

## Acute Dialysis Quality Initiative

### 2<sup>nd</sup> International Consensus Conference

#### REVIEWS

*ADQI workgroup reports were sent to leading experts who served as external reviewers.*

*Reviewers were asked to provide reviews and editorial comment on the workgroup reports.*

*Martine Leblanc*

### Workgroup 3: Physiological Endpoints for Acute Renal Failure Studies

#### **GFR markers**

Among newer GFR markers in ARF, serum cystatin C deserves evaluation since it has been shown more sensitive and accurate than serum creatinine in several settings, but has not been validated as a GFR indicator in ARF (1-2). Another endogenous marker,  $\beta_2$ -microglobulin, has been suggested as a GFR estimate (3). Measuring tubular enzymuria could facilitate the early detection of renal impairment at low costs (4). Future research is certainly required in this area.

#### **Renal blood flow**

Although a decreased renal perfusion has been directly related to ARF development only in animals, it has been related at least indirectly in humans (vasopressors and fluid resuscitation). Despite no controlled human data to define the renal effects of norepinephrine, many series show a positive impact on GFR and urine output (5-6). Renal physiology also teaches the importance of renal flow as a main determinant of renal function.

#### **Urine markers**

Urine sodium and fractional excretion of sodium ( $FE_{Na}$ ) are useful indices to help distinguish a functional from an installed ATN (7).  $FE_{urea}$  becomes a more sensitive and specific index in presence of diuretics. On urine microscopy, finding dirty brown casts (oftentimes abundant) is strongly indicative of ATN.

#### **Urine output**

Diuretics have generally been found detrimental in animal models of ARF. In human, loop diuretics (as well as low-dose dopamine) may facilitate ARF management, but the available evidence does not support routine use (8). A recent study showed worse outcome in ARF patients receiving diuretics (9). The better prognostic of non-oliguric ARF is attributable to spontaneous forms rather than to those for which diuresis is forced.

### **Serum markers of RRT**

Delivering a larger dose of renal replacement seems to have a positive impact on ARF outcome. It is prudent to prescribe at the very least to ARF patients the minimum dialysis dose consistent with adequate therapy in ESRD. The DOQI guidelines recommend for ESRD a delivered single-pool Kt/V of 1.2 (equivalent to a 65% URR) per hemodialysis session thrice weekly. To avoid falling below the minimum, prescription should aim for a single-pool Kt/V of 1.3 (URR of 70%). No firm recommendation on a double-pool Kt/V to achieve in ESRD has been released so far despite the recent HEMO study (10). Since regional flows and compartment effects might be even more confounding in ARF, and because continuous and longer intermittent treatments (EDD/SLED) are performed for ARF, single-pool kinetics remain more appropriate (11). "Equivalent urea clearance" is an appealing and practical concept in the ICU (e.g. useful for medication dosing).

Ronco et al. showed that CVVH with an ultrafiltration of 35 ml/kg/h (in post-dilution) was associated with a better outcome. The same ultrafiltration performed in pre-dilution leads to reductions in solute clearances (12); this factor is to consider to match doses rather than volume exchanges. CRRT can deliver higher cumulative solute removal than conventional hemodialysis, but daily/longer treatments such as EDD/SLED can achieve quite impressive epuration. However, the spectrum of molecules removed, although poorly defined, might be different between convective and mainly diffusive methods. Should we have an index of middle molecule removal?

### **Non-renal markers of RRT**

Many factors may confound the assessment of bleeding parameters in the ICU. Encephalopathy is oftentimes multifactorial, and rarely only due to the underlying uremic milieu. Would the ability to remove extra fluid/edema, and restore a normal fluid balance be a useful clinical marker of the the benefits of renal replacement?

### **References**

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### Workgroup 3: Physiological Endpoints for Acute Renal Failure Studies

No treatment has ever been unequivocally shown to improve outcome in acute renal failure (ARF). Therefore from a therapeutic standpoint we are still at the stage of testing candidate treatments in phase two studies of ARF, rather than confirming early reports of efficacy in large multicenter phase three trials. Couple this with the fact that we do not know when it is best to start dialytic therapy, nor do we know how much, of what type, for how long and in what manner to administer dialysis, and we can see why we have made so little progress in the past 30 years. We have been unable to describe either the disease or its treatment, and we cannot agree even on when it is present. The Acute Dialysis Quality Initiative (1) draws together those with an interest in this problem in order to approach ARF with an organized plan of investigation. Consensus will be reached on definitions, research priorities and a rational scientific approach to the problem using the principles of evidence based medicine. In particular, this workgroup addresses the place of physiological surrogate endpoints in ARF trials.

The principal objective in clinical studies of ARF is to discover treatments that might improve outcomes in three patient domains: mortality, morbidity and cost of delivered care (2). The majority of the studies published in the ARF literature have not been sufficiently powerful to detect a real difference between treatment groups, nor to safely exclude the chance of such a difference. Most reports have focused on the use of surrogate endpoints because they are easier to measure, generally require fewer patients in order to achieve a P value of less than 0.05 (and thus increase the chance of subsequent publication) and have substantial precedent in the literature. However, responsible clinicians wish to know which treatments will reduce the three clinically important endpoints above. Given this apparent paradox, how can the continued use of physiological surrogates as endpoints in clinical trials be justified?

Large multicenter phase three clinical trials are very expensive to organize and perform. It is therefore irresponsible to commit significant resources to such a project unless there is a good chance that a treatment will be effective. We have very few candidates for such a trial in ARF, and it is no surprise therefore that the first of these trials will focus on a non-pharmacological treatment problem which all agree needs to be addressed— namely how much of what type of dialysis is best. Suitable candidates for coordinated large phase three trials will come from carefully planned phase two trials of candidate therapies. These studies will not be powerful enough to detect a difference in clinical endpoints, but should be able to detect important changes in surrogates. Dr Murray and colleagues elegantly summarize the question of which endpoints to measure in this workgroup report.

Such surrogate endpoints should be clinically useful in their own right, should allow real time tracking of renal function, be easily standardized across investigational centers, be objective and lastly be easily measured. No such surrogate physiological endpoint currently exists. Of those that do, the two hour creatinine clearance estimation probably represents our best effort, since it allows semi-real time GFR

estimation, can be trended, allows for a changing baseline and is easy to standardize across sites. In concert with an absolute serum creatinine value it is more informative since this information provides an estimate of the starting point. Other markers of clearance such as the housekeeping protein cystatin C, (3) and exogenously administered Iohexol (4) are promising and should certainly be investigated for future use.

We assume that maintenance of the usually high flow of blood to the kidney is a desirable endpoint in the management of ARF. This may be true (we do not know) in the case of ischemic renal disease, but it may worsen nephrotoxic renal disease if the end result is delivery of more toxin to the relevant biosite. We have very poor tools with which to study renal blood flow clinically, and this should be a priority for future research. BOLD MRI, tissue harmonic Doppler ultrasound and PET scanning all offer possibilities and studies of the utility of these techniques are to be welcomed. It is probable that maintenance of renal perfusion is important during periods of potential or actual renal compromise, and that when we have adequate tools with which to study this issue we will be able to work out the true relationship between renal blood flow, glomerular perfusion pressure, renal oxygen delivery, urine output and solute clearance for example. We still do not know what the “right” mean arterial pressure is for example, nor do we know whether avoidance of high central venous pressures in an attempt to improve renal perfusion pressure is advantageous or not. These issues are relevant when considering the type and amount of fluid resuscitation to administer.

Before we can study the efficacy of a treatment in a given disease state, we need to be able to control the dose, the schedule and the manner in which the treatment is applied. In terms of endpoints for dialytic dose estimation, measurement of solute clearance is currently best achieved using calculation of equivalent renal urea clearance in the ARF setting, since it permits analysis of dialytic dose independently of type of dialysis or administration schedule. Once consensus is achieved on dose measurement, we may then begin to study schedule and type of dialysis.

Lastly, future studies should not ignore the effect of genetic variation in patients with ARF. Certain genotypes are known to segregate with renal (5) and other critical care (6) disease phenotypes, and there is every reason to suspect that this will be the case in both susceptibility to ARF, response to treatment, and also in long-term outcome. Gene-disease association studies bring their own technical complexities, such as the need for meticulous statistical analysis (7-8) to control for multiple comparisons, but will provide additional insight into the observed variability of the clinical syndrome of acute renal failure.

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