

# Acute Dialysis Quality Initiative

## Workgroup 2

### Selection of patients for acute extracorporeal renal support in general and CRRT in particular

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## Introduction

Practice patterns for CRRT are extremely variable. Broadly speaking, CRRT is almost exclusively applied to ICU patients. However, beyond this, there are large variations in practice. The evidence for this comes from two patient-level epidemiologic studies,<sup>1,2</sup> one US physician survey of self-reported practice patterns,<sup>3</sup> and several large case series.<sup>4,5</sup> In 1996, Mehta surveyed 2000 nephrologists in the US and found that less than 25% of patients with ARF were treated with CRRT.<sup>3</sup> The use of CRRT is much more common in Europe, although its use is highly variable between centers, while CRRT is the predominant (>90%) choice in Australia.<sup>2</sup>

In general, it appears that the decision to use CRRT is affected by strongly held physician beliefs as well as a number of patient and organizational characteristics. Patient characteristics may include age, race, illness acuity, and co-morbidities. Organizational characteristics may include country, type of institution, type of ICU, type of physician or insurance provider, and perceived cost of therapy. However, the strength of association of these characteristics with decision to use CRRT is not fully understood. Further large epidemiological studies are needed to establish which factors are most important in determining practice patterns, and whether there are important access to care issues.

## Patient selection for acute extracorporeal renal support in general

### **What are the indications for renal replacement therapy in patients with ARF?**

An operative definition of severe acute renal failure (ARF) in which renal replacement therapy is appropriate is needed to address this question. For the purpose of this document, a patient has ARF requiring renal support or replacement therapy when he or she has an acute fall of GFR and has developed, or is at risk of, clinically significant solute imbalance/toxicity or volume overload. The standard of care for

such patients is dialytic therapy. This standard has been widespread in the developed world for 40 years. As with penicillin for pneumococcal pneumonia, evidence for the benefit of acute dialysis is based on the known highly lethal outcome of untreated ARF before the availability of dialysis, early case series,<sup>6</sup> and experience in end stage renal failure. However, information on long-term follow-up is limited.<sup>7</sup> The major trend in practice that may be emerging is to commence therapy earlier.

Summary: Dialysis improves short-term survival in severe ARF (Level III evidence, but unlikely that higher level studies will ever be conducted). There is no consensus on the exact indications for renal replacement therapy. Recommendations for clinical practice: Patients with severe ARF should be treated with acute renal replacement therapy (Grade D). Recommendations for future research: Epidemiological studies to document long-term outcomes (survival, quality of life, renal function, and need for chronic renal replacement) and the prognostic factors for these outcomes, in patients who developed severe ARF.

### **When should acute extracorporeal renal support be initiated?**

The timing of the intervention may have a profound effect on outcome. There is no accepted definition of what “timing of initiation” means (time from admission to hospital? ...from admission to ICU? ...from time of acute insult?), and there is wide variation in clinical practice.<sup>2,8-10</sup> A single retrospective, non-randomized cohort study used BUN as a surrogate of “timing of intervention”.<sup>8</sup> In this study from a large trauma center, patients who were started on Renal Replacement Therapy (RRT) at a mean BUN of 42.6 mg/dl had a 39% survival compared to a 20% survival in those who started RRT at a mean BUN of 94.5 mg/dl. However, because the BUN may reflect many factors other than time of initiation, this approach is likely to be seriously flawed. No randomized controlled trials have specifically addressed the effect of timing of intervention on outcome.

Summary: There are significant differences in the timing of intervention using BUN, creatinine, or urine output with up to two-fold differences in their reported values at the time of initiation of RRT among series.<sup>2,8-10</sup> Recommendations for clinical practice: No recommendations on the timing of initiation of renal replacement therapy are possible beyond those defined by the conventional criteria that apply to chronic renal failure patients (diuretic unresponsive pulmonary edema, hyperkalemia, uremic complications, etc.) (Grade D). However, since the consequences of these complications are likely to be more severe for critically ill patients with ARF, renal replacement therapy should usually begin prior to their development (Grade E). Recommendations for future research: Observational studies of the early natural history of ARF are needed. An ideal population would be one in which the timing of the insult is easily identifiable (e.g., ruptured AAA or major trauma). A trial would feature careful “phenotyping” of patients using several markers at many time points, and study the relation of such markers to timing and course. If differences in timing are associated with differences in outcome, a subsequent randomized controlled trial of the effect of alternative initiation times on outcome should be conducted.

## Patient selection for CRRT

### **Are there non-ARF indications for CRRT?**

There are no established non-ARF indications for CRRT. There are several case series of CRRT use in a variety of non-ARF conditions including intoxication with dialyzable/filterable drugs or toxins,<sup>11;12</sup> cardiac failure,<sup>13;14</sup> ARDS,<sup>15</sup> and pediatric cardiac surgery<sup>16</sup> or sepsis and systemic inflammation.<sup>5</sup> The two common rationales for use of CRRT in non-ARF indications are continuous tightly-controlled adjustment of volume balance and removal of biologically active, and presumably deleterious, substances

Recommendations for clinical practice: There is insufficient evidence to recommend the use of CRRT for non-ARF indications outside clinical investigation (Grade E). Recommendations for future research: We recommend no further observational case series on the above indications. Rather, we recommend further evaluation by randomized controlled trials.

### **What patient and/or environmental characteristics make CRRT desirable?**

This is the most pressing clinical question regarding the use of CRRT. Specifically, does CRRT offer an important survival advantage over IHD in the management of ARF? There are only three prospective randomized trials comparing CRRT to other forms of renal replacement and none are published except in abstract form.<sup>17-19</sup> In addition, there are several observational studies.<sup>20-29</sup> Most observational studies have reported improved survival with CRRT, even though CRRT patients were often sicker at baseline.<sup>20-22</sup> However, some reported worse outcomes.<sup>27;29</sup> In the largest RCT (n= 166) to date, there was no difference in outcome but there were significant baseline differences in severity of illness between groups, making comparison difficult.<sup>18</sup> There are small controlled randomized trials suggesting that, compared to IHD, CRRT has a beneficial physiologic effect on cerebral edema in ICU patients with ARF when compared to intermittent therapy.<sup>30-32</sup>

Summary: In keeping with the rationale for its development, CRRT use has generally been reported in severely ill ICU patients. In particular, CRRT is selected for patients with ARF who have hemodynamic instability and for patients in whom continuous removal of volume or toxic substances is thought desirable. The latter might include patients with ARF who also have septic shock, ARDS, burns, or conditions with or, at risk for, cerebral edema. Recommendations for clinical practice: No firm overall recommendations for patient selection can be made. However, CRRT use may be advantageous in the management of ICU patients with ARF (Grade E). CRRT is recommended over IHD for patients with ARF who have, or are at risk for, cerebral edema (Grade C). Recommendations for future research: A large prospective RCT of CRRT vs. IHD in ICU patients with ARF is needed. This study should feature careful "phenotyping" of patients, stratified randomization of key sub-groups (e.g., severity of illness), standardization of dialytic treatment (including dose and membrane), and co-interventions (including drug use, nutrition, and non-renal organ support). Of note, the consistent difference in baseline severity of illness, where CRRT patients

are sicker, raises concern that physicians involved in the study of CRRT may be reluctant to randomize sicker patients to IHD. Thus, analogous to evaluation of the pulmonary artery catheter, significant dedication to developing investigator equipoise and rigorous adherence to study design will be essential.

**When and how (transition to different modality or cessation of treatment) should a course of acute extracorporeal renal support including CRRT be stopped?**

Whereas weaning from mechanical ventilation is a crucial aspect of pulmonary support that has been extensively investigated, it is unfortunate that no such studies exist for renal replacement in general, and CRRT in particular. It is likely that appropriate cessation (which includes both when and how) of CRRT is critical to clinical and economic outcomes. No studies have specifically addressed these issues. Personal experience and anecdotal information suggest that the decision to stop a course of treatment or to change modality of treatment is influenced by a variety of factors including patient characteristics (hemodynamic status, urine output, volume status) and logistic characteristics (staff availability, cost, circuit clotting).

Recommendations for clinical practice: Renal replacement therapy should continue as long as the criteria defining severe ARF are present (Grade E). No further recommendations can be made. Recommendations for future studies: 1. A survey of physician and nurse opinion about current practice patterns; 2. observational studies of the clinical decision making process in relation to stopping or transition to a different modality; 3. Observational studies of physiologic status at time of cessation or transition; and 4. study of the consequence of physiologic variations on outcome.

**Should CRRT be available at all institutions caring for critically ill patients with ARF?**

There is no information regarding the need for and the effect of CRRT availability. CRRT availability varies widely and depends on logistic factors, availability of resources and expertise as well as perceived need. This information is based upon epidemiological surveys, case series and personal experience (level IV-V evidence). Recommendations for clinical practice: Because there is insufficient evidence for the effectiveness of CRRT over IHD in large classes of patients with ARF, no firm recommendations can be made.

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