Blood Purification

Hemodialysis - Guidelines

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Nomenclature of Extracorporeal Blood Purification Therapies for Acute Indications: The Nomenclature Standardization Conference

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Keywords
Extracorporeal blood purification · Adsorption · Hemoadsorption · Renal replacement therapy · Precision medicine · Blood purification

Abstract
The development of new extracorporeal blood purification (EBP) techniques has led to increased application in clinical practice but also inconsistencies in nomenclature and misunderstanding. In November 2022, an international consensus conference was held to establish consensus on the terminology of EBP therapies. It was agreed to define EBP therapies as techniques that use an extracorporeal circuit to remove and/or modulate circulating substances to achieve physiological homeostasis, including support of the function of specific organs and/or detoxification. Specific

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acute EBP techniques include renal replacement therapy, isolated ultrafiltration, hemoadsorption, and plasma therapies, all of which can be applied in isolation and combination. This paper summarizes the proposed nomenclature of EBP therapies and serves as a framework for clinical practice and future research.

Introduction

Significant advances have been made in extracorporeal blood purification (EBP) due to new technologies, refined biomaterials, an improved understanding of the benefits and challenges of these techniques, and new indications [1–9]. However, large-scale randomized clinical trials are lacking for most technologies, and major variability exists in current practice worldwide [10, 11]. Furthermore, there is considerable misunderstanding of EBP therapy, which is exacerbated by significant inconsistencies in terminology used for the different techniques, devices, and components. In 2016, a conference was held in Vicenza, Italy, to gather experts in renal replacement therapy (RRT) and members of companies manufacturing RRT machines and hardware to establish consensus on technical terminology and definitions relevant to basic principles of RRT and related technologies [12, 13]. In November 2022, a second consensus conference was organized by the International Renal Research Institute of Vicenza in collaboration with industry partners relevant to the field of EBP to establish consensus on the terminology for a broader range of EBP therapies. International experts from diverse professional backgrounds (nephrology, critical care, and anesthesia, including both adult medicine and pediatrics, and industry representatives) reviewed the existing literature, debated the terminology, and proposed consensus definitions for acute and chronic EBP techniques, the components and their application [41, 42]. This review summarizes the conclusions and suggests a standardized nomenclature of acute EBP therapies to harmonize clinical practice and future research in this field.

Consensus Recommendations

1. The term EBP encompasses techniques that use an extracorporeal circuit to remove and/or modulate circulating substances to achieve physiological homeostasis, including support of the function of specific organs and/or detoxification. Table 1 provides an overview of different EBP techniques.
2. We suggest that the term "hybrid therapy" be replaced by "multi-modality therapy," defined as the application of >1 mechanism of EBP (i.e., diffusion, convection, and/or adsorption) or >1 EBP therapy (i.e., continuous renal replacement therapy [CRRT] plus plasmapheresis, or hemoadsorption plus CRRT).

Description of Different EBP Techniques

Continuous Renal Replacement Therapy

CRRT comprises several strategies for EBP, including continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), and continuous veno-venous hemodiafiltration (CVVHDF). In many nephrology-based journals, especially in the USA, the term continuous kidney replacement therapy is also used. However, the term CRRT is more accepted internationally and across disciplines. Descriptions of CRRT hardware, including pumps, monitors and membranes, and ultrafiltration are provided in the previous consensus papers [12, 13] (for more information, see also online suppl. material: see https://doi.org/10.1159/000533468).

Continuous Veno-Venous Hemofiltration

Definition. CVVH uses convection for clearance (Fig. 1). A hydrostatic pressure gradient across a semipermeable membrane leads to fluid movement from the blood to the effluent side. The ultrafiltrate is removed and wholly or partially replaced with a solution containing a desirable concentration of organic and inorganic solutes before, after, or on both sides of the filter. The solvent drag phenomenon leads solutes to the effluent side across the membrane [14].

Continuous Veno-Venous Hemodialysis

Definition. CVVHD uses diffusion for clearance (Fig. 2). Using a dialysate with a desirable concentration of solutes, net solute movement occurs down a concentration gradient across a semipermeable membrane. Volume removal is achieved by generating a hydrostatic pressure gradient across the membrane which acts as a filter (i.e., ultrafiltration). Clearance depends on the dialysate flow rate, calculated as milliliters of dialysate per kilogram of the patient's ideal or adjusted body weight per hour of treatment.

Continuous Veno-Venous Hemodiafiltration

Definition. CVVHDF combines convection and diffusion for clearance (Fig. 3). In this mode, the replacement fluid and dialysate contain a desirable concentration

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Table 1. Overview of EBP techniques

EBP modality (preferred term)	Abbreviation	Terms to avoid	Main mechanism of solute removal				Duration	Technical characteristics
			diffusion	convection	adsorption	centrifugation		
Whole blood therapies								
Continuous veno-venous hemofiltration	CVVH			x	(x)		Continuous	
Continuous veno-venous hemodialysis	CVVHD		X		(x)			
Continuous veno-venous hemodiafiltration	CVVHDF		X	x	(x)			
Prolonged intermittent renal replacement therapy	PIRRT	SLEDD, EDD	X	(x)	(x)		Intermittent (6–24 h)	PIRRT can be performed using IHD or CRRT machines
Isolated ultrafiltration		SCUF		x			Intermittent or continuous	Removal of fluid without significant solute clearance
Intermittent hemodialysis	IHD	IRRT	X		(x)		Intermittent (usually 4–6 h but can be shorter if needed)	Higher dialysate flow-to-blood flow rate ratio compared to CRRT
Extracorporeal CO_2 removal	$ECCO_2R$		X				Continuous	CO_2 removal with little or no impact on oxygenation
Extracorporeal membrane oxygenation	ECMO		X				Continuous	Oxygenation and CO_2 removal
Hemoadsorption	HA	Hemoperfusion			x		Intermittent or continuous	Different materials can be used for adsorption (online supplementary Table S1)
Albumin-based therapies								
Molecular adsorbent recirculating system	MARS		X				Intermittent	
Single-pass albumin dialysis	SPAD		X				Continuous	

Table 1 (continued)

EBP modality (preferred term)	Abbreviation	Terms to avoid	Main mechanism of solute removal				Duration	Technical characteristics
			diffusion	convection	adsorption	centrifugation		
Plasma therapies								
Plasma exchange therapies								
Plasmapheresis				x	(x)	(x)	Intermittent	Plasma removal
Therapeutic plasma exchange	TPE			x		(x)	Intermittent	Plasma removal and replacement
Double filtration plasmapheresis	DFPP			x			Intermittent	Plasma removal and replacement
Plasma adsorption therapies								
Plasma adsorption filtration	PAF			x	x	(x)	Intermittent	Plasma removal, adsorption, and return
Coupled plasma filtration and adsorption	CPFA			x	x		Continuous	Plasma removal, adsorption, and return
Plasma filtration adsorption dialysis	PFAD		X	x	X	(x)	Intermittent	Plasma filtration, adsorption, dialysis, and return
Double plasma filtration molecular adsorption system	DPMAS	Plasma filtration and double molecular adsorption system		x	X		Intermittent	Plasma adsorption on two different adsorbers and return
Heparin-induced extracorporeal LDL precipitation	HELP		X	x	X		Intermittent	Plasma removal, adsorption, and return

"x" symbols denote the main mechanisms of solute removal for each EBP modality. "(x)" symbols under whole blood therapies denote secondary mechanisms that certain filters may display (e.g., additional adsorptive capacity due to surface modification, such as AN69-PEI or PMMA filters). "(x)" symbols under plasma exchange therapies and plasma adsorption therapies denote alternate mechanisms for the modality. AN, acrylonitrile; CO_2, carbon dioxide; EBP, extracorporeal blood purification; EDD, extended daily dialysis; IRRT, intermittent renal replacement therapy; LDL, low-density lipoprotein; PEI, polyethyleneimine; PMMA, poly (methyl methacrylate); SCUF, slow continuous ultrafiltration; SLED, sustained/slow low-efficiency daily dialysis.

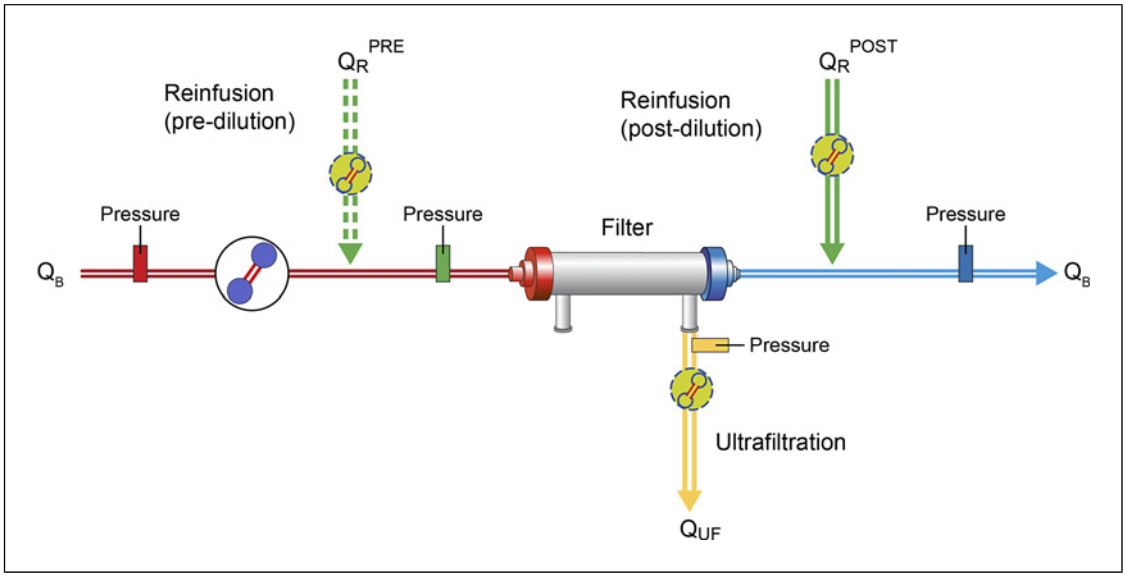

Fig. 1. Hemofiltration. Typical parameters in adults: Q_B = 150–250 mL/min; $Q_R^{PRE+POST}$ = 20–35 mL/kg/h; $Q_{UF} = Q_R + Q_{UF}^{NET}$; $Q_{UF}^{NET} = Q_{UF} - Q_R$. Q_B, blood flow; Q_R, reinfusion flow; Q_R^{PRE}, pre-filter reinfusion flow; Q_R^{POST}, post-filter reinfusion flow; Q_{UF}, ultrafiltration flow; Q_{UF}^{NET}, net ultrafiltration flow or volume of fluid removed from the patient substracted by volume of fluid infused to the patient per unit of time. Pressure = pressure detection.

of solutes (electrolytes and bicarbonate). Hydrostatic and concentration gradients across a semipermeable membrane lead to solute movement across the filter. Volume removal is achieved by generating a hydrostatic pressure gradient across the filter. Achieved clearance depends on the sum of dialysate and effluent flow rate (the dose applied corrected for pre-dilution if required), solute molecular weight, membrane characteristics, and additional mechanisms of solute removal, such as adsorption to the membrane.

Indications for CRRT in Clinical Practice. CRRT is indicated in patients with acute kidney injury (AKI) who have hemodynamic instability, are at risk of cerebral edema, or suffer from intracranial hypertension [3, 10, 15]. CVVH, CVVHD, and CVVHDF can be used interchangeably, but some specific aspects must be considered. CVVH requires a high-permeability membrane and is thought to have a higher ability to remove middle molecular weight molecules than modalities based on diffusion alone. In CVVHD, the fluid shift across the membrane is lower than in CVVH as the technique depends on diffusion rather than convection. Thus, the degree of hemoconcentration on the membrane's blood side is substantially lower than in CVVH. CVVHDF provides a higher total dose than CVVH alone without raising the filtration fraction which is the fraction of plasma that is removed from blood during hemofiltration. It is defined as the ratio of the total ultrafiltration flow to the plasma flow [12]. A higher filtration fraction can lead to hemoconcentration in the filter, increasing the risk of filter clotting.

Isolated Ultrafiltration

Definition. Isolated ultrafiltration describes ultrafiltration without the administration of replacement fluid. It can be performed intermittently or continuously which is often referred to as continuous isolated ultrafiltration (Fig. 4). It is purely intended for the treatment of fluid overload or maintenance of fluid balance [16, 17]. Clearance of solutes is negligible.

Indication. Isolated ultrafiltration is only used when the aim is to remove fluid, for instance, in patients with advanced heart failure who have failed to respond to diuretic-based strategies [16, 18].

Intermittent Forms of Renal Replacement Therapy

Intermittent Hemodialysis

Intermittent hemodialysis (IHD) uses diffusion for clearance. It is characterized by the countercurrent/concurrent flow of blood and dialysate (a solution with a desirable concentration of solutes). Solute clearance is provided by solute movement across a semipermeable

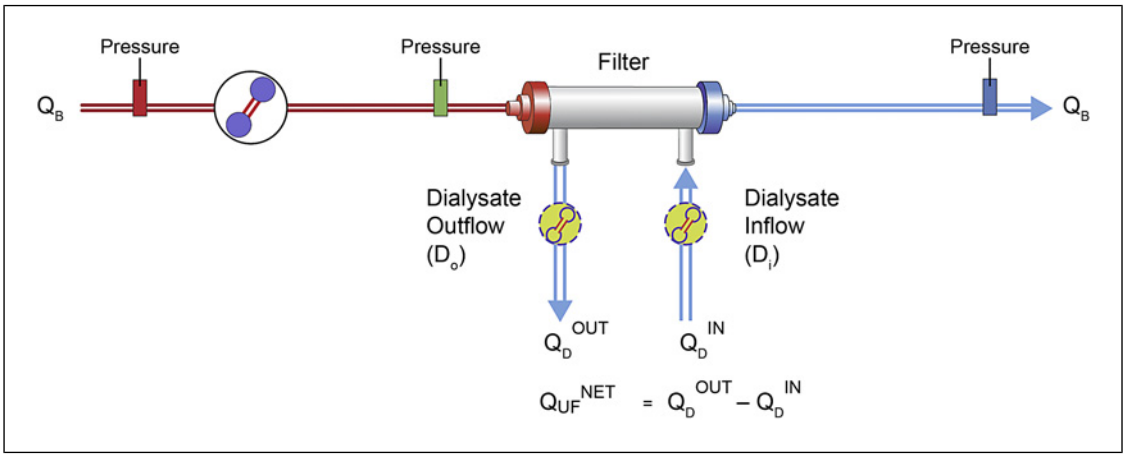

Fig. 2. Hemodialysis for acute indications. Typical parameters in adults: **CVVHD** – Q_B = 80–150 mL/min, Q_D^{IN} = 20–35 mL/kg/h, sterile bagged dialysate; **PIRRT** – 6–12 h sessions usually daily, Q_B = 150–200 mL/min, Q_D^{IN} = 200–400 mL/min, online or bagged dialysate; **IHD** – <6 h sessions daily or alternate days, Q_B = 200–350 mL/min, Q_D^{IN} = 400–800 mL/min, online dialysate. CVVHD, chronic veno-venous hemodialysis; IHD, intermittend hemodialysis; PIRRT, prolonged intermittend renal replacement therapy; Q_B, blood flow; Q_D^{IN}, flow of dialysis solution at the inlet; Q_D^{OUT}, flow of dialysis solution at the outlet; Q_{UF}^{NET}, net ultrafiltration flow or volume of fluid removed from the patient substracted by volume of fluid infused to the patient per unit of time. Pressure = pressure detection.

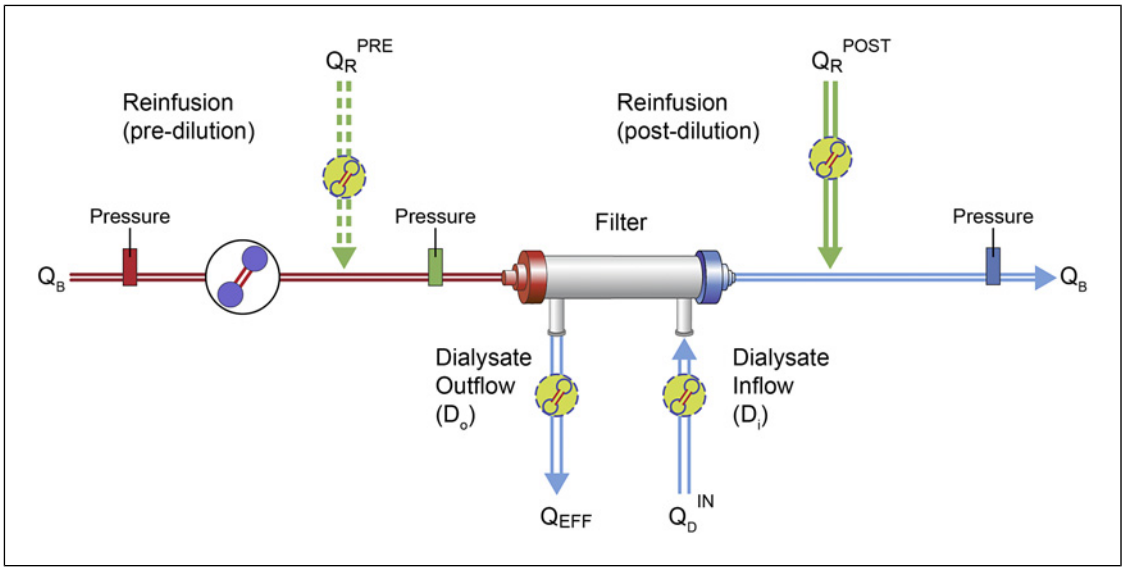

Fig. 3. Hemodiafiltration. Typical parameters in adults: **CVVHDF** – Q_B = 150–250 mL/min, $Q_{EFF} = Q_{UF}^{NET} + Q_D + Q_R^{PRE} + Q_R^{POST}$ (typically 20–35 mL/kg/h), $Q_{UF}^{NET} = Q_{EFF} - (Q_D^{IN} + Q_R)$. If applied in **PIRRT** over 6–12 h, Q_{EFF} typically 30–60 mL/kg/h. CVVHDF, chronic veno-venous hemodiafiltration; PIRRT, prolonged intermittend renal replacement therapy; Q_B, blood flow; Q_D, dialysate flow; Q_D^{IN}, flow of dialysis solution at the inlet; Q_{EFF}, effluent flow; Q_R^{PRE}, pre-filter reinfusion flow; Q_R^{POST}, post-filter reinfusion flow; Q_{UF}^{NET}, net ultrafiltration flow or volume of fluid removed from the patient substracted by volume of fluid infused to the patient per unit of time. Pressure = pressure detection.

membrane according to a concentration gradient on the two sides of the membrane. Volume removal is achieved by generating a hydrostatic pressure gradient across the membrane. The relationship between blood flow rates and dialysate flow rates in intermittent therapies differs from the CRRT. In IHD, dialysate flow rates are usually

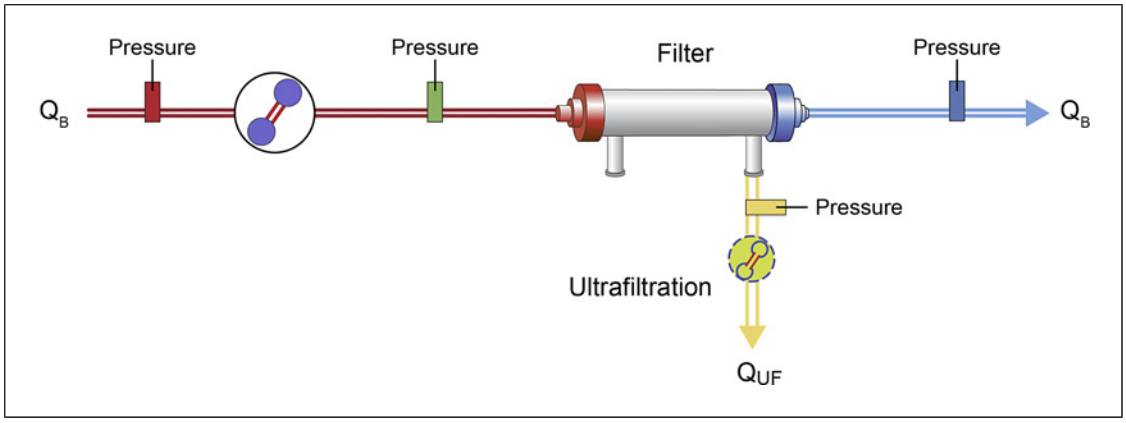

Fig. 4. Isolated ultrafiltration. Typical parameters in adults: **Continuous isolated ultrafiltration** – Q_B = 50–150 mL/min; **Intermittent isolated ultrafiltration** – Q_B = 150–300 mL/min. Q_B, blood flow; Q_{UF}, ultrafiltration flow. Pressure = pressure detection.

much greater than blood flow rates; consequently, the dialysate may not saturate. In IHD, higher clearance is achieved at the expense of large quantities of dialysate being used. In specific settings (e.g., home hemodialysis), dialysate flow may be reduced so that it becomes fully saturated in order to use less dialysate. Other intermittent dialysis modalities use convection or a combination of convection and diffusion for clearance, for instance, intermittent hemodiafiltration or intermittent high-flux dialysis use higher flux dialyzers for diffusive or convective therapies.

Indications. IHD is the standard modality for patients with dialysis-dependent chronic kidney disease (together with peritoneal dialysis). It is also used for patients with AKI but is less tolerated in conditions associated with hemodynamic instability, acute liver failure, cerebral edema, or intracranial hypertension [3]. Other indications for IHD may include situations where rapid clearance is required, for instance, life-threatening acid-base or electrolyte disturbances, specific intoxications, or situations where drugs with low protein binding need to be removed urgently (i.e., bleeding caused by novel oral anticoagulants).

IHD can be applied as a stand-alone modality [19]. More commonly, patients are transitioned from CRRT to IHD when they are no longer hemodynamically unstable and/or fluid-overloaded, and mobilization and rehabilitation are priorities.

Prolonged Intermittent Renal Replacement Therapy

Definition. Prolonged intermittent renal replacement therapy (PIRRT) is a mode of RRT that lasts longer than a traditional 4-h IHD session but less than 24 h. Thus, it includes some of the advantages of intermittent and continuous RRT. It is often provided on IHD platforms with extended time and lower blood and dialysate/replacement fluid flow rates but can also be administered with CRRT machines [20]. There is considerable heterogeneity in the terminology related to PIRRT, including sustained/slow low-efficiency daily dialysis, sustained low-efficiency dialysis, extended daily dialysis, "go-slow dialysis," slow hemodialysis, extended daily veno-venous high-flux hemodialysis, daily shift CVVHD (for diffusion therapies), accelerated veno-venous hemofiltration (for convective therapies), sustained low-efficiency daily diafiltration, and sustained hemodiafiltration for mixed diffusive and convective therapies [20]. Compared with CRRT, PIRRT provides shorter treatment, allows higher patient mobility, and offers some of the benefits of slow and long therapies, including slower osmolar and fluid shifts and less hemodynamic instability than traditional IHD.

Hemoadsorption Techniques

Definition

Hemoadsorption (formerly referred to as hemoperfusion) is the passage of blood through a sorbent-containing cartridge or a hemofilter for selective or broad-spectrum solute removal via direct contact of the blood with the sorbent material or the filter membrane surface (Fig. 5). Different cartridges are available (online supplementary Table S1). Hemoadsorption has the advantage of removing molecules through competitive binding, including plasma protein-bound and lipophilic molecules. Endotoxin, inflammatory cytokines, and other toxins such as bilirubin and myoglobin

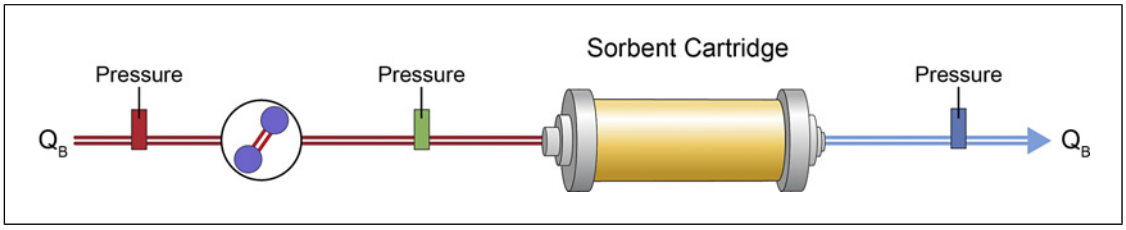

Fig. 5. Hemoadsorption. Typical parameters in adults: Q_B = 100–250 mL/min (may be provided continuously or intermittently over 6–24 h). Q_B, blood flow. Pressure = pressure detection.

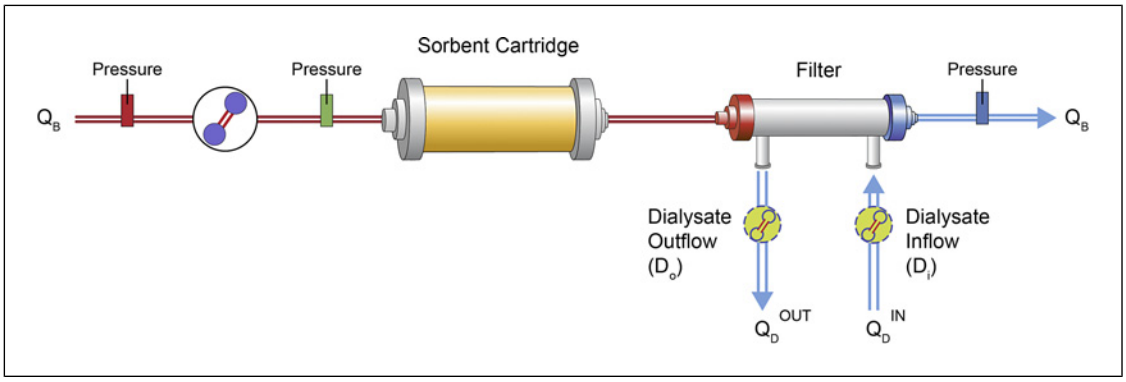

Fig. 6. Combined hemoadsorption and CRRT. Typical parameters in adults. Q_B = 100–250 mL/min. (1) Sorbent cartridge in series with CRRT circuit (may be pre- or post-filter). (2) CRRT can be provided as CVVHD (as shown in figure), CVVH, or CVVHDF. (3) Adsorption may be applied intermittently during CRRT. (4) Some devices may employ CRRT filter with intrinsic adsorptive capacity (see online suppl. Table S1). CRRT, continuous renal replacement therapy; CVVHF, chronic veno-venous hemofiltration; CVVHD, chronic veno-venous hemodialysis; CVVHDF, chronic veno-venous hemodiafiltration; Q_B, blood flow; Q_D^{IN}, flow of dialysis solution at the inlet; Q_D^{OUT}, flow of dialysis solution at the outlet. Pressure = pressure detection.

are common targets for removal [21]. Adsorption therapies can be applied alone and with other EBP techniques (concurrently or sequentially) (Fig. 6). Overall, the prescription depends on the type of sorbent cartridge used.

Indications in Clinical Practice

The clinical applications are expanding. Hemoadsorption has been used to achieve immunomodulation in inflammatory conditions such as sepsis, cardiac surgery, and organ transplant, and to remove specific solutes, such as bilirubin, myoglobin, endotoxin, drugs, or other toxins [22].

Plasma Therapies

Apheresis

The term "apheresis" refers to the process of using a machine to separate from the whole blood (a) the plasma (plasmapheresis), (b) blood cells (cytapheresis), or (c) other blood-soluble components. Cytapheresis involves separating red blood cells (i.e., erythrocytapheresis) or white blood cells (i.e., leukapheresis). Importantly, selective apheresis techniques remove specific molecules, antibodies, or cellular elements that are considered to be particularly pathogenic in specific diseases. Selective cytopheretic device is a specific type of cytapheresis that aims to target activated neutrophils and monocytes selectively.

Plasmapheresis. Plasmapheresis separates the plasma from the blood by centrifugation or filtration [23] (Fig. 7). It can be performed in healthy donors to obtain plasma only, used for transfusion to patients, or as a source for other preparations, e.g., albumin and clotting factors. In this case, donors usually give only 1 unit of plasma (approximately 500 mL).

Plasmapheresis may also be administered therapeutically to remove various deleterious substances (e.g., autoantibodies, immune complexes) that circulate in the plasma and may contribute to life-threatening diseases [23, 24]. In this case, large volumes of plasma are removed repeatedly, and patients are transfused with a plasma-replacing solution (i.e., fresh frozen plasma or albumin

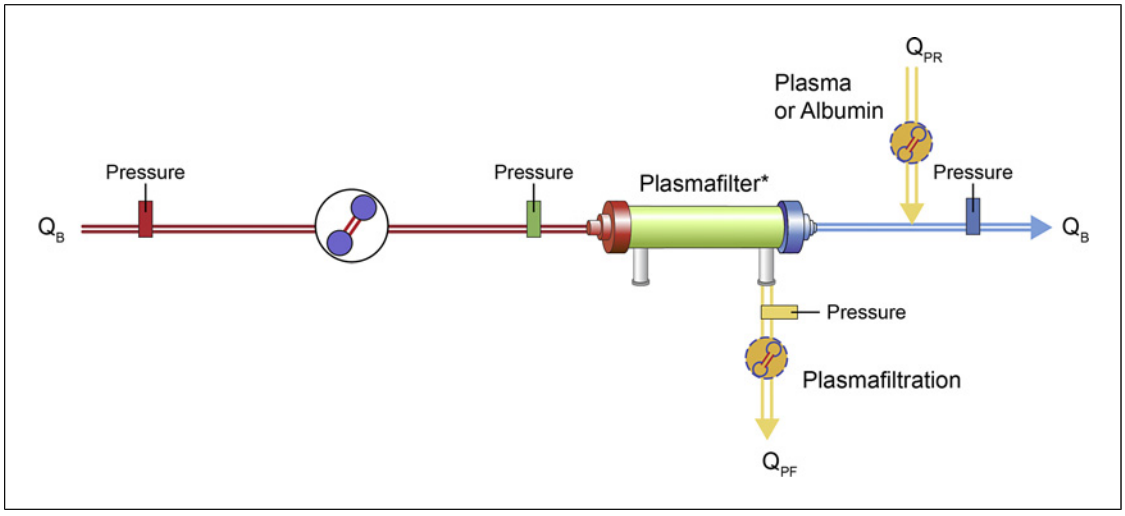

Fig. 7. Plasmapheresis. Typical parameters in adults: Given intermittent sessions over 3–4 h – Q_B = 100–200 mL/min; Q_{PF} = Q_{PR} = 10–20 mL/min; Q_{UF}^{NET} = 0 mL/min. *Plasma separation may also be achieved with a centrifugal apheresis device. Q_B, blood flow; Q_{PF}, plasmafiltration flow; Q_{PR}, flow of reinfusion of endogenous plasma or albumin solution. Pressure = pressure detection.

solutions) from healthy donors, hence the term "therapeutic plasma exchange." Although plasmapheresis is commonly used, various gaps in knowledge remain [25].

Double Filtration Plasmapheresis

Double filtration plasmapheresis or cascade filtration, refers to using a primary membrane plasma separator to isolate the plasma, followed by a secondary plasma fractionator to remove target solutes based on molecular size and weight. Double filtration plasmapheresis is also called "rheopheresis" since it changes blood viscosity by removing components such as fibrinogen, α2-macroglobulin, low-density lipoprotein (LDL) cholesterol, and immunoglobulins. This may be helpful in diseases associated with microcirculatory dysfunction, including dry age-related macular degeneration, diabetic foot, peripheral arterial occlusive disease, cerebrovascular stroke, and sudden sensorineural hearing loss [26]. Other indications include hypercholesterolemia, cryoglobulinemia, and Waldenstrom's macroglobulinemia [27].

Heparin-Induced Extracorporeal LDL Precipitation Apheresis

Heparin-induced extracorporeal LDL precipitation apheresis selectively removes lipoproteins containing apolipoprotein B100 in patients with severe dyslipidemia who show progressive atherosclerotic cardiovascular disease despite optimal treatment [28]. In addition to lowering lipids, heparin-induced extracorporeal LDL precipitation apheresis is thought to exert pleiotropic effects by modifying blood components other than lipids (cytokines, pro-thrombotic factors).

Combination EBP Therapies

Combination EBP therapy uses two or more EBP techniques in a definite time interval, depending on a patient's condition and the need to use the same circuit or via separate circuits. Further, the different therapies can be applied simultaneously or sequentially (Fig. 8, 9) [2]. When a single circuit is used, the techniques can be applied in series or parallel. The specific indication and the technical requirements determine the timing of combination therapies. Combination therapies may be considered to address different targets matched to the technique.

When used, the onset and end of each therapy determine the duration and should be recorded for each therapy individually. The therapeutic goal determines the duration of each therapy. Examples of combination therapies include the utilization of CRRT and plasmapheresis, CRRT and hemoadsorption, CRRT and extracorporeal membrane oxygenation, or CRRT and extracorporeal CO_2 removal ($ECCO_2R$) [1, 29] (Fig. 10).

Plasma Filtration Adsorption Dialysis

Plasma filtration adsorption dialysis combines a plasma adsorption circuit with a CRRT device (Fig. 11). In the first stage, plasma separation is immediately

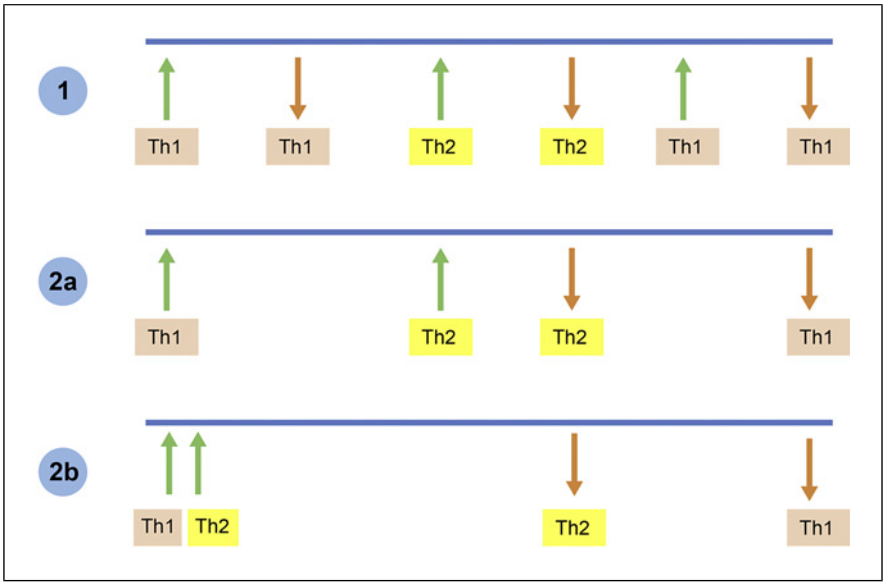

Fig. 8. Combination therapies. Option 1: sequential application. Option 2a: simultaneous application at different start times. Option 2b: simultaneous application at same start time. Green arrow denotes start of therapy. Orange arrow denotes end of therapy. Th1, therapy 1; Th2, therapy 2.

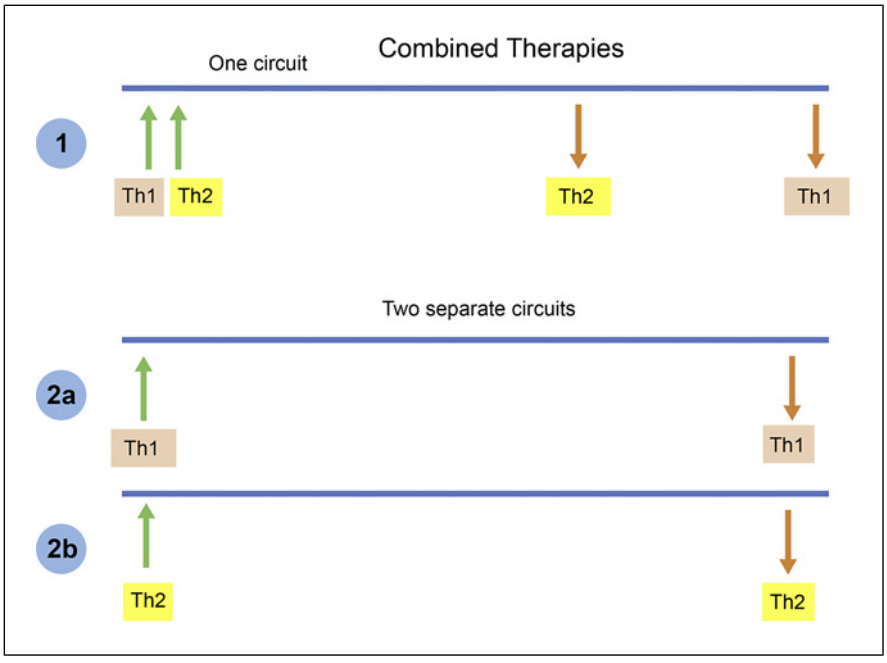

Fig. 9. Integration of combined therapies. Option 1: combined simultaneous application in series with single circuit. Option 2a and option 2b: combined simultaneous application in parallel with two circuits. Green arrow denotes start of therapy. Orange arrow denotes end of therapy. Th1, therapy 1; Th2, therapy 2.

followed by plasma adsorption of various disease-associated molecular patterns and/or toxins, and in the second stage, CRRT is provided. It differs from other types of EBP in that the upper part of the circuit can be considered a "closed loop" [30]. In this manner, the plasma separated by the plasma filter passes through an adsorbent cartridge containing a resin with a high affinity to many cytokines, mediators, and toxins/poisons. After passing through the cartridge, the purified plasma is returned to the patient. The second part consists of the CRRT, which can then be used to remove small toxins not adsorbed by the resin or to remove fluid. Plasma filtration adsorption dialysis is proposed for inflammatory states with AKI [31]. Plasma filtration adsorption can be combined with dialysis in series or in a single device [32].

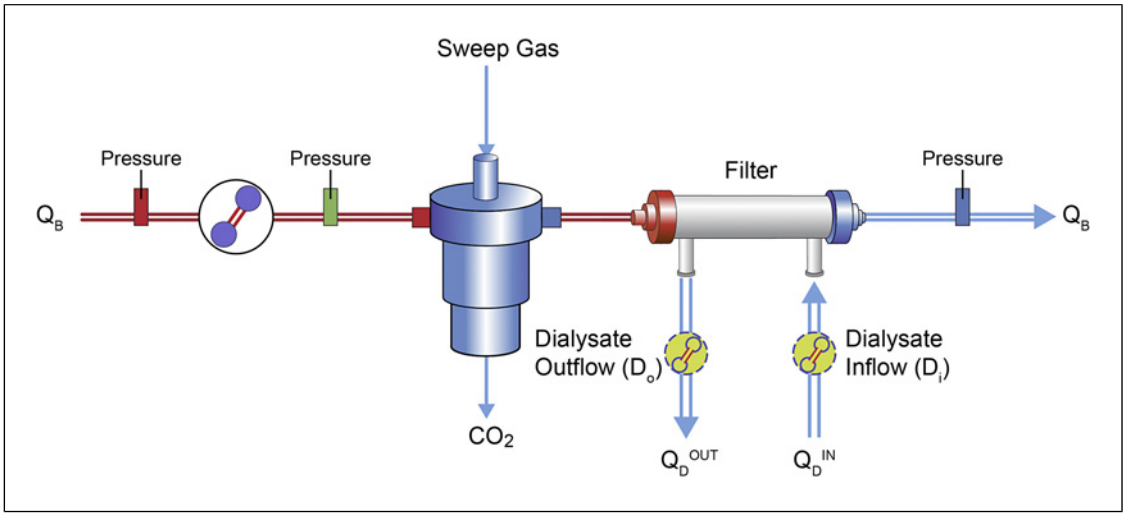

Fig. 10. Combined $ECCO_2R$ and CVVHD. Typical Q_B = 250–450 mL/min. Sweep flow = 8–10 L/min. CVVHD is shown but any form of CRRT can be combined with $ECCO_2R$. CO_2, carbon dioxide; $ECCO_2R$, extracorporeal carbon dioxide removal; CRRT, continuous renal replacement therapy; CVVHD, continuous veno-venous hemodialysis; Q_B, blood flow; Q_D^{IN}, flow of dialysis solution at the inlet; Q_D^{OUT}, flow of dialysis solution at the outlet.

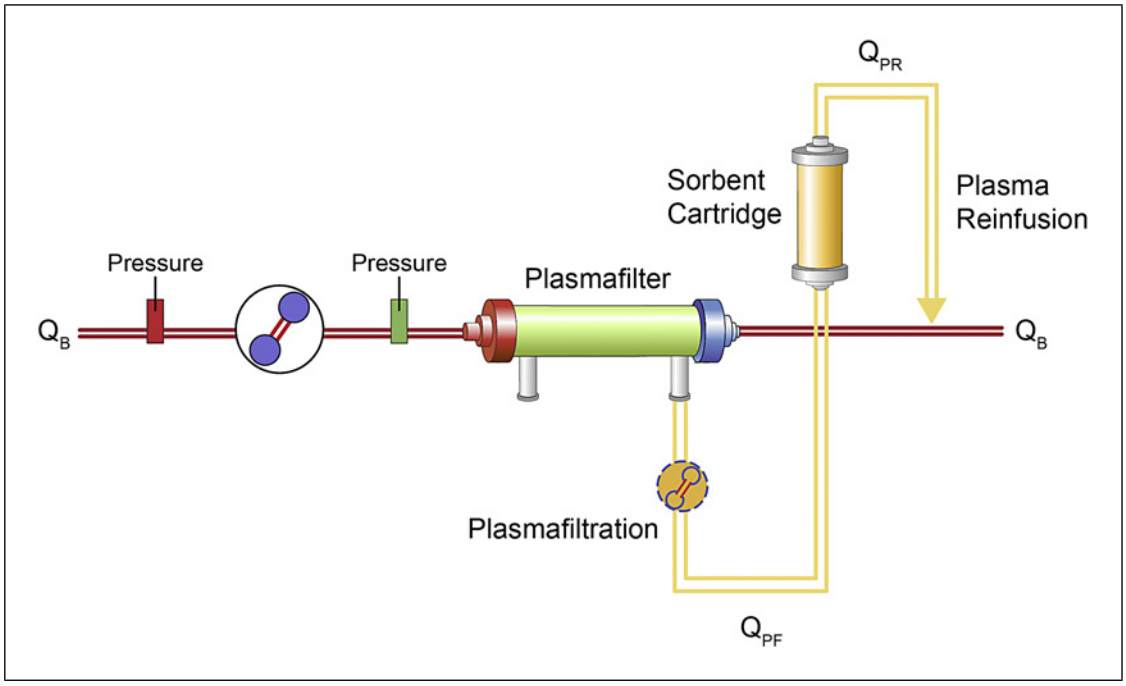

Fig. 11. Plasma filtration adsorption dialysis. Typical parameters in adults: Q_B = 100–200 mL/min, Q_{PF} = Q_{PR} = 10–30 mL/min. If needed, >1 sorbent cartridge with specific characteristics can be applied in series to achieve therapeutic goals. Q_B, blood flow; Q_{PF}, plasmafiltration flow; Q_{PR}, flow of reinfusion of endogenous plasma.

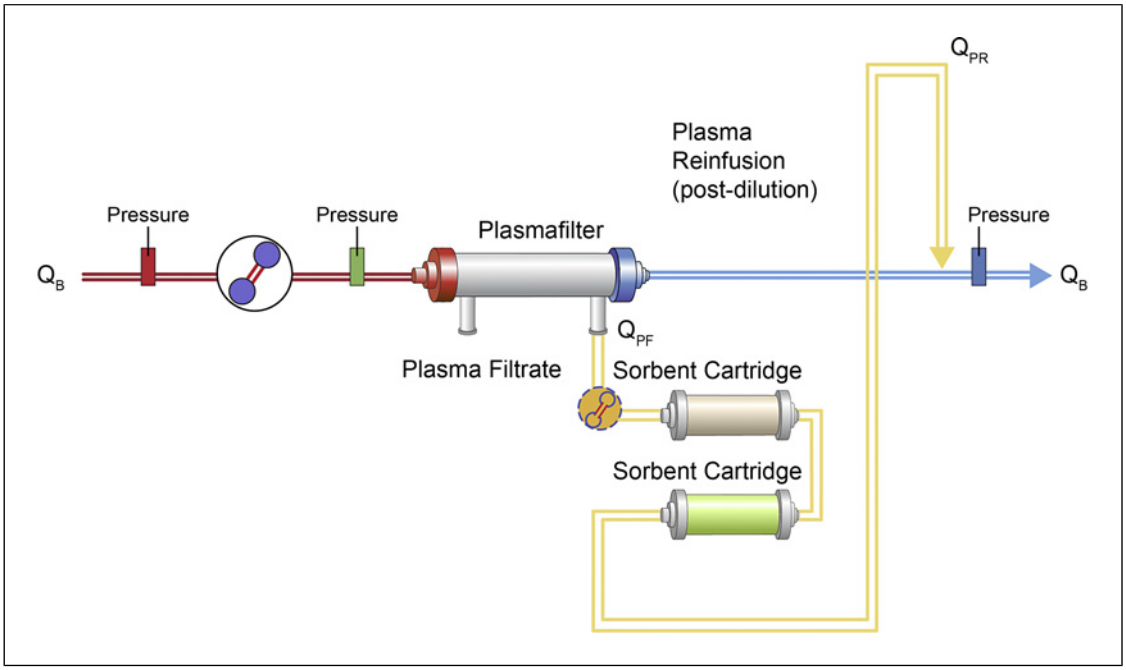

Fig. 12. Double plasma filtration molecular adsorption system. Typical parameters in adults: Q_B = 100–150 mL/min, $Q_{PF} = Q_{PR}$ = 10–30 mL/min, Q_{UF}^{NET} = 0 mL/min. Q_B, blood flow; Q_{PF}, plasmafiltration flow; Q_{PR}, flow of reinfusion of endogenous plasma.

Double Plasma Filtration Molecular Adsorption System

The double plasma filtration molecular adsorption system, also known as plasma filtration and double molecular adsorption system, is an artificial liver support composed of anion exchange resin (specific adsorption of bilirubin) and neutral microporous resin (adsorption of inflammatory mediators) (Fig. 12). This extracorporeal therapy is proposed to manage acute-on-chronic liver failure [33].

Immunoadsorption

The principles of immunoadsorption techniques relate to the ability of immobilized antibodies on immunoadsorption columns to bind to a circulating molecule selectively and to remove it from the plasma [34]. The antibodies are covalently bound to an inert, insoluble matrix in gel beads. Plasma is initially separated and then passed over a column containing anti-immunoglobulin antibodies immobilized on sepharose, selectively removing IgG, IgA, and IgM. In addition, the online regeneration of the columns allows for large volumes of plasma to be processed, thus making immunoglobulin removal more effective.

Extracorporeal CO_2 Removal

$ECCO_2R$ is a form of extracorporeal gas exchange that allows CO_2 removal from the blood typically using a gas exchange membrane while not affecting oxygenation [35]. Different devices and membranes are available (online supplementary Table S2). The components of an $ECCO_2R$ device and principles are explained in the online supplement.

The main characteristic that separates $ECCO_2R$ from other extracorporeal life supports is the ability to use a significantly reduced cannula caliber for vascular access due to low blood flow requirement through the gas exchange membrane. $ECCO_2R$ can be categorized into low-flow (<500 mL/min), mid-flow (500–1,500 mL/min), and high-flow $ECCO_2R$ (>1,500 mL/min), although no clear-cut definitions exist. Vascular access for $ECCO_2R$ is most often achieved through a veno-venous configuration, most often using a dual-lumen catheter. As RRT equipment and expertise are available, low-flow $ECCO_2R$ using RRT machines as a stand-alone therapy or in combination with RRT offers an alternative to mid-flow and high-flow $ECCO_2R$ devices.

Indications

Potential indications for $ECCO_2R$ include acute hypercapnic respiratory failure and acute exacerbations of chronic obstructive pulmonary disease with the aim to

improve dyspnea symptoms, prevent mechanical ventilation, or allow mechanical ventilation with lower tidal volumes and/or inspiratory pressures.

Specific Considerations in Children

Providing acute pediatric CRRT (pCRRT) can be challenging and technically complex. As a result, pCRRT circuits are mostly pediatric adaptations of adult machines. Although these machines have continued to evolve and expand for safe use in children, most pCRRT remains off-label, particularly in patients weighing less than 10 kg. The exception is the Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM), specifically dedicated to newborns and small infants [36]. The nomenclature of acute EBP techniques discussed in this article is similar in adults and children. However, there are discrete differences in filter selection, dosing, and circuit configurations that are important to highlight.

Filter Selection

The filter selection in children begins with the important consideration of extracorporeal volume concerning a patient's total blood volume. This relationship affects the priming practices of each circuit. Extracorporeal volumes >10% of the patient's total blood volume require careful consideration of blood priming to avoid clinically significant dilution of hematocrit and cardiovascular instability.

A small selection of filters has been authorized for use in pediatric patients in some countries, i.e., the HF20 filter. In addition, plasma filters have been utilized in Europe, often in larger children. However, the primary method for plasma purification in the USA is via centrifugal methods [37, 38]. For adsorption techniques, new pediatric cartridges have recently become available (i.e., Jafron HA60 and BS80).

Circuit Configurations

Pediatric patients may need multiple EBP techniques that often require several circuits connected in series or parallel. Integrating multiple circuits further complicates the mechanical aspects of blood flow rates required for therapeutic benefits. There are no specific guidelines for safe and efficacious circuit configurations and combinations in pediatric patients, including the integration with other extracorporeal life support circuits [39, 40].

Conclusions

Application of EBP technology at the bedside requires full knowledge of the basic principles and the operating mechanisms of the different techniques. We suggest a framework for standardization 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 clinical outcomes of the different techniques in clinical reports and scientific journals, ultimately allowing for improvements in clinical practice and patient outcomes.

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Conflict of Interest Statement

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Author Contributions

Claudio Ronco conceived the topic of the manuscript and oversaw the development of the manuscript. Ghada Ankawi, Vincenzo Cantaluppi, Rajasekara Chakravarthi, Faeq Husain-Syed, Kianoush Kashani, Ravindra Mehta, John Prowle, Thiago Reis, Thomas Rimmele, Marlies Ostermann, and Alexander Zarbock reviewed the literature, summarized the data, and created the figures and the table. Marlies Ostermann wrote the first draft. Kristin Dolan reviewed the pediatric literature and wrote the pediatric section. John A. Kellum contributed to the table and critically reviewed several versions of the manuscript. All authors revised the manuscript several times and approved the final version.

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