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doi: 10.1093/ndt/gfn390

Advance Access publication 5 September 2008

Reply

Sir,

In reply to the comments by Morgan, we generally concur and offer the following additional commentary.

We agree that the addition of patient weight, hourly urine output and baseline serum creatinine as core variables to the Australia New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD) would have tremendous value and certainly advance its capability for additional evaluation of acute kidney injury (AKI) and other kidney-related issues.

At the time of analysis, however, these variables were not available [1]. Accordingly, assumptions about the data and their application to calculate the RIFLE categories were necessary. We recognize these assumptions potentially introduce some misclassification of the cohort and, as expected, influence incidence and outcome estimates. We, however, contend that any bias introduced due to misclassification resulting from these assumptions was likely to be balanced given they were applied systematically across the entire cohort.

Moreover, the validated collection of these variables (i.e. patient weight, urine output, baseline serum creatinine) can be problematic. For example, the measurement of weight in critically ill patients is highly variable and context specific (i.e. ideal versus actual). Accurate estimates of pre-hospitalization baseline creatinine (or estimated glomerular filtration rate), in particular for those with chronic kidney disease, in critically ill patients are often impossible. Moreover, values at the time of ICU admission may be grossly modified by factors such as acute resuscitation. Likewise, the urine output can be modified by factors independent of kidney injury or function (i.e. fluid therapy, diuretic therapy). However, we also recognize that while the urine output

criteria proposed for the RIFLE classification likely have significance, they have yet to be prospectively evaluated and validated. We appropriately acknowledge and discuss these limitations in our manuscript [2,3].

We are further reassured, however, by additional epidemiologic investigations that have found relative consistency in incidence rates and effect estimates for AKI and associated clinical outcomes with the RIFLE criteria (many having modified the original RIFLE criteria or omitting the urine output criteria altogether) [4,5]. We contend that our study is strengthened by inclusion of a very large heterogeneous cohort (over 120 000 critically ill patients) from multiple centres across Australia. As such, in the very least, it provides a broad estimate of the burden of early AKI (within 24 h of ICU admission) in critically ill patients. Finally, we certainly agree and would welcome additional prospective evaluation of the performance of the RIFLE criteria in similar cohorts of critically ill patients.

Conflict of interest: None declared.

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doi: 10.1093/ndt/gfn396

Advance Access publication 5 September 2008

Spontaneous remission of hyperparathyroidism

Sir,

We read with great interest the case report concerning spontaneous remission of severe hyperparathyroidism published by our Japanese colleagues [1].

We wish to underscore two things from their report.

Firstly, 17 years ago we presented a chronic kidney disease patient with spontaneous inflammation remission of a parathyroid tumour. By fine-needle aspiration biopsy, an inflammatory process was proven [2]. In the next 5 years, three more patients with similar clinical symptoms were observed [3]. In two of them, inflammatory changes of

parathyroid glands were proven by cytology, and in one, after surgery, a haemorrhage with subsequent fibrosis and spontaneous sclerosis of the parathyroid gland was proven. Remission of hyperparathyroidism was not observed due to the enlargement of the other parathyroid glands. In all of the patients, before spontaneous pathological changes, an enlarged volume of the parathyroid gland was detected by ultrasound, from 3.92 cm³ to 32.5 cm³. In our patients, secondary hyperparathyroidism due to nodular parathyroid gland hyperplasia was considered, and in a case described by Komaba *et al.*, primary adenoma was considered. Spontaneous changes of the parathyroid gland were due to autoinfarction in the Japanese case. Regardless of the pathological changes, it appears that enlarged parathyroid glands, i.e. adenoma or nodular hyperplasia, are susceptible to autoinfarction, necrosis and haemorrhage of even spontaneous inflammation. As we have concluded previously, our knowledge of parathyroid pathology is insufficient at this time [3].

Secondly, in our patients we were not able to use a new third-generation PTH assay. From the report of Komaba and his colleagues, as well from some others, it appears that a new assay could be a marker of more severe hyperparathyroidism [4]. We agree with the statement that we need more data to elucidate the relationship between the third-generation PTH assay and the severity of secondary hyperparathyroidism. In our view, parathyroid sonography and the new PTH assay could be useful in an evaluation of the severity of hyperparathyroidism. Unfortunately, in our opinion parathyroid sonography as an inexpensive and non-invasive method still does not have a significant place in the daily work of many hospitals [5].

Conflict of interest statement. None declared.

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doi: 10.1093/ndt/gfn391

Reply

Sir,

We thank Dr Pavlovic *et al.* for their interest in our recent case report [1]. As indicated, spontaneous pathological changes of parathyroid glands have rarely been reported in dialysis patients [2,3], including those reported by Dr Pavlovic *et al.* [4,5]. Interestingly, their data on four patients with unusual changes in parathyroid glands were consistent with the notion that a large gland is susceptible to spontaneous pathological changes. Our case of spontaneous autoinfarction was also associated with an enlarged parathyroid gland, which was clinically considered as primary adenoma. We believe that excessive parathyroid growth may have outstripped vascular supply, thereby resulting in autoinfarction. Ultrasonography was highly helpful not only for the evaluation of parathyroid volume, which appears to be a useful indicator of autonomous parathyroid cell proliferation [6], but also for the diagnosis of parathyroid infarction. It was, however, very difficult to pathologically confirm the diagnosis of adenoma, as well as the aetiology of autoinfarction in our patient. In this regard, we agree with their comments that our knowledge of parathyroid pathology is still insufficient. Further studies with new diagnostic methods are required to elucidate these issues.

As we have previously reported [7], the third-generation PTH/second-generation PTH ratio is usually 0.6–0.7 in dialysis patients. However, we observed the paradoxically reversed third-generation PTH/second-generation PTH ratio in our patient, which dramatically normalized after spontaneous infarction of the enlarged gland. It is noteworthy that most patients with the reversed third-generation PTH/second-generation PTH ratio showed marked parathyroid enlargement associated with severe hyperparathyroidism [8]. Moreover, we would like to point out the possibility that a high third-generation PTH/second-generation PTH ratio, even if it is not reversed, might indicate a certain amount of new N-form of PTH in the sera. In relation to such a possibility, we are currently considering that the third-generation PTH/second-generation PTH ratio could be a useful predictor of severe hyperparathyroidism [9]. Further studies with information by ultrasonography and pathology are needed to clarify the clinical impact of the third-generation PTH/second-generation PTH ratio. And ultimately, development of a new assay that directly detects N-form of PTH would be mandatory to confirm these findings.

Conflict of interest statement. None declared.

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