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REVIEW

Renal replacement therapy for acute renal failure on the intensive care unit: coming of age?

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ABSTRACT

The introduction and development of continuous renal replacement therapy (CRRT) represents one of the most substantial changes in patient management on the intensive care unit (ICU). Several issues, however, are still unresolved. Adequacy of dialysis in critically ill patients involves more than simple control of urea (although considered reflective of toxic uraemic compounds). It also concerns various (other) biochemical and clinical parameters. This article addresses important questions such as the different aspects of 'adequate' dialysis and its timing and intensity ('dialysis dosing'). Dialytic treatment should now be tailored to the patient, influenced by patient characteristics, urgency of treatment, haemodynamic tolerance and vascular access. For this, intermittent haemodialysis and CRRT should be regarded as complementary techniques, to be used interchangeably in critically ill patients with acute renal failure (ARF) according to circumstances. While awaiting scientific criteria for the initiation of renal replacement therapy in ARF patients, it seems reasonable to prefer prevention of physiological derangements to their *post-hoc* correction. This would mean early initiation of dialytic treatment as renal support rather than its initiation as renal replacement therapy for uraemic complications. The amount of dialysis ('dialysis dose') should preferably be prescribed on an individualised basis, especially when considering that the delivered dialysis dose may make a difference. Despite its limitations, simplified urea kinetic modelling, as outlined in this article's appendix, may be used as a bedside method to establish the required dose with CRRT. If not, at least the weight-adjusted ultrafiltration (UF) flow rate should be used as a surrogate for the prescribed dialysis dose (i.e., ml/kg/h). As the prescribed dialysis dose is usually less than the delivered dose, this should also be taken into account. In addition, nutrition should be viewed as an integral part of the dialysis prescription. Continuing effort should be made to develop 'evidence-based' guidelines for the appropriate prescription and delivery of renal replacement therapy to treat ARF in the ICU. This should include efforts to determine a validated dialysis dose methodology in ARF patients to address further the dose/outcome relationship. Based on existing data, some guidelines for the prescription and delivery of adequate (C)RRT are provided.

INTRODUCTION

Although in part masked by a change in the patient population, adequate comparative data indicate that outcome of acute renal failure (ARF) patients has improved over the last two decades.[1,2] Advances in resuscitation techniques, mechanical ventilation, nutrition and haemodynamic monitoring which we have seen during the last two decades may explain this better outcome. In addition, we now have a complete armamentarium of extracorporeal techniques available to replace renal function in the critically ill patient with ARF.

Indeed, the introduction and development of continuous renal replacement therapy (CRRT) represents one of the most substantial changes in patient management on the ICU.[3] However, despite more than 250 published papers concerning the various aspects of CRRT, some important questions still need to be answered. This particularly

concerns aspects of 'adequate' dialysis and the timing and intensity ('dialysis dose') of dialytic treatment. This article addresses these questions and, as an increasing number of nondialysis hospitals are implementing CRRT,[2] attempts to provide some guidelines for internists providing nephrological care on the ICU.

ADEQUACY OF DIALYSIS

In contrast to end-stage renal disease (ESRD) patients, there is no definition of 'adequate' dialysis in critically ill patients. We can only rely on personal experience, clinical intuition and some preliminary data to define adequacy. Of course, adequacy of dialysis in critically ill patients concerns more than simple control of urea (although considered reflective of toxic uraemic compounds). It also concerns various other biochemical and clinical parameters (*table 1*).

Table 1
Different aspects of adequate dialysis in acute renal failure

BIOCHEMICAL PARAMETERS	CLINICAL PARAMETERS
Adequate small-solute clearance	Control of fluid balance
Correction of electrolyte disturbances	Cardiovascular stability
Attaining acid-base homeostasis	No respiratory compromise
Adequate clearance large(r) solutes?	Adapted to nutritional needs
No depletion syndrome	No aggravation of renal/ splanchnic ischaemia

Biochemistry

Accumulating data suggest that CRRT is superior to intermittent haemodialysis (IHD) in terms of control over the patient's biochemistry and fluid status.[3-5] One factor is that the 'dialysis dose' actually delivered with IHD is less than that prescribed, predominantly due to repeated hypotensive episodes necessitating a decrease in blood flow or earlier termination of the procedure.[4,5] Recirculation is another important factor, depending on site, blood flow and reversal of lines.[4,5] CRRT not only enables a significantly higher dialysis dose to be delivered when compared with IHD, more mass of urea is also removed in CRRT than in IHD at similar Kt/V_{urea} (mathematical expression of dialysis dose, where K represents clearance, *t* time and V volume distribution of urea) (see *appendix* on page 246).[4,5] This apparent inefficiency of IHD compared with CRRT is related to the nonlinearity of diffusion-based solute removal, compartmentalisation phenomena and flow-related disequilibrium.[4] However, the prescribed dialysis dose with CRRT is also less than the delivered dose. As the actual mean duration of CRRT often does not exceed 18 to 19 hours (e.g. due to filter clotting, surgical procedures), a prescribed UF rate of 33 ml/min is not necessarily equivalent to a delivered dialysis dose of 48 l/day.[3,5]

Fluid balance

The amount of fluid removed during IHD is also limited to approximately two to three litres a day. This contrasts sharply with CRRT which, by providing the option of being able to remove fluid any time of the day or night, gives us the potential for continuous fine-tuning of the intravascular volume.[3,5] This is also important in view of the often massive fluid resuscitation required in the early phase of septic shock; fluid which is sequestrated in part into the interstitial tissue because of capillary leakage. During recovery from sepsis and re-establishment of capillary integrity, sequestrated fluid shifts back from the interstitial space into the vascular space. In this stage, high negative fluid balances are required if renal failure (i.e. oliguria) is still present, which can only be attained with CRRT.[6]

Acid-base homeostasis

Adequacy of dialysis also concerns the adequate correction of acid-base homeostasis. Lactate-based CRRT is associated with superior correction of acidosis in comparison with standard bicarbonate-based IHD. As lactic acidosis is often present in concurrence with decreased lactate metabolism, one may question whether bicarbonate – although more costly – should (also) be preferred as the buffering anion with CRRT.[3,5,7] In one prospective, randomised trial comparing continuous venovenous haemofiltration (CVVH) with either bicarbonate-based or lactate-based replacement fluid, superior acidosis correction and reduced cardiovascular events were observed with use of the bicarbonate-based replacement fluid.[8] Others have noted an increased urea generation rate with use of lactate-buffered replacement fluid, possibly because of a catabolic effect of D-lactate.[9,10] Lactate can be used safely as the buffering anion in most patients; no hyperlactataemia has been reported with a lactate flux of up to 65 mmol/h in ICU patients.[3] However, no data exist on the effect of a large lactate load with CRRT using high UF flow rates (>4 l/h). In cases of severe liver dysfunction (e.g. cirrhosis, fulminant liver failure) bicarbonate should preferentially be used as the buffering anion. Of note, high dialysate or ultrafiltration flow rates with CRRT may result in alkalosis, which may complicate weaning the patient from the ventilator.

Choice of membrane

Adequacy of dialysis also concerns the choice of the membrane. Blood-membrane interactions may lead to several unwanted effects; the less biocompatible the membrane, the more unwanted effects will occur.[11,12]

Several data suggest that use of bioincompatible cellulosic membranes (cuprophane) with IHD is associated with delayed recovery of renal failure and decreased survival in ICU patients compared with the use of biocompatible low- and high-flux synthetic membranes.[13] No superiority of synthetic membranes compared with modified cellulosic membranes (cellulosic tri-acetate) in terms of renal or patient outcome with IHD has been observed.[11,14] Although the use of high-flux synthetic or modified cellulosic membranes is advocated with IHD, this issue is still much debated.[15] With the exclusive use of (semi)synthetic membranes in CRRT and despite potential differences in characteristics (e.g. adsorptive *vs.* nonadsorptive membrane surfaces), no superiority of any specific membrane has been demonstrated.[3,11]

Anticoagulation

Ongoing anticoagulation is needed with CRRT to prevent clotting of the extracorporeal circuit. Frequent filter clotting is one of the most important factors decreasing the delivered dialysis dose, thereby jeopardising the adequacy of dialysis with CRRT.[16] In patients who are often at high risk of bleeding, finding the optimal anticoagulation regime which leads to prolonged filter life (≥24 hours) while preventing (aggravation of) bleeding is an important part of the dialysis prescription with CRRT. Given the association of new haemorrhagic episodes and even haemorrhage-associated death with use of conventional low-dose heparin in high-risk patients treated with CRRT,[16,17] regional citrate anticoagulation is being increasingly used.[18] Besides a lower risk of bleeding, it is also associated with increased filter life and avoidance of heparin-induced thrombocytopenia.[16,18] However, whatever the anticoagulation regime, proper monitoring and adequate vascular access are of utmost importance in preventing filter clotting with CRRT.[16] Contrary to CRRT, IHD can be safely and adequately performed with or without anticoagulation. As such, it may be an alternative for CRRT in patients at high-risk of bleeding. Pros and cons of the different anticoagulation regimes are beyond the scope of this article and the reader is referred to some excellent reviews on this subject.[16,17,19]

Complications

In addition to being superior as renal replacement *per se*, CRRT avoids complications such as (aggravation of) hypotension, cardiac arrhythmias, an increase in oxygen consumption or cerebral oedema and splanchnic ischaemia, which may be seen with IHD.[3,5] However, while significant improvements in intermittent treatment may ameliorate some of these complications (*table 2*), CRRT may offer some potential disadvantages (*table 3*). Indeed, sustained low-efficiency dialysis (SLED) may be seen as the ultimate hybrid technique, combining advantages of conventional dialysis with those of CRRT.[20]

Table 2

Improvements in intermittent treatment of acute renal failure on the intensive care unit

Sequential ultrafiltration/dialysis
Volumetric-controlled ultrafiltration
High-flux biocompatible membranes
Sodium profiling[@]
Low-temperature dialysate
Intermittent haemofiltration
On-line blood volume monitoring
Acetate-free biofiltration[#]
SLED (sustained low-efficiency dialysis)*

[@] Use of variable dialysate sodium concentration with mirrored UF.
[#] Complete avoidance of acetate may result in improved haemodynamics.
** Extended duration of IHD to 6-12 hours with decreased blood (100-200 ml/min) and dialysate flow rate (200-300 ml/min).*

Table 3

Potential disadvantages of continuous renal replacement therapy

Need for continuous anticoagulation
More difficult drug dosing
Prolonged immobilisation of patient
Low efficiency in terms of unit/time (e.g. severe hyperkalaemia)
Hypophosphataemia/(ionised) hypocalcaemia more frequent
Nonselective solute removal: depletion syndrome with prolonged use of high Q_f ?[@]
Adverse effects hyperlactataemia with lactate-based continuous renal replacement therapy using high Q_f ?[@]

[@] Few if no data available concerning these important issues, Q_f = ultrafiltration flow rate.

The IHD *versus* CRRT debate

Some still consider the choice of treatment modality on the ICU a matter of ongoing debate. While a protagonistic view as to the preferential use of CRRT on the ICU is supported by several clinical data, antagonists of the preferential use of CRRT on the ICU point to the similar mortality of ARF patients in studies comparing IHD with CRRT, including three prospective randomised trials and two meta-analysis.[21-25] However, guidelines for providing adequate dialysis should direct the choice of treatment modality. Defining a superior treatment modality based on often biased views and inconsistent data (e.g. intensivists *vs.* nephrologists; physicians from nondialysis *vs.* dialysis hospitals) will hamper establishing valid guidelines. Most would agree that CRRT is the preferred treatment modality for a significant proportion of haemodynamically unstable ICU patients. In patients stable enough to tolerate either form of dialysis treatment, benefits and complications of

both treatment modalities should be weighed carefully against each other. Therefore, a reasonable approach is to regard IHD and CRRT as complementary techniques, to be used interchangeably in critically ill patients with ARF according to circumstances (*figure 1*).

WHEN TO START RENAL REPLACEMENT THERAPY?

The optimal 'timing' of renal replacement therapy is not known. Several earlier studies, including one prospective, randomised trial, comparing outcome of ARF patients who were dialysed on established indications with the outcome of ARF patients who were dialysed 'early' (i.e. at a lower serum urea level), showed a clear survival advantage of patients who were dialysed 'early' (*table 4*). However, lack of adjustment to differences in case mix, illness severity, nondialytic therapies and/or dialysis intensity may have confounded these positive results.[12,23,26,27] There are no recent studies investigating the timing of renal replacement therapy in a controlled fashion. In a retrospective comparative study, a shorter time interval from ICU admission to start of CRRT was found in surgical ARF patients who survived compared with similar patients who died (4.5 *vs.* 6.8; p=0.01).[7] These findings were not observed in ARF patients treated

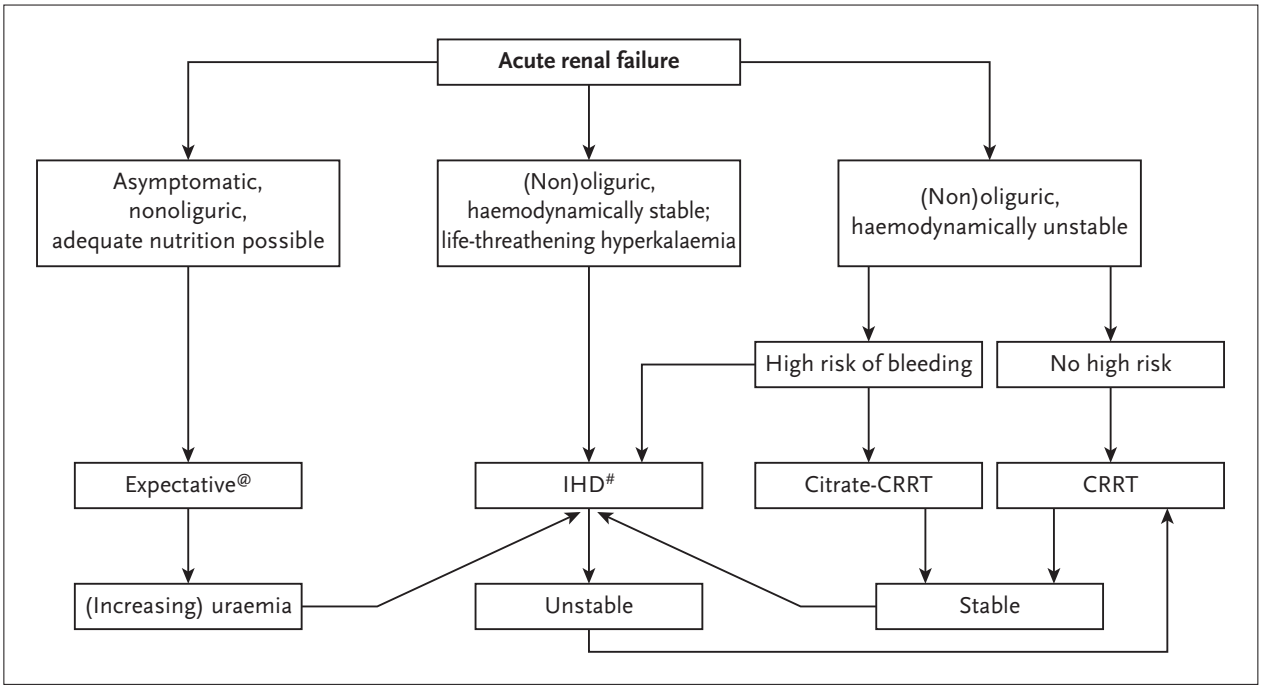

Figure 1

Algorithm for the dialytic treatment of acute renal failure according to circumstances

IHD = intermittent haemodialysis, CRRT = continuous renal replacement therapy. @ Delay initiation of dialytic treatment to maximise the odds of native renal recovery, # if no citrate-protocol for CRRT, heparin-free IHD may be used as alternative treatment.

Table 4

Impact of early ('prophylactic') dialysis on outcome in acute renal failure

AUTHOR, YEAR	PREDIALYSIS UREA (MMOL/L)		MORTALITY (%)	
	CONTROLS#	EARLY	CONTROLS#	EARLY
Parsons, 1961	71	43	15/17 (88)	4/16 (25)
Balslφv, 1963	67	52	22/42 (52)	31/54 (57)*
Fischer, 1966	83	54	65/84 (77)	40/78 (51)
Kleinknecht, 1972	58	33	73/173 (42)	43/147 (29)
Conger, 1975[27]	43	18	8/10 (80)	3/8 (36)

*# Historical controls treated with intermittent haemodialysis for clinical deterioration (severe electrolyte, acid-base or fluid disturbances) and/or very high urea levels, * no significant difference.*

with contemporary IHD. There was no difference in serum creatinine levels between survivors and nonsurvivors upon initiation of CRRT.[7] In another retrospective study, 'early' start (mean urea 15.2 ± 4.6 mmol/l) of CRRT was associated with a shorter time interval between hospital admission and initiation of renal replacement therapy (10.5 *vs.* 19.4 days; p=0.01) and improved outcome (39% *vs.* 20%; p<0.0001) when compared with 'late' starters (urea 33.7 ± 10.1 mmol/l).[28]

It may be that patients treated later developed ARF with a more protracted course or developed ARF as part of multi-organ dysfunction syndrome (MODS). Otherwise, one might suggest that earlier intervention with CRRT favourably affects outcome. Commonly observed cardiac and/or pulmonary system failure accompanying ARF may be exacerbated (or provoked) by overhydration and increases the risk of dying.[5,7] Therefore, the prevention or rapid reversal of any existing overhydration with the early initiation of CRRT may lead to a diminution of additional vital organ dysfunctions. The 'early' institution of CRRT may also down-modulate the body's exaggerated response to severe septic or nonseptic insults for which various mechanisms may be responsible: reduction of interstitial oedema by continuous intravascular 'refilling'; decrease in core body temperature in hyperthermic patients; correction of (lactic) acidosis; and perhaps the continuous removal of toxic substances (urea, proteases, inflammatory mediators, myoglobin, and maybe others.[29,30] All this may lead to less established organ damage (ARDS, acute tubular necrosis) and a more favourable clinical course. Indeed, while awaiting scientific criteria for the initiation of renal replacement therapy in ARF patients, it seems reasonable to prefer prevention of physiological derangements to their *post-hoc* correction. In recent years, indications and timing of dialysis seems to be shifting from renal replacement *per se* to renal support, the latter eventually being more targeted – although unproven[31] – for overall support.

WHAT DIALYSIS DOSE SHOULD BE PROVIDED?

Dialysis intensity

The issue of dialysis intensity ('dialysis dosing') has been studied extensively in patients with chronic renal failure (see *appendix* on page 246). Indeed, a consistent correlation has been shown between dialysis dose (expressed as Kt/V_{urea}) and survival, even after adjusting for important comorbid factors, such as diabetes, nutritional status and hypertension.[27-31] Based on these data, it is advised to deliver a Kt/V of at least 1.2 per session to chronic dialysis patients.[32-36] However, little attention is paid to the intensity of dialysis in ARF. A controlled study from the 1980s, comprising only a small number of patients, failed to show any significant benefit from intensive IHD using cuprophane membranes in ARF patients.[37] However, it may be that the possible beneficial effects of this approach were offset by the side effects associated with IHD using bioincompatible (BIC) membranes, such as hypotension and the prolongation of ARF. Indeed, some data do suggest that the dialysis dose may affect patient outcome. Tapolyai *et al.*[38] found a higher delivered dialysis dose in ARF patients treated with (more) contemporary IHD (bicarbonate-based, synthetic membranes) who survived compared with similar patients who died (Kt/V_{urea} 1.09 *vs.* 0.89; p<0.05).

In a prospective randomised study comparing daily with alternate-day intermittent haemodialysis in ARF patients (n=160), intensive haemodialysis (weekly Kt/V_{urea} 5.8 ± 0.4 *vs.* 3.0 ± 0.6) reduced duration of renal failure (9 ± 2 *vs.* 16 ± 6 days; p=0.01) and improved survival (72% *vs.* 54%; p=0.01).[39]

Diffusive or convective clearance ?

Another important question concerns the principal method of solute removal, i.e. diffusion or convection. Some retrospective data suggest a correlation between the ultrafiltration volume (i.e. convective purification rate) and recovery rate of renal failure and patient outcome, respectively.[40] Paganini and co-workers found an inverse correlation between the delivered dialysis dose (expressed as Kt/V_{urea}) and mortality in patients with intermediate illness severity, whether treated with contemporary IHD or CRRT.[41] As might be expected, this impact of a higher delivered dialysis dose on outcome was not seen at either extremes of illnesses.[41] Improved survival was also observed in a prospective randomised study in CVVH-treated ARF patients (n=425) with increasing ultrafiltrate volumes.[42] Data suggested that the weight-adjusted UF volume should be at least 35 ml/h/kg.[42] An 'attractive' explanation often put forward is an improved clearance of toxic middle- and large-molecular-weight solutes with convection-based techniques, from which the patient with an exaggerated inflammatory response (e.g. septic shock) may benefit.[29,30] However, as data suggest a correlation between dialysis dose and patient outcome with both diffusion-based and convection-based techniques, more data are needed to substantiate this point. In addition, data from formal comparisons of convection-based and diffusion-based CRRTs, e.g. CVVH *vs.* CVVHD (continuous venovenous haemodialysis) or low *vs.* high volume CVVH in ARF patients have yet to be published. Nevertheless, if not using more 'sophisticated' dialysis dosing, it seems appropriate to use the weight-adjusted UF volume as a surrogate for the dialysis dose (ml/kg/h *vs.* ml/h). Using the above-mentioned UF flow rate of 35 ml/kg/h one can easily see the difference in required dialysis dose,

depending on the patient's weight: e.g. a daily clearance of 71 l/day for a patient with a bodyweight of 85 kg and 57 l/day for a patient with a weight of 68 kg.

PROTEIN AND CALORIE ADMINISTRATION DURING RENAL REPLACEMENT THERAPY

Nutritional support directly influences the required dialysis dose and amount of fluid removal with renal replacement therapy. Both the amount of nonprotein calories administration and the amount of protein administration correlate strongly with the urea generation rate, thus influencing the required dialysis dose.[43] In contrast to IHD, CRRT facilitates the unrestricted supply of protein and energy sources without the risk of exacerbating azotaemia or fluid overload. However, these techniques also have an impact on nutrient balance itself. Urea nitrogen losses with the ultrafiltrate represent 70 to 80% of the eliminated nitrogen.[44,45] Non-urea nitrogen losses occur as a result of convective removal of free amino acids (AA)(MW 75-240 Da),[44,45] their clearance being directly proportional to the serum concentration and ultrafiltration/dialysate flow rate (≈ 10 to 12% of nutritional input). Therefore, although AA losses with CRRT are not great, this should be taken into account when prescribing nutritional support.

Thus far, protein requirements of ARF patients receiving renal replacement therapy have not been studied carefully. Some studies suggest that positive nitrogen balance can not be achieved with full (par)enteral nutrition.[44-46] However, levels of protein administration in these studies were relatively low (0.5-1.0 g/kg per day). It is suggested that a positive nitrogen balance may be achieved with the administration of 1.5 to 1.8 g protein/kg per day.[47] Of note, at this increased level of protein administration, lower levels of energy administration (25 to 35 kcal/kg per day) appeared to be associated with improved nitrogen retention and a more favourable nitrogen balance.[47] Recent data in highly catabolic ARF patients treated with CVVHDF (continuous venovenous haemodiafiltration) suggest that even higher levels of protein administration (2.5 g/kg/day) may be required to improve nitrogen balance.[48]

Although benefits of aggressive nutritional therapy in ARF for renal recovery are unknown and its impact on morbidity and mortality remains unproven, it seems intuitive that early initiation of nutritional support is warranted. Indeed, pre-existing and/or hospital-acquired malnutrition have been identified as important factors contributing to the persistent high mortality of ARF patients.[49]

Therefore, the dose of dialytic therapy – whether IHD or CRRT – should always be adapted to the nutritional needs (i.e. no protein restriction to avoid daily haemodialysis; no 'standard' UF volume without considering the amount of calories and protein administration). However, one must also realise that any excess protein intake beyond basic requirements will result in an additional increase in urea production, the production of other nitrogenous waste products and in potentially more pronounced negative nitrogen balance.[44-46]

In short, nutrition should be viewed as an integral part of the dialysis prescription (*table 5*). Most authors suggest administration of at least 1.4 g protein and 35 to 45 kcal/kg a day in patients with complicated urea ARF (for instance a highly catabolic patient with severe septic shock) receiving renal replacement therapy.[26,44,47] Urea kinetic modelling (UKM) may also assist in establishing protein requirements through determination of the protein catabolic rate (see *appendix* on page 246). It should be noted that dialysis – particularly CRRT – may have an impact on other nutritional substrates as well (e.g. vitamins, minerals).[44-46]

Table 5
Factors influencing prescription of dialysis dose

Patient size and weight[@]
Degree of catabolism (assumed or calculated PCR)
Amount of protein and calorie administration
Delivered dose < prescribed dose
Desired level of metabolic control

[@] Adjust ultrafiltration rate to the patient's weight (ml/kg/h) or use Kt/V. PCR = protein catabolic rate (see appendix).

ADEQUATE PERFORMANCE OF CRRT

Inadequate knowledge of or expertise with CRRT will directly affect its performance and impact negatively on the adequacy of dialysis. For example, repeated filter clotting – the Achilles' heel of CRRT – may not be related to the anticoagulation regime *per se* but more often to incorrect monitoring and absence of standardised procedures.[50] For all people involved (intensivists, nephrologists, renal and critical care nurses), it is important to recognise each other's responsibilities and expertise.[50,51] Regardless of the ICU format (closed *vs.* open), severely ill and complex patients with ARF offer ample opportunity for a collaborative interaction between the nephrologist and intensivist.[52,53] Unlike CRRT, IHD is performed by renal nurses under the direct supervision of the nephrologist and requires no active participation from the critical care nurse in the dialytic care of the patient.

However, what about hospitals without non-CRRT dialysis facilities and absence of nephrologists (and renal nurses)

with extensive knowledge of and experience with different dialytic treatment modalities? The first and most important question is the required minimal number of patients to be treated on a yearly basis to safely adopt CRRT on the ICU. In other words, how many patients should be treated to gain (and keep) enough experience with the technique? To date, no such practice guideline exists but is urgently needed. In addition, all measures should be taken to keep pace with (rapid) changes in technology and technique, to provide adequate and continuously updated protocols, and to establish areas for potential improvement.[50,54] These and other important issues that need to be considered are summarised in *table 6*. The mere implementation of some form of CRRT ('Wow, a new technique, let's do it')[55] without considering or adhering to these issues is to be strongly discouraged.

CONCLUSIONS

It seems as if renal replacement therapy for the treatment of ARF on the ICU is coming of age. Dialytic treatment can now be tailored to the patient, influenced by patient characteristics, urgency of treatment, haemodynamic tolerance and vascular access. However, current practice at many institutions is still to prescribe generally similar amounts of renal replacement therapy to ARF patients regardless of patient size and degree of catabolism.
The amount of dialysis ('dialysis dose') should preferably be prescribed on an individualised basis, especially when considering that the delivered dialysis dose may make a difference (*table 5*). Despite its limitations,[56-61] simplified UKM may be used as a bedside method to establish the required dose (see *appendix* on page 246). If not, at least the weight-adjusted UF flow rate should be used as a surrogate for the prescribed dialysis dose (i.e., ml/kg/h). As the prescribed dialysis dose is usually less than the delivered dose, this should also be taken into account.
It is the author's view that improved clearance (particularly of larger solutes), better control of blood flow and ultrafiltration rate and avoidance of arterial cannulation make pump-driven venovenous techniques the treatment of choice in critically ill haemodynamically unstable patients. Since the blood pump can augment blood flow and thus the ultrafiltration rate, it seems inefficient to add dialysate before the blood flow is maximised. In addition, CVVHD and CVVHDF are more labour intensive than CVVH. Results from a Dutch survey indicate that this judgement is shared by others.[2] One should also recognise that there are still specific situations for the preferential use of intermittent techniques on the ICU (*figure 1*).
Continuing effort should be made to develop 'evidence-based' guidelines for the appropriate description and delivery of renal replacement therapy to treat ARF in the ICU. This should include efforts to determine a validated dialysis dose methodology in ARF patients to address further the dose/outcome relationship.[8,59] Based on existing data, some guidelines for the prescription and delivery of adequate CRRT are suggested (*table 7*).

Table 7
Some guidelines to deliver adequate CRRT on the ICU

Start '*early*': oliguria >24 hours or anuria ≥12 hours; uraemia ≥25-30 mmol/l
Prescribe '*adequate*' dialysis dose: daily K*t*/V ≥1.2; UF volume ≥35 ml/kg/h
Use (semi)synthetic biocompatible high-flux membranes
Use the venovenous approach, preferably internal jugular vein[#]
Maximise UF flow rate, before adding slow-dialysis
In case of severe liver dysfunction, use bicarbonate as buffering anion
Judicious use of anticoagulation to improve delivered dialysis dose[@]
Prescribe ≥1.2-1.4 g protein/kg/day to improve nitrogen balance
If the patient is stabilised, switch to intermittent treatment

CRRT = continuous renal replacement therapy, IHD = intermittent haemodialysis, UF = ultrafiltration. [#] Canulation of jugular vein associated with less recirculation, hence improved dialysis adequacy, [@] if repeated clotting consider switch therapy (e.g., post- to predilution CVVH; other filter type; CVVH to CVVHDF) or switch to other anticoagulation protocol.

Table 6
Factors affecting successful implementation and continuation of CRRT

FACTORS AFFECTING POTENTIAL IMPLEMENTATION OF CRRT	FACTORS AFFECTING PERFORMANCE OF CRRT
# intensive care unit beds; # acute renal failure patients on intensive care unit/year; # dialysed patients on intensive care unit/year	Clear delineation of nursing responsibilities (e.g. CRRT set-up, initiation, monitoring, trouble shooting)
Dialysis services (non-CRRT dialysis facilities, nephrological support, renal nurses)	Physician's responsibilities and interaction
Intensive care unit staffing support (# intensivists, # part-time critical care nurses)	Formal and continuous instruction (lectures, 'hands-on' training, skill assessment, patient care experience)
Intensive care unit staff training support	Standardised and updated protocols
Level of intensive care unit (CBO terms)	Continuous identification of areas for improvement (e.g. new knowledge)

Appendix

UREA KINETIC MODELLING (UKM)

Mathematically derived biochemical concept of adequacy of intermittent dialysis in end-stage renal disease (ESRD), assuming:[35,36]

1. a steady-state process;
2. negligible urea generation during dialysis;
3. eubolic state (protein catabolic rate reflects daily protein intake);
4. absence of residual renal function;
5. with 'single-pool' kinetics, it is also assumed that urea is distributed in one well-mixed pool of volume.

Dialysis dose is expressed as Kt/V_{urea}, where:
K = diffusive and/or convective clearance, derived from the manufacturer's specifications of the dialyser clearance with actual delivered blood- and dialysate flow rates (ml/min);
t = time (min);
V_{urea} = urea distribution volume (L), for which different equations are available.

Intensifying dialysis by increasing Kt/V per dialysis session is consistently associated with lower morbidity and mortality in ESRD patients. It is suggested that the target dialysis dose, as assessed by UKM-derived single-pool Kt/V, should be increased from the traditional 1.0 to 1.2 and even 1.4 per session. No further improvement in outcome was noted beyond a Kt/V of 1.5.

Several simplified formulas are now available to evaluate Kt/V of intermittent treatment at the bedside. For several reasons calculation of Kt/V with CRRT is much easier (continuous nature, exact body clearance, linearity of treatment). Of note, Kt/V is only a marker of treatment efficiency of small molecules.[56-59]

Hypothesis: In the absence of other data, ARF patients should at least receive a similar dialysis intensity per dialysis session to that recommended for ESRD patients: Kt/V ≥1.2.[56-59]

Limitations of using UKM in ARF patients:[56-60]

- no steady-state situation;
- only crude approximation of variables (e.g. fluid overload, hypercatabolism);
- prescribed dialysis dose usually less than actually delivered;
- high(er) and variable urea generation rate (PCR 1.0 *vs.* >1.4 g/kg/day).

CLEARANCES WITH CONTINUOUS THERAPIES

CAVH/CVVH

Clearance, $K = Q_f \times C_f/C_{pi}$, where:
Q_f = ultrafiltration flow rate (ml/L);
C_f and C_{pi} = ultrafiltrate and prefilter plasma solute concentration (mmol/L).
Sieving coefficient, SC (C_f/C_{pi}) for urea = 1.0 so $C_f = C_{pi}$.

(1) $K_{urea} = Q_f$

CAVHD/CVVHD

$K = (Q_{do} \times C_{do}) - (Q_{di} \times C_{di})/ C_{pi}$, where:
Q_{di} and Q_{do} = dialysate inflow and outflow rate (ml/min);
C_{di} and C_{do} = solute concentration in inflowing and outflowing dialysate (mmol/L).
If $C_{di} = 0$ (e.g., urea) then $K = Q_{do} \times C_{do}/C_{pi}$.
If $Q_b >> Q_d$ almost complete (90-95%) small solute saturation of outflowing dialysate occurs[61] and therefore
$C_{do} = C_{pi}$,
$Q_{do} = Q_{di}$.

(2) $K_{urea} = Q_{do}$

CAVHDF/CVVHDF

$K = (Q_{di} \times C_{do}/C_{pi}) + (Q_f \times C_{do}/C_{pi})$.

(3) $K_{urea} = Q_{di} + Q_f = Q_{do}$

Kt/V with CRRT

Example (1): female patient 73 kg, CVVHDF; Q_d 1 l/h, Q_f 0.5 l/h.
K_{urea}= 1.5 l/h = 25 ml/min;
t = 1440 min;
V_{urea}= 0.58 x G = 42.3 L, where G is pre-ICU weight with added resuscitation fluid and estimated oedema component (kg).
Prescribed daily Kt/V_{urea} = 0.86 (weekly Kt/V 6.0).
Note: if G 85 kg then prescribed Kt/V_{urea} is lower: 0.72.
Note: if actual duration 18 hours (e.g., due to filter clotting), delivered dialysis dose is significantly lower: Kt/V_{urea} = 0.6.

Example (2): male patient 89 kg, CVVH; Q_f 3 l/h.
K_{urea} = 3 L/h = 50 ml/min;
t = 1440 min;
V_{urea} = 0.58 x G = 51.6 L.
Prescribed daily Kt/V_{urea} = 1.4 (weekly Kt/V 8.8).
Note: if actual duration 19 hours, delivered dialysis dose is lower: Kt/V_{urea} = 1.1.

UREA GENERATION RATE AND DIALYSIS DOSE

Another approach to determine the required dose makes use of the urea generation rate.[57]
For IHD with significant variations of urea concentrations, urea generation can not be readily assessed at the bedside. For continuous techniques, however, assuming that no significant alterations in urea concentrations occur during the day (i.e., after 48 to 72 hours of treatment), the rate of urea removal from the body can be determined as:

(4) R_{urea} (mmol/min) = C_{urea} (K_{urea} - Q_{net}) , where:
C_{urea} = serum urea concentration (mmol/L);
K_{urea} = urea clearance (ml/min);
Q_{net} (ml/min) = net rate of plasma volume reduction or the rate of ultrafiltration (Q_f) minus the rate of substitution fluid replacement (i.e. to correct for haemoconcentration).

At steady-state urea levels and assuming negligible residual renal function, urea generation rate equals urea removal rate (G_{urea} = R_{urea}) or:

(5) G_{urea} (mmol/min) = C_{urea} (K_{urea} - Q_{net})

The steady-state serum urea level (C_{ss}, mmol/l) equals the ratio between G_{urea} (mmol/day) and K_{urea} (L/day):

(6) C_{ss} = G_{urea}/K_{urea}

This equation can be inverted to determine the necessary clearance to obtain a certain 'goal' steady-state urea concentration (C_{goal}):

(7) K_{urea} = G_{urea}/C_{goal}

Example (3): patient 85 kg,3[d] of CVVH; Q_f 2 L/h; net ultrafiltration 200 ml/h.
K_{urea} = 2 L/h or 48 L/day;
C_{urea} = 20 mmol/L or 56 mg/dl ('steady-state');
Q_{net} = 200 ml/h or 4.8 L/day.
Current G_{urea} = 20(48-4.8) = 864 mmol/day (0.6 mmol/min) or 560(48-4.8) = 24 g/day
If desired serum urea level (C_{goal}) is 16 mmol/L and assuming stable urea generation, than required clearance is:
Desired K_{urea} = 864/16 = 54 L/day or 38 ml/min.
Knowledge of G_{urea} (g/day) permits the protein catabolic rate (PCR) to be derived :

(8) G_{urea} = 0.154 x PCR (g/day) - 1.7 or PCR = (G_{urea} + 1.7)/0.154

For this patient PCR = 24 + 1.7/0.154 = 167 g/day or 1.9 g/kg/day.
Note: all this implies a simplified approach to UKM using some crude approximations to provide a bedside method to determine the required dialysis dose. More sophisticated methods of UKM are beyond the scope of this article and the reader is referred to other articles on this subject.[57,58]

CAVH = continuous arteriovenous haemofiltration, CVVH = continuous venovenous haemofiltration, CAVHD = continuous arteriovenous haemodialysis, CVVHD = continuous venovenous haemodialysis, CAVHDF = continuous arteriovenous haemodiafiltration, CVVHDF = continuous venovenous haemodiafiltration.

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