C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140:346–355.
[6] Toyoda H, Kumada T, Tada T, Hayashi K, Honda T, Katano Y, et al. Predictive value of early viral dynamics during peginterferon and ribavirin combination therapy based on genetic polymorphisms near the *IL28B* gene in patients infected with HCV genotype 1b. J Med Virol 2012;84:61–70.
[7] Tanaka Y, Nishida N, Sugiyama M, Tokunaga K, Mizokami M. Λ-interferons and the single nucleotide polymorphisms: a milestone to tailor-made therapy for chronic hepatitis C. Hepatol Res 2010;40:449–460.
[8] Thompson AJ, Muir AJ, Sulkowski MS, Ge D, Fellay J, Shianna KV, et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. Gastroenterology 2010;139:120–129.

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Encephalopathy or hepatic encephalopathy?

To the Editor:

We read with interest the paper by Ginès and co-authors on the management of critically-ill cirrhotic patients [1]. However, we have some concerns on the section on management of hepatic encephalopathy. The authors seem to base their recommendations on a 'statistical' rather than a pathophysiological definition of the syndrome, grouping under the heading 'severe hepatic encephalopathy' a set of different neuropsychiatric symptoms arising in critically-ill cirrhotic patients, to include mental abnormalities relating to sepsis, electrolyte imbalance, and even the side- or desired-effects of drugs such as opioids and benzodiazepines. Within this frame, they state that ammonia levels should not be measured, as they provide no clinical information nor do they relate to clinical outcomes. While we agree with the authors that patients with cirrhosis, especially if critically-ill, may present with more than one metabolic encephalopathy, and these may all contribute and worsen the clinical picture, it seems to us that an effort should be made to differentiate *hepatic* encephalopathy from other forms of metabolic/toxic neuropsychiatric disturbance. For example, we need to be reasonably sure that the encephalopathy we refer to in order to define fulminant hepatic failure is *hepatic* encephalopathy, as we would not want to list for transplant a patient with hepatitis who is confused because of hypoglycaemia, or opioid/benzodiazepine overdose. In this respect, ammonia levels seem useful, as they reflect hepatic failure and portal-systemic shunting [2], they correlate with recognised, quantified indices of hepatic encephalopathy, and they predict the development of hepatic encephalopathy over time [3]. Notably, sepsis, electrolyte imbalance, and psychoactive drugs cause neuropsychiatric abnormalities in critically-ill patients with no liver dysfunction [4]: we would not diagnose these patients with hepatic encephalopathy, we would not expect them to be hyperammonaemic and we would not treat them with ammonia-lowering drugs such as non-absorbable disaccharides/antibiotics. Critically-ill cirrhotic patients are no exception. Should they present with more than one potential cause for neuropsychiatric dysfunction, each cause should be identified and treated according to its pathophysiology. Finally, there seems to be some confusion in Table 2, in relation to the West Haven criteria [5]. These are clinical criteria and they are described, although not in their exact, original form [5], in columns 2 and 3 of the table. However, the table also depicts stages, characterized by parallel alterations in consciousness, cognitive/behavioural features, neurological findings, and electroencephalographic changes. Such correspondence has never been established, which is the reason why Conn and co-workers proposed the use of an index, not unlike the Child–Pugh score, combining the independent scores of five dimensions (mental state based on the West Haven criteria, Trail Making Test A, asterixis, electroencephalographic slowing and arterial ammonia levels) [5]. In addition, the classification of electroencephalographic changes reported in column 5 of the table does not correspond to either the one proposed by Conn *et al.* [5] or to more modern ones [6], most likely in relation to a typo or an alignment problem. An *errata corrige* on the involuntarily misleading information provided in Table 2 of the paper might be necessary.

Conflict of interest

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References

[1] Gines P, Fernandez J, Durand F, Saliba F. Management of critically-ill cirrhotic patients. J Hepatol 2012;56:S13–S24.
[2] Watanabe A. Portal-systemic encephalopathy in non-cirrhotic patients: classification of clinical types, diagnosis and treatment. J Gastroenterol Hepatol 2000;15:969–979.
[3] Montagnese S, Biancardi A, Schiff S, Carraro P, Carla V, Mannaioni G, et al. Different biochemical correlates for different neuropsychiatric abnormalities in patients with cirrhosis. Hepatology 2011;53:558–566.
[4] van den Boogaard M, Pickkers P, Slooter AJ, Kuiper MA, Spronk PE, van der Voort PH, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. BMJ 2012;344:e420.
[5] Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-

systemic encephalopathy. A double blind controlled trial. Gastroenterology 1977;72:573–583.
[6] Amodio P, Pellegrini A, Ubiali E, Mathy I, Piccolo FD, Orsato R, et al. The EEG assessment of low-grade hepatic encephalopathy: comparison of an artificial neural network-expert system (ANNES) based evaluation with visual EEG readings and EEG spectral analysis. Clin Neurophysiol 2006;117:2243–2251.

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Reply to: "Encephalopathy or hepatic encephalopathy?"

Management of critically-ill cirrhotic patients

To the Editor:

In response to Montagnese *et al.* [1], we fully agree that hepatic encephalopathy is a multifactorial syndrome which may result from impaired liver function, portosystemic shunts as well as from non-hepatic factors including sepsis, electrolyte imbalance, and sedative agents. None of the manifestations of hepatic encephalopathy are specific to any of the mechanisms involved. Although we do not clearly understand what a "statistical definition" means in this context, we also agree that, as it is multifactorial and non-specific, "hepatic encephalopathy" might be better termed as "encephalopathy" in critically-ill cirrhotic patients who frequently have several precipitating factors. Elevated blood ammonia levels are the hallmark of encephalopathy in cirrhosis. However, the correlation between blood ammonia and severity of encephalopathy is weak [2]. In addition, due to a marked impairment in liver function, any critically-ill cirrhotic patient is expected to have elevated blood ammonia levels, whatever the severity of encephalopathy. Practically, the findings of elevated blood ammonia levels in this population may not exclude the contribution of non-hepatic factors in the occurrence of neuropsychiatric changes. This is the reason why, in line with others [3], we have suggested that the systematic determination of blood ammonia levels is unlikely to be useful in the management of critically-ill cirrhotic patients [4].

As pointed out by Montagnese *et al.* [1], whether or not non-hepatic factors are involved in the occurrence of encephalopathy, in patients with acute liver failure, is a crucial issue. Indeed, while the prognostic value of "spontaneous" encephalopathy (i.e. encephalopathy only related to impaired liver function) is unequivocally poor in acute liver diseases, it would be highly questionable to consider transplantation if encephalopathy is only related to non-hepatic factors. However, the issue of patients with acute liver failure is clearly different from that of critically-ill cirrhotic patients. In addition, any patient with acute liver failure is expected to have high blood ammonia levels, whatever non-hepatic factors are involved in the mechanisms of encephalopathy [5]. No threshold value of blood ammonia would allow a clear differentiation between "hepatic encephalopathy" and "non-hepatic encephalopathy". Careful analysis of the potential contributing factors is still essential in the management of patients with acute liver failure as well as critically-ill cirrhotic patients.

Finally, Montagnese *et al.* raise concerns about the variables to be included in the West-Haven criteria [1]. Indeed, the criteria presented in Table 3 [4] do not correspond to the "original" West Haven criteria [6]. Unfortunately, numerous studies have employed variations of these criteria [7]. In this review, we have selected one of these criteria including level of consciousness, intellectual behavior, neurological findings, and electroencephalographic (EEG) abnormalities [8] in an attempt to be exhaustive. Montagnese *et al.* are right in that there may not be a parallel between consciousness, behavior, other neurological findings, and EEG changes, which represents a limitation of these criteria. An index score comparable to the Child–Pugh score, combining the independent scores of these variables could be more accurate [6]. However, no consensus exists yet on an optimal scoring system.

Conflict of interest

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References

[1] Montagnese S, Merkel C, Amodio P. Encephalopathy or hepatic encephalopathy?. J Hepatol 2012;57:928–929.
[2] Kramer L, Tribl B, Gendo A, Zauner C, Schneider B, Ferenci P, et al. Partial pressure of ammonia versus ammonia in hepatic encephalopathy. Hepatology 2000;31:30–34.
[3] Bajaj JS. Review article: the modern management of hepatic encephalopathy. Aliment Pharmacol Ther 2010;31:537–547.
[4] Gines P, Fernandez J, Durand F, Saliba F. Management of critically-ill cirrhotic patients. J Hepatol 2012;56:S13–S24.
[5] Rolando N, Wade J, Davalos M, Wendon J, Philpott-Howard J, Williams R. The systemic inflammatory response syndrome in acute liver failure. Hepatology 2000;32:734–739.
[6] Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. Gastroenterology 1977;72:573–583.
[7] Blei AT, Cordoba J. Hepatic encephalopathy. Am J Gastroenterol 2001;96:1968–1976.