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Hybrid Therapies for Supporting Critically Ill Patients with Acute Kidney Injury: When, how, and for Whom?

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ABSTRACT

Acute kidney injury (AKI) is common in critically ill patients. There is no specific pharmacological treatment for established severe AKI. Therefore, the conventional therapeutic strategy is limited to the use of kidney replacement therapy (KRT) to maintain homeostasis. Hybrid therapies optimize the advantages of intermittent and continuous modalities of KRT, combining lower hourly efficiency, longer application time, at lesser cost, but also adding different physicochemical principles of extracorporeal clearance. The sum of convection and diffusion, with or without adsorption or apheresis, and in different time combinations gives hybrid techniques great flexibility in prescribing a personalized treatment adapted to the needs of each patient at any given time. Hybrid therapies are increasingly being used due to their flexibility, which is determined by the combination of equipment, membranes, and available resources (machines and health-care personnel experience). The required technology is widely available in most intensive care units and uses low-cost consumables compared to other types of AKI treatment modalities, favoring its widespread use. Hybrid therapies are feasible and provide a viable form of KRT, either alone or as a transition therapy from continuous kidney replacement therapy to intermittent hemodialysis. (REV INVEST CLIN. 2023;75(6):337-47)

Keywords: Hybrid therapies. Acute Kidney Injury. PIRRT. Critical care.

INTRODUCTION

"Female, 67 years old, por acute renal failure (ARF) due to septic DOMS, anuria, hyperkalemia 13.5 mEq/l, azotemia >5 g/l, poor general condition, neurological compromise, unstable hemodynamics. Hemodialysis was started for 11.5 h with a blood flow of 116 ml/min, achieving a urea reduction rate of 69%. Daily hemodialysis was maintained with the same characteristics and the patient improved, left the hospital, and is still alive after 7 months." Willem J. Kolff, 1945[1-3].

Acute kidney injury (AKI) is common in critically ill patients, with approximately 50% of patients developing AKI at some point during their ICU stay and 10-20% ultimately requiring kidney replacement therapy (KRT)[4-7]. Regardless of the cause and associated comorbidities, the more severe the renal injury,

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the greater the adverse outcomes, morbidity, and mortality[5]. Sepsis, shock, need for mechanical ventilation, and surgery are high-risk settings for developing AKI[8]. Severe AKI in critically ill patients is associated with high mortality. There is no specific pharmacological treatment for established severe AKI. Therefore, the conventional therapeutic strategy is limited to the use of KRT to maintain homeostasis of the internal environment (nitrogen metabolism, electrolytes, acid-base, and body volume) until resolution of the underlying disease and eventual recovery of renal function sufficient to meet the metabolic demands of the patient[9].

KRT for AKI raises many important questions, including the type of dialysis, timing of initiation, and the dose to be prescribed. The requirements, indication, and goal of dialysis treatment may change in the same patient during his or her hospital stay. A change in strategy or technology applied is required very frequently throughout the disease and is sometimes determined by metabolic demand and kidney physiological capacity.

One of the goals of KRT is to avoid episodes of arterial hypotension and organ ischemia during treatment. Arterial hypotension reduces oxygen delivery to tissues and leads to organ dysfunction. This is particularly important at the renal level in patients with AKI due to impaired autoregulation of renal blood flow. Hypotension induces further ischemic tubular damage and compromises the recovery of renal function. Therefore, to avoid delayed recovery of renal function and exacerbation of an other organ failure, KRT should be as safe as possible[10]. One of the most important aspects, but also one of the most difficult challenges, is to maintain hemodynamic stability.

Extracorporeal clearance procedures for AKI can be classified according to the predominant physicochemical principle, treatment time, or combinations of these options.

Physicochemical principles of extracorporeal depuration

The physicochemical principles on which extracorporeal depuration techniques in nephrology are based are diffusion, convection, adsorption, and plasmapheresis[11].

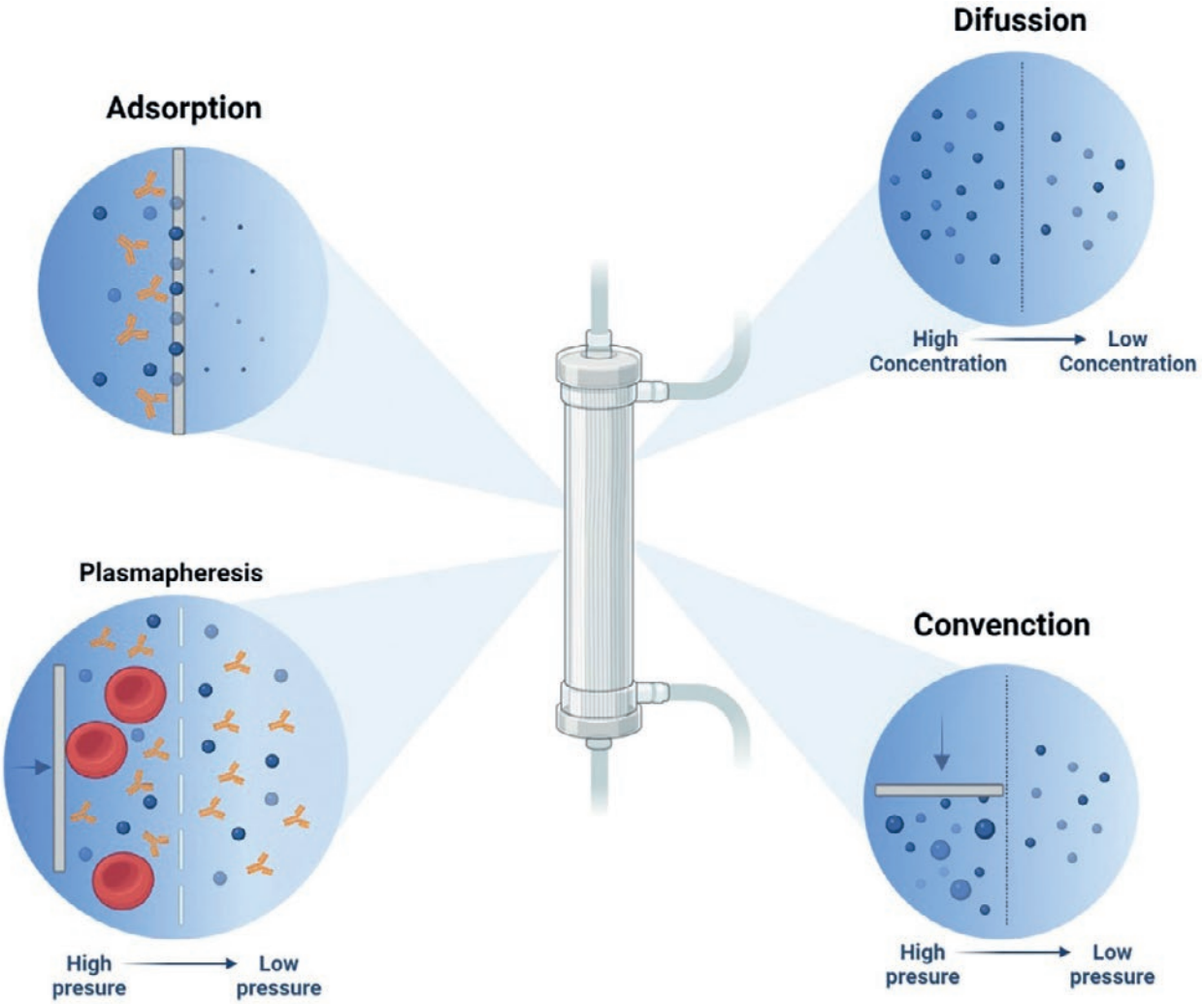
Diffusion is the principle that prevails in intermittent hemodialysis (IHD) and consists of the transport of solutes across a semipermeable membrane in favor of a concentration gradient. The diffusion capacity is limited by the permeability of the membrane to the solute (pore size and thickness of the membrane) and the molecular weight, and the geometry of the molecules. Lower molecular weight solutes such as urea and potassium are removed more efficiently in IHD, which is less effective in removing larger molecular size molecules such as beta 2-microglubulin or inflammatory mediators such as interleukins.

Convection or ultrafiltration (UF) is the movement of water-soluble solutes driven by a hydrostatic pressure gradient across a semipermeable membrane, with UF being the volume of fluid removed from the blood through the dialysis membrane by this mechanism. In this mode, molecules are "washed" from one side of the membrane to the other. The clearance of substances is proportional to the ultrafiltrated volume: Large volumes of UF (several times the total extracellular volume) are required to achieve solute removal by this mechanism, far in excess of the target UF required to achieve adequate fluid balance (up to 100 l in 24 h).

The ultrafiltrated volume must be replaced and reinfused into the patient's bloodstream and therefore must meet certain characteristics of physicochemical composition and bacteriological safety[12,13]. The effectiveness of the technique is determined not only by the amount of volume ultrafiltrated and reinfused but also by where in the extracorporeal circuit the replacement occurs, whether it is before the dialyzer or membrane (pre-dilutional) or after (post-dilutional). The pre-dilution system incorporates the reinfusion fluid before the dialyzer, which reduces cell and solute concentrations, decreases viscosity, and thus improves rheology within the dialyzer at the expense of reduced clearance efficacy of the extracorporeal circuit. Anticoagulation is, therefore, an important pillar of treatment, whether by systemic (heparin) or regional (citrate) administration, combined with the pre-dilution replacement mode, which favors "fiber flushing" with high replacement volumes when anticoagulation is limited by the risk of bleeding.

Adsorption is the physicochemical process by which substances of high molecular weight or high absorption

Figure 1. Physicochemical principles of extracorporeal purification techniques.



to plasma proteins are purified, through the ability to adhere to an artificial membrane to which the patient's blood is exposed. The most commonly adsorbed substances are inflammatory mediators, bilirubin, bile acids, and exogenous toxins with high absorption to plasma proteins.

The adsorption capacity of a standard dialyzer is very limited; to remove substances by adsorption, it is necessary to resort to processes using cartridges with substances of high adsorption capacity[14]. The devices used are composed of materials such as activated carbon, ion exchange resins, or albumin, which, due to their physicochemical properties, adsorb on their surface medium- and high-molecular-weight molecules dissolved in plasma or bound to proteins.

Plasmapheresis is the process of separating plasma from the formed elements of the blood using extracorporeal centrifugation or filtration (plasma filters). In therapeutic plasma exchange (TPE), purification is achieved by eliminating the protein structures that make up the plasma proteins (antigens, immunoglobulins, antibodies, and others) or substances adhering to them, particularly to albumin (endogenous or exogenous toxins). This procedure requires the replenishment of volume with fluids, albumin and/or globulins, removed during the procedure, usually in equal amounts. Experimental and clinical studies have shown that plasma exchange reduces circulating levels of endotoxins and cytokines and restores levels of immunoglobulins, coagulation factors, protein C, antithrombin III, and the opsonic and bactericidal

capacity of serum, improving disseminated intravascular coagulation and the humoral inflammatory response. Plasma filtration may be combined with adsorption alternating with hemofiltration (HF) or hemodialysis, continuous or intermittent, simultaneous or in tandem[15]. Other therapeutic apheresis techniques (cytapheresis) are not commonly used in nephrology and are therefore beyond the scope of this review. Figure 1 summarizes the physicochemical principles of extracorporeal purification techniques.

Extracorporeal treatment time

At present, different modalities of extracorporeal blood purification are used in severe AKI, which correspond to two types of procedures, classified according to the duration of treatment[11,16,17].

Continuous kidney replacement technique (CKRT), mainly based on the physicochemical principle of convective clearance, is applied slowly and continuously throughout 24 h of the day for several days. CKRT offers better hemodynamic tolerance due to the characteristics of the blood flow in the extracorporeal circuit and the ultrafiltrate flow, both of which are designed to achieve the best possible hemodynamic tolerance[13,18]. CKRT is the treatment of choice in neurocritical patients and those with severe hemodynamic instability because the removal of extracellular fluid and the osmotic changes in plasma occur slowly and persistently over several days. However, the availability of the technique is dependent on the availability of machines and replacement solutions, which are brand and distribution chain dependent and more costly than other dialysis treatment modalities. The use of commercial replacement fluids makes the technique independent of the use of tap water and pure and ultrapure water production systems, which may not be available in some contexts. The main difficulty of CKRT is that it is a continuous treatment, which requires persistence over time without interruption to reduce the likelihood of suboptimal dialysis doses that do not meet therapeutic goals.

Intermittent hemodialysis (IHD), based mainly on the physicochemical principle of diffusive clearance, is applied daily or every other day for <6 h. IHD remains the cornerstone of extracorporeal KRT in the ICU, either as first-line therapy for AKI or as second-line therapy when patients are transitioning from continuous or extended intermittent therapy[19]. In this context, IHD is usually performed 3 days per week, as no clinical benefit has been demonstrated with more frequent treatments. This should not detract from the need to continuously evaluate and refine the hemodialysis prescription (including the need for additional treatments) based on dynamic changes in extracellular volume and other parameters and to ensure that an adequate dose of hemodialysis is administered to the patient. Compared to other modalities, the main challenge of IHD is hemodynamic instability. This phenomenon occurs when reductions in intravascular volume due to UF and/or osmotic changes exceed compensatory plasma replenishment from the extravascular space. Myocardial stunning induced by IHD and independent of UF may also contribute. The hemodynamic effect of IHD is likely to be magnified in critically ill patients due to the inability to mount sufficient compensatory physiological responses in the context of multiorgan dysfunction[19]. IHD machines are capable of modifying dialysis liquid composition in a wide range of sodium and bicarbonate concentrations, as well as temperature and volume, allowing for a good match between the patient electrolyte and acid-base status and fluid composition.

Combinations of physicochemical principles and times: hybrid techniques for acute kidney injury and multiorgan support

Hybrid techniques (HT) optimize the advantages of intermittent and continuous modalities of KRT, combining lower hourly efficiency, and longer application time, and lower cost[20]. More recently, the term hybrid techniques have also been coined to refer to the possibility of combining not only different times but also adding diverse physicochemical principles of extracorporeal blood purification. The sum of convection and diffusion, with or without adsorption or apheresis, and in different time combinations, greatly expand the therapeutic possibilities according to the etiology, pathogenic process, predominant pathophysiological imbalance, need for other associated therapeutic maneuvers, and evolutionary profile of the patient. The range of therapeutic possibilities resulting from these combinations is enormous and easily adaptable to the changing needs of the individual critically ill patient at different times during the disease[17]. This "à la carte" therapeutic modality must be standardized according

Table 1. Characteristics of extracorporeal purification techniques dived by treatment time

	Key characteristics	Advantages	Disadvantages
Continuous kidney replacement techniques	– Based on the principle of convective clearance. – High intensity (time), low efficiency. – Continuous treatment for 24 h a day over several days.	– Better hemodynamic tolerance. – Suitable for neurocritical patients. – Gradual removal of extracellular fluid and osmotic changes in plasma. – Independence from pure and ultrapure water systems thanks to the use of commercial replacement fluids.	– Special machines and replacement solutions. – Requires continuous persistence without interruption. – Possibility of suboptimal dialysis doses if continuity is not maintained. – High cost.
Intermittent hemodialysis	– Based on the principle of diffusive clearance. – Applied daily or every other day for <6 h. – Generally performed 3 days a week.	– Allows a wide range of modifications in dialysis fluid composition. – Requires a conventional HD machine. – Can be tailored to the patient's electrolyte, acid-base status, and fluid composition needs. – Low cost.	– Hemodynamic instability due to reductions in intravascular volume. – Possible induction of myocardial stunning. – Greater likelihood of hemodynamic instability in critically ill patients. – Requires portable osmosis machines or water treatment plants.
Hybrid techniques	– Combining lower hourly efficiency with longer application time. – Generally performed 3-6 days a week, and 6-12 h.	– Allows a wide range of modifications in dialysis fluid composition. – Requires a conventional HD machine. – Low cost. – Better hemodynamic tolerance.	– Some critically ill patients present hemodynamic instability during treatment. – Requires portable osmosis machines or water treatment plants.

to the best available evidence to achieve an appropriate balance between individualized treatment and therapeutic efficacy. The combination of technologies is not an end in itself but a means to achieve the best possible health status in patients with highly variable pathophysiological disorders, metabolic needs, and residual renal function. Table 1 summarizes the characteristics of extracorporeal purification techniques divided by treatment time.

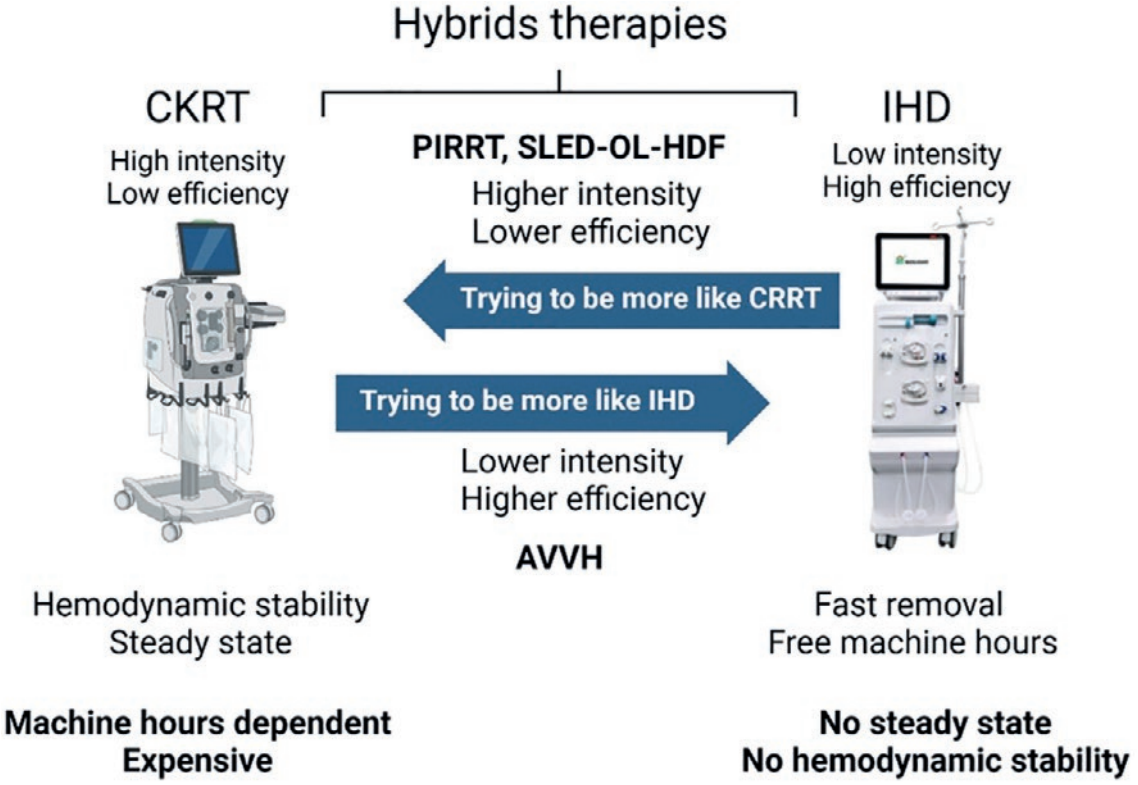
Mixed time: prolonged intermittent renal replacement therapy (PIRRT) and slow low-efficiency dialysis (SLED)

PIRRT and SLED are almost interchangeable terms. These procedures can be delivered using a standard IHD machine (connected to a central purified water supply or using a portable/installed reverse osmosis machine) or a CKRT machine using standard commercial CKRT solutions[21]. Adjustments are made to the blood flow rate and dialyzate and/or replacement fluid rates. These modifications are made to reduce the efficiency of solute clearance relative to standard IHD (and provide it for a longer duration) or to increase clearance relative to CKRT (and provide it for a shorter duration)[22]. When using a conventional IHD machine to provide HT, the machine software may not allow the dialyzate flow to be reduced enough to significantly reduce the efficiency of solute clearance. In such cases, a CKRT or pediatric IHD dialyzer (filter) with a relatively small surface area may be used to further reduce time-adjusted efficiency[23]. Figure 2 summarizes the characteristics of hybrid therapies.

Mixed physicochemical principles: extended hemodiafiltration (HDF) with online liquid replacement

HDF is the combination of diffusion and convection. This combination increases the removal of small and

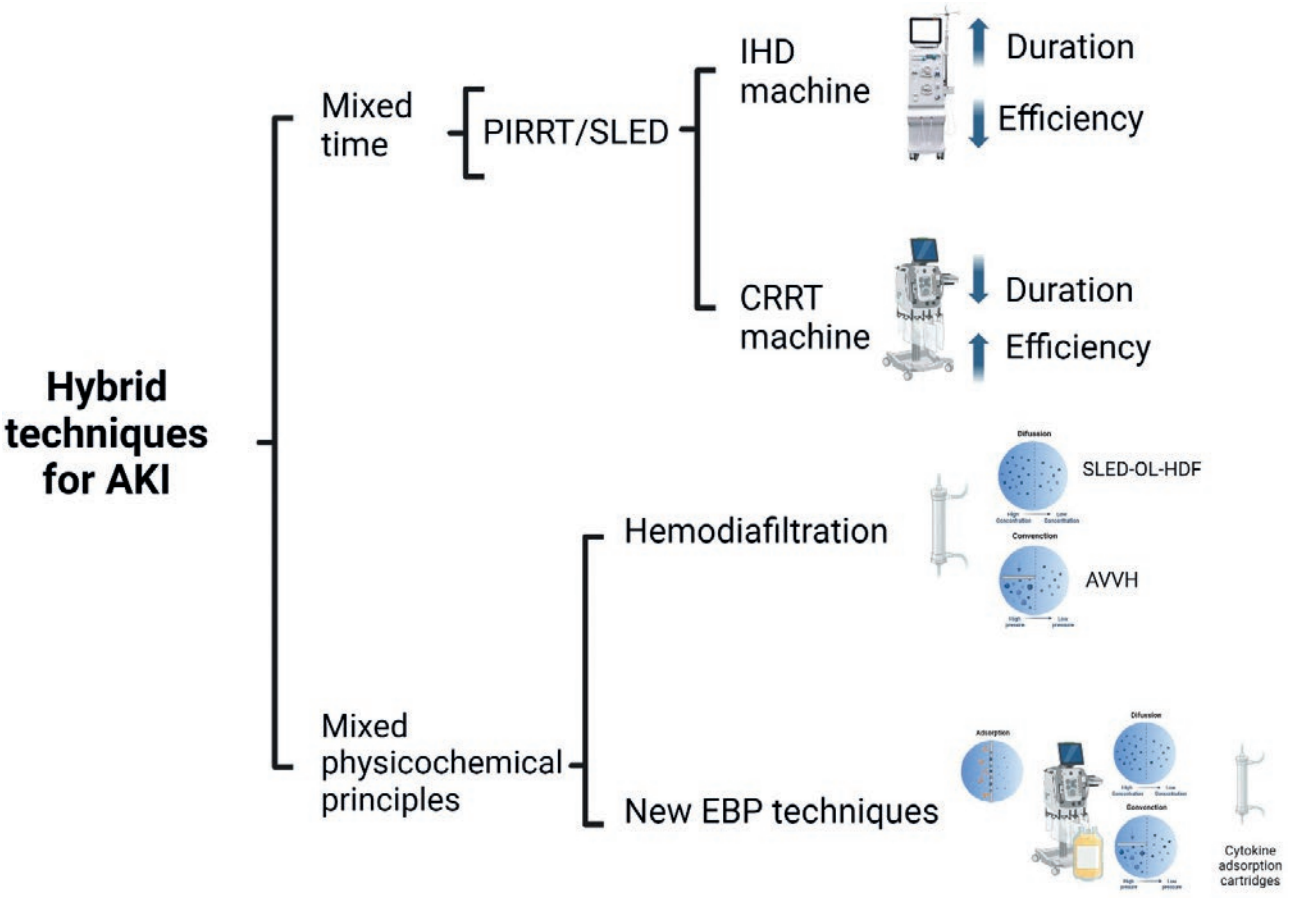
Figure 2. Main characteristics of hybrid therapies *(figure kindly provided by Dr Pablo Galindo, Centro Médico ISSEMYM, State of Mexico, Mexico).*



medium-molecular-weight molecules compared to each modality separately. Although HDF can be administered as a continuous or intermittent techniques, hybrid techniques refer to intermittent procedures[22]. Depending on the machines used and local experience, the case of PIRRT may utilize diffusive clearance (i.e., sustained low-efficiency [daily] dialysis [SLED/SLEDD]), convective clearance (i.e., HF, accelerated veno-venous hemofiltration [AVVH]), or a combination of these principles (i.e., HDF, sustained low-efficiency [daily] diafiltration [SLED-f/SLEDD-f])[24]. Intermittent SLED-HDF has recently been incorporated into the treatment of AKI as an extension of the successful experience in the treatment of chronic kidney disease (CKD) on dialysis[25]. HDF provides enhanced removal of small and medium-molecular-weight uremic toxins compared to other techniques such as HF or IHD. *In vivo* and *in vitro* studies have demonstrated its efficacy in reducing the inflammatory response by decreasing cell activation[26,27].

Due to the loss of several liters of extracellular fluid volume in HDF, it is necessary to replace it by administering solutions in premade bags or by reinfusion solution prepared simultaneously from the dialysis fluid itself, a process called HDF with online replacement (OL-HDF). In OL-HDF, the production of an appropriate replacement fluid requires a system for obtaining a sterile, non-pyrogenic replacement solution. For this purpose, ultrapure water must first be obtained by means of special water treatment equipment (double-pass osmosis) and final filtration of the replacement fluid with endotoxin filters in each dialysis machine to ensure the production of apyrogenic and sterile fluid[22,28]. The feasibility to use replacement fluid produced online with ultrapure water makes it possible to obtain a large volume of replacement fluid at a much lower cost than using commercial replacement fluid, as needed for CKRT. The combination of OL-HDF and SLED (SLED-OL-HDF) has the theoretical advantage of incorporating the physicochemical processes of convection and diffusion, reducing the solute transfer rate per unit of time, extending the treatment time, with free intervals to perform other procedures (without affecting the dialysis dose administered), with ample availability of low-cost replacement fluid. The association of HDF with SLED may allow for better hemodynamic

Figure 3. Hybrid therapies combine physicochemical principles, time, and technologies.



tolerance by achieving adequate clearance of small and medium molecules. These characteristics make SLED-OL-HDF a valid alternative for the treatment of severe AKI in the critical care setting, with minimal additional investment in equipment[29].

OL-HDF has recently been added to the therapeutic armamentarium for the treatment of AKI, with several reports demonstrating its safety and efficacy[24,25]. However, this technique, which has been shown to be safe in achieving therapeutic goals in several reports, has not yet been widely adopted. OL-HDF is a safe procedure with no increase in infectious complications or adverse events. In particular, the combination of SLED with OL-HDF has been shown to be safe for the treatment of AKI[30]. In critically ill patients with multiple organ dysfunction syndrome (MODS) requiring resuscitation with vasopressors. Theoretically, the combination of diffusion and convection allows the efficient clearance of a wider range of small and medium molecular weight substances. Among them, some inflammatory mediators, such as TNF-alpha, IL-6, and IL-18, play a pathogenic role in critical MODS in patients, as well as in the hemodynamic compromise with tissue oxygen extraction deprivation[26]. Thus, SLED-HDF-OL can be used in patients with severe AKI in the context of MODS. This modality may represent a new therapeutic and cost-effective alternative to RRT in critically ill patients with severe AKI.

Mixed physicochemical principles: diffusion and/or convection associated with adsorption/hemoperfusion and/or TPE

In recent years hemoperfusion, apheresis or adsorption devices and membranes have been developed that can be inserted into the extracorporeal circuit originally designed for HDI, PIRRT, or CKRT[31]. These technological developments greatly expand the

possibilities of extracorporeal blood purification (EBP) into the world of large molecules (e.g., free light chains and cytokines), molecules with adsorption to plasma proteins (e.g., digoxin and paraquat), or molecules with specific adsorption to certain cartridges (antibodies and toxins)[16]. Having reached a therapeutic ceiling with diffusive and convective techniques, apheresis, and in particular adsorption, promises significant advances in the multiorgan support of the critically ill patient. The use of single-pass albumin dialysis (SPAD), the use of TPE combined with adsorption (CPFA), and cytokine adsorption cartridges (Polimixin-B®, CytoSorb®, Oxiris®) associated with convection or diffusion technology are being extensively evaluated (Fig. 3). New fiber technology may allow the application of selective immunomodulatory therapy. There is insufficient evidence to recommend the use of hemoperfusion in sepsis and septic shock, but it opens a promising area of development and research.

WHEN TO ADMINISTER HYBRID THERAPIES FOR ACUTE KIDNEY INJURY

As defined by KDIGO guidelines[32], the indication of KRT is generally established with a stage III AKI. Some situations may recommend its early initiation, even without renal dysfunction. These are critical electrolyte alterations, fluid overload, or poisonings. Hybrid techniques are used in the treatment of the hemodynamically unstable critically ill patient as a valid alternative to CKRT, especially when planned interruptions are expected (i.e., surgery and diagnostic procedures). It is also proposed as a transitional therapy from CKRT to IHD[33], in patients still dependent on vasopressors, or in patients in whom the combination of physicochemical principles is indicated. Hybrid techniques are a valid alternative in resource-poor regions or in situations of supply shortage, as occurred during the COVID-19 pandemic[34].

HOW TO ADMINISTER HYBRID THERAPIES FOR ACUTE KIDNEY INJURY

Most machines designed for IHD and CKRT allow hybrid procedures to be performed at a lower cost and with similar results to CKRT. Treatments are provided for a longer duration than typical IHD treatments (6-12 h vs. 3-4 h, respectively) but not 24 h per day as is done for CKRT. Vascular access considerations for patients with AKI are like when prescribing IHD or CKRT[35].

Unlike dosing recommendations for CKRT and IHD, there is no standard recommendation for dosing HT. Reports on hybrid methods in critically ill patients are very heterogeneous, and the use of Kt/V, urea clearance, and/or convective volume to assess the dialysis dose is not routinely performed in most of the reference studies, being an area under investigation. Despite significant pitfalls in its use, urea kinetics remain the mainstay to determine adequacy of clearance during KRT, even in AKI. When prescribing PIRRT as a substitute for CKRT, a minimum weekly standard Kt/Vurea of 3.6 may be required. If used as a substitute for IHD or as a transition therapy, then lower flow rates or decreased frequency of treatments may suffice, as the weekly standard Kt/Vurea recommendations for IHD is 2[36]. Finally, there is less need for anticoagulation with the use of PIRRT compared with CKRT, largely due to the higher blood flow. In the absence of another indication for anticoagulation, PIRRT can be prescibed without any anticoagulation (i.e., saline flushes only). When anticoagulation is indicated due to issues with filter clotting or otherwise, unfractionated heparin is most used. If CKRT machines are used to provide PIRRT and regional citrate anticoagulation is possible, it is the option of choice.

Table 2 compares the standard prescriptions for IHD, hybrid, and CKRT modalities.

FOR WHOM TO ADMINISTER HYBRID THERAPIES FOR ACUTE KIDNEY INJURY TREATMENT?

AKI is a pro-inflammatory state in which all these mechanisms are enhanced, even more so when diuresis does not meet the patient's fluid balance needs. Despite its ability to remove inflammatory mediators, KRT has not been shown to have a favorable impact on the outcome of MODS without AKI or in patients with early-stage AKI who do not meet the classic criteria for initiation of KRT. Severe AKI in the setting of MODS has a greater impairment of fluid distribution between the different compartments compared to the healthy individual.

Table 2. Standard prescriptions for IHD, hybrid, and CKRT modalities

Parameter	Modality IHD	Hybrid therapies		Standard CKRT
		Using IHD machine	Using CKRT machine	
Blood flow rate	> 300 mL/min	100-300 mL/min	100-200 mL/min	100-200 mL/min
Duration	3-4 h	6-12 h	8-12 h	Continuous
Frequency	3-4 days/week	3-7 days/week	3-7 days/week	Continuous
Dialyzate rate	300-800 mL/min	300-500 mL/min	–	10-30 mL/min
Need for anticoagulation	±	±	++	+++
Dialyzate Na+	130-155 mmol/L	130-155 mml/L	140 mmol/L	140/mmol/L
Dialyzate K+	2.5-4 mmol/L	2.5-4 mmol/L	2-4 mmol/L	2-4 mmol/L
Dialyzate Ca+	1.5 mmol/L	1.5 mmol/l	1.75 mmol/L (0 mmol/L if using citrate anticoagulation)	1.75 mmol/L (0 mmol/L if using citrate anticoagulation)
Dialyzate HCO_3	24-36 mmol/L	24-36 mmol/L	32 mmol/L	32 mmol/L

To date, no single extracorporeal technique has been shown to be superior to another in terms of survival or renal recovery[16,17]. The modalities are not mutually exclusive but complementary in the treatment of AKI: The prescription pattern (type of physicochemical principle, procedure duration, clearance rate, and mass transfer) must be individualized and related to the indication, and depends mainly on the advantages and disadvantages of each technique adapted to the patient's needs, as well as its availability in the patient's setting (availability of resources, cost, and staff training). In general, in hemodynamically unstable patients, slow convection-based techniques (CKRT) or time prolongation with low-efficiency IHD (SLED and PIRRT) are recommended, although there is no high-level evidence to support one over the other[37].

Hybrid therapies are increasingly being used due to its flexibility, which is determined by the combination of equipment, membranes, and available resources (machines and health-care personnel)[24]. On the other hand, PIRRT and SLED are feasible and provide a viable form of KRT in a resource-limited setting[38].

Several clinical trials have already shown that the duration of dialysis treatment or the technique used would not affect mortality or kidney function recovery[37]. In a randomized trial in critically ill patients with AKI[39], intensive versus non-intensive dialysis treatment with different modalities (IHD, SLED, and continuous HDF) was indicated and no difference in mortality was found with any of the techniques. In a recently published meta-analysis of randomized controlled trials comparing the efficacy and safety of different modalities of KRT in critically ill patients with AKI, mortality was observed at 40%, with no difference between patients treated with CKRT and IHD, although a lower risk of mortality was observed in patients treated with SLED combined with hemofiltration. The average convective volume achieved was 19 l in most cases with post-dilution replacement and only 2 procedures with pre-dilution replacement[37]. In contrast to the CKD patient, there is no convective volume that has been shown to improve mortality; it is thought that the higher the volume, the greater the clearance of medium molecules and this may have a benefit in controlling the inflammatory response in patients with sepsis, for example.

When using a conventional IHD machine with the online generation of dialysate, solute levels might also be reduced to allow for the generation of dialysate sodium and bicarbonate concentrations at the lower end of what the machine allows (typically ~ 130 mmol/L and 24 mmol/L, respectively). Similarly, when prescribing dialysate potassium concentration, it is safest to assume that complete balance will occur before the end of the treatment. Thus, unless the patient is profoundly hyperkalemic

and/or more rapid correction is mandated (i.e., serum potassium ≥ 6.5 mmol/L or acutely rising), then dialysate potassium of 4 mmol/L can be used routinely to avoid precipitating hypokalemia. Just as interleukins are removed, more phosphate is removed and so is the removal of drugs such as sedatives and especially antibiotics[40]. As in other modalities, increased drug clearance, without additional antibiotic dosing during or after HDF, may adversely affect the patient's prognosis and outcome[41,42]. While hyperphosphatemia is not a problem in AKI patients, critically ill patients often have hypophosphatemia and this has been shown to be associated with a worse prognosis, so it is important to consider phosphate depletion, especially in patients treated daily with HDF, to monitor, prevent, and treat hypophosphatemia[43].

CONCLUSIONS

Clinicians must know the advantages and disadvantages of each KRT technique and adapt it to the clinical characteristics of the individual, the local resources (availability and cost), and their experience[44,45].

The combination of extracorporeal treatment time and the physicochemical bases gives hybrid techniques great flexibility in prescribing a personalized treatment adapted to the needs of each patient at any given time. The required technology is widely available in most intensive care units and uses low-cost consumables compared to other types of AKI treatment modalities, favoring their widespread use.

These are lessons learned from the early days of KRT, when the first patient successfully treated with hemodialysis survived a severe episode of AKI in 1945.

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