

## Acute Dialysis Quality Initiative

Workgroup 3

Solute Control (Treatment Dose)

*Tom Depner*

*Emil Paganini\**

*David Wensley*

### Introduction

The management of renal failure requires the removal of toxins as well as the restoration and maintenance of fluid and electrolyte balance. Renal replacement therapy utilizes diffusion or filtration across a semi-permeable membrane to eliminate toxins that are normally removed by the native kidney. One measure of this blood purification effect is the clearance (removal rate/concentration) of these toxins, which is an instantaneous measurement (K). The overall solute elimination is defined by the product of clearance and time (Kt), which is usually normalized for the volume of distribution (V) of the solute as "Kt/V." The search for specific toxins has not been successful despite over 30 years of research, so "surrogate" or "marker" solutes (e.g., urea and creatinine) are used to measure renal replacement clearance for renal failure. While available evidence does not allow direct correlation of the degree of uremia with outcome, in the absence of a specific toxin, clearances of urea and creatinine can be used in chronic or "end stage" renal disease (ESRD) to guide treatment dose. Most of the previous work has been done in patients with ESRD where urea clearance (or more precisely the fractional clearance compared to body volume of distribution =  $Kt/V$ ), correlates with outcome. Hence,  $Kt/V$  is widely applied clinically in patients with ESRD, but its application to patients with acute renal failure requiring emergent dialysis has not been rigorously validated.

With the application of continuous renal replacement therapy (CRRT) for patients with acute renal failure (ARF), reports have appeared describing better hemodynamic stability, less restriction on fluid delivery, and better control of electrolytes and uremia. The continuous nature of the technique offers certain advantages over the more traditional intermittent delivery of renal replacement. A key issue is how CRRT techniques compare to intermittent techniques for removal of solutes and what parameters should be used to compute a "dose of dialysis". Despite the development of new dialyzer membrane materials, sophisticated dialysis machinery, varying and tailored dialysate composition, and the continuous methodology of dialysis delivery, a relationship between dialysis intensity and patient outcome has not been fully established. Indeed, the very concept of dialysis dosage in acute renal failure has not been

validated. Critically ill patients with ARF are frequently catabolic and have highly labile fluid volumes. These and other variables confound classic methods for estimating both the required and the delivered dialysis dose. In contrast to chronic dialysis where Kt/V has demonstrated utility in defining a delivered dialysis dose, no prospective studies have attempted to classify the acuity of the patient population or to quantify the delivered dialysis dose in patients with ARF. To quantify dialysis in patients with ESRD, the traditional approach is urea kinetic modeling utilizing the urea reduction ratio to calculate clearance, or for research purposes, the clearance can be measured using direct dialysate quantification. Improved survival in ESRD patients who received a higher delivered dialysis dose has been described. Similar information is required for patients with ARF and in whom specific parameters for measuring the dose of dialysis are lacking.

### **Does the process of renal replacement therapy improve patient outcome (mortality & morbidity)?**

*Current practice:* Life sustaining therapy is provided for patients with either end-stage renal disease (ESRD) or acute renal failure (ARF) as either replacement or as a bridge to transplant or renal recovery.

Dialysis has been shown to improve patient outcome in both ARF and ESRD. Level III evidence dating back to the Korean<sup>1</sup> and Vietnam war<sup>2</sup> eras and a strong consensus among clinicians supports improved patient outcomes with renal replacement therapy. Conversely there is Level IV evidence suggesting a risk to renal recovery with hemodialysis.<sup>3</sup> However, in most surviving patients, acute renal failure resolves.

Recommendations for clinical practice: Some form of renal replacement therapy is recommended when a decision is made to support patients with ESRD or persistent ARF (Grade D). No further recommendations can be made (*see also Workgroup 2*).

Recommendations for future research: It is necessary to better understand the influence of co-morbidity on outcome of patients requiring renal support.

### **Which solutes are responsible for the adverse effects of uremia?**

*Current practice:* Many clinicians continue to use blood levels of urea and/or creatinine as reliable indicators of the adverse effects of uremia. The exact identity and relative importance of all uremic toxins is not known. Despite many years 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.<sup>4-5</sup>

Recommendations for clinical practice: It is inappropriate to equate the clinical diagnosis of uremia with isolated blood levels of urea or creatinine (Grade C).

Recommendations for future research: Biochemical identification, isolation, and characterization are needed to identify the uremic toxin(s) and to understand the mechanism(s) of toxicity.

### **Do surrogate toxin (marker) levels correlate with outcome (morbidity & mortality)?**

*Current practice:* Many clinicians use absolute levels or a rate of change in levels of urea and/or creatinine as markers of patient outcome or severity.

Absolute levels of urea and creatinine are difficult to interpret as both high and low levels may indicate poor outcome.<sup>4</sup> The rates of change of urea or creatinine levels may better reflect severity of renal failure (i.e. rapid increases suggesting severe renal dysfunction).<sup>6-9</sup>

Recommendations for clinical practice: There is broad consensus that serum levels of urea or creatinine should be interpreted in the context of their rates of change over time (Grade C).

Recommendations for future research: Studies are needed to more precisely relate the rate of change in marker substances (e.g. urea, creatinine) to severity and to guide initiation of renal replacement therapy.

### **Which best reflects the dose of RRT; markers of solute concentration (mg/ml) in the serum, markers of removal rate (mass transfer, mg/min) or markers of clearance (ml/min)?**

*Current practice:* Clinicians use all of the above methods to assess therapy dose. Target blood levels are frequently used as therapy goals. No consensus exists on which approach is best.

Marker clearance seems to be the best measurement of therapy dose since mass transfer must be interpreted with steady state blood levels to reflect clearance. Fractional clearance may be even more appropriate. In addition to the relative change in blood concentration to assess clearance, the absolute concentration must be considered to measure solute generation rates.<sup>10-14</sup>

Recommendations for clinical practice: Marker clearance should be used as a basis for CRRT dosing (Grade C).

Recommendations for future research: Further evaluation of the distribution and kinetics of various marker solutes in patients with ARF undergoing a variety of treatment modalities and their application.

### **How do the continuous nature and technique of the RRT (CVVH, CVVHD, and CVVHDF) affect the methods for measuring and expressing clearance?**

*Current practice:* The methods for measuring and expressing CRRT clearance vary widely in clinical practice [Kt (ml per dialysis), Kt/V (fractional clearance per dialysis), K/SA ( $\text{ml}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ ), Solute Removal Index (SRI), and ultrafiltration rate for CVVH]. Different techniques alter different parameters for prescription changes but no consensus exists as to which technique should be used in clinical practice. Emerging evidence suggests the importance of using standardized Kt/V or equivalent renal clearance to compare disparate therapies and different frequencies of treatment.<sup>15</sup>

Recommendations for clinical practice: For pure hemofiltration the ultrafiltration rate and sieving coefficient for a marker can be used to measure clearance. For other modalities, dialysate + ultrafiltrate flow and concentration are required to measure clearance (Table 1) (Grade C).<sup>16-18</sup> Clearance should be

factored for body surface area, similar to native kidney clearance, or for urea distribution volume, similar to chronic dialysis. Residual renal function must also be accounted for (Grade E).

Recommendations for future research: Establish the efficacy of various markers for each modality and the relationship of marker clearance to clearances of other substances. Establish a means of comparing clearance in disparate therapies and/or to identify the best parameter by which to measure dialysis dose.

**Table 1. Variables used to measure clearance for the different forms of RRT.**

Variable	CVVH	CVVHD	CVVHDF
Qb	_*	_*	_*
Qd	-	++	+
Quf	++	+/-	+
Solute concentration	-	+	+

(Qb) Blood flow rate; (Qd) Dialysis flow rate; (Quf) Ultrafiltration rate. (-) Not recommended; (+) Recommended; (++) Best; (\*) Effect of pre-dilution.

**What is the dose relationship (response curve) to outcome (morbidity & mortality) and is the relationship patient and/or disease specific?**

*Current practice:* The relationship is often assumed to be linear. Aside from the adjustments for patient size and volume control, other adjustments are rarely made.

For stable patients with ESRD, a dose response relationship has been shown for delivered clearance versus outcome.<sup>19</sup> Recent (level I and level III) evidence supports a similar relationship for patients with ARF.<sup>20-21</sup> However, a dose range has not been established.

Recommendations for clinical practice: Consensus does not exist. Based on evidence from ESRD, a minimum Kt/V of 1.2 thrice weekly should be delivered to patients with ARF (Grade A). However, higher doses of dialysis may be beneficial in critically ill patients with ARF based on studies where CRRT was used (Grade B). Specifically, an intensity of CVVH of 35mL/kg/hr is associated with improved survival compared to 20mL/kg/hr in critically ill patients with ARF.<sup>20</sup> Delivered clearance should be monitored daily during all continuous therapies (Grade E). No recommendations can be made for specific dialysis dosing for patient with specific diseases at this time.

Recommendations for future research: A minimum dose of RRT needs to be established for ARF. This may be best achieved by adequately powered observational multi-centered prospective studies of delivered dose and outcome in patients with varied co-morbidity followed by severity stratified prospective randomized

trials of varying delivered dose and modality versus outcome. Prospective studies of outcome comparing intermittent and continuous therapy with similar dose and technique are also needed.

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**Authors:**

In alphabetic order:

Thomas Depner, M.D. Division of Nephrology, University of California at Davis. Email: [tadepner@ucdavis.edu](mailto:tadepner@ucdavis.edu)

Emil P. Paganini, MD. Department of Hypertension/Nephrology, The Cleveland Clinic Foundation. Email: [paganie@cesmtp.ccf.org](mailto:paganie@cesmtp.ccf.org)

David Wensley, MD. Pediatric ICU, Children's Hospital, Vancouver, Canada. Email: [Dwensley@cw.bc.ca](mailto:Dwensley@cw.bc.ca)