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Should non-oliguric acute renal failure be treated with renal replacement therapy?

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INTRODUCTION

It is incontrovertible that renal replacement therapy (RRT) can be life-saving in oliguric acute renal failure (ARF). In non-oliguric ARF (where urine output exceeds 400 ml/day), the indications for RRT are much less clear, and many cases may be managed without RRT. This article examines the evidence for and against RRT in non-oliguric ARF.

In the pre-RRT era, many patients with oliguric ARF died of hyperkalaemia or fluid overload. With the advent of RRT, it quickly became apparent that these complications could be averted or treated by the initiation of RRT[1]. However, just as in chronic renal failure, precise indications for initiation of RRT have never been established[2]. In the modern era, it is conventional to initiate RRT when oliguria persists after correction of reversible factors such as hypovolaemia, hypoxia and hypotension. How long one should wait after these factors have been corrected remains uncertain, and for many physicians, the decision to initiate RRT depends on the perceived likelihood, or otherwise, that renal function will return rapidly, and the presence or absence of complications of ARF such as hyperkalaemia, fluid overload, or severe metabolic acidosis. No adequate randomised controlled trial (RCT) of initiation of dialysis in ARF has been performed but, in oliguric ARF, the 'time window' before onset of severe complications is usually short (of the order of 1 or 2 days) and it seems unlikely that the precise timing is crucial. In non-oliguric ARF, this 'time window' may be much longer, and many more patients may recover renal function without RRT, or die of causes unrelated to ARF. A careful evaluation of the indications for RRT is therefore much more important in non-oliguric ARF to avoid unnecessary use of RRT, with its attendant potential complications, and to avoid unnecessary transfer of patients to centres providing RRT.

Non-oliguric ARF has usually been regarded as having a better outcome than oliguric ARF[3,4]. One study challenges this view, demonstrating that higher urine output at first nephrologic consultation was associated with a worse outcome[5]. However, this study included only a subpopulation of intensive care patients subsequently treated with intermittent dialysis, so the generalisability of the findings is questionable. The recently developed RIFLE classification[6] includes reduced urine output as an indicator of increased severity, and in a recent large study of critically ill patients with ARF, urine output was among the most important variables associated with a reduced risk of in-hospital death[7]. In general, therefore, non-oliguric ARF should still be regarded as a less severe condition than oliguric ARF.

The epidemiology of ARF is changing. Many more patients are developing ARF in the context of multiple organ failure in the intensive care unit (ICU). Many ICUs initiate RRT without seeking the opinion of a nephrologist. Many of the patients are not oliguric at the time of initiation of RRT. In the absence of clear guidelines for initiation of RRT, wide variations in practice exist[8]. This is clearly unsatisfactory for the ICU community and also has adverse consequences

for the accuracy of information about the incidence and outcome of ARF, and the ability to estimate the resources required for the provision of expensive treatments for ARF. It may be that RRT is not necessary for some ICU patients who currently receive it; at the very least, this would be a waste of resources and, given the potential complications of RRT, it may also be harmful to some patients.

INDICATIONS FOR RRT IN ARF[2]

Current, 'conventional' major indications for RRT in ARF include:

Hyperkalaemia
Fluid overload
Severe metabolic acidosis (particularly in the presence of fluid overload)
Uraemic features such as vomiting, pericarditis and encephalopathy (unexplained by other illnesses)

Other possible indications include:

High serum urea concentration
Need for fluid removal to allow administration of nutritional fluids, inotropes and other drugs
Non-renal indications such as the treatment of sepsis
Treatment of poisoning with agents such as lithium, salicylate, methanol or ethylene glycol

These indications will be considered in turn for the particular context of non-oliguric ARF. Treatment of poisoning will not be considered as this is clearly indicated in some cases of non-oliguric ARF.

Hyperkalaemia

In the absence of drugs such as potassium sparing diuretics, angiotensin converting enzyme-inhibitors or angiotensin receptor blockers, severe hyperkalaemia is relatively rare in non-oliguric ARF[9]. Where it occurs, and cannot be easily controlled by medical treatment including correction of acidosis with sodium bicarbonate, it is appropriate to use RRT, probably in the form of intermittent haemodialysis, until it resolves.

Fluid overload

By definition, patients with non-oliguric ARF pass at least 400 ml of urine per day and many pass considerably more than this – indeed in patients with stable non-oliguric ARF, the daily urine output is usually around 2 litres for an adult, given the usual requirement to excrete about 600 mosmol/day of solutes. Taking into account insensible and other losses, this should allow the intake of at least 1 litre of fluid per day, and usually more than 2 litres per day, which is sufficient for the administration of nutrition and medications in the majority of cases. Patients who are volume overloaded, often as the result of injudicious administration of intravenous fluids as a response to rising urea and creatinine concentrations, may be treated with high-dose loop diuretics, which have been shown to be effective in increasing urine output in ARF, despite the lack of any overall effect on outcome in most studies[10-12]. Some studies have suggested an adverse effect of diuretics on outcome of ARF[13,14], and there are understandable concerns about the effects of very high-dose loop diuretics on auditory function, but high doses of loop diuretics in the licensed ranges have rarely been reported to cause any lasting harm.

Overall, fluid overload cannot be regarded as a major indication for RRT in a well-managed patient with non-oliguric ARF.

Severe metabolic acidosis

It is conventional opinion that lactic acidosis in the context of tissue hypoxia, due to shock for example, should *not* be corrected by administration of alkali, as this paradoxically worsens tissue acidosis. So, RRT, which effectively administers bicarbonate in this setting, is not indicated in patients with this type of lactic acidosis. Diabetic ketoacidosis is also not usually treated by alkali administration or RRT, and patients with acidosis related to poisoning are excluded from this review. What remains are patients with severe metabolic acidosis due primarily to renal failure. If it is deemed necessary for this acidosis to be treated, then most patients with non-oliguric ARF can safely receive intravenous sodium bicarbonate[2]. Those few who are also volume overloaded may represent a specific case for the initiation of RRT, but the risks should be carefully weighed against the putative benefits, given the absence of good evidence in this area.

Uraemic features such as vomiting, pericarditis and encephalopathy

When such features are unequivocally present then it would appear reasonable to start RRT. The incidence of uraemic features in non-oliguric ARF is not well documented but is not high, so they represent rare indications for RRT in non-oliguric ARF.

High serum urea concentration

There is no strong evidence for a threshold level of urea above which RRT is indicated in ARF, nor is there good evidence for any other marker of renal function. Widely quoted blood urea nitrogen concentration (BUN) thresholds of 80 or 100 mg/dl (29 or 36 mmol/l) are largely based on poorly-controlled or observational studies. A recent observational study showed a higher risk of death for patients starting RRT with a BUN >76 mg/dl than those starting RRT with a BUN below this value (RR 1.85)[15]. The median urine output at the start of RRT in each group was 424 and 423 ml/day respectively so just over half the patients were non-oliguric and there was no difference in urine output between the groups. However, because of the nature of the study, the authors concluded that these results could represent 'residual confounding by severity of illness'. They rightly state that they provide a rationale for an RCT to test whether a BUN threshold is justifiable.

Removal of fluid to allow administration of nutritional fluids, inotropes and other drugs

As has been stated earlier, with judicious fluid management it should be possible to administer appropriate nutritional fluids, inotropes and other drugs to patients with stable non-oliguric ARF as they usually pass at least 2 litres of urine per day. In patients with urine output between 400 ml and 2 litres per day, who require multiple intravenous drugs, there may be difficulty in administering the volume of fluid required for nutrition. However, as this is an unstable state, it is likely to persist only for a relatively short time, and such patients usually move fairly rapidly from this state into established oliguric ARF, stable non-oliguric ARF, renal recovery or death.

There is evidence that adequate enteral nutrition is beneficial in patients with critical illness in general but few data relates specifically to patients with ARF. There are proponents of 'permissive underfeeding' who claim that giving only 15-20 kcal/kg per day for up to the first 5 days of critical illness is beneficial[16] so it seems unlikely that a short period of underfeeding, while it becomes clear which course ARF is taking, would be harmful to most patients with non-oliguric ARF.

'Non-renal' indications for RRT

RRT has been proposed as a treatment for conditions such as sepsis, rhabdomyolysis, congestive heart failure, hepatic failure, tumour lysis syndrome, and adult respiratory distress syndrome, in the absence of ARF. A recent review concluded that there are currently insufficient data for RRT to be 'the standard of care for these conditions'[17].

IS THERE ANY OTHER EVIDENCE FOR 'EARLY-START' OF RRT IN ARF, WHICH MIGHT POINT TO A BENEFIT FOR RRT IN NON-OLIGURIC ARF?

There is a trend towards 'early start' of RRT in ARF[18], in the belief that it might improve outcome. Inevitably, this approach leads to larger numbers of patients with non-oliguric ARF being treated with RRT. This fashion seems to be particularly prevalent in the treatment of patients with ARF after cardiac surgery and a recent publication claimed to show benefit for an early start of RRT in this setting[19]. However, this study compared patients in two consecutive periods of 4 and 5 years and patients also differed in other important respects. Other studies claiming benefit from early initiation of RRT were conducted over 30 years ago and are generally small or not well controlled[20-22]. Just as in chronic renal failure[23], there is no compelling evidence in favour of a policy of early initiation of dialysis in ARF.

COULD RRT BE HARMFUL IN NONOLIGURIC ARF?

The main potential risks of RRT in ARF include:

Complications of central venous access
Cardiovascular instability
Anticoagulation
Membrane bio-incompatibility

In addition, specifically for non-oliguric ARF, there is the risk of conversion to oliguric ARF.

Complications of central venous access

Many patients with non-oliguric ARF will have multi--lumen central venous catheters (CVCs) in place, which can be used for RRT without the need for placement of additional CVCs. However, some will need the insertion of a CVC specifically for RRT, either because they do not have a CVC or because the CVC already in place is required for other purposes. The risk of CVC-related sepsis with its attendant considerable morbidity and mortality is related to both the number of CVCs and the duration of CVC use[24] so this is an important consideration when considering the overall risk-benefit of RRT for non-oliguric ARF.

Cardiovascular instability, Anticoagulation, Membrane bio-incompatibility

Cardiovascular instability during RRT is a particular concern in non-oliguric ARF as repeated hypotension/hypoperfusion episodes may lead to conversion from non-oliguric to oliguric ARF, with its attendant higher risks. However, in the modern era, with controlled ultrafiltration, biocompatible membranes, pure water and bicarbonate-based dialysate, cardiovascular instability is probably not a major factor in the analysis of risk-benefit of RRT for non-oliguric ARF. The relatively small risks of anticoagulation and membrane bio-incompatibility are also probably not of major significance.

Risk of conversion to oliguric ARF

Of more importance may be the potential for conversion of non-oliguric ARF to oliguric ARF as a consequence of the removal of water and solute by RRT. The failing kidney loses the ability to concentrate or dilute the urine. In stable ARF or CRF, this leads to the production of a fixed urine volume which represents the volume required for the obligatory excretion of a solute load of about 600 mosmols per day for an average adult human at a urine osmolality matching plasma osmolality (usually around 300 mosmol/L), that is about 2 litres per day. If water and solutes are removed by RRT then there is likely to be a consequent reduction in the amount of urine produced. This may exacerbate tubular obstruction, which is one of the injurious mechanisms in ARF[25].

CAN RCTs SHOWING BENEFIT OF HIGHER DOSES OF RRT IN ARF PROVIDE ANY RELEVANT INFORMATION?

Two major RCTs have shown significantly better outcomes in ARF with higher 'doses' of RRT[26,27]. In one[26], all the patients were oliguric at time of initiation of RRT but, in the other[27], only 46% were oliguric. It is tempting to regard the fact that a higher dose of RRT improved outcome in this study as indirect evidence that RRT is beneficial in non-oliguric ARF. However, because the study was not designed to answer this question and did not include a control group of non-oliguric patients treated without RRT, it cannot be interpreted in this way. For example, it is possible that RRT is harmful at all doses, but relatively less harmful at higher doses, in non-oliguric patients. It is interesting to note that oliguria was very significantly associated with an increased risk of death with an odds ratio of 3.02 ($p<0.007$) which was similar to the odds ratios for lower dialysis dose (OR 3.92) and the presence of sepsis (OR 3.27).

CONCLUSIONS

There is no good evidence for initiating RRT in non-oliguric ARF simply because of worsening biochemistry and there is no 'threshold' for serum urea or BUN at which RRT should be started. In properly-managed patients with non-oliguric ARF, RRT should only very rarely be indicated for hyperkalaemia or volume overload. Most patients should be able to receive adequate nutrition during non-oliguric ARF treated without RRT. If this is not possible, then it is reassuring that undernutrition for a few days has not been shown to be harmful. Loop diuretics may be used if necessary but very high doses should be avoided.

There is a need for further research in this area. An appropriate RCT would randomise patients who satisfy criteria for non-oliguric ARF, including thresholds of renal function deterioration, into groups to be treated with or without RRT (unless complications arise). Outcomes such as survival should be determined from the date of randomisation to avoid lead time bias. The study should include a cost-effectiveness analysis as RRT incurs significant extra expense, even in critically ill patients. The study would have to be adequately powered to detect a meaningful difference in outcomes.

Given the absence of adequate RCT evidence, and given that RRT is often initiated in the ICU by non-nephrologists, clearer guidelines are required for the treatment of non-oliguric ARF. These should emphasise the importance of accurate management of fluid and electrolyte balance and should discourage the use of RRT in the majority of patients.

Conflicts of interest. None declared.

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