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Reply from the Author

I thank Professors Kashtan and Rizzoni and Dr. Massella for their comments. They rightly point out the value of immunostaining of renal biopsies for the diagnosis of X-linked and autosomal Alport syndrome and the utility of skin immunofluorescence in diagnosis of many cases of X-linked Alport syndrome. The use of confocal laser scanning microscopy (CLSM) [1–3] is an elegant technique to improve the spatial resolution of α5(IV) chain distribution in basement membranes.

Ueda et al [3], also using CLSM, have reported that compared with α2(IV), α5(IV) expression in GBM is reduced in patients with TBMD. The reduction in α5(IV) but not α3(IV) and α4(IV) is difficult to reconcile with the genetic evidence implicating mutations of COL4A3 and COL4A4 in TBMD.

Confirmation and clarification of the results of CLSM of EBM and GBM is eagerly awaited. Until sequencing of the relevant collagen genes or other comprehensive genetic testing is routinely and readily available, immunofluorescence of skin biopsies is a minimally invasive means for diagnosis of many cases of X-linked Alport syndrome. If quantitative comparisons of the different α(IV) chains in GBM permit a positive diagnosis of TBMD, this will further strengthen our diagnostic hand.

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Dialysis dose and gender: A different hypothesis

To the Editor: A recent report [1] suggested that females who are smaller than males need higher dialysis dose (Kt/V) than males. The idea that smaller persons require higher Kt per L of V is not new [2], and suggests that a 0-intercept rule for judging Kt per unit of V is incorrect [3].

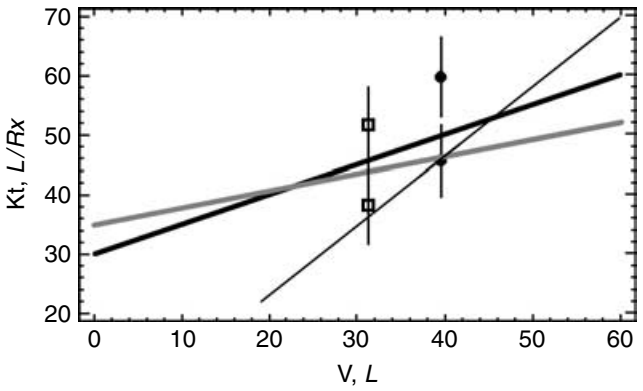

Fig. 1. Illustration of three relationships discriminating the high (upper symbols) and low (lower symbols) Kt/V groups for males (solid circles) and females (open squares) in the HEMO study. The relationships are 1) Kt = 1.16 V (thin black line) representing the low dose HEMO study Kt/V for both genders, 2) Kt = 30 + 0.5 V (thick black line), and 3) 35 + 0.3 V (thick gray line).

Figure 1 illustrates a non-0 intercept rule (thick black line: Kt = 30 + 0.5 V) [3]. The mean Kt ± SD (Table 3) [1] is shown for females (squares) and males (circles) at the mean V (Table 2) [1] for the high (upper symbols) and low (lower symbols) hemodialysis (HEMO) treatment groups. The steep, thin black line is a 0-intercept Kt/V rule (Kt = 0 + 1.16 V) [1]. All groups were treated at or above the Kt for their V by that rule. Females in the low treatment group (Kt = 38.2; eKt/V = 1.17), however, had marginally worse ($P = 0.02$) survival than females in the high treatment group [1].

The gray line (Kt = 35 + 0.3 V) is a rotation of the earlier black line [3], and better discriminates among groups according to outcome. Only low Kt/V females received substantially suboptimal therapy according to this illustrative rule.

The point of this exercise was not to recommend a new rule for judging treatment. It only shows that one need not resort to speculations about different uremic toxin generation in males and females [1] to explain this marginal survival difference. All one needs to do is accept the possibility that a 0-intercept Kt/V rule may be suboptimal.

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Reply from the Authors

We appreciate the attempts by Lowrie and others to explain the suspected gender effect as simply reflecting the difference in body size. In the analysis of our findings we explored functions of body size that might diminish or erase the difference between the genders in their response to the dialysis dose, expressed either as Kt or Kt/V. As detailed in our paper [1], the dependence of the dose effect on gender was not explained by differences in body size expressed as several different parameters, including weight, height, body surface area, water volume, and body mass index (Table 6). The dose effect was not significantly associated with any of these size parameters. In fact, the nonsignificant weak trends that were detected were further diminished by correction for gender (Table 5). Furthermore, the suggested increased mortality of males treated at the higher dose could not be explained by any consideration of body size.

A non-0 intercept for a linear relationship between body size and required solute clearance is a clear mathematic concept that is difficult to understand physiologically. It implies an enormous amount of dialysis (or kidney function) for very small people, and a near infinite amount for even smaller biological organisms. Probably the relationship is nonlinear but with a 0 intercept (e.g., a power function of body mass). This is consistent with the universal scaling law that relates physiologic functions to the 3/4 power of body mass and to the current practice of correcting the creatinine clearance or GFR for body surface area (2/3 power of body mass) [2, 3, 4].

The effect of body size as an independent mortality risk factor in hemodialyzed patients reported by Lowrie et al [5] is now commonly accepted, and was also observed in the HEMO Study (Table 4). However, the marked rotation of the line depicting dose versus size in the graph provided by Lowrie et al suggests that the relationship of size with outcome can be altered by changing the dose. Post-hoc analyses of our data [1] do not support such a dependence of the effect of dose on the risk associated with body size in a range of eKt/V from 1.16 to 1.53, but do indicate that women were more responsive to the dose effect than men. The risk associated with female gender, in contrast to small body size, can be viewed as favorable because females appeared to respond to the higher dose, whereas both small patients and males did not.

Finally, we must reiterate two important limitations that we noted in our paper. First, the finding of a different dose effect in men and women must be viewed as a suggestion only because the level of significance was not high in the context of multiple subgroup analyses. Second, because the power of the study to detect effects in subgroups is limited, it cannot rule out the possibility of an undetected dependence of the dose effect on body size.

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Prevention of acute renal failure with N-acetylcysteine—Enough is enough?

To the Editor: As clinicians in daily practice we would like to comment on the enormous amount of publications published in the last three years on the prevention of radiocontrast-induced nephropathy (RCIN) by N-acetylcysteine (NAC). Just recently, the last of four meta-analyses was completed [1–4].

The dilemma a clinician faces is the enormous amount of data in this field, and deciding if the information is clinically valid or not. Traditionally, meta-analyses have been the key tool in estimating a treatment benefit of contradictory randomized controlled trial (RCT) results. However, even at this evidence level results are inconclusive. How is the clinician going to solve this problem?

From a practical point of view, it seems to be more sensible to use the drug. A physician who is trying to prevent RCIN in his patient is likely to administer a drug if there is any evidence for a beneficial effect, especially given the low adverse event profile for many years and low cost of the drug.