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Medical management of hepatorenal syndrome

Sir,

We have read with great interest the manuscript from Davenport *et al.* [1], concerning the medical management of patients with hepatorenal syndrome. We request the clarification of components in Table 4 which may be labeled incorrectly. The authors reported survival rates from Esrailian *et al.* [2] as 43% in patients receiving combination octreotide and midodrine therapy versus 71% control group. Based on our review of this trial, we find that the reported values represent mortality rates instead of survival. Given this finding, the survival rates in Table 4 should be modified to 57% in the treatment group versus 29% in the control group which further demonstrates benefit from this combination therapy.

On Page 38, Davenport *et al.* [1] referenced Pomier-Layrargues *et al.* [3] as having a higher survival rate in patients treated with the midodrine and octreotide combination compared with the combination of dopamine and albumin. Review of this reference reveals a double-blinded crossover comparison of octreotide versus placebo to evaluate the improvement in renal function at 8 days. We suggest that the authors may have intended to credit Angeli *et al.* [4] with this trial review and summation. Angeli *et al.* [4] compared the effects of dopamine and the combination of midodrine and octreotide in patients diagnosed with hepatorenal syndrome (HRS) Type 1. Upon our review of this reference, we find that patients in both groups received albumin. We suggest that a more accurate description of this trial in Table 4 might reflect dopamine alone in the comparator group column and 20–40 g/day in the albumin administration column.

Table 4 notes a study by Wong *et al.* [5] correctly as a prospective trial that examines the role of transjugular intrahepatic portosystemic stent shunt with background midodrine, octreotide and albumin therapy in HRS Type 1 patients. It was reported in the study by Davenport *et al.* [1] that reference 72 reflects this citation instead of the noted reference

61, a study of HRS Type 2 patients not included in this table. Further review of Wong *et al.* [5] reveals that all patients received albumin 50 g/day for 5 days prior to trial initiation and were subsequently continued on albumin 50 g/day for the trial duration (median 14 ± 3 days, range 5–47 days). Table 4 might be modified to remove a treatment duration of 5 days from the albumin administration column.

In conclusion, we appreciate the work that the authors have undertaken to bring us the review. However, we find the above-noted values and citations may not be entirely correct. We hope that these items do not alter treatment suggestions offered in the Davenport *et al.* [1] recommendations for the clinical practice section of this article. However, we request the authors to confirm the assigned levels of evidence recommendations, particularly for North American readers who do not have access to terlipressin.

Conflict of interest statement. None declared.

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Reply

Sir,

Octreotide infusions have been used in the management of patients with hepatorenal syndrome Type 1 (HRS-1), due to their effects on portal blood flow. When used alone, octreotide has not been shown to significantly improve renal function [1]. However, there are a number of small studies reporting a beneficial effect when combined with midodrine, and standard medical therapy (SMT) including albumin used either at the initiation of supportive care or during the ongoing treatment. We wish to thank Nguyen and colleagues for drawing our attention to the study from Esrailian *et al.* [2], which reported a 30-day 40% improvement in renal function in patients with HRS-1 treated with

the combination of midodrine and octreotide compared with 10% with SMT, and both the earlier study from Angeli *et al.* [3] who reported an improvement in renal function in five patients with midodrine doses titrated to achieve an increase in mean arterial blood pressure of 15 mmHg, and the later report from Wong *et al.* [4] of 10 of 14 responding to treatment. However, none of these positive reports was a large study or a truly randomized prospective study, and as such, there may be an element of publication bias towards reporting positive findings in small case series. Unfortunately, the evidence-based literature in treating patients with HRS-1 is somewhat lacking as pointed out in our review [5], although treatment with vasopressin analogues in combination with SMT would appear to be currently the most promising option.

Conflict of interest statement. None declared.

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Calciphylaxis in end-stage renal disease patients

Sir,

In a recent paper, Hayashi *et al.* [1] reviewed the cases of calciphylaxis in the Japanese dialysis population. They conducted a survey case-control study to identify the characteristics and risk factors for the development of calciphylaxis in chronic haemodialysis patients in Japan. The study identified warfarin therapy and lower albumin concentration as the strong risk factors for the development of calciphylaxis.

In 2008, our group analysed a series case report [2] of eight calciphylaxis cases diagnosed by skin biopsy in our hospital between January 2001 and December 2006. In our case report, all patients were female, obese, met the established criteria for the cardiometabolic syndrome and all developed hypotensive episodes during haemodialysis sessions. We propose the reduction of blood pressure

during haemodialysis treatment that impairs perfusion in the vascular bed of the subcutaneous adipose compartment as a major mechanism for inducing calciphylaxis in our obese patients. Hypotension and subsequent hypoperfusion of subcutaneous adipose tissue (increased in these obese patients) may be responsible for inducing calciphylaxis. Our patients presented lesions proximally in the regions of greatest adiposity which supports our hypothesis [3].

As in Hayashi's study, our patients also had low serum albumin levels and most of them were undergoing treatment with warfarin. We did not find any association with levels of serum calcium or phosphate levels or parathyroid hormone levels [4] as in Hayashi's study.

We consider calciphylaxis as a severe complication of obese female patients on haemodialysis. Based on our data, the risk factors for developing calciphylaxis are female gender, obesity associated with type 2 diabetes and anticoagulant therapy with warfarin. In these patients hypotensive episodes during dialysis treatment should be avoided because it may favour a subcutaneous adipose tissue ischaemia and the development of calciphylaxis.

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Reply

Verdalles *et al.* suggest that the hypotensive episode impairs perfusion in the vascular bed of subcutaneous adipose tissue and results in calciphylaxis. In addition, obesity may deteriorate the tissue hypoperfusion, further. This hypothesis seems very attractive for the etiology of calciphylaxis. In consistent with Verdalles's report, previous case studies also identified female gender and obesity as risk factors for calciphylaxis as described in Verdalles's previous report. Our recent