Continuous renal replacement therapy: forty-year anniversary

Claudio Ronco¹,²

¹Department of Nephrology, Dialysis and Transplantation, St. Bortolo Hospital, Vicenza - Italy
²International Renal Research Institute of Vicenza (IRRIV), St. Bortolo Hospital, Vicenza - Italy

ABSTRACT

In 1977 Peter Kramer performed the first CAVH (continuous arteriovenous hemofiltration) treatment in Göttingen, Germany. CAVH soon became a reliable alternative to hemodialysis or peritoneal dialysis in critically ill patients. The limitations of CAVH spurred new research and the discovery of new treatments such as CVVH and CVVHD (continuous veno-venous hemofiltration and continuous veno-venous hemodialysis). The alliance with industry led to development of new specialized equipment with improved accuracy and performance in delivering continuous renal replacement therapies (CRRTs). Machines and filters have progressively undergone a series of technological steps, reaching a high level of sophistication. The evolution of technology has continued, leading to the development and clinical application of new membranes, new techniques and new treatment modalities. With the progress of technology, the entire field of critical care nephrology moved forward, expanding the areas of application of extracorporeal therapies to cardiac, liver and pulmonary support. A great deal of research made extracorporeal therapies an interesting option for the treatment of sepsis and intoxication and the additional use of sorbents was explored. With the progress in understanding the pathophysiology of acute kidney injury (AKI), new guidelines were developed, driving indications, modalities of prescription, monitoring techniques and quality assurance programs. Information technology and precision medicine have recently contributed to further evolution of CRRT, with the possibility of collecting data in large databases and evaluating policies and practice patterns. This is likely to ultimately result in improved patient care. CRRTs are 40 years old today, but they are still young and full of potential for further evolution.

Keywords: AKI, CRRT, CRRT machine, Hemofiltration, Precision CRRT, Ultrafiltration

Introduction

Exactly forty years ago Peter Kramer treated the first patient with continuous arteriovenous hemofiltration (CAVH) in the intensive care unit (ICU) of Göttingen, Germany (1). Acute renal failure was mostly treated with peritoneal dialysis or haemodialysis, but in critically ill patients, these modalities were often contraindicated or precluded due to severe cardiovascular instability. CAVH was well tolerated and easy to institute in ICUs where haemodialysis was not routinely performed. In the year following the first description of CAVH, a significant evolution of acute renal replacement therapy (ARRT) and related technology occurred, leading to the modern techniques of continuous renal replacement therapy (CRRT). In this process of evolution, the centre of Vicenza has always been leading the edge and it has significantly contributed to the birth of a new speciality called Critical Care Nephrology. In Figure 1 we report the history timeline of CRRT as seen from our point of observation. It may be incomplete or partial, but certainly every single minute of this history has been personally lived with passion and dedication.

The era of CAVH

The introduction of CAVH made it possible to perform renal replacement therapy even in ICUs not fully equipped or trained for haemodialysis. Our first patient was treated in Vicenza with the original Amicon 20 dialyser in 1978. We further refined our understanding and knowledge of CAVH by collaborating with Juan Bosch at the Mount Sinai Hospital in New York (2). In the late 1970s we extended the use of the technique used in adults to neonates with the use of specific Minifilters (Fig. 2) (3, 4). We developed specific filters with reduced flow resistance, suitable for operating in arterio-venous mode that are today preserved in our Vicen-
za Dialysis Museum. In spite of several advantages, CAVH soon demonstrated limitations in efficiency and frequent complications due to the need for arterial cannulation. This spurred new research for alternative techniques.

The discovery of CAVHD and CAVHDF

A remarkable increase in treatment efficiency and urea removal was achieved with the addition of diffusion. New filters with 2 ports in the dialysate/filtrate compartment allowed the use of counter-current flow of dialysate, giving birth to continuous arteriovenous hemodiafiltration or hemodialysis (CAVHDF or CAVHD) (5). CAVHD-CAVHDF made it possible to treat hypercatabolic patients, simply by increasing dialysate the flow rate up to 1.5 or 2 L/h. In the case of excessive ultrafiltration, fluid losses were partially or completely replaced, allowing accurate fluid balance control. The problem of arterial cannulation was still the main drawback of the technique.

Fluid balance control

Manual control of ultrafiltration was initially achieved by positioning the filtrate bag at different heights, thus modifying the negative (suction) pressure generated by the filtrate column. Delivery of replacement fluid was initially regulated manually and later new systems were designed to provide automatic fluid balance (6). The systems operated by gravity, using scales and electronic clamps, although peristaltic pumps soon replaced these simple mechanisms with more advanced equipment.

CVVH, CVVHD and CVVHDF

Because arterial-venous techniques were associated with significant complications related to arterial cannulation and low blood flow in the extracorporeal circulation, continuous veno-venous hemofiltration (CVVH) or hemodialysis (CVVHD)
hemodiafiltration (CVVHDF) took over thanks to the availabil-
ity of double lumen venous catheters and machines with a
peristaltic blood pump (7-10). These changes improved the
safety and performance of extracorporeal treatments in the
ICU, allowing the use of high blood flows (>150 mL/min) and
large dialyzers (>1.0 m²). This resulted in better control of hy-
per-catabolic states and other severe pathophysiological de-
rangements. Initially veno-venous circuits took advantage of
already existing technology, often creating a combination of
devices (blood pump, UF pump, reinfusion pump, anticoagu-
lation, etc.) that were not integrated and, therefore, unable
to communicate and operate together, with the possibility of
amplifying errors and complications. Adoptive technology al-
lowed significant advances to be made, but it soon proved
inadequate when a clear need for integrated and safer de-
vices became evident in clinical practice.

Integrated technology

In Vicenza we started the process of integration of blood
dialysate filtrate pumps in a single machine and pushed
the industry of the field toward new research to create dedi-
cated devices for CRRT. With this effort, companies mostly in-
volved in chronic hemodialysis began to collect components
from chronic machines and to integrate them into machines
for CRRT (11, 12). Using this approach, several companies
made new equipment: B. Braun moved from TRIO (3 separate
pumps) to the compact ECU Carex machine (Fig. 1) designed
by the engineer, Mr. Frigato, in Mirandola. Baxter moved to
the integrated BM 25; and Hospal generated the DM 32 from
the blood module of the Monitril machine. Medica built an
integrated version of the Equipump and Equaline, while in
Germany, Fresenius Medical Care commercialized the DM08
with 1 blood pump and 2 pumps for dialysate or fluid bal-
ance (13-15). Bellco utilized the blood module of the Multi-
mat chronic machine to create the Multimat B Acute version,
and Gambro adjusted a special version of the AK 10 module
for continuous dialysis. All these machines derived from the
technology generated for chronic hemodialysis, but they re-
presented the seeds for the upcoming generation of specific
CRRT equipment (16, 17).

The PRISMA® revolution

With the progress in understanding the pathophysiol-
ogy of AKI and its clinical implications, the targets for renal
replacement therapy became clearer (18-25). The indica-
tions for CRRT were defined and the practice of CRRT was
better identified in the first edition of the book Critical Care
Nephrology, edited by Bellomo and Ronco. New standard of
treatments were required as well as new simplified meth-
ods to expand the application of CRRT to all ICUs. Special
requirements for easier institution of CRRT and easier mon-
toring of treatment had led to the development of the first
generation of CRRT integrated machines with several pumps
and different technique capabilities. It was now the time for
a revolution with a second-generation CRRT machine, and
this happened with the launch of the PRISMA®, the first in-
tegrated CRRT platform designed specifically for Acute RRT in
intensive care. The pre-assembled circuit and the auto-prim-
ing feature, together with the 4 pumps made CRRT possible
in almost every ICU, with improved safety and performance
even when performing complex techniques such as CVVHDF.

CRRT dose quantification

Started in 1995, in Vicenza we concluded the first ran-
domized trial on treatment dose in the year 2000 (26). We
underlined the importance of a minimum quantity (dose) of
treatment and we indicated 35 mL/kg per hour as the op-
timal target according to the trial result. This target, with a
minimum of 80% delivery of the prescribed dose, began the
golden standard for adequate CRRT and improved clinical
outcomes. Subsequent studies have demonstrated that low-
er doses can be equally safe and successful in treating the
critically ill patient (27-33), although effective delivery often
differs significantly from the prescription (34-37). The new
machines developed by industry with the possibility of mov-
ing toward more sophisticated techniques such as coupled
plasma filtration-adsorption (CPFA) and high-volume hemofil-
tration (HVHF) fulfilled these new performance requirements
(38-41). Improved usability and user-friendly interfaces with
systematic instructions made CRRT machines popular and
widely used in every ICU (17).

CRRT in sepsis

The original observation that higher doses of treatment
could be beneficial in patients with sepsis introduced the
rationale for HVHF and CPFA with the intent to remove chem-
ic mediators (42-45). HVHF or CPFA showed potent immu-
nomodulatory effects in sepsis. Since a cytokine network that
is synergistic, redundant, autocatalytic and self-augmenting
characterizes sepsis and systemic inflammatory response
syndrome, it is unlikely to achieve the control of such a non-
linear system by simple blockade or elimination of some
specific mediators. Thus, we hypothesized that the unselect-
ive nature of mediator removal by extracorporeal therapies
could be a potential advantage, capable of reconstituting
the immune-homeostasis of the septic patient, as suggested by
the ‘peak concentration’ hypothesis (42). Higher volumes and
complex techniques were made possible by the third gen-
eration of CRRT machines such as the Prismaflex (Gambro),
the Equasmart (Medica), The Lynda (Bellco), The Multifil-
trate (Fresenius Medical Care), The Acquarius (Edwards Life
Sciences) and others.

From renal replacement to multiple organ
support therapy

The effect of different modalities of CRRT on length of stay
and recovery of renal function in the general population is still
under evaluation, since the case mix changes in every study
and the population treated is not homogeneous. Further re-
search is needed in this field, although it has become evident
that Precision CRRT (personalized prescription) should be ad-
opted in order to optimize results in single patients, even in
the absence of the documented benefits of 1 specific technol-
ogy for the general population. Adequate technological sup-
port becomes mandatory to fulfil all these expectations and
new machines have been upgraded with specific circuits to support organs other than the kidney. The possibility of supporting or partially replacing the function of organs such as the liver, the lung and the heart with modified extracorporeal circuits, make multiple organ support therapy (MOST) a reality in the critical care setting. CRRT machines become platforms for multiple organ support via extracorporeal therapies carried out with specific biomaterials and devices (45, 46).

Sorbent therapies

Hemoperfusion has been available for detoxification purposes since the second part of the last century. Zeolites and charcoal were the most common sorbents, although soon a new generation of more hemocompatible materials became available. In recent years, cartridges with polymixin-B-coated polystyrenic fibres designed for the adsorption of endotoxin have been used for the treatment of sepsis. This therapy seems particularly beneficial in patients with post-surgery abdominal septic shock (47, 48). New sorbents, derived from the original experience carried out by our group in the early years of the new century, are today appearing as a new option for the treatment of sepsis (49-53).

Latest generation of CRRT machines

The latest generation of machines available on the market today, which represent the evolution of the past 4 decades of research and development is shown in Figure 3. Specific machines have now been designed to permit safe and reliable performance and monitoring. The apparent complexity of the circuit is made simple by a self-loading circuit or a cartridge that includes the filter and the blood and dialysate lines. Priming is performed automatically by the machine and pre- or post-dilution (reinfusion of substitution fluid before or after the filter) can easily be performed by changing the position of the reinfusion line. These new machines permit all CRRT techniques to be performed by programming the flows and the total amounts of fluid to be exchanged or circulated as a counter-current dialysate throughout the session.

Precision CRRT

The Acute Disease Quality Initiative consensus group has stressed the importance of applying the principles of precision medicine to CRRT (54). The group has invited CRRT experts and manufacturers to utilize a standardized nomenclature and sign a document called “Charta of Vicenza” (55) agreeing to follow the recommendations proposed by 2 detailed publications (56, 57). This was a starting point to generate a harmonized terminology and to advance in a standardized environment for the generation of useful pragmatic trials. Today we have several examples of new machines that include software and terminology coherent with the recommended nomenclature.

The consensus group also focused on the identification of patients requiring CRRT and the correct timing of application, technological needs and expected advances, pointing out the desirable characteristics of new equipment, membranes and the importance of integration of information technology into the process of patient care and decision-making (58-61).
Information technology and connectivity

The ADQI group has recently recommended the use of modern information technology (IT) tools to improve practice and patient care. Such tools can be used for data acquisition and storage but also for treatment monitoring (62). Manual, authorized or automatic feedback technology is available today in chronic dialysis machines and has been advocated for CRRT machines as well. Integration of patient and machine signals through IT tools and connectivity with electronic health record (EMR) and data collection systems will be required to allow pragmatic trials and make big data registries available for analysis. Data can then be used for Quality Assurance (QA) and for Continuous Quality Improvement (CQI) purposes in the centre, in the region and even in multinational data collection studies.

Machine connectivity can be provided via different tools. Machine and patient chip-cards can be used to extract data from single treatments from the front-end terminal (CRRT machine). Cable or wireless connectivity may permit the download of technical and clinical parameters from single or multiple machines and to analyse single treatment data as well as trends or statistics in multiple treatments. Cloud-based connectivity could help clinicians to generate virtual registries and analyse the performance of single treatments or centres in absolute terms, or relative to other units. This may result in important feedback to clinicians, to either strictly control outliers, or to change policies and procedures in the event of repeatedly unsatisfactory results.

Data collected and stored in EMRs may be rapidly evaluated and managed by ad hoc designed electronic snippets that can alert clinicians about dangerous trends or unwanted effects of CRRT. Solutions to the problem may be listed as suggestions or even automatically fed back into devices such as pumps and CRRT machines. The feedback may either require manual application of the necessary change by a nurse/physician, authorization of an operational change proposed by the system, or operate automatically.

Current and future perspectives

There are several areas of investigation where evolution in new therapeutic options and new devices is likely to occur. Different biomaterials and surface modifications have been introduced on semipermeable membranes to increase biocompatibility, to reduce thrombogenicity and the tendency toward fouling, and finally to modify sieving and adsorption properties. Vitamin E-coated membranes represent an example in which alpha-tocopherol has been covalently bound to a polysulfone membrane to reduce oxidant stress (63). These and other new membranes should be further investigated to elucidate the potential for improving the inflammatory pattern in sepsis.

Software integration should become a tool for new equipment to perform safer and more efficient CRRT treatments. The integration of bioimpedance and on-line haematocrit measurements may result in important effects on hemodynamic stability and treatment delivery (64). The integration of blood temperature monitoring may have the potential to control thermal energy balance and the patient’s temperature. This could allow a specific energy balance (KJ/h) or a target temperature control to be achieved by adjusting the dialysate or replacement fluid temperature according to signals coming from temperature sensors placed on blood and dialysate lines. A significant heat loss can in fact occur when the extracorporeal circuit is exposed to room temperature (65).

Automated circuit pressure control with flow adjustment feedback could provide the best possible blood flow in presence of a malfunctioning catheter or could provide early warning of access malfunction, preventing inadequate treatment delivery.

On-line chemical sensors for acid-base and electrolytes may provide the basis for continuous control via biochemical feedback on dialysate and replacement fluid composition.

Miniaturized and wearable technology

There is a great deal of interest in applying nanotechnology, microfluidics and other emerging sciences to the field of renal replacement. In Vicenza we tested the first wearable system for ultrafiltration (66). For the original wearable belt, we mostly used components off the shelf, but we recently made new developments by creating a new design and applying newly conceived, dedicated technology (67-69). Wearable devices are mostly conceived for ambulatory care and out-of-hospital patients. Nevertheless, it seems that miniaturized systems may become useful even in the acute patient, allowing mobility, low-priming-volume extracorporeal circuits and better care at the bedside.

Specific technology for small infants and paediatric applications

An interesting development in the process of machine and device miniaturization is the application of small-sized components for infants and children for whom the adult technology seems to be clearly inadequate. The requirement for specific technology in the field of paediatric CRRT emerged in the early 1980s (70). Over the years we personally contributed to a significant evolution of the field (71-74) and the historical milestones of paediatric CRRT are reported in Figure 3. Quite recently, based on the observation that every CRRT machine is conceived for adult patients and the use in neonates and small infants is precluded or off-label, we decided to undertake a special project for the creation of miniaturized equipment specifically designed for these small patients. We started from scratch and we moved, through artisanal design and rough assembly of prototypes, to an industrially designed machine called CARPEDIEM (Cardio Renal Pediatric Dialysis Emergency Machine). This evolution has captured new interest in the treatment of AKI in neonates and has allowed different techniques to be performed with the possibility of precisely adjusting the treatment dose and fluid balance in babies with body weights as low as 1.5 kg (75, 76) (Fig. 4). There is a consensus that such a specific technology will probably modify the outcome of AKI in neonates and small infants.

Conclusions

Over the last 40 years, CRRT has been widely utilized for the management of AKI in critically ill patients (77-79). The Vicenza Centre has heavily contributed to important tech-
Continuous renal replacement therapy

Fig. 4 - First CRRT treatment with CARPEDIEM (Cardio renal Pediatric Dialysis Emergency Machine).

Ronco C, Fabris A, Feriani M, et al. Technical and clinical evaluation of a new system for ultrafiltration control during hemodialysis. ASAIO Trans. 1988;34(3):613-616.

Zobel G, Ring E, Kuttnig M, Grubbauer HM. Five years experience with continuous extracorporeal renal support in paediatric intensive care. Intensive Care Med. 1991;17(6):315-319.

Better OS. Acute renal failure in casualties of mass disasters. Kidney Int Suppl. 1993;41:S235-S236.

Werner HA, Herbertson MJ, Seear MD. Operating characteristics of pediatric continuous arteriovenous hemofiltration in an animal model. Pediatr Nephrol. 1993;7(2):189-193.

Heinrichs W, Mönk U, Fauth U, Halmágyi M. An automatic system for fluid balance in continuous hemofiltration with very high precision. Contrib Nephrol. 1991;93:167-170.

Alkhasheyn F, Vincent HH, van Ittersum FJ, van Duyl WA, Schalekamp MA. A mathematical model of continuous arterio-venous hemodiafiltration (CAVHD). Comput Methods Programs Biomed. 1990;31(3-4):215-224.

Barber ND, Gibbs JS, Barrett P, Fox KM. Quality of haemofiltration fluids: a potential cause of severe electrolyte imbalance. Br Med J (Clin Res Ed). 1987;295(6605):1025.

Colton CK. Analysis of membrane processes for blood purification. Blood Purif. 1987;5(4):202-51.

Macias WL, Mueller BA, Scarim SK, Robinson M, Rudy DW. Continuous venovenous hemofiltration: an alternative to continuous arteriovenous hemofiltration and hemodiafiltration in acute renal failure. Am J Kidney Dis. 1991;18(4):451-458.

Yorgin PD, Krensly AM, Tune BM. Continuous venovenous hemofiltration. Pediatr Nephrol. 1990;4(6):640-642.

Ricci Z, Bonello M, Salvatori G, et al. Continuous renal replacement technology: from adaptive devices to flexible multipurpose machines. Crit Care Resusc. 2004;6(3):180-187.

Ronco C, Bellomo R. The evolving technology for continuous renal replacement therapy from current standards to high volume hemofiltration. Curr Opin Crit Care. 1997;3:426-433.

Tan HK, Baldwin I, Bellomo R. Continuous veno-venous hemofiltration without anticoagulation in high-risk patients. Intensive Care Med. 2000;26(11):1652-1657.

Abramson S, Niles JL. Anticoagulation in continuous renal replacement therapy. Curr Opin Nephrol Hypertens. 1999;8(6):701-707.

Böhler J, Donauer J, Keller F. Pharmacokinetic principles during continuous renal replacement therapy: drugs and dosage. Kidney Int Suppl. 1999;(72):S24-8.

Jacka MJ, Ivancanova X, Gibney RT. Continuous renal replacement therapy improves renal recovery from acute renal failure. Can J Anaesth. 2005;52(3):327-332.

Gillespie RS, Seidel K, Symons JM. Effect of fluid overload and dose of replacement fluid on survival in hemofiltration. Pediatr Nephrol. 2004;19(12):1394-1399.

Luyckx VA, Bonventre JV. Dose of dialysis in acute renal failure. Semin Dial. 2004;17(1):30-36.

Clark WR, Turk JE, Kraus MA, Gao D. Dose determinants in continuous renal replacement therapy. Artif Organs. 2003;27(9):815-820.

Liao Z, Zhang W, Hardy PA, et al. Kinetic comparison of different acute dialysis therapies. Artif Organs. 2003;27(9):802-807.

Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous venovenous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet. 2000;356:26-30.

Ricci Z, Salvatori G, Bonello M, et al. A new machine for continuous renal replacement therapy: from development to clinical testing. Expert Rev Med Devices. 2005;2(1):47-55.

Garzotto F, Ostermann M, Martin-Langerwerf D, et al. DoReMiFA study group. The Dose Response Multicentre Investigator
29. Lorenzini A, Garzotto F, Alghisi A, et al. CVVHD treatment with CARPEDIEM: small solute clearance at different blood and dialysate flows with three different surface area filter configurations. Pediatr Nephrol. 2016;31(10):1659-1665.

30. Villa G, Ricci Z, Romagnoli S, Ronco C. Multidimensional Approach to Adequacy of Renal Replacement Therapy in Acute Kidney Injury. Contrib Nephrol. 2016;187:94-105.

31. Swartz R, Pasko D, O’Toole J, Starmann B. Improving the delivery of continuous renal replacement therapy using regional citrate anticoagulation. Clin Nephrol. 2004;61(2):134-143.

32. Ricci Z, Ronco C. Renal replacement therapy in the critically ill: getting it right. Curr Opin Crit Care. 2012;18(6):607-612.

33. Ricci Z, Ronco C. Timing, dose and mode of dialysis in acute kidney injury. Curr Opin Crit Care. 2011;17(6):556-561.

34. Vesconi S, Cruz DN, Fumagalli R, et al. DOSe ReSPonse Multicentre International Collaborative Initiative (DO-RE-MI Study Group). Delivered dose of renal replacement therapy and mortality in critically ill patients with acute kidney injury. Crit Care. 2009;13(2):R57.

35. Ronco C, Cruz D, Oudemans van Straaten H, et al. Dose of dialysis in acute renal failure: in vitro studies. Nephrol Dial Transplant. 2004;19(2):245-250.

36. Ricci Z, Bellomo R, Ronco C. Dose of dialysis in acute renal failure: practical applications. Crit Care. 2017;21:244-245.

37. Ronco C, The Charta of Vicenza. Blood Purif. 2015;40:1-5.

38. Neri M, Villa G, Garzotto F, et al. Nomenclature Standardization Initiative (NSI) Alliance. Nomenclature for renal replacement therapy in acute kidney injury: basic principles. Crit Care. 2016;20(1):318.

39. Villa G, Neri M, Bellomo R, et al. Nomenclature Standardization Initiative (NSI) Alliance. Nomenclature for renal replacement therapy and blood purification techniques in critically ill patients: practical applications. Crit Care. 2016;20(1):283.

40. Moruigan R, Hoste E, Mehta RL, et al. Acute Disease Quality Initiative (ADQI) Consensus Group. Precision Fluid Management in Continuous Renal Replacement Therapy. Blood Purif. 2016;42(3):266-278.

41. Cerda J, Baldwin I, Honore PM, Villa G, Kellum JA, Ronco C. ADQI Consensus Group. Role of Technology for the Management of AKI in Critically Ill Patients: From Adaptive Technology to Precision Continuous Renal Replacement Therapy. Blood Purif. 2016;42(3):248-265.

42. Bagshaw SM, Chakravartli MR, Ricci Z, et al. ADQI Consensus Group. Precision Continuous Renal Replacement Therapy and Solute Control. Blood Purif. 2016;42(3):238-247.

43. Kellum JA, Ronco C. The 17th Acute Disease Quality Initiative International Consensus Conference: Introducing Precision Renal Replacement Therapy. Blood Purif. 2016;42(3):221-223.

44. Clark WR, Garzotto F, Neri M, Lorenzini A, Zaccaria M, Ronco C. Data analytics for continuous renal replacement therapy: historical limitations and recent technology advances. Int J Artif Organs. 2016;39(8):399-406.

45. Yamashita A, Masaki H, Kobayashi E, Sukegawa T. Evaluation of solute penetration across the polysulfone membrane with vitamin E coating. Hemodial Int. 2015;39(2):520-525.

46. Chen H, Wu B, Gong D, Liu Z. Fluid overload at start of continuous renal replacement therapy is associated with poorer clinical condition and outcome: a prospective observational study on the combined use of bioimpedance vector analysis and serum N-terminal pro-B-type natriuretic peptide measurement. Crit Care. 2015;19:135.

47. Rahmati S, Ronco F, Spittle M, et al. Validation of the blood temperature monitor for extracorporeal thermal energy balance during in vitro continuous hemodialysis. Blood Purif. 2003;19(2):245-250.

48. Gura V, Ronco C, Nalesso F, et al. A wearable hemofilter for continuous ambulatory ultrafiltration. Kidney Int. 2008;73(4):497-502.

49. Tetta C, Bellomo R, Formica M, et al. Use of adsorbents in ARF therapy. Contrib Nephrol. 2002;137:181-8.

50. Cantaluppi V, Weber V, Lauritano C, et al. Protective effect of resin adsorption on septic plasma-induced tubular injury. Crit Care. 2010;14(1):R4.

51. Zhang J, Peng Z, Maberry D, et al. Effects of hemoadsorption with a novel adsorbent on sepsis: in vivo and in vitro study. Blood Purif. 2015;39(1-3):239-249.

52. Rimmele T, Kaynar AM, McLaughlin JN, et al. Leukocyte capture and modulation of cell-mediated immunity during human sepsis: an ex vivo study. Crit Care. 2013;17(2):R59.

53. Honore PM, Jacobs R, Joannes-Boyau O, et al. Newly designed CRRT membranes for sepsis and SIRS: a pragmatic approach for bedside intensivists summarizing the more recent advances: a systematic structured review. ASAIO J. 2013;59(2):99-106.

54. Forni LG, Chawlila L, Ronco C. Precision and improving outcomes in acute kidney injury: Personalizing the approach. J Crit Care. 2017;32:244-245.

55. Ronco C. Renal replacement therapy in the critically ill: getting it right. Curr Opin Crit Care. 2012;18(6):607-612.

56. Ricci Z, Ronco C. Timing, dose and mode of dialysis in acute kidney injury. Crit Care. 2011;17(6):556-561.

57. Villa G, Neri M, Bellomo R, et al. Nomenclature Standardization Initiative (NSI) Alliance. Nomenclature for renal replacement therapy in acute kidney injury: basic principles. Crit Care. 2016;20(1):318.

58. Forni LG, Chawlila L, Ronco C. Precision and improving outcomes in acute kidney injury: Personalizing the approach. J Crit Care. 2017;32:244-245.

59. Ronco C. The Charta of Vicenza. Blood Purif. 2015;40:1-5.

60. Neri M, Villa G, Garzotto F, et al. Nomenclature Standardization Initiative (NSI) Alliance. Nomenclature for renal replacement therapy and blood purification techniques in critically ill patients: practical applications. Crit Care. 2016;20(1):283.

61. Moruigan R, Hoste E, Mehta RL, et al. Acute Disease Quality Initiative (ADQI) Consensus Group. Precision Fluid Management in Continuous Renal Replacement Therapy. Blood Purif. 2016;42(3):266-278.

62. Clark WR, Garzotto F, Neri M, Lorenzini A, Zaccaria M, Ronco C. Data analytics for continuous renal replacement therapy: historical limitations and recent technology advances. Int J Artif Organs. 2016;39(8):399-406.

63. Yamashita A, Masaki H, Kobayashi E, Sukegawa T. Evaluation of solute penetration across the polysulfone membrane with vitamin E coating. Hemodial Int. 2015;39(2):520-525.

64. Chen H, Wu B, Gong D, Liu Z. Fluid overload at start of continuous renal replacement therapy is associated with poorer clinical condition and outcome: a prospective observational study on the combined use of bioimpedance vector analysis and serum N-terminal pro-B-type natriuretic peptide measurement. Crit Care. 2015;19:135.

65. Rahmati S, Ronco F, Spittle M, et al. Validation of the blood temperature monitor for extracorporeal thermal energy balance during in vitro continuous hemodialysis. Blood Purif. 2003;19(2):245-250.

66. Gura V, Ronco C, Nalesso F, et al. A wearable hemofilter for continuous ambulatory ultrafiltration. Kidney Int. 2008;73(4):497-502.

67. Armignacco P, Garzotto F, Neri M, Lorenzini A, Ronco C. Wak engineered evolution. Blood Purif. 2015;39(1-3):110-104.
68. Armignacco P, Lorenzin A, Neri M, Nalesso F, Garzotto F, Ronco C. Wearable devices for blood purification: principles, miniaturization, and technical challenges. Semin Dial. 2015;28(2):125-130.

69. Kim JC, Garzotto F, Nalesso F, et al. A wearable artificial kidney: technical requirements and potential solutions. Expert Rev Med Devices. 2011;8(5):567-579.

70. Ronco C, Brendolan A, Bragantini L, et al. Treatment of acute renal failure in newborns by Continuous Arterio-Venous Hemofiltration. Kidney Int 1986;29(4):908-915.

71. Ronco C. Evolution of Technology for Continuous Renal Replacement Therapy: Forty Years of Improvements. Contrib Nephrol. 2017;189:114-123.

72. Ronco C, Ricci Z, Goldstein SL. (R)evolution in the Management of Acute Kidney Injury in Newborns. Am J Kidney Dis. 2015;66(2):206-211.

73. Ronco C, Ricci Z. Pediatric continuous renal replacement: 20 years later. Intensive Care Med. 2015;41(6):985-93.

74. Garzotto F, Zanella M, Ronco C. The evolution of pediatric continuous renal replacement therapy. Nephron Clin Pract. 2014;127(1-4):172-175.

75. Ronco C, Garzotto F, Brendolan A, et al. Continuous renal replacement therapy in neonates and small infants: development and first-in-human use of a miniaturised machine (CARPEDIEM). Lancet. 2014;383:1807-1813.

76. Ronco C, Garzotto F, Ricci Z. CA.R.P.E.D.I.E.M. (Cardio-Renal Pediatric Dialysis Emergency Machine): evolution of continuous renal replacement therapies in infants. A personal journey. Pediatr Nephrol. 2012;27(8):1203-1211.

77. Kellum JA, Ronco C, Bellomo R. Acute kidney disease and the community. Lancet. 2016;14;387(10032):1974-1976.

78. Ronco C, Ricci Z, De Backer D, et al. Renal replacement therapy in acute kidney injury: controversy and consensus. Crit Care. 2015;19:146.

79. Bellomo R, Ronco C, Mehta RL, et al. Acute kidney injury in the ICU: from injury to recovery: reports from the 5th Paris International Conference. Ann Intensive Care. 2017;7(1):49.

80. Ronco C, Bellomo R. Acute renal failure and multiple organ dysfunction in the ICU: from renal replacement therapy (RRT) to multiple organ support therapy (MOST). Int J Artif Organs. 2002;25(8):733-747.

81. Mehta R, Bihorac A, Selby NM, et al. Acute Dialysis Quality Initiative (ADQI) Consensus Group. Establishing a continuum of acute kidney injury - tracing AKI using data source linkage and long-term follow-up: Workgroup Statements from the 15th ADQI Consensus Conference. Can J Kidney Health Dis. 2016;3:13.

82. Siew ED, Basu RK, Wunsch H, et al. 15th ADQI Consensus Group. Optimizing administrative datasets to examine acute kidney injury in the era of big data: workshop statement from the 15th ADQI Consensus Conference. Can J Kidney Health Dis. 2016;3:12.

83. Sutherland SM, Chawla LS, Kane-Gill SL, et al. 15th ADQI Consensus Group. Utilizing electronic health records to predict acute kidney injury risk and outcomes: workshop statements from the 15th ADQI Consensus Conference. Can J Kidney Health Dis. 2016;3:11.

84. Hoste EA, Kashani K, Gibney N, et al. 15 ADQI Consensus Group. Impact of electronic-alerting of acute kidney injury: workshop statements from the 15th ADQI Consensus Conference. Can J Kidney Health Dis. 2016;3:10.

85. James MT, Hobson CE, Darmon M, et al. Acute Dialysis Quality Initiative (ADQI) Consensus Group. Applications for detection of acute kidney injury using electronic medical records and clinical information systems: workshop statements from the 15th ADQI Consensus Conference. Can J Kidney Health Dis. 2016;3:9.

86. Bagshaw SM, Goldstein SL, Ronco C, Kellum JA. ADQI 15 Consensus Group. Acute kidney injury in the era of big data: the 15th ADQI Consensus Conference of the Acute Dialysis Quality Initiative (ADQI). Can J Kidney Health Dis. 2016;3:5.