Letters and Replies

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The Hannover Dialysis (extended dialysis) study and the dose-outcome relation

Sir,

The investigators participating in the Hannover Dialysis Outcome (HANDOUT) study [1] deserve enormous credit for the important results of their prodigious comparison of standard versus intensified extended dialysis treatment of ICU patients with severe acute kidney injury (AKI). However, a number of issues related to patient characteristics and to study design mandate some caution in interpreting their results and applying them to other patient populations.

The failure of the study to show non-inferiority of standard dialysis in terms of survival by Day 28 and renal recovery amongst survivors by Day 28 may have more than one explanation. First of all, compared to other dose/outcome studies [2], the patients of the HANDOUT study had higher APACHE II scores (over 30), sepsis rate (70%), percentage of oliguria (70%) and should consequently have a higher mortality rate (60%). Paganini et al. retrospectively evaluated 844 patients with AKI requiring renal replacement therapy (RRT) and found that when patients were stratified for disease severity, the dialysis dose did not affect outcome in patients with high or very low scores, but did correlate with survival in patients with intermediate degrees of illness [3]. Thus, the overall high level of illness severity in this study might have overridden a potential dose effect. Secondly, initiation of RRT was dictated in the majority of patients by anuria/oliguria and both treatments were started very early as evidenced by low urea levels. Numerous retrospective and prospective cohort studies suggest that the timing of RRT might exert an important influence on AKI patient survival independent of the dose of RRT [4]. Thirdly, the extended dialysis regimen in each group provided adequate doses in both groups, which may explain the findings of this study compared to our earlier study [5]. Comparing conventional IHD (prescribed sp Kt/V urea 1.2) performed every other day with daily IHD (prescribed sp Kt/V urea 1.2) resulted in an underdialysis of the less intensive treatment arm (delivered sp Kt/V urea 0.9), characterized by high time-averaged BUN values, and high morbidity and mortality of our patients [5].

There is a broad consensus that determinations of plasma urea concentrations cannot be used as surrogate for measurements of the RRT dose. This approach is likely to be seriously flawed. Patient-related factors, such as body size, volume overload and urea generation rate, are also critical determinants of plasma urea concentrations. Clearance measurements should be used for the calculation of the RRT dose, multiplied by treatment duration and divided by the volume of urea distribution. Despite the limitations of blood-based formal variable pool urea kinetic modelling, Kt/V urea has appeared to be a predictor of adequacy of the RRT dose in AKI.

The results of the HANDOUT study do not imply that the dose of RRT is not important, and they do not contradict those of previous studies. The dose/outcome domain map in RRT of AKI seems to display a linear and steep dose region until the curve reaches a plateau, after which further increases in dose do not result in further benefits [6]. The crucial points are that neither the inflection point of the curve has been established nor whether the plateau is identical for different groups of patients.

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Department of Nephrology, KfH Nierenzentrum München-Laim

Munich, Germany

E-mail: hschiffel@hotmail.com


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Reply

Sir,

We thank Dr Schiffl for his comments on the HANDOUT study, which compared mortality of critically ill patients, randomized to either standard or intensified extended dialysis [1]. Dr Schiffl extends our discussion on the numerous limitations of the study focusing on three points: (i) severity of illness defined by APACHE, (ii) timing of treatment initiation and (iii) adequacy of dose and its surrogate parameters, which in his view mandate some caution in interpreting the results and applying them to other patient populations.

The severity of illness unfortunately reflects the everyday life in our tertiary care centre. Also the rate of septic patients in our study (~70%) is in line with the results of recently published multi-centre trials on the causes of acute renal failure [2]. Despite the rather high APACHE II score of 31, the patients’ mortality at Day 28 was 39% and 45% and not 60% as suggested by Dr Schiffl. Also, when