Title: Urea Reduction Ratio May be a Simpler Approach for Measurement of Adequacy of Intermittent Hemodialysis in Acute Kidney Injury

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Author’s response to reviews:

Reviewer reports:

Bart De Moor (Reviewer 1): General remarks:

This paper is a statistically correct exercise on the comparison of Kt/V with URR in the ICU setting. Nothing more and nothing less. Therefore I would suggest making the abstract more informative.

For the abstract:

1. The KDIGO-AKI guideline suggests a weekly Kt/V of 3.9. In a thrice weekly schedule, this means a Kt/V of 1.3 by a single dialysis session. Could the authors mention the URR that can guarantee this aim in a thrice weekly as well as in a 6/7 day schedule.

Thank you for bringing up this concern. Unfortunately, we believe this aspect of the KDIGO guideline is in error. Kt/V is not an arithmetic function; hence a delivered Kt/V of 1.3 three times per week is not equivalent to a delivered Kt/V of 0.65 six times per week, even though both add up to 3.9 per week. Using a model, such as Gotch’s standard weekly Kt/V, to establish equivalency between dialysis provided on different schedules, a Kt/V of 0.65 delivered 6-times per week is a substantially greater weekly dose than a Kt/V of 1.3 delivered 3-times per week. It is not certain what the minimum necessary Kt/V is for a schedule other than three times per week, and we believe that the KDIGO guideline should have stated that when IHD is delivered on the three times per week schedule that the minimum delivered Kt/V should be at least 1.3 per treatment and that the optimal delivered dose on other treatment schedules is unknown. We therefore do not believe it appropriate to provide specific guidelines for delivered URR on other schedules. In addition, since the data used is derived from the ATN study, in which the target delivered Kt/V was 1.2-1.4 for patients assigned to either a three times per week and six times per week hemodialysis schedule, our data are not robust for substantially lower Kt/V values. We
therefore believe that it is not appropriate to include any statement that there is a cutoff URR corresponding to a minimum Kt/V that can be considered acceptable for a daily or 6-times per week dialysis schedule.

In the methodology section:

2. Renal replacement therapy in ICU is usually performed via a temporary catheters. Do the authors have information on insertion sites, especially the quantity of femoral catheters. We wonder how recirculation can hamper correct post-dialysis urea measurements with this access site. In the original paper, supplements included, no information on vascular access was included.

We appreciate the reviewer’s comment on how recirculation can affect post-dialysis urea measurements and therefore calculation of URR. However, we do not believe the data that the reviewer is requesting, i.e., information on insertion sites and particularly femoral catheters, is germane to this analysis. While elevated recirculation will reduce overall clearance during treatment, it will not alter the relationship between Kt/V and URR. Furthermore, the measurement of post-dialysis BUN was carefully protocolized using slow flow (blood pump at <100 mL/min) or stop pump sampling techniques with blood sampling from the arterial port/needle to minimize any effects of recirculation on measurement of the post-dialysis BUN. In addition, if the delivered Kt/V was low, the Standard Operating Procedures instructed that recirculation was to be assessed and the catheter replaced if recirculation exceeded 15%. Furthermore, the location of a catheter in the femoral site does not definitely increase the risk of recirculation. We have included a statement in the manuscript’s Discussion section under limitations (p. 11) addressing this concern, but the lack of information on insertion sites does not impact the conclusions drawn from our study.

In the conclusion section:

A warning may be added. Maintaining an adequate fluid balance is an important problem in AKI-settings. Focusing on URR and delivering shorter dialysis treatments might counteract the planned fluid removal.

On the other hand, delivering long and efficient dialysis treatments can remove antibiotics and as such, influence the recovery from sepsis.

While we agree with this concern, we believe that these issues are beyond the scope of the current manuscript. In order to acknowledge this concern, we have added an additional brief statement to the conclusion addressing these issues (p. 12).

Casper Franssen (Reviewer 2): In this post-hoc study of the ATN study, the authors compared the urea reduction ratio (URR) with single pool Kt/Vurea. They found a tight correlation and
provide detailed information on the sensitivity and specificity of URR for corresponding Kt/V in the clinically relevant range. Since the URR is much easier to calculate in an ICU setting compared with Kt/V, this study may help to provide adequate acute dialysis with regard to small solute removal.

Comments to the authors

1. In patients with morbid obesity, Vurea was adjusted by taking 55% of the ideal body weight plus 25% of the difference between ideal and actual pre-morbid weight. What is the rationale for using this specific correction factor? Which proportion of patients in this study had morbid obesity? Are the results in this study comparable for patients with and those without morbid obesity?

We appreciate the concerns raised by the reviewer about the correction factor used in calculating Vurea in morbid obesity. The rationale for this correction is based on the reduction in the percentage body weight comprised by water (and hence Vurea) as the percentage body fat increases. Since estimation of the volume of distribution of urea based on body weight is only a crude approximation, this adjustment in the ATN Study protocol was a pragmatic first-order adjustment in the small number of patients enrolled in the trial with morbid obesity. The entry criteria for the study also limited the maximal weight of patients to 128.5 kg based on limitations of the equipment used for CVVHDF at the majority of study sites at the time of study initiation in 2003. Thus, the number of patients with morbid obesity (>130% of IBW) represented only a small percentage of total enrolled patients (mean weight 84 ± 19 kg). The data set used for this analysis included only the study calculated Kt/V values and the pre- and post-dialysis BUNs and did not include patient weight. However, given the underlying mathematical relationships between Kt/V and URR, the minimum URR required to achieve the target Kt/V should not be affected by alterations in the estimation of Vurea based on body weight. We have addressed the rationale for the adjustment for morbid obesity in the Methods section of the revised manuscript (p. 6-7).