Letters to the Editor

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Reply from the Author
We agree with Dr. Cuhaci that underlying severity of illness is a strong determinant of outcome from acute renal failure requiring dialysis. As discussed in our article [1], the study was powered for an effect size of 20% reduction in mortality (from 70% to 50%) and we did not include hypotensive patients to avoid biasing the study in favor of continuous renal replacement therapy (CRRT). We did not standardize timing and indication or dose of dialysis as these factors are not well defined even today and were even less appreciated when the study was initiated. Despite its limitations, we believe that our study is still relevant to modern-day practice. It highlights the importance of standardizing an approach for dialysis in acute renal failure as there is wide variation in the timing and indications for dialysis and choice of modality [2]. Recognition of the underlying severity of illness and its effect on outcomes should promote a change in our paradigms for the appropriate selection of dialysis modality and its application for renal support rather than replacement [3]. Our results also support the need for further research to establish standards for timing, indications, dose of dialysis, and then for an individualized approach for management of acute renal failure before embarking on future randomized controlled trials. The Acute Dialysis Quality Initiative (ADQI) is an initial attempt, which we hope will serve as a starting point for future research and development of practice guidelines in this field [4].

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Fragmentation of filtered proteins and implications for glomerular protein sieving in Fanconi syndrome

To the Editor: The calculations of glomerular sieving coefficients in Fanconi syndrome by immunoassay [1] have not considered the effects of the relatively large quantities of protein fragments [2] that arise by degradation of filtered protein during renal passage [3, 4]. The fragments do not arise in plasma of non-filtered kidneys nor are they at sufficient concentration in the circulation to account for the material in urine [4]. Fragments are not detected by immunoassays [5]. It is clear that any estimation of protein glomerular sieving coefficient has to take into account these fragments. Furthermore, esti-
mates of glomerular sieving coefficients used by Nordon et al [1] still rely on the amount of material measured post glomerular capillary wall. There is an urgent need to confirm the underlying assumption that this represents the actual quantity of material that has left the capillary and has been filtered.

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Red blood cells and thin basement membrane disease

To the Editor: The article by Collar et al entitled, “Red cell traverse through thin glomerular basement membranes” illustrates a red blood cell (RBC) passing through a small gap in the glomerular endothelium and basement membrane in a patient with thin basement membrane disease [1].

Phase contrast microscopy has demonstrated that up to 10,000 RBC/mL are normally present in the urine and that this number often increases to about 30,000 RBC/mL with vigorous exercise. The RBCs that occur normally and after exercise are dysmorphic in appearance, reflecting their glomerular origins [2, 3]. The basement membrane gaps described in thin basement membrane disease in Collar et al’s report [1] may very well represent the normal means of RBC egress, and the increase associated with exercise could result from an increased number of membrane gaps or from the passage of more RBCs through each.

Although long suspected, the escape of RBCs through gaps in the glomerular membrane into Bowman’s space has proved difficult to capture on electron microscopy. Most of our patients with thin basement membrane disease lose about 100,000 RBC/mL urine [4], which represents $2 \times 10^8$ RBCs a day. If a kidney has a million glomeruli, then on average 100 RBCs pass through the membrane of each glomerulus daily. Ultrastructural kidney sections comprise only a few glomerular loops, and Collar et al reflect that the membrane gaps are present for only 10 minutes [1]. Even with macroscopic hematuria, which corresponds to at least 5,000,000 RBC/mL urine [5], only 5000 RBCs pass through each glomerulus daily.

Can Collar et al also explain why many patients with thin basement membrane disease have hematuria but no proteinuria, which is different from the situation with most other glomerular lesions? Are the gaps in the membranes in thin basement membrane disease so small that negatively-charged plasma proteins are repelled from margins of the endothelial aspect of the similarly-charged membranes?

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ANCA-associated renal vasculitis

To the Editor: The Nephrology Forum discussed by Professor Savage reminded us of two items about ANCA-associated renal vasculitis (ARV): (1) the complex patho-