The first international consensus conference on continuous renal replacement therapy

JOHN A. KELLUM, RAVIDRA L. MEHTA, DEREK C. ANGUS, PAUL PALEVSKY, and CLAUDIO RONCO, for the ADQI WORKGROUP

Departments of Critical Care Medicine and Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA; Department of Medicine, University of California, San Diego, CA; Veterans Administration Pittsburgh Healthcare System, Pittsburgh, PA; Department of Nephrology, St. Bortolo Hospital, Vicenza, Italy; and Renal Research Institute, New York, NY, USA

The first international consensus conference on continuous renal replacement therapy.

Background. Management of acute renal failure (ARF) in the critically ill is extremely variable and there are no published standards for the provision of renal replacement therapy in this population. We sought to review the available evidence, make evidence-based practice recommendations, and delineate key questions for future study.

Methods. We undertook an evidence-based review of the literature on continuous renal replacement therapy (CRRT) using MEDLINE searches. We determined a list of key questions and convened a 2-day consensus conference to develop summary statements via a series of alternating breakout and plenary sessions. In these sessions, we identified supporting evidence and generated practice guidelines and/or directions for future research.

Results. Of the 46 questions considered, we found consensus for 20. We found inadequate evidence for 21 questions and for the remaining five we found data but no consensus. Full versions of workgroup findings are available on the Internet at www.ADQI.net.

Conclusions. Despite limited data, broad areas of consensus exist for use of CRRT and guideline development appears feasible. Equally broad areas of disagreement also exist and additional basic and applied research in acute renal failure is needed.

Acute renal failure (ARF) is a common complication of critical illness [1, 2] and mortality remains over 50%. Despite several advances in treatment, consensus over the optimal way to deliver care does not exist. Today, approximately one fourth of all patients in the United States with ARF are treated with continuous renal replacement therapy (CRRT) [3] and use of this therapy is increasing worldwide. However, there are no standard guidelines for the application of CRRT and practice patterns vary widely between individual centers. Results from recent clinical trials on selection of dialysis membranes [4–7] and dialysis dose [8, 9] provide important evidence to guide therapy. Yet important questions remain unanswered. Finally, the method by which acute organ support is provided can have a profound effect on patient mortality (e.g., transfusion thresholds [10] and ventilator management [11]) supporting the need to identify practice standards and key research questions. The purpose of this consensus conference was to review the available evidence regarding the optimal provision of CRRT, make evidence-based practice recommendations, and delineate key questions for future study.

METHODS

Our consensus process relied on evidence where available and, in the absence of evidence, consensus expert opinion where possible [12]. This combined approach has led previously to important practice guidelines with wide adoption into clinical practice [13]. In contrast, expert opinion alone can ignore important evidence while evidence-based reviews can be conceptually flawed without expert opinion [14]. We conducted the consensus process in three stages: (1) pre-conference, (2) conference, and (3) post-conference.

Prior to the conference, we identified seven topics of CRRT practice (Table 1). We selected these topics based on (1) the prevalence of the associated clinical problem; (2) known or suspected variation in clinical practice; (3) potential importance for clinical outcome; (4) potential for development of evidence-based medicine guidelines; and (5) availability of scientific evidence. For each topic, we outlined a preliminary set of key questions. We then invited an international panel, predominantly from the
fields of nephrology and intensive care, based on their expertise in CRRT. Panelists were assigned to three-person workgroups, with each workgroup addressing one key topic. Each workgroup conducted literature searches related to their topic questions via MEDLINE, bibliographies of review articles, and participants’ files. Searches were limited to English language articles. However, articles written in other languages were used when identified by workgroup members. During this stage, the scope of the conference was also defined and some topics were excluded (Table 1).

We conducted a 2-day conference in August 2000, in New York, NY. We developed summary statements through a series of alternating breakout and plenary sessions. In each breakout session, the workgroups refined the key questions, identified the supporting evidence, and generated practice guidelines and/or directions for future research as appropriate. We classified evidence by levels according to evidence-based medicine methodology (Table 2) and provided qualitative commentary as necessary. However, we deferred critical appraisal of individual studies to a later stage. We considered physiologic, clinical, and economic outcomes separately. We generated future research questions by identifying deficiencies in the literature and debating whether more evidence was necessary. Where possible, we also considered pertinent study design issues. Workgroup members presented their findings during the plenary sessions, rotating responsibility for presenting to ensure full participation. The workgroups then revised their drafts as needed until a final version was agreed upon.

A writing committee assembled the individual reports from the workgroups and each report was edited to conform to a uniform style and for length. The final reports were mailed to each participant for comment and revision.

**RESULTS**

We considered a total of 46 questions and our results are summarized in Table 3. We report a summary of each individual workgroup below. Full versions of workgroup findings are available on the Internet at www.ADQI.net.

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**Table 1.** Topics covered and not covered in the consensus conference

<table>
<thead>
<tr>
<th>Topics Included</th>
<th>Topics Excluded</th>
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<tbody>
<tr>
<td>Definitions/nomenclature</td>
<td>Indications for renal replacement therapy</td>
</tr>
<tr>
<td>Patient selection for CRRT</td>
<td>Costs</td>
</tr>
<tr>
<td>Solute control in CRRT</td>
<td>Drug dosing</td>
</tr>
<tr>
<td>Membranes</td>
<td>Blood purification in non-renal failure conditions</td>
</tr>
<tr>
<td>Operational characteristics</td>
<td>Withholding and withdrawing dialysis</td>
</tr>
<tr>
<td>Access and anticoagulation</td>
<td></td>
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<tr>
<td>Fluid composition and management</td>
<td></td>
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</tbody>
</table>

**Table 2.** Evidence-based medicine levels and grades

<table>
<thead>
<tr>
<th>Levels of Evidence</th>
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</thead>
<tbody>
<tr>
<td>Level I: Randomized trials with low false positive (α) and low false negative (β) error (i.e., high power)</td>
</tr>
<tr>
<td>Level II: Randomized trials with high α error or low power</td>
</tr>
<tr>
<td>Level III: Non-randomized concurrent cohort studies</td>
</tr>
<tr>
<td>Level IV: Non-randomized historic cohort studies</td>
</tr>
<tr>
<td>Level V: Case series, case reports, expert opinion</td>
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</tbody>
</table>

**Grades of Recommendations**

| Grade A: Supported by at least two level I studies                                   |
| Grade B: Supported by only one level I study                                         |
| Grade C: Supported level II studies                                                  |
| Grade D: Supported by at least one level III study                                   |
| Grade E: Supported by only level IV or V studies                                     |

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**Assessment of consensus and recommendations for clinical practice**

*Selection of patients for CRRT.* Dialysis improves short-term survival in severe ARF (level III evidence, but it is unlikely that higher level studies will ever be conducted) [15, 16]. Although there is no consensus on the exact indications for renal replacement therapy, there is consensus that patients with severe ARF should be treated with acute renal replacement therapy (grade D). There is significant variation in the timing of intervention using blood urea nitrogen (BUN), creatinine, or urine output with up to twofold differences in the reported values of these variables at the time of initiation of renal replacement therapy [1, 6, 17, 18]. Thus, 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). Renal replacement therapy should continue as long as the criteria defining severe ARF are present (grade E). No further recommendations as to discontinuation of renal replacement therapy can be made.

In keeping with the rationale for its development, CRRT use has generally been reported in severely ill patients in the intensive care unit. In particular, CRRT is most often 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, acute respiratory distress syndrome (ARDS), burns, or conditions with or, at risk for, cerebral edema. In the absence of definitive evidence comparing CRRT to intermittent hemodialysis, no firm overall recommendations for patient selection can be made. However, CRRT use may be advantageous in the man-
agement of intensive care unit patients with ARF (grade E) and CRRT is recommended over intermittent hemo-
dialysis for patients with ARF who have, or are at risk for, cerebral edema (grade C) [19–21]. There is insufficient
evidence to recommend the use of CRRT for non-ARF indications outside clinical investigation (grade E).

Solute control (treatment dose). The exact identity and
relative importance of all uremic toxins is unknown.
Despite many decades of research, no single substance
or group of substances have been directly related to
adverse effects. Urea is only a marker substance for
the clinical condition known as uremia [22]. Thus, it is
inappropriate to equate the clinical diagnosis of uremia
with isolated blood levels of urea or creatinine (grade
C). Absolute levels of urea and creatinine are difficult
to interpret as both high and low levels may indicate
poor outcome [23]. The rates of change of urea or creati-
nine levels may better reflect severity of renal failure
(i.e., rapid increases suggesting severe renal dysfunction)
[24–27]. Accordingly, there is broad consensus that se-
rum levels of urea or creatinine should be interpreted in
the context of their rates of change over time (grade C).
Similarly, during treatment, clearance of various marker
substances appears to be the best measurement of ther-
apy dose since mass transfer must be interpreted with
steady-state blood levels to reflect clearance. Fractional
clearance may be even better. Furthermore, the use of
blood solute concentrations to assess clearance must con-
sider solute generation rates [28–30]. Therefore, marker
clearance should be used as the primary basis for CRRT
dosing (grade C), excepting that during pure filtration,
dose is proportional to ultrafiltration rate. Methods for
measuring and expressing CRRT clearance vary widely
in clinical practice and include clearance (K) times dial-
ysis duration (t) divided by the volume of distribution
(V) to yield Kt/V (fractional clearance), or divided by
the body surface area (K/SA). Other measures include
the solute removal index (SRI), or simply ultrafiltration
rate for hemofiltration. There is no consensus as to which
technique should be used in all clinical situations. Emer-
ing evidence suggests the importance of using standard-
ized Kt/V or equivalent renal clearance to compare dis-
parate therapies and different frequencies of treatment
[31]. For pure hemofiltration the ultrafiltration rate and
sieving coefficient for a marker can be used to measure
clearance. For other modalities, dialysate plus ultrafil-
trate flow and concentration are required to measure
clearance (grade C). Clearance is typically factored for
surface area, similar to kidney clearance or for urea
distribution volume similar to chronic dialysis (grade E).

Table 3. Summary of findings

<table>
<thead>
<tr>
<th>State of Consensus</th>
<th>Number of Questions</th>
<th>Action/Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consensus exists</td>
<td>20</td>
<td>EBM process*</td>
</tr>
<tr>
<td>Data available but no consensus</td>
<td>5</td>
<td>Statistical meta-analysis</td>
</tr>
<tr>
<td>Consensus exists</td>
<td>1. Cellulose-based vs. synthetics membranes</td>
<td>Systematic review</td>
</tr>
<tr>
<td></td>
<td>2. CRRT vs. intermittent hemodialysis</td>
<td>Guideline development (further study in IHD)</td>
</tr>
<tr>
<td></td>
<td>3. Dialysis dose</td>
<td>Guideline development</td>
</tr>
<tr>
<td></td>
<td>4. Catheter design and location</td>
<td>Guideline development</td>
</tr>
<tr>
<td></td>
<td>5. Catheter insertion</td>
<td>Future research objectives outlined</td>
</tr>
</tbody>
</table>

* A formal evidence-based medicine (EBM) process was not undertaken as part of the consensus conference. However, in five key areas we determined that sufficient evidence exists to warrant such a process. In the case of dialysis membranes, a statistical meta-analysis was recommended, while in the area of catheter design and insertion site, a comprehensive systematic review will be necessary to integrate the data on safety, patency, and recirculation. With regard to dialysis dose and catheter placement, sufficient data exist to establish formal guidelines, although some further study is still required; while, in the case of continuous (CRRT) vs. intermittent therapy, an EBM process will be useful in designing a definitive trial.

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the use of synthetic in favor of cellulose-based membranes is appropriate [4–7, 34, 35] (grade B). Although not demonstrated conclusively to be of benefit, transmembrane pressure monitoring and measurement of urea sieving coefficient, urea equilibration ratio, and filtration fraction may all be employed to assess filter function (grade E). Filter choice requires special consideration for proper implementation of certain modalities, such as high-volume hemofiltration, slow low-efficiency dialysis (SLED), and extended daily dialysis (EDD). In general we recommend the use of filters with higher water permeability for high-volume hemofiltration and dialyzers with large surface areas for SLED and EDD (grade E). Finally, hypersensitivity reactions may occur with certain types of filters. However, there is insufficient evidence to produce specific recommendations regarding this issue.

Operational characteristics. Based on the available data, no recommendations regarding the use of predominantly convective therapies (i.e., CVVH) as compared to diffusive therapies [i.e., continuous venovenous hemodialysis CVVHD]) can be made. Efficiency of removal of low-molecular-weight solutes is similar with convection and diffusion. Efficiency of middle- and high-molecular-weight solute removal is greater with convective therapies; however, there is no evidence that this enhanced solute removal influences clinical outcomes. The clinical relevance of differences in solute adsorption is also unknown. Venovenous therapies are preferred to arteriovenous therapies due to the ability to provide higher rates of solute clearance [36] and a reduced risk of complications [36, 37] (level III). Arteriovenous therapies should be reserved for settings in which venovenous therapy cannot be provided due to the absence of adequate equipment or personnel (grade D). There is no consensus regarding the appropriate qualifications for personnel performing CRRT other than demonstration of competency. Specifically, there are no data to support the exclusive performance of these therapies by either intensivists or nephrologists, or by critical care or nephrology nurses. We believe that these decisions need to be resolved at individual health-care facilities, based on available resources and the local competency and credentialing of physicians and nurses (grade E). The criteria for this competency and credentialing have been addressed by medical and nursing professional societies.

Vascular access. There is currently no consensus on vascular access, although the majority of recently published reports suggest that most centers are now using single dual-lumen venous catheters. Venous access sites include the subclavian, internal jugular, and femoral veins. The optimal site in any given patient is determined by the risks of thrombosis and infection, ease of placement, and adequacy of function [38–45]. Due to the risk of thrombosis and late stenosis, if possible, subclavian veins should be avoided for CRRT access in adults (grade C). Femoral vein thrombosis is a significant problem in neonates and young children and, thus, these vessels should be avoided if possible (grade D). Based on available evidence, no recommendation can be made regarding the risk of infection with various sites of catheter placement. Recirculation is likely to be significant for blood flow rates in excess of 200 mL/min, but will vary depending on catheter design and location. Internal jugular locations are generally superior (grade C). Polyurethane catheters are preferable for CRRT access (grade D). Silver coating is currently not effective and antibiotic coating/impregnation has not been studied for this indication. Vascular access sites should be managed in accord with previously published recommendations [46].

Ultrasound guidance has been reported in level II and III studies to reduce the failure and complication rates of central venous catheter insertion [47–50]. Similarly, infection rates and placement failure rates are less when catheters are placed by specialized/experienced vascular access teams [51, 52]. Thus, the use of ultrasound guidance and specialized access teams is encouraged (grade C).

Anticoagulation. The choice of anticoagulant for CRRT should be determined by patient characteristics, local expertise, ease of monitoring (bed side vs. specialized laboratory tests), and pharmacy issues (including preparation of specialized replacement solutions) (grade E). Systemic anticoagulation with heparin (standard unfractionated, low-molecular-weight, or synthetic heparinoids), or direct thrombin inhibitors (hirudin and argatroban) should probably be avoided in patients at high risk of bleeding (grade E). There is no consensus currently on which anticoagulant should be the first choice for all CRRT patients. In patients who are auto-anticoagulated, or are at high risk of bleeding, consensus exists that anticoagulation should be resolved at individual health-care facilities, based on available evidence, no recommendation can be made regarding the risk of infection with various sites of catheter placement. Recirculation is likely to be significant for blood flow rates in excess of 200 mL/min, but will vary depending on catheter design and location. Internal jugular locations are generally superior (grade C). Polyurethane catheters are preferable for CRRT access (grade D). Silver coating is currently not effective and antibiotic coating/impregnation has not been studied for this indication. Vascular access sites should be managed in accord with previously published recommendations [46].

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When anticoagulation is used, safety monitoring is recommended (grade E) although consensus does not exist on the frequency or method. During heparin anticoagulation, measurement of activated clotting times (ACT) or systemic partial thromboplastin time (PTT) are readily available. In addition, routine measurement of platelets should be made to monitor for heparin-induced thrombocytopenia. During citrate anticoagulation, frequent measurements of post-filter and serum-ionized calcium should be done to appropriately titrate the dose of citrate and calcium replacement solutions (grade E). Monitoring of systemic acid-base balance is also advisable in patients at high risk for citrate accumulation. Without additional safety data, regional anticoagulation using heparin-protamine cannot be recommended given the risk of protamine accumulation in patients with ARF. Low-molecular-weight heparins and synthetic heparinoids require regular monitoring of anti-factor Xa activity (grade E).
There is insufficient evidence to recommend specific monitoring strategies for these agents. Similarly, there is no consensus on whether or how to monitor for filter performance during CRRT.

Fluid composition and management. Dialysate or substitution fluid used during CRRT should contain physiologic concentrations of electrolytes, except in patients with extreme imbalances (grade E). Supra-physiologic concentrations of glucose found in some dialysis or substitution fluids frequently result in excessive glucose intake and hyperglycemia [54, 55] and therefore should be avoided (grade E). Both lactate and bicarbonate are able to correct metabolic acidosis in most CRRT patients [56] (level II). Worsening of acidosis has been noted when lactate was used in patients with lactic acidosis or liver failure [57] (level V). The use of citrate, mostly not titrated to pH but for anticoagulation, has been associated with both metabolic alkalosis and metabolic acidosis [58] (level IV). Thus, either lactate or bicarbonate can be used as buffer in most CRRT patients (grade C), whereas bicarbonate is preferred in patients with lactic acidosis and/or liver failure (grade C) and in high-volume hemofiltration (grade E). Fluids administered before the hemofilter (pre-dilution) appear to enhance the achievable ultrafiltration rate (this may be especially important in high-volume CVVH) and may also be useful in patients with frequent filter clotting (grade E) or, in combination with post-dilution, when extracorporeal clearance is limited by the achievable blood flow (grade E). However, no controlled studies provide adequate comparisons among these techniques.

While the use of sterile fluid for replacement is imperative, the bacteriological requirements for CRRT dialysate are less clear, except in high-flux dialysis where dialysate should probably be sterile because of backfiltration (grade E). Although reductions of body temperature below 35°C should probably be avoided (grade E), available data do not allow us to make recommendations on whether CRRT fluids should be warmed. Integrated fluid balancing systems have important, albeit theoretical, advantages. While there is no evidence that fluid removal, per se, improves outcome in critically ill patients with or without ARF, there is limited evidence that volume overload is associated with adverse outcomes. There is level II evidence to suggest that maintaining negative fluid balance decreases length of stay in the intensive care unit in patients with acute lung injury [59]. Therefore, volume overload should be avoided (grade D), especially in patients with acute lung injury (grade C). Since adaptive use of intravenous infusion pumps for CRRT has been shown to risk significant errors in fluid balance, these systems should be discouraged when devices specifically designed for CRRT are available [60] (grade D).

Recommendations for reporting of CRRT in the medical literature

CRRT is defined as any extracorporeal blood purification therapy intended to substitute for impaired renal function over an extended period of time and applied for, or aimed at being applied for, 24 hours per day. Conversely, intermittent therapies are those usually prescribed for a period of 12 hours or less and include techniques classified as EDD and SLED. While the current definitions for the basic modes of CRRT (arterial or pump driven, filtration or dialysis, or both) should continue to be used (Table 4) [61], definitions for new techniques follow.

Continuous venovenous high-flux dialysis. Continuous venovenous high-flux dialysis (CVVHFD) is defined as a technique that uses a highly permeable dialyzer with blood and dialysate flowing countercurrent. In this technique, blood pumps control ultrafiltrate production and there is a balance of filtration and back-filtration with ultrafiltrate produced in the proximal portion of the fibers and reinfused by back-filtration in the distal portion of the fibers so that replacement fluid is not required [62, 63].

Continuous high-volume hemofiltration. Continuous high-volume hemofiltration is a variant of CVVH, which requires higher surface area hemofilters and employs ultrafiltration volumes greater than 35 mL/hour/kg [63–65].

Plasma therapies. The term “plasma therapies” should be used for any extracorporeal therapy that requires the separation of plasma from the formed elements of blood. The term “hemoperfusion” should be reserved for treatment in which blood or plasma is exposed to an adsorptive substance (charcoal, protein A, synthetic materials, monoclonal antibodies, etc.) to remove toxins, solutes, or other materials.

To achieve status of a “new” CRRT technique, it should be substantially different from existing modalities. Otherwise these approaches should be classified as a subgroup of an existing modality. Our suggested “minimal acceptable parameters” for reporting studies involving CRRT are shown in Table 5 and are critical for evaluation of studies using CRRT and comparisons between CRRT and intermittent therapy. It is recognized that technical reports describing technique modifications without outcome data may only report operational characteristics.

Recommendations for future research in CRRT

Observational/epidemiological studies

- Long-term outcomes (survival, quality of life, renal function, and need for chronic renal replacement) of ARF, including assessment of the prognostic factors for these outcomes
- Early natural history studies of ARF; ideal charac-
### Table 4. CRRT nomenclature

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
<th>Description</th>
</tr>
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</table>
| CAVH         | Continuous arteriovenous hemofiltration | Driving force is patient’s blood pressure  
Circuit is arteriovenous  
Ultrafiltrate produced is replaced with a replacement solution  
Ultrafiltration in excess of replacement results in patient volume loss  
Solute removal is through convection |
| CVVH         | Continuous venovenous hemofiltration | Driving force is external pump  
Circuit is venovenous  
Other features similar to CAVH |
| SCUF         | Slow continuous ultrafiltration | Form of CAVH or CVVH not associated with fluid replacement  
Primary aim is to achieve fluid removal in fluid overloaded states |
| CAVHD        | Continuous arteriovenous hemodialysis | Driving force is patient’s blood pressure  
Circuit is arteriovenous  
Dialysate solution is delivered across membrane countercurrent to blood flow at a rate substantially slower than blood flow rate; typical dialysate flow rates are 1 to 2 L/hour  
Fluid replacement is not routinely administered  
Solute removal is by diffusion  
Other features similar to CAVH |
| CAVHDF       | Continuous arteriovenous hemodiafiltration | Driving force is patient’s blood pressure  
Circuit is arteriovenous  
Dialysate solution is delivered across membrane countercurrent to blood flow at a rate substantially slower than blood flow rate; typical dialysate flow rates are 1 to 2 L/hour  
Ultrafiltration volumes are optimized to exceed desired weight loss and enhance solute clearance from convection  
Fluid losses are replaced in part or completely with replacement solution  
Solute removal is both diffusive and convective |
| CVVHDF       | Continuous venovenous hemodiafiltration | Driving force is external pump  
Circuit is venovenous  
Other features similar to CAVHDF |


### Table 5. Minimal reporting criteria for CRRT studies

<table>
<thead>
<tr>
<th>Define operational characteristics of treatments</th>
<th>Report patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane/dialyzer/filter</td>
<td>Measure of time actually spent on therapy</td>
</tr>
</tbody>
</table>
| Delivery device Anticoagulation and monitoring Access and blood flow | Surgical/trauma/medical/other Co-interventions  
Measure of severity of illness (e.g., APACHE II, SOFA, Liano, CCF Score) at start of therapy* |
| Ultrafiltration rates and technique for fluid balance Replacement fluid composition and administration | Indication/s for CRRT  
Reporting of integrated hemodynamic status and vasopressor treatment |
| Dialysate fluid composition and administration | Outcomes, especially survival, short and long term, morbidity and return of renal function |
| Complications of therapy                          | Functional status and quality of life |

*The most appropriate score remains to be determined*

Points and study of the relation of such markers to timing and course

- Optimal frequency of filter changes in specific populations in terms of filter clotting, activation of complement and leukocytes

**Interventional trials**

- Randomized controlled trial (RCT) of the effect of dialysis intensity (including alternative initiation times and dose) on clinical outcomes
- RCT of CRRT versus intermittent hemodialysis in intensive care unit patients with ARF
- RCT comparing convective and diffusive therapies
- Further study to assess the benefits or lack of benefit of tunneling catheters, topical antimicrobials to the exit site, and use of antibiotic and/or antiseptic packs in patients treated with EDD/SLED, where there is continual connection and disconnection of the CRRT circuit and antibiotic-coated venous dialysis catheters
- Compare different anticoagulation regimes on filter performance and circuit longevity with analysis of cost and safety
- Compare lactate and bicarbonate-based fluids in high-volume hemofiltration
**Practice variations**
- A survey of physician and nurse opinions about current practice patterns
- Observational studies of the clinical decision-making process in relation to stopping or transition to a different modality
- Observational studies of physiologic status at time of cessation or transition

**CRRT in sepsis**
- No further observational case series on the use of conventional CRRT in sepsis
- Recommend further evaluation by suitably powered randomized controlled trials

**Mechanistic/physiologic studies**
- Identification of the mechanism(s) of toxicity
- Biochemical identification, isolation and characterization of the uremic toxin(s)
- Distribution and kinetics of various marker solutes in patients with ARF undergoing different treatment modalities
- Establishment of methodology to compare clearance in disparate therapies and/or identify the best parameter by which to measure dialysis dose
- Better definition of kinetics of inflammatory mediators (generation and removal), with special consideration of the effect of adsorption and back-transport of solute
- Effects of filter characteristics (high permeability, high adsorptivity) on middle/large molecule removal

**Meta-analysis/systematic review**
- Better characterization of the potential for adverse events related to blood-membrane interactions in specific patient populations and with specific filters; conflicting evidence needs to be reconciled
- The risks of vascular thrombosis and infection with vascular access for CRRT in adults and children along with the effects of different catheter designs, insertion site, catheter tip location and anticoagulation on catheter performance and recirculation rates; existing evidence needs to be integrated

**DISCUSSION**

After nearly a quarter of a century of clinical use and despite growing acceptance, there remain significant deficiencies in our knowledge regarding CRRT and this has led to variation in practice. However, despite a paucity of level I evidence, there are broad areas of consensus in the practice of CRRT. There are also limited areas where adequate data exist but where controversy persists. In some cases (membrane biocompatibility, catheter design and insertion site) standard evidence-based medicine techniques are needed to summarize and combine the results of existing, albeit small, studies. In other cases (treatment dose and catheter placement methods), existing evidence should be translated into clinical practice guidelines. Finally, in the case of deciding between available modalities (CRRT, intermittent hemodialysis, EDD), further clinical trials are necessary with careful attention to issues of patient selection and study design [66].

One clear conclusion of this Acute Dialysis Quality Initiative (ADQI) is that more basic and applied research in CRRT is necessary. Our results detail 21 recommendations for future studies. However, first and foremost, a uniform “working” definition/classification of ARF for future studies is urgently needed [67]. More than 30 biochemical definitions of ARF exist in the literature and none has achieved wide acceptance. Research and patient care are equally compromised by this lack of consensus.

Beyond existing evidence and future research, the practical matter of providing care for patients with ARF must be addressed. Strategies are needed for developing consensus and recommendations in the absence of evidence. At present, practice patterns for CRRT are extremely variable. Evidence from patient-level epidemiologic studies [17, 26] show that there is large variation in the practice of CRRT. Surveys of United States [3] and Australia physicians [17], as well as several large case series [68], support this conclusion [69].

Uncertainty exists as to when to begin renal replacement therapy and when to stop. In the absence of evidence, issues of timing, dose, and technique remain not only variable, but also extremely controversial. CRRT is sometimes used for non-ARF indications, even though there are no established non-ARF indications. Perhaps the most pressing clinical question regarding the use of CRRT is to determine what patient and/or environmental characteristics make CRRT desirable. Specifically, does CRRT offer an important survival advantage over intermittent hemodialysis in the management of ARF [70]? Although combining evidence from multiple small reports appears to demonstrate a small survival advantage with CRRT versus hemodialysis [66], definitive evidence is lacking. Thus, a large prospective RCT of CRRT versus intermittent hemodialysis in intensive care unit patients with ARF is urgently needed. This study should feature careful “phenotyping” of patients, stratified randomization of key subgroups (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 intermittent hemodialysis. Thus, analogous to evaluation of the pulmonary artery
catheter, significant dedication to developing investigator equipoise and rigorous adherence to study design will be essential.

**APPENDIX**

**Members of the ADQI Workgroup**

Derek Angus, M.D., M.P.H., Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA; Rinaldo Bellomo, M.D., Department of Intensive Care, Austin & Repatriation Medical Centre, Melbourne, Australia; Timothy Bunchman, M.D., Department of Pediatrics (Nephrology), University of Alabama Medical Center, Birmingham, AL; William Clark, M.D., Hemodialysis Research, Renal Division, Baxter Healthcare Corporation, McGaw Park, IL; Andrew Davenport, M.D., Department of Nephrology, Royal Free Hospital, London, UK; Thomas Depner, M.D., Division of Nephrology, University of California at Davis, Davis, CA; R.T. Noel Gibney, M.D., Division of Critical Care Medicine, University of Alberta, Edmonton, Canada; John A. Kellum, M.D., Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA; Paul Kimmel, M.D., National Institutes of Health, Bethesda, MD; J. Michael Lazarus, M.D., Fresenius Medical Care North America, Lexington, MA; Martine Leblanc, M.D., Nephrology Center, Maisonneuve-Rosemont Hospital, University of Montreal, Montreal, Quebec, Canada; Nathan Levin, M.D., Renal Research Institute, New York, NY; Ravindra L. Mehta, M.D., Division of Nephrology, University of California–San Diego Medical Center, San Diego, CA; Sangeeta Mehta, M.D., Department of Critical Care Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada; Patrick T. Murray, M.D., Section of Nephrology, University of Chicago Hospitals, Chicago, IL; Emil P. Paganini, M.D., Department of Hypertension/Nephrology, The Cleveland Clinic Foundation, Cleveland, OH; Paul Pavelsky, M.D., Division of Nephrology, University of Pittsburgh School of Medicine, Pittsburgh, PA; Claudio Ronco, M.D., Department of Nephrology, St. Bortolo Hospital, Vicenza, Italy; Miet Schetz, M.D., Department of Intensive Care, Gasthausberg University, Lowen, Belgium; Robert A. Star, M.D., National Institutes of Health, Bethesda, MD; Ciro Tetta, M.D., Clinical and Laboratory Research Department, Bellico SpA, Mirandola, Italy; David Wensley, M.D., Pediatric Intensive Care Unit, Children’s Hospital, Vancouver, Canada.

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Reprint requests to John A. Kellum, M.D., University of Pittsburgh Medical Center, Department of Critical Care Medicine, 200 Lothrop Street, Pittsburgh, PA 15213-2582, USA.

E-mail: kellumj@anes.upmc.edu

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