups (median days 5, IQR 2-12, p=0.845)(**Figure 1**). We reported a late CRRT initiation in the SA-AKI group (3 vs 1 days, p=0.002). In-hospital mortality was reported in 221 patients (69%), with impressive percentages in the SA-AKI group (82.45 vs 69.3%, p<0.001). KFR at 28 days from CRRT initiation was significantly higher in the NS-AKI (28.5%) compared to the SA-AKI group (13.7%, p=0.002). Multivariate Cox Regression analysis showed that only SA-AKI (HR 1.442, 95%CI 1.052-1.978, p=0.023) was independently associated with increased risk of mortality.

Conclusions: Sepsis-associated AKI was associated with high mortality rate and lower likelihood of renal recovery compared to non-septic AKI in critically ill patients requiring RRT.

Figure 1. Main clinical outcomes and Kaplan-Meier analysis among SA-AKI and NS-AKI patients



	All AKI patients (n=320)	SA-AKI (n=131)	NS-AKI (n=189)	P-value
Days on RRT, days, median (IQR)	5 (2-12)	5 (2-11)	5 (2-13)	0.845
Time from ICU admission to CRRT start, days, median (IQR)	1 (0-7)	3 (1-11)	1 (0-4)	0.002
28-day renal recovery, n(%)	72 (22.5%)	18 (13.7%)	54 (28.5%)	0.002
Overall Renal recovery after AKI, n (%)	86 (26.8%)	21 (16%)	65 (34.4%)	0.001
Time of renal recovery from CRRT start, days, median (IQR)	7 (4-16)	7 (4-12)	7 (3.5-17.5)	0.833
Dialysis dependence at hospital discharge, n (%)	16 (5%)	3 (2.3%)	13 (6.8%)	0.059
Length of ICU stay, days, median (IQR)	12 (4-25)	13 (5-26)	11 (3-23)	0.422
28-day mortality, n (%)	184 (57.5%)	92 (70.2%)	92 (48.6%)	<0.001
Overall mortality, n (%)	221 (69%)	108 (82.4%)	113 (69.3%)	<0.001

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HIGHER BUN/ALBUMIN RATIO PREDICTS MORTALITY IN CHRONIC CRITICALLY ILL PATIENTS

E. Holndonner-Kirst[a,b] , *I. K. Karpathi** [a,c], *L. K. Kophazi* [b,c] , *V. Kesztyus*[c,d], *G. Karvaly*[e], *Cs. Hermann*[d,e]

[a] Gottsegen National Cardiovascular Center; [b] Department of Intensive Care, Semmelweis University, [c] Doctoral College, Semmelweis University, [d] Petz Aladár County Teaching Hospital, [e] Department of Laboratory Medicine, Semmelweis University, [e] Széchenyi István University

Background: A high proportion of critically ill patients fail to improve and leave the ICU after the first week of ICU stay. In this late period, persistent inflammation and catabolism characterize the clinical picture. The definition of chronic critical illness (CCI), or persistent critical illness is not well clarified. Usually, it is based on the length of ICU treatment, prolonged mechanical ventilation, and organ dysfunction. The mortality of CCI is high, and, due to the prolonged ICU treatment and several complications, imposes a huge medical challenge and financial burden. High blood urea nitrogen (BUN) implies elevated protein catabolism, kidney injury or impaired fluid balance. Low serum albumin levels are frequently seen in severe inflammation, due to impaired synthesis or capillary leakage. The BUN to albumin ratio (BA) was reported as a predictor of adverse prognosis in critically ill patients. Our aim was to evaluate the prognostic role of BA in chronic critical illness.

Methods: In our prospective, observational study, we included adult patients admitted to our tertiary intensive care unit from February 2022 to June 2023. Primary inclusion criteria were informed consent and need for mechanical ventilation for at least 2 days. CCI was defined as at least 8 days of mechanical ventilation. Extensive laboratory tests were made on admission, and on the 3rd, 7th, 14th, 21st, and 28th of ICU care. CCI and non-CCI patients were compared using chi-square test and Mann-Whitney U-test. We used logistic regression analysis to predict ICU mortality.

Results: 62 patients were included in the study. Overall ICU mortality was 25.8% (16 patients), four patients died during the first eight days of ICU treatment, 12 in the CCI phase. 15 patients were discharged within 8 days, 43 patients met the CCI criteria. Serum albumin levels on day 3 and 7 were lower and BA ratio on day 7 was significantly higher in CCI patients. According to our multivariate analysis, higher BA levels on day 7 and 14 were associated with higher ICU mortality in CCI patients (OR=1.09; 95% CI:1.01-1.17; p=0.022 and OR=1.11; 95% CI:1.00-1.24; p=0.050, respectively). Other renal markers, as creatinine did not influence the outcome in the CCI period.

Conclusion: During chronic critical illness several changes, partially independent of the admission diagnosis influence the outcome. According to our results, blood urea nitrogen to serum albumin ratio is a promising marker of adverse outcome in

the chronic phase of critical illness, but creatinine not. From this point of view, we should reassess the role of traditional renal parameters in this population. Loss of muscle mass plays important role in the pathophysiology of CCI, thereby reducing the sensitivity of the creatinine level. Furthermore, the blood urea nitrogen to serum albumin ratio is a promising marker of the persistent inflammation and catabolism that supports the PIICS hypothesis in the aetiology of CCI.

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ACUTE KIDNEY INJURY IN HIV-INFECTED PATIENTS ADMITTED TO THE ICU

*Bruno Pepe** [ab], *Inês Palmares* [b], *Anna Sukhoviy* [b], *Catarina Morgado* [b], *João Pedro Santos* [b], *Francisco Faustino* [b], *Paulo Freitas* [b], *Silvia Coelho* [b]

[a] Nephrology Department, Hospital de Santa Cruz, Lisboa, Portugal; [b] Intensive Care Departmente, Hospital Fernando Fonseca, Amadora, Portugal;

Background: Acute Kidney Injury (AKI) is characterized by a sudden and often reversible decline in kidney function, with negative impact in short- and long-term patient outcomes. Human immunodeficiency virus (HIV)-infected patients are at an increased risk of developing AKI, particularly for those who are hospitalized. While the widespread use of antiretroviral therapy in the treatment of HIV-infected patients lead to a significant reduction of their morbidity and mortality, Intensive Care Unit (ICU) admission remains frequent. We aim to characterize the epidemiology and outcomes of HIV-infected patients admitted to the ICU with AKI.

Methods: A single-center, retrospective, observational study of HIV-infected patients admitted to the ICU between the 1st March 2019 and the 1st March 2024, including repeat admissions. AKI stage was defined by serum creatinine (sCr) according to the KDIGO classification.
Statistical analysis was performed by IBM SPSS Statistics.

Results: During the study period, there were 75 admissions involving 69 HIV-infected patients, of which 16% were newly diagnosed. The median age was 56 years, with 64% being male and 65% caucasian. The majority of ICU admissions were for non-AIDS-defining conditions (89,3%), mainly sepsis/septic shock (28%), respiratory illness (25,3%), and neurological disorders (16%).

During their ICU stay, 60% of patients required vasopressors and/or inotropes, 64% mechanical ventilation, and 23% renal replacement therapy (RRT). AKI was present in 57,3% of patients upon admission, predominantly at stage KDIGO 2 or 3 (67,4%). Among those with AKI, 39.5% required RRT during their ICU stay, with the majority (88,2%) undergoing continuous renal replacement therapy (CRRT).

Comparison between patients with and without AKI revealed no statistically significant differences in terms of age, gender, ethnicity, or previously known HIV infection. AKI patients had higher values of basal serum creatinine (0.98±0.50 vs

0.76±0.23 mg/dl, p=0.022), but no other statistically significant findings were observed in terms or other laboratory finding, namely viral HIV load or CD4 cells.

The severity of illness, as indicated by a higher APACHE II score (17.4±7.7 vs. 24.2±8.5, p=0.002), was greater in patients with AKI, leading to a higher predicted ICU mortality rate, although no significant differences were identified in terms of SAPS II score (p=0.270).

During the hospital stay, patients with AKI had a higher requirement for vasopressor/inotropic therapy (37.5% vs. 76.7%, p<0.001), invasive mechanical ventilation (50.0% vs. 74.4%, p=0.029), and RRT (0% vs. 39.5%, p<0.001), ultimately resulting in higher ICU mortality (12.5% vs. 32.6%, p=0.044).

After conducting linear regression analysis, AKI emerged as a statistically significant predictor of ICU mortality in HIV-infected patients(p=0.045).

Conclusion: AKI is prevalent among HIV-infected patients in the ICU, and significantly impacts prognosis. Despite the quality of care and interventions, higher illness severity contributes to increased ICU mortality. Early recognition, diagnosis, and targeted interventions, including renal support are crucial for improving outcomes in this population. Future studies should focus on developing biomarkers to detect AKI, as these are pivotal to enhance patient care and outcomes.

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TREATMENT OF OVERDOSE OLENZAPINE AND ARIPIPRAZOL POISONING WITH HEMOPERFUSION.

Oktay Demirkirana, Oguzhan Kayhana, Mert Katilmisa.

aIstanbul University- Cerrahpasa, Cerrahpasa Medical School, Department of Anaesthesiology and Reanimation, Intensive Care Unit.

Background: Olanzapine is one of the newer atypical antipsychotic agents which is being increasingly used, as it is effective in the maintenance treatment of chronic schizophrenia. Olanzapine is associated with toxicity in certain overdose situations, but evidence of any relation is limited and likely influenced by the higher rates of cardiovascular disease and sudden death (1,2). We report succesful treatment with hemoperfusion in olenzapine and apipiprazol overdose intoxicated patient.

Case presentation: 41 year old woman admitted to emergency service following an overdose of 50 tablets of olanzapine and 20 tablets of aripiprazol with an initial Glasgow Coma Scale (GCS) of 15. After gastric lavage in this local hospital the patient developed GCS deteriorated to 7, and she was intubated in view of a deteriorating level of consciousness. Then she transferred to our intensive care unit for critical care. When she admitted to ICU, GCS was 3. She was mechanically ventilated. Oxygen saturation and arterial blood gases were in normal ranges. Further examination revealed a heart rate of 65 beats/ min, blood pressure of 80/50 mmHg and bilaterally constricted pupils, light reflex was bilaterally positive but weak. Noradrenaline started due to hypotension. In addition to conservative treatment the patient received hemoperfusion HA 230 (Jafron) cartidge for 6 hours. Respiratory, cardiovascular, neurological functions returned to normal within 15 hours of ICU admission. She was extubated without any complication. And discharged from ICU on the third day of admission.

Discussion: Possible toxic effects of olenzapin and are likely to be extrapolated from other similar drugs: CNS depression, convulsions and coma, prolonged QT interval and a-v block, hypotension and the development of neuroleptic malignant syndrome. The patient had only CNS depression, with hypotension.

Conclusion: Large overdose involving olanzapine alone that was associated with tachypnia, sinus tachycardia, fluctuating blood pressure, and brief hypoxemia. Aripiprazole led to more gastrointestinal disturbances (nausea, and constipation) (2). In this case the use of hemoperfusion improved the recovery, and prevented the possible severe cardiovascular side effects.

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HEMOPERFUSION TECHNIQUE AS ADJUVANT THERAPY IN MULTIORGAN FAILURE DUE TO SEVERE LEPTOSPIROSIS INFECTION IN HEMODIALISYS PATIENT: CASE REPORT

Vargas, Francisco [a,b] Tomlinson, Jermaine [b,c]*

[a.] Section of Nephrology, Department of Medicine, Hosp. Dr. Ezequiel Abadía, C.S.S, Veraguas, Panama;
[b.]Grupo Nephron, The Panamá Clinic, Pacific Center Tower B.
[c.]Section of Nephrology, Department of Medicine, Hosp. Dr Manuel Amador Guerrero, C.S.S, Colon, Panama.

Background: Severe leptospirosis is a medical emergency and a life-threatening zoonosis; Life-threatening conditions such as Weil's disease (jaundice and acute kidney failure), pulmonary hemorrhage, and central nervous system involvement may develop.
The development of more severe outcomes likely depends on factors related to host and pathogen virulence. Patients with severe leptospirosis experience an uncontrolled immune response, a systemic inflammatory syndrome involving hyperactivation of immune cells and an increase in circulating cytokines (IL-6, IL-10, and TNF-α).
The kidney is the primary target of leptospirosis, with clinical presentations ranging from mild to acute renal failure requiring renal replacement therapy. However, there is little information on the effect of infections by this type of spirochetes in subpopulations such as patients on chronic hemodialysis.
The initial clinical suspicion of leptospirosis is based on the patient's risk factors (potential exposure) and the development of symptoms. It is important to initiate antimicrobial and supportive therapy early, especially in patients with more severe presentations of the disease.
There is evidence that PCR detection in blood samples collected at the time of hospital admission may be more sensitive than culture, and that IgM antibodies are detectable in the blood between 5 and 7 days after the onset of symptoms.
In patients with a severe presentation of leptospirosis, in addition to standard supportive treatment, other alternatives have been proposed such as pulsed steroids, cyclophosphamide, and hemoperfusion membranes.

Methods: A 63-year-old hemodialysis patient presented with chest pain, malaise, and sudden onset dyspnea during his renal replacement therapy. On physical examination, he did not present hypotension, but developed pulmonary crackles, fever, and associated hypoxemia. The patient and family members denied symptoms in the previous days. During the first hours of admission, acute coronary syndrome and Covid -19 were ruled out. Empirical antibiotics were started due to suspicion of an infectious process (pneumonia or bacteremia related to vascular access) and complementary tests were requested (blood cultures, viral serologies and angiotomography).

The admission laboratories showed leukocytosis with neutrophilia (WBC: 28,000; NEU: 95%), severe anemia (HGB: 4.9 g/dl) and hyperbilirubinemia (total bilirubin: 3.70; indirect bilirubin 3.49) and the transaminases showed a slight increase (AST: 323UL) An angiotomography was performed, which ruled out pulmonary thromboembolism, and a brain tomography showed no ischemic or hemorrhagic lesions or findings suggestive of neuroinfection.
Twenty-four hours after admission to the hospital, the patient developed neurological deterioration, characterized by delirium and dilutions, subsequently progressing to moderate encephalopathy. Analysis on the second day of hospital admission showed a significant increase in bilirubin and transaminases (total bilirubin: 8.65; indirect bilirubin: 7.17; AST: 3183 UL; ALT: 1079 UL), evidencing hepatocellular damage.
Due to the clinical presentation and a subsequent epidemiological report on exposure to rats in the patient's area of residence, we requested PCR and serology for leptospira, and ELISA to detect IgM antibody for hantavirus.
Given the patient's clinical evolution, we decided to add a sorbent membrane to the intermittent hemodialysis treatment.

Results and Discussion: We performed hemodialysis with hemoperfusion with HA380 filter on two consecutive days without complications and showing notable clinical improvement after each treatment. At the end of the first IHD + HP, the patient's encephalopathy went from moderate to mild. In addition, markers of liver damage began to decrease (total bilirubin: 7.68; indirect bilirubin: 4.94; AST: 813 UL; ALT: 755 UL).
We gave the patient 24 hours of rest from dialysis therapies, to perform a third IHD + HP on the sixth day of hospital admission. At this time, the patient was fever-free, alert, and without significant neurological alterations.
Confirmatory PCR results for leptospirosis were received and Hantavirus was ruled out. Subsequent analyzes showed a new decrease in bilirubin (total bilirubin: 2.41) and transaminases (AST: 88 UL; ALT: 165 UL).
The rapid deterioration of the general condition in a patient with severe leptospirosis is largely a consequence of the cytokine storm that triggers this type of infection. In these patients, adequate and early treatment is essential, but conventional protocols (supportive therapies) do not involve intervening in the autoimmune cascade. We consider that a large part of our patient's improvement was due to the treatment with sorbent membranes (targeted at the cytokine cascades), even before having the definitive molecular diagnosis.

Conclusion: In patients with leptospirosis with multiorgan involvement, adjuvant treatment with hemoperfusion membranes may be considered due to the development of the cytokine storm that these patients can develop. This phenomenon of exaggerated immune response is one of the factors that can lead to fatal outcomes.

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HEMOADSORPTION (JAFRON HA230) AND APITOXIN POISONING SYNDROME (APIS MELLIFERA). CASE REPORT.

D, Ballesteros[a] *, A Mantilla*[a] *, I Palechor*[b]*, D Rodriguez*[b]

[a] Universidad del Cauca – Colombia

[b] Hospital Universitario San José de Popayán

Background: Wasp and bee stings are associated with a wide range of reactions, ranging from mild local responses (such as swelling, redness, and hives) to life-threatening systemic complications (such as anaphylactic shock, rhabdomyolysis, acute kidney injury, myocardial infarction, acute liver failure and encephalitis). More than 50% of people affected by multiple wasp or bee stings develop acute renal failure, and most of these patients require extracorporeal organ supportive therapies. Currently, there is no established standard treatment; However, the scientific literature has shown that extracorporeal multiorgan support therapies, such as continuous veno-venous hemodiafiltration, hemoadsorption and hemodialysis, have shown benefits in patients who have suffered traumatic contacts with Hymenoptera, with evidence of renal recovery after the medium.

Methodology: A total of four patients undergoing extracorporeal multiorgan support therapy were included, using hemoadsorption with HA-230 cartridge and hemodiafiltration with ST-150 filter, who experienced traumatic contact due to multiple bee stings, during the period between July and September 2023. The procedure consisted of hemoadsorption for six hours a day, followed by continuous veno-venous hemofiltration for 24 hours a day, for a period of three days. Monitoring of patients' clinical characteristics and serum laboratory tests were carried out.

Results: The four patients came from rural areas (100%), all were older adults and worked as farmers. Two of the four patients survived throughout the 90-day observation period (50%). After receiving hemoadsorption therapy followed by continuous veno-venous hemodiafiltration, significant improvements were observed in indicators of liver function, renal function, state of consciousness, and mediators in blood circulation, including creatine kinase (CPK), blood urea nitrogen (BUN).), serum creatinine (CR), C-reactive protein (CRP), among others. In patients who survived, acid-base balance returned to normal levels and kidney function recovered.

Conclusion: Our findings indicate that hemoadsorption with the HA-230 cartridge with continuous veno-venous hemodiafiltration using the ST-150 filter can be effective in the treatment of patients with poisoning syndrome after multiple bee stings, through non-specific elimination. of bee venom and inflammatory cytokines, favoring the improvement of the internal environment and renal recovery.

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NEW KIRPA KIT: A MANUAL DIALYSIS DEVICE FOR LOW- AND MIDDLE-INCOME COUNTRIES IN CATASTROPHIC ENVIRONMENTS

Rizo-Topete Lilia[a], Borbolla- Flores Paola[a], Garza-Treviño Ricardo[a], Gòmez- Villarreal Juan Pablo[a], Hasson Denis[b], Giovanni Ceschia[c].*

[a] Hospital Universitario "Dr. José Eleuterio González", Nephrology department.
[b] Pediatric Critical Care Faculty Group at NYU Langone Hassenfeld Children's Hospital and Bellevue Hospital.
[c] Cincinnati Children's Hospital

Background: The alarming data about the increased incidence of AKI in low - and middle - income countries around the globe is a trigger for research. Not only preventive interventions but also easy and economic performance of renal replacement therapies provide opportunities for treatment in limited environments. On the other hand, natural catastrophes such as earthquakes, hurricanes, heatwaves, and sadly, war environments are other adverse situations that increase AKI with difficult RRT opportunities. After some research, we decided to join forces and work together with Dialysis Without Borders to find a way to help this vulnerable population.

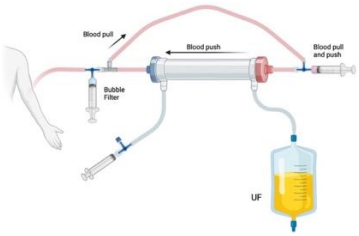
Introduction: Last year, we witnessed in our own hospital an increase in the incidence of AKI for heatwaves, and even if we have most of the essential types of RRT, it is also common to have late arrival and treatment, especially for patients who come from rural centers without resources. Also, in Mexico, we live in the Otis Huracan, which leaves multiple consequences with an inability to perform RRT to victims of AKI and other patients with CKD. To help and improve possibilities, we look forward to using manual dialysis equipment for acute ultrafiltration and, if necessary, offering dialysis to improve the urgent indications of dialysis like hyperkalemia, acidosis, and uremia, as a temporary treatment or a bridge therapy for the treatment needed.

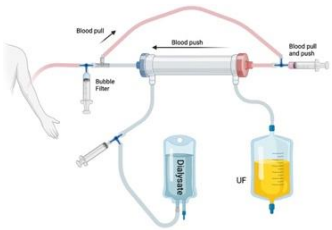
Methods: We introduce the new KIRPA Kit, a manual dialysis device in which we can give ultrafiltration and hemodialysis without the need for electricity and at a very low cost. The miniaturized configuration is shown in Figure 1. As shown, we can pump out blood (60 ml) from the patient through the syringe, which should be in approximately 15 s. Blood passes through the bypass lumen and enters the syringe. Then, the blood will be pumped out of the syringe through the filter to the other side of the filter, ready to return to the patient. When the blood passes through the filter, the dialysate (when HD is performed) will

come from the X syringe through the filter. The ultrafiltration will reach the effluent bag. For patient protection, the bubble filter is a syringe located proximal to the patient that provides bubble protection where the bubbles are trapped.

Results / Discussion: The KIRPA KIT will be a life-changing treatment in clinical scenarios where renal replacement therapy is not accessible treatment, as well as where the patient needs time to get to the final treatment, so KIRPA KIT will work as a bridge therapy to provide time to the patient. It is quite important to perform capacitation before using KIRPA. Although it is simple and quick, one must be able to perform manual dialysis adequately.

Conclusion: The manual dialysis kit is an excellent tool for patients who do not have the necessary and timely access to renal replacement therapy. It is a new and innovative therapy for clinical scenarios where deficiencies, sometimes even of light, wreak havoc on patients with fluid overload or requiring renal replacement therapy.





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ULTRASOUND GUIDED DESCONGESTION IN CRRT AND ITS IMPACT ON KIDNEY RECOVERY

Emmanuel Sigfred Villalobos Arreola Sergio Vazquez Olvera*

Kidney Health Institute. Querétaro Mexico

Background: There is evidence of the damage caused by fluid overload in patients with acute kidney injury and an association with less recovery of kidney function and greater mortality when there is a fluid balance greater than 10% of their weight. In current conceptual models, particularly in the post-resuscitation period, the use of POCUS in the evaluation of venous congestion, performing standardized reassessments for the adjustment of net fluid removal goals, could limit the impact of CRRT ultrafiltrate on perfusion renal, drive diuretic use and biomarkers for withdrawal of renal replacement therapy.

Methods: All patients requiring acute renal replacement therapy will be evaluated in a prospective multicenter manner in second-level hospitals in the city of Querétaro. The patients will be divided into two groups randomly, the first group to the ultrafiltration strategy guided by ultrasound, with two measurements every 24 hours of cardiac output, systolic function of the right ventricle and diastolic dysfunction, plus the VEXUS protocol, the second group to the conventional ultrafiltration strategy guided by hemodynamic parameters, using the Goldstein formula, matching according to severity by Charlson index, SAPS II and APACHE III, without exceeding the ultrafiltration rate 1.01 to 1.75 ml/kg/hr.

At the time of improving renal perfusion by ultrasound, measuring NGAL in the post-phase of resuscitation, initiation of diuretics and withdrawal of renal replacement, comparing major adverse renal events, mortality at 7, 14, 21, 28 and 90 days in both groups.

Results: Male patient, 79 years old, weight 58 kg, height 1.65 m, BMI 21.3, history of hypothyroidism, hypertension and cardiac pacemaker, admitted for abdominal septic shock secondary to post-laparoscopy Candida Glabrata infection, persistent fever 39 to 40 C, ventilation mechanics to nephrology evaluation, with acute kidney injury KDIGO 3, anuria for 36 hours, fluid overload 10 liters in relation to body weight on admission, no response to high dose of diuretic for renal metabolic demand, urinary flow 0.2 ml/kg/hr, upon admission SOFA 12, SAPS-II 71,

APACHE II 31, norepinephrine 0.15 mcg/kg/min, accumulated fluid balance 10 liters on day 13 of admission, NT pro BNP 7866 pg/ml, bilateral pleural effusion 30%, microalbuminnuria in isolated urine >65 mg, urinary sodium 89, basal NGAL 100 ng/ml, at the time of connection 233 mg/ml, IL- 6, 719.12 pg/ml and CRP 321 mg/l, CRRT was started in CVVHDF modality due to fluid overload, persistent fever and inflammatory response, Oxiris membrane is used due to inflammatory state, dose calculated 30 ml/kg/hr and delivered 27 ml/kg/hr, regional anticoagulation with citrate at a dose of 2.8 mmol/l, achieving net ultrafiltration – 2100 a 2300 ml every 24 hours, until remission of overload and extubating, reduction of sepsis parameters and inflammatory response, IL-6 127.9 pg/ml and CRP 82.7 mg/l, spontaneous uresis and response to diuretic infusion, allowing change of modality to online hemodiafiltration and continued support as required due to acute pancreatitis such as complication, transferring the patient to a tertiary hospital for bile duct reconstruction, being the first patient randomized to conduct the study.

Conclusion: After 6 days of treatment with CRRT, due to a non-classical indication of renal replacement, volume overload that exceeds metabolic demand, inflammatory response and persistent fever, the need and addition of POCUS in the nephrologist's evaluation is evident as a promising tool to individualize decisions related to the ultrafiltration rate, the development of dynamic protocols for the adjustment of net fluid removal objectives is required. Ultrafiltration rate and fluid clearance tolerance could be better predicted using dynamic ultrasound markers that influence renal recovery.

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AN EXPLAINABLE MACHINE-LEARNING MODEL FOR PREDICTING PERSISTENT SEPSIS ASSOCIATED ACUTE KIDNEY INJURY: DEVELOPMENT, VALIDATION, AND COMPARISON WITH CCL14

Wei Jianga,b, Yaosheng Zhangc, Jiayi Wengd, Lin Songa,b， Siqi Liud， Siqi Xu a,b, Xianghui Lib, Quan Yuanc, Keran Shia,b, Luanluan Lia,b, Chuanqing Zhanga,b, Jing Wanga,b, Yongwei Zhang, Quan Yuanc, Jun Shaob, Jiangquan Yu b& Ruiqiang Zhengb

a Medical College, Yangzhou University, Yangzhou 225001, China
b Department of critical care medicine, Clinical medicine College, Yangzhou University &Intensive Care Unit, Northern Jiangsu People's Hospital, Yangzhou 225001, China
c School of Clinical and Basic Medicine, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan 250000, China
d School of Economics and Management, Beijing Jiao Tong University, Beijing 100044, China

Background: Persistent sepsis-associated acute kidney injury (SA-AKI) portends worse clinical outcomes and remains a therapeutic challenge for clinicians. Early identification and prediction of persistent SA-AKI is crucial. The aim of this study was to develop and validate an interpretable machine learning (ML) model that predicts persistent SA-AKI.

Methods: Four retrospective cohorts and one prospective cohort were used for model derivation and validation. The derivation cohort utilized the MIMIC-IV database, randomly split into 80% for model construction and 20% for internal validation. External validation is conducted using subsets of the MIMIC-III dataset, the e-ICU dataset, and retrospective

cohorts from the ICU of a Northern Jiangsu people`s hospital. Prospective data from the same ICU were used for validation and compared with urinary CCL14 biomarker measurements. AKI was defined based on serum creatinine and urine output, using the kidney disease: Improving Global Outcomes (KDIGO) criteria. Routine clinical data within the first 24 hours of ICU admission were collected, and eight ML algorithms were utilized to construct the prediction model. Multiple evaluation metrics, including the area under the receiver operating characteristic curve (AUC), were employed to compare predictive performance. Feature importance was ranked using SHAP, and the final model was explained accordingly.

Results: Among eight ML models, the Gradient Boosting Machine (GBM) model demonstrated superior discriminative ability. Following feature importance ranking, a final interpretable GBM model comprising nine features was established. The final model accurately predicted the occurrence of persistent SA-AKI in both internal (AUC = 0.872) and external validation cohorts (MIMIC-III subset: AUC = 0.889, e-ICU dataset: AUC = 0.930, North Jiangsu people`s Hospital retrospective cohort: AUC = 0.942). In the prospective cohort, the GBM model outperformed urinary CCL14 in predicting persistent SA-AKI (GBM AUC = 0.850 vs. CCL14 AUC = 0.821). Additionally, the model has been transformed into an online clinical tool to facilitate its application in clinical settings.

Conclusions: Our interpretable GBM model successfully and accurately predicts the occurrence of persistent SA-AKI, alleviating concerns regarding the "black box" nature of ML techniques through non-direct interpretation

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EXPLORING THE ROLE OF FREE FRACTION *PROTEIN-BOUND SOLUTES* IN PREDICTING IMMUNE-RELATED COMPLICATIONS IN CHRONIC KIDNEY DISEASE

Valentina Corradi[a,b], Carlotta Caprara[a,b], Elena Barzon[c], Nenzi Marzano[b], Cecilia Mattarollo[c], Fiammetta Zanetti[b,d], Fiorenza Ferrari[b,e], Faeq Husain-Syed[b,f], Davide Giavarina[c], Claudio Ronco[b,g], Monica Zanella[a,b]*

[a]Department of Nephrology, Dialysis and Transplantation, Ospedale San Bortolo, AULSS8 BERICA Vicenza, Italy, [b]International Renal Research Institute of Vicenza IRRIV Foundation, Ospedale San Bortolo, AULSS8 BERICA Vicenza, Italy, [c]Department of Laboratory Medicine, Ospedale San Bortolo, AULSS8 BERICA Vicenza, Italy [d]Department of Behavioural and Cognitive Sciences, University of Luxembourg, Esch-sur-Alzette, Luxembourg, [e]Department of Emergency-Urgency, IRCCS Ca' Granda Foundation - Ospedale Maggiore Policlinico, Milan, Italy, [f]Department of Internal Medicine II, University Hospital Giessen and Marburg, Justus-Liebig-University Giessen, Klinikstraße 33, 35392, Giessen, Germany, [g]University of Padova, Department of Medicine (DIMED), Padova, Italy

Background: The activity, distribution, and clearance rate of the biologic compound are limited by its albumin-binding, determining its free fraction concentration. Some *protein-bound solutes* are bonded to the transport protein Human Serum Albumin (HAS), the most abundant (50%) in human plasma. Organic-anionic uremic toxins, such as indoxyl sulfate (IXS) and p-cresyl sulfate (pCS), have low molecular weight, which should be removed by HD. Their quantification is not always available in routine clinical practice due to its cost and the need for specific technologies. Despite their interest as therapeutic targets, knowing the ratio of free plasma fractions of protein-bound solutes, might provide valuable insights to stratify the risk of immune-mediated complications in CKD. Additionally, a multilevel understanding of the different elements involved (e.g., diet, individual microbiota composition, genetic background) may facilitate a personalized approach, especially considering multiple variables that impact uremic toxins levels, as well as recent adsorptive membrane-based strategies targeting *protein-bound solutes* removal.

In the present study, total (t) and free fractions (f) of p-cresyl sulfate (pCS) and indoxyl sulfate (IXS) were measured to evaluate their role as surrogate markers of renal function according to the GFR (G) categories using contemporary eGFR equations.

Methods: We performed an observational, prospective, single-center study involving CKD patients not on maintenance dialysis. We enrolled patients aged ≥18 years who visited our outpatient nephrology clinic at the Department of Nephrology, Dialysis, and Transplantation, San Bortolo Hospital, Vicenza, Italy. Liquid chromatography/tandem mass spectrometry has been applied for the identification and quantification of total (t) and free fractions (f) of p-cresyl sulfate (pCS) and indoxyl sulfate (IXS). All reagents (mobile phases, precipitant solution, internal standards, calibrator and control set), analytical column and filters, were provided by the FloMass®paraCresylSulphate/IndoxylSulphate kit (BSN Srl Biological Sales Network, Castelleone, Cremona, Italy).

Results: We evaluated 80 patients (55±13 years); 41 M. We found a statistically significant increase of total and free fractions of pCS and of IXS across the CKD spectrum according to the GFR (G) categories using contemporary eGFR equations. ($p<0.001$). A significant negative correlation was observed between eGFR (any equations) and plasma concentrations of pCS and IXS (all p-values < 0.001). The increase of pCSf and IXSf, and their correlations are represented in Figure 1. Representative ion chromatograms of one sample obtained from analysis of pCS and IXS, are shown in Figures 2 and 3 respectively.

Conclusions: Our results show that free fraction as well as total concentrations of pCS and IXS, are negatively correlated with eGFR (any equations) in CKD patients, not on maintenance dialysis. The correlation remained good using all three equations for eGFR estimation. In this study, we clinically validated a fast and sensitive LC-MS/MS method to identify and quantify the total and free fraction of IXS and pCS in plasma. Mass spectrometry allows the identification of compounds in very minimal concentrations and with a limited sample quantity, making the technique optimal for the detection of these uremic toxins. Particularly, the significant increase of free fractions of pCS and IXS, across the CKD spectrum defined by GFR (G) categories, suggests the possibility of identifying better patients at risk, in the challenge to predict renal function and CKD progression. We highlight the use of mass spectrometry in exploring the role of free fraction of protein-bound solutes, facilitating the development of further therapies by their monitoring, considering its capability to detect very low concentrations. Hemoadsorption combined with Hemodialysis (HA-HD) might be the most appropriate method to correct this retention and further study will be necessary to clinically demonstrate its efficacy.

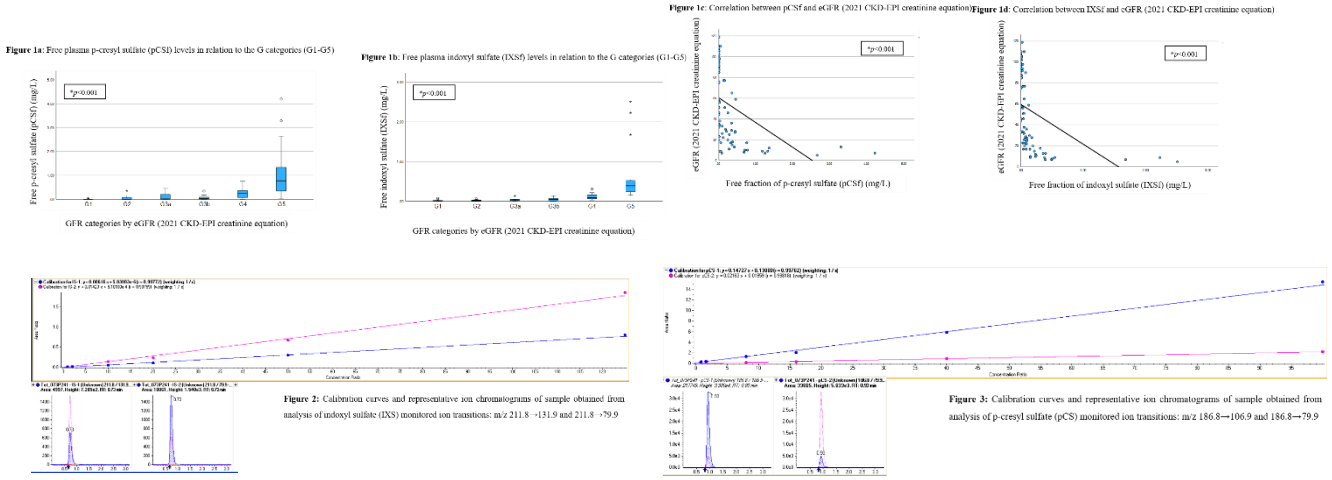

Figure 2: Calibration curves and representative ion chromatograms of sample obtained from analysis of indoxyl sulfate (IXS) monitored ion transitions: m/z 211.8→131.9 and 211.8→79.9

Figure 3: Calibration curves and representative ion chromatograms of sample obtained from analysis of p-cresyl sulfate (pCS) monitored ion transitions: m/z 186.8→106.9 and 186.8→79.9

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THE IMPLEMENTATION OF ACUTE KIDNEY INJURY ELECTRONIC ALERT AND CARE BUNDLE SYSTEM IN A TERTIARY CARE CENTRE

*Toh Jia Pei April[a], Liew Zhong Hong[a], Kaushik Manish[a], Leong Yun Zhen Nicholas[b], Lew Suet Fen Nancy[b], Koniman Riece [a], Tan Han Khim[a], Teo Su Hooi[a]

[a] Department of Renal Medicine Singapore General Hospital; [b] Medical Informatics Office Singapore General Hospital

Background: The growing interest in electronic notifications or alerts in the management of acute kidney injury (AKI) has led to numerous studies on its implementation and effects on patient outcomes. Despite the promise of technological advancement in improving healthcare delivery, most trials evaluating AKI electronic alert (e-alert) have failed to demonstrate major impact on clinical outcomes. We aim to describe the implementation of an AKI e-alert system in order to aid in timely detection of AKI.

Methods: We developed an automated electronic alert system using the KDIGO definitions of AKI in our electronic health record system (EHR system). The AKI e-alert interrogates serum creatinine for each inpatient once a day and detects any creatinine changes consistent with AKI, including resolving AKI (improvement of serum creatinine ≥ 26.5 µmol/L over the past 48 hours). The non-interruptive alert encompasses an AKI Care Bundle consisting of good clinical practices of AKI including volume assessment, avoidance of nephrotoxic agents, escalation of therapy or referral to a nephrologist if necessary. We randomly selected 108 inpatient adults aged 21 years or older from various wards and specialties in Singapore General Hospital in March 2024 and ran AKI e-alert algorithm to detect any occurrence of AKI. We reported the sensitivity and specificity of our AKI e-alert system.

Results: Median age of patients was 67 years old and 58 (53.7%) were male. Majority were Chinese (76 or 70.4%), followed by Malay (16 or 14.8%) and Indian (12 or 11.1%). Majority had no underlying chronic kidney disease (CKD) (63.0%), and 27

(25%) of patients had CKD stage 3 and above. Of the 108 patients, 51 patients had AKI and 4 had resolving AKI detected by AKI e alert system. The most frequent cause of AKI was noted to be multifactorial (27.5%), followed by sepsis-associated (9.8%), cardiorenal syndrome (5.8%) and hemodynamic instability (3.9%). In-hospital mortality was 23.2% (25 patients). Median length of hospitalization was 18 days. If resolving AKI is excluded as true AKI, our AKI e alert had 100% sensitivity and 93.0% specificity.

Conclusions: The timely detection of AKI by AKI e-alert system allows timely administration of AKI care bundle and can potentially improve the outcomes of inpatient AKI. Further studies should be carried out to evaluate the long-term outcomes of resolving AKI that are not referred to nephrology or general medicine. This study demonstrated that an automated algorithm on delta check of serum creatinine can detect and alert AKI to the managing team. However, future studies should be carried out to evaluate the utility of AKI e-alert system in improving patient outcomes with the understanding of potential for alert fatigue among practitioners.

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LINEZOLID CONCENTRATION AT DIFFERENT RENAL FUNCTION AND DURING CONTINUOUS VENO-VENOUS RENAL REPLACEMENT THERAPY: A RETROSPECTIVE STUDY

**Beatrice Brunoni[a], Stefano Agliardib, Leonardo Baggioa, Irene Sironia, Roberto Fumagallia,c, Thomas Langera,, c*

aDepartment of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy; bDepartment of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy; cDepartment of Anesthesia and Intensive Care Medicine, Niguarda Ca' Granda, Milano, Italy.

Background. Variability in plasma drug levels, including antimicrobials, is a significant concern in critical care settings due to factors such as volume of distribution of patients, albumin concentration, kidney function, and use of extracorporeal blood purification systems. Linezolid, a low molecular weight oxazolidinone, has a volume of distribution of 0.5-0.6 L/Kg in adult patients. It is primarily metabolized by the liver and excreted only partially (33%) by the kidneys. The therapeutic window for Linezolid is narrow, between a Therapeutic Drug Monitoring (TDM) of 2 to 7, mg/L, and no adjustment for renal function are required.

Few studies reported different percentual of thrombocytopenia at different renal functions. This study aims to explore TDM across varying levels of renal clearance and in CRRT.

Methods. This retrospective study was conducted in the General Intensive Care of Niguarda Hospital from January 1 to December 30, 2023. We included all patients with Linezolid TDM analyzed on the third day of antibiotic therapy. Linezolid was administered either as a bolus or via continuous infusion, at a daily dose of 1200 mg. TDM was measured by the central laboratory. The total clearance of Linezolid was calculated as dose (mg/die) divided by TDM (mg/L). The area under the

curve (AUC) was expressed in mg * h/L. Data on measured creatinine clearance, weight, albumin concentration, and episodes of thrombocytopenia were collected. Patients were stratified into four groups based on measured creatinine clearance, with a separate group for CRRT patients. Details on CRRT machine modalities and characteristics such as citrate infusion rate, reinfusion fluid rate, and dose were documented.

Results. A total of 48 patients were included, according to creatinine clearance 11 patients with clearance ≤ 30 ml/min; 12 patients with clearance of 31-100 ml/min, 5 patients with a clearance > 100 ml/min, and 20 undergoing CRRT. All patients in the CRRT group were treated with Continuous venovenous hemofiltration (CVVH) using the Prismaflex system with diluted citrate in pre-infusion (1385 ± 104 ml/h) and reinfusion fluid (1360 ± 167 ml/h) at a dose of 34± 6 ml/Kg/h. All patients in this group were oligoanuirc with diuresis <0.5 ml/kg/h. The main characteristics of patients and antibiotics therapy are described in Table 1.

Conclusion. The TDM in our critical care populations demonstrates considerable variability. Our findings indicate significant differences in Linezolid plasma levels depending on renal function, necessitating close monitoring to optimize therapeutic dose.

Table 1. *Characteristics of patients and antibiotic plasma level and kinetic in population divided for creatinine clearance and CRRT.*

	$Cl_{creatinine}$ ≤30 ml/min (11 patients)	$Cl_{creatinine}$ 31-100 ml/min (12 patients)	CRRT (20 patients)	$Cl_{creatinine}$ > 100 ml/min (5 patients)	p-value
Weight (Kg)	78 ± 15	77 ± 15	87 ± 24	81 ± 27	0.54
Female n (%)	3 (27%)	3 (25%)	9 (45%)	2 (40%)	0.673
Albumin (g/dL)	2.4 ± 0.5	2.6 ± 1.9	2.6 ± 0.5	2.7 ± 0.7	0.58
TDM (mg/L)	14.1 ± 12.5	4.5 ± 3.8	6.5 ± 4.6	2.6 ± 1.6	0.007
Cl tot (L/h)	8.7 ± 10.6	27.9 ± 46.7	15.3 ± 17.5	27.4 ± 9.6	0.02
AUC (mg * h/L)	339 ± 299	116 ± 7	155 ± 110	61 ± 3	0.07
Thrombocytopenia n (%)	2 (18%)	0 (0%)	4 (20%)	0 (0%)	

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PROENKEPHALIN AND VITAMIN D METABOLISM IN CRITICALLY ILL PATIENTS WITH MULTIORGAN FAILURE

Cameron L1, Hartmann O2, Schulte J2, Ledwaba-Chapman L3, Forni LG4, Seylanova N1, Wang Yanzhong3, Arlt B2, DAmato F1, Kosifidou E1, Engelhard C1, Radcliffe G1, Ostermann M1

1 Department of Critical Care, Guy's & St Thomas' NHS Foundation Trust, London, UK;
2 SphingoTec GmbH, 16761 Hennigsdorf, Germany;
3 Department of Population Health Sciences, King's College London, London, UK;
4 School of Medicine, University of Surrey, Guildford, Surrey, UK

Background: Vitamin D deficiency is associated with a higher risk of mortality in critically ill patients and worse outcomes. The final conversion and bioactivation from 25(OH) to 1,25(OH)2 vitamin D takes place in proximal tubular cells. Critically ill patients with moderate to severe acute kidney injury (AKI) have been shown to have significantly lower serum 1,25(OH)2 vitamin D concentrations than similarly sick patients without AKI. Whether serial levels of the AKI biomarker proenkephalin A 119-159 (penKid) correlate with vitamin D metabolism and affect kidney function is unknown.

Methods: In this prospective, observational study in two centers in the UK, critically ill patients with and without AKI according to Kidney Disease Improving Global Outcomes (KDIGO) criteria underwent serial measurement of 25(OH) vitamin D, 1,25(OH)2 vitamin D, creatinine and penKid in serum or plasma for five days.

Results: Serial data of 137 patients with multiorgan failure were analysed. Seventy-one patients had AKI stage II/III of whom 23 recovered kidney function during the 5-day period. Sixty-six patients did not have AKI at enrolment of whom 14 developed new AKI. PenKid was increased in patients with AKI at enrolment (Figure 1) and decreased over time in patients who recovered kidney function (Figure 2). Correlations between AKI trajectories, penKid trajectories and 1,25(OH)2 vitamin D metabolism were observed (Figures 1-3).

Conclusion: PenKid and 1,25(OH)2 vitamin D are altered in AKI patients. Further research is needed to investigate the role of penKid in identifying patients with progressive vitamin D deficiency during critical illness.

Figure 1. Proenkephalin by AKI at enrolment

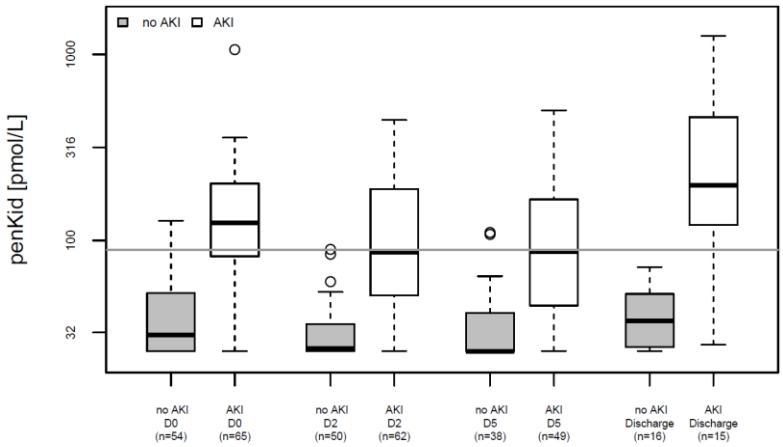


Figure 2 Proenkephalin concentrations by kidney function trajectories

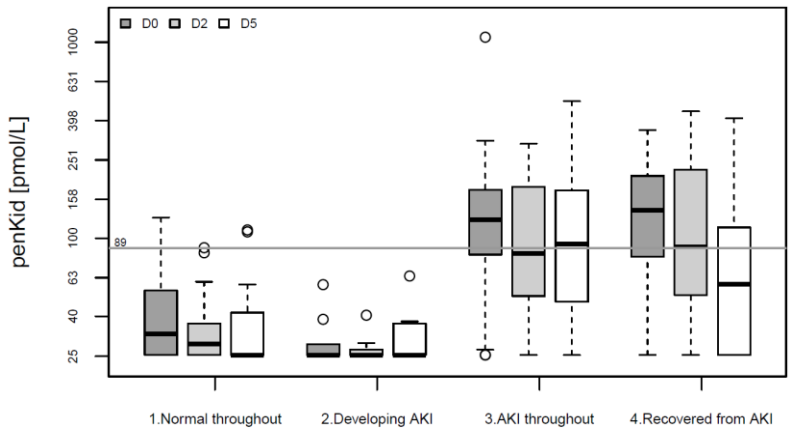
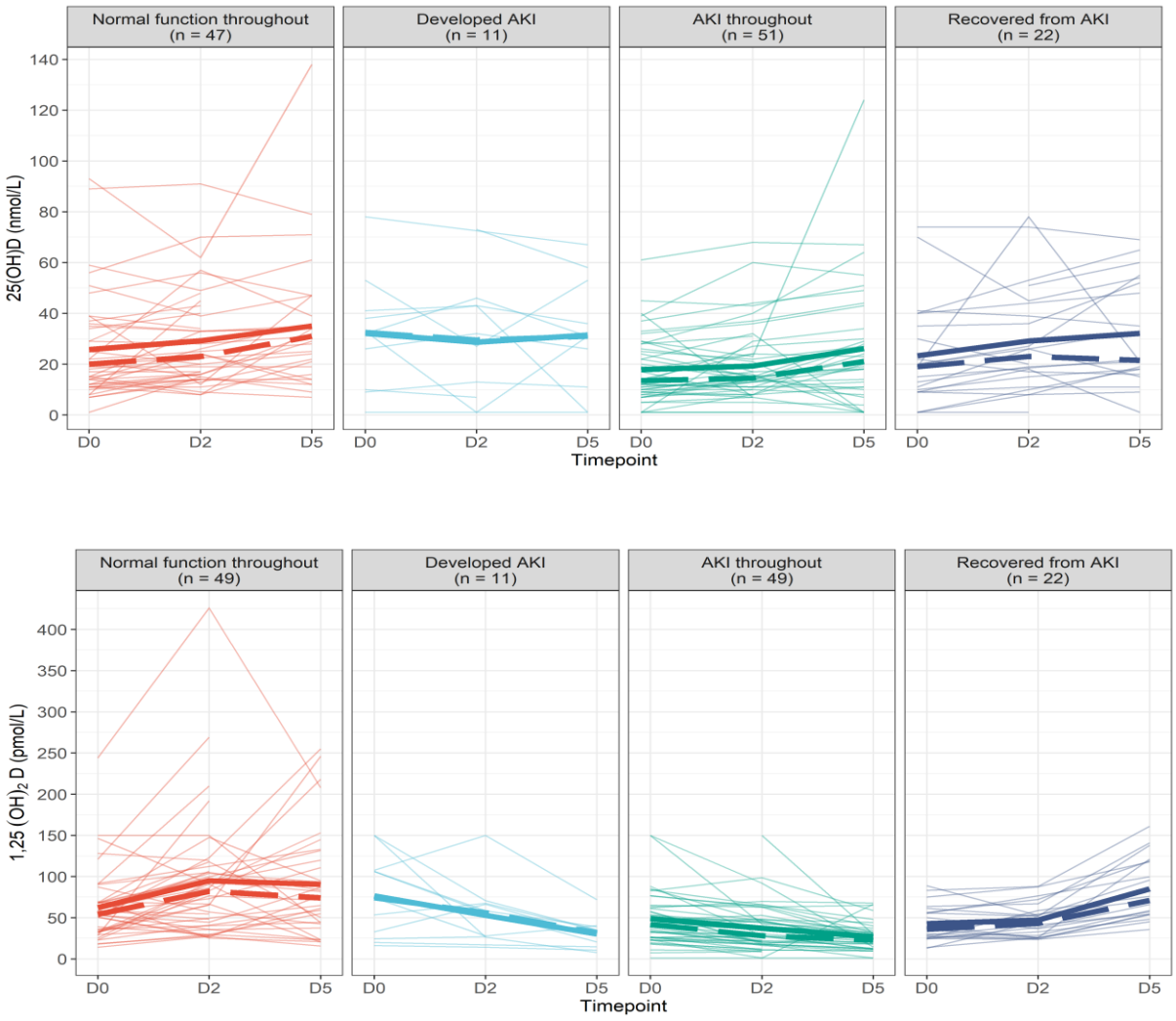


Figure 3 25(OH) and 1.25 (OH)2 vitamin D by kidney function trajectories



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EFFICACY OF HEMADSORPTION WITH HA-330 ADSORBER IN INTRAABDOMINAL SEPSIS

Oktay Demirkiran a, Oguzhan Kayhan a, Mert Katilmis a

a Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Department of Anaesthesiology and Reanimation, Intensive Care Unit

Background: Severe sepsis has a very poor prognosis, and the mortality rate varies between 30 and 70% during the first 7–14 days. Early and effective treatment is very important to improve the survival. Hemadsorption is a spesific treatment in septic shock which allows to remove cytokines, and restore the organ dysfunction and improve the outcomes. In this case, we present the efficacy of early and long duration of hemadsorption treatment in intraabdominal sepsis patient.

Case presentation: A 72-year-old female patient admitted to ICU after major gynecological operation due to overian cancer. She was intubated, and hemodynamically unstable. Blood pressure was 90/50 mmHg, HR 140/min. In arterial blood gases (ABG); pH: 7.29, pO2: 92,1 mmHg, pCO2: 37,6 mmHg, sO2: 94%, Lactate:7.1 mmol/L, HCO3: 18.1 mmol/L, BE: -7.7 mmol/L. There was grade 3 mottling. Noradrenaline and dopamin used for hemodynamic management during the operation, and the doses increased (noradrenaline-1,0 mcg/kg/min, dopamin-5 mcg/kg/min) in ICU. There was no response to fluid resuscitation. Leucocyte, serum C-Reactive Protein (CRP) and serum procalcitonin levels were high (25230/mm3, 367 mg/L, 57 ng/mL respectively). SOFA Score was 11, APACHE II score was 20. Empiric antibiotherapy (meropenem, teikoplenin and anidulafungine) was started. This patient was diagnosed with septic shock, and her clinical conditions gradually worsened despite the antibiotic and the supportive therapy. She had olguria. Continuous renal replacement therapy

(CRRT) with hemadsorption filter (Jafron® HA330) was started. Hemadsorption therapy (HA) was performed for 3 consecutive days for 24 hours. In microbiological culture results, Kleibsiella, MDR Acintobacter, enteroccci were isolated in intraabdominal material, and MDR Acinetobacter in blood culture, and the antibiotherapy revised (meropenem, teikoplenin, kolistin) due to the results. Acute phase reactants regressed, hemodynamic, and oxygenation improvement was observed gradually (Table 1). The hemodynamic support discontinued at the end of hemadsorption therapy. On the 18th day the patient discharged to ward.

Conclusion: HA330 is characterized by a hemoperfusion cartridge with an electrically porous resin used specifically to remove cytokines, complements, and other endotoxins with molecular weight of 10–60 kDa. It is used primarily during acute and severe clinical conditions associated with a cytokine storm, as it can occur during sepsis. In this case we suggested that the hemoadsorption with HA330 cartridge may be an effective and relatively safe adjunctive treatment to counterbalance the cytokine storm in septic patients in rapid hemodynamic stabilization and increased survival, particularly in patients in whom therapy was started early. We believe that long duration use is more effective in improvement and stabilization.

Table 1. Major clinical and laboratory results.

	Before HA	1st day HA	2nd day HA	3rd day HA	After
MAP (mmHg)	55	60	65	70	75
HR (/min)	125	115	106	95	80
Noradrenaline (mcg/kg/min)	1.0	0,9	0,6	0,1	-
Dopamine (mcg/kg/min)	5	5	5	-	-
CRP (mg/L)	367	393	407	363	158
PCT (ng/mL)	57	23	10	5,74	1,48
Ferritin (ng/mL)	501	1728	851	640	500
SOFA score	10	9	6	5	4
Hb (g/dL)	9,7	11,8	9,9	10,0	10,2
Htc (%)	29,4	35,9	33,4	29	31,1
PaO_2/FiO_2	170	195	233	232	250