ABSTRACT—Acute renal failure (ARF) is a common event in critical patients usually taking place in a multiorgan failure context. This disorder implies a great clinical challenge. ARF could be defined as a sudden deterioration of the renal function that results in a loss of electrolyte, acid-base and fluid balance control, with subsequent accumulation of nitrogen wastes. Although ARF can appear in a wide range of patients and conditions, its physiopathological bases is shared by most episodes with the hipoperfusion and/or renal ischemia as a triggering of the injury. Shock, and specially septic shock is the main cause of ARF leading to renal replacement techniques. Though in the last twenty years continuous extracorporeal purification techniques have experienced an extraordinary growth, mortality remains high (50-70%). At present predominance of the continuous renal replacement therapy (CRRT) versus intermittent hemodialysis (IHD) is based on its better hemodynamic stability, great versatility in the hydroelectrolytic handling, favored gaseous exchange and improvement of the ventricular filling pressures, low extracorporeal blood volume, smaller activation of the complement, preferred elimination of fluids from the interstitial space, low rate of complications, control of uremia and the intravascular volume without protein or hydric restriction, possibility of elimination of certain toxics, good tolerance in patients with intracranial hypertension and no need of specialized personnel. CRRT and related procedures are an effective and feasible treatment in patients with acute renal failure, severe cardiovascular instability, multisystem organ failure or politraumatized patients, being a simple and easy choice to implement and monitor.

ACUTE KIDNEY INJURY AND RENAL REPLACEMENT TECHNIQUES

ACUTE RENAL FAILURE (ARF) IS A common event in critical patients usually taking place in a multiorganic failure context. The estimated incidence is 5-6% (8.6% excluding coronary patients), usually taking place in a multiorganic failure context. This disorder implies a great clinical challenge and resource consumption, remaining mortality rates in the range of 50-70%. In the last twenty years continuous extracorporeal purification techniques have experienced an extraordinary growth, with a more trustworthy procedures and a better tolerance for them. CRRT and related procedures are an effective and feasible treatment in patients with acute renal failure, severe cardiovascular instability, multisystem organ failure (MSOF) or multiple trauma, being a simple and easy choice to implement and monitor. Nowadays, the available techniques combine diffusion with convection, extracorporeal pump with spontaneous circulation, etc. Surely the use and knowledge of these methods will broaden in the future. It is necessary to underline the important conceptual different that exists between the chronic renal patient, in whom delay to the maximum the beginning of the extracorporeal purification is attempted, and the patient with ARF in whom minimizing metabolic complications that could affect the patient evolution is required. In the last 20 years the continuous extracorporeal purification techniques have experienced an amazing growth, being fundamental the development of more trustworthy procedures and a good tolerance for them.

At present predominance of CRRT versus IHD is based on the following points: 1) More hemodynamic stability, allowing its use in unstable patients, in whom the IHD is very difficult to carry out. 2) Great versatility in the hydroelectrolytic handling. 3) Gaseous exchange is favored by reduction of the hydrostatic pressure and improvement of the ventricular filling pressures. 4) Low extracorporeal blood volume. 5) Smaller activation of the complement thanks to the use of biocompatible membranes. 6) Preferred elimination of fluids from the interstitial space. 7) Low rate of complications. 8) Control of uremia and intravascular volume without protein or hydric restrictions. 9) Possibility of elimination of certain toxics. 10) Better tolerance in patients with intracranial hypertension. 11) Specialized personnel in dialysis techniques is not needed. Also, it is reasonable to conclude that in the absence of evidence the elimination of inflammatory mediators may benefit patients with MODS (Multiple Organ Dysfunction Syndrome), it seems that the elimination of inflammatory mediators (IL-1, IL-6, TNF, etc.) can benefit to those patients with MODS.

ACUTE RENAL FAILURE: CONCEPT AND DIAGNOSIS

Although total consensus has not yet been reached on the issue, ARF could be defined as a sudden deterioration of the renal function that results in a loss of electrolyte, acid-base and fluid balance control, with subsequent accumulation of nitrogen wastes.

ARF can be classified into prerenal, postrenal and parenchymal:
- Prerenal ARF: The most frequent (30-60%) can be due to hypovolemia, hypotension, or excessive vasodilatation. It can progress to ischemia and acute tubular necrosis (ATN).
- Postrenal ARF: Extrarrenal or intrarrenal obstruction to the urine flow. Its frequency varies from 5 to 25%, and it is associated with a very low mortality.
- Parenchymal ARF: It can be originated in renal vessels (vasculitis...), great vessels (thrombosis, emboli), glomerulopathy or interstitial injury (drugs, infection, lymphomas...), and it also can be an ATN secondary mainly to hypoperfusion, nephrotoxics or pigments. Besides, shock and specially septic shock is the main cause of ARF leading to renal replacement techniques. Urine assessment can be useful to classify ARF since before prerenal ARF arises, urinalysis will show a low sodium concentration (<20), a high osmolarity (>500), a high urinary creatinine/plasmatic creatinine ratio and a low (<1) fractional excretion of sodium (FENa). If the insult persists and ATN appears, the concentration capacity is lost, and a high FENa (>1), a high sodium concentration (>40) and a reduction in urine osmolarity (<400) can be found. In view of previous renal dysfunction or use of diuretics these determinations lack validity.
FENa = \[100 \times \frac{\text{UrNa/SrNa}}{\text{UrCr/SrCr}}\]

Although it is not an exact equivalent to assess the renal function, the glomerular filtrate is the most accepted parameter and can be estimated by means of physiological parameters (the urine flow is used), by the calculation of certain molecules clearance or by the elevation of plasmatic concentration of molecules of renal elimination as expression of the deterioration of the glomerular filtration (urea/BUN or serum creatinine). Oliguria (urinary flow less than 0.5ml/kg/h or 5ml/kg/day) is a poor specific marker of residual glomerular function except for extreme oliguric situations, but it is very sensitive for renal hemodynamic changes, and even able to precede biochemical markers.5

We can estimate the glomerular filtration rate (GFR) by means of calculation of the clearance of certain molecules, as long as they show an exclusive renal elimination, a steady production rate and an absence of metabolization and tubular excretion. Although inulin clearance is the gold standard for GFR determination, the estimation of the 24 hour creatinine clearance (CrCl) is the most widely accepted method for GFR evaluation in clinical practice, even though it has two main limitations. Firstly, there are factors like malnutrition, gender, race or muscular mass which can cause important variations in serum creatinine levels without relationship with GFR changes. Secondly, in order to consider CrCl as valid, GFR must be stable, which is infrequent in the ARF. When GFR descends the active secretion of creatinine is stimulated, increasing its urinary concentration and overestimating the GFR.

GFR can also be estimated from formulas which are based on demographic characteristics and biochemical data, that predict the CrCl avoiding the need of collect urine samples, although knowledge of serum creatinine levels (CrSr) is required, this is the reason why these formulas present the same disadvantages as the estimation of the GFR carried out by means of the levels of CrSr. The most used formula to assess GFR in the case of acute renal failure is the calculation of 24 hours renal clearance:5

\[
\text{CrCl} = \frac{\text{UCr (mg/dl)} \times \text{Vu (ml)} \times 1.73}{\text{SCr (mg/dl)} \times 1.440 \times S}
\]

Cystatin-C is a very potentially useful marker, that has proved to be a better marker of the GFR than the CrSr. It is produced at a constant rate and independently of the age, sex or muscular mass. Not only is a good marker of renal failure, but it can detect acute renal failure between one and two days before the CrSr. However, the age, sex, smoking habit, and inflammatory states can interfere with its results. It is important to emphasize that, except on rare exceptions, it is more important to know the evolution of the renal function that its quantification at a certain moment, although at the moment static parameters like the CrSr, urine flow or even the CrCl are used. The introduction of evolutionary parameters, like the elevation of CrSr of 0.5 mg/dl or to double the basal levels suffer from lack of consensus, although recent reports confirm the validity of RIFLE scale (Table 1)7 to adequately classify ARF patients to their prognosis.

### Prevention of the Acute Kidney Injury

Although ARF can appear in a wide range of patients and conditions, its physiopathological bases is shared by most episodes (hipoperfusion and/or renal ischemia as a triggering of the injury); an important number of factors that increase the susceptibility of the inpatient population to develop renal dysfunction have been described. The knowledge of these injuring factors will allow us to elaborate strategies of prevention directed to specific risk groups in order to reduce their effects as well as to implement each insulting agent.

Hypoperfusion will be our first prevention target, since in situations of hypovolemia, hypotension, low cardiac output and vasodilatation; the response of renal adaptation is based on a regulation of renal flow and glomerular filtrate to maintain this latter at a constant level. If this situation prolongs or other insults are added to the process, the failure of the compensating mechanisms results in severe blood vessel constriction, cellular damage and eventually the development of established renal dysfunction (ATN).
This hypoperfusion will be corrected by measures like a suitable hydration (the unique universally accepted measure to avoid the development of ATN) and the optimization of the hemodynamic parameters. Dopamine, furosemide, mannitol or natriuretic atrial peptide is not indicated. There is no enough evidence to consider the use of fenoldopam.8

There is a long list of factors that can increase the susceptibility to the development of renal dysfunction or increase the negative effects of the causal agents of the injury. Although many of these factors are not modifiable, awareness of them will allow us to establish populations at risk like elderly patients, those with a previous history of heart or liver disease, diabetes and/or chronic renal dysfunction who present with dehydration/hypoperfusion, and who require diagnostic procedures involving iodinebased contrast media, who are going to have surgery or who present with sepsis requiring nephrotoxic antibiotics.9

Although factors predisposing to ARF are many, the most frequent are the following:

**SEPSIS**

ARF appears in 19% of the cases of sepsis, and in more than 50% in septic shock. Furosemide, dopamine, fenoldopam or analogs of atrial natriuretic peptide have not demonstrated any utility.9 Maintenance of a correct perfusion and hydration is fundamental in these patients, without being able to define concrete objectives, although could be adapted the existing recommendations for the patient with severe sepsis, beginning resuscitation as soon as the syndrome is recognized. An elevated serum lactate concentration identifies tissue hypoperfusion in patients at risk who are not hypotensive. During the first 6 hrs of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as one: Central venous pressure between 8 and 12 mmHg a mean arterial pressure ≥65 mmHg, an urine output ≥0.5 ml/kg/hr and a central venous (superior vena cava) or mixed venous oxygen saturation ≥70%.10 No advantage for the use of colloids or crystalloids use can be defined, but it is possible that the use of starch derivatives should be avoided in high risk patients.11 A close relationship between other high risk pathological processes like cardiac surgery and major trauma and ARF it also has been reported. Dopamine has traditionally been used in these patients but a definitely positive role on their prognosis has not been found.12

**IODINE BASED CONTRAST MEDIA**

Contrast-induced nephropathy is the third cause of ARF in hospitalized patients. It is defined as an elevation of previous CrSr >0.5 g/dl during the 48 hours following i.v. contrast administration, being detectable in up to 45% of the procedures in high risk patients, though only less than 3% need purification techniques.13 The injury by mechanisms of vascular constriction directly related to the contrast and the high osmolarity usually presents. Avoiding hyperosmolar contrasts is one of the therapeutic measures to carry out, although the preventive measure that has proved more effective is the patient hydration before the procedure (administration of 1 ml/kg/h of saline i.v. between six and twelve hours before the infusion).14 N-acetylcyestein (600 mg/12 hours the

### Table 1. RIFLE Classification.

<table>
<thead>
<tr>
<th>Category</th>
<th>GFR and Serum creatinine criteria</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>GFR down by &gt; 25%. Creatinine up 1.5 times baseline</td>
<td>&lt; 0,5 mL/kg/hr for 6 hr</td>
</tr>
<tr>
<td>Injury</td>
<td>GFR down by 50%. Creatinine up 2 times baseline</td>
<td>&lt; 0,5 mL/kg/hr for 12 hr</td>
</tr>
<tr>
<td>Failure</td>
<td>GFR down by 75%. Creatinine up 3 times baseline</td>
<td>&lt; 0,3 mL/kg/hr for 24 hr or anuria for 12 hr</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent complete loss of kidney function for &gt; 4 wd</td>
<td></td>
</tr>
<tr>
<td>End stage</td>
<td>End-stage kidney disease (&gt;3 months)</td>
<td></td>
</tr>
</tbody>
</table>

GFR: Glomerular Filtration Rate
RIFLE: Risk, Injury, Failure, Loss and End Stage
day before and after the procedure) reduces the incidence of AKI, although over the last years the most strongly supported hypothesis is that it directly influences on the serum levels of creatinine without relationship with the changes in the GFR.\textsuperscript{15} The pre-procedure xanthin administration is another effective method to avoid the increase in serum creatinine levels.\textsuperscript{16} Although a possible beneficial effect of fenoldopam (selective agonist of the dopamine-1 receptors) has been confirmed, its usefulness has not been clearly defined.\textsuperscript{17} No beneficial effect of dopamine, calcium-antagonists, atrial natriuretic peptide or diuretics has been reported, the latter being able to worsen renal function. Based upon a JAMA article,\textsuperscript{18} bicarbonate may have a potential renal protective role in the contrast-induced nephropathy.

**Nephrotoxic Drugs**

In the development of an ATN other factors than the drug itself have a key role. These are age, sex, previous acute renal failure, diabetes, or depletion of sodium. There is no convincing data that diuretics are beneficial, but whether they are harmful is controversial. In the presence of a risk patient who needs a nephrotoxic drug is essential to look for an alternative, and should this not be feasible to follow an approach to minimize the risk: 1) withdrawal of other nephrotoxic drugs or other risk associations, 2) suitable hydration and 3) close follow-up of the patient’s renal function. Finally we should implement specific measures for each drug:

- Calcineurin inhibitors: They bring about renal damage by vessel constriction and intracellular calcium accumulation, and calcium antagonists being able to counteract such effects.
- NSAIDs: They inhibit the synthesis of prostaglandins by inhibiting ciclooxigenase, being necessary to limit its use in the presence of hyponatremia, use of diuretics, surgical stress or decreased cardiac output.
- B Amphotericin: Although the appearance of new preparations and the administration of this drug in low doses is important to reduce its nephrotoxicity, a correct hydration is the most efficacious preventive measure.
- Aminoglycosides: With a very extended use in the handling of sepsis caused by intrahospital gram-negative bacteria of nosocomial origin, where the incidence of ARF is high, they injure the kidney by direct action and by means of alterations in plasma flow. For this reason dehydration increases its toxicity and therefore concomitant furosemide use is not recommended. Apart from a suitable hydration, the only measure that has been effective with a risk decrease is the administration in a single daily.\textsuperscript{19}
- Rhabdomyolysis: Myoglobin and creatinkinase, released before an extensive muscular injury are proteins with nephrotoxic effect that bring about blood vessel constriction, direct tubular toxicity, secondary damage to oxidation and tubular obstruction. Renal prophylaxis is not recommended if the quantity of creatinkinase does not exceed 5000 U/l. Hydration is the only effective method in clinical practice, and urine alkalinisation or manitol have not usefulness.\textsuperscript{20}

**Conservative Management of Acute Renal Failure**

In a patient in ARF the logical approach is to begin by carrying out procedures of renal replacement or intermittent hemodialysis, techniques of continuous extracorporeal purification or peritoneal dialysis being this last one relegated at present to the pediatric setting.

Nevertheless, either in very elderly patients and/or those with a very bad prognosis, or in those with a good prognosis (for example in a patient without failure of another organ, like in the cases of ARF due to contrasts or aminoglycosides), we will show preference for a conservative treatment, whose objectives will be the following:

1. Providing enough volume of diuresis: The role of Henle’s loop diuretics in ARF remains controversial, as well as their role in a potential increase in mortality rates.\textsuperscript{21} However, these are powerful diuretics able to improve metabolic acidosis although they can cause toxicity (especially ototoxicity) and allergies, trombopenia, hemolytic anemia and metabolic disorders (hypokalemia, metabolic alkalosis, hyponatremia). Dopamine, by means of DA, receptors, produces mesenteric, coronary and splancnic circulation vasodilatation, achieving a renal vasodilatation with diuretic effects without hemodynamic significative actions at low doses. Two methanalysis have demonstrated that dopamine has no role in

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**Key Points**

- A correct hydration is essential to reduce nephrotoxicity.
- Bicarbonate may have a potential renal protective role.
- Calcineurin inhibitors and NSAIDs are harmful but not clearly defined.
- B Amphotericin is contraindicated in ARF.
- Rhabdomyolysis requires specific treatment.
- Conservative management is preferred in elderly patients.
- Hydration is critical in preventing ARF.
- Dopamine is ineffective in the treatment of ARF.
AKI prevention, even though it increases the urinary output without increasing GFR in a significant way. The optimal blood pressure level that enhances the kidney in a shock situation is not known, but that if mean blood pressure is less than 65 mmHg, the Odds Ratio for ARF raises to 15. Noradrenaline is the vasoactive amine of choice in septic shock (in α dose). For the time being, attitudes directed towards a reduction in renal metabolism, like 33-34°C cooling for a 12-24 hours period, thyroxin use or Insulin-Like-Growing-Factor have not showed any benefits.

2. Monitoring of nitrogen products: The fall in glomerular filtration results in a namely urea. The hypercatabolic state that usually accompanies the critically ill patient and the physiopathological response to renal hypoperfusion, consisting in a water and urea resorption through the nephron, will aggravate the severity of uremia. Unless nutrition is provided, malnutrition and negative nitrogen balance may ensue. An early replacement therapy may be of interest in order to provide adequate nitrogen intake in critically ill. Nevertheless, even in hypercatabolic condition, like sepsis and MOF, the energetic needling usually doesn’t exceed 1.3 times basal needs. In ARF a 25 to 35 kcal per day ingest is recommended, depending on the catabolism rate. There are enteral preparations with nitrogen, fosforum and potassium that can be useful in the conservative management of ARF. Anyway, urea levels higher than 200 mg/dl usually indicate the need of dialysis.

3. Maintaining a correct electrolytic balance: The most frequent electrolytic disorders in the ARF are hyperkalemia, hypocalcemia, hyperphosphoremia and metabolic acidosis. Hyperkalemia correction is summarized in Table 2. For hypocalcemia management calcium will be administered in gluconate, glucobionate or chlorure forms, monitoring phosphorus levels not to exceed calcium × phosphorus product over 70 (mg/dl)² and thus, avoiding metastatic calcifications. It is absolutely necessary to be very careful with the bicarbonate administration, understanding the consequences of Na and CO2 overload due to its administration, replacing 50% of the deficit in the first 12 or 24 hours to avoid rebound alkalosis or abrupt pH variations.

4. Not worsening the prognosis of the patient because of delaying hemodialysis or hemofiltration.

### Basic Concepts in Molecule Purification

The dialysis is a process by which the composition of solutes of a solution A modifies when exposing itself to a solution B through a semipermeable membrane, considering this one like a layer perforated by holes or pores. The water molecules and the low molecular weight solutes can pass through the membrane pores and mix up, but the higher molecular weight solutes, like proteins, can’t pass through the semipermeable membrane, keeping their concentration unchanged at both sides of the membrane.

The solutes that can pass through the membrane are transported by three different mechanisms: diffusion, ultrafiltration (convection) and adsorption. Diffusion consists of molecule displacement between the blood compartment and the fluid compartment until a balance is achieved, and depends on the concentration of the substance, the thickness of the membrane, and the available area. Ultrafiltration and convective transport refers to the difference of pressures between both sides of the membrane, which produces a fluid exit from the compartment to the blood, depending on the efficacy of the transmembrane pressure and permeability and area of the membrane. Adsorption consists in the molecule trapping in the membrane surface. Its efficacy depends on the pore surface of the membrane. The membrane water permeability is indicated by its ultrafiltration coefficient (Kuf). Kuf is the volume of fluid ultrafiltered per hour at a transmembrane pressure of 1 mmHg. For more porous membranes, Kuf is higher for the same dialyzer surface area.

### Extracorporeal Purification Techniques in ARF

An important percentage of the patients who currently develop ARF in the intensive care units receive extracorporeal purification techniques, being the continuous procedures the most widely used, due to the better hemodynamic stability achieved with its use, allowing its implementation in unstable patients, in whom intermittent
dialysis is difficult to apply. Besides, gradual elimination of water and toxic metabolites allow a great flexibility in the hydroelectrolytic management, generating “space” for the administration of artificial nutrition and intravenous medication. Besides, it can also improve the gas exchange by a reduction in the hydrostatic pressure and by the enhancement of the ventricular filling pressures. Other advantages are the preferential elimination of interstitial fluids, a lower complement activation rate, a low extracorporeal blood volume, low complication rate and the chance of a good uremic and intravascular volume control without any protein intake or fluid restriction.

There are several studies that support the utility of this technique in ARF, not only by the high fluid elimination, but also, and although this point is more discussed, by the clearance of solutes which is necessary to achieve a better metabolic control for the patient. In addition, evidence exists that the metabolic control achieved by extracorporeal purification (venovenous or arteriovenous with diafiltration) is superior to that obtained with conventional hemodialysis, because of the rebound effect in the solutes concentration which is produced in the intermittent techniques. Nevertheless, although they improve very much the management of this patients, it has not been proved clearly that this techniques increase survival, although in a recent metaanalysis published with all the studies published up to present (13 studies, including 1400 patients) it has been found that when patients with a similar severity level, the reduction in hospital mortality with continuous techniques is clearly significant, and the recovery of ARF is significantly better and faster.

The continuous techniques used at present are the following:

**SLOW CONTINUOUS ULTRAFILTRATION (SCUF)**
This technique consists of passing a certain blood flow through a high permeability filter. The extracorporeal circuit can be impelled by the arterial pressure of the patient (arteriovenous circuit) or by a pump to perfuse the hemofilter.

### Table 2. Hyperkalemia emergency treatment.

<table>
<thead>
<tr>
<th>Mild hyperkalemia (&lt;6.5 meq/l):</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cation exchange resin such as sodium polystyrene sulfonate (Kayexalate)</td>
<td></td>
</tr>
<tr>
<td>Diuretics alone may suffice with a level of less than 6.0 meq/l</td>
<td></td>
</tr>
<tr>
<td>Maintenance: low-potassium diet and discontinuation of offending drugs</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severe or symptomatic hyperkalemia (&gt;6.5 meq/l):</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuevers that effect K⁺ transit into cells:</td>
<td></td>
</tr>
<tr>
<td>Calcium (1 ampule of 10% calcium gluconate) stabilizes cell membranes, acting within minutes but with a short-lived effect. Should not be given in bicarbonate-containing solutions or in patients taking digoxin</td>
<td></td>
</tr>
<tr>
<td>Insulin (10 U or regular) and glucose (50 ml of 50% solution) can decrease potassium levels by 0.5 to 1.5 meq/l, begin its effect within 15 minutes and lasting for several hours. In an hyperglycemic diabetic patient, use insulin alone</td>
<td></td>
</tr>
<tr>
<td>Sodium bicarbonate (one ampoule of 7.5% sodium bicarbonate solution). Begins acting within 30 to 60 minutes, and the effect lasts for several hours. Works best in patients with metabolic acidosis but is less effective in renal failure</td>
<td></td>
</tr>
<tr>
<td>Albuterol (20 mg in 4mL of saline by inhalation or 0.5 mg i.v. can lower plasma potassium concentration by 0.5 to 1.5 meq/l within 30 to 60 minutes</td>
<td></td>
</tr>
<tr>
<td>Increasing K⁺ excretion (slower but longer-lasting effect):</td>
<td></td>
</tr>
<tr>
<td>Loop or thiazide diuretics facilitate urinary potassium excretion</td>
<td></td>
</tr>
<tr>
<td>Cation exchange resins cause potassium loss in the stool by exchanging potassium for sodium. It can be given orally or by retention enema, though intestinal necrosis or volume overload can potentially complicate treatment</td>
<td></td>
</tr>
<tr>
<td>Dialysis should be considered in case of previous measures failure, severe hyperkalemia, and massive tissue destruction with release of large amounts of potassium</td>
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</tbody>
</table>
Venovenous circuit. The physical membrane mechanism used in this technique is the convection, and its greater utility lays in the control of fluid in situations of hydric overload (congestive heart failure resistant to the conventional treatment), since its objective consists of simply eliminating the leftover liquids, using high flow membranes.

**VENOVOENOUS/ARTERIOVENOUS CONTINUOUS HEMOFILTRATION (VVHF/AVHF)**

It is the most commonly implemented technique in intensive care units, being very helpful in acute renal failure, hyperkalemia, intoxications, volume overload, etc. The main difference with the previous technique is the need of reposition, allowing to balance the volume loss at our will. The physical mechanism employed is convection, using a high permeability filter. The system works by the pressure difference between both sides of the membrane.

**VENOVOENOUS/ARTERIOVENOUS CONTINUOUS HEMODIALYSIS (VVHD/AVHD)**

It consists in passing a continuous dialysis fluid flow through the effluent compartment which circulates cross-current to blood flow; this way we can face the blood to the dialysis bath through a low permeability membrane, generating a small size molecule diffusion phenomenon (urea, creatinine, etc.), ineffective for big molecules. The dialysis fluid passes only once through the filter, so that its composition remains unaltered and more diffusion capacity can be achieved. In parallel with the ultrafiltrate produced, which is also saturated to 100% with urea, an additional convective clearance is generated. Being the action mechanism predominantly diffusive, the pass of water through the membrane is small, without being necessary fluid reposition.

**VENOVOENOUS/ARTERIOVENOUS CONTINUOUS HEMODIAFILTRATION (VVHDF/AVHDF)**

A combination of the two previous ones. It consists of a continuous hemodialysis where a filter with a membrane of high permeability is used to eliminate molecules of high molecular weight apart from molecules of low molecular weight eliminated by diffusion. Due to the high rate of ultrafiltration generated in these membranes, replacement is necessary to secure a suitable balance of fluid.

**HIGH-VOLUME HEMOFILTRATION (HV-HF)**

High permeability membranes through which blood is passed are used. Dialysis fluid must be simultaneously and concurrently flushed through the ultrafiltrate at a high flow rate; the possibility of making it recirculate (adding to the mechanisms of diffusion and convection one of retrofiltration) must be considered. This consists of passing through the distal end of the ultrafiltrate in an inverse direction so that it can return to the blood compartment of the filter. Thus we achieve an adequate volume of the ultrafiltrate which can be altered based on the type of balance which is considered most appropriate (positive, negative or neutral) by either an increase or decrease of the dialysis fluid. With this technique the highest clearance rates are elicited with an optimization of the diffusive and convective mechanisms.

### DOSAGE AND START/WITHDRAWAL CRITERIA

Regarding criteria of “dosage” of the extrarrenal purification, it seems that the greater the purification volume the better prognosis. In a prospective randomized study by Ronco a significant reduction of the mortality of patients (<0.0007) with an hourly hemofiltrate volume higher than 35 ml/kg using polysulphone membranes was concluded. In other studies it have been stated that in septic patients with ARF and treated with depuration techniques very high convection doses (60-130 ml/kg/h) implemented in short periods of time and followed by more conventional doses due to the inherent difficulties to the handling of very high convection doses, improve the hemodynamics and mortality in these patients. This principle is also applicable to the intermittent techniques, also being effective in this context.

An early beginning of the hemofiltration in an ARF situation seems to bring a better prognosis. In a study including a group of 100 traumatized patients with ARF the start of the kidney purification with urea levels lower than 10 mmol/L improved their survival. Though this issue is controversial, other authors also found
a better outcome in patients treated with an earlier extracorporeal purification, as well as a higher mortality in a diuretic-treated group of patients. In situations of lactic acidosis it is possible to administer high doses of bicarbonate without any risk of hypernatremia. In intoxications, continuous techniques show the advantage with regard to intermittent methods a reduction of the “rebound effect” that occur in the latter. It is mainly used with greater efficiency for lithium, fenformine and N-acetyl procaainamide intoxications.

In the context of hepatic encephalopathy in patients with fulminant hepatic failure, the continuous techniques have demonstrated to produce a reduction in the increase of intracranial pressure (ICP) and cerebral perfusion pressure compared to conventional techniques.

In the post-operative liver transplant care the continuous venovenous hemodiafiltration allows to eliminate great volumes of fluids without any hemodynamic repercussion.

ARF appears in 15-30% of the cases of traumatic rhabdomyolisis, specially related to the “crush syndrome”. In this setting the role of renal replacement techniques seems to be limited to the established ARF.

The externalization of the extracorporeal circuits and the dilution with fluids at a controlled temperature allows the treatment of both hyperthermia and hypothermia. Cardiopulmonary bypass is considered as the most effective heating method in severe hypothermia, and in pathological situations like severe head injury the temperature control seems to have prognostic importance.

The seriously burned patient is a special kind of severe traumatized patient in whom hypercatabolic features as special conditioners for fluid management (capillary leak) turn extracorporeal purification into a reasonable alternative. Current experience in these kind of patients is good though conclusive data in patients without ARF are lacking.

Continuous replacement techniques are generally well tolerated, with a low rate of complications:

Complications of continuous techniques

Continuous replacement techniques are generally well tolerated, with a low rate of complications:

Vascular complications
The most severe complications are associated with the arterial access for the continuous arteriovenous hemofiltration (CAVHF). Venovenous access reduces these complications substantially. Percutaneous puncture and introduction of great caliber catheters by the modified Seldinger technique can produce bleeding episodes or even blood vessel perforation. In atheromatous blood vessels important hemorrhages can arise due to damage in the vessel wall and plaque detachment. During hemofiltration, a careful control of anticoagulation may reduce the bleeding risk. At the end of the procedure, bleeding can appear because of arterial cannula withdrawal; careful management and continuous compression are encouraged. If bleeding persists surgery could be necessary.

Local thrombosis of the arterial cannula is a frequent event. Occasionally this situation can critically decrease leg perfusion and make urgent surgery necessary. A frequent control of the perfusion of the leg is recommended. Similar complications have been described at a lower rate for venous access.

In the case of venovenous therapies, the positive pressure in the venous line rises and the extracorporeal pump automatically stops. The filter and the vascular lines can completely become coagulated without any complication or thrombosis of the catheters or the cannulated vessels.

INFECTIOUS COMPLICATIONS
In order to prevent infection and sepsis due to the extracorporeal circuit, sterile manipulation of the circuit is essential, even if it is working correctly. In patients with CRRT the antimicrobial treatment should be adapted to the patient clinical needs and to the drug extracorporeal clearance. In some situations an increase in drugs dosage is recommended, whereas for binded-to-proteins substances the extracorporeal clearance and the dose must be reduced compared to the patients with a normal renal function.40

CIRCUIT DISCONNECTION
Any accidental disconnection of the extracorporeal circuit can be life-threatening. It is always necessary to make sure that all the connections are firmly set and that all the parts of the circuit are visible. The majority of the disconnections used to occur with the old circuits, not specifically designed for this function. Nowadays these problems are unusual.

AIR EMBOLISM
In the modern systems this problem is prevented with a special monitoring and the pump-incorporated alarms, which immediately interrupt the fluid perfusion when air inside the circuit is detected.

HYDRIC OVERLOAD
Accidental hydric overload is a very serious risk to be kept in mind in the hemofiltration techniques, especially when there is a high fluid refill. Monitoring and meticulous register of the entrance and exit of liquids are essential.

HYPOPHOSPHATEMIA
Just like with other electrolytes, drugs or nutrients, phosphorus deficiency can only be detected by biochemical monitoring of the patient.

HYPOThERMIA
Due to the big amount of fluid exchanged, hypothermia can occasionally be observed. This problem can be avoided by heating the fluids of reposition. Nevertheless, continuous hemofiltration can be used to decrease the body temperature in hypothermia.

Depending on their composition, membranes are classified into cellulosic (cellulose and derivatives like hemofan, cellulose diacetate, cellulose triacetate) characterized by their thinness (appropriate for diffusion) low resistance and lack of adsorptive capacity due to their hydrophilic features, synthetic (PMMA, poliamide, polysulphone, AN69, poliacrilonitrilo) can support high difference of pressures presenting a high permeability (hydrophobic composition) and a variable adsorption capacity depending on each compound. Mixed synthetic (poliflux) are hydrophilic-hydrophobic membranes with intermediate characteristics of the previous ones, being water permeable, resistant, and with good adsorptive properties. According to their permeability the membra-
nones are classified into low permeability membranes (not apt for convection) which include cellulose, hemofan and cellulose diacetate made and high permeability ones (suitable for hemofiltration) including synthetic, mixed and cellulose triacetate made. Permeability is measured by means of ultrafiltration coefficient (\(K_{uf} = \text{Volume of ultrafiltrate in ml/mMg/m}^2/\text{hour}\)).

The contact of the blood against the membrane generates a patient’s response, demonstrated as the activation of very different biologic systems (complement activation, stimulation of the cytokine production, leukocyte attachment, etc.). In the biocompatible membranes (synthetic, mixed, cellulose triacetate) induce a less activation of these mechanisms, whereas the bioincompatible membranes (cellulose derivatives) active complement in a very intensive way. Though the negative physiologic consequences of this event have been proved, there is no evidence in favor of biocompatible membranes in order to improve prognosis, with completely discordant results in recent meta-analysis.\(^{41}\) Depending on each treatment and patient we can choose certain types of membranes:

- **Dialysis:** Low flow membranes (cellulose derivatives) are suitable for intermittent dialysis, whereas for slow dialysis high flow membranes could be more appropriate if dialyzer low flows are used (<30ml/h).
- **Hemofiltration:** We need a high flow membrane for continuous hemofiltration. Any synthetic membrane could be used (for example cellulose triacetate).
- **Hemodiafiltration (diffusion+convection):** The right membrane would be hydrophilic-hydrophobic (poliflux) though if we use a slow flow dialyzer (<30ml/min) we can manage with a high flow membrane.
- **Adsorption:** Although mixed synthetic components have shown great adsorptive capacity, AN69 is the best material for adsorptive treatment.\(^{42}\)

Reposition and dialysis fluids composition must be similar to plasma (potassium 3,5-5 meq/l, clorur 100-110 meq/l, calcium 3-4 meq/l, bicarbonate 25-30 meq/l and sodium 135-145 meq/l). Though we can change both solutions composition depending on the patient needs, the same solution can be used both as replacement or dialyzer.\(^{43}\) However, all these solutions lack for phosphorus. These molecules are generally present at high levels in patients with renal failure and continuous renal replacement needs, but rapidly decreases by the great elimination capacity of these procedures that is why it is necessary to contribute it by dialysis fluid addition or nutrition. During renal replacement procedures high concentrations of aminoacids and glucose are eliminated, being necessary their reposition despite the fact that at this moment we cannot define the precise reposition doses. It has not proved either the need of replace vitamins, folic acid or oligoelements, being not possible nowadays to implement any specific recommendation. Sterility is an essential requirement for these fluids. Solutions containing bicarbonate tend to get more contaminated during their storage, that is why avoiding the delay in their administration once prepared is an important measure. Retrodiffusion is a typical mechanism of bacterial contamination in dialysis that is why sterility requirements in dialysis must be as strict as in hemofiltration, or even more when bicarbonate is used as buffer. The use of the buffer substance is a controversial issue. We have 4 choices:

- **Acetate:** Fallen in disuse due to its bad metabolic control and hemodynamic tolerance profile, with severe myocardial depression effects.
- **Citrate:** It is used as circuit anticoagulant, existing little experience with its use as buffer.
- **Lactate:** It is a well tolerated molecule by its good metabolic tolerance, but increases lactate serum levels, has catabolic effects and presents metabolic difficulties in liver failure.
- **Bicarbonate:** It has the same buffer power as lactate, but it is used instead of this one in hyperlactatemia, liver failure or high volume hemofiltration treatments. It presents difficulties related to its manipulation and commercialization, because of its crystallization ease when is mixed with the calcium included in the fluids, that is why is fundamental to mix the components shortly before its administration.

The venous access is an outcome decisive factor in continuous purification techniques. Point of access choice must be individualized, avoiding subclavia vein due to its latter stenosis complications. We will need two-lumen catheters ≥12 F and ≥13 F if we plan high volume treatment. The length ranges 15-18 cm, and 20-
25 cm for the femoral vein. The use of permanent arteriovenous fistula is not recommended.

CIRCUIT ANTI-COAGULATION

Premature circuit clotting is a major problem in daily practice of continuous renal replacement therapy. It means an important waste of material, nursing time, blood loss (at least 200 ml every coagulated filter) and hours of treatment. Some factors help pro-coagulant trend in the extracorporeal circuit: Firstly, the contact of the blood with a stranger material activate blood cells, making platelets and polimorphonuclear cells aggregates and activating the proteic cascade until the clot is formed. Secondly this process is activated by means of the contact of the blood with air bubbles caught in some parts of the circuit. Third, the blood reologic features can determine coagulation. The blood viscosity depends on its hematocrit. With a normal hematocrit, relative viscosity (to water) ranges between 3 and 4, in anemia around 2, and with an hematocrit of 60% can raise up to 8 or 10. High hematocrit can be found at the exit of the filters in policitemia or when the ultrafiltration is important. Temperature can always affect viscosity since low temperatures increase viscosity (2% by each degree that descends). The speed of the blood flow also influences on viscosity, decreasing with microcirculation slow flows (as happens in shock).

Tisular factor triggers extrinsic pathway, whereas contact with collagen or a strange surface (filter’s membrane) activates XII factor and platelets, activating intrinsic pathway. This pathway is slower, needing some minutes to get activated. Extrinsic pathway is explosive: gets activated in only seconds. Routine coagulation tests include:
- Platelet count: Normal value between 130000 and 400000/µl.
- Partial thromboplastin time (APPT): Normal value ranges 25-35 seconds.
- Prothrombin time (PT) and International Normalized Ratio (INR). This last one is the quotient between patient’s prothrombin time and laboratory control (normal value ranges 0.9-1.2).
- Calcium concentration: Calcium plays an important role accelerating reactions in extrinsic or intrinsic (except the two first steps) pathway. That is why hypocalcemia can generate coagulation disorders.
- Activated clotting time: Little used. Normal value ranges 110-190 seconds.
- Antithrombin III levels: Normal value ranges 80-120%. It is an alpha-globulin or antithrombin-heparin cofactor. 90% of thrombin formed in a clot originated in prothrombin is absorbed. Rest of it is rapidly combined with antithrombin III.

Ultrafiltration flow rates are directly related to transmembrane pressure (TMP) and a constant: the hydraulic permeability coefficient (Kf) of every membrane, which is valid for certain flow, pressure and hematocrit values. An increase in TMP implies a decrease in permeability coefficient. In other words it expresses a partial coagulation of membrane’s surface or capillary, or an accumulation of a proteic layer decreasing its permeability. In order to avoid circuit coagulation there are two types of measures to be implemented:

TECHNICAL MEASURES

The circuits must be designed without obstacles, twists or turns. Catheter length and caliber must be adapted to the vein and flow required. Though there is no evidence related to survival enhancement with high compatibility membranes these are desirable because the more biocompatible the membrane is the less gets coagulated. Besides, we can reduce filtration fraction (FF) by an increase in the blood flow rate and prefilter reinfusion and a reduction in ultrafiltration flow rates. Fabricants advice to change the circuits every 48 or 72 hours, but it seems that more frequent changes (still not defined) improve some substances purification, specially some types of proinflammatory mediators. Anyway we can go ahead the coagulation events controlling TMP since TMPs >200 indicate the routine filter removal.

PHARMACOLOGICAL MEASURES

- Not fractionated heparin (sodium heparin): The present consensus recommends low sodium heparin doses at the circuit input. After a 2000-5000 units at initial dose follows a perfusion of 5-10 international units/kg/hour. Our strategy consists in diluting 5 ml of 1% heparin (5000 U) in 15 ml of 0.9% saline solution, resulting in
Eliminate certain components selectively. Once processed, plasma is reinfused to the patient. Main indications are thrombotic thrombocytopenic purpura, Guillain Barré syndrome, myasthenia gravis crisis, Goodpasture syndrome, Eaton-Lambert syndrome, sepsis, intoxications and drug overdose. CPFA is a blood purification modality in which plasma filtration obtained plasma is passed through a hydrophobic resins filter, producing a non-selective adsorption of sepsis mediators, improving survival in animal trials and hemodynamics in clinical trials.

Molecular Adsorbent Recirculating System (MARS)

Acute liver failure is characterized by encephalopathy, jaundice and coagulopathy and can be produced by virus, drugs or toxins. Infections and gastrointestinal bleeding can also intensify a chronic liver failure in patient with a known liver disease. Though liver transplant is the only treatment that cures 90% of patients, it is necessary to develop a liver support system to keep the patient in better possible conditions until his liver recovers or transplant can be done. Due to the liver failure a wide variety of toxic substances get accumulated, leading to brain and renal dysfunction. Most of these substances are lipophilic and are albumin-binded. The MARS purifies patients blood by means of passing it through a filter and uses 15% albumin as dialysis fluid. These treatment decreases serum bilirubin levels in 18%, biliar acids in 44% and normalizes aminoacids balance. Nowadays the established indications are acute liver failure over healthy liver, acute liver failure over known chronic liver disease and intractable pruritus.

List of abreviations:
AKI: Acute kidney injury.
ARF: Acute renal failure.
CRRT: Continuous renal replacement therapy.
IHD: Intermittent hemodialysis.
MSOF: Multisystem organ failure.
MODS: Multiple organ dysfunction syndrome.
ATN: Acute tubular necrosis.
FENa: Fractional excretion of sodium.
GFR: Glomerular filtration rate.
CrCl: Creatinine clearance.
CrSr: Serum creatinine levels.
Kuf: Ultrafiltration coefficient.
SIRS: Systemic inflammatory response syndrome.
CPFA: Coupled plasma filtration-adsorption.
MARS: Molecular Adsorbent Recirculating System.

250 U/ml. Heparin should not be used in heparin induced trombopenia and APPT levels must be determined, with target levels between 35 and 45 seconds (1.4 times control). Every 10 seconds we raise APPT the life of the filter prolongs 25% at the expense of hemorrhagic complications. Dose adjustment must be individualized being aware of hematocrit falls, concomitant bleed-inducing drugs, etc.

- Fractionated heparin: There is much less experience with low molecular weight heparins but it seems that heparin induced trombopenia risk is lower than sodium heparin induced (though exists). Dalteparin (a 15-25 U/kg initial dose followed by 5U/kg/hour) and enoxaparin (a 0.15 mg/kg initial dose followed by 0.05mg/kg/hour) have been used. Monitoring anti-Xa levels is necessary, being 0.25-0.35 UI/ml the recommended range in continuous renal replacement techniques.

- Citrate: It can cause complications (metabolic alkalosis, hypernatremia, hypomagnesaemia) due to the great amount of sodium that provides as well as the citrate converts to bicarbonate (1:3 ratio), decreasing calcium and magnesium concentrations using it as prefilter reinfusion fluid an easy and safe way to avoid complications. 3-5mmol/l would be the concentration target in the circuit.

- Prostaglandins: Indicated in heparin contraindications (heparin induced trombopenia, high risk of bleeding, severe trombopenia, etc.) and short life filters (less than 16-24hours), being prostacyclin the most commonly used. Sodium epoprostenol dose varies between 4 and 8 nanograms/kg/min, being 5ng the most recommended dose. Hypotension as main adverse effect, high price and difficult administration are its great inconvenient, not being able to use it associated with C activated protein.

- Thrombin inhibitors: Human recombinant hirudin, argatroban and dermatan sulfate. Little experience at this moment about them exists.

Other Extracorporeal Purification Models

Plasmapheresis and Coupled Plasma Filtration-Adsorption (CPFA)

Plasmapheresis is the procedure in which plasma is separated from blood and processed to