Optimizing continuous renal replacement therapy in the ICU

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Chapter 2

Acute kidney injury and renal replacement therapy in the intensive care unit

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Defining acute renal failure

Acute renal failure in the intensive care unit (ICU) is common and carries a high mortality risk. The reported incidence of acute renal failure in the critically ill varies from 1-25% with a hospital mortality of 28-90%.[1-5] The reason of these wide ranges is the lack of consensus definition for acute kidney injury (AKI). A uniform definition and classification system of course is necessary for standardizing entry criteria and endpoints in clinical trials. The Acute Dialysis Quality Initiative Group developed the RIFLE classification system through broad consensus by experts (Fig. 1).[6,7] The RIFLE criteria have been validated in several studies and appeared useful in predicting hospital outcome.[8,9] RIFLE is an acronym for three levels of severity: risk, injury and failure and two outcomes: persistent acute renal failure for more than 4 weeks termed loss and renal function loss for more than three months termed end-stage renal disease.

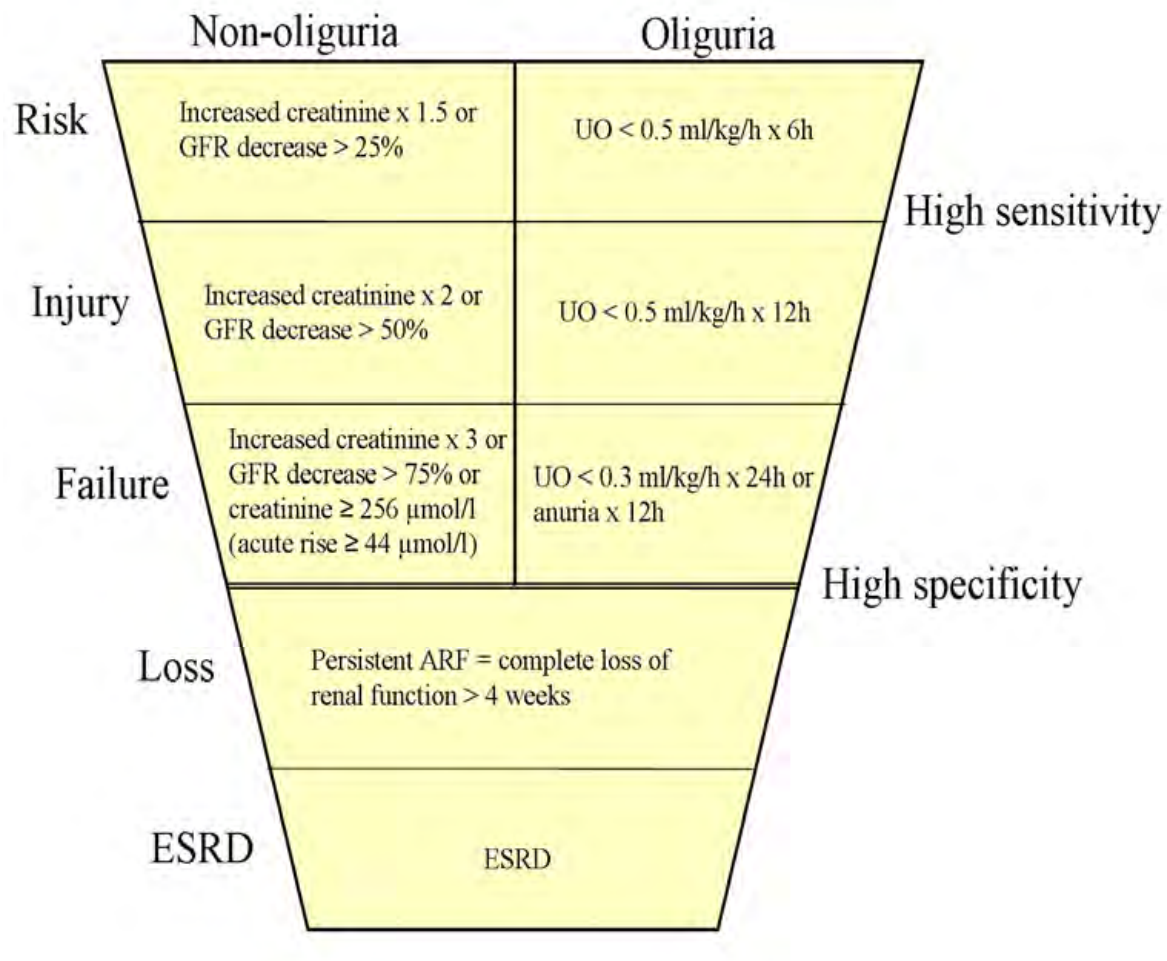

Fig. 1. RIFLE criteria for classification of acute renal failure. GFR: glomerular filtration rate; UO: urine output; ARF: acute renal failure; ESRD: end-stage renal disease; RRT: renal replacement therapy.[6] (Reproduced with permission)

As this definition was developed, several studies showed the clinical importance of renal dysfunction even before reaching the stage of failure. Mild renal function loss seems to be associated with adverse outcomes.[8,10] These new insights have led the Acute Kidney Injury Network to propose some small modifications to the RIFLE criteria (Table 1).[11] The diagnostic criteria for AKI were broadened: an abrupt (within 48 hours) reduction in kidney function defined by an absolute increase in serum creatinine of more than or equal to 26.4 μmol/l, a percentage increase in serum creatinine of more than or equal to 50%, or a reduction in urinary output (documented oliguria of less than 0.5 ml/kg per hour for more than 6 hours). Also, the staging system was altered. The "Risk" category has the same criteria for the diagnosis of stage 1 AKI. The "injury" and "failure" category are now stages 2 and 3 of AKI. Patients receiving renal replacement therapy are categorized as stage 3. The new system has yet to be validated.

Table 1. Classification/staging system for acute kidney injury.[11] (Reproduced with permission)

Classification/staging system for kidney injury [a]		
Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of more than or equal to 26.4 μmol/l (≥ 0.3 mg/dl) or increase to more than or equal to 150% to 200% (1.5- to 2 fold) from baseline	Less than 0.5 ml/kg per hour for more than 6 hours
2	Increase in serum creatinine to more than 200% (> 2 to 3 fold) from baseline	Less than 0.5 ml/kg per hour for more than 12 hours
3[b]	Increase in serum creatinine to more than 300% (> 3 fold) from baseline (or serum creatinine of more than or equal to 354 μmol/l (≥ 4.0 mg/dl) with an increase of at least 44 μmol/l (0.5 mg/dl)	Less than 0.3 ml/kg per hour for 24 hours or anuria for 12 hours
[a] Modified from RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) criteria. Only one criterion (creatinine or urine output) has to be fulfilled to qualify for a stage. [b] Individuals receiving renal replacement therapy (RRT) are considered to have met the criteria for stage 3 irrespective of the stage they are in at the time of RRT		

Pathogenesis and prevention of acute renal failure

The cause of acute renal failure can be classified into three broad categories: prerenal, postrenal and intrinsic renal. The pathogenesis of acute renal failure depends on its aetiology, varying from immune or infection mediated-glomerular damage to drug-induced tubulo-interstitial nephritis (Fig. 2).

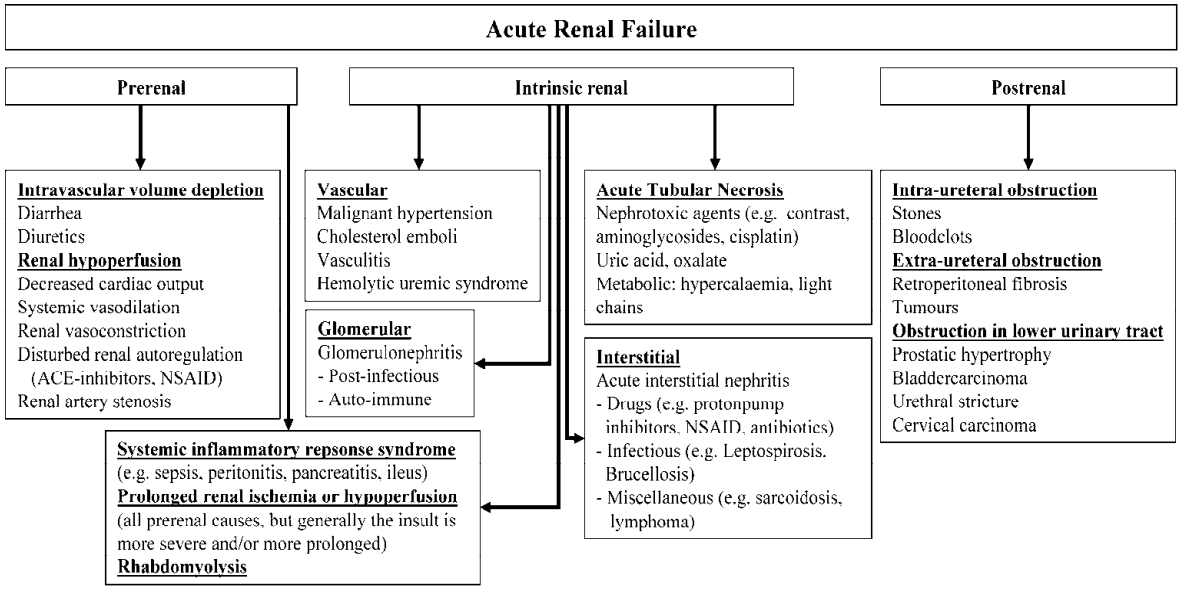

Fig. 2. Classification of acute renal failure. ACE: angiotensin converting enzyme; NSAID: non-steroidal anti inflammatory drugs.

Pathogenesis

In the ICU the prerenal form is by far the most common cause of acute renal failure, associated with diminished renal perfusion, yet in the absence of tissue damage. There are several conditions that can cause a decreased renal perfusion, such as reduced cardiac output and any cause of shock or intravascular volume depletion. These conditions will typically result in oliguric acute renal failure. If renal hypoperfusion is prolonged, tissue injury will eventually occur resulting in acute tubular damage (resulting in apoptosis or necrosis and AKI). The mechanisms of acute intrinsic renal failure involve both vascular and tubular factors. In view of medullary hypoxia, the proximal tubule and the thick ascending limb of the loop of Henle appear to be particularly susceptible to ischaemia.[12] The tubular ischaemia results in apoptosis with rapid loss of cytoskeletal integrity and cell polarity. Some cells manifest ischemic necrosis. The cells are desquamated and normal ion transport is disturbed. Sodium chloride is pumped back into the tubular lumen and ultrafiltrate diffuses back into the interstitium causing interstitial oedema.[13] The tubuloglomerular feedback causes constriction of afferent arterioles due to high distal sodium chloride delivery, with subsequent decrease in glomerular filtration rate and urinary output. Tubular obstruction will occur as the damaged and necrotic cells and cellular debris form casts. Renal ischaemia also induces an inflammatory response in which endothelial and epithelial cells, leucocytes and T-lymphocytes are involved. The inflammatory cells are recruited during reperfusion and release several chemokines and cytokines that further fuel the inflammatory cascade.[14,15]

Prevention

The most important measure in preventing acute renal failure, especially acute tubular necrosis, is optimization of intravascular volume and cardiac output. Furthermore, nephrotoxic agents such as radiocontrast and aminoglycoside should be avoided as much as possible. These measures are especially important in those patients in whom renal function and blood flow are already compromised. Drugs that intervene with renal autoregulation (angiotensin converting enzyme inhibitors, non-steroidal anti-inflammatory drugs, angiotensin-II receptor blockers) should be used with caution. There is much debate concerning the type of fluid to be used to restore intravascular volume. Resuscitation with crystalloids is not associated with an improved survival compared to colloids.[16] The use of starch-containing volume expanders should be avoided, especially in sepsis, since it may be associated with irreversible kidney injury.[17,18] Especially in case of oliguria or anuria, caution is warranted with excessive volume expansion, which may cause pulmonary oedema. If hypotension persists in spite of adequate volume expansion, vasopressors should be considered in order to preserve renal perfusion. In patients with septic shock, norepinephrine is preferable to dopamine.[19]

In the past, several pharmacological agents had been assigned renoprotective capacities, but up till now it remains unclear whether or not these agents are of benefit for the kidney. The use of "renal dose" dopamine was an accepted strategy to prevent or even treat renal dysfunction, by increasing renal blood flow and resulting in short-term increases of glomerular filtration rate with an increased urinary output. Prospective trials and meta-analyses, however, have shown that the use of dopamine is not associated with reduced mortality and totally ineffective for preventing or treating renal dysfunction.[20] Fenoldopam, a selective dopamine-1-receptor agonist, has been shown to increase renal blood flow and glomerular filtration rate.[21] There are some promising reports that this agent might be useful in preventing AKI from other causes than contrast exposure and in reducing mortality.[22,23] However, data concerning this issue are conflicting.[24] Future studies will hopefully give some clarifications; hypotension as an important side effect is, however, a major drawback. Loop diuretics have the potential to alter an oliguric state to a non-oliguric state. Several trials and meta-analysis, however, did not reveal any beneficial effects of these agents in acute renal failure. Loop diuretics are not associated with diminished need for renal replacement therapy or decreased mortality, but there is an association with a shorter duration of RRT and increased urinary output.[25] There are conflicting data whether the use of diuretics in acute renal failure is associated with increased mortality.[26,27] Moreover, high dose furosemide may

cause serious adverse events such as tinnitus and deafness. Hence, caution is warranted when administering loop diuretics in the critically ill with acute renal failure. Mannitol has only proven benefit in preventing acute renal failure, when administered just before clamp release during cadaveric renal transplant surgery.[28] Though never formally investigated, the preventive use of mannitol together with forced alkaline diuresis is generally accepted as a preventive measure of acute renal failure in rhabdomyolysis.[29] By virtue of its ability to inhibit apoptosis and to enhance tubular epithelial regeneration, erythropoietin seems a promising agent to protect the kidney against ischaemia/reperfusion injury in animal studies.[30-32] The effectiveness of this agent in acute renal failure in humans has to be proven yet.

Contrast-induced nephropathy (CIN)

A type of acute renal failure that deserves separate discussion in the context of critical illness is contrast-induced nephropathy (CIN). Indeed, critically ill patients frequently undergo diagnostic and interventional radiographic procedures in which iodinated radiocontrast media are used. Administration may result in a usually reversible form of acute renal failure. Contrast-induced acute renal failure accounts for a significant number of cases of hospital-acquired AKI.[33] CIN is the third commonest cause of AKI in hospitalized patients accounting for 11% of cases. The European Society of Urogenital Radiology precisely defined CIN as an absolute increase of serum creatinine level of ≥ 44 μmol/l (= 0.5 mg/dl) or a 25% increase from baseline within 72 hours after contrast administration.[34] The definition of acute kidney injury as proposed by The Acute Kidney Injury Network is a rise in serum creatinine of 26.4 μmol/l (= 0.3 mg/dl) with oliguria (table 1). So, a rise in creatinine of 26.4 μmol/l (AKI stage 1) after contrast exposure in the ICU theoretically fulfils the criterion for CIN; this, of course, is debatable.

Pathophysiology

The pathogenesis of CIN is unclear. Altered renal haemodyamics and direct tubular toxicity are potential contributory factors, as outlined in Fig. 3. After injection of contrast there is an acute and transient increase in renal plasma flow, diuresis and natriuresis. These effects activate the tubuloglomerular feedback which is responsible for renal vasoconstriction. These processes increase the renal demand for oxygen; in case of sepsis or hypovolemia the contrast-induced increased oxygen demand may cause medullary ischaemia. If the release of

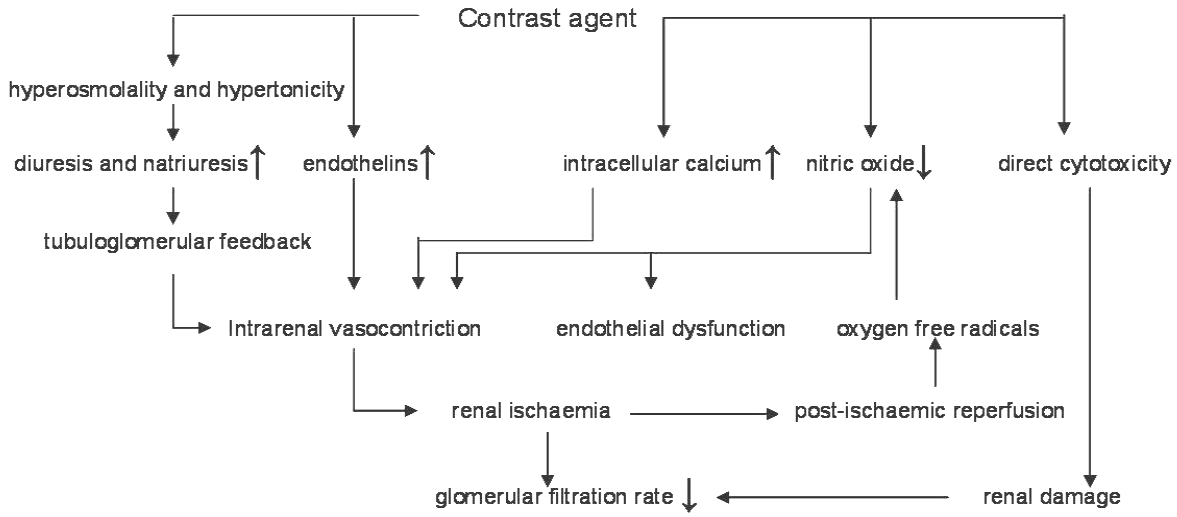

Fig 3. Possible mechanisms of contrast-induced nephropathy. Adapted from Meschi et al..[35] (Reproduced with permission)

protective endogenous vasodilators (such as nitric oxide and prostaglandins) is inhibited (for example by non-steroidal anti-inflammatory drugs), medullary ischaemia and tubular necrosis may develop. In animal studies, contrast agents may have a direct tubular toxic effect due to the release of oxygen free radicals. Medullary ischaemia may also result in the formation of reactive oxygen species leading to injury.

Epidemiology and risk factors

The reported incidence of CIN greatly varies in the literature and ranges from zero to 50%, depending on study population, definition of CIN, the amount and type of contrast used, and the radiologic procedure. Even though the mortality rate is about 14%,[36] several studies reported attributable mortality in patients developing CIN.[37-39] After adjusting for comorbidity, patients developing CIN had a more than 5-fold increased risk of death compared to those without.[40] Futhermore, the development of CIN is associated with an increased risk for adverse cardiovascular outcome and a prolonged hospital stay.[41-44]

Patients developing CIN have more comorbidity than patients exposed to contrast who do not develop CIN. Pre-existing renal impairment is associated with the highest risk for developing CIN.[45] The higher the baseline creatinine level the higher the risk: 2% in patients with a serum creatinine of < 132 μmol/l and 20% in patients with a serum creatinine level of > 220 μmol/l.[46] Historically, diabetes was known to be associated with an increased risk. However, the risk of developing CIN in diabetic patients without renal impairment is similar to that in healthy individuals.[47] Many elderly patients develop CIN, but they also have

extensive comorbidity such as atherosclerosis and renal impairment. Multiple myeloma is often regarded as a risk factor, but this can be doubted, in the absence of hypovolaemia. All conditions leading to hypovolaemia or hypotension, such as heart failure, cirrhosis and sepsis are considered as risk factors for CIN. The conditions result in a compromised renal perfusion rendering the kidneys susceptible to contrast-induced injury. Others conditions and drugs inhibiting of protective renal vasodilators can contribute to CIN.

Iodinated contrast agents are either ionic or non-ionic also having variable osmolality. A general rule is that the higher the osmolality of the agent the greater its nephrotoxic effects.[48] The non-ionic low osmolality contrast agents still have an osmolality of 500-850 mosmol/kg (iohexol, iopamidol, iopromide), which is significantly higher than plasma. The iso-osmolar contrast agents (290 mmol/kg) such as iodixanol, seem to be the least nephrotoxic as demonstrated in a pooled analysis of 16 trials in which the compound was compared with low osmolality contrast agents.[49] This advantage of iso-osmolar contrast may only pertain to high risk patients. In a trial in which iso-osmolar contrast was compared with low-osmolar agent in low risk patients, the rate of CIN was comparable.[50,51] However, a randomized double-blind trial, comparing low-osmolar with iso-osmolar contrast agents in patients with diabetes and chronic kidney disease at risk for CIN, suggested that the incidence of CIN was similar in both groups.[52] Several studies have finally shown a relationship between the volume of contrast and the incidence of CIN. However, even small volumes of contrast can be nephrotoxic in the high risk patient.

Clinical characteristics

CIN typically develops within 24 hours after exposure. The AKI is usually non-oliguric and recovery may occur within three to five days. In high risk patients the decline in renal function may temporarily require renal replacement therapy. Occasionally, renal failure is persistent, especially in patients with pre-existent severe chronic kidney disease and extensive comorbidity (for example diabetic nephropathy or heart failure). The diagnosis of CIN is usually made in the absence of any other causes of AKI. There are no diagnostic tests to confirm the diagnosis. After percutaneous arterial interventions, AKI can also be caused by atheromatous or cholesterol emboli or by haemorrhagic shock.

Preventive strategy

There are few modifiable risk factors which can be used to lower the risk for CIN. In high risk patients it is preferable to use small volumes of low- or iso-osmolar contrast agents.

Furthermore, dehydration and hypovolemia should be pretreated. Isotonic saline seems more effective than half normal saline.[53] In small trials, isotonic bicarbonate seems superior to isotonic saline in preventing CIN.[54,55] However, sodium bicarbonate was associated with an increased incidence of CIN in a retrospective study,[56] so that further study is needed. There is no consensus concerning the optimal rate and duration of infusion. In elective procedures, it is recommended to administer isotonic saline 12 hours before until 12 hours after exposure to contrast at a rate of 1 mL/kg/h.[55,57] In urgent situations, sodium bicarbonate (a mixture of 154 mL sodium bicarbonate (1000 mmol/L) and 846 mL Dextrose 5%) can be administrated at a rate of 3 mL/kg/h, starting 1 hour prior to the procedure and 1 mL/kg/h for 6 hours afterwards.[55] If rehydration prior to the procedure is not possible, it is recommended to administer isotonic saline after the procedure for several hours. Clearly, there is a need for randomized trials addressing issues like rate, duration and composition of volume expansion.

Several pharmacological agents have been tried to prevent CIN. Vasodilators such as dopamine, fenoldopam, calcium channel blockers and theophylline proved ineffective. N-acetylcysteine has gained wide popularity because of its anti-oxidative effects and negligible side effects. Data and numerous meta-analyses concerning its effectiveness are conflicting, however. After deciding to use the agent despite doubtful effects, the most frequently prescribed dosage is 600-1200 mg orally twice a day, before and on the day of the procedure. Other agents, such as statins, ascorbic acid and atrial natriuretic peptide have been tried to prevent CIN, all without success.[58-60] The concept of removing the toxic contrast with dialysis or filtration is charming, but there are no convincing data to show a decrease in the incidence of CIN.[61]

Renal replacement therapy

Historical background

Renal replacement therapy became feasible when Kolff developed the artificial kidney in the mid 1940's. In the 1950's haemodialysis was not widely used yet and still considered as an emergency treatment in near-hopeless situations. In the 1960's several chronic dialysis programmes were initiated in the developed countries, but the availability was still limited. The increasing application of renal replacement caused the mortality from acute renal failure to drop from 90% to 30%. At the end of the 1960's well structured intensive care units were introduced in hospitals worldwide. Haemodialysis was the dominant form of renal replacement in the 1970's. Major drawbacks of this technique, however, were acute

hypotension and difficulties in fluid management; also the rapid electrolyte shifts were considered undesirable. Because of these shortcomings, Kramer developed in 1977 a system called continuous arteriovenous haemofiltration (CAVH).[62] The major advantages, as he described, are low stress of the cardiovascular system, high effective fluid withdrawal, absence of danger for air embolism, and no need for electricity, for highly specialised staff and for high investments. The disadvantages are, however, limited urea clearance due to low filtration rate and lack of its applicability in patients with atherosclerosis.[63] The introduction of continuous arteriovenous haemodialysis (CAVHD) and continuous arteriovenous haemodiafiltration (CAVHDF) increased azotemic control. With continuous venovenous haemofiltration (CVVH), continuous venovenous haemodialysis (CVVHD) and continuous venovenous haemodiafiltration (CVVHDF) the urea clearance was guaranteed, because the extracorporeal blood flow no longer depended on the arterial pressure. With the venovenous technique, however, renal replacement therapy became more complicated as compared to the arteriovenous technique, because of the introduction of a pump and a balancing system.

Renal replacement therapy (RRT) modalities are categorized by intermittent versus continuous techniques and by mechanisms of solute and fluid removal. There is yet no clarity on what renal replacement mode is best considering patient-centered outcomes, so that the choice is mainly dictated by availability, expertise, haemodynamics, vascular access and reasons to start renal replacement therapy.

Diffusion versus convection

Ultrafiltration is the term used to describe fluid removal in renal replacement therapy, a process by which plasma water and ultrasoluble solutes are removed from whole blood across a semi-permeable membrane driven by pressure. The two primary principles of solute removal are diffusion and convection. Diffusion concerns solute transport across a semi-permeable membrane generated by a concentration gradient; molecules move from the compartment with a high concentration to the compartment with a low concentration (Fig. 4A). In general, solutes move from the blood compartment to the dialysate compartment. In haemodialysis, solutes are removed by diffusive clearance. The dialysate fluid generally containing sodium, chloride, bicarbonate, calcium and magnesium runs countercurrent to the blood flow thereby maximizing the concentration gradient. Factors affecting the rate of solute removal are the solute molecular weight, concentration gradient across the membrane, dialysis duration, blood and dialysate flow rates, and surface area and permeability of the haemofilter.

Small molecular weight solutes (< 500 dalton), such as blood urea nitrogen, potassium creatinine and some drugs such as lithium, are most effectively cleared by haemodialysis.

Convection concerns solute transport across a semi-permeable membrane generated by a hydrostatic pressure gradient; molecules move from the compartment with a higher pressure to the compartment with a lower pressure together with the solvent (solvent drag) (Fig. 4B). During haemofiltration, solutes are removed by convective clearance. Solute removal is primarily dependent on the ultrafiltration rate, the concentration in plasma water, and the surface area and permeability of the haemofilter. Apart from the small molecular weight solutes, medium molecular weight molecules are removed as well by haemofiltration. It requires to use a replacement solution to prevent acidosis, electrolyte disturbances and excessive fluid removal. The replacement solution generally contains sodium, chloride, magnesium, calcium, glucose, and bicarbonate/lactate and some potassium. Hence, the concentration of solutes in plasma is gradually decreased during haemofiltration and the concentrations of electrolytes gradually move towards the concentration in the replacement solution. The replacement solution can be delivered prefilter (predilution) or postfilter (postdilution). The prefilter administration decreases the plasma solute concentration and thereby solute clearance. However, diluting the plasma by replacement solution may increase the filter life, which has a favourable effect on uraemic control. Conversely, postdilution continuous RRT may be associated with a reduced filter life without any beneficial effects on metabolic control, as compared to predilution continuous RRT.[64] Worldwide, both pre- and postdilution continuous RRT remain widely practiced. In haemodiafiltration, diffusive and convective clearances are combined allowing improved clearance of both small and large molecular weight substances.

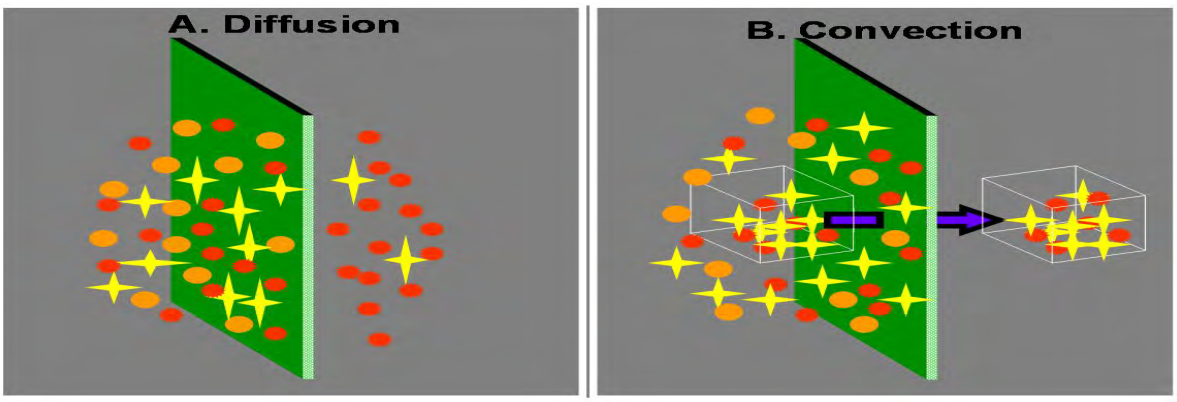

Fig 4. Principles of solute removal. A: Diffusion: removal of solutes across a semi-permeable membrane by a concentration gradient. B: Convection: removal of solutes across a semi-permeable membrane by filtration (solvent drag); solutes together with the solvent are dragged from a high hydrostatic pressure compartment to a low pressure compartment.

Renal replacement therapy modalities

There are several options for renal replacement therapies. The three primary modalities are intermittent haemodialysis (IHD), sustained low extended dialysis (SLED) and the continuous forms of renal replacement therapy (CRRT). Peritoneal dialysis which is a commonly used modality in chronic renal failure is generally not used in the critically ill. In IHD, solutes are removed by diffusion and fluid by ultrafiltration. In AKI, IHD is generally prescribed for 3-6 hours per session for 3-4 times a week. The major advantages of IHD include rapid solute or fluid removal, relatively low costs and complexity and less anticoagulation requirements. The major disadvantages are the risk for haemodynamic instability and the desequilibrium syndrome. SLED is a form of IHD where treatment time is prolonged to 8-12 hours per session. In SLED, the blood flow is lowered and the fluid and solute removal is slower as compared to IHD. CRRT is performed continuously through arteriovenous or venovenous access. The blood flow rate used in CRRT is much lower than in IHD.

The most commonly applied submodalities of CRRT are CVVH, CVVHD and CVVHDF (Fig. 5) and characteristics are described in Table 2. The arteriovenous techniques are not frequently applied anymore, because of the high access complication rates and the development of external circuit pumps. CRRT provides slower solute clearance per unit of time compared with IHD, but the 24 hrs clearance may exceed that provided by intermittent techniques. Fluid is also removed more slowly as compared to IHD. A major drawback of continuous techniques is the use of continuous anticoagulation to prevent clotting of the filter; this, of course, carries an increased bleeding risk.

Table 2. Different modes and characteristics of continuous venovenous renal replacement techniques.

	Solute transport	**Blood flow**	**Dialysate flow**	**Replacement solution**	**Ultrafiltration flow**
Continuous venovenous haemofiltration (CVVH)	Convection	100-200	---------	Yes	Equal to replacement solution flow. More ultrafiltration results in volume loss
Continuous venovenous haemodialysis (CVVHD)	Diffusion	100-200	1-2 L/h	No	No ultrafiltration. Ultrafiltration results in volume loss.
Continuous venovenous haemodiafiltration (CVVHDF)	Convection and diffusion	100-200	1-2 L/h	Yes	Equal to replacement solution flow. More ultrafiltration results in volume loss

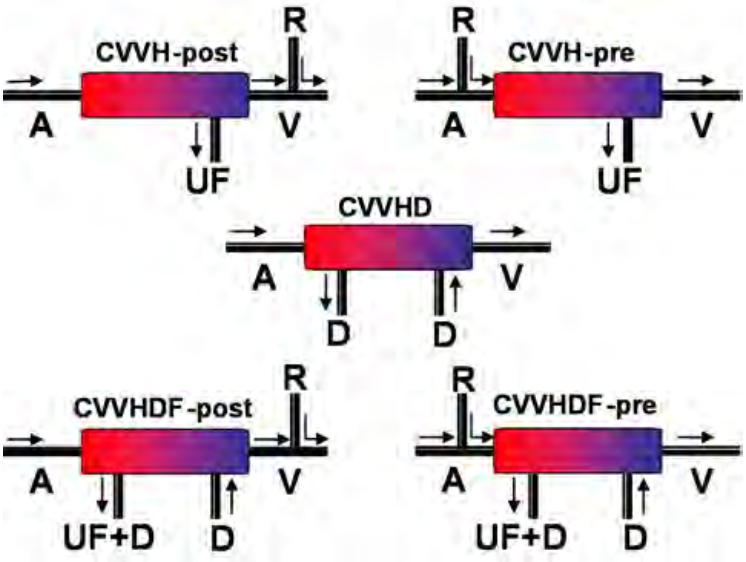

Fig. 5. Different types of CRRT. CVVH-post: postdilution continuous venovenous haemofiltration ; CVVH-pre: predilution continuous venovenous haemofiltration; CVVHD: continuous venovenous haemodialysis; CVVHDF-post: postdilution continuous venovenous haemodiafiltration; CVVHDF-pre: predilution continuous venovenous haemodiafiltration; A: blood in; V: blood out; R: replacement solution, UF: ultrafiltration; D: dialysate.

Indication, timing, modality and dialysis dose

The way RRT is practiced around the world greatly varies, particularly when indications, timing, modality and dialysis doses are concerned.

Indication and timing

There is no doubt that volume overload, uraemic complications, severe electrolyte disturbances and overt metabolic acidosis due to renal failure are clear reasons to start RRT. Moreover, RRT has to be initiated before these complications arise. The exact timing of RRT, however, is unclear and randomized trials addressing this issue are scarce. In one trial, the effects of the initiation time of CVVH were studied in critically ill patients, developing early oliguric acute renal failure.[65] Thirty five patients were treated by early high volume haemofiltration (72-96 L per 24 hrs) and 35 patients received late and low volume haemofiltration (24-36 L per 24 hrs). Early was defined as a start within 12 h after a 6 h period of oliguria (< 30 mL per h). Thirty six patients were treated by late low volume haemofiltration (24-36 L per 24 hrs), starting when patients fulfilled the conventional criteria for RRT, including a plasma urea level > 40 mmol/L, potassium > 6.5 mmol/L or severe pulmonary oedema. Survival at 28 days and recovery from renal function did not differ between the groups. Data from an observational study nevertheless suggest that mortality of patients starting RRT with a urea less than 27 mmol/L is lower than in patients with a urea of more than 27 mmol/L. It cannot be excluded that the results were confounded by severity of illness, however.[66] One major concern in starting RRT early, is that spontaneous recovery of renal function in about 10% of patients is not awaited for.[65]

Modality

As outlined before, there are different modalities of RRT. The continuous techniques have beneficial effects over IHD regarding haemodynamic stability, solute clearance and ultrafiltration capacity. These advantages are, however, limited when compared to slow haemodialysis. There are not many randomized trials comparing IHD to CRRT. In one study, the 28 day mortality rate was lower in IHD as compared to CRRT (42% versus 60%).[67] Unfortunately, randomization appeared unbalanced; patients in the CRRT group had higher disease severities and prevalence of liver failure. There are few randomized trials showing no differences in outcome between CRRT and IHD.[68,69] One large prospective randomised multicenter study has been performed comparing CVVHDF with IHD for acute renal failure in patients with multi-organ dysfunction syndrome: the rate of survival at 60 days was comparable.[70] In the multicenter observational study on AKI, CRRT seemed associated with an increased mortality as compared to IHD. Several meta analyses could not demonstrate convincing benefits of CRRT over IHD with regard to mortality and/or recovery of renal function.[71-73] Taken together, there are no data proving benefits of CRRT as compared to IHD in the critically ill.

Dose

The issue of dosage is controversial. The dosage is defined as the amount of blood purification achieved by RRT techniques per unit of time. Uniformly, in chronic dialysis urea clearance is used as a marker of small solute removal. In patients with end stage renal disease the correlation between dialysis intensity and mortality has been extensively studied and there is consensus that intensity really matters up to a certain level.[74] In chronic dialysis, the dose is expressed as Kt/V urea (K is the dialyser urea clearance, t represents time on dialysis and V is the volume of distribution for urea). It is advised to deliver an equilibrated Kt/V of at least 1.2 per session to chronic IHD patients. However, the Kt/V as a dose representative is not applicable in critically ill patients with AKI: there is uncertainty about the volume of distribution of urea. Also, the generation of urea varies and is not in a steady state, and some residual renal function may be present. Furthermore, the delivery of dose in AKI is difficult to predict because it depends on technical issues such as malfunctioning catheters, variable blood flows and off time due to filter clotting or transport of patients (for radiology or surgery). Therefore, treatment dose in CRRT is expressed as effluent rate per kilogram body weight per h with postfilter replacement. In a landmark study in 2000, Ronco et al. demonstrated an association between CRRT dose and mortality.[75] Survival in a group

assigned to an ultrafiltration rate of 20 ml/kg/h was lower (41%) than in groups assigned to 35 mL/kg/h (57%) and 45 mL/kg/h (58%). The recommendation was to prescribe ultrafiltration dose according to patient's body weight, i.e. 35 mL/kg/h at minimum and many ICU's have changed their policies accordingly. Because of several drawbacks of the study, the controversies concerning CRRT dose remain, with persistent variations in prescribed dosed of CRRT worldwide, as demonstrated in Fig. 6.[76]

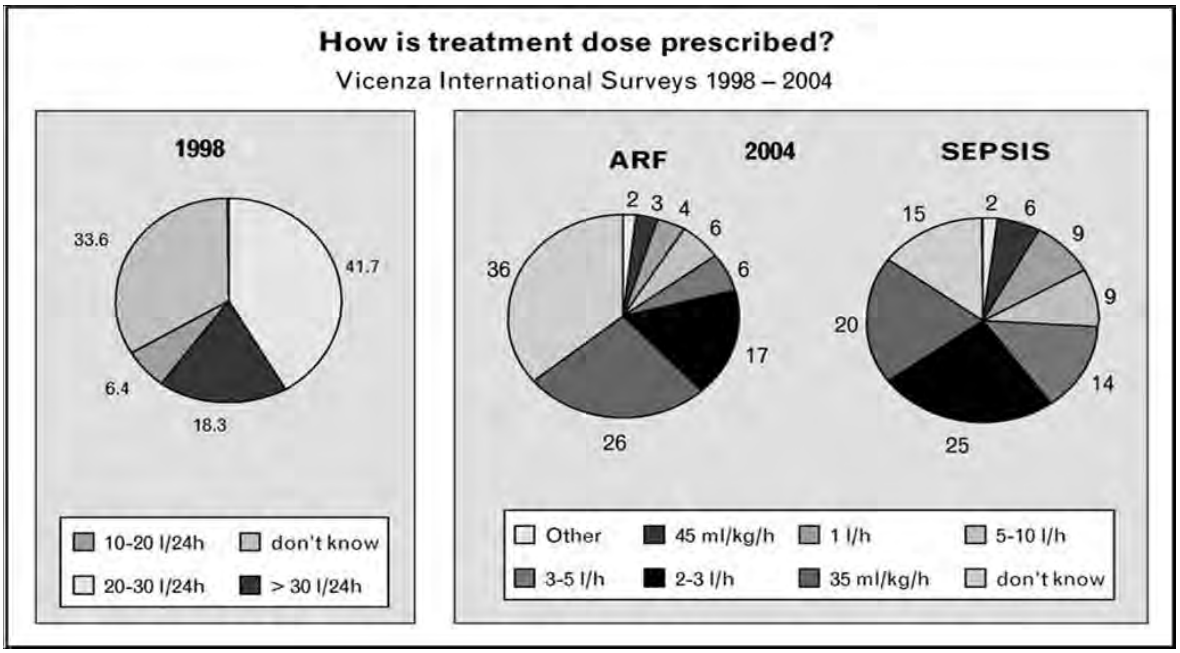

Fig 6. Results from the Vicenza International Surveys on CRRT carried out in 1998 and 2004. Adopted from Ronco et al..[76] (Reproduced with permission)

Indeed, Bouman et al. did not observe a difference in mortality between high (48.2 mL/kg/h) and low (20.1 mL/kg/h) ultrafiltration rates in a randomised trial.[65] Saudan et al. showed that increasing the renal replacement dose by adding a dialysis dose to CVVH improved survival.[77] However, in a recent comparison between high (35 mL/kg/h) and standard dosage (20 mL/kg/h) CVVHDF, no difference in survival was found.[78] The Acute Renal Failure Trial Network also gave answers on the dosage issue.[79] In this large multicenter randomised trial, a comparison was made between intensive renal replacement therapy (IHD or SLED 6 times per week or CVVHDF with an ultrafiltration of 35 mL/kg/h) and less intensive renal replacement therapy (IHD or SLED 3 on alternate days or CVVHDF with ultrafiltration rate of 20 mL/kg/h). The intensive treatment strategy did not decrease mortality nor accelerated renal function recovery and changed the rate of non-renal organ failure, as compared to the less-intensive strategy. The main conclusion of the authors is that other treatment strategies will be necessary to decrease mortality in the critically ill with AKI.

Expected are the results of the RENAL trial (Randomized Evaluation of Normal versus Augmented Level of RRT). In this large randomized trial also a comparison is made between normal dose (25 mL/kg/h) and augmented dose (40 mL/kg/h) CRRT.

Non-renal indications for continuous renal replacement therapy

The renal indications for CRRT are based on the capability of convective and diffusive techniques to remove substances from plasma, which normally should have been removed by the kidneys. By these extracorporeal treatments it is also possible to remove substances that even normal kidneys would not remove. This feature forms the cornerstone of the so called non-renal indications for CRRT. These indications are less well established as compared to the classic ones. Non-renal indications are based on the removal of pro-inflammatory mediators in sepsis or sepsis-like syndromes, the removal of fluid in chronic heart failure, the removal of endogenous toxins or the removal of drugs in intoxications.

Removal of inflammatory mediators.

Infection, tissue injury and ischaemia evoke a systemic inflammatory response as part of the body's defence mechanism. The production by macrophages, monocytes, lymphocytes and neutrophils of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β) and IL-6 initiate an inflammatory cascade involving the complement, coagulation and fibrinolytic systems. The pro-inflammatory response will be counterbalanced by inhibitors of inflammation: the compensatory anti-inflammatory response syndrome. Anti-inflammatory mediators such as IL-10 and soluble cytokine receptors are produced. Sepsis is a syndrome in which the pro-inflammatory mediators lead to a generalized inflammatory response overwhelming the anti-inflammatory response and is a major cause of mortality in adult and paediatric populations worldwide. Conventional treatment of sepsis consists of timely measures to eradicate infection by antibiotics, haemodynamic and respiratory support. Early initiation of adequate antibiotics, however, appears to have little immediate effect on the course and outcome of septic shock. Several strategies have been developed to target the pro-inflammatory response such as anti-cytokine or anti-endotoxin therapy, unfortunately all without any beneficial effects on mortality and morbidity. Several decades ago, it was hypothesised that CRRT could play a role in attenuating the inflammatory response by extracorporeal removal of harmful cytokines and other mediators.[80] Most of the immune mediators are water soluble with a middle molecular weight; theoretically these mediators can be removed by convection as in haemofiltration. Filters utilized in standard CRRT usually

have a molecular weight exclusion limit of 50.000 daltons. Considering their molecular weight, thromboxane A2, leukotrienes, prostaglandins, histamine, serotonin and platelet activated factor (all < 1000 D) are likely to be removed. Also complement 3a (10000 D), C5a (11200 D), IL-1β (16800 D) and IL-6 (22000 D) can theoretically be removed if there are no interactions with the filter. One should bear in mind, however, that removal of these substances is highly variable because of interaction with proteins and cells. Based upon this rationale, several investigators have investigated the effects of CRRT in animal models of sepsis and demonstrated beneficial effects.[81-83] Studies have demonstrated that inflammatory mediators can be removed during CRRT, a little by convection, but mainly by membrane adsorption.[84] Optimal mediator removal may thus be obtained by frequent filter changes, which is both expensive and impractical. Up to date, it is, however, still controversial whether it makes sense and does no harm to non-specifically remove inflammatory mediators from the blood. In a trial performed in 2002, patients with sepsis were randomized to receive CVVH at 2 L/h or no CVVH.[85] In this trial, CVVH failed to reduce the circulating concentrations of several cytokines and anaphylatoxins associated with septic shock, or to attenuate the organ dysfunction that followed severe sepsis. Earlier, Cole et al. showed a beneficial effect of high volume haemofiltration (HVHF) (6 L/h) compared to standard CVVH (1 L/h) regarding vasopressor requirements. Also, HVHF was associated with greater removal of C3a and C5a, mostly due to absorption rather than filtration.[86]

An alternative approach to increase cytokine removal is to increase the porosity of the haemofilter with a cut off point varying between 50 en 100 kD. Treatment using high cut-off filters has beneficial effects on immune cell function and increases survival in animal models of sepsis. Preliminary clinical studies show that these filters decrease plasma cytokine levels and the need for vasopressor therapy. Firm data considering clinical course and outcome are, however, still lacking.[87] A drawback of this technique is the loss of several proteins such as albumin, protein C and antithrombin, which all have a molecular weight of approximately 66 kD. Another rather new technique is coupled plasma filtration and adsorption. In this system plasma filtration and adsorption, using a sorbent cartridge, is combined with standard renal replacement therapy (Fig. 7). The isolated plasma is redirected trough a synthetic sorbent in which inflammatory mediators are non-selectively removed; after adsorption the endogenous plasma is returned to the blood and because of coupling with a haemofilter, further renal replacement therapy can be provided. Animal studies have already shown the efficacy of this technique regarding removal of inflammatory mediators, modulation of immune system and survival.[88] Human studies are scarce but promising.[89,90]

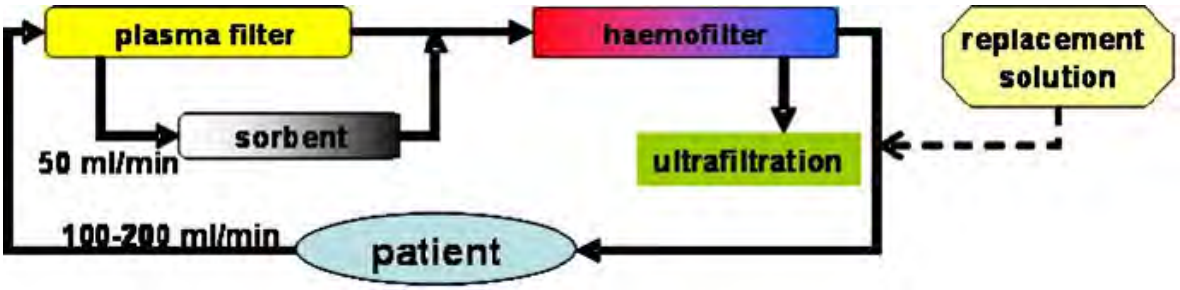

Fig. 7. Coupled plasma filtration and adsorption. After isolation in the plasmafilter, the endogenous plasma is directed to the sorbent in which inflammatory mediators are adsorbed; the plasma then reunites with blood. Because of coupling with a haemofilter, standard renal replacement therapy can be provided.[91] (Reproduced with permission)

In 2004, Ronco et al. developed the "peak concentration hypothesis".[92] During systemic pro- and anti-inflammatory responses, systemic mediator overflow may result in immunodysregulation. There are two theories: in the sequential theory, peaks of pro-inflammatory mediators are followed by peaks of anti-inflammatory mediators; in the parallel theory, a mixture of pro- an anti-inflammatory mediators coexists. In both theories the hypothesis is that by non-selectively removing the excess of pro- and anti-inflammatory mediators (peak concentration) a situation of immunohomeostasis is restored (Fig. 8).

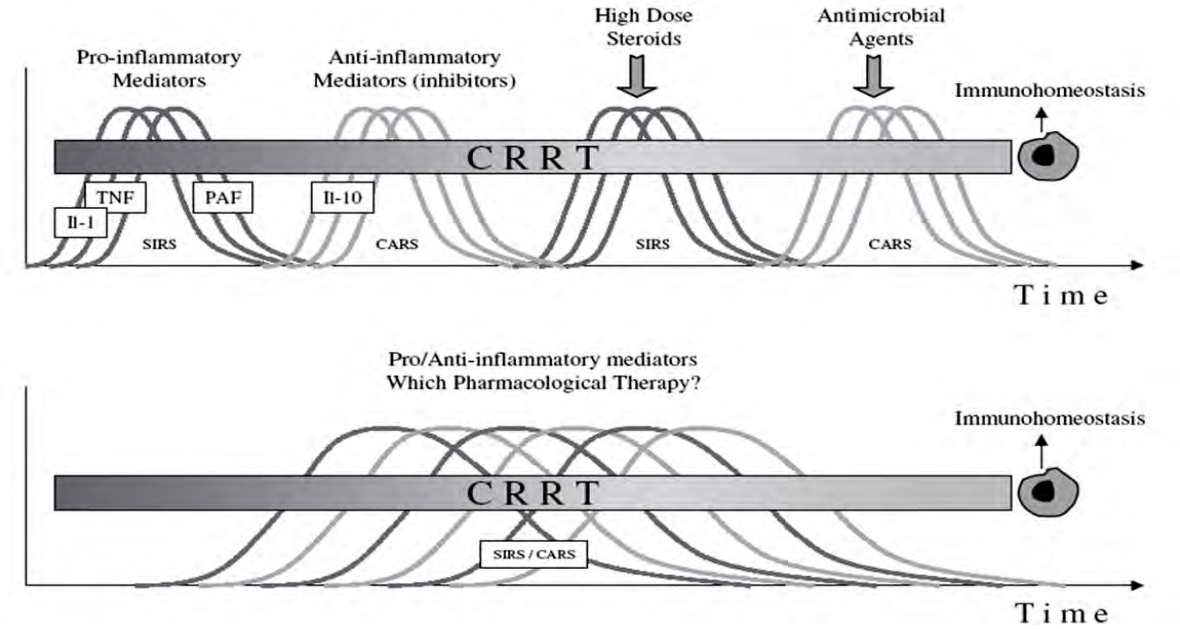

Fig. 8. The peak concentration hypothesis. In the sequential as well as in the parallel theory the hypothesis suggests that by non-selective removal by CRRT, excess of pro- and anti-inflammatory mediators a situation of immunohomeostasis is restored. SIRS = systemic inflammatory response syndrome; CARS = compensatory anti-inflammatory response syndrome. (Adopted from Ronco et al.[92]). (Reproduced with permission)

With CRRT, it is possible to remove excess pro- and anti-inflammatory mediators, but HVHF and frequent filter changes are mandatory. There are, however, some major technical requirements of HVHF: high blood flow and tight ultrafiltration control, necessitating large amounts of costly replacement fluids. These requirements combined with the crucial frequent filter change render HVHF labour-intensive. Moreover, there are increased losses of beneficial substances such as electrolytes, vitamins, trace elements and amino acids during HVHF. To reduce costs and workload several non-controlled small trials were performed with pulse-HVHF: for example an ultrafiltration rate of 85 mL/kg/h for 6 hours per day followed by standard CVVH. Several of the studies concerning HVHF or pulse-HVHF showed promising results.[93-95] Up to date, however, the evidence is too low to propagate haemofiltration as an adjunctive therapy in critically ill patients with sepsis.[96] The use of HVHF in sepsis with or without AKI must be considered experimental and large scale randomized studies are urgently needed. The IVOIRE (hIgh Volume in Intensive CarE) study perhaps will give some answers considering this issue.

Removal of fluid

Patients on the ICU with compromised cardiac function and renal failure are best treated by CRRT. In patients with heart failure resistant to diuretics, CRRT is the best technique to restore dry body weight and improve diuresis and heart function. In congestive heart failure, the decreased effective circulating volume results in the activation of several neurohumoral systems such as the sympathetic system and the renin-angiotensin-aldosteron system and in the release of vasopressin. In case of refractory congestive heart failure, ultrafiltration by CRRT can decrease neurohumoral activation by removal of fluid and sodium.[97]

Removal of uric acid and phosphate

Patients treated for malignancies may develop tumor lysis syndrome, which may result in AKI due to tubular obstruction by uric acid crystals or hyperphosphataemia with deposition of calcium phosphate crystals in renal interstitium and tubuli. Hyperhydration, and allopurinol or rasburicase may help to prevent AKI. If, however, AKI still develops, renal function recovery depends on normalization of phosphate and uric acid levels. Both phosphate and uric acid are small molecules and are easily be removed by diffusive clearance; in this setting conventional haemodialysis seems more effective than haemofiltration.[98,99] The major advantage of CRRT is the absence of a rebound hyperphosphataemia which is often seen after

intermittent haemodialysis. CRRT can also be used to prevent AKI due to tumor lysis syndrome.[100]

Removal of drugs in intoxications

In the intoxicated patient, IHD has several advantages over CRRT. Especially the relatively slower clearance rate in CRRT is a major drawback in patients intoxicated with a dialyzable substance. In haemodynamic unstable patients, however, CRRT is a more attractive renal replacement modality. There are no randomized controlled trials addressing this issue, however. Hence, the optimal method of extracorporeal blood purification is frequently a matter of debate. In each situation, a clinical judgement has to be made, to see if extracorporeal blood purification is beneficial and if so which modality is best. One has to keep in mind that in case of an intoxication, rapid blood purification may be beneficial.[101,102]

Practical issues: vascular access, haemofilter, replacement/dialysate solution, anticoagulation and complications

Vascular access

For arteriovenous circuits (CAVH, CAVHD, CAVHDF), where the blood pressure is the driving force for blood flow, large bore, small length catheters are inserted, usually in the femoral artery and vein. With use of arteriovenous circuits, they carry a high risk for arterial thrombosis. In pumped systems (CVVH, CVVHD, CVVHDF, IHD) double lumen catheters are usually used. The size depends on the localization of insertion: the subclavian, jugular or femoral vein. If possible, insertion in the subclavian vein should be avoided because of a high incidence of subsequent stenosis.[103] Use of short catheters in the femoral vein may result in significant blood flow recirculation but this can be avoided by using longer catheters (19-15 cm).[104]

Haemofilter

Adequacy of renal replacement therapy also concerns the choice of the haemofilter. Haemofilters used for IHD and CRRT are characterized in terms of flux (the permeability to water and solutes) and biocompatibility (degree to which complement is activated by exposing the membrane to blood). Despite the facts that there is no evidence for its superiority compared to low-flux filters, high-flux (high permeable) filters are generally recommended for CRRT, since increased permeability to water facilitates haemofiltration. The solute

removal capacity of a filter (KoA = mass transfer area coefficient) is of minor importance in CRRT, since solute clearance is largely determined by ultrafiltration/dialysate flow rate. In IHD, where therapy is given over a relatively short period, the KoA is important. Blood-filter contact may cause several undesirable effects; there are data suggesting that the use of bio-incompatible cellulose (cuprophane) haemofilters with IHD is associated with delayed recovery of renal failure and decreased survival in the critically ill compared with the use of more biocompatible filters.[105]

Replacement/dialysate solutions

Dialysate for haemodialysis is produced by the dialysis machine from a combination of ultra pure water and several electrolytes. The ultra pure water, which does not have to be sterile, is purified by treatment with reverse osmosis, deionization and the use of charcoal filters. Replacement solutions used for haemofiltration are in fact administered directly to the blood compartment and have to be sterile. The replacement solutions consist of balanced electrolyte solutions that closely resemble the composition of the ultrafiltrate minus the waist products which accumulate in renal failure. They contain sodium, chloride, magnesium, calcium, glucose and some potassium. These solutions also contain a buffer to correct for the metabolic acidosis. The buffer can be either bicarbonate, acetate, lactate or citrate. Acetate, lactate and citrate are converted to bicarbonate; in multiorgan failure the conversion can be limited. Trials comparing lactate with acetate and lactate with bicarbonate did not demonstrate any difference in the risk of death.[106,107] It is, however, clear that lactate or bicarbonate solutions offer a better control of acid-base balance and improved cardiovascular stability compared to acetate buffered solution.[108] The composition of the replacement solution can vary extensively in order to achieve specific metabolic goals; by varying specific electrolytes for example, imbalances can be corrected.

Anticoagulation

During RRT, the patient's blood is in the extracorporeal circuit and in contact with artificial tubing and haemofilters. The passage of blood through the extracorporeal circuit results in activation of platelets, coagulation proteins, complement and white blood cells resulting in microthrombus formation with subsequent platelet and fibrin deposition on the surface of the dialyser membrane.[109,110] To maintain dialyser efficacy and circuit longevity, adequate anticoagulation is important. Inadequate anticoagulation results in deterioration of filter performance, the filter may eventually clot contributing to blood loss. Excessive

anticoagulation, however, may result in bleeding complications reported to occur in 5-26% of treatments.[111,112] Ideally, the anticoagulation is delivered regionally, which means that only the extracorporeal circuit is anticoagulated.

As with IHD, many anticoagulation strategies have been pursued for CRRT, including low dose heparin, low molecular weight heparin, prostanoids, mesylates and regional citrate anticoagulation.[113-115] Heparin continues to be the most commonly used anticoagulant for CRRT. It is relatively easy to use and to monitor its effect. It provides adequate extracorporeal anticoagulation. However, there is a high risk of bleeding and the development of heparin-induced thrombocytopoenia and thrombosis.[116] Low molecular weight heparin is infrequently used due to the need to monitor factor Xa levels; and once a bleeding occurs it is difficult to counteract the effects. Citrate offers an anticoagulant effect through its ability to chelate calcium. Calcium has an essential role in activation of several clot factors (II, V, VII, VIII, IX, X, XIII) and in the conversion of fibrinogen to fibrin. Citrate acts regionally when administered pre-filter and thus reduces the risk of bleeding. The anticoagulant effect is overwhelmed and neutralized when citrated blood from the extracorporeal circuit returns and mixes with central venous blood containing sufficient amounts of calcium. Citrate is cleared by the tricarboxycyclic acid pathway in the liver, skeletal muscles and renal cortex producing bicarbonate. Thus, citrate can be used to anticoagulate an extracorporeal circuit, without systemic anticoagulation, resulting in regional anticoagulation. The method carries the risk of hypocalcaemia when insufficiently counteracted by calcium infusion after passage of blood through the filter. Also, metabolic alkalosis may develop when too much citrate enters the blood. Citrate has been widely used for conventional IHD and has been successfully adapted for use in CAVHD/F and CVVH(DF).[117] Two methods of regional citrate anticoagulation are being used effectively. The first and most frequently used method employs concentrated trisodium citrate together with the use of hypotonic alkali-free replacement solution c.q. dialysate as reported by Mehta et al. and Kutsogiannis et al..[118,119] The second method employs trisodium citrate containing replacement solution that is isotonic and has an adjusted concentration of citrate, so that the amount of bicarbonate equivalent is similar to that employed when lactate or bicarbonate-buffered solutions are used.[120,121] Citrate CRRT carries the potential risk of citrate accumulation. Accumulation can occur as free citrate or as calcium citrate complexes. The main dangers are those of hypocalcaemia.[122] When free citrate accumulates, there is a rise in the anion gap. Accumulation of calcium citrate complexes will increase the total to ionised calcium ratio.[123] There is accumulating evidence that citrate anticoagulation is at least equivalent or even superior to heparin in CRRT concerning filter

life and/or transfusion rate.[124-126] If regional anticoagulation with citrate is associated with a lower mortality compared to heparin has not been proven yet. The advantages of citrate must be balanced against its increased complexity and its potential for metabolic complications.

In the absence of a citrate protocol, thrombin inhibitors such as argatroban or hirudin are good alternatives to heparin, especially in case of heparin induced thrombocytopenia.[127,128] Currently, none of the anticoagulants is ideal and the choice is frequently influenced by patient factors. The experiences of the ICU staff with the different anticoagulants are major determinants of the success of any anticoagulation regimen.

Complications

Renal replacement therapy is not free of any risks. Since timing and sometimes indications are issues of great controversy, one has to consider the adverse effects of initiating renal replacement therapy. These consists the potential complications of inserting the catheters (such as bleeding, pneumothorax, air embolism, thrombosis and infection), the hazards of continuous anticoagulation and the risk if significant blood loss in case of filter clotting. After initiating CRRT drug dosing becomes more difficult, in general.

Future trends: renal cell therapy and the bioartificial kidney.

In chronic renal failure, transplantation is the best form of renal replacement, if possible, because normal kidney function is closely mimicked. A simplified comparison is that haemofiltration mimics the glomerulus and haemodialysis the diffusive transport in the tubules. However, the tubules do have more functions than solely passive diffusive exchange of solutes, such as active bicarbonate and glucose transport, glutathione degradation, ammonia production and activation of vitamin D. A less known feature of the kidney is its immunologic function. The renal proximal tubules possess antigen-presenting capacities and they produce several inflammatory mediators.[129-131] Proximal tubular cells have a pivotal role in the metabolic, endocrinologic and immunologic functions of the kidney. In end-stage renal disease as well as in AKI these functions are compromised and simply cannot be replaced by an artificial, synthetic haemofilter. End-stage renal disease is associated with a state of chronic inflammation. It is also hypothesized that the propensity of patients with AKI to develop sepsis suggests that renal function, specifically renal tubule cell function secondary to ATN, plays a critical immunomodulating role in stress.[132] Humes et al. developed a method to isolate and culture renal proximal tubule cells and used these to create the renal tubule cell

assist device (RAD).[133] The RAD is in fact a haemofilter containing over 109 human renal tubule cells grown as confluent monolayers along the inner surface of the hollow fibers. These cells remain immunoprotected from the patient's blood by a semi-permeable membrane. By coupling the RAD to a conventional CVVH system, a bioartificial kidney was created as outlined in Fig. 9. Blood pumped out of the patient first passes through the haemofilter where ultrafiltrate is formed; this process mimics the glomerular function. This ultrafiltrate then passes through the hollow fibers of the RAD, where it is in close contact with the renal tubule cells. The filtered blood coming from the haemofilter enters the RAD through the extracapillary port. The process in the RAD mimics tubular function. The blood coming from the RAD returns to the patient and the processed ultrafiltrate is a waist product just like urine. Preclinical and animal studies have demonstrated that the tubule cells maintain their transport, endocrinologic as well as metabolic activities.[133,134] A phase II, multicenter, randomized controlled open-label trial comparing CVVH + RAD with CRRT revealed a reduced mortality rate in the first treatment group. RAD therapy was also associated with more rapid recovery of renal function. The treatment was well tolerated.[135]

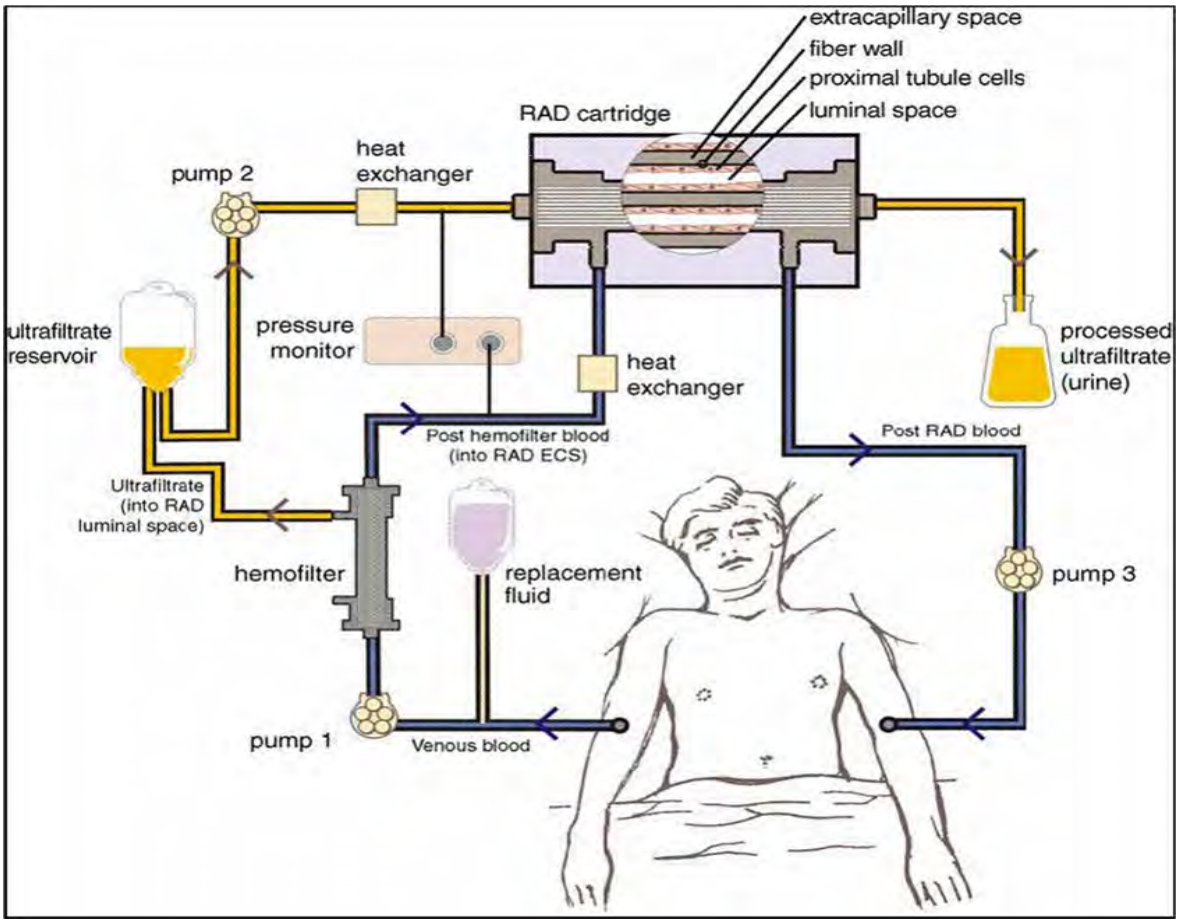

Fig. 9. Scheme of the extracorporeal circuit for the bioartificial kidney consisting of a haemofilter and a renal assist device cartridge.[136] (Reproduced with permission)

Prognosis

Patients with AKI are amongst the most severely ill in the ICU. The mortality of patients admitted to the ICU with AKI being treated by RRT is approximately 60%.[137] After an initial decline in mortality during the last decades, the mortality from acute renal failure has climbed considerably despite increasing clinical experience and knowledge. The explanation of this phenomenon is that the population in the ICU's has changed with time. More patients are surviving trauma, acute coronary and vascular events and serious infections. Also, surgeons can perform more complicated surgical procedures in older patients with a considerable risk of developing acute renal failure. While dying in the past, these patients nowadays survive but develop acute renal failure.[138] As a consequence more patients develop renal failure. Conversely, the observed mortality in patients with AKI is significantly higher than predicted from the underlying disease. Therefore, AKI is an independent risk factor for mortality.[5] Even minor deterioration of renal function is associated with an increased mortality rate in ICU and non-ICU patients.[8,10,40] The majority of patients surviving the ICU and hospital stay regain normal or near-normal renal function. The long term effects of AKI are still unclear, because of the paucity of long-term follow-up studies. The long-term mortality, however, in those patients who survived AKI is higher when compared with critically ill patients without AKI. This could be explained by the fact that a great deal of survivors of AKI, varying between 19%-31%, will eventually develop chronic kidney disease.[139] Because of the increased risk for mortality and development of chronic kidney disease, patients with partial recovery of renal function should be monitored closely at the outpatient clinic.[140,141] Approximately 13% of patients will remain on renal replacement therapy because of the development of end stage renal disease.[137]

Case presentation

A 29 year old woman presented at the emergency department because of shortness of breath. Four weeks earlier she gave birth to a healthy son. Because some neck pain she used ibuprofen daily for several days. For about two weeks she had complaints of nausea and vomiting. Two days prior to her presentation she developed shortness of breath. There was no fever or coughing. At physical examination a pale young woman was seen with a blood pressure of 144/95 mmHg, a heart rate of 88 beats and a respiratory rate of 30 breaths per minute. She had no fever. The examination of the thorax, abdomen and extremities were without abnormalities. The labarotory analysis revealed the following abnormalities:

haemoglobin: 3.6 mmol/l, WBC: $13.7x10^9$/L, reticulocytes: 184 ‰; potassium: 7.8 mmol/l, creatinine: 1851 μmol/l, BUN: 35.6 mmol/l, phosphorus: 3.17 mmol/l, lactate dehydrogenase: 1786 U/L. The arterial blood gas measurements showed: pH: 7.23, PO_2: 73 mmHg, PCO_2: 20 mmHg, base excess: -17.4 mmol/l. The blood smear demonstrated schizocytes. The chest X-ray showed bilateral pulmonary oedema. The electrocardiogram demonstrated peaked T-waves. Because of anuria there was no urinary analysis. The diagnosis was a postpartum haemolytic uraemic syndrome. Because of respiratory failure she was intubated for mechanical ventilation and sedation. Renal replacement was initiated; in order to lower the potassium and to remove the excess of fluid rapidly, the first choice of modality was haemodialysis. After the haemodialysis, daily plasma exchange therapy was started combined with IHD. Recovery to spontaneous ventilation was rapid and smooth. Unfortunately, the renal failure persisted and the patient remained dependent on IHD.

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