Evolution of the Management of AKI in Neonates

By Claudio Ronco and Zaccaria Ricci

1983–1988: Technology and bioengineering

We in Vicenza began studies on buffers in peritoneal dialysis (PD), leading the pathway toward the use of bicarbonate in fluids (1–3). We analyzed the pathophysiological pathways of neurotransmission, measuring several substances in the cerebrospinal fluid before and after dialysis (4, 5). In those days, the pressure to shorten hemodialysis treatments provided the impetus for studies on dialysis tolerance. We therefore focused on developing technology to make short dialysis efficient and safe (6). We studied fluid mechanics and flow distribution in dialyzers and mechanisms of solute transport in hollow fibers, and we applied all of this information to support rapid hemodialysis (7) and continuous arteriovenous hemofiltration (CAVH) (8). We developed new filters (9), described the adsorption process onto the membrane, and made the first filters with two ports in the filtrate compartment so that we could perform the first hemodiafiltration treatment (10). At the same time, we developed new fluid balance devices to be applied in intensive care patients (11).


During the years after the rapid evolution of dialysis and consequent technologic improvement, we started to consider that urea was just one aspect of treatment adequacy, and we began to promote a more holistic approach to the patient. In 1992, I felt compelled to start exploring the true integration between intensive care medicine and nephrology for better outcomes in critically ill patients. In 1998, Rinaldo Bellomo and I published “Critical care nephrology: the time has come” (12). This editorial, together with the first textbook on critical care nephrology (13), paved the way toward a new modern discipline. In the meantime, other studies were published by our group on new hemodialysis membranes, the low-flux polysulfone (14), the use of adsorption (15), and the mechanics of cross-filtration in hollow fiber dialyzers (16). These and other studies paved the way for the Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM).

2006–2010: The years of multiple organ support therapy, the wearable artificial kidney (WAK), and cardiorenal syndrome

Once the research group had been established in Vicenza, a continuous rotation of fellows made the Vicenza center a vibrant and energetic environment for new projects. We had already proposed the concept that although a single organ failure like acute kidney injury (AKI) requires specific organ replacement and thus dialysis/hemofiltration, multiple organ dysfunction syndrome in the critically ill patient may require multiple organ support therapy (MOST) (17). Thus, we advocated the transformation of the continuous renal replacement therapy (CRRT) machine into a platform for any extracorporeal therapy that can provide organ support. Techniques such as hemodiafiltration for the kidney, slow continuous ultrafiltration for the heart, plasmafiltration and albumin dialysis for the liver, and extracorporeal CO2 removal for the lung were conceived and clinically applied with success (18).

2011–2013: The CARPEDIEM project (Cardio-Renal Pediatric Dialysis Emergency Machine): a journey into pediatric nephrology

In 1984, we pioneered new techniques for neonates: CAVH. We published a series of four neonates treated with an extracorporeal circuit in which blood was circulated through a permeable filter by the pressure gradient generated by the heart (19). Our expertise with the technique in adults and in bioengineering of low-flow fiber hemodialyzers allowed us to open the way to pediatric hemofiltration, thanks to the development of minifilters—a scaled-down version of adult filters used for artificial kidney technology (20). In the neonate, it was important to develop a tool with appropriate dimensions and extremely low extracorporeal volumes; the neonate has approximately 300 mL of blood in the body. Shifts of even small volumes into the extracorporeal circulation can create major hemodynamic derangements (2).

Figure 1. First continuous arteriovenous hemofiltration (CAVH) treatment at San Bortolo Hospital

Our experience suggested that the simplicity, rapid application, and good clinical tolerance demonstrated by CAVH in adults could make it a reliable treatment also for infants and children (10). In these patients, the technique could offer significant advantages in terms of low priming volume of the extracorporeal circuit, low heparin requirements, low blood flow, and slow continuous removal of isotonic fluid. We treated four small infants with a modified CAVH circuit with shortened blood lines and connected the small filter (Minifilter) and the circuit to an artery and a vein (19). Such a circuit was able to run for 48 to 72 hours in the fourth patient treated in Vicenza for the first time in the world. Heparin and substitution fluids were administered according to the fluid balance requirements. An average ultrafiltration rate of 0.9 mL/min was achieved by this pioneering system.

Figure 1 shows the image of the first CAVH treatment carried out at the San Bortolo Hospital in Vicenza. The results in the four patients were subsequently published as the first application of CAVH in neonates (19). As a consequence, CAVH in neonates became a routine treatment in the world during the following years. The continuous evolution of the technique in the adult led to modified and specific machines with special blood and ultrafiltrate pumps that were designed to optimize the performance of the extracorporeal circuit (21). These machines, however, have proved to be suboptimal for pediatric use, even in the presence of customized circuits. In fact, the current equipment is mostly used off label in patients <15 kg of body weight and often provides significant challenges in their neonatal application (21). A major obstacle, in fact, is the small size of the catheter used in the very small patient and the low accuracy of flow control in the blood circuit and fluid balance control in the dialyze circuit.

The increase in the incidence of AKI and its association with poor outcomes in the general population (22) has led to a call for action to make an early diagnosis, institute new preventive measures, and implement new therapies to improve clinical outcomes (22). In fact, increased focus on AKI has occurred in adult patients, and to a lesser extent in children, with the development of standardized AKI classification systems (23), assessment of novel AKI biomarkers (24), and assessment of the association between AKI and the development of chronic kidney disease (25). However, such progress has not been made for infants and neonates. As a result, the National Institute of Diabetes and Digestive and Kidney Disease convened a workshop in 2013 (26) to review the state-of-the-art knowledge of AKI in neonates and to determine the feasibility of studying this group in an organized prospective manner.

In children, AKI is a complicated clinical syndrome requiring careful clinical management. In recent years, despite significant advances in critical care technology, a truly pediatric CRRT system has not been developed (2). Current CRRT machines present significant limitations for children, and in some cases, severe complications have occurred (27).

In current practice, clinical application of dialysis equipment is adapted to smaller patients, with great concern about outcomes and side effects (28). Whereas critically ill adults receive renal support with modern devices and very strict safety features, smaller children must rely on very accurate delivery of therapy, especially where fluid balance is concerned. Yet current CRRT machines are not designed to treat a small infant with accurate blood flow rates in the range of 10 to 50 mL/min and hourly ultrafiltration error <5 g/h (2). The accuracy of current systems does not meet these tolerances: a recent analysis of most commonly used machines in the adult setting showed balance errors in the range of 20 to 190 g depending on the machine and treatment flow rate (29).

CRRT devices also have different “reaction times” before a fluid balance error occurs (in the range of 10 to 20 seconds). In a worst-case scenario, more than 500 mL could be excessively removed from a patient in only a couple of minutes after three or four unchecked, alarm overrides (29). Remarkably, third-generation machines automatically stop CRRT sessions when a fluid balance error (typically 60 to 500 mL) has been reached within the adjustable time unit (typically 3 hours) (2). Before this feature was applied, fatal errors occurred in the very small child. Furthermore, because manufacturers of dialysis or CRRT machines do not perform specific tests for treatments in patients smaller than 10 to 15 kg, and safety features in these patients are not specifically created, legal concerns may arise when operators decide to prescribe these therapies (2). Thus, although current CRRT machines have been equipped with “modified” or
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“adapted” circuits for children, they are not reliable for patients weighing <15 kg. Moreover, a specifically designed neonatal machine had never been conceived. The small number of cases, together with the limited interest by industry in developing a fully integrated device specifically designed for small children, made AKI/acute renal failure in infants and neonates an “orphan disease” (2).

With this in mind, in 2008 we undertook a new journey into this area of “orphan” medicine to develop dedicated technology. We started a fundraising campaign to engage a team of experts to develop a miniaturized device for renal support in the neonate. The CARPEDIEM project was designed to create the conceptual basis for renal replacement therapy equipment specifically dedicated to newborns and small infants in a weight range of 1.5 to 10 kg and with an approximate body surface area of 0.15 to 0.5 m². In these patients, the total blood volume ranges from <200 mL to about 1 L, meaning that total body water content varies from 1 to 5 L. In such conditions, circuit priming volumes should be reduced to a minimum level and roller pumps should be able to run at slow speeds, guaranteeing the integrity of lines (small roller pumps running small tubes are expected to cause a quick decline in their performance) and maintaining an excellent level of flow and balance accuracy. The ambition of the CARPEDIEM project was to reconsider the technical and clinical expertise accumulated during the pediatric CAVH era and to design, with the help of modern miniaturization engineering skills, the first neonatal CRRT device. The project was carried out with the collaboration of many experts, including Luciano Fecondini (Medica, Medolla, Italy) and Domenico Cianciavicchia (Bellco, Mirandola, Italy), together with our engineering team leader, Francesco Gazzotto, who conceived and built the machine.

A prototype was created in record time and immediately tested in our laboratory. The machine was subsequently manufactured by Bellco. CARPEDIEM received the European Community (CE) mark in 2012 conceived and built the machine.

Cianciavicchia (Bellco, Mirandola, Italy), together with ciano Fecondini (Medica, Medolla, Italy) and Domenico

A newborn girl had a subgaleal hemorrhage resulting from vacuum extraction and consequent hemorrhagic shock. The patient received several transfusions (28 units of packed red cells and platelets); she was intubated and mechanically ventilated. She had severe thrombocytopenia, acidosis, and severe fluid overload (60 percent of baseline body weight; body weight at birth, 2.9 kg; body weight at start of CRRT, 5.2 kg) with hyponatremia.

On day 2, a 4-French dual-lumen catheter was surgically placed into the femoral vein because of the lack of any other possible vascular access resulting from severe edema. Because she had oliguric AKI, she was given postdilution CVVH with the CARPEDIEM machine. The blood pump flow rate ranged from 9 to 13 mL/min, postdilution CVVH with the CARPEDIEM machine. The blood pump flow rate ranged from 9 to 13 mL/min, and daily clearance ranged from 2.2 to 2.8 L (a volume exchange close to the patient’s total body water). The extracorporeal priming volume of the circuit was 27 mL, allowing maximal hemodynamic tolerance (Figure 3). Whereas creatinine and fluid overload began to be slowly but effectively corrected (Figure 4), the baby experienced severe hyperbilirubinemia (up to 54 mg/dL) resulting from combined liver dysfunction, and the hemofiltration treatment was subsequently alternated with other modalities aimed at bilirubin removal such as blood exchange in three sessions with 475 mL blood volume exchange at an isovolumetric exchange rate of 5 mL/min, single-pass albumin dialysis in three sessions of 10 hours with 4 percent albumin dialyze, and finally plasma exchange in four sessions with 670 mL plasma volume exchange. CVVH with additional bilirubin-targeted treatments led to progressive normalization of the bilirubin levels (Figure 5). The patient was supported with parenteral nutrition and supplementation with calcium, phosphate, and intravenous infusion of antibiotics and antifungal drugs because of her positive bacterial and fungal cultures. After 7 days of CRRT, her urine output partially recovered to 1.2 mL/kg/h and ultimately reached 3.2 mL/kg/h at 20 days. Hemofiltration was discontinued 25 days after the start of renal replacement therapy. Three days later, she was extubated, and she started to advance to complete oral alimentation. The extracorporeal treatment was carried out for 25 days, constituting more than 400 hours of extracorporeal circulation, stabilization of vital indicators, and correction of fluid overload, in conjunction with stabilization of serum creatinine at 2.8 mg/dL. After she reached her ideal body weight, she subsequently achieved physiologic weight gain, always while daily fluid balance was being monitored.

Finally the neonate was considered to be in stable condition, breathing normally without supplemental oxygen, making adequate amounts of urine, and displaying normal liver function, and she was therefore discharged from the intensive care unit. Twenty days later she was discharged from the hospital. The patient still had significant chronic kidney dysfunction, with a serum creatinine of 2.2 mg/dL. However, without a dedicated CRRT platform, renal replacement therapy would have been impossible because of technical and clinical contraindications to PD and inability to achieve a reliable vascular access for the use of traditional machines. We hypothesize that an inevitable fatal outcome would have occurred a few days after birth.

The CARPEDIEM technology applied in this case report represents a potential paradigm shift in the treatment of the neonate with AKI. Whereas PD will remain an important therapy for the uncomplicated case of neonatal AKI, the ability to accurately prescribe clearance and fluid balance will usher in a new era of renal replacement therapy and will provide a method of renal

![Figure 2. Components of the CARPEDIEM machine](https://example.com/image2.png)
supportive therapy in neonates with common technical contraindications to PD. In addition, the ability to combine extracorporeal therapies, such as plasma exchange, single-pass albumin dialysis with CRRT extends the spectrum of support to critically ill infants. The CARPEDEM technology is the first CRRT platform designed and developed for small pediatric patients, and very likely this machine will change the destiny of many infants and children.

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References
Figure 6. Timetable in development of the CARPEDIEM machine

- 2008: Review of unmet clinical needs
- 2009: Analysis of technical requirements
- 2010: Initial drawing
- 2011: Professional drawing, technical planning
- 2012: 3D project of the prototype
- 2013: Final product

**3D project of prototypes with miniaturized circuits and size calculation**

**Presentation of the functioning prototype of the CARPEDIEM machine**

**Final product CE Mark, Machine licensed for human use**

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