Personal Opinion

Acute renal failure in the intensive care unit: adequacy of dialysis and the case for continuous therapies

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Introduction

The importance of delivering 'adequate' dialysis to patients with end-stage renal failure is widely recognized [1-4]. Despite this, little attention has been paid to the concept of 'adequacy of dialysis' in acute renal failure patients, particularly where it is likely to matter most: the intensive care unit. There are several explanations for this. Firstly, conventional forms of renal replacement with bioincompatible membranes are associated with so many technical and pathophysiological problems [5-9] that providing a treatment which controlled hyperkalaemia, limited oedema and acidosis, and lowered the blood urea concentration to 'acceptable' levels (similar to that of end-stage renal failure patients) was considered an achievement.

The heterogeneity of the patient population makes it difficult to evaluate the impact of different approaches to dialytic therapy. The variability in illness severity, the many confounding factors inherent to ICU therapy, and the small numbers obtained in single institutions, further aggravate the problem.

While the problems described above remain, there has been progress. There now are several safe, effective, and flexible forms of renal replacement therapy [10-12]. Illness severity scores have been developed and validated [13,14]. More accurate comparisons of populations of critically ill patients from the same or different ICUs are now possible. Ventilator techniques, haemodynamic manipulations, and approaches to the management of sepsis are increasingly performed according to consensus principles [15-18]. Finally, the ability to organize multicentre studies is increasing because of recent advances in telecommunications.

Despite such advances, any discussion of the concept of adequacy of dialysis in the critically ill with acute renal failure continues to have to rely on indirect information and on physiological principles. Such physiological principles are important in defining a priori the necessary properties of an adequate renal replacement therapy.

The first principle in the management of critically ill patients is that the degree of physiological derangement in the first 24 h after admission to the ICU determines prognosis to hospital discharge. This principle has been widely tested and demonstrated by multiple studies of illness severity scoring systems which evaluated it prospectively in thousands of ICU patients [13,14]. Early correction or prevention of any physiological derangements is, therefore, an important therapeutic goal in critical care medicine. Acute renal failure should be no exception. Renal replacement therapy is adequate if it is applied early to prevent hyperkalaemia, hyponatraemia, uraemia, acidosis, and pulmonary and peripheral oedema. In addition, such renal replacement therapy must not generate physiological derangements of its own.

The second principle is that the adequacy of any artificial organ support in the ICU is measured by how closely such support mimics the flexibility, versatility, and efficacy of the organ system it seeks to replace. This is true for mechanical ventilation, cardiac assist devices, and artificial oxygenators. It should be true of any artificial kidney.

The third principle is that the use of any artificial organ support should not delay the recovery from injury of the native organ.

The fourth principle is that, particularly in the setting of multisystem organ failure, any organ replacement therapy must have maximal biocompatibility.

Another observation is important in understanding adequacy of dialysis in the ICU. In critically ill patients, the time frame of renal support delivery is different from the ambulatory setting. While in the former situation it is important to deliver treatment over a relatively short period of time to achieve as normal a lifestyle as possible, in the latter, no such time constraints exist. What matters to the patient and the treating physician is that recovery should be speedy and outcome favourable.

Pathophysiological derangements and renal replacement

In critically ill patients, uraemia develops rapidly and is sustained by the need to administer full nutritional
support, and by a high degree of catabolism. Physiological adequacy of renal replacement in this setting implies early and steady control of uraemia.

It makes little physiological sense to delay treatment until the blood urea nitrogen concentration has risen above some scientifically untested and biologically magical number such as 100 or 120 mg/dl. It makes no sense at all to delay it until clinical manifestations of uraemia appear. One of the major reasons for the existence of ICUs is the maintenance of homeostasis. Acute renal failure should be no exception.

A delay in the dialytic treatment of acute renal failure means that acid–base derangements inevitably develop. Adequate dialysis means their early treatment or their prevention. If acetate is used as dialysate buffer during intermittent haemodialysis a number of therapy-induced acid–base derangements may be added to those already present in the critically ill patient [19]. If bicarbonate is used as a buffer the correction of metabolic acidosis is more physiological and predictable. However, because of the intermittent nature of treatment, metabolic acidosis will redevelop and re-balance serum electrolytes, total body water, and total body sodium. The 'conventional' indications for initiating dialytic treatment, when applied to critically ill patients, are physiologically suboptimal. Intermittent therapy is also physiologically undesirable. In fact, the concept that any artificial form of renal support should closely mimic the features of the native organ is an important criterion for the assessment of adequacy.

In the case of the kidney, replacement therapy should ideally provide steady control of uraemia, acid–base balance, serum electrolytes, total body water, and total body salt content. It should also provide an adequate stimulus to erythropoiesis, participate in the control of mineral balance and bone physiology, assist in the control of vascular tone and contribute to the elimination of a variety of middle molecules, including cytokines. It should do all this to a degree similar to that of the human kidney and provide such therapy 24 h a day. No such replacement therapy currently exists but any renal replacement that more closely approaches these goals can also be said to more closely approximate the concept of adequacy.

Of the techniques of renal replacement currently available (intermittent haemodialysis, peritoneal dialysis, and continuous haemofiltration/haemodiafiltration) only continuous forms offer renal replacement close to 24 h a day. Peritoneal dialysis, however, is often insufficient to achieve the small-molecular clearances and daily nitrogen extraction rates needed to optimally control uraemia [21]. Accordingly, supplemental haemodialytic therapy is often required. Modern techniques of haemofiltration, such as continuous arteriovenous haemodialfiltration (CAVHDF), continuous venovenous haemofiltration (CVVH), and continuous venovenous haemodiafiltration (CVVHD), on the other hand, have been shown to predictably and steadily control uraemia in critically ill patients irrespective of their nutritional therapy [22–24]. They also permit rapid and steady control of total body water and salt content according to clinical needs. Such ability to control extracellular fluids may have powerful positive implications in the management of patients with pulmonary oedema and the acute respiratory distress syndrome. In both of these conditions, the achievement of a negative fluid balance has been associated with improved outcome [25].

Standard intermittent haemodialysis fails this test of adequacy because of its episodic nature. The need to remove volume over a short period of time in patients who require at least 2 litres per day of intravenous fluids for nutritional and pharmacological purposes is frequently associated with hypotension. Often, in order to avoid such hypotension, fluid removal is suboptimal, resulting in the persistence of oedema [26].

A superficial analysis of continuous versus intermittent therapies would reveal that the latter achieve a significantly greater Kt/V, and must therefore offer superior control of uraemia. In fact, however, prescription and delivery of intermittent dialysis often differ even in end-stage renal failure patients [27,28] for reasons that vary from changes in actual therapy time to solute disequilibrium. The use of the Kt/V in comparing continuous therapy to intermittent therapy is misleading [29].

The rapid fall in blood urea nitrogen concentration during intermittent haemodialysis, the failure of extracirculatory body pools of urea to rapidly equilibrate, and the regional blood flow dependence of such re-equilibration (particularly in critically ill patients) mean that, for an equal Kt/V, a continuous form of therapy would remove vastly more urea nitrogen from the total body pool and accomplish much greater blood purification [29].

We recently, retrospectively analysed two cohorts of critically ill patients treated with either intermittent haemodialysis or CVVHD. Despite similar baseline values, after the first 24 h of treatment, CVVHD-treated patients had a significantly (P<0.0001) lower mean plasma urea concentration. This difference persisted throughout therapy. The mean urea level during intermittent haemodialysis was 35 mmol/l vs 23.4 mmol/l for CVVHD (P<0.0001).

Continuous therapies are rarely at work for the full 24 h a day as intended. The mean operational time per day has recently been reported at 21.8 h [30]. Despite
this, CAVHD and CVVHD offer high small-molecular clearances with a weekly urea nitrogen extraction averaging 196 g [30]. It would theoretically take approximately 7 h of intermittent haemodialysis each day to achieve such levels of blood purification. Intermittent haemodialysis would start to look remarkably like a continuous therapy!

In addition, the time-honoured criteria for the initiation of renal replacement therapy are associated with a physiologically unacceptable degrees of derangement from homeostasis in critically ill patients. More aggressive criteria appear physiologically superior. We offer a set of criteria (Table 1) that we believe more closely approximate the needs of critically ill patients.

If adequate renal replacement means early intervention, clearly, techniques associated with earlier application of replacement therapy are preferable. Once again available data support the use of continuous therapies [31]. The reasons for earlier intervention with haemofiltration include the ease of implementation within the ICU, the rapid preparation of the extracorporeal circuit, the lack of a need for surgical intervention, and the ability to start therapy at any time of day and night without concerns about personnel availability.

The haemodynamic consequences of renal replacement therapy constitute an important aspect of clinical 'adequacy'. The evidence that standard haemodialysis is associated with the induction of clinically important hypotension is overwhelming [32,33]. This hypotensive effect of haemodialysis was the prime stimulus to the development of continuous therapies. Such therapies have been shown to lead to outstanding haemodynamic stability [34-41], an important measure of dialytic adequacy in the ICU. It has been argued [42] that the use of several techniques (bicarbonate dialysis, high-sodium dialysate, cold dialysate, and the like) will result in the maintenance of haemodynamic stability during intermittent haemodialysis [43-45]. This may be true in chronic patients but remains to be proved in critically ill patients with acute renal failure. Current evidence continues to suggest that continuous therapies are superior.

Another important aspect of adequacy relates to the effect of therapy on renal recovery. There are no data available to prospectively compare the effects of standard haemodialysis and continuous therapies on the rate of renal recovery, although retrospective data suggest a trend in favour of continuous therapies [31]. Recent work indicates that renal injury occurs during and after intermittent haemodialysis and could result in deterioration of residual renal function.

This adverse effect may be independent of any decrease in blood pressure and simply relate to the use of bioincompatible membranes (cuprophane) as suggested by recent laboratory and clinical studies [46-50].

The issue of biocompatibility stretches beyond that of immunological dysfunction into the area of nutrition. Simple exposure (not dialysis) to cellulosic membranes may result in net protein catabolism [51] which continues for up to 9 h after exposure to the bioincompatible membrane. In addition, the dismal nitrogen balances achieved with standard approaches (low-protein diet and conventional haemodialysis) to the nutritional management of these patients [52] are unacceptable in view of current thinking in the area of nutrition for the critically ill [53-59] and acute renal failure [60,61]. With the use of continuous therapies and the increased administration of protein nitrogen, patients with critical illness can move progressively toward the nutritionally important goal of a near neutral nitrogen balance. Adequate protein supplementation does not only have positive repercussions on the maintenance of respiratory muscle mass and function [62,63] but is likely to have a favourable effect on renal recovery [64], another important aspect of clinical adequacy.

Unique issues of dialytic adequacy apply to neurosurgical and liver failure patients. Such patients have a high incidence of cerebral oedema. They require a dialytic therapy that can both deal with their extreme nutritional needs and prevent swings in intracranial pressure. There is strong evidence that intermittent haemodialysis induces measurable increases in intracerebral water [65]. Such changes are likely to aggravate cerebral oedema and pose a serious threat to the life of such patients. No changes in intracranial pressure or cerebral perfusion pressure occur during continuous therapies in high-risk patients [66-68]. In addition, continuous haemofiltration therapies have never been reported to induce the disequilibrium syndrome and may have further beneficial effects in liver failure patients by removing noxious middle molecules from the circulation [69].

### Table 1. Proposed criteria for the initiation of renal replacement therapy in critically ill patients

| 1. Oliguria (urinary output < 5 ml/kg per day) |
| 2. Anuria (no urinary output for > 12 h) |
| 3. Serum creatinine concentration > 600 μmol/l (> 6.7 mg/dl) |
| 4. Plasma urea concentration > 35 mmol/l (> 100 mg/dl) |
| 5. Hyperkalaemia (serum potassium concentration > 6.5 mmol/l) |
| 6. Pulmonary oedema not responsive to conventional therapy and diuretics |
| 7. Metabolic acidosis (pH < 7.2) |
| 8. Uraemic encephalopathy |
| 9. Uraemic pericarditis |
| 10. Uraemic neuropathy |

N.B. The presence of one of the above criteria is sufficient grounds for the initiation of renal replacement therapy in critically ill patient. The presence of two of these criteria makes renal replacement urgent and mandatory.

**Whither renal replacement therapy in the ICU?**

In the absence of prospective controlled randomized studies and accepted definitions of dialytic adequacy in acute renal failure in the ICU, one option is to continue to apply the therapies of the 1970s (standard cellulose-based intermittent haemodialysis) until such trials are performed and definitions become estab-
Acute renal failure in the ICU

This option is wrapped in the cloak of scientific righteousness. It ignores the fact, however, that if critical care physicians and nephrologists had steadfastly refused to implement therapies that had not been tested and proved to increase survival under prospective, controlled and randomized conditions, all intensive care units around the world would have to be dismantled and haemodialysis for acute renal failure stopped. More to the point, such widely embraced technologies as volume-cycled ventilators, the pulmonary artery catheter and the pulse oximeter have never been shown, in controlled trials, to affect patient outcome favourably.

A less scientifically 'pure' but more pragmatic option is likely to emerge: a progressive shift toward continuous therapies.

The trend in this direction is essentially complete in Australia and very strong in Europe where continuous haemofiltration techniques are now the most common form of renal replacement therapy in the ICU. The USA has lagged behind such trends for a number of complex medical and non-medical reasons. Other trends are also emerging. They include an earlier start of renal replacement therapy, a tighter control of blood urea concentration, and the provision of more aggressive, nitrogen rich, nutritional support.

Despite all the above changes, it seems unwise to move to continuous therapies by attrition and to other newer therapeutic options without some documentation of their impact. We need to test the wisdom of tentative definitions of dialytic adequacy and that of new criteria for the initiation of dialysis (see Table 1). We have a unique opportunity to tackle these issues in a more systematic way than has been possible for chronic haemodialysis, and we should not miss it.

References

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