Editorial

Timing of RRT initiation in critically-ill patients: time for precision medicine

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Recently published randomized controlled trials have brought a focus upon the timing of renal replacement therapy (RRT) initiation in critically-ill patients (1,2). The AKIKI study randomized 620 ICU patients with severe acute kidney injury (AKI) [kidney disease improving global outcomes (KDIGO) classification, stage 3] to either immediate initiation of RRT or delayed initiation according to predetermined mandatory RRT criteria (1). Gaudry *et al.* found no significant difference in mortality between early and delayed RRT initiation strategies in critically-ill patients results, suggesting that careful monitoring of patients for predetermined mandatory RRT criteria may safely allow delaying RRT in ventilated and/or catecholamine-dependent patients with severe AKI. To a more detailed unadjusted subpopulation analyses however, it seems that results may have been influenced by differences in patient outcomes within the delayed-RRT group. Indeed, among patients in the delayed group, those without RRT had a significantly decreased risk of death [hazard ratio =0.71 (0.52;0.97); P=0.031] while those who received delayed RRT had significantly increased risk of death [hazard ratio =1.40 (1.08;1.8); P=0.011]. These results suggest that patients who will never have required RRT probably benefit from not being exposed to potential complications of RRT while patients who definitely required RRT suffer from delayed initiation. The authors mitigate these results by performing an adjustment to baseline severity, after which differences were no longer significant. Given the important implications of the unadjusted subpopulation analysis, adjustment to baseline severity may not have been sufficient to completely describe results and the related phenomena. Rather, studies show that even when adjusting for severity, fluid accumulation remains a major risk factor for death in ICU patients with AKI (3-6). Therefore, adjusting-to or stratifying-by fluid accumulation could have confirmed or accentuated the opposite behaviors observed within the delayed-RRT group. Although no data on fluid accumulation was provided aside from pulmonary edema incidence, increased diuretic use in the delayed-RRT group [4 patients (1.3%) *vs.* 112 patients (36.5%); P<0.001] shows that fluid accumulation was a major issue nonetheless.

Fluid accumulation was among inclusion criteria in the recent ELAIN trial which randomized 231 critically-ill patients with AKI (KDIGO stage 2) to either early (within 8 hours of diagnosis of KDIGO stage 2 AKI; n=112) or delayed (within 12 hours of stage 3 AKI or no initiation; n=119) initiation of RRT (2). The use of biomarkers was also among inclusion criteria in the ELAIN trial: plasma neutrophil gelatinase–associated lipocalin (NGAL) >150 ng/mL. Zarbock *et al.* found increased survival in early versus delayed-RRT suggesting that "early" RRT-initiation earlier than the in the AKIKI trial (KDIGO stage 2 *vs.* stage 3) in patients with both fluid accumulation and NGAL-positive AKI is beneficial.

Given possible risks to patient subpopulations when delaying RRT initiation in KDIGO stage 3 patients and the benefits of early RRT-initiation in NGAL-positive/KDIGO stage 2 patients with fluid accumulation, and the limited risk involved in today's practice of CRRT, we feel compelled to recommend a personalized approach considering early RRT-initiation in the critically-ill. This has been proposed recently by the acute disease quality initiative (ADQI)

consensus group (7-11) suggesting that precision CRRT should start from a truly personalized prescription of timing of initiation of the extracorporeal therapy. This has been derived from several previous observations and the analysis of the literature (12-14). Thus, the answer to the frequently asked question: "When to start CRRT in AKI patients?" is probably "Not too early, not too late, but just at the right time for each specific patient".

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Footnote

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