“CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY in BUCHAREST
DOCTORAL SCHOOL
GENERAL MEDICINE

EXTRA-RENAL PURIFICATION METHODS IN NEONATES AND INFANTS

PhD THESIS ABSTRACT

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Contents of PhD Thesis Abstract

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Introduction

Acute kidney injury (AKI) has an incidence in the paediatric population of up to 5%, but in patients admitted to intensive care units it can reach up to 50% [1]. A special category is represented by neonates, in whom the diagnosis and treatment of AKI is a continuous challenge. This fact is the consequence of the variability of renal function in relation to gestational age and postnatal age.

For a long time, peritoneal dialysis was the only modality for acute renal replacement. Recently, in developed countries, Continuous Renal Replacement Therapy (CRRT) is increasingly used, while peritoneal dialysis has remained an option, especially for chronic renal replacement or in patients with very low body weight, in whom it is not technically possible to initiate the CRRT.

Since 2015, the "Maria Sklodowska Curie" Emergency Clinical Hospital for Children in Bucharest is the only centre in South-Eastern Europe where CRRT is practiced in neonates. The idea of this study came from the desire to deepen and improve renal replacement techniques. To our knowledge, there is no similar study including neonates and infants conducted in recent years in this part of Europe. Some data on neonatal CRRT are provided by The Prospective Paediatric Continuous Renal Replacement Therapy (ppCRRT) Registry [2].

This paper consists of two parts, a theoretical part and a special part. The first part includes a brief presentation of the diagnostic features of AKI in neonates and infants, the main aetiologies of AKI in this age group and renal replacement therapy. The principles, technical modalities, dialysis parameters, monitoring, complications, but also certain features of renal replacement methods according to the AKI aetiology are described. For CRRT, the technique and prescription were taken and adapted from the experience gained in adults. Currently, internationally, there are no regulations regarding the use of CRRT in neonates. Technical difficulties continue to exist and special efforts are being made to create equipment dedicated to these patients.

In the special part, a detailed, comparative analysis is made of classical renal replacement therapy (peritoneal dialysis) versus CRRT. Advances in cardiovascular surgery have created a new category of patients who developed AKI and required extensive intensive care measures. The group of patients who developed AKI after cardiovascular surgery was analysed and an attempt was made to establish the risk factors for the development of AKI, the optimal renal replacement method, the technical features and the subsequent evolution

of these patients. Other revolutionary intensive care techniques (extracorporeal membrane oxygenation - ECMO and cytokine filter) used in conjunction with CRRT were also analysed.

The findings of this study will contribute to better care of neonates and infants with AKI. Treatment of AKI was until recently a missing link in the care of critically ill neonates. The improvement of renal replacement techniques and the early initiation of this therapy will increase the survival rate of these patients. In practice, most of the time, this technique was used “as a therapeutic last resort”

Chapter I - GENERAL PART

Acute kidney injury (AKI) represents an acute reduction in renal function, followed by progressive retention of creatinine and nitrogenous products, making it impossible to regulate the homeostasis of fluids and electrolytes. In the case of neonates, the diagnosis of AKI is sometimes difficult to establish due to their peculiarities related to renal blood flow, glomerular filtration rate, serum urea and serum creatinine values and the ability to concentrate urine, which are in a permanent change.

A comprehensive review by The Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) determined that the incidence of AKI is high in the neonatal population (30% of neonates hospitalized in tertiary care centres) and is associated with increased mortality [3]. The aetiology of renal dysfunction in this population is represented in 85% of cases by prerenal events. At the same time, it is known that 20-25% of the medication prescribed in paediatric intensive care units has nephrotoxic potential [4].

An important category is *post-cardiovascular surgery AKI*. Current data show a global incidence of AKI after cardiovascular surgery of 30-40% of cases [5]. In the case of neonates, the percentage is higher, reaching 64% [6] and even 71% [7], depending on the complexity of the surgery. Renal replacement therapy is required in only 1% of paediatric patients who underwent surgery, but may be as high as 10% in the neonatal population [7].

Sepsis is another important aetiology for AKI. AKI occurs in 26% of neonatal patients with sepsis and mortality can reach 70% [8].

Abdominal compartment syndrome can cause AKI primarily by decreasing renal arterial and venous flow, which associates congestion and renal oedema, and secondarily a direct compressive effect on the kidneys. At their level, there is thus a double injury, the so-called "compartment included in another compartment syndrome*"* [9].

Fluid overload (FO), regardless of whether it is caused by renal dysfunction or not, can degrade renal function by causing renal interstitial oedema, with increased renal venous pressure and decreased renal arterial flow. It is important to know the percentage of fluid overload (FO) [10][11]. When the FO value exceeds 20%, it is associated with increased mortality, as shown by a study carried out by the Prospective Paediatric Continuous Renal Replacement Therapy (ppCRRT) Registry [12]. Mortality appears to increase by 3% for

every 1% “fluid overload” [13]. Piggot et al. claim that a percentage of FO greater than 30% is associated with 100% mortality [14]. The most recent recommendations are that, until KDIGO (Kidney Diseases Improving Global Outcomes) criteria are met for the diagnosis of AKI, to consider that small variations in FO may be a warning signal and initiate early diuretic treatment or renal replacement therapy [7].

The incidence of *AKI post neonatal asphyxia* is 41.6%, as shown in the AWAKEN analysis **Error! Reference source not found.**, but there are authors who claim that up to 70% of neonates with perinatal asphyxia may develop AKI of various degrees [16].

Preemies represent another category at increased risk for the occurrence of AKI. It is known that nephrogenesis continues even 40 days after a premature birth, but the morphology of the nephrons is abnormal in a high percentage [17][18]. AKI is found in association with many of the pathologies specific to prematurity. Thus, the incidence of AKI in neonates with patent ductus arteriosus is 20-40% [19], more than 50% of preemies with cerebral haemorrhage will develop AKI [20] and 50% of preemies with necrotizing enterocolitis may develop AKI [21][22]. Many authors have found a close association between AKI and chronic lung disease [23]. Other authors claim that retinopathy of prematurity and AKI have similar mechanisms of occurrence explained by microangiogenesis caused by reactive oxygen species and VEGF (vascular endothelial growth factor) [24].

In the neonatal period, AKI appears very rarely as a single pathology. Most of the time, AKI is part of a set of multiorgan conditions. The therapeutic strategy, in this context, targets several areas. In the first stage, the specific treatment of the cause that led to the AKI is attempted. Then increased attention is paid to fluid and electrolyte management, nutritional support, and medication adjustment based on the glomerular filtration rate.

Renal replacement therapy is instituted when medical treatment has failed. It is estimated that in the paediatric population with AKI, approximately 5.8% of patients require renal replacement therapy [25]. In neonates, the percentage can reach 10% depending on the AKI aetiology [7]. An extensive ESCAPE Network analysis from 2019 that included 35 Paediatric Nephrology centres in Europe concluded that the most used acute renal replacement methods are peritoneal dialysis (PD) 39.4% and continuous renal replacement therapy (CRRT) 38.2%, followed by haemodialysis 22.4% [26].

Peritoneal dialysis in neonates and infants involves a technique similar to the procedure used in the case of adults, but adapted to the lower weight of the patient. A number of pathologies are absolute contraindications to peritoneal dialysis. We are talking about:

congenital defects of the diaphragm and defects of the abdominal wall (omphalocele, gastroschisis, bladder exstrophy). The procedure should be performed with caution in patients with ventriculo-peritoneal drainage, "Prune belly" syndrome, acute abdomen, recent abdominal surgery or respiratory failure in the absence of mechanical ventilation [27]. Also, this procedure has reduced effectiveness in the case of patients with low cardiac output when the splanchnic circulation is compromised. The presence of gastrostomies, ileostomies, colostomies or vesicostomies is not a contraindication for performing peritoneal dialysis.

Continuous Renal Replacement Therapy (CRRT) has been used in adult therapy since 1977, and in 1985 the first neonate patient who underwent continuous arteriovenous haemofiltration (CAVH) was reported (Ronco C-Vicenza, Italy). Later, the technique was improved by introducing a blood pump that draws blood into the circuit, so that the arterio-venous gradient was no longer necessary. This allowed the simplification of the technique, using only the venous vascular access. Over time, more and more efficient equipment was developed. Initially, for paediatric use, it was attempted to fit paediatric circuits into adult equipment. In 2015, the first case of a neonate in whom special equipment created for this age category was used was published, and since then there has been a permanent concern in this direction [28]. Unfortunately, the initiation of continuous renal replacement therapy (CRRT) in neonates and young infants is associated with a number of technical difficulties related in particular to the vascular access, and there are very few centres internationally where this procedure is performed.

The goal of continuous renal replacement therapy is to mimic the role of the kidney by removing toxic substances produced and fluids that have accumulated in excess. A semipermeable membrane is used, which allows the passage of water and low to medium molecular weight molecules according to a concentration and/or pressure gradient. Together with the unwanted dissolved substances, other useful substances for the body are also extracted. These, together with part of the extracted water, are reintroduced into the body using the replacement solution. There are several subcategories of CRRT, illustrated in [Figure 1].

- *Slow continuous ultrafiltration (SCUF)*. In this technique, only ultrafiltration is used, without liquid replacement. It is indicated in the treatment of refractory fluid overload, with or without renal dysfunction.
- *Continuous veno-venous haemofiltration (CVVH)*. This technique is characterized by an increased clearance of dissolved substances and requires replacement fluid.

- *Continuous veno-venous haemodialysis (CVVHD).* This technique uses a diffusion process, that is, the movement of molecules across the membrane according to a concentration gradient created by the dialysis fluid.
- *Continuous veno-venous haemodiafiltration (CVVHDF).* Both dialysis fluid and replacement fluid are required to perform this technique.

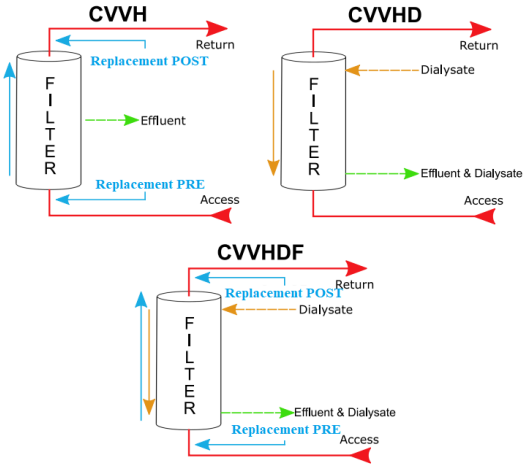

Figure 1: Schematic diagram of the main therapeutic modalities used in CRRT.
CVVH (Continuous veno-venous haemofiltration). CVVHD (Continuous veno-venous haemodialysis).
CVVHDF (Continuous veno-venous haemodiafiltration).
(Adapted from Sethi SK [29])

The success of CRRT is highly dependent on vascular access. The internal jugular vein is preferred, especially the right one, because it is wider and has a direct path into the superior vena cava [29]. The femoral veins are the second option because, although they are more accessible, they have a greater potential for recirculation, interfere with patient movement and increase intra-abdominal pressure. They also appear to be at increased risk of infection and thrombosis [30].

The prescription is sometimes difficult to establish and is adapted according to the pathology and the characteristics of the patient. The values used in paediatric practice are extrapolated from adults. Thus: the *blood flow rate* (is between 3-10 ml/kg/min [29], the *dialysate rate* is around **15-25 ml/min/m^2** [8] or **2.5-3 l/1.73 m^2**, the *replacement* rate is **20-30 ml/kg/hour** [8], the *effluent dose*, which in practice represents the clearance of low molecular weight substances such as urea, is **20-25 ml/kg/hour** [30][31], *fluid removal* is **0.5–2 mL/kg/h** or 1–3% of blood volume/hour, *ultrafiltration rate* is **10–20 mL/kg/hour** [30]. All this must lead to a *filtration fraction* (the fraction of water that is removed from the blood) of less than 20-25%, avoiding haemoconcentration and the risk of thrombi in the circuit [32].

Anticoagulation of the system is another important factor on which the success of the CRRT procedure depends. Thrombi in the extracorporeal circuit can be small, reducing the clearance of substances, or large, leading to the compromise of the filter and, implicitly, of the circuit [33]. Both in adults and in children, numerous strategies have been tried to slow down the formation of thrombi in the circuit by changing the technique (adequate blood flow, decrease in the haemoconcentration in the filter) but also different anticoagulation methods (systemically administered unfractionated heparin, regional citrate, prostacyclin, bilavirudin or argatroban) [34][35][36].

CRRT is not a risk-free procedure. Arterial hypotension is the most frequent complication (30% of cases [37]) and represents a 20 mmHg decrease in mean blood pressure compared to the previous value in the first 60 min after connection. During CRRT, fluid and hydro-electrolyte imbalances (hypocalcaemia, hypokalaemia, hypophosphatemia), complications related to the dialysis catheter, complications related to anticoagulant treatment, and infections may also occur. Global mortality in case of AKI is 15.3%, and for the paediatric population it can reach 42% [38]. When using CRRT in preemies, mortality can reach 85% [55].

The combined use of different extracorporeal therapies is a practice that has only come into use in recent years, because they are trying to save some patients who until recently were classified as “no chance”. The most common combination is ECMO (extracorporeal membrane oxygenation) and CRRT. It is estimated that between 25-68% of patients on ECMO also need renal replacement therapy [39][40]. In more than 50% of them, the indication was fluid overload [41]. There are several technical ways to use ECMO and CRRT concurrently, either using separate vascular accesses or inserting the CRRT machine into the ECMO circuit at different levels. In his meta-analysis, Chen noted that the combination of ECMO and CRRT increases the risk of haemolysis in extracorporeal circuits [42][43]. The use of CRRT in ECMO is proven to be associated with an increased need for inotropic support and the need for blood product transfusions [44][45].

The cytokine filter represents another extracorporeal therapy and is used with good results in the haemodiafiltration circuit [46], after the dialysis filter, for patients with infectious or hepatic impairment of various aetiologies. Studies have shown good absorption of bilirubin, [47][48], pro- and anti-inflammatory cytokines after cardiopulmonary bypass [49], bacterial toxins, myoglobin and activated complement. The concern is that it also absorbs therapeutic substances such as prostaglandin or antibiotics, and serum levels thereof should be monitored where possible [50].

Renal replacement therapy is also accompanied by a number of ethical dilemmas. Sometimes the initiation decision is difficult in front of a patient with comorbidities that affect survival and quality of life, but according to the Code of Medical Deontology, “The professional act and the entire activity of the physician will be exercised, respectively carried out without any kind of discrimination, including in what concerns the patient’s state of health or chances of recovery”. Also, discontinuing proven ineffective therapy is an equally difficult decision. In Romania, a physician is prohibited from terminating the life of a terminally ill patient, regardless of the costs.

Chapter II - SPECIAL PART

1. Hypothesis and Research Objectives

In the "Maria Sklodowska Curie" Emergency Clinical Hospital for Children - Neonatal Intensive Care Unit, neonates with acute kidney injury are cared for, receiving both drug treatment and renal replacement therapy. The idea of this observational study came from the desire to deepen this pathology and to improve the continuous renal replacement techniques still in the pioneering stage in this age category. By establishing some parameters and calculating some risk scores, this study creates the premises of an effective therapy through early initiation, improvement of the renal replacement technique and associated treatment.

1.1 General Research Methodology

This research represents a descriptive observational, non-randomized study, both retrospective and prospective. In this survey, patients from the Neonatal Intensive Care Clinic within the "Maria Sklodowska Curie" Emergency Clinical Hospital for Children in Bucharest were enrolled, in whom renal replacement therapy was practiced between January 2013 and June 2021.

The following criteria were applied for patient selection:

Inclusion criteria:

- renal replacement therapy – peritoneal dialysis and/or CRRT
- duration of the procedure longer than 6 hours
- procedure carried out in the "M.S. Curie" Neonatal Intensive Care Unit

Exclusion criteria:

- duration of therapy less than 6 hours

Data collection was performed on the basis of medical data from consultation sheets, from the hospital IT system, and data from the history of the CRRT equipment.

1.2 Reasearch objectives

The aspects pursued were: establishment of the AKI aetiology, influence of pathology on the occurrence of AKI, establishment of the most effective method of acute renal replacement therapy, influence of the technical aspects of the procedure on survival, establishment of the incidence of complications, role of drug and substitute treatment in extra-renal purification therapy.

The general objectives are the early diagnosis of AKI, the early initiation of renal replacement therapy and also the improvement of the renal replacement technique.

2. Statistical Analysis and Processing

The processing and statistical interpretation of the obtained data was carried out with the help of software Microsoft Excel 2007 (part of the graphics for descriptive statistics), SPSS Statistics 15.0.0 (SPSS Inc. - 2006 for ANOVA analysis, Crosstabulation - Chi square, Kaplan Meier and some of the graphs) and MedCalc 14.8.1 (MedCalc software - 2014 for ROC analysis and estimated OR risk calculation). A value of **$p<0.05$** was considered statistically significant. We specify that the names **p-value** and **Sig** are similar and represent statistical significance.

2.1 Study Group

The methods of extra-renal purification therapy used in the Neonatal Intensive Care Unit – "M.S. Curie" Emergency Clinical Hospital for Children are peritoneal dialysis (PD) and continuous renal replacement therapy (CRRT).

Among the types of CRRT, only Continuous Veno-Venous Haemodiafiltration (CVVHDF) was used. 2 patients who had CRRT duration less than 6 hours were excluded from the study (one patient had intraoperative CRRT with the diafiltration filter mounted in the ECMO circuit for 60 min, the second patient died 2 hours after initiation of the CRRT procedure). Thus, 34 patients were included in the study, of which 6 patients underwent PD and 28 patients underwent CRRT. Two of the CRRT patients required two CRRT sessions separated by time because a complication occurred in the course of the disease that prompted the initiation of a new CRRT procedure. Among the CRRT patients, 8 patients initially underwent PD, but since this was ineffective, therapy was continued with CRRT. We specify that in a first stage we analysed a group of 44 procedures, as follows: PD (6 cases), PD that was continued with CRRT, marked PD-CRRT (8 cases) and CRRT (30 cases). We sought to determine whether there are correlations between certain factors and the ineffectiveness of the PD-CRRT procedure. In the second part of the study, the 44 procedures were divided into two groups, PD (14 cases) and CRRT (30 cases). We made this separation in order to be able to also analyse the possible risk factors (OR – Odd Ratio) for the two therapeutic methods and/or other statistical analyses.

CRRT was found to be the most frequently used renal replacement procedure (**68.18%**).

2.2 Distribution by Year of Renal Replacement Procedures

[Figure 2] illustrates the distribution by year of renal replacement procedures, while the change in the approach to renal replacement therapy is noted. Thus, if until 2015 peritoneal dialysis was exclusively used, at present CRRT represents the first-line technique for acute renal replacement.

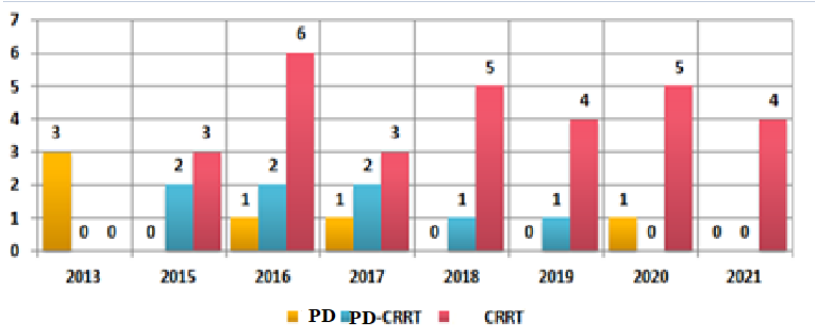

Figure 2: Distribution by year of renaı replacement procedures

PD - peritoneal dialysis, PD-CRRT- peritoneal dialysis followed by CRRT, CRRT- haemodiafiltration

2.3 AKI Aetiology in the Study Group

Renal impairment occurring in neonates and infants requiring renal replacement therapy can have different aetiologies, an important category being represented by cardiac pathology. Thus, in this study, **56.8%** of the total renal replacement procedures were performed on patients who underwent cardiovascular surgery [Figure 3a].

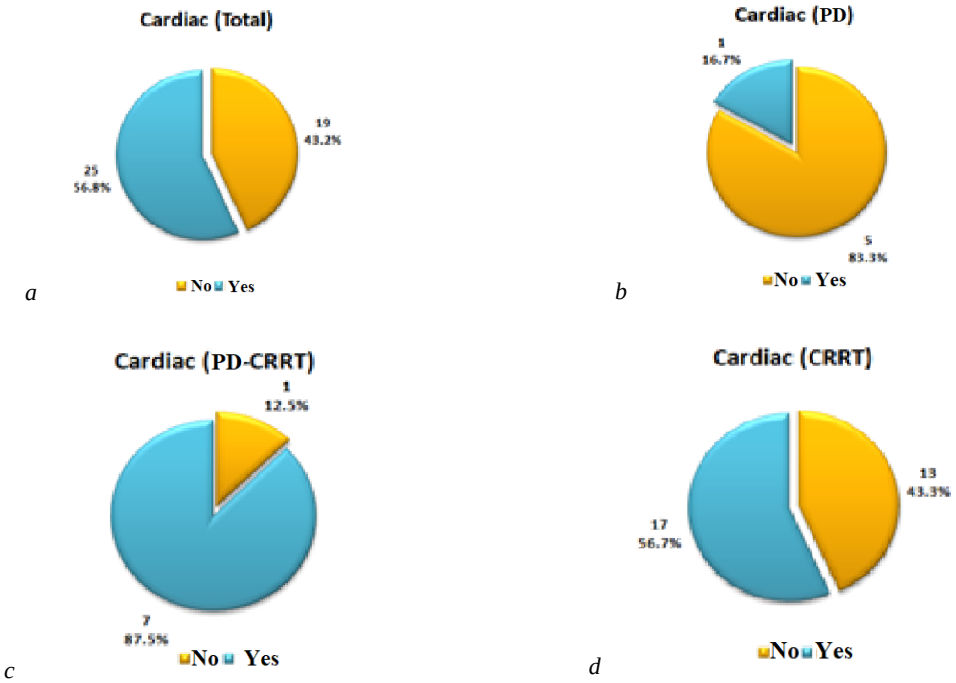

Figure 3: Distribution of renal replacement procedures according to cardiac status: a - total, b - PD, c - PD-CRRT, d - CRRT

PD - peritoneal dialysis, PD-CRRT- peritoneal dialysis followed by CRRT, CRRT- haemodiafiltration

PD proved ineffective for patients with cardiac pathology (cardiac pathology accounted for only **16.7%** of PD [Figure 3b], whereas patients who benefited from PD but which proved ineffective and who were converted to CRRT had cardiac pathology in **87.5%** of cases [Figure 3c]). This aspect can be explained by the occurrence of a low cardiac output and decreased mesenteric perfusion. Among the patients in whom CRRT was used, **56.7%** had cardiac pathology [Figure 3d] and a positive statistical correlation was found between the presence of cardiac pathology and CRRT as the method used for acute renal replacement (Sig=0.030).

The occurrence of AKI in the group of patients with cardiac pathology correlated with the degree of complexity of the cardiac malformation. Individual operative risk was classified into 6 categories using the Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1) score [51][52][53]. A score of 1-2 represents low risk, a score of 3-4 represents medium risk and a score of 5-6 represents high risk. It was found that most renal replacement procedures were performed for medium risk cardiac pathologies and the number of CRRT procedures was directly proportional to the RACHS-1 score [Figure 4].

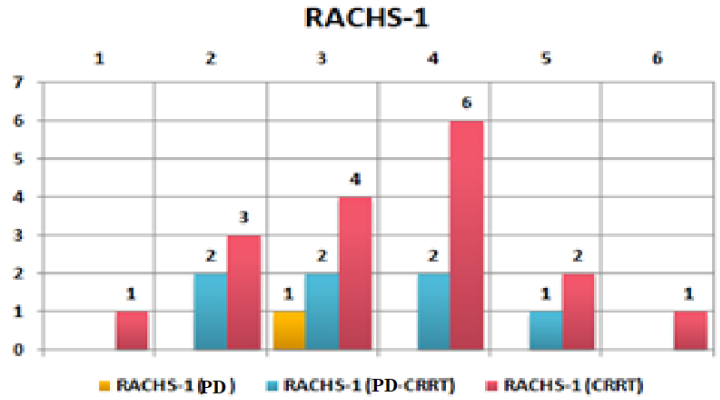

Figure 4: Distribution of renal replacement procedures according to RACHS-1 score
PD - peritoneal dialysis, PD-CRRT- peritoneal dialysis followed by CRRT, CRRT- haemodiafiltration

The degree of complexity of the malformation is translated into the duration of the surgical intervention. Analysing extracorporeal circulation time (ECT) and aortic cross-clamp time, it emerged that the patients included in the study group had an average ECT time of **185.39 min** [36-341 min] and an average aortic cross-clamp time of **110 min** [3-186 min]. Studies have shown that ECT duration of more than 180 min causes AKI in approximately 70% of patients [54] and an aortic cross-clamp time of more than 57 min causes AKI in 64% of patients [6]. In the case of patients included in this study, who benefited from CRRT, it was found that both operative times were longer compared to the operative times of patients who underwent PD.

43.2% of acute renal replacement procedures were performed on patients who presented pathologies other than cardiac ones. Two patients presented primary renal pathology (polycystic kidney), the rest were secondary renal diseases. Gastroschisis and sepsis were the main diagnoses for which acute renal replacement therapy was performed in this group of patients. For gastroschisis, only CRRT was performed, the abdominal wall defect contraindicating performing PD. Patients with sepsis benefited from both PD (40%) and CRRT (60%).

2.4 Survival Rate in the Study Group

The survival rate was **16.67%** for patients who underwent PD and **20%** for patients who underwent CRRT. In our study, the overall survival rate (**18.18%**) is lower compared to data reported in the literature. The results of the statistical analysis showed that the survival rate was not influenced by the diagnosis of heart impairment or the method of renal replacement (Sig=0.692 for PD and 0.531 for CRRT), knowing that survival is lower in the case of neonates and infants with post-cardiovascular surgery AKI and when renal replacement is performed in patients weighing less than 3 kg or preemies [7][33][55][56]. Our opinion is that mortality rate was increased in the study group because the extra-renal purification procedure was initiated late, in very complex cases.

2.5 Physiological Antecedents

Approximately 60% of the births were performed by caesarean section (83.3% for PD, 50% for PD-CRRT and 56.7% for CRRT). Caesarean section could represent a risk factor for the occurrence of AKI, if it had as an indication a medical cause (maternal pathology: arterial hypertension, diabetes mellitus, HELLP syndrome, etc. or foetal pathology: acute foetal distress, macrosomia, prematurity). However, the statistical analysis did not establish a correlation between the mode of birth and the renal replacement procedure (Sig=0.406). It is possible that this result is consistent with the global trend of increase in the number of caesarean births noted in recent years.

Male gender was dominant for all types of renal replacement procedures (Sig=0.05). Gender difference is a common phenomenon in many conditions, both in the neonatal period and later. It seems that even in the case of severe renal impairment, the male gender is more frequently predisposed. There are numerous studies that suggest the existence of a protective effect for the female gender due to the production of oestrogens [57].

Apgar Score is an independent risk factor for the development of AKI. Low Apgar values in AKI patients beyond the neonatal period may suggest that kidney injury continues

beyond the hypoxic event [58][59]. In the study group, **69%** of patients had a Apgar greater than 7. In this context, AKI is most likely due to other causes and not to perinatal hypoxia. A statistically significant correlation was established between the type of procedure and the Apgar Score value (Sig=0.010). Thus, PD dominated in patients with Apgar<7, while CRRT was predominantly used in patients with Apgar≥7.

Starting from the gestational age, the patients were structured into two categories: those with GA<37 weeks and those with GA≥37 weeks. Preemies have a smaller number of nephrons and are prone to develop AKI much more easily. In the study group, a rather large percentage was represented by preemies (**33%** respectively 14 out of 42, for 2 of the patients there is no data). As a result of low birth weight, preemies requiring acute renal replacement therapy are rather referred for PD, due to the technical difficulties of performing CRRT. In the studied group, **83.3%** (5 out of 6) of those who underwent PD were preemies, compared to **27,58%** of those with CRRT (8 out of 29). A positive correlation was established between prematurity and PD and between GA≥37 weeks and CRRT (Sig=0.016).

2.6 Age of Patients

The patients included in the study were divided into two groups: age less than or equal to 30 days and age greater than 30 days. **63%** of patients were less than 30 days old (respectively 28 out of 44). No correlation could be established between the patient's age and the type of renal replacement method used (Sig=0.985). CRRT was used more frequently for both age categories.

The survival rate was higher among patients older than 30 days (**45.45%** respectively 5 out of 11) compared to the survival rate among patients younger than 30 days (**10.7%** respectively 3 out of 28). This is similar to data reported in the literature of high mortality among neonates with AKI receiving acute renal replacement therapy [7][33][55].

No patient included in the study younger than 30 days old who received PD survived. This result is unexpected because in many international clinics only PD is used as an extra-renal purification method in neonates.

2.7 Peritoneal Dialysis - Technique

Peritoneal dialysis was performed using catheters inserted either at the patient's bedside by the intensive care physician, or intraoperatively (simultaneously with the cardiovascular surgery or later by the general surgeon).

The PD procedure was done manually by the nurse. Glucose was used as dialysate in concentrations of 1.5% and 2.3%. It was started at **10-15ml/kg/shift** (mean **11.9ml/kg/shift**)

and was increased to a maximum of **21ml/kg/shift**. The time to introduce the dialysate solution was generally **10 min**, but there were also cases when the introduction of the dialysate liquid lasted 60 min. The contact time in all cases was 30 min with only one exception when it had to be extended to 60 min. The type of emptying (drainage time) varied for PD between 20-60 min with a mean of **36.42 min** and for PD-CRRT between 20-30 min with a mean of **26.66 min**.

2.8 CRRT - Technique

Prismaflex Gambro Set HF20 equipment, *AN69ST membranes* were used. The HF20 disposable set is specially designed for the treatment of patients weighing less than 8 kg and the circuit has an extracorporeal volume of 58 ml [60]. Circuit priming was done using normal saline solution and then packed red blood cells. Blood heating was done with a Prismacomfort cuff heating system that was mounted on the return line, set to a temperature of 40^{o}C. The settings of the CRRT equipment were set by the neonatologist/intensivist and values were recorded similar to the recommendations of other clinics for blood flow rate, effluent dose, ultrafiltration dose and filtration fraction. Instead, for the rate of fluid removal from the patient, dialysate and replacement fluid, values different from those recommended were obtained, an aspect explained by the existence of an important fluid overload in the study group.

Vascular access for the CRRT procedure was obtained through a double-lumen catheter inserted by the Seldinger technique at the patient's bedside, under ultrasound guidance. Catheters between 6-8 Fr inserted into the jugular and femoral veins were used. In no patient was the subclavian vein used for the access. The CRRT circuit was inserted into the ECMO circuit in one case. Catheter insertion for CRRT was found to be predominantly in the femoral veins (36.7% RFV and 30% LFV). Jugular veins were the second option (20% RIJV and 10% LIJV). These results are in opposition to what was obtained by Guzzo et al. in an extended analysis of acute dialysis used in children (internal jugular veins 68.6%, femoral veins 25.7% and subclavian veins 5.7%) [26]. Subject to increased consumption of sedation medication, we preferred this access which affords easier patient handling and better equipment operation without interruptions associated with alarms.

Analysing statistically the influence of cardiac pathology on the vascular access used, it was found that even in the case of patients with cardiac pathology, the vascular access at the level of the femoral veins was predominantly used (29.5% RFV and 35.29% LFV). However, no correlation could be established between the presence of cardiac pathology and the vascular access used (Sig=0.256).

Regarding the survival rate, it is noted that the patients who survived only had femoral venous access (66.6% RFV and 33.3% LFV), without being able to establish a correlation between the type of vascular access and survival (Sig=0.358). We would have expected that in patients with cardiac impairment associated with low cardiac output syndrome, the access to the femoral vessels would not be functional, yet the surviving patients had only femoral catheters.

2.9 Duration of the Acute Renal Replacement Procedure

Acute renal replacement procedures were discontinued either when they were no longer necessary (as the patient resumed diuresis, nitrogen retention products normalized, and fluid overload entered remission) or when it was no longer feasible from the technical point of view or the patient has died.

In the study group, PD lasted an average of **5.64 days** and CRRT an average of **8.63 days**. The longest PD duration was **18 days**, the longest CRRT duration was **20 days**, and the longest CRRT duration for a surviving patient was **16 days**.

Analysing the survival rate using the Kaplan Meier method [Survival time
Figure 5] it is noted that the estimated average duration for PD was approximately **7 days** and for CRRT approximately **10 days**.

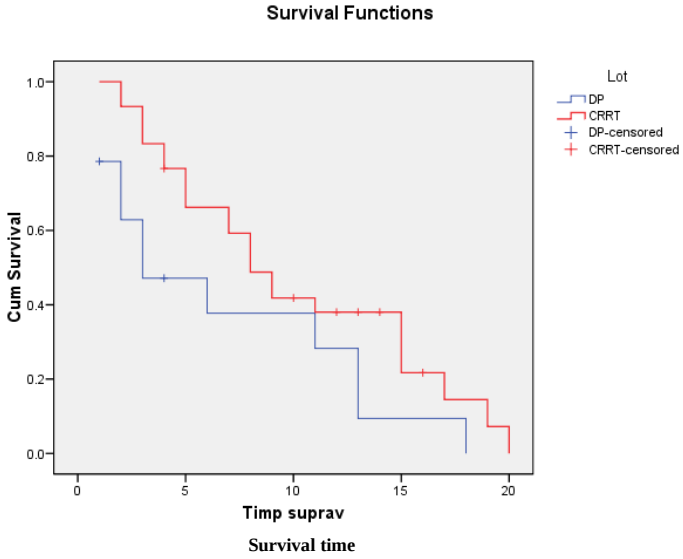

Figure 5: Survival in renal replacement therapy related to duration of therapy

The differences are statistically significant according to Overall Comparisons tests (Sig=0.055 for Log Rank, Sig=0.028 for Breslow and Sig=0.39 for Tarone-Ware). It can be concluded, in this study, that CRRT was more effective compared to PD.

2.10 Clinical Aspects

In the study group, at the initiation of **PD**, the patients had an average weight of **2,946.83 g** [1,200-4,860g]. Patients who started **CRRT** had an average weight of **4,490g** [2,730-13,000g]. Following the statistical analysis, a correlation was found between the weight at the time of initiation of the procedure and the type of procedure used (Sig=0.008). Thus, PD was practiced in patients with low weight, in whom it was technically difficult to perform CRRT. The ROC analysis of the patients' weight at the time of initiation of the renal replacement procedure established as the tie-breaking criterion for CRRT the value of **CW>2,670.88 g**, with statistical significance (p=0.001) with the sensitivity of 100.00% and the specificity of 34.69%, AUC 0.681 and 95%CI AUC 0.575-0.774. Current weight was the patient's weight prior to fluid retention plus fluid overload.

The percentage of fluid overload (FO) for all patients included in the study was calculated using the formula: FO= [Current Weight - Admission Weight]/Admission Weight x100 [61]. For the CRRT procedure, the average FO was 16.5% and for the PD procedure, **31.8%.**

A correlation was found between the lower value of FO and the CRRT procedure (Sig=0.016), so it can be concluded that CRRT is a more effective method in decreasing FO compared to PD.

In the studied group, diuresis had a mean value for **PD** of **2.01 ml/kg/h** [0.05-6.2 ml/kg/h], for **PD-CRRT** of **0.36 ml/kg/h** [0.05-0.9 ml/kg/h] and for **CRRT** of **0.85 ml/kg/h** [0-5.9 ml/kg/h]. In the case of the PD-CRRT group, 4 patients were anuric and 4 oliguric. The absence of a diuresis greater than 1 mg/kg/hour was one of the criteria that contributed to the decision to change the procedure to CRRT.

For PD, the mean AV values during the procedure were **157 beats/min** and for CRRT **149 beats/min**. There is a positive correlation between higher values of AV and PD (Sig=0.002). Literature data indicate that arterial hypotension, haemodynamic instability, and secondary tachycardia may occur in patients in whom CRRT was initiated. This association was not found in our study. On the contrary, an increase in AV values is noted in the case of patients who benefited from PD. This aspect can be explained by increased intra-abdominal pressure and decreased venous return.

Heart rhythm disorders occurring in patients with cardiac pathology, especially postoperatively, can be a cause of renal dysfunction through atrioventricular asynchrony. The assessment of rhythm disturbances revealed that the most frequent patients presented a junctional rhythm (JET). In patients in whom sinus rhythm did not resume, a temporary

peacemaker was used on epicardial electrodes. It was noted that patients who benefited from PD had predominantly sinus rhythm. In the case of patients who had JET or required a temporary peacemaker, the CRRT method was used either as first intention or after the failure of using PD (PD-CRRT). It is found that there is a statistically significant correlation between the type of procedure and heart rhythm (Sig<0.001). We can conclude that the absence of sinus rhythm is associated with the increased need to initiate CRRT. A direct causal relationship between heart rhythm disturbances and the occurrence of AKI cannot be established. Most likely, we can raise the suspicion of the existence of complex cardiac pathologies, which required surgical interventions with extended operative times and complex postoperative therapy. Only one patient from the studied group required a permanent peacemaker [62].

In our study, it was found that arterial hypotension occurred in all three groups, but it was most common in patients who received CRRT. The most hemodynamically stable renal replacement method was PD.

2.11 Paraclinical Aspects

The CRRT method is associated with a lower blood pH value, which is consistent with AKI severity, case complexity and therapeutic needs (Sig<0.001).

In the study group, the mean values of serum urea and serum creatinine were lower in the group of those who benefited from CRRT. It can be concluded that CRRT is a much more efficient method of purification of serum urea and serum creatinine compared to PD. For patients in whom PD was used but continued with CRRT (PD-CRRT), the serum creatinine level increases or remains unchanged, representing another indication for procedure switch from PD to CRRT. Serum creatinine is rapidly dialyzable and cannot be used to estimate AKI remission. The decrease in serum creatinine during dialysis is instead an indicator of the efficiency of the procedure.

Analysing the mean glycaemia values for each patient included in the study, it was noted that in the PD group the mean value was **116.28 mg/dl**, higher than in the CRRT group, where the mean value was **102.7 mg/dl**. Although these differences are not statistically significant (Sig=0.209), the higher value found in the group that benefited from PD can however be explained by the fact that glucose was used as dialysate and thus its serum value also increased. Only one patient in the PD group required the administration of insulin to normalize glycaemia.

Between the mean values of Hb and Ht determined in the 3 groups of patients, no statistically significant differences were found. The values of Hb and Ht were similar for all

types of procedures. The mean value for Hb in the patients in the study who had benefited from renal replacement therapy was **11.58 mg/dl**, corresponding to a mean haematocrit of **34.44%**. An attempt was made to maintain Hb and Ht within normal limits by administering packed red blood cells. Blood transfusion is a frequent and necessary practice in neonates undergoing CRRT-type renal repletion therapy, due to the destruction of haemoglobin in the CRRT circuit, frequent blood sampling, repetitive bleeding secondary to anticoagulant medication and the need to support the delivery of oxygen to the tissues. ELSO (Extracorporeal Life Support Organization) recommends maintaining a target haematocrit (Ht) of 40% for neonates undergoing ECMO. There is no consensus regarding the administration of transfusions during renal replacement procedures.

In the study group, it was found that the highest requirement of packed red blood cells was found in the CRRT group (Sig=0.954). On average, the patient who benefited from the CRRT method received the equivalent of **68 ml/kg**. The only study found on the paediatric population that we could refer to is the one carried out by Redant et al. They administered packed red blood cells during ECMO at doses of 34 ml/kg, and when ECMO and CRRT were combined, the doses increased to 114 ml/kg [45].

Similar to packed red blood cell transfusions, platelet transfusions are also commonly given during the CRRT procedure. These are the result of the persistent consumption of platelets in the haemodiafiltration circuits to which is added the consumption due to the associated pathology. Because haemorrhagic complications are an important and frequent source of increased mortality, it is recommended to maintain platelet counts at higher values for CRRT patients compared to other critically ill patients. ELSO recommends maintaining a platelet count threshold of approximately 100,000/μL.

In the study group, a lower mean value of the platelet count was noted in the group of patients in whom CRRT was used, of **98.2** [10-564] X $10^3/mm^3$ compared to PD or PD-CRRT (**179** respectively **133** X $10^3/mm^3$). There is a statistically significant correlation (Sig<0.001) between low platelet count and CRRT administration. To maintain the platelet count at these values, platelet transfusions were required. On average, a platelet concentrate volume of **93.3 ml/kg** was administered. This value is higher compared to that obtained by Redant et al. in their study. The authors stated that in patients who required ECMO and CRRT, the mean volume of platelet concentrate was 83 ml/kg [47].

In the studied group, a mean serum lactate value of **4.3 mmol/l** was obtained for patients undergoing PD and **8 mmol/l** for those undergoing CRRT. A statistically significant positive correlation was established between CRRT and high serum lactate values

(Sig=0.001). The higher value of lactate in the group of patients who underwent CRRT can be explained by the existence of a low cardiac output, postoperative status and an increased need for inotropic and vasoactive medication.

High values of transaminases were recorded (ALT had a mean value of **298.86 U/L** in patients who underwent PD and **244.77 U/L** in those who benefited from CRRT; AST had a mean of **508.2 U/L** in patients who underwent PD and **484.98 U/L** in patients who underwent CRRT), with no statistically significant differences between the types of renal replacement procedures (Sig=0.910).

A much higher value for direct bilirubin was noted in the group of patients who benefited from CRRT compared to those in whom the technique used was PD. This difference is explained by the existence of more accentuated haemolysis in the CRRT circuit but also by intrinsic hepatic impairment due to heparin, medication or total parenteral nutrition. Another risk factor is the presence of a higher percentage of fluid overload in these patients, which associates hepatic congestion and cholestasis.

In the study undertaken, C-reactive protein (CRP) values were considered positive at more than 5 mg/l. It was found that the value of this marker was increased in both types of renal replacement procedures. A higher value of CRP was noted for patients in the CRRT group (**62.28 mg/l**) compared to those in the PD group (**22.67 mg/l**), and there is a statistically significant positive correlation between CRRT and the increased CRP value (Sig<0.001). CRP values in patients with cardiac pathology were similar to those in the group of patients without cardiac impairment and cannot be associated with a presumed inflammatory response given by ECT. The higher mean CRP value for the CRRT group could still be the consequence of the inflammatory phenomena due to the haemodiafiltration circuit, but an infection cannot be excluded.

For the CRRT procedure, the anticoagulant medication used was heparin and was administered in the CRRT circuit as a continuous infusion. It was aimed to keep the ACT value in the range of 180-220s and the aPTT value in the range of 60-80s. For ACT values lower than 180s, heparin bolus of 10-20 U/kg was administered, followed by increasing heparin doses by 1 U/kg/hour. For ACT values higher than 250s, the heparin dose was decreased, until stopped, using in some cases the specific antidote Protamine □.

In 6 patients, during the use of CRRT, aPTT values were monitored, in 2 patients, only ACT values were monitored and in 22 patients both determinations were used. In the study group, the mean value for ACT was **209.77s**, and for aPTT the mean value was **77.67s**. In 4 patients it was necessary to administer the antidote for heparin (protamine).

In the case of patients who underwent PD, only the determination of aPTT was used, within the regular health assessment, recording a mean value of **39.29 s**.

Ensuring effective anticoagulation is the main requirement imposed to extend the lifetime of the circuit for CRRT.

The manufacturer recommends that the Prismaflex disposable set be changed after 72 hours of use. In a 2017 meta-analysis by Brain M et al., it was shown that the average lifetime of a circuit for CRRT was 21.92 hours [64].

In the study group, the average lifetime of a circuit for CRRT was **81.44 hours** (representing 3.39 days).

In patients with sepsis, circuit lifetime is unpredictable because of coagulation disorders that can occur at any time.

And the consumption of fresh frozen plasma in the group of patients who underwent CRRT was much higher compared to what Redant identified in the conducted study (**88 ml/kg** in our study compared to 36 ml/kg for patients who required ECMO and CRRT in the study by Redant et al.)

2.12 Mechanical Ventilation

In the study group, all patients receiving renal replacement therapy were mechanically ventilated. Conventional ventilation was mainly used in 77.2% of cases (respectively 34 out of 44). The ventilation modes used were: SIMV - Synchronized Intermittent Mandatory Ventilation, CMV - Continuous Mandatory Ventilation, and APRV - Airway Pressure Release Ventilation. High Frequency Oscillatory Ventilation (HFOV) was used in 22.8%. Only one patient who benefited from PD (representing 2.2% of patients) was ventilated with HFOV. The remaining patients (20.5%) in whom HFOV was used underwent renal purification using the CRRT or PD-CRRT procedure. It should be noted that a significant number of patients (27.27%, i.e. 12 out of 44) developed pulmonary hypertension. In their case, inhaled nitric oxide was used. There were no significant differences between mean values of oxygen saturations, mean values of partial pressure of oxygen and mean values of partial pressure of carbon dioxide.

2.13 Medication and Nutrition

The inotropic support used in the patients in our study was assessed using the Vasoactive Inotropic Score (VIS). There are studies showing that a VIS score higher than 15-20 after cardiac surgery is associated with a higher mortality rate [66]. In the studied group, the VIS score had a mean of **25.28** for patients in whom PD was initiated and **111.2**

for those with CRRT. This shows that patients who required CRRT required more inotropic and vasoactive support than those who underwent PD. Many patients who received CRRT underwent cardiovascular surgery and required intensive inotropic and vasoactive support. The increased value of the VIS score may be partly due to the CRRT procedure predisposing to arterial hypotension and increased need for vasoactive medication. There is a positive correlation between increased VIS score and CRRT, with statistical significance (Sig<0.001). Following the ROC analysis, the **VIS>48** value was established as the tie-breaking criterion for CRRT, with a sensitivity of 62.16% and a specificity of 90.67%. The test has statistical significance (p<0.0001) with diagnostic value (AUC 0.836, 95% Confidence interval 0.792-0.874).

With the initiation of renal replacement therapy, diuretic treatment should be discontinued. For many of the patients included in our study, diuretic therapy was continued as a result of no diuresis. The medication used consisted of: Furosemide in continuous infusion, Myofilin in continuous infusion and ethacrynic acid (Reomax) administered intermittently. The need for diuretic medication administration was higher for patients who benefited from CRRT compared to those in the PD group.

Since all patients in the study group were intubated and mechanically ventilated, opioids were used for analgesia, benzodiazepines and propofol for sedation, and sometimes a neuromuscular blocker was added to them. For patients who benefited from CRRT, higher doses of this medication were used for a longer period.

In the study group, several peculiarities of the nutrition of patients who benefited from renal replacement therapy were identified. In the vast majority of patients included in the study, nutrition was achieved parenterally. Enteral nutrition is contraindicated in conditions of haemodynamic instability with arterial hypotension requiring inotropic and vasopressor support. Some patients on PD have developed increased intra-abdominal pressure with impaired mesenteric perfusion. Many patients included in the CRRT group experienced gastrointestinal bleeding in the context of the initiated anticoagulant medication. However, some patients received “trophic enteral nutrition” during the renal replacement procedure, representing a minimum amount of milk of approximately 10 ml/kg/day that ensured the trophicity of the intestinal villi, thus preventing intestinal atrophy. Breast milk is preferred.

2.14 Complications of Acute Renal Replacement Procedures

In patients who benefited from PD, the most common complications were: fluid loss around the catheter insertion site (35.71%), hyperglycaemia (21.42%) and arterial hypotension (14.28%).

In the patients who benefited from CRRT, the occurrence of arterial hypotension was noted in two thirds of the patients (66.66%), which required an increase in the doses of inotropic and vasopressor drugs. 50% of patients experienced gastrointestinal bleeding and 30% endotracheal bleeding. Haemorrhagic complications were the consequence of the anticoagulant medication that the infants received, of thrombocytopenia, but also of changes in coagulation factors in the context of sepsis, asphyxia and postoperative status. In a small percentage of 3%, haemorrhagic complications resulted in death.

Although the overall survival rate among patients who underwent the renal replacement procedure was low, **18.18%** (8 out of 44 patients), it was noted that **56.81%** of patients (25 out of 44 patients) were alive at the end of the renal replacement procedure. This aspect supports the efficiency of the renal replacement procedure, but the complexity and severity of the cases ultimately did not allow the survival of some patients (17 patients). Only 2 deaths occurred during PD and 17 deaths out of 24 during CRRT.

The efficiency of the renal replacement procedure was assessed by the decrease in the serum creatinine value, the decrease in the serum urea value, the resumption of diuresis, the reduction in fluid overload and finally the survival.

2.15 Associated Extracorporeal Therapies

In the case of 4 patients included in the study, the CRRT procedure was associated with ECMO. These patients had cardiac pathology and veno-arterial ECMO was performed.

For patients who received ECMO associated to CRRT, the mean haemoglobin value was found to be **10.65 g/dl** [9.3-11.31], lower than the mean haemoglobin value for CRRT patients (11.57 g/dl). This fact supports the statement that the concomitant use of ECMO and CRRT increases the risk of haemolysis and the need for packed red blood cell transfusions [42][43]. The ECMO procedure lasted an average of **11 days** [7-16 days]. None of the patients survived.

In the case of 5 patients included in the current study, a cytokine filter (Cytosorb) was used. ECMO, CRRT, and Cytosorb were used concurrently in two of these patients. The main indications for fitting the cytokine filter were sepsis (Candida and Staphylococcus) and multiple organ failure. In the case of a single patient, the cytokine filter was used for severe hyperbilirubinemia (total bilirubin 52 mg/dl). The cytokine filter was mounted in the CRRT circuit after the haemodiafiltration filter. In all 5 cases, significant arterial hypotension was found at the beginning of the procedure, which required an increase in inotropic and vasopressor support. The cytokine filter was maintained between 30 min and 3 days, with change every 24 h.

3. Conclusions and Personal Contributions

- AKI has an important role in the evolution of the critically ill neonatal patient.
- Renal replacement therapy is the only proven effective treatment for advanced stage AKI.
- CRRT was the most used acute renal replacement method. Romania thus aligns with the practices of developed countries regarding the approach to extra-renal purification therapy.
- Post-cardiac surgery AKI was the most common aetiology (56.8%). Renal replacement therapy was influenced by the degree of complexity of the cardiac malformation (RACHS-1) and correlated with increased operative times: ECT and aortic cross-clamp time. PD proved ineffective in this group of patients.
- On the other hand, preemies and low-weight patients, in whom it is not technically possible to perform CRRT, mainly benefited from PD.
- The male population was dominant in the study group.
- The overall survival rate was low (18.8%) compared to the data reported in the literature, the explanation being the late initiation of the procedure in the case of some patients with complex pathology.
- Patients older than 30 days at the initiation of renal replacement therapy had a higher survival rate compared to those younger than 30 days at the initiation of the procedure.
- CRRT is more effective than PD in decreasing fluid overload, purification of serum urea, serum creatinine, and serum potassium.
- CRRT is associated with increased acute phase reactants, lactate and direct bilirubin.
- CRRT increases the need for inotropic and vasoactive medication, the need for blood products (packed red blood cells, platelet concentrate, fresh frozen plasma) and medication for analgesia and sedation.
- There were no significant complications during extra-renal purification procedures resulting in patient death.
- Extracorporeal therapies (ECMO, CRRT, cytokine filter) can be used in combination for complicated cases.

4. Limitations

- The study group consisted of a relatively small number of procedures to allow extensive statistical analysis, therefore some results may be erroneous. However, considering that it is a complex, unusual procedure and being a unicentric study, the results obtained are very valuable from a clinical point of view.
- Considering the complexity of the pathology that requires the use of acute renal replacement procedures, we specify that a randomized trial is extremely difficult to perform because it would not be ethical for the patient.
- There is no local or national standardization of initiation of renal replacement therapy in the neonate and infant.
- There is no local or national standardization of discontinuation of renal replacement therapy that proves to be ineffective.
- The medication used during renal replacement therapy could not be monitored by determining serum levels to determine the degree of nephrotoxicity.
- We did not have available data from a similar centre in Romania with which to compare the data from the current study.

5. For the Future

- We aim for early diagnostic and initiation of renal replacement procedures. This objective can be achieved by using in practice the scores that determine the risk of AKI development in the paediatric population (RAI, FOKIS and the STARZ score); the use of NIRS (Near Infrared Spectroscopy) to monitor renal oxygenation for selected patient populations: prematurity, arterial canal, post-cardiovascular surgery, post-abdominal surgery (diaphragmatic hernia, gastroschisis, omphalocele), post-asphyxia; the use of biomarkers for an earlier diagnostic of AKI, before the reduction of diuresis and the increase in nitrogen retention.
- Use of the VVR (Vasoactive-Ventilation-Renal) score to assess the AKI prognosis.
- Limitation of the need for transfusions with blood products by using more specific investigations such as TEG or ROTEM that accurately specify the affected stage in the coagulation process.

- Use of regional citrate as an anticoagulation method to avoid the systemic effects of unfractionated hepatrine.
- We want to purchase miniaturized equipment for preemies.
- We intend to create and implement CRRT training programmes for physicians and nurses.
- Continuation of research on the methods of acute renal replacement in neonates and infants by resuming the study with a larger number of patients (e.g. 100).
- Registration of these cases from Romania in the Renal Replacement Therapy Registry of the International Paediatric Nephrology Association (IPNA International Paediatric Nephrology Association - Global RRT Registry).

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Annexes

Scientific papers published:

1. **Bizubac M**, Cirstoveanu C, Plesca DA, Mustea C, Davițoiu AM, Filip C, Nicolescu A, Spataru R. *Heparin Provides Long Time Survival for Circuits in the Neonatal and Infant Continuous Renal Replacement Therapy*. Farmacia, 2021, Vol 69 (1): 75-81, January-February 2021; ISI indexation; ISSN: 0014-8237. eISSN: 2065-0019; Impact Factor: 1.433; WOS:000623961800010
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2. **Bizubac M**, Cirstoveanu C, Filip C, Nicolescu A, Barascu I, Chirca R, Gaiduchevici A, Plesca DA. *Multiple Renal Injuries Lead to Death in Postoperative Cardiac Surgery even with Precocious Hemodiafiltrations.* Romanian Journal of Pediatrics. 2021, Vol. 70 Issue 1, pp. 63-74. 12p. doi: 10.37897/RJP.2021.1.12; BDI indexation;
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3. Cirstoveanu C, **Bizubac M**, Plesca D, Bărăscu I, Manolache Ș, Nine L, Istrate-Bârzan A, Herișeanu C. *Hemodiafiltration at Neonates and Small Infants. A Small Retrospective Case Series.* Co-author. Critical Care volume 157, Issue 6, Supplement, A120, June 01, 2020. CHEST Congress, Bologna, Italy, June 25th – 27th, 2020, DOI: https://doi.org/10.1016/j.chest.2020.05.134; ISSN: 0012-3692. eISSN:1931-3543, Impact Factor: 9.410, WOS:000546434900121
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Papers presented at scientific events organized by national and international professional associations

1. **Bizubac M**, Cirstoveanu C, Plesca D, Bărăscu I, Manolache Ș, Nine L, Herișeanu C, Istrate-Bârzan A, Gaiduchevici A. "Epurarea extrarenală la nou-născut - o continuă provocare [Extrarenal Purification in Neonates - A Continuing Challenge]" - Lecturer, 21th National Conference of Neonatology with international participation - "Actualități în neonatologie [Novelties in Neonatology]" – September 6th -7th, 2019, Brașov, Romania.

2. Cirstoveanu C, **Bizubac M**, Bărăscu I, Manolache Ș, Nine L, Herișeanu C, Gaiduchevici A. "Canularea și setarea corectă a unui aparat pentru CRRT la nou-născuții cu insuficiență renală nu sunt suficiente pentru salvarea unei vieți [Cannulation and Proper Setting of a Machine for CRRT in Neonates with Kidney Injury is not Enough to Save A Life]" - the experience of the Neonatal Intensive Care Unit at "M.S. Curie" Emergency Clinical Hospital for Children in Bucharest over 3 years - Co-author, National Conference "Actualități și interdisciplinaritate în boala cronică de rinichi la copil [Novelties and Interdisciplinarity in Chronic Kidney Disease in Children]", National Institute of Statistics, Bucharest, October 24th, 2018.

3. Cirstoveanu C, Barăscu I, Manolache Ș, **Bizubac M**, Gaiduchevici A, Nine L. "Renal Failure and Hemodiafiltration in the Neonatal ICU at MS Curie Children's Hospital Bucharest" – Co-author, National Paediatric Nephrology Conference "Cum diagnosticăm și cum tratăm bolile reno-urinare la copil [How We Diagnose and Treat Kidney-Urinary Diseases in Children]", Bucharest, October 20th – 22th, 2016.

4. Cirstoveanu C, Nicolae R, Manolache Ș, **Bizubac M** "Ornithine transcarbamylase deficiency. Acute and long-term management" poster- Co-author, National Neonatology Conference, Oradea, September 29th- October 2th, 2022