6 February 2009

Renal replacement therapy in acute kidney injury

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INTRODUCTION

Renal replacement therapy (RRT) has progressed rapidly over the past 50 years from the Kolff twin coil tank to some very sophisticated machines capable of performing a variety of therapies. Our understanding of renal function and the response to dialysis has also expanded such that it is now an integral part of medical care.
5% to 6% of critically ill patients develop acute kidney injury (AKI) and 70% of them require the application of RRT. However, even the best centers in the world typically report mortalities of 50 – 70%[22].
In the past, the paradigm for management of severe AKI was that patients died *with*, but did not die *of* their renal failure, so long as acute uraemic complications were prevented. Over the past decade, this paradigm has been challenged by data demonstrating that AKI is an independent risk factor for mortality. RRT however is not innocuous and associated with its own complications. Therefore specific management of RRT may impact greatly on the outcomes of AKI.
RRT is an expansive topic which cannot be covered in its entirety in a single lecture.
I will attempt to briefly clarify some of the basic concepts but will focus on a few of the current controversies surrounding renal replacement therapy.

WHAT IS RENAL REPLACEMENT THERAPY?

RRT is a therapy which assumes all or part of the blood purification as well as balance of water and electrolytes, a function usually performed by the kidney.
The use of artificial kidneys began during the Korean War, when it was called “dialysis”, derived from Greek and meaning “to pass across”. We have since moved on to using the term “renal replacement therapies (RRT)” to describe haemodialysis as well as other modes of treatment including peritoneal dialysis, continuous haemofiltration and continuous haemodiafiltration.

There are two key principles that must be understood to differentiate the modes of renal replacement. These are **DIFFUSION**, which should strictly be used when referring to dialysis, and **ULTRAFILTRATION**, which is convection.

Diffusion is the movement of solutes along an electrochemical gradient, from an area of high concentration to one of lower concentration. During dialysis, an electrolyte solution or dialysate (usually containing sodium, bicarbonate, chloride, magnesium, and calcium) runs in a counter-current

direction to the patient’s blood flowing on the opposite side of a semipermeable membrane. Small molecules in the blood, such as urea, move along the concentration gradient passing through the membrane into the dialysate fluid. Larger molecules are poorly removed by this process. The rate of diffusion of a given solute depends on a number of factors including its charge and molecular weight, the surface area, membrane porosity, thickness and amount of protein binding, the blood flow rate and dialysate flow rate.

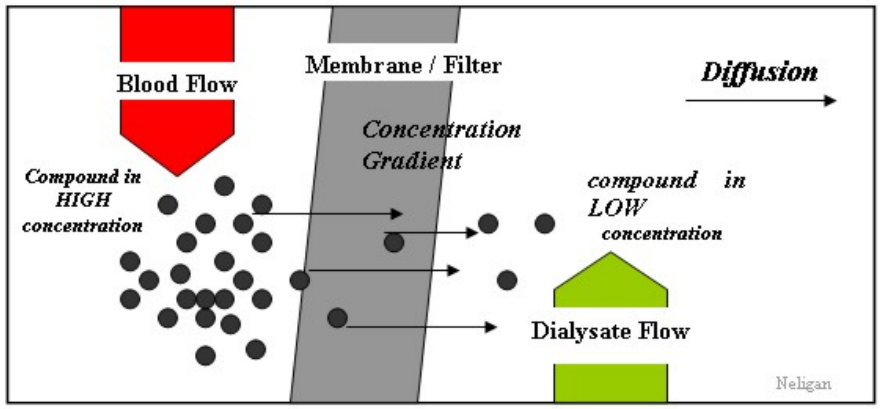

Fig.1 Dialysis[13]

Conversely with ***ultrafiltration***, solute is carried in solution across a semi-permeable membrane in response to a transmembrane driving pressure (also called solvent drag). This is more effective for removal of fluid and middle sized molecules.
The rate of ultrafiltration depends on the permeability of the membrane, transmembrane pressure and the surface area of the membrane.

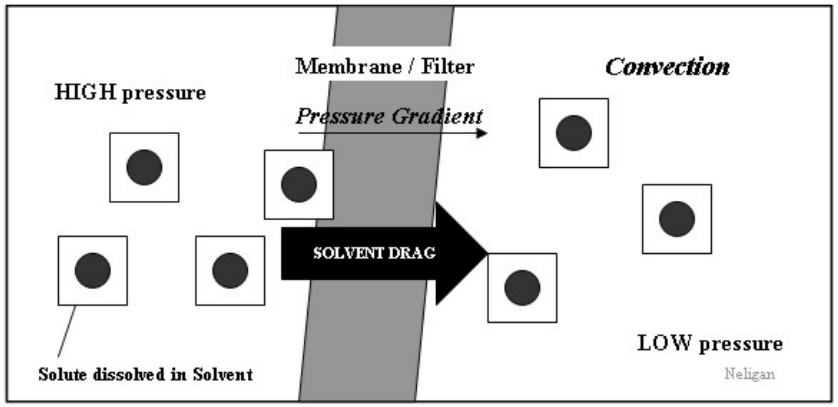

Fig.2 Ultrafiltration[13]

MODES OF RENAL REPLACEMENT THERAPY

RRT may be further subdivided into intermittent and continuous techniques.

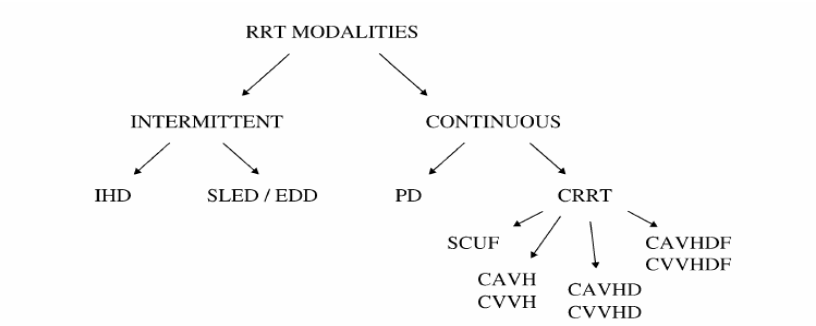

Fig. 3. Renal replacement modalities for acute renal failure. CRRT, continuous renal replacement therapy; CAVH, continuous arteriovenus hemofiltration; CAVHD, continuous arteriovenous hemodialysis; CAVHDF, continuous arteriovenous hemodiafiltration; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; EDD, extended daily dialysis; IHD, intermittent hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy; SCUF, slow continuous ultrafiltration; SLED, sustained low-efficiency dialysis.

Fig. 3 RRT Modalities of RRT[3]

Intermittent Haemodialysis

Haemodialysis is mainly based on the diffusion principle discussed previously. It is very effective in the rapid removal of small molecules. To enable rapid corrections to volume and electrolyte status, high blood flow rates and dialysate flow rates are required. In conventional haemodialysis, the dialysate flow rate is usually 500 mL/min, which makes on-line dialysate production necessary. The dialysis machine requires concentrated solutions of electrolytes and buffers in order to produce the dialysate. Therefore, haemodialysis is technically complex and needs to be performed by highly trained nursing staff. Sessions usually last 3-5 hrs and occur 2-4 times a week but there is high variability regarding individual patients with some units preferring daily dialysis.

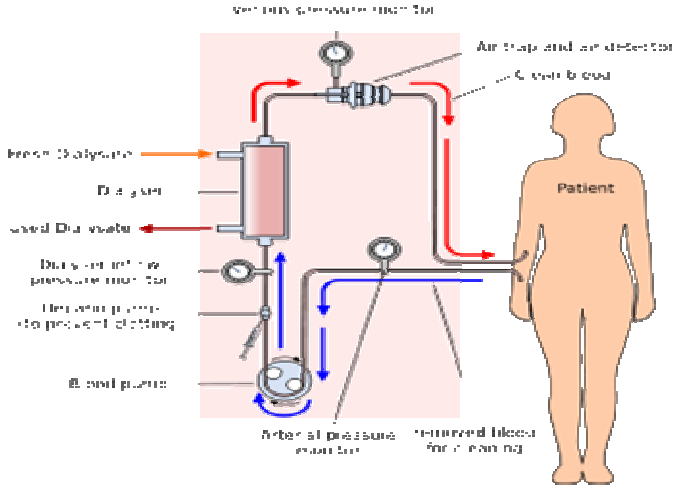

Fig. 4 Intermittent Haemodialysis

Continuous Renal Replacement Therapy

CRRT encompasses techniques that slowly correct physiological derangements.
The most commonly used method of CRRT is continuous venovenous haemofiltration **(CVVH).** Here the process of ultrafiltration is used. The volume of the ultrafiltrate is continuously substituted by replacement fluids that can be delivered in ready-to-use bags. Haemofiltration is technically easier to perform than haemodialysis. Since, in comparison to diffusive methods, the clearance for small molecules per unit time is lower, haemofiltration has to be delivered continuously for 18 to 24 h per day. Because of the slower flow rates and the longer duration of therapy, CRRT

CRRT usually requires prolonged exposure to the extracorporeal membrane and to anticoagulation to prevent clotting of the filters.
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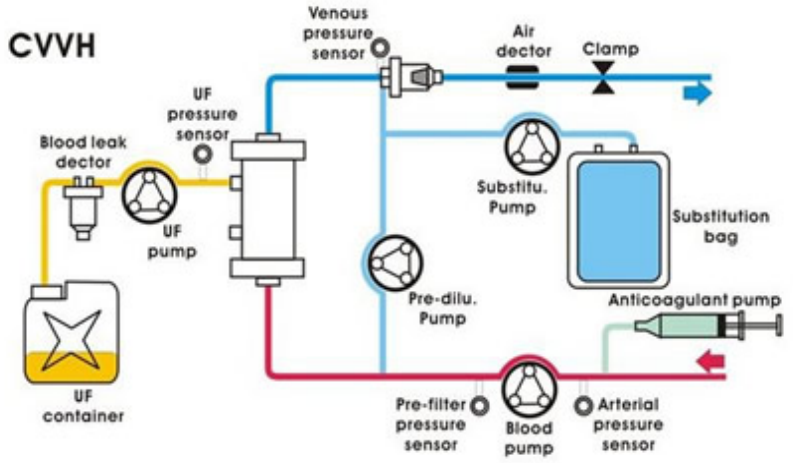


Fig. 5 Continuous veno-venous haemofiltration

IHD	CVVH
Diffusive transport	Convective transport
High clearance for small molecules	Clearance for small and middle seized molecules
Dialysate production and high dialysate flow required 2–8 h/d, intermittently	Large amounts of substitution fluid in bags required 18–24 h/d, continuously
Technically demanding	Technically less difficult
Personnel with "renal" qualification required	ICU-trained personnel sufficient
Low work load	High work load for 24 h a day
Relatively cheap	Three to five times more expensive
Possible without anticoagulation	Usually continuous anticoagulation required

Fig. 6 Major Differences between IHD and CVVH[21]

There are a variety of methods of RRT that may be encountered.

RRT Modality	Transport Principle	Comment
IRRT		All intermittent therapies
IHD	Diffusion	"Classic" hemodialysis
EDD	Diffusion	Longer dialysis times, slower blood and dialysate flows
SLEDD	Diffusion	Longer dialysis times, slower blood and dialysate flows
SCUF	Mainly convection	Only UF with conventional dialysis machines
CVVHDF	Convection and diffusion	Hemofiltration combined with dialysis (low dialysate flow)
EIHF	Convection	Early hemofiltration in septic shock with high UF rates (like HVHF) but without volume loss
HVHF	Convection	Hemofiltration with high UF rates (equal to high RRT dose; allows intermittent therapy)
CAVH	Convection	Without pumps, allows UF rates of only 10–15 L/d
CVVH	Convection	"Classic" hemofiltration
CRRT		All continuous therapies

Fig .7 Different RRT Modes in the Critical Care Setting[21]

EIHF - early isovolemic haemofiltration, HVHF – high volume haemofiltration

A few of the more commonly encountered methods include:

Continuous arterial venous haemofiltration (CAVH) – this merely describes the mode of vascular access as being arterial to create the driving pressure. This technique is seldom used now with the improved development of venous pumps and greater morbidity of arterial cannulation.

Continuous veno-venous haemodiafiltration (CVVHDF) – this method employs a combination of dialysis and ultrafiltration. The use of this method is increasing as it is said to be more efficient in solute and fluid clearance than CVVH.

Sustained low efficiency daily dialysis (SLEDD) - This technique is very much like prolonged IHD and uses the same machines and dialysates. The main difference is that longer sessions (usually 6–12 h) enable slower blood and dialysate flow rates. As with IHD this technique is excellent for solute clearance and fluid may also be removed. The slow continuous removal of solute and water tends to offer greater haemodynamic stability than a conventional haemodialysis treatment. Clinical trials comparing SLEDD to CRRT have failed to demonstrate a survival difference when adjusting for disease severity.[20] The benefit is in being able to use one type of machine for any renal replacement therapy, instead of one machine for haemodialysis and a different machine for CRRT. SLEDD therapies are also less expensive as there is no requirement for large volumes of customised fluids. Besides, there is greater flexibility in terms of the ability to move patients out of the intensive care unit for investigations or interventions by allowing a scheduled down time.

Slow continuous ultrafiltration (SCUF) - Fluid removal at a constant rate is targeted with this therapy. No dialysate or replacement fluid is used; hence solute clearance is negligible. It is very effective when fluid removal is the only goal in patients who are not azotemic. Patients who would benefit from SCUF are those with fluid overload that is resistant to diuretic therapy as in refractory cardiac failure or in patients with ARDS who require fluid removal. Excess fluid removal may benefit by improving gas exchange as well as haemodynamic parameters.

High volume haemofiltration (HVHF) - Haemofiltration can be used intermittently when higher ultrafiltration rates are applied. HVHF is defined as flow rates in excess of 35ml/kg/min.

Peritoneal dialysis (PD). This mode is used more in chronic settings as opposed to AKI. PD utilizes the peritoneal epithelial lining as a natural semi-permeable membrane. Blood flow is rich to this area and dialysate is inserted via a catheter through the abdominal wall. This technique is most often used by patients with chronic renal failure in the community but has been used in the AKI setting when haemodialysis facilities are not available. The efficiency of solute clearance is variable. Fluid removal is determined by the concentration of glucose in the dialysate fluid, with fluid shifts generated by osmotic pressure differences between the dialysate and patients blood.

INDICATIONS FOR RENAL REPLACEMENT THERAPY

There are numerous well recognized indications for RRT in the critical setting. These mainly stem from the need to maintain fluid, electrolyte and acid-base homeostasis. Some of these may be urgent indications presenting on admission while at other times, RRT is instituted in the ICU patient with renal failure as a planned component of overall supportive care. The following represents the most commonly described indications for RRT.

Renal (AEIOU)		
	Uremia	Azotemia >30 mmol/L
		Neuropathy, myopathy
		Encephalopathy
		Pericarditis
	Overload of fluids	Volume removal
		Pulmonary edema
		Oliguria with < 200 mL of urine output in 12h
		Anuria with < 50 mL urine output in 12 h
	Electrolytes	Hyperkalemia (K > 6.5 mmol/L)
		Sodium abnormalities (Na< 115 or >160 mol/L)
	Acid-base	Metabolic acidosis (pH < 7.0)
	Intoxications	With dialyzable toxin
Nonrenal		Allowing administration of fluids and nutrition
		Hypo/hyperthermia
		? Elimination of inflammatory mediators in sepsis

Fig 8 Indications for RRT in AKI[21]

Depending on the guidelines used, these absolute values may differ with different authors.

Uremia - RRT is generally indicated with marked uremia. Cut off values are usually quoted as 30mmol/L but this varies with different references. RRT is also necessary when uremia becomes symptomatic in the form of neuropathies, pericarditis or encephalopathy.

Fluid Balance - In order to preserve tissue perfusion in patients with AKI, it is important to optimize fluid balance by removing excess water without compromising the effective circulating fluid volume. It is still a matter of controversy as to which clinical parameters should be utilized in order to uniformly define the concept of ‘‘volume overload’’. Most physicians use a

combination of clinical signs as well as fluid balance to decide on the amount of fluid to be removed.

Electrolytes - Dialysis provides a very effective way to correct symptomatic electrolyte imbalance not responsive to medical therapy.
Acid Base - Correction of marked derangements in plasma pH may facilitate the function of inotropic infusions, as well as improving cardiac function in severe shock states.
Intoxication - With acute intoxication, dialysis often provides the most effective way to remove these toxins from the blood. Dialyzable toxins include: **lithium, ethanol, methanol, salicylates, theophylline, sodium valproate and barbiturates**.
Temperature regulation - Extreme hypo or hyperthermia may be rapidly corrected with the passage of blood through an extracorporeal circuit where the blood temperature may be manipulated.
Nutrition - When volemic and uremic control can be manipulated by RRT, an aggressive, protein-rich nutritional policy can be implemented in ICU patients resulting in a marked improvement in daily nitrogen balance with possible favorable effects on immune function and overall outcome.
Sepsis - The host response to infection in patients with septic shock involves the generation of pro and anti-inflammatory molecules. This response may be responsible for the development of organ dysfunction in patients with sepsis. It has been hypothesized that CRRT may modulate the inflammatory response by removal of cytokines and other mediators from the circulation. This hypothesis was largely based on animal studies where high-volume haemofiltration (6 L/h) applied early in the course of porcine sepsis resulting in haemodynamic improvement. It is important to note that the ultrafiltration volumes required to replicate this technique are massive: 200 ml/kg per hour, or 14 L/h in a 70-kg human, compared with 15-30 ml/kg per hour, or 1-2 L/h that are used. The rates used regularly do not significantly augment inflammatory mediator clearance. With the development of HVHF, higher filtration rates are now possible. Some small studies have suggested improved haemodynamic stability in septic patients but these needs to be substantiated by larger randomized control trials. Further research is needed here to improve mediator removal and to decide on which mediators should be removed without depleting valuable nutrients, albumin, hormones, vitamins, trace elements.

TIMING OF RRT

While most of the conventional indications for RRT are relatively well accepted, they also are subject to interpretation. How severe a degree of volume overload, uremia, or metabolic acidosis do we accept? Do we use

these values commonly quoted as strict guidelines? What, if any, medical therapies should be tried before initiating RRT?
These questions often arise as there is no uniform standard of care and wide variations in clinical practice prevail as to what constitutes AKI. This has been the source of much debate as well as whether to initiate RRT early or later.

The concept of early dialysis was used to describe the initiation of RRT before nitrogenous waste products had reached some arbitrary predefined cutoff value.
There have been numerous articles, majority being retrospective trials, examining this concept. The most recent are summarized as follows.

Study	Yr	Mode	Study	No	Criteria for Initiation of RRT		Survival	
					Early	Late	Early	Late
Bouman et al (12)	2002	CRRT	RCT	106	<12 hrs after meeting AKI definition	BUN >112 mg/dL, S_K >6.5 mmol/L, or pulmonary edema	LV: 69 HV: 74	LV: 75
Demirkiliç et al (26)	2004	CRRT	Retrospective	61	UOP <100 mL/8 hr	S_{Cr} >5.0 mg/dL or S_K >5.5 mmol/L	77	45
Elahi et al (27)	2004	CRRT	Retrospective	64	UOP <100 mL/8 hr	BUN ≥4 mg/dL, S_{Cr} >2.8 mg/dL, or S_K >6 mmol/L	78	57
Piccinni et al (28)	2006	CRRT	Retrospective	80	<12 hrs after ICU admission	"Conventional" indications	55	28
Liu et al (29)	2006	IHD & CRRT	Observational	243	BUN ≤76 mg/dL	BUN >76 mg/dL	65	59

IHD, intermittent hemodialysis; CRRT, continuous renal replacement therapy; RCT, randomized controlled trial; BUN, blood urea nitrogen; S_{Cr}, serum creatinine; AKI, acute kidney injury; UOP, urine output; ICU, intensive care unit; S_K, serum potassium; LV, low-volume hemofiltration; HV, high-volume hemofiltration.

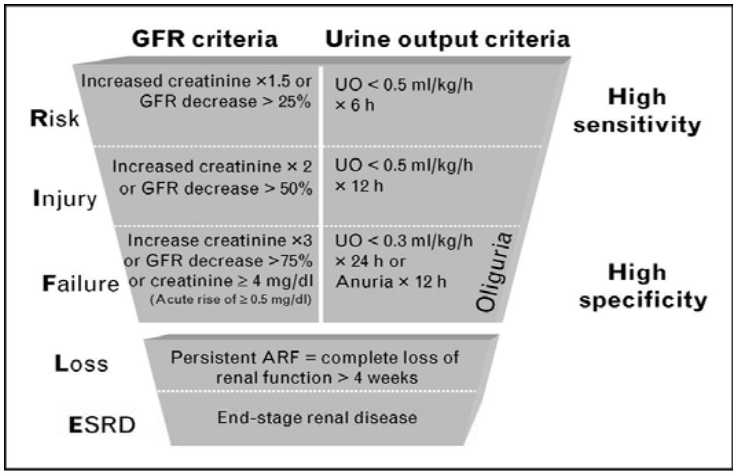
Fig. 9 Summary of recent studies evaluating the timing of initiation of renal replacement therapy.[17]

As can been seen, majority of these results showed lower mortality rates in the patients where RRT was started earlier.
However, a few problems are evident when trying to compare these results. Most obvious is the lack of definition for what is considered early and late criteria. No two studies have used the same values. The use of urea as a marker in critical care is not as accurate as its use in chronic renal failure. There may be a bias with regard to choice of therapy as the reasons for early or late therapy often differ eg. in 2 studies oliguria was used in early therapy while azotaemia or hyperkalaemia in late, and when oliguria is used as a marker, the presence of adequate fluid volume or diuretic use was not always commented on.

Only one recent study has attempted to address the timing of CRRT prospectively.
Bouman and colleagues randomized 106 critically ill patients to 1 of 3 groups - early high-volume CVVHDF, early low-volume CVVHDF, and late low-volume CVVHDF. Treatment was initiated in the two early groups within 12 hrs of meeting study inclusion criteria (the presence of oliguria for 6 hrs despite hemodynamic optimization or a measured creatinine clearance of 20 mL/min on a 3-hr timed urine collection), while in the late group renal support was not initiated until urea was 112 mg/dL, potassium was 6.5 mmol/L, or pulmonary edema was present.
No significant differences in survival were observed among the three groups.
Of note, however, the overall 28-day mortality for subjects in this study was only 27%, substantially lower than mortality rates reported in most other studies of critically ill patients with AKI, suggesting a lower disease burden in this cohort.

Despite these flaws in the studies, majority have suggested that earlier initiation of RRT improves survival and the recovery of renal function. Similar findings were reflected in the most recent meta analysis of the subject in American Journal of Kidney Diseases - Volume (August 2008).

In response to the need for a common definition and classification of acute renal failure, the Acute Dialysis Quality Initiative developed a consensus definition that goes under the acronym of **RIFLE** (**R**isk of renal dysfunction, **I**njury to the kidney, **F**ailure of kidney function, **L**oss of kidney function and **E**nd-stage kidney disease).
Since then, several clinical studies have shown that the proposed RIFLE classification is suitable for definition of AKI in the ICU and correlates with hospital mortality as the RIFLE class goes up.[23 24]



The classification system includes separate criteria for serum creatinine and urine output (UO). The criteria that lead to the worst possible classification should be used. Note that RIFLE-F is present even if the increase in serum creatinine is below 3-fold so long as the new serum creatinine is 4.0 mg/dl (350 μmol/l) or above in the setting of an acute increase of at least 0.5 mg/dl (44 μmol/l). The shape of the figure denotes the fact that more patients (high sensitivity) will be included in the mild category, including some without actually having renal failure (less specificity). In contrast, at the bottom, the criteria are strict and therefore specific, but some patients will be missed. GFR, glomerular filtration rate; ARF, acute renal failure. From Bellomo *et al.* [18]; used with permission.

Fig 9 RIFLE criteria for AKI

Given the importance of early recognition of AKI, the **A**cute **K**idney **I**njury **N**etwork (**AKIN**) recently modified the RIFLE classification. AKI is classified in three stages. Stage 1 is slightly more sensitive than risk, stages 2 and 3 correspond to injury and failure.

AKI stage	Serum creatinine	Urine output (ml/kg/h)
1	Absolute increase $\geq$ 0.3 mg/dl[a] or increase above baseline $\geq$ 1.5–2×	<0.5 for 6 h
2	Increase above baseline $\geq$ 2–3×	<0.5 for 12 h
3	Increase above baseline $\geq$ 3× or sCr $\geq$ 4 mg/dl[b] with an acute rise of 0.5 mg/dl[c] in $\leq$24 h Patients receiving RRT	<0.3 for 24 h or anuria for 12 h

The time constraint of the changes is 48 h or less. AKI, acute kidney injury; sCr, serum creatinine; RRT, renal replacement therapy. Reproduced from [42••].
[a] 26.4 μmol/l.
[b] 350 μmol/l.
[c] 44 μmol/l.

Fig 10 AKIN criteria for AKI

The AKIN criteria have also been clinically tested, most recently in an article in Critical Care Medicine – May 2008. 470 patients admitted to ICU were examined and they found a significant correlation with the AKIN classification and mortality and the need for initiation of RRT.

In addition to renal criteria, the decision of when to start RRT should also consider the severity of other organ failure. Renal function is unlikely to recover spontaneously if circulation remains vasopressor dependent with the presence of other organ failure as well. Involvement of other organ systems may prompt earlier initiation of RRT.

Optimally, the question of timing of initiation of RRT in AKI will need to be addressed in a prospective randomized trial. The design of such a trial, however, poses significant challenges – most critically, the need for early identification of patients who will have persistent and severe renal injury requiring renal support. Without reliable markers to identify this population, a substantial number of patients who would not otherwise be started on RRT will need to be randomized into an early therapy arm and subjected to the risks of RRT. Thus, robust biomarkers and clinical predictors of the course of AKI are needed before conducting such a study.

The introduction of various biomarkers for AKI is an exciting new area of research. The use of biomarkers may prove to be helpful in detecting AKI at an early stage, to describe the type of AKI, to evaluate preventive strategies

and to decide when to start or stop RRT. Biomarkers that are currently generating interest include: NGAL, IL8, KIM 1 and Cystatin C.

So in summary regarding timing of RRT, there is a trend to starting RRT earlier in patients with AKI. This is supported by numerous retrospective trials however there is no conclusive RCT's to back this up. As a result, no consensus has been reached on guidelines for timing of RRT. The RIFLE and AKIN criteria have begun to establish a clear definition for AKI and further RCT using these criteria are needed. The role of biomarkers for AKI is eagerly awaited.

IHD VS CRRT

CRRT first made an appearance in 1977. Since then it has been adopted in numerous centres especially in developed countries. The differences in the two modalities described earlier largely influence the choice of therapy chosen in different centres and in different patients. But which therapy has a better overall outcome? When assessing this, most of the studies mainly focused on the following issues: haemodynamic stability, mortality, time to renal recovery and the need for anticoagulation in CRRT.

Proponents of CRRT suggest that it is superior to IHD for the management of AKI, particularly in haemodynamically unstable patients. The slower, more gradual removal of fluid and solute is said to enhance haemodynamic stability and increased net salt and water removal permits better treatment of volume overload.
Because of its rapid changes in fluid status and plasma osmolality, IHD induces a decrease in venous return and cardiac index. This may cause renal ischemia and delay renal recovery after AKI. This concern initially came from experiences in combat casualties in Vietnam. Tissues from biopsies and postmortem studies in patients who had prolonged AKI requiring dialysis showed the presence of focal areas of fresh tubular necrosis estimated to be 48 or 72 hrs old following dialysis. Haemodynamic instability may also contribute to other organ dysfunction.

A number of observational studies compared haemodynamics in IHD and CRRT, all of which showed that CRRT had better haemodynamic stability. Although some of the RCT conducted showed mixed results when comparing the two modes, the general consensus appears to be that CRRT offers better haemodynamic stability compared with IHD and therefore should be considered in unstable patients.[18]

Because CRRT is a continuous modality, there is less fluctuation of volume status, solute concentrations, and acid-base status over time. It represents the superior method in patients with cerebral edema because of the avoidance of osmotic cellular shifts.
In contrast, IHD is highly effective in removing small solutes from the circulation.

Because of reported haemodynamic stability in CRRT, it would stand to reason that outcome would be better in the CRRT group. Numerous meta-analyses and prospective trials have failed to prove significant difference in mortality when comparing IHD and CRRT.[2]

However, lack of survival benefit does not imply that IHD and CRRT are equal.
Renal recovery is another important outcome for patients with AKI.
End-stage kidney disease requiring long-term haemodialysis is known to cause significant limitations in health related quality of life. Furthermore, long term dialysis is costly. Because of its rapid changes in fluid status and plasma osmolality, intermittent renal replacement therapy induces a decrease in venous return and can induce intrarenal hypotension. Because of this effect, intermittent renal replacement therapy may cause renal ischemia and delay renal recovery. A few observational studies suggest that continuous renal replacement therapy may be able to reduce chronic dialysis dependence. On the other hand, randomized controlled trials conducted so far do not support an effect of continuous renal replacement therapy over intermittent renal replacement therapy in relation to renal recovery.[18]

Table 2. Randomized controlled trials comparing renal recovery between intermittent (IRRT) and continuous (CRRT) renal replacement therapies

Author	Published Year	Reference No.	No. of Centers	Sample No. (IRRT:CRRT)	Severity (IRRT:CRRT)	Dialysis Dependence, %, IRRT:CRRT	*p* Value
Mehta	2001	5	4	166 (82:84)	87.7:96.4[a]	7.0:13.8	.43
Augustine	2004	6	1	80 (40:40)	12.0:11.6[b]	66.7:61.5	>.99
Uehlinger	2005	7	1	125 (55:70)	55:55[c]	3.7:2.7	>.99
Vinsonneau	2006	8	21	359 (184:175)	63.7:64.7[c]	0:1[d]	?

[a]Acute Physiology and Chronic Health Evaluation III, $p < .045$; [b]Cleveland Clinic Foundation severity score; [c]Simplified Acute Physiology Score II; [d]No. of patients is shown because hospital mortality is not provided. Dialysis dependence is rate of patients who remained on dialysis at hospital discharge among survivors.

Fig. 11 RCT comparing IHD vs. CRRT

So, no conclusive evidence favours one modality over another with regard to all cause mortality or recovery of renal function.

One of the main disadvantages of CRRT includes filter clotting due to prolonged exposure to the extracorporeal circuit necessitating anticoagulation. This may present a significant problem in trauma or operative patients. Although most centres also use anticoagulation for IHD, this is for a considerably shorter time. If contraindicated, IHD can also be performed without anticoagulation. In this respect, certain units may favour IHD for patients at risk of bleeding.

One also needs to consider the availability of CRRT. More resources are needed to conduct this in terms of cost, trained personnel, more machines per unit and the lack of flexibility to move patients for procedures, interventions etc while on continuous therapies. If mortality outcomes have not shown much difference and there isn't overwhelming evidence favouring renal recovery with CRRT, its routine use for all patients cannot be justified.
This has resulted in the increasing use of "hybrid" therapies such as SLEDD that try to match the advantages offered by both CRRT and IHD. Data comparing the hybrid modes of RRT are still lacking.

DOSE

As with any other therapy administered, any kind of dialysis has its "dosage." The dose of RRT is a measure of the quantity of blood purified of waste products and toxins. There are different methods used to define dose in IHD and CRRT.

With IHD, dose is assessed in chronic renal failure patients most commonly using the **urea kinetic model (Kt/V).**
The term Kt/V is a unitless measure of dialysis dose based on urea removal. K is the urea clearance of the dialysis membrane used (ml/min), t is the duration of dialysis (min), and V is the volume of distribution of urea in the patient (ml) where V is assumed to be total body water: 0.5-0.6 L/kg. Thus, Kt/V is a measure of the volume of plasma cleared of urea during a haemodialysis session. Larger Kt/V values signify greater haemodialysis dose.
The recent Dialysis Outcomes Quality Initiative recommendations defined a Kt/V of 1.2 as the minimum acceptable dialysis dose in chronic IHD patients. No such dosing guidelines have been established for the ARF population.

There are problems trying to extrapolate the use of this model in AKI patients.
Measurement of the urea kinetic model assumes a steady state of urea production and urea removal. Patients with AKI are not in a steady state; they have a greater protein catabolic rate and are in a negative nitrogen balance. Furthermore, urea kinetic modeling assumes the volume distribution of urea is equal to total-body water. Because patients with AKI have excess extracellular fluid volume and reduced lean body mass, true total-body water and urea distribution are variable. In spite of the above, and there being a lack of tools to quantify dose in AKI, a Kt/V of 1.2-1.4 is still considered the minimum dose that should be delivered per session. It is also suggested that treatment be at least 3 times a week.

In 2002, Schiffl focused on frequency of treatment. He randomized 2 groups in a prospective study to determine the effect of daily IHD as compared with conventional (alternate day) IHD on survival in patients with AKI. He demonstrated that daily IHD resulted in better control of uremia, fewer hypotensive episodes during IHD, and more rapid resolution of AKI than did alternate-day IHD thus favouring a more intensive approach.[6]

Dose in CRRT is more simply assessed by the ultrafiltration rate. In a randomized trial Ronco compared ultrafiltration rates of 20, 35 and 45 ml/kg/h with CVVH in 425 ICU patients with oliguric acute renal failure. It was shown that 35 and 45 ml/kg/h were of equal utility but both doses were superior to 20 ml/kg/h with respect to survival 15 days after CRRT was ceased (41%, 57%,58% respectively). Again this favoured a relatively more intensive approach.[21]

However, the largest addressing this aspect was published recently (NEJM July 2008). The Acute Renal Failure Trial Network (**ATN**) Study,[8] was designed as a multicenter, randomized trial in 1160 critically ill. The patients were randomized into 2 treatment groups: intensive and less-intensive dialysis therapy. The intensive group received IHD or SLEDD of Kt/Vurea targeting 1.2 to 1.4 per session with a frequency of 6 times a week, or CVVHDF with combined rates of 35 mL /kg/hr. The less-intensive group received IHD or SLED targeting the same Kt/Vurea dose, 1.2 to 1.4 per session, but with a frequency of 3 times a week, or CVVHDF with total effluent rate of 20 mL/kg/h. The primary end point was 60-day all-cause mortality rate.

Unfortunately the results were disappointingly similar. The mortality rate at 60 days was 53.6% in the intensive group and 51.5% in the less-intensive group. Recovery of renal function was also similar between the 2 groups. Of

note, more episodes of hypotension, hypophosphatemia, and hypokalemia occurred in the intensive group. The study concluded that increasing rates in critically ill patients with AKI over current adequate dialysis dosing schedules had no effect on clinical outcome in this disease process.

So what should we do? No strict recommendations can be made for specific dialysis dosing at this time. A minimum dose of RRT, however, needs to be delivered for AKI: the best evidence to date supports the use of at least 20 mL/hr/kg although most centres still tend towards 35mL/kg/hr for CVVH or CVVHDF, or Kt/V of 1.2 at least 3 times a week for IHD. One must also take into account the actual doses delivered as therapy may be interrupted for many reasons like diagnostic studies, surgery, clotting of filters etc.

CONCLUSION

Advances in RRT in the last few years have resulted in multiple RRT modalities available for treating ARF in the ICU. There is little data as to the best modality of RRT. Many confounders exist, such as severity of illness and etiology of renal failure, which are probably the most important factors affecting outcome in ICU patients with ARF. RRT strategies should be tailored to the needs of the individual patient.

In view of the above information, these general practical guidelines have been suggested.
• Initiate RRT early, once indications for RRT exist. Potential advantages of earlier RRT initiation must be set against the hypothetical risks of dialysis induced complications, bleeding due to anticoagulation, and complications associated with central venous access
• Adequate double-lumen venous catheters must be used to guarantee optimal extracorporeal blood flow and filter performance
• If RRT is implemented, make sure an adequate treatment dose is delivered. In otherwise stable patients, alternate-day IHD treatments of 4 or more hours using blood flows of 250 mL/min or greater are usually sufficient. More frequent heamodialysis may be required in highly catabolic patients or to achieve treatment targets for fluid, electrolyte, or acid-base management.
• If haemodynamic instability is present, longer therapies, such as CRRT or SLEDD, should be implemented. If CRRT is used, the target dose should be 20 - 35 mL/kg/hour.
• Low-dose unfractionated heparin, aiming for a slightly above normal APTT, is recommended. If risk factors for bleeding exist and the filter continues to clot, consider pre-dilution haemofiltration, regional

anticoagulation with heparin and protamine, citrate anticoagulation or prostacyclin.

• If the choice is possible, select biocompatible high-flux membranes.

• When intracranial pressure control is vital consider implementing CRRT early if there is coexistent AKI. Volume and electrolyte control will help intracranial pressure control

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