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Nomenclature for renal replacement therapy in acute kidney injury: basic principles

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Abstract

This article reports the conclusions of a consensus expert conference on the basic principles and nomenclature of renal replacement therapy (RRT) currently utilized to manage acute kidney injury (AKI). This multidisciplinary consensus conference discusses common definitions, components, techniques, and operations of the machines and platforms used to deliver extracorporeal therapies, utilizing a "machine-centric" rather than a "patient-centric" approach. We provide a detailed description of the performance characteristics of membranes, filters, transmembrane transport of solutes and fluid, flows, and methods of measurement of delivered treatment, focusing on continuous renal replacement therapies (CRRT) which are utilized in the management of critically ill patients with AKI. This is a consensus report on nomenclature harmonization for principles of extracorporeal renal replacement therapies. Devices and operations are classified and defined in detail to serve as guidelines for future use of terminology in papers and research.

Keywords: Terminology, Diffusion, Convection, Ultrafiltration, Transmembrane pressure, CRRT membranes, CRRT modalities, Dose, CRRT efficiency, Clearance

Background

The management of critically ill patients with acute kidney injury (AKI) requiring renal replacement therapy (RRT) demands a multidisciplinary approach. In spite of previous efforts at harmonization, the terminology used to describe the different aspects and modalities of RRT is often confusing. A consensus conference on RRT terminology was organized to develop common definitions for the components, techniques, and operation of the machines and platforms used for acute extracorporeal therapies.

In this article, we report the conclusions of the consensus group on the basic principles underlying RRT technologies and the application of those principles to patient care, using "machine-centric" rather than "patient-centric" terminology. We provide a detailed description of the performance characteristics of membranes and filters, solute and fluid transport mechanisms across membranes, flow rate parameters, and methods of treatment evaluation, focusing on the continuous RRT (CRRT) used in the treatment of critically ill patients.

Methodology

A conference was organized in Vicenza, Italy, to gather experts in CRRT and members of CRRT manufacturing companies to establish consensus on technical terminology and definitions relevant to basic principles of CRRT and related technology [1]. The conference provided the background for a modified Delphi consensus methodology as previously utilized for the Acute Disease Quality initiative consensus sessions [2]. Prior to the conference, participants screened the literature of the last 25 years and previous taxonomy efforts [3–5]. Keywords included "*continuous renal replacement therapy*", "*dialysis*", "*hemofiltration*", "*convection*", "*diffusion*", "*ultrafiltration*", "*dose*", "*blood purification*", "*renal support*", "*multiorgan dysfunction*", together with the

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relative MeSH terms. Abstracts of 707 articles were screened and more than 300 papers were read in full and analyzed. Based on this literature search, a series of definitions and terms were proposed and consensus was achieved from the majority of experts who participated in the conference. Where consensus was lacking, different statements were created after two-thirds of the audience expressed a positive vote. We present the results of this effort of terminology harmonization called NSI (Nomenclature Standardization Initiative).

Characteristics of the membrane and filter

Geometric characteristics

The main one-dimensional geometric characteristics of hollow fiber membranes are length (L), mean inner radius (r_i^-), wall thickness (t), and number of pores (N_p). The membrane surface area depends on the number of fibers (N_f). Using these parameters, multidimensional characteristics [6] can be expressed as listed in Table 1.

Performance characteristics

The performance characteristics define the potential applications of each membrane.

Membrane ultrafiltration coefficient and filter ultrafiltration coefficient

The membrane ultrafiltration coefficient (K_{UF}) represents the water permeability of the filter membrane per unit of pressure and surface. It depends on both the dimensions of the membrane and the number of pores and is measured as:

$$K_{UF} = \frac{Q_{UF}}{TMP} \cdot \frac{1}{A}$$

where Q_{UF} is the ultrafiltration flow rate, TMP is the transmembrane pressure, and A is the membrane surface area. The unit of measurement is ml/h/mmHg/m^2. Treatment parameters that enhance or reduce pore blockage induce changes in the K_{UF}.

The filter ultrafiltration coefficient (DK_{UF}) is defined as the product of the K_{UF} and membrane surface area (A):

$$DK_{UF} = K_{UF} \cdot A$$

The unit of measurement is ml/h/mmHg. Membrane manufacturers measure DK_{UF} as the ratio of the Q_{UF} per unit of applied TMP.

The K_{UF} is used to define "high-flux" or "low-flux" membranes. Although there is no definitive consensus in the literature about the K_{UF} cut-off value [7], it is generally assumed that a K_{UF} <10 ml/h/mmHg/m^2 identifies a low-flux membrane, a K_{UF} of 10–25 ml/h/mmHg/m^2 identifies middle-flux membranes, and a K_{UF} >25 ml/h/mmHg/m^2 identifies high-flux membranes.

The term high-flux has been generally used to define a membrane with an ultrafiltration coefficient >25 ml/h/mmHg/m^2. This mainly describes the hydraulic permeability of the membrane (permeability to water). However, hydraulic permeability does not necessarily correspond to the permeability to solutes, which instead depends on the density of pores, the mean size of pores, and the distribution of pores. For this reason the terms high-flux and highly permeable membrane are not interchangeable.

Mass transfer area coefficient

The mass transfer area coefficient (K_0A) represents the overall capacity of the membrane to provide diffusive removal of solutes over the entire filter surface. It is defined as the product of the solute flux per unit of membrane area (K_0) and the membrane surface area. The unit of measurement is ml/min.

The K_0A value can change during dialysis as a result of changes in membrane permeability or a loss of membrane exchange surface area.

Membrane sieving coefficient/rejection coefficient

The sieving coefficient (SC) is the ratio of a specific solute concentration in the ultrafiltrate (removed only by a convective mechanism), divided by the mean plasma concentration in the filter:

$$SC = \frac{C_{UF}}{(C_{Pi} + C_{Po})/2}$$

where C_{UF} is the solute concentration in the ultrafiltrate, and C_{Pi} and C_{Po} the plasma solute concentrations at the inlet and outlet of the filter, respectively. A true calculation would require measurement of the solute concentration in plasma water rather than plasma to avoid interference of proteins. Nevertheless, for practical purposes, plasma concentration is normally accepted.

SC is correctly measurable only in the absence of a gradient for diffusion (no concentration gradient through the membrane). Measurement of the SC varies during treatment because the characteristics of the membrane change.

Table 1 Multidimensional characteristics of the membranes

Multidimensional characteristic	Symbol	Formula
Surface area	A	$A = 2 \cdot N_f \cdot L \cdot \pi \cdot r^-{}_i$
Filter priming volume	V_b^F	$V_b^F = N_f \cdot L \cdot \pi\, r_i^{-2}$
Total priming volume	V_b^{TOT}	$V_b^{TOT} = V_b^F V_b^{TOT}$ + volume of tubes
Membrane porosity	ρ	$\rho = N_p \cdot \pi \cdot r_p^{-2}$

L membrane length, N_f Number of fibers in the filter, N_p number of pores in the filter, $r^-{}_i$ mean inner radius of the fibers, $r^-{}_p$ mean inner radius of the pores

SC is specific for each solute and for every membrane (Fig. 1). The formula is commonly simplified to the ratio between the concentration in the ultrafiltrate and the concentration in pre-filter plasma.

The rejection coefficient (RC) is defined as:

$$RC = 1 - SC$$

Cut-Off

For a specific membrane, the cut-off represents the molecular weight of the smallest solutes retained by the membrane. Taking into account the normal distribution of membrane pore size, the statistical cut-off value is identified as the molecular weight of a solute with a SC of 0.1. For a specific membrane, the retention onset (cut-off 90 % or 0.9) represents the molecular weight of a molecule with a SC of 0.9. For a complete understanding of the performance characteristics of a membrane, the cut-off value and the retention onset both need to be taken into account, allowing evaluation of the profile of the SC curve for each membrane (Fig. 1) [8].

Clinically, the expression "high cut-off membrane" describes membranes with a cut-off value that approximates the molecular weight of albumin (before exposure to blood or plasma).

Mechanisms of solute and fluid transport

Solute transport occurs mainly by two phenomena: convection and diffusion. Fluid transport across semipermeable membranes is driven by ultrafiltration. Adsorption influences removal of hydrophobic (lipid-soluble) compounds by attachment of solute to the membrane. When solute removal rate (mass/time) is normalized by the concentration of blood/plasma entering the filter (mass/volume), the correct term to be used is "solute clearance" which is expressed in ml/min and describes the volume of blood completely purified by the solute in the unit of time.

Ultrafiltration and convection

Ultrafiltration describes the transport of plasma water (solvent, free of cells and colloids) through a semipermeable membrane, driven by a pressure gradient between blood and dialysate/ultrafiltrate compartments. It is influenced by the intrinsic properties of the filter, such as the DK_{UF}, and the operating parameters (e.g., TMP) [9]. Quantitatively, ultrafiltration is defined by the ultrafiltration rate (Q_{UF}):

$$Q_{UF} = DK_{UF} \cdot TMP$$

The term ultrafiltration requires some specifications depending on the context in which it is utilized. When

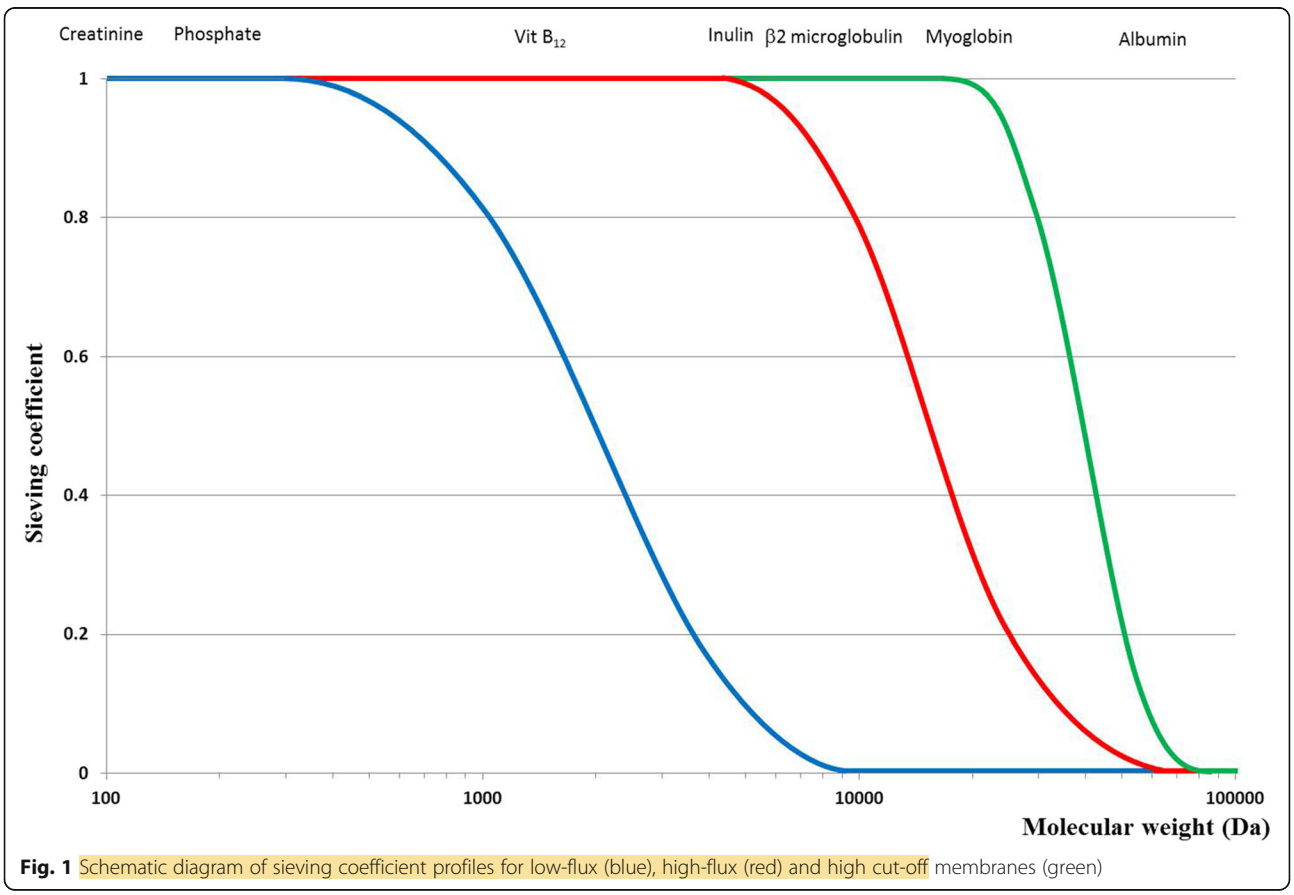

Fig. 1 Schematic diagram of sieving coefficient profiles for low-flux (blue), high-flux (red) and high cut-off membranes (green)

ultrafiltration is applied to a circuit or a CRRT treatment, specifications should be made using terms such as total ultrafiltration (UF = overall ultrafiltration volume produced during treatment) and net ultrafiltration (UF^{NET} = net ultrafiltrate volume removed from the patient by the machine). In the first case, the overall volume can be completely replaced, partially replaced, or not replaced at all. UF^{NET} is the difference between UF and the volume replaced in the circuit (Table 2).

When techniques are discussed, ultrafiltration may be isolated (no other mechanism is utilized in the treatment and only volume control is achieved), be used as part of hemofiltration (the ultrafiltrate is partially or completely replaced achieving volume and solute control), or combined with diffusion in treatments such as hemodialysis (HD) or hemodiafiltration (HDF). Different membranes are utilized for different techniques.

Convection is the process whereby solutes pass through membrane pores, dragged by fluid movement (ultrafiltration) caused by a hydrostatic and/or osmotic transmembrane pressure gradient.

The convective flux (J_c) of a solute depends on the Q_{UF}, the membrane surface area (A), the solute concentration in plasma (C_{Pi}) and the solute SC:

$$J_c = \frac{Q_{UF}}{A} \cdot C_{Pi} \cdot SC$$

Compared to diffusive transport, convective transport permits the removal of higher molecular weight solutes at a higher rate [10].

Transmembrane pressure

In hollow fiber filters, the TMP is the pressure gradient across the membrane. The terms that define this gradient are the hydrostatic pressure in the blood compartment (P_B), the hydrostatic pressure in the dialysate/ultrafiltrate compartment (P_D) and the blood oncotic pressure (π_B). The TMP value varies with length (l) along the whole filter length (L):

$$TMP(l) = P_B(l) - P_D(l) - \pi_B(l)$$

Generally, TMP is expressed using a simplified formula:

$$TMP^* = \frac{P_{Bi} + P_{Bo}}{2} - \frac{P_{Di} + P_{Do}}{2} - \frac{\pi_{Bi} + \pi_{Bo}}{2}$$

where P_{Bi} is the blood inlet pressure, P_{Bo} the blood outlet pressure, P_{Di} the dialysate/ultrafiltrate inlet pressure, P_{Do} the dialysate/ultrafiltrate outlet pressure, π_{Bi} the

Table 2 Fluids and flows in continuous renal replacement therapy

Flowrate	Symbol	Unit of measure	Definitions and comments
Blood flowrate	Q_B	ml/min	Depends on: - modality - vascular access - hemodynamic stability of the patient
Plasma flowrate	Q_P	ml/min	Approximated as: $Q_P = (1 - HCT) \quad Q_B$ where HCT = hematocrit
Ultrafiltration flowrate	Q_{UF}	ml/h	Total volume of fluid removed in the filter by positive TMP per unit of time: $Q_{UF} = Q_{UF}^{NET} + Q_R$. Depends on: - blood flow rate - filter and membrane design - transmembrane pressure (TMP) - membrane ultrafiltration coefficient and surface area
Net ultrafiltration flowrate (Δ weight flowrate) (weight loss flowrate)	Q_{UF}^{NET}	ml/h	Net volume of fluid removed from the patient by the machine per unit of time
Plasma ultrafiltration flow rate	$Q_{P\text{-}UF}$	ml/h	Total volume of plasma removed in the plasma filter by TMP per unit of time
Replacement flowrate (Substitution flow rate) (Infusion flowrate)	Q_R^{PRE} Q_R^{POST} $Q_R^{PRE/POST}$	ml/h	Sterile fluid replacement can be: - upstream of filter (pre-replacement, pre-infusion or pre-dilution): reduced depurative efficiency but better filter life - downstream of filter (post-replacement, post-infusion or post-dilution): higher depurative efficiency but lower filter life - both upstream and downstream of filter (pre-post replacement, pre-post infusion or pre-post dilution): compromise between the two modalities
Replacement plasma flow rate	$Q_{P\text{-}R}$	ml/h	Replacement of plasma downstream of the plasma filter
Dialysate flowrate	Q_D	ml/h	Volume of dialysis fluid running into the circuit per unit of time
Effluent flowrate	Q_{EFF}	ml/h	Waste fluid per unit of time coming from the outflow port of the dialysate/ultrafiltrate compartment of the filter: $Q_{EFF} = Q_{UF} + Q_D = Q_{UF}^{NET} + Q_{R\ +}\ Q_D$

oncotic pressure of the inlet blood, and π_{Bo} the oncotic pressure of the outlet blood. It must be stressed that the TMP* is a positive, averaged value along the length of filter, and does not reflect the true local pressure profile in the filter. In other words, a positive TMP* does not imply a positive TMP (l) at each point in the filter.

Furthermore, CRRT machines do not usually directly measure the P_{Di} or the oncotic pressure, so the TMP is *estimated* using an even simpler formula:

$$TMP^* = \frac{P_{PRE} + P_{OUT}}{2} - P_{EFF}$$

where P_{PRE} is the pre-filter pressure, P_{OUT} the post-filter pressure, and P_{EFF} the pressure measured in the effluent line (all three measured by the machine). In the most common configuration, as blood flows down the filter, plasma water is removed and eliminated with the spent dialysate (if present), which flows in a counter-current direction. This ultrafiltration, called direct (or internal) filtration, identifies the one-directional movement of plasma water from the blood side to the dialysate/ultrafiltrate compartment of the filter due to a local positive TMP(l):

$$P_B(l) > P_D(l) + \pi_B(l)$$

At a critical point on the filter, where $P_B(l) = P_D(l) + \pi_B(l)$, equilibrium is achieved. After this point, the TMP (l) may become negative (even if TMP* is positive) allowing dialysate fluid to flow back into the blood compartment, resulting in so-called back filtration [11]. Back filtration describes the movement of fluid from the dialysate compartment to the blood compartment.

Diffusion

Diffusion is a process whereby molecules move randomly across a semipermeable membrane. Solute movement occurs from a more concentrated to a less concentrated area, until an equilibrium is reached between the two compartments. The concentration gradient ($C_1 - C_2 = dc$) is the driving force. The unidirectional solute diffusive flux (J_d) through a semipermeable membrane follows Fick's law of diffusion, being directly proportional to the diffusion coefficient (D) of the solute and inversely proportional to the distance between the compartments (dx) [10]:

$$J_d = -D\left(\frac{dc}{dx}\right)$$

The diffusivity coefficient D can be approximated using the Stokes-Einstein equation:

$$D = \frac{k_B T}{6\pi\mu R}$$

where k_B is the Boltzmann constant, T the absolute temperature, μ the viscosity of the medium, and R the effective radius of the molecules. Assuming that most molecules are globular and their effective radius is proportional to the cube root of their molecular weight, D is higher for smaller molecular weight solutes [12].

Adsorption

Adsorption is an extracorporeal process in which molecules dissolved in plasma or blood (in particular peptides and proteins) bind to the membrane structure or to other adsorbing substances such as charcoal, resins, or gels. The characteristics that influence molecule-membrane interaction are typical for each molecule (i.e., dimension, charge, and structure) and for each particular membrane (i.e., porosity, composition, hydrophobicity, surface potential). Adsorption cartridges should be evaluated in terms of their device adsorption capability (DAC) and their selectivity. DAC represents the total quantity of a specific molecule that the device is able to adsorb, and should be of the same order of magnitude as the blood concentration of that molecule multiplied by the blood volume. Selectivity is a safety parameter: it defines what the device does *not* adsorb.

Modalities of extracorporeal RRT

Hemodialysis

The main mechanism of solute removal in hemodialysis is diffusion, which is chiefly effective in the removal of small solutes. Hemodialysis involves the use of a *hemodialyzer*, where blood and dialysate solution circulate counter-current or co-current. A counter-current configuration is preferred because the average concentration gradient is kept higher along the whole length of the dialyzer. Conversely, a co-current configuration guarantees better stability and control of hydrodynamic conditions, and better air removal during the priming phase [13]. High-flux filters permit achievement of significant convective transport: this modality is called high-flux hemodialysis [14].

Hemofiltration

Hemofiltration is an exclusively ultrafiltration/convection treatment in which high-flux membranes are utilized in the absence of dialysis fluid. Infusion of a sterile solution into the blood circuit reconstitutes the reduced plasma volume and reduces solute concentration. Infusion of a sterile solution (replacement fluid) can replace totally or partially the filtered volume. Replacement fluid can be infused pre-filter (*pre-dilution*) or post-filter (*post-dilution*). In terms of solute clearance, post-dilution is more efficient than pre-dilution, but can lead more easily to membrane fouling due to hemoconcentration [9].

Hemodiafiltration

Hemodiafiltration combines hemodialysis and hemofiltration, whereby the mechanisms involved in solute removal are both diffusive and convective. Since this modality utilizes high-flux membranes, adequate amounts of sterile solution must be infused to replace the removed volume (pre-filter or post-filter) [15].

Isolated ultrafiltration

The main goal of ultrafiltration is to remove fluid using semipermeable membranes without volume replacement, thus achieving volume but not solute control in the patient [16].

Plasmapheresis

Membrane plasmapheresis filters the plasma through plasma filters and replaces it with plasma-derived products, such as fresh frozen plasma, albumin, or other fluids. Alternatively, plasma can be extracted gravimetrically from whole blood using a centrifuge pump. Plasmapheresis is used to remove hydrophilic and lipophilic high molecular weight pathogenic substances [17].

Hemoperfusion/plasmaperfusion

In hemoperfusion or plasmaperfusion, blood or plasma circulates through a column containing specific sorbents, with adsorption as the only removal mechanism. Usually combined with other modalities, hemoperfusion and plasmaperfusion are used to remove specific hydrophobic (lipid-soluble) substances, toxins, or poisons [18].

Fluids, volumes and flows

Solute transport during extracorporeal treatments strictly depends on the operating conditions including blood flow rate, dialysate, net ultrafiltration, and replacement flow rates, designed to achieve the desired clearance performance. These typical CRRT parameters (fluids and flows) are listed in Table 2.

Filtration fraction and concentration ratio

The filtration fraction (FF) is defined as the ratio between the ultrafiltration flow rate (Q_{UF}) and the plasma flow rate (Q_P):

$$FF = \frac{Q_{UF}}{Q_P}$$

Filtration fraction can also be measured by the following equation:

$$FF = \frac{1-Prot_{IN}}{Prot_{OUT}}$$

where $Prot_{IN}$ is the protein concentration in plasma entering the filter and $Prot_{OUT}$ is the protein concentration in plasma exiting the filter.

A directly measured FF can be expressed as a fraction:

$$FF = \frac{Q_{UF}}{Q_P} = \frac{Q_{UF}}{Q_B(1-HCT) + Q_{R^{PRE}}}$$

where Q_R^{PRE} is the pre-replacement flow rate and Q_B the blood flow rate.

For practical clinical purposes (as often used in CRRT machines) it is useful to define the concentration ratio (CR), which quantifies the magnitude of hemoconcentration inside the filter:

$$CR = \frac{Q_{UF}}{Q_B + Q_{R^{PRE}}} = \frac{Q_R^{POST} + Q_{UF}^{NET} + Q_{R^{PRE}}}{Q_B + Q_{R^{PRE}}}$$

where Q_R^{POST} is the post-replacement flow rate, Q_R^{PRE} is the pre-replacement flow rate, and Q_{UF}^{NET} the net ultrafiltration flow rate (all of which sum to Q_{UF}). Clinically, while the filtration fraction should be kept ideally below 30 %, the CR should be kept below 20–25 % [19], depending on initial hematocrit, to reduce hemoconcentration and mitigate protein-membrane interactions.

Treatment evaluation methods: the "dose" of RRT

Although the most appropriate dose has not been established for specific patients, large studies have demonstrated in the general population a direct relationship between dose and survival for both intermittent and CRRT modalities [20–26]. Today, a growing body of evidence suggests the use of precision CRRT, which is characterized by the need to pay great attention to the balance between demand (of blood purification) and capacity (of the native kidney). In these circumstances, personalized prescription and monitoring of treatment dose is highly recommended [27–30]. Although treatment adequacy should be considered more appropriately as a composite of different elements rather than an index based solely on urea kinetics, in CRRT a treatment efficiency equal or higher than 25 ml/kg/h is commonly considered adequate. This will approximately result in a daily standardized Kt/V = 1 which describes the efficacy of treatment for a specific patient.

Dose identifies the volume of blood cleared of waste products and toxins by the extracorporeal circuit per unit of time. In practice, it is measured as the rate of removal of a representative solute. Urea is the solute most commonly used to quantify dose [31] because it is an indicator of protein catabolism and is retained in kidney failure [12]. Originally, this solute-based approach was developed to measure the dose of dialysis prescribed to patients with end-stage renal disease. In these patients, application of this approach is relatively simple and correlates well with patient outcomes [20]. However, when

using CRRT to treat critically ill patients, other measures of adequacy and dose should also be considered. One potentially easier and more reproducible means of estimating dose is incorporating the measurement of flow rates provided by the dialysis machine [32].

Multiple different definitions and formulas to calculate RRT "dose" have been proposed [33, 34]. In this section, we try to clarify the concept. During RRT, the definition of dose must include: target (patient), target (machine), current, average, projected, current effective delivered doses, and average effective delivered doses. Starting from these definitions, therapies should be identified by their efficiency, intensity, and efficacy.

Target dose (prescribed)

The target dose (prescribed) is the clearance prescribed for a specific patient in his/her specific clinical condition and represents the clearance the prescribing clinician wants to achieve in that patient.

Target machine dose (set)

The target machine dose is the clearance that the prescribing clinician wants to achieve from the machine. It is usually set as a target machine efficiency or by specifying the flow rate settings and RRT modality. The target machine dose can be modified during the treatment to reduce the mismatch between the target dose (prescribed) and the average effective delivered dose (measured).

Current dose (estimated from treatment parameters)

The current dose (estimated from treatment parameters) is the clearance at the present time estimated from the flow rates in the extracorporeal circuit. During downtime, when the machine treatment is stopped, the current dose is zero. Interruptions during the treatment can occur because of machine alarms, circuit clotting, vascular access malfunctions, or interruptions when the patient must leave the intensive care unit (ICU), such as for surgery or radiological investigations.

Average dose (measured/calculated)

The average dose is the clearance calculated for the current dose applied over the total treatment time. The total time of treatment is defined as the sum of the effective time of treatment and downtime. The effective time of treatment is the cumulative time during which the effluent pump is working. The average dose is usually an overestimate of the average effective delivered dose.

Projected dose (calculated/estimated)

The projected dose is the weighted-mean clearance that will theoretically be obtained at the end of the treatment. If the target machine dose is kept constant during treatment, the projected dose and the average dose will align. If the target machine dose is modified, the projected dose will depend on the average dose obtained until that moment and the new set target machine dose. The projected dose is usually an overestimate of the average effective delivered dose.

Current effective delivered dose (measured)

The current effective delivered dose (measured) is the clearance observed at every moment during the treatment. Unlike the current dose (estimated from treatment parameters), it is based on blood concentrations. The current effective delivered dose depends mainly on the specific RRT modality, treatment settings, and other technical and clinical issues that qualitatively and quantitatively affect clearance. The major determinants are differences between the displayed and real blood or effluent flow rates, inadequate vascular access, incorrect priming procedure, loss of surface area (clotting, air), loss of permeability (clotting of the membrane, protein cake deposition on the inner surface of membranes, concentration polarization), high blood viscosity and hematocrit, and excessive FF.

Average effective delivered dose (measured)

The average effective delivered dose (measured) or real dose is the clinically relevant (measured) clearance delivered to the patient. It is calculated on the basis of the weighted-mean of the current effective delivered dose, over the total time of treatment until that specific moment. The average effective delivered dose is the average of the current effective delivered dose during the time of treatment, and not of the current dose, because the latter is plagued by errors during times in which flow may be occurring with no solutes clearance, (e.g., bag changes, recirculation procedures). The largest discrepancies between the target dose and the average effective delivered dose are found in predominantly diffusion-based CRRT (i.e., continuous veno-venous hemodialysis and continuous veno-venous hemodiafiltration) [33].

In an ideal treatment, during which downtime and technical and/or clinical hindrances do not influence clearance, the target, target machine, current, average, projected, current effective delivered dose, and average effective delivered doses will be equal.

Efficiency, intensity and efficacy

Identified as a clearance (K), the efficiency represents the volume of blood cleared of a solute over a given period of time. It can be expressed as the ratio of blood volume over time (ml/min, ml/h, l/h, l/24 h, etc.) and is generally normalized to ideal patient weight (ml/kg/h). Efficiency depends on the reference molecules chosen (molecular size), removal mechanisms (diffusion, convection or both), and circuit operational characteristics (i.e., flow rates and type of filter). Efficiency can be used to

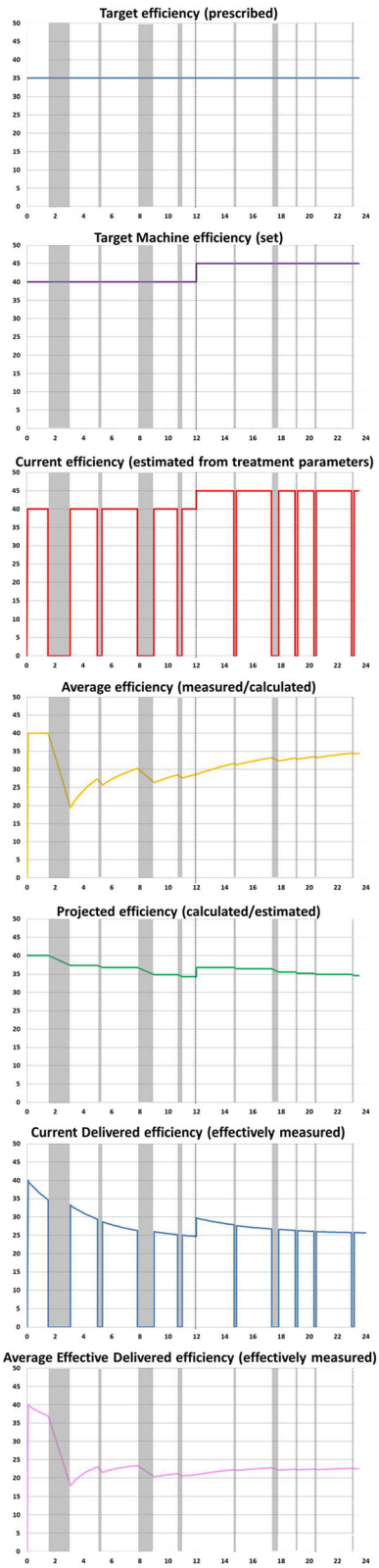

Fig. 2 Practical example showing the different trends in efficiency (ml/kg/h, *y* axis) vs treatment time (h, *x* axis) during treatment with continuous renal replacement therapy (CRRT). *Target efficiency (prescribed)*: "It is the amount of clearance prescribed for the specific patient in his/her specific clinical condition, and represents the amount of clearance that the doctor wants to achieve in that patient. Example: according to literature, the doctor decides that a dose of 35 ml/kg/h is the most adequate for his patient". *Target machine efficiency (set)*: "It is the amount of clearance that the physician wants to achieve in the machine. It is the only value that can be set in the machine. Example: taking into account the average downtime, the doctor sets the target machine dose to reach the target dose (prescribed). For example, to obtain a target dose (prescribed) of 35 ml/kg/h, the doctor sets flow rates and modalities to achieve a target machine dose of 40 ml/kg/h". *Current dose (estimated from treatment parameters)*: "It is the clearance at the present time, estimated considering the set flows in the extracorporeal circuit. During downtime, the current dose is zero. Example: based only on the instantaneous flow rates, the machine calculates the current dose at every moment of the treatment. A current dose of zero allows the user to recognize downtime". *Average dose (measured/calculated)*: "It is the clearance calculated for the current dose applied over the total time of treatment. Example: based on the total time of treatment and the current dose calculated at every moment, the machine displays the average dose. At a particular moment of the treatment, if the average dose equals 35 ml/kg/h (the target dose prescribed), the physician can assume that the patient is undertreated". *Projected dose (calculated/estimated)*: "It is the weighted-mean clearance that will theoretically be obtained at the end of the treatment. Example: based on the average dose obtained until a specific moment and the set target machine dose, the machine estimates the dose that theoretically will be obtained at the end of treatment session (24 h). At a particular moment during the treatment, if the projected dose is less than 35 ml/kg/h (target prescribed dose), the physician can assume that the patient will be undertreated at the end of the treatment". *Current effective delivered dose (measured)*: "It is the amount of clearance observed at every moment during treatment time. Unlike the current dose, it is based on blood concentrations. Example: the doctor now calculates actual blood clearance based on concentrations of solute markers. He often finds differences with the current dose (estimated from treatment parameters) because technical issues in the measurement of flow rates limit the accuracy of the estimation". *Average effective delivered dose (measured)*: "It is the clinically relevant amount of (measured) clearance delivered to the patient. It is calculated on the basis of the weighted-mean of the current effective delivered dose, over the total time of treatment until that specific moment"

compare different RRT treatments applied with the same modality using different settings and operational characteristics. Efficiency can be further categorized and defined as target efficiency, target machine efficiency, current efficiency, average efficiency, projected efficiency, current effective delivered efficiency, and average effective delivered efficiency. In Fig. 2, the different categories of efficiency during CRRT are illustrated with examples.

Intensity can be defined by the product "efficiency × time". In practice, intensity represents the blood volume cleared of a solute after a certain period of time; it can be expressed as ml or l. When comparing RRT modalities with different duration times, the use of intensity is more

appropriate than the use of efficiency. For example, despite its low efficiency, use of CRRT for a long period of time results in increased treatment intensity.

Renal failure patients frequently require more than a single treatment; therefore, frequency of treatment should be considered when assessing dose. Specifically, the product of intensity times frequency (measured as treatment days/week) is useful to obtain information beyond a single treatment. Although intensity allows comparison between different treatments, it does not take into account the volume of the solute pool.

Efficacy measures the removal of a specific solute achieved by a given treatment in a given patient. It can be identified as the ratio of the entire volume cleared during the treatment to the volume of distribution of that solute. In practice, efficacy is a dimensionless number and can be numerically defined as the ratio between intensity and the volume of distribution of a specific solute.

Definitions of efficiency, intensity, and efficacy, together with the related formulas and abbreviations, are given in Table 3.

Conclusions

Understanding the basic mechanisms underlying the process of RRT is essential to be able to make appropriate treatment choices for individual patients. Although apparently simple, those choices are in reality complex, and specific to each clinical situation.

Table 3 Definitions and formulas for efficiencies, intensities and efficacies

Measurement	Name	Symbol	Unit of measure	Formula
Efficiency	Target (prescribed)	K_T	ml/kg/h	Assuming that the patient's clinical condition does not change, K_T is a constant value throughout the treatment
Efficiency	Target machine	K_{Tm}	ml/kg/h	Considering the downtime and the reduction in clearance properties of the membranes during treatment, K_{Tm} is usually set at a greater value than K_T
Efficiency	Current	K_{Cr}	ml/kg/h	$K_{Cr} = \frac{\left(Q_{RPRE}+Q_D+Q_{UF}^{NET}+Q_R^{POST}\right)}{B.W.} \cdot \frac{Q_B}{Q_B+Q_{RPRE}}$
Efficiency	Average	K_{Am}	ml/kg/h	$K_{Am} = \frac{1}{t_1} \cdot \int_0^{t_1} KCrdt$
Efficiency	Projected	K_{Pr}	ml/kg/h	$K_{Pr} = \frac{\int_0^{t_1} K_{Cr}dt + (t_{tot}-t_1)\cdot K'_{Tm}}{t_{tot}}$ where K'_{Tm} is the new target machine efficiency set
Efficiency	Current effective delivered	K_{Cd}	ml/kg/h	$K_{Cd} = \left(Q_B \cdot \frac{C_{Bi}-C_{Bo}}{C_{Bi}} + Q_{UF} \cdot \frac{C_{Bo}}{C_{Bi}}\right) \cdot \frac{1}{B.W.}$
Efficiency	Average effective delivered	K_{Aed}	ml/kg/h	$K_{Aed} = \frac{1}{t_1} \cdot \int_0^{t_1} K_{Cd}dt$
Intensity	Target (prescribed)	I_T	ml/kg	Blood volume that should be cleared applying K_T during the total time of treatment
Intensity	Target machine	I_{Tm}	ml/kg	Blood volume that should be cleared applying K_{Tm} during the total time of treatment
Intensity	Current	I_{Cr}	ml/kg	$I_{Cr} = K_{Cr} \cdot t_{tot}$
Intensity	Average	I_{Am}	ml/kg	$I_{Am} = K_{Cm} \cdot t_1 = \int_0^{t_1} K_{Cr}dt$
Intensity	Projected	I_{Pr}	ml/kg	$I_{Pr} = K_{Pr} \cdot t_{tot} = \int_0^{t_1} K_{Cr}dt + (t_{tot}-t_1)\cdot K'_{Tm}$
Intensity	Current effective delivered	I_{Cd}	ml/kg	$I_{Cd} = K_{Cd} \cdot t_1$
Intensity	Average effective delivered	I_{Aed}	ml/kg	$I_{Aed} = K_{Ced} \cdot t_1 = \int_0^{t_1} K_{Cd}dt$
Efficacy	Target (prescribed)	E_T	Dimensionless	Solute removal obtained applying I_T to the volume of distribution of the solute
Efficacy	Target machine	E_{Tm}	Dimensionless	Solute removal obtained applying I_{Tm} to the volume of distribution of the solute
Efficacy	Current	E_{Cr}	Dimensionless	$E_{Cr} = \frac{I_{Cr}}{V} = \frac{K_{Cr} \cdot t_{tot}}{V}$
Efficacy	Average	E_{Am}	Dimensionless	$E_{Am} = \frac{I_{Cm}}{V} = \frac{1}{V}\int_0^{t_1} K_{Cr}dt$
Efficacy	Projected	E_{Pr}	Dimensionless	$E_{Pr} = \frac{I_{Pr}}{V} = \frac{1}{V} \cdot \left[\int_0^{t_1} K_{Cr}dt + (t_{tot}-t_1)\cdot K'_{Tm}\right]$
Efficacy	Current effective delivered	E_{Cd}	Dimensionless	$E_{Cd} = \frac{I_{Cd}}{V} = \frac{K_{Cd} \cdot t_1}{V} = \frac{1}{V} \cdot \left(Q_B \cdot \frac{C_{Bi}-C_{Bo}}{C_{Bi}} + Q_{UF} \cdot \frac{C_{Bo}}{C_{Bi}}\right) \cdot \frac{1}{B.W.} \cdot t_1$
Efficacy	Average effective delivered	E_{Aed}	Dimensionless	$E_{Aed} = \frac{I_{Ced}}{V} = \frac{K_{Ced} \cdot t_1}{V} = \frac{1}{V} \cdot \int_0^{t_1} K_{Cd}dt$

B.W. ideal body weight, C_{Bi} pre-filter blood concentration of the reference solute, C_{BO} post-filter blood concentration of the reference solute, *dt* delta time, Q_B blood flow rate, Q_D dialysate flow rate, Q_R^{POST} post-replacement flow rate, Q_R^{PRE} pre-replacement flow rate, Q_{UF}^{NET} net ultrafiltration flow rate, Q_{UF} ultrafiltration flow rate, t_{tot} total time of treatment, *V* volume of distribution of the reference solute

The aim of this consensus is to standardize the nomenclature used by all parties involved in planning and delivering RRT at any level. We hope that the industry will also adopt this standard terminology in the future.

Abbreviations

$\bar{r_i}$: Mean inner radius of the fibers; $\bar{r_p}$: Mean inner radius of the membrane pores; ρ: Membrane porosity; π_B: Oncotic pressure in the blood; π_{Bi}: Oncotic pressure of blood inlet; π_{Bo}: Oncotic pressure of blood outlet; A: Membrane surface area; AKI: Acute kidney injury; B.W.: Ideal body weight; C_{Bi}: Pre-filter blood concentration of the reference solute; C_{Bo}: Post-filter blood concentration of the reference solute; C_{Pi}: Pre-filter plasma concentration of the reference solute immediately before the filter; C_{Po}: Post-filter plasma concentration of the reference solute immediately after the filter; CR: Concentration ratio; CRRT: Continuous renal replacement therapy; C_{UF}: Concentration of the reference solute in the ultrafiltrate; D: Diffusion coefficient; DAC: Device adsorption capability; dc: Concentration gradient; DK_{UF}: Filter ultrafiltration coefficient; dx: Distance between compartments; E_{Aed}: Average effective delivered efficacy; E_{Am}: Average efficacy; E_{Cd}: Current effective delivered efficacy; E_{Cr}: Current efficacy; E_{Pr}: Projected efficacy; E_T: Target efficacy; E_{Tm}: Target machine efficacy; FF: Filtration fraction; HCT: Hematocrit; I_{Aed}: Average effective delivered intensity; I_{Am}: Average intensity; I_{Cd}: Current effective delivered intensity; I_{Cr}: Current intensity; ICU: Intensive care unit; I_{Pr}: Projected intensity; I_T: Target intensity; I_{Tm}: Target machine intensity; J_c: Convective flux; J_d: Diffusive flux; K: Clearance; K_0: Solute flux per unit of membrane area; K_0A: Mass transfer area coefficient; K_{Aed}: Average effective delivered efficiency; K_{Am}: Average efficiency; k_B: Boltzmann constant; K_{Cd}: Current effective delivered efficiency; K_{Cr}: Current efficiency; K_{Pr}: Projected efficiency; K_T: Target efficiency (prescribed); K'_{Tm}: New target machine efficiency set at time t_1; K_{Tm}: Target machine efficiency; K_{UF}: Membrane ultrafiltration coefficient; l: Infinitesimal part of the membrane's length; L: Length of the membrane; N_f: Number of fibers in the filter; N_p: Number of pores in the membrane of the filter; P_B: Hydrostatic pressure in the blood compartment; P_{Bi}: Hydrostatic pressure in the inlet part of the blood compartment; P_{Bo}: Hydrostatic pressure in the outlet part of the blood compartment; P_D: Hydrostatic pressure in the dialysate/ultrafiltrate compartment; P_{Di}: Hydrostatic pressure in the inlet part of the dialysate compartment; P_{Do}: Hydrostatic pressure in the outlet part of the dialysate compartment; P_{EFF}: Pressure in the effluent line; P_{OUT}: Pressure in the out-flow line; P_{PRE}: Blood pre-filter pressure measured by the machine; $Prot_{OUT}$: Protein concentration in plasma exiting the filter; $Prot_{IN}$: Protein concentration in plasma entering the filter; Q_B: Blood flow rate; Q_D: Dialysate flow rate; Q_{EFF}: Effluent flow rate; Q_P: Plasma flow rate; $Q_{P\text{-}R}$: Replacement plasma flow rate; $Q_{P\text{-}UF}$: Plasma ultrafiltration flow rate; Q_R: Total replacement flow rate; Q_R^{POST}: Replacement flow rate post-filter; Q_R^{PRE}: Replacement flow rate pre-filter; Q_{UF}: Ultrafiltration flow rate; Q_{UF}^{NET}: Net ultrafiltration flow rate; R: Radius of the molecules; RC: Rejection coefficient; RRT: Renal replacement therapy; SC: Sieving coefficient; T: Absolute temperature; t: Thickness of the fibers; t_1: Treatment elapsed time ($0 < t_1 < t_{tot}$); TMP*: Approximated cumulative pressure gradient across the entire membrane; TMP: Transmembrane pressure; t_{tot}: Total time of treatment; UF: Overall ultrafiltration volume produced during treatment; UF^{NET}: Net ultrafiltrate volume removed from the patient by the machine; V: Volume of distribution of the reference solute; V_b^F: Filter priming volume; V_b^{TOT}: Total priming volume; μ: Viscosity

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REVIEW Open Access

Nomenclature for renal replacement therapy and blood purification techniques in critically ill patients: practical applications

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Abstract

This article reports the conclusions of the second part of a consensus expert conference on the nomenclature of renal replacement therapy (RRT) techniques currently utilized to manage acute kidney injury and other organ dysfunction syndromes in critically ill patients. A multidisciplinary approach was taken to achieve harmonization of definitions, components, techniques, and operations of the extracorporeal therapies. The article describes the RRT techniques in detail with the relevant technology, procedures, and phases of treatment and key aspects of volume management/fluid balance in critically ill patients. In addition, the article describes recent developments in other extracorporeal therapies, including therapeutic plasma exchange, multiple organ support therapy, liver support, lung support, and blood purification in sepsis. This is a consensus report on nomenclature harmonization in extracorporeal blood purification therapies, such as hemofiltration, plasma exchange, multiple organ support therapies, and blood purification in sepsis.

Keywords: Terminology, Pump, Pressure sensor, CRRT machine, Continuous veno-venous hemodialysis, Continuous veno-venous hemofiltration, Continuous veno-venous hemodiafiltration, High volume hemofiltration, Continuous plasmafiltration coupled with adsorption, Hemoperfusion

Abbreviations: AKI, Acute kidney injury; AVVH, Accelerated veno-venous hemofiltration; CPE, Continuous plasma exchange; CPFA, Continuous plasmafiltration coupled with adsorption; CRRT, Continuous renal replacement therapy; CVVH, Continuous veno-venous hemofiltration; CVVHD, Continuous veno-venous hemodialysis; CVVHDF, Continuous veno-venous hemodiafiltration; CVVHFD, Continuous veno-venous high-flux dialysis; ECMO, Extracorporeal membrane oxygenation; ED, Extended dialysis; EDD, Extended daily dialysis; EDDf, Extended daily dialysis with filtration; FPSA, Fractionated plasma separation and adsorption; HVHF, High-volume hemofiltration; ICU, Intensive care unit; IHD, Intermittent hemodialysis; IHDF, Intermittent hemodiafiltration; IHF, Intermittent hemofiltration; IHFD, Intermittent high-flux dialysis; MARS, Molecular adsorbent recirculating system; MOST, Multiple organ support therapy; PIRRT, Prolonged intermittent renal replacement therapy; PMX, Polymyxin; RRT, Renal replacement therapy; SCUF, Slow continuous ultrafiltration; SLED, Sustained low-efficiency dialysis; SLEDD, Slow low-efficiency extended daily dialysis; SPAD, Single pass albumin dialysis; TMP, Transmembrane pressure; TPE, Therapeutic plasma exchange; VHVHF, Very high-volume hemofiltration

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Background

The use of renal replacement therapy (RRT) in the management of acute kidney injury (AKI) requires a multidisciplinary approach. It is, therefore, essential that all members of the team use the same terminology, but the terms used to describe the different modalities of RRT often vary and can be confusing. In this article, we provide an updated consensus nomenclature to help navigate this complex field. We review the practical applications of transmembrane solute and fluid transport principles and the control mechanisms for RRT devices. The article focuses on continuous renal replacement therapies (CRRTs), which are commonly used in the treatment of critically ill patients. We hope that this standardized terminology will be adopted by all involved in this field, including industry as they develop new devices.

Methodology

A conference was organized in Vicenza, Italy, to gather experts in CRRT and members of companies manufacturing CRRT hardware and devices to establish consensus on technical terminology and definitions relevant to basic principles of CRRT and related technologies [1]. The conference provided the background for a modified Delphi consensus methodology as previously utilized for the Acute Disease Quality initiative consensus sessions [2]. Prior to the conference, participants screened the literature of the last 25 years and previous taxonomy efforts [3–5]. Keywords included "continuous renal replacement therapy", "dialysis", "hemofiltration", "convection", "diffusion", "ultrafiltration", "dose", "blood purification", "renal support", "multiorgan dysfunction", together with the relative MeSH (Medical Subject Headings) terms. Abstracts of 707 articles were screened and more than 300 papers were read in full and analyzed. Based on this literature search, a series of definitions and terms were proposed and consensus was achieved from the majority of experts who participated in the conference. Where consensus was lacking, different statements were created after two-thirds of the audience expressed a positive vote. We present the results of this effort of terminology harmonization called the Nomenclature Standardization Initiative (NSI).

Hardware and devices

CRRT "hardware" includes the machine and all dedicated disposables. Knowledge of the nomenclature and the functions of the machine and its main components is extremely important, not only for nurses and technicians but also for clinicians.

Figure 1 depicts a standard CRRT machine equipped with current technology and characteristics [6, 7]. Its main components include:

1. *Screen*: the monitor through which the user interacts with the machine.

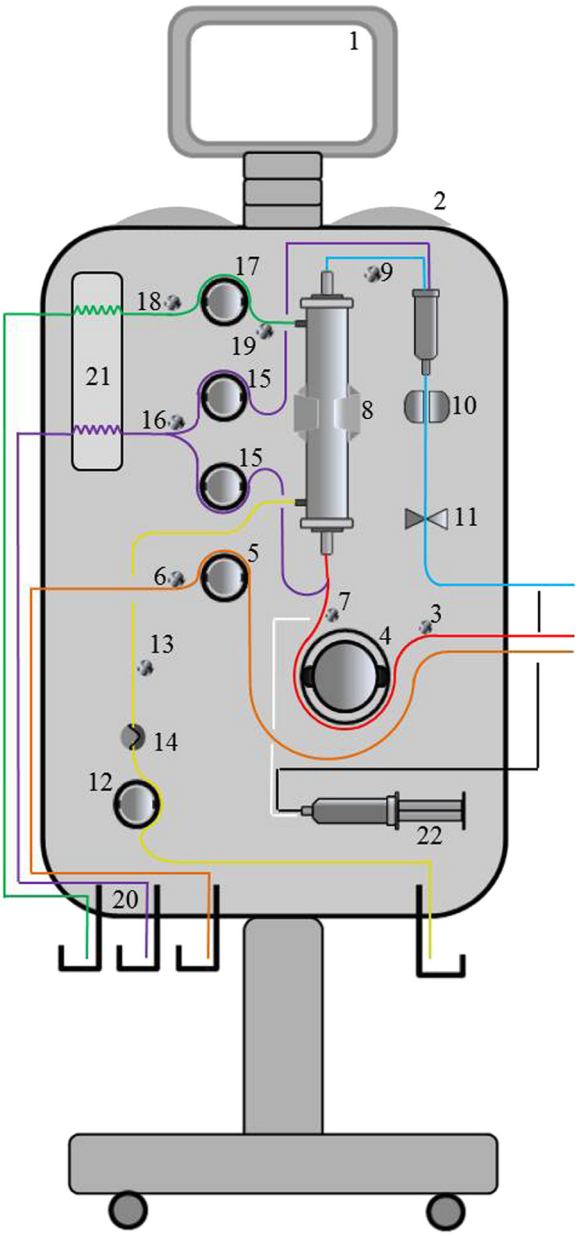

Fig. 1 The CRRT machine (see the text for explanation of numbered components)

2. *Alarm light and sound indicators*: visual and auditory alarms must be clear and comprehensive. The alarm settings should be unequivocally categorized according to a specific standard.
3. *In-flow pressure (P_{IN}) sensor* (upstream of blood pump): monitors the negative pressure in the blood in-flow line between the patient's vascular access and the blood pump.
4. *Blood pump*: pump that controls the blood flow rate through the extracorporeal circuit.

5. *Pre-blood pump*: pump that controls the flow rate of solutions, mainly regional anticoagulants (e.g., citrate), into the blood in-flow line before the blood pump.
6. *Pre-blood pump pressure sensor*: monitors the pressure before the pre-blood pump.
7. *Pre-filter pressure (P_{PRE}) sensor* (downstream of blood pump): located in the blood flow line between the blood pump and filter, this sensor monitors the positive pressure and enables calculation of the transmembrane pressure (TMP) and pressure drop (P_{DROP}) in the filter.
8. *Filter holder*: holds the filter or the entire filter-tubing kit on the machine.
9. *Out-flow pressure (P_{OUT}) sensor*: monitors the positive pressure between the filter and the patient vascular access. This sensor is used to calculate the TMP and pressure drop in the filter.
10. *Bubble detector*: a transducer that detects the presence of air in the blood out-flow line.
11. *Safety out-flow electroclamp*: a mechanism that produces occlusion of the blood out-flow line.
12. *Effluent/ultrafiltrate pump*: pump that controls the rate of total fluid removal from the filter.
13. *Effluent/ultrafiltrate pressure (P_{EFF}) sensor*: monitors the pressure in the effluent compartment of the filter. This sensor is placed before the effluent pump and allows calculation of the TMP.
14. *Blood leak detector (BLD)*: placed along the effluent line, it identifies unwanted blood leaks from the blood compartment of the filter.
15. *Replacement/infusion pump*: the pump that controls the rate of replacement fluid flow into the blood in-flow line (pre-dilution, usually between the blood pump and the filter) and/or into the blood out-flow line (post-dilution, usually in the blood out-flow chamber, such as the deaeration or venous drip chamber).
16. *Pre-replacement pump pressure sensor*: monitors the negative pressure before the replacement pump.
17. *Dialysate pump*: the pump that controls the rate of dialysate flow into the filter.
18. *Pre-dialysate pump pressure sensor*: monitors the negative pressure before the dialysate pump.
19. *Post-dialysate pump pressure (P_{Di}) sensor*: monitors the pressure in the dialysate line before the connection with the filter. Permits a better estimate of TMP.
20. *Fluid control system*: allows direct monitoring of the fluid balance related to fluids exchanged by the CRRT machine during the treatment. It can be gravimetric, volumetric, fluximetric, or a combination of these mechanisms.
21. *Heater*: heats the dialysate/replacement fluids or the blood flowing through the blood out-flow line of the extracorporeal circuit.
22. *Anticoagulant pump*: infuses anticoagulants into the blood circuit. Depending on the anticoagulation modality chosen, this pump can be a single unit (systemic anticoagulation, e.g., heparin) or be a part of a more complex infusion system with multiple pumps. In fact, in cases of regional anticoagulation (heparin-protamin or citrate-calcium) a second pump is necessary to infuse the antagonist of the selected anticoagulant into the blood out-flow line.

CRRT machine: procedures and phases of treatment

The different procedures performed by the machine [8] include:

Prescription phase: this phase consists of decisions by the prescribing clinician about the required modality and related operational parameters and includes periodic reassessment and/or change of the prescription.
Preparation phase: this phase consists of collection of necessary disposable material, identification and checking of the disposable set, set loading (cassette tubing), connection to the filter, positioning of the tubing, and hanging of bags.
Priming phase: priming solution is infused into the extracorporeal circuit in order to remove air and impurities remaining after sterilization of the set. When heparin anticoagulation is used, it is usually added to the priming solution. During this phase, the machine makes a general check of all components and sensors.
Connection to the patient: this phase consists of the connection of the extracorporeal lines to the patient's vascular access.
Treatment phase: net ultrafiltration and diffusive and/or convective solute transport are activated (all the pumps are working) and blood purification is performed. The patient's vital signs and circuit pressures must be monitored throughout the treatment phase.
Special procedures: during treatment, special procedures can include replenishment of dialysate, replacement fluid, and citrate bags (when citrate anticoagulation is used), change of syringes (when using heparin anticoagulation), repositioning of the vascular access, and temporary disconnection, recirculation, and replacement of filter and kit.
Blood return, disconnection and unload: the blood return procedure returns the blood to the patient. This is usually done by connecting a saline solution bag to the in-flow blood line and running the blood pump. When the circuit is flushed, the blood pump is stopped, the blood outflow line disconnected, and the tubing and filter unloaded.

CRRT disposables

Disposables (single-use components of the extracorporeal circuit) are specific for every machine and are usually designed for a specific treatment modality. The main disposables [9] and color codes that should mark each tubing line are listed in Table 1.

During CRRT, the filter is the key disposable through which blood or plasma is effectively purified by ultrafiltration, convection, and/or diffusion. Historically, the designation "filter" describes the entire purifying extracorporeal device system (i.e., membranes, housing, etc.). Among the different types of filters, hemofilters, hemodialyzers, and hemodiafilters should be used when exclusively convective, diffusive, or convective plus diffusive modalities, respectively, are applied. In this article we use these terms distinctly, taking into account the different CRRT modalities. A plasma filter is defined as a specific filter that allows the separation of plasma from cellular elements. Sorbents, cartridges, and adsorbers do not belong to the category of filters; in this case, adsorption is the only purifying modality. The only available type of CRRT filter that can perform diffusive and/or convective transport is shaped as a collection of parallel "hollow fibers". The filters can be mainly identified by membrane geometrics and performance characteristics [10–12].

Volume management and fluid balance

Fluid management during CRRT must take into account the volume and hemodynamic status of the patient. The machine fluid balance error is the fluid management error caused by CRRT machine malfunction. Based on the inherent variability ("tolerances") in the performance of the fluid pumps, scales, and other components of a CRRT machine's fluid management system, the manufacturer provides a specified limit ("specification") beyond which a fluid imbalance is considered an error. Fluid imbalances can be due to hardware (scales, pumps, tubes) or software (control system and protective subsystem) errors. Various systems have been proposed for fluid balancing in CRRT machines:

- Gravimetric fluid balancing, using one or more scales, is most commonly used in CRRT because it is the most reliable technique during long treatment intervals. A fundamental aspect of this type of system is the continuous weighing of the effluent along with replacement fluid and/or dialysate, with weight acting as a surrogate for fluid flow rate. The machine software analyzes these scale data on an ongoing basis and any discrepancies between prescribed and actual values lead to adjustments in pump rates based on a servo-feedback mechanism. Disadvantages include limitations in scale capacity, user errors, and other disturbances of the operating environment.
- In volumetric fluid balancing, a system of balancing chambers and valves is used. During long treatments, volumetric balancing is less accurate than gravimetric balancing because of systematic, cumulative errors, as there is no continuous servo-feedback safeguard for this approach. The advantage of this system is that it eliminates the need to collect effluent and thus reduces the frequency of fluid-related interventions.
- Fluxometric fluid balancing requires the application of accurate but expensive flow meters (electromagnetic, ultrasonic and Coriolis flow meters).

All these methods can be applied individually or in combination.

Extracorporeal therapies and treatments

Extracorporeal therapies can be categorized according to session frequency and duration.

Continuous therapies

CRRT is any extracorporeal technique that replaces kidney function and more generally provides blood purification for an extended period of time. CRRT is considered by many clinicians to be the most appropriate modality for the management of hemodynamically unstable patients with AKI, promoting better hemodynamic stability, reduced transcellular solute shifts, and better tolerance to fluid removal than intermittent extracorporeal therapies. The need for expertise, the necessity of continuous anticoagulation, the nursing workload, the continuous alarm vigilance, and the higher costs are some of the limitations of this approach. CRRT can be provided in various forms depending on resources, patient needs, and staff skills [5, 13, 14] (Fig. 2).

Prescription should be reviewed regularly.

CRRT treatments are currently performed using a double lumen catheter as vascular access, a "veno-venous" technique whereby blood is driven from a vein and, after being purified, returned to the same vein. "Arterio-venous" circuits have been virtually abandoned.

Slow continuous ultrafiltration

Slow continuous ultrafiltration (SCUF), based only on slow removal of plasma water, is used for patients with refractory fluid overload, with or without renal dysfunction. Its primary aim is to achieve safe and effective correction of fluid overload.

Continuous veno-venous hemofiltration

Continuous veno-venous hemofiltration (CVVH) uses convection, with ultrafiltrate replaced in part or completely with appropriate replacement fluids, to achieve solute clearance and volume control. Replacement fluid can

Table 1 Main disposables and their components with associated color code in a CRRT extracorporeal circuit (modified from [45])

Tubes	
Blood in-flow line (red; previously known as access or arterial line)	Segment connecting the patient's vascular access to the filter
	Segment for pressure measurement (upstream blood pump): segment of the blood in-flow line connected to the in-flow pressure sensor
	Pump segment line: segment inserted between the rotor and the stator of the blood pump
	Blood in-flow air removal chamber: allows removal of light air bubbles before the blood enters the filter
	Segment for pressure measurement (downstream blood pump): segment of the blood in-flow line connected to the pre-filter pressure sensor
Blood out-flow line (dark blue; previously known as return or venous line)	Segment connecting the filter to the patient's vascular access
	Segment for pressure measurement: segment of the blood out-flow line connected to the out-flow pressure sensor
	Blood out-flow air removal chamber: allows removal of light air bubbles before the blood returns to the patient
Effluent/ultrafiltrate line (yellow)	Segment that allows the flow of waste fluids from the filter
	Pump segment line: segment inserted between the rotor and the stator of the effluent/ultrafiltrate pump
	Segment for pressure measurement: segment of the effluent line connected to the effluent/ultrafiltrate pressure sensor
Dialysate line (green)	Segment that allows the flow of incoming dialysate into the filter
	Pump segment line: segment inserted between the rotor and the stator of the dialysate pump
	Segment for pressure measurement (if present): segment of the dialysate line connected to the dialysate pressure sensor
	Heater line: segment of the dialysate line placed in contact with the heater
Replacement line (purple or light blue)	Segment that allows the flow of replacement fluid into the blood in-flow and/or blood out-flow lines
	Pump segment line: segment inserted between the rotor and the stator of the replacement pump
	Segment for pressure measurement (if present): segment of the replacement line connected to the replacement pressure sensor
	Heater line: segment of the replacement line placed in contact with the heater
Pre-blood line (orange)	Segment that allows the flow of specific fluids (mainly regional anticoagulants) into the blood in-flow line before the blood pump
	Pump segment line: segment inserted between the rotor and the stator of the pre-blood pump
	Segment for pressure measurement (if present): segment of the pre-blood line connected to the pre-blood pressure sensor
Anticoagulant and specific antagonists line	Segments connecting the anticoagulant/specific antagonist bag or pump to the main blood circuit
	Citrate line (orange): segment for citrate infusion (i.e., pre-blood line)
	Heparin line (white): segment connecting the heparin syringe pump to the blood in-flow line
	Specific antagonist line (black): segment connecting the specific antagonist syringe pump to the blood out-flow line
Filter	
Fiber (membranes)	Every fiber, hollow and of cylindrical shape, allows the transport of fluids and solutes through their porous semi-permeable surface
Bundle	Entire number of fibers inside the housing
Housing	Plastic casing containing a single membrane fiber bundle
	Blood in-flow port: entrance port of blood entering into the filter
	Blood out-flow port: exit port of blood leaving the filter
	Dialysate in-flow port: entrance port of fresh dialysate
	Effluent/ultrafiltrate out-flow port: exit port of waste solution
Potting	Polyurethane component fixing the bundle within the housing and embedding the bundle at both ends of the filter

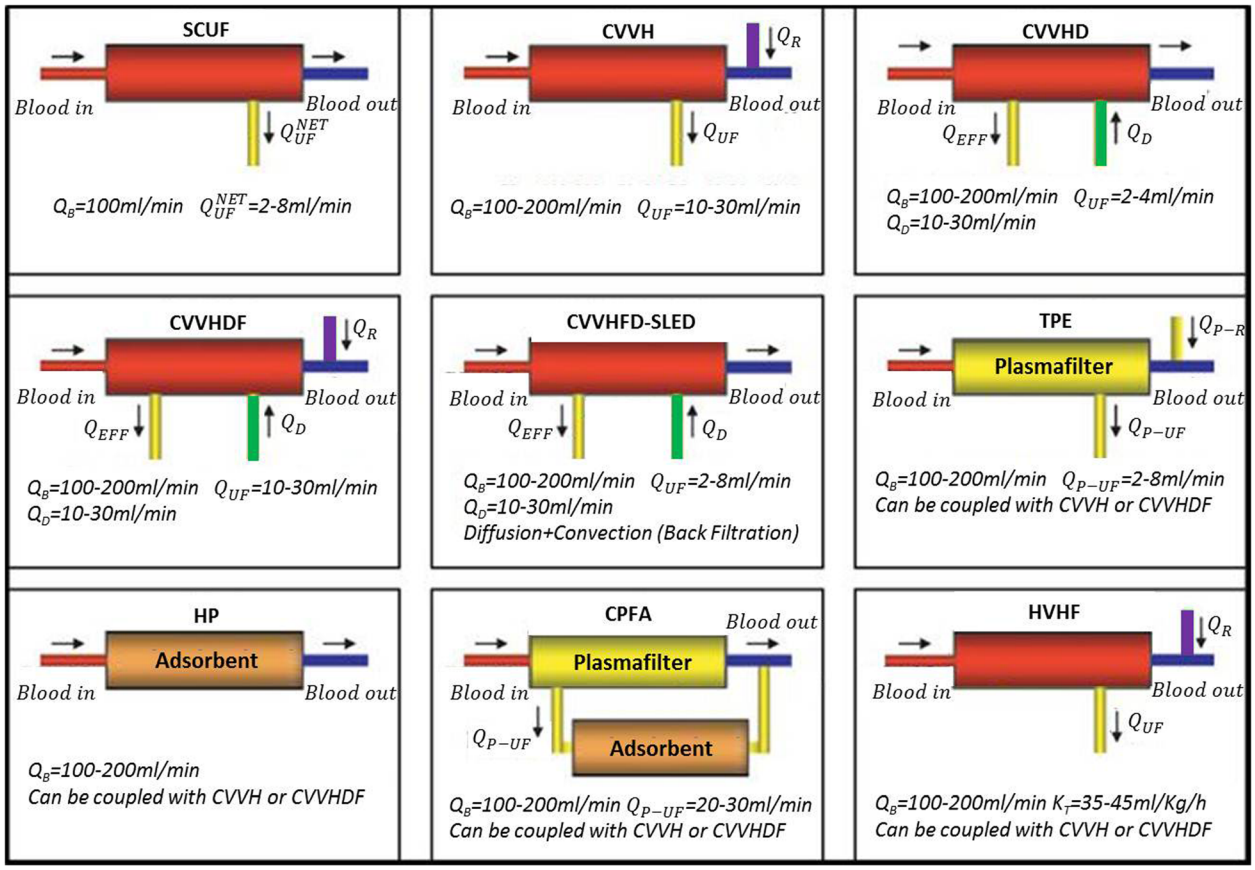

Fig. 2 Main extracorporeal therapies and treatments (modified from [5]) *Abbreviations*: Q_B blood flow rate, Q_{UF}^{NET} net ultrafiltration flow rate, Q_{UF} ultrafiltration flow rate, Q_D dialysate flow rate, Q_R total replacement flow rate, Q_{EFF} effluent flow rate, $Q_{P\text{-}R}$ replacement plasma flow rate, $Q_{P\text{-}UF}$ plasma ultrafiltration flow rate, *SCUF* slow continuous ultrafiltration, *CVVH* continuous veno-venous hemofiltration, *CVVHD* continuous veno-venous hemodialysis, *CVVHDF* continuous veno-venous hemodiafiltration, *CVVHFD-SLED* continuous veno-venous high-flux dialysis–sustained low-efficiency dialysis, *TPE* therapeutic plasma exchange, *HP* hemoperfusion, *CPFA* continuous plasma filtration coupled with adsorption, *HVHF* high-volume hemofiltration

be infused before (predilution) and/or after (postdilution) the hemofilter.

Continuous veno-venous hemodialysis

Continuous veno-venous hemodialysis (CVVHD) is a form of continuous hemodialysis characterized by counter-current/co-current dialysate flow rate into the dialysate compartment of the hemodialyzer. The main mechanism of transmembrane solute transport is diffusion.

Continuous veno-venous hemodiafiltration

Continuous veno-venous hemodiafiltration (CVVHDF) combines hemodialysis and hemofiltration modalities. Ultrafiltrate is replaced in part or completely by replacement fluid (pre- or post-infusion) and counter-current/co-current dialysate flow into the dialysate compartment. Solute clearance is achieved via diffusive and convective clearance.

Continuous veno-venous high-flux hemodialysis

Continuous veno-venous high-flux hemodialysis (CVVHFD) consists of the same treatment as in CVVHD but carried out using high-flux membranes. Due to the high-flux properties of the membrane, a convective component of solute clearance is achieved even if replacement fluid is not infused.

Intermittent therapies

Intermittent therapies are carried out in sessions of 3–5 h. They require adequate vascular access, specially trained nurses, and water processing and sterilization that produces pure water for dialysate. Since treatment times are relatively short, the depuration rate must be higher than that of CRRT. The most commonly prescribed intermittent therapies are intermittent hemodialysis (IHD), intermittent hemofiltration (IHF), intermittent hemodiafiltration (IHDF), and intermittent high-flux dialysis (IHFD). Other therapies are available combining different

modalities but these are not usually performed in the intensive care unit (ICU), so are not discussed here.

Hybrid therapies

With respect to frequency and duration, the term "hybrid therapies" relates to the blending of characteristics from both intermittent and continuous modalities. These therapies attempt to optimize the advantages and minimize the disadvantages of both modalities: efficient solute removal, slower ultrafiltration rates for hemodynamic stability, less anticoagulant exposure, shorter duration, lower costs, decreased nurse workload, and improved ICU workflow. Hybrid therapies encompass various specific "discontinuous" RRT modalities: sustained low-efficiency dialysis (SLED), slow low-efficiency extended daily dialysis (SLEDD), prolonged intermittent RRT (PIRRT), extended daily dialysis (EDD), extended daily dialysis with filtration (EDDf), extended dialysis (ED), "go slow dialysis", and accelerated veno-venous hemofiltration (AVVH).

Hybrid therapies are usually performed with standard intermittent hemodialysis equipment, including machines, filters, extracorporeal blood circuits, and, in some cases, online fluid production for dialysate and ultrafiltrate infusion. Solute removal is largely diffusive but variants with a convective component, such as EDDf and AVVH, are possible.

The most commonly prescribed hybrid therapy is SLED, a technique that uses reduced blood and dialysate flow rates and is usually limited to 8–12 h. Data from appropriately powered studies on the application of these techniques are limited [15].

Other extracorporeal therapies

Other blood purification techniques are also performed in the ICU to clear toxins and solutes generally not removable by "classic" RRT or to support single or multiple organ dysfunction. While the delivery of CRRT may be achieved without anticoagulation in some patients, these therapies typically require some form of anticoagulation.

Therapeutic plasma exchange

Therapeutic plasma exchange (TPE) consists of the automated removal of plasma (plasmapheresis) and its replacement (exchange) with a suitable fluid composed of fresh frozen plasma or albumin.

TPE is performed using a centrifugal-based system or a very highly permeable membrane that allows separation of plasma from the cellular elements of blood. In membrane-based TPE, pore sizes ranging between 0.2 and 0.6 microns allow a sieving coefficient of 0.9–1.0 for molecules with a molecular weight greater than 500 kDa [16].

Continuous plasma exchange (CPE) is a therapy derived from TPE that is performed with lower flow rates and for a longer period of time. Single or repeated sessions can be performed as pure CPE or in conjunction with other purification techniques.

Multiple organ support therapy

Recently, CRRT has been used in a wide range of "non-renal applications", including multiple organ support therapies (MOSTs), to manage patients with multiple organ dysfunction syndrome [17]. MOST requires a complex extracorporeal support system with a multi-tasking machine platform and multiple devices. The type and intensity of organ support therapy can be modulated according to the number and severity of organ dysfunctions.

Heart support In myocardial dysfunction, right and left ventricular dysfunction can be complicated by severe fluid overload [18]. SCUF, performed in patients with or without AKI, can reduce fluid overload, improve cardiac filling volumes and contractility and is usually well tolerated among hemodynamically unstable cardiac failure patients [19]. It may be especially worthy of consideration in patients with severe diuretic resistance and cardiorenal syndrome, for whom therapeutic options are limited.

Liver support Artificial liver support includes "cell-based" and "non-cell-based" devices, including conventional IHD, CRRT, and devices specifically designed to clear accumulated toxins associated with liver dysfunction [20, 21] (Table 2). In many non-cell-based systems, an albumin-enriched dialysate is necessary to remove such toxins (e.g., fatty acids, hydrophobic bile acids, and nitric oxide), which are highly albumin-bound. This "albumin dialysis" concept forms the basis of single pass albumin dialysis (SPAD) and the molecular adsorbent recirculating system (MARS) while Prometheus (Fresenius Medical Care, Bad Homburg, Germany) is based on fractionated plasma separation and adsorption (FPSA) [22].

Table 2 Liver support systems in the hepato-renal syndrome (modified from [20])

Non-cell-based systems	Intermittent, extended and continuous dialysis techniques
	Hemoperfusion techniques
	Plasma exchange techniques
	Plasmapheresis
	Plasma filtration/adsorption
	Albumin dialysis • MARS • SPAD
	Prometheus
Cell-based systems (Bioartificial liver support systems)	Human hepatocytes (bioartificial liver support system)
	Porcine hepatocytes

1. *Single pass albumin dialysis*
   In SPAD, albumin is used as a component of the dialysate for more effective protein-bound toxin removal. The blood is placed in contact with a standard albumin-impermeable high-flux membrane and is dialyzed against an albumin-containing dialysate. Protein-bound molecules that are small enough to pass from the blood compartment through the membrane pores are dialyzed and then bound to albumin in the dialysate. SPAD provides a single pass of fresh albumin dialysate; this characteristic constitutes the major difference between SPAD and MARS [23, 24].
2. *Molecular adsorbent recirculating system*
   MARS uses a hemodialyzer in a primary circuit, which is connected to a secondary circuit composed of a standard hemodialyzer, an activated carbon adsorber and an anion exchanger. In the primary circuit, the patient's blood is pumped into the MARS hemodialyzer and water-soluble substances diffuse through the dialysate solution. This membrane has a size selection threshold of less than 60 kDa, thus retaining albumin on the blood side; only the free fraction of toxins can cross the membrane in a manner similar to SPAD. The dialysate compartment of the MARS hemodialyzer is part of a secondary circuit, where a 20 % albumin solution circulates in a counter-current flow. Toxins can bind to the free albumin in the secondary circuit, while clearance of water-soluble substances occurs in a standard CRRT hemodialyzer. Hydrophobic albumin-bound toxins are then extractedby passage through activated charcoal and anion exchange columns, thus regenerating the albumin binding sites. The reconstituted albumin is then recirculated to maintain a transmembrane concentration gradient in the primary circuit hemodialyzer.
3. *Prometheus FPSA*
   The Prometheus system is based on FPSA combined with hemodialysis. The patient's blood is pumped toward a specific albumin-permeable membrane with a size-selection threshold of 250 kDa. The albumin fraction of blood is selectively filtered and albumin-bound toxins can freely pass the membrane by convection. In a secondary circuit, the filtered albumin-rich plasma fraction is treated by two absorber columns: a neutral resin absorber and an anion exchanger for removal of negatively charged toxins. The purified albumin-rich plasma fraction is re-infused into the primary circuit where, in a second step, conventional hemodialysis is performed to eliminate water soluble molecules [25, 26].

Lung support There is well-established evidence of interaction between lung and kidney functions and many critically ill patients may require concomitant extracorporeal kidney and lung support [27, 28]. In most cases, CRRT can be performed with the same vascular access used for extracorporeal lung support therapies, both for therapies requiring high blood flows (extracorporeal membrane oxygenation (ECMO) [29]) and, more recently, for therapies requiring low blood flows. ECMO is frequently performed in conjunction with CRRT and different circuit configurations can be used [27]. Conventional ECMO systems typically require blood flow rates substantially higher than those used in CRRT, although new therapies using lower blood flows may even be sufficient to achieve adequate extracorporeal oxygenation [30]. On the other hand, new lung support modalities utilizing blood flow rates similar to those applied in CRRT (and capable of being provided by CRRT machines) are sufficient to perform extracorporeal CO_2 removal [31].

Blood purification in sepsis In patients with hyperinflammation (mainly during sepsis), extracorporeal blood purification therapies have the potential to modulate the host inflammatory response through the removal of inflammatory mediators and/or bacterial toxins.

1. *High-volume hemofiltration*
   Although not unequivocally defined in the medical literature, high-volume hemofiltration (HVHF; Fig. 2) is identified as continuous treatment with a convective target dose (prescribed) greater than 35 ml/kg/h [32, 33]. Continuous treatments with a dose greater than 45 ml/kg/h identify very high-volume hemofiltration (VHVHF) modalities. Intermittent procedures with brief, very high-volume treatments at 100 to 120 ml/kg/h for 4–8 h, followed by conventional CVVH, are identified as pulse HVHF [34].
   However, there is no evidence that HVHF, when compared with standard dose hemofiltration, leads to a reduction in mortality [35]. There is insufficient evidence to routinely recommend the use of HVHF in critically ill patients with severe sepsis and/or septic shock except as interventions being investigated in the setting of a randomized clinical trial.
2. *Continuous plasmafiltration coupled with adsorption*
   Continuous plasmafiltration coupled with adsorption (CPFA) is a blood purification therapy (Fig. 2) that combines the advantages of CRRT and continuous plasma filtration without requiring large amounts of plasma substitutes. In the first step of CPFA, a plasma filter separates plasma from the blood cellular component and the plasma filtrate is pumped through a sorbent. The purified plasma is then returned to the main circuit where blood is

reconstituted and treated with standard CRRT modalities. There is no evidence that CPFA reduces mortality in patients with septic shock or that it positively affects other important clinical outcomes [36].

3. *Hemoperfusion*
Continuous hemoperfusion involves placement of a sorbent cartridge in series with the filter (Fig. 2) in order to remove those toxins that are not removable by classic CRRT. The sorbent is placed in direct contact with blood and adsorbs solutes through hydrophobic interactions, ionic attraction, hydrogen bonds, and van der Waals interactions [37]. Hemoperfusion requires an extremely biocompatible sorbent coated with a surface that prevents platelet adhesion and clotting activation. The removal characteristics of hemoperfusion are dependent on the different types of sorbent used, with effective surface area playing an important role. Polymyxin (PMX)-hemoperfusion is a technique based on the use of a cartridge containing fibers coated with PMX B, an antibiotic with high affinity for lipopolysaccharide. The aim is to remove circulating endotoxin. Results from studies of PMX-hemoperfusion have been controversial. Nevertheless, the most recent results seem to suggest no improvement in organ failure in patients treated with PMX-hemoperfusion [38, 39].

Conclusions

Application of technology at the bedside requires full knowledge of the basic principles and the operating mechanisms for every technique. When faced with a complex patient, practitioners can use a growing variety of extracorporeal treatment options. For patients with multiple organ failure, an increasingly rich panoply of options is being developed, including extracorporeal treatments for sepsis and for cardiac, pulmonary, and liver failure [40–44]. In this complex scenario, a multidisciplinary clinical care team composed of specialists from different disciplines and highly trained nurses is crucial to the success of the treatment. We suggest a framework for harmonization of terminology to reduce the errors and complications that can result from poor understanding and inadequate delivery of the prescribed therapies. Homogenized nomenclature is also important when reporting machine functions and clinical parameters to enable study comparisons and advance our understanding in this field, ultimately allowing for improvements in clinical practice and patient outcomes.

We trust that new publications, electronic medical records, and machine software will be designed and operated in compliance with the agreed terminology to enable consistent data collection and comparison.

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