

opportunity to expand our discussion on the pathogenesis of HRS as well as on the therapeutic resources.

The fact that volume expansion is an essential component in the prevention and treatment of HRS has been confirmed in the past several years. For example, albumin is able to prevent HRS in patients with spontaneous bacterial peritonitis (SBP),<sup>1</sup> and its prolonged administration is necessary to improve the efficacy of terlipressin or midodrine in reversing HRS type 1.<sup>2-4</sup> This does not exclude, however, that simple volume expansion is insufficient to correct glomerular filtration rate in such patients.

From a pathogenetic standpoint, there are two types of functional renal failure in cirrhotic patients: one that is caused by an absolute loss of volume, as can occur after over-zealous diuretic use, gastrointestinal bleeding, diarrhoea or other dehydrating events. In these cases, renal failure is regarded as prerenal azotaemia, as hypovolaemia with reduced renal perfusion pressure is the only cause of renal failure.<sup>5,6</sup> This type of renal failure is easily resolved by correction of the trigger and by volume restoration using albumin as well as crystalloids or colloids. The second type of renal failure is caused by renal vasoconstriction and this is what is defined as HRS.<sup>7</sup> These patients have severe effective hypovolaemia that is not due to absolute volume loss, but rather to a maldistribution of the total blood volume with an excess of blood preferentially located in the dilated splanchnic vessels.<sup>8</sup> The absolute blood volume of these patients is not necessarily decreased and the circulatory dysfunction is attributed to an exaggerated stimulation of cytokines, many of which are vasodilators, such as that occurs with bacterial peritonitis.<sup>9</sup> The reason why fluid administration corrects prerenal azotaemia but not HRS is probably due to the fact that in prerenal failure, the intravenous fluids administered are partly retained in the central circulation, thereby improving the total and the effective blood volume; whereas in the latter, the intravenous fluids are rapidly sequestered into the splanchnic circulation, or third spaced into the peritoneal cavity as increased ascites, rather than staying in the circulation to improve the effective blood volume.<sup>10</sup> Accordingly, the response to blood volume expansion in cirrhotic patients has become one of the widely accepted criteria to separate HRS from other forms of functional renal failure.

Recent investigations suggest that, in addition to peripheral vasodilation, the already elevated cardiac output as observed in patients with decompensated cirrhosis, is relatively insufficient for the extent of arterial vasodilatation and this may also contribute to the effective hypovolaemia in cirrhotic patients.<sup>11</sup> The issue deserves new accurate investigations.

HRS type 1 is a rapidly progressive form of renal failure, and if it is not responsive to early treatment, the patient may develop acute tubular necrosis and die within a few days due to multi-organ failure. This justifies the indication to liver transplantation for the patients who survive the initial insult of renal failure.

From a practical point of view, we agree that many previous investigations might have used insufficient volume expansion to diagnose HRS and that some of those patients might have been misdiagnosed as having HRS. This was the reason why we decided to update the criteria of diagnosis of HRS, replacing crystalloids with albumin, since it seems to be the most effective colloid in cirrhotic patients.<sup>12</sup> In order to establish the daily doses and total amount of albumin to be administered, we did take into account the importance of balancing the need to improve the accuracy of the diagnosis of HRS with the need to avoid any delay in providing potentially effective treatment. This led us to establish that a 2-day administration was a sufficient time in most cases, so that vasoconstrictors (or other forthcoming therapies) are not unduly delayed. The dose of albumin (1 g/kg b.w.) was chosen according to the collective experience of the experts in our panel and also to the results of one previous trial.<sup>1</sup> We were concerned that a greater amount of albumin could increase portal pressure with the associated risk of variceal haemorrhage.<sup>13</sup> However, table 3 of our paper states that the infusion of albumin should be given for "at least" 2 days, thereby allowing the physician to prolong the volume expansion in individual cases for a sufficient time to correct the intravascular volume deficit. However, we are confident that a more prolonged or greater infusion of albumin could not be of benefit in treating patients with HRS type 1, without the co-administration of a vasoactive drug such as terlipressin. This opinion is supported by the previous experience that other manoeuvres such as the insertion of a peritoneovenous shunt, which provided more volume expansion than intravenous fluids, did not improve renal function in patients with HRS.<sup>14</sup> Furthermore, a recent Spanish trial reports that only 9% of patients with a traditional diagnosis of HRS responded to the administration of albumin for more than 7 days, whereas 44% of similar patients responded to terlipressin combined with albumin.<sup>15</sup>

With respect to the investigation of a goal-directed circulatory treatment, we agree with this proposal entirely, but such investigations must have predefined endpoints in order to demonstrate the efficacy or failure of any step of therapy. Accordingly, in our paper, we advised that doses and frequency of vasoconstrictors administration should be adjusted according to blood pressure and creatinine changes, and suggesting that

## Authors' response

Umgelter and colleagues have reported that there is a general reluctance to treat cirrhotic patients with renal failure with volume resuscitation. Moreover, they are critical of the accuracy of diagnosing hepatorenal syndrome (HRS) using the infusion of pre-defined doses of albumin as recommended in our paper.<sup>1</sup> Finally, they do not seem to share the opinion that HRS, once established, is no longer responsive to simple volume expansion, and therefore suggest investigating a goal-directed approach of treatment. We would like to take the

other simple measures such as plasma sodium and urine excretion could also be of help.

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## Authors' response

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