

was not designed for this purpose (it does not describe the use of anti-inflammatory drugs, for example). In fact, what this paper shows is that four patterns of inflammation can be found in hemodialysis patients during follow-up—stable-low, decrease, increase and stable-high—, and that persistent elevation and increases of C-reactive protein, interleukin-6 and tumor necrosis factor (TNF)- α over a short period of time is associated with a worse outcome.

Your statement about inadequate dialysis in the pentoxifylline (PTX) group is a little bit confusing. Even though the control group had higher equilibrated Kt/V_{urea} than PTX group, both groups had values considered as adequate [4]. Supposing, without accepting, that PTX patients had inadequate dialysis, according to your statement, this group would have higher inflammation than controls throughout the study; however, patients in the PTX group decreased all the studied inflammation markers, whereas they remained roughly the same or increased in the controls (without changes of dialysis dose in both groups throughout the follow-up). Moreover, one has to be cautious extrapolating data from *in vitro* studies to *in vivo* situations; the study that you are referring to [5] was performed *in vitro* and only measured IL-12p70.

Finally, as you stated, PTX has been shown to increase values of hemoglobin by means of decreasing TNF- α values; however, this is not the only factor influencing hemoglobin levels in patients on hemodialysis [6]. These latter factors may have influenced hemoglobin values in our study, and more importantly, as we recognized in the discussion, this issue cannot be appropriately evaluated as erythropoietin dose was not controlled by researchers, and its use is still a matter with local economical implications.

All these issues were appropriately considered and discussed in the paper; therefore, the conclusions are sustained.

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Immunostaining findings in IgA nephropathy: correlation with histology and clinical outcome in the Oxford Classification patient cohort

Sir,

I have read with interest the article by Bellur *et al*. [1] published recently in your premier journal. It describes the immunohistological findings of IgA nephropathy (IgAN) and their correlation with the clinical and histological features of this disease at the time of renal biopsy and the final renal outcome. The study cohort used for this study is the same as that used for the development of original Oxford Classification of IgAN. The study may be considered as an important adjunct to the original Oxford Classification of IgAN, which was entirely based on the pathological evaluation of morphological features [2, 3]. It is worth mentioning here that soon after its publication, some investigators raised the point of lack of immunofluorescence (IF) or electron microscopic (EM) findings in the original classification and their correlation, if any, with the morphological and clinical features at the time of diagnosis and the final outcome [4].

In the backdrop of the above facts, the study is certainly welcome addition to the Oxford Classification of IgAN. However, there is one caveat. The subject study is entirely based on careful scrutiny of the original renal biopsy reports and not on the re-examination of the archived frozen renal biopsy material by the IF test. I have the experience of working on one such project nearly 2 years ago at the Pathology Department of Academic Medical Center (AMC), Amsterdam, under the supervision of Prof. Sanderine Florquin and Dr. Joris Roelofs, which involved repeat IF study of the archived frozen tissue of all IgAN cases in AMC Pathology Department files (M. Mubarak, unpublished data). As I have first hand experience of working on this subject, I have a couple of points to make about this study, the clarification of which will be helpful for all the renal pathologists in their routine practice as well as future research projects on this subject. The points are as follows:

- As we all know, the interpretation of capillary wall IF positivity is quite subjective and shows marked inter-observer variability. It is worth reiterating here that I have not come across a single case of IgAN with the IF findings similar to those shown in Figure 1B of the subject study. On the other hand, the majority of cases showed peripheral capillary positivity of IgA as shown in Figure 1A. Obviously, the question arises of the definition of capillary wall positivity of IgA staining here. For that matter, do the authors recommend using an immunohistochemical approach for determining the accurate capillary wall positivity?

- (2) The definitions of IF distribution pattern and intensity also need to be vigorously defined. In this context, the precise definitions of morphological lesions used in the original Oxford Classification can serve as a template [3]. I know, a circulation of IF-stained material among the pathologists is difficult, this can be done with high-quality images in Internet-based surveys, as has recently been done for polyoma virus nephropathy (PVN) classification by the Banff working group on PVN.
- (3) The authors will agree that similar work needs to be done on ultrastructural findings in this disease and their correlation with morphological and IF findings to further refine the original classification.
- (4) Finally, although the authors conclude that the evidence from their study is insufficient to justify inclusion of the immunostaining data in the Oxford Classification at the present time, there is a clear need for further studies incorporating all the pathological data from light microscopic, IF and EM studies of renal biopsies, along with clinical investigations, in prospective cohorts. These can then be carefully scrutinized by multivariate analysis for the relative importance of each of the above features in better prognostication of individual patients, and especially, for the selection of suitable patients for optimal treatment.

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Reply

Sir,
As Dr Mubarak correctly observes, the study of immunohistological findings in the Oxford Classification of IgA

nephropathy cohort [1] is based on review of the original pathology reports and not of the slides. This was necessary, as there was no access to the original diagnostic material which, in almost all cases, was immunofluorescence (IMF) on frozen sections. As a result, the quality of immunohistological data was potentially limited by inter-observer variation between the reporting pathologists. In view of this methodological flaw, it is particularly impressive that strong correlations were found between the IMF findings and light microscopical changes.

We agree that if immunohistology is to be included in a classification of IgA nephropathy, then the issue of IMF definitions and reproducibility first needs to be addressed. Whilst there are several studies that have assessed interobserver agreement in the interpretation of the histological changes in renal diseases [2–4], there are few such studies applied to renal immunohistology. Interobserver concordance in the interpretation of C4d and SV40 T-antigen positivity in renal transplant biopsies has recently been reported [5, 6]. Similar studies applied to glomerular IMF and immunohistochemistry in native renal disease are lacking. Some researchers suggest that image analysis is superior to subjective interpretation of renal IMF. Interestingly, a recent study reported that, in IgA nephropathy, the presence of adverse histological prognostic features correlated with intensity and total optical density of fluorescence measured using image analysis software, but not with semiquantitative scoring [7].

Electron microscopy (EM) was not included in the Oxford Classification because neither the reports nor the images were available for most biopsies. We agree that further investigation of the ultrastructural changes in IgA nephropathy is required, in particular correlation with light microscopy and clinical outcome. The future inclusion of ultrastructural features in the Oxford Classification will depend on evidence that EM provides added clinical value. Such evidence is lacking at present, reflected in the limited use of EM in many centres.

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Cardiopulmonary assessment of patients with end-stage kidney disease

Sir,

The recent investigation by Agarwal highlights the need to consider pulmonary disease as part of the cardiovascular disease spectrum among end-stage renal disease (ESRD) patients. The prevalence of pulmonary hypertension (PHT) was present in 38% of a large ESRD cohort and was associated with poor survival [1]. There are a number of intriguing observations.

The observation that patients with PHT had a greater midwall fractional shortening and cardiac index but had a greater mortality rate is interesting. The correlation between PHT and left atrial diameter strongly suggests a cardiac aetiology to PHT. In the context of an increased left atrial diameter and an associated increase in mortality, the greater midwall fractional shortening and cardiac index are likely to represent greater myocardial workload rather than better myocardial systolic function. It therefore seems plausible that patients with PHT may have reduced cardiopulmonary functional reserve and consequently a greater mortality. A reduced cardiopulmonary functional status is evident in paediatric and adolescent patients with ESRD who have a limited cardiorespiratory capacity just 16 months after starting haemodialysis compared to their counterparts with normal renal function [2]. As the author points out, the similarity in left ventricular mass index suggests that diastolic dysfunction is not a likely explanation of the increased cardiovascular events.

The observation that a lower diastolic blood pressure was associated with mortality is unsurprising. Patients with ESRD are prone to arterial stiffness, which results in a lower diastolic blood pressure. These in turn result in reduced coronary blood flow, compounding any increase in cardiac workload, and may ultimately lead to an increase in cardiovascular mortality [3].

The association between PHT and patients who were not on a vitamin D receptor activator may relate to endothelial dysfunction associated with vitamin D deficiency [4, 5]. Prospective studies to investigate the beneficial effect of therapeutic vitamin D supplementation on cardiovascular disease among chronic kidney disease patients are crucial.

The challenge that lies ahead is to identify an integrative approach to cardiac investigations that is most likely to yield a practical approach to the management of an individual patient. Consideration of PHT as part of the cardiovascular disease spectrum among ESRD patients is crucial.

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