Continuous renal replacement therapy

To the Editor:

We read the article by Jacka et al.1 with interest. This manuscript is provocative and novel but raises potentially significant methodological questions.

First, the issue of crossovers between treatment groups makes it difficult to conclude which modality was responsible for favourable or adverse outcomes. Was continuous renal replacement therapy (CRRT) still associated with better renal recovery if only patients treated with a single modality were included?

Second, comparing renal recovery in survivors is of questionable validity as the sole renal outcome. Specifically, the “advantage” of CRRT was observed only after excluding those who died – and as Jacka et al. note, death in the intensive care unit (ICU) was significantly more frequent in the CRRT group. Since death and dialysis-dependence are competing risks, the composite of both outcomes would seem more appropriate. This outcome does not appear to significantly differ between the two modalities, which is unsurprising. Although the largest randomized study to date actually showed significantly increased in-hospital mortality due to CRRT use,2 this may not have resulted from the effect of treatment per se. As noted by Jacka et al. in their article, the underlying illness probably influences prognosis to a far greater extent than the dialytic modality.

Third, impaired kidney function at baseline is strongly associated with the need for chronic dialysis in people with acute renal failure.3 In the study by Jacka et al., patients who received intermittent hemodialysis (IHD) had significantly higher serum creatinine at ICU admission, suggesting that they were more likely to have pre-morbid chronic renal insufficiency. Unfortunately, analyses evaluating renal recovery by treatment modality did not control for this difference, which may have influenced the findings.

Finally, a pooled analysis of four randomized studies including more than 400 patients showed no renal benefit of CRRT (and a slight trend towards harm).4 Although meta-analysis has its limitations, none of the four included studies showed a renal benefit of CRRT. Jacka et al. do not discuss why their retrospective study might differ from the available randomized trials. We speculate that the discrepancy is due to bias resulting from the non-randomized design.

Multiple non-randomized studies over the last 20 years have been used to support the theoretical benefits of CRRT, and to justify its higher costs. However, randomized studies have not demonstrated that CRRT is superior. Even for surrogate outcomes such as intradialytic hypotension, no good quality data support the use of this indisputably more expensive treatment.

We agree with Jacka et al. that larger randomized trials should be performed, but respectfully disagree that their article helps to inform debate in the interim. Since the best available data do not indicate that dialytic modality influences outcome in critically ill patients, we suggest that the least costly therapy should be used until new randomized trials demonstrate otherwise.

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References
1 Jacka MJ, Ivancinova X, Gilmey RT. Continuous renal replacement therapy improves renal recovery from acute renal failure. Can J Anesth 2005; 52: 327–32.
2 Mehta RL, McDonald BR, Babhai FB, et al. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. Kidney Int 2001; 60: 1154–63.
3 Silvester W, Bellomo R, Cole L. Epidemiology, management, and outcome of severe acute renal failure of
critical illness in Australia. Crit Care Med 2001; 29: 1910–5.
4 Tonelli M, Manns B, Feller-Kopman D. Acute renal failure in the intensive care unit: a systematic review of the impact of dialytic modality on mortality and renal recovery. Am J Kidney Dis 2002; 40: 875–85.

Reply:

We thank Tonelli et al. for their interest in our study showing improved renal recovery among patients treated with continuous renal replacement therapy (CRRT).1

As we described, ours was a non-randomized observational study. The ‘issue of crossover’ should not affect interpretation, even adopting a ‘worst case scenario’. Crossovers were very few and occurred only among patients who had stabilized on CRRT from the indications precluding intermittent hemodialysis (IHD). Crossovers would be a concern in a randomized trial, among patients assigned to IHD but who required CRRT due to hemodynamic instability, and who would probably die without renal replacement.

Second, the risks of dialysis-dependence and death might be an appropriate composite outcome measure in a prospective randomized analysis. In our study, as we pointed out in the methods and discussion, CRRT was applied to patients who had sufficient hemodynamic instability, intracranial hypertension, or liver failure that made use of IHD impossible. The finding of any survivors among these CRRT patients supports the use of CRRT, making randomized evaluation unethical.

Third, most studies comparing CRRT and IHD have used mortality and renal recovery as separate outcome measures, rather than composites. Tonelli et al. have suggested that studies comparing modes of RRT should concentrate on renal recovery.2 No study has found hospital mortality ‘due’ to CRRT as implied by Tonelli.

Fourth, although serum creatinine was higher at intensive care unit admission among IHD patients, careful examination of our tables shows that at the time of institution of RRT, and as we pointed out in our discussion, serum creatinine was similar between groups.

Fifth, we agree that meta-analysis has limitations. Although Tonelli failed to find a benefit from CRRT, Kellum showed lower mortality with CRRT when patients were stratified according to severity of illness.3,4

Sixth, CRRT has been shown to have specific advantages over IHD. CRRT minimizes hemodynamic fluctuation in unstable patients and prevents further elevation of intracranial pressure in patients with fulminant liver failure.4 CRRT is superior in correcting azotemia and acidosis and is recommended for patients with severe sepsis.5,6

While we support Tonelli et al. in their advocacy of the least costly alternative, insistence on minimizing cost in the face of evidence of benefit represents an inappropriately regimented approach. Finally, we thank Tonelli et al. for helping us to stimulate and inform debate on the issue of renal replacement among the critically ill, along with our descriptive study.

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References
1 Jacka MJ, Ivancinova X, Gibney RT. Continuous renal replacement therapy improves renal recovery from acute renal failure. Can J Anesth 2005; 52: 327–32.
2 Tonelli M, Manns B, Feller-Kopman D. Acute renal failure in the intensive care unit: a systematic review of the impact of dialytic modality on mortality and renal recovery. Am J Kidney Dis 2002; 40: 875–85.
3 Kellum JA, Angus DC, Johnson JP, et al. Continuous versus intermittent renal replacement therapy: a meta-analysis. Intensive Care Med 2002; 28: 29–37.
4 Davenport A, Will EJ, Davison AM. Early changes in intracranial pressure during haemofiltration treatment in patients with grade 4 hepatic encephalopathy and acute oliguric renal failure. Nephrol Dial Transplant 1990; 5: 192–8.
5 Uchino S, Bellomo R, Ronco C. Intermittent versus continuous renal replacement therapy in the ICU: impact on electrolyte and acid-base balance. Intensive Care Med 2001; 27: 1037–43.
6 Dellinger RP, Carlet JM, Masur H, et al.; Surviving Sepsis Campaign Management Guidelines Committee. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004; 32: 858–73.

Sulfadiazine-induced methemoglobinemia in a boy with thalassemia

To the Editor:

Drug-induced methemoglobinemia has been well documented,1–3 but an acute episode of sulfadiazine-induced arterial desaturation during emergence from anesthesia has never been reported. A three-year-old boy (14 kg, 90 cm) suffered scalding injury (55% of body surface area) and was scheduled for debridement. Family history was positive for a dominant β-thalassemia trait. Physical examination revealed no