

An Important, Potentially Life-Threatening Cause of Acute Adult Disorders of Consciousness Is Missing From the Evaluation Done by Chang et al

To the Editor:

We recently read a comprehensive review by Chang et al (1) on acute adult disorders of consciousness (DoC) for intensivists, but we noticed that a crucial cause of DoC was not mentioned. Severe liver failure is a common cause of hyperammonemia in ICU patients and requires urgent treatment to avoid neurologic complications and even death (2). However, nonhepatic hyperammonemia in ICU patients can pose diagnostic and management challenges for clinicians (2–4). Nutritional and metabolic factors can also contribute to these complex disorders and need to be considered in management (2–4). Causes of nonhepatic hyperammonemia, such as drugs, infection, and inborn errors of metabolism may be unfamiliar to clinicians and may be overlooked. Although cirrhotic patients may tolerate high ammonia levels, other causes of acute severe hyperammonemia can result in fatal cerebral edema as noncirrhotic do not tolerate hyperammonemia for more than 6 hours when the concentrations are greater than 150 $\mu\text{mol/L}$ in adults. In case of levels above 150 $\mu\text{mol/L}$ in adults, they are associated with intracranial hypertension and those patients do need urgent blood purification (2–4). Therefore, any coma of unclear cause should prompt immediate measurement of ammonia and severe elevations should be treated with protective measures and renal replacement therapy to avoid neurologic injury (2–4). Ammonia is a small, water-soluble molecule that can be cleared using renal replacement therapy, with similar properties to urea (2–4). Although diffusive therapies may have some theoretical advantages, there is no clear evidence that any particular modality is superior. Peritoneal dialysis and exchange transfusion have both been DoC as inferior treatment strategies and the role of more complex blood purification methods is still unclear (2–4). Conventional hemodialysis can rapidly reduce ammonia concentrations. However, continuous modalities may be preferable in the critical care setting as they are less likely to result in rebound hyperammonemia, exacerbation of cerebral edema, and potential hemodynamic instability (2–4). Continuous modalities of renal replacement therapy also offer benefits such as fever prevention, management of electrolyte and acid-base balance, and drainage of dangerous fluid accumulation that may exacerbate cerebral edema (2–4). In situations where treatment begins with conventional dialysis, it is important to follow-up with continuous renal replacement therapy to maintain biochemical control. Avoiding delays in the initiation of therapy is crucial as vulnerable patients can experience sudden onset of permanent neurologic injury (2–4).

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The correlation between plasma ammonia and the severity of encephalopathy and cerebral edema is somewhat variable (5). Levels of more than 100 $\mu\text{mol/L}$ are highly predictive of encephalopathy in hepatic hyperammonemia, while ammonia concentrations over 150 $\mu\text{mol/L}$ in adults are associated with intracranial hypertension that may lead to neurologic injury and death from brainstem herniation (2–4).

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The authors reply:

We thank Honoré et al (1) for their comments that further highlight hyperammonemia as a potential cause of an acute disorder of consciousness (DoC). We appreciate the need to assess for an elevated ammonia level and to consider a comprehensive differential diagnosis that includes nutritional, metabolic, and nonhepatic causes of hyperammonemia. Given the nature of a Concise Definitive Review (CDR), we briefly mentioned hyperammonemia as an important metabolic cause of DoC (2), fully anticipating that clinicians evaluating an acute DoC would initiate a detailed investigation if hyperammonemia were discovered. We thank Honoré et al (1) for providing this thorough and thoughtful discussion as a complement to the framework within the CDR. Furthermore, they importantly underscore the dangers of resultant cerebral edema and acute treatment imperatives that include renal replacement therapy to prevent death or permanent neurologic injury.

This letter to the editor provides an opportunity to reinforce that there are a plethora of metabolic etiologies that may impact consciousness. Our CDR addressing evaluation of acute adult DoCs was intended to provide a structured approach from which to initiate a thorough evaluation of potential etiologies that would inform subsequent therapy undertaken by bedside clinicians. Honoré et al (1) have done precisely what we hoped readers would do—expand on that structure in a fashion that is directly translatable to the bedside, and in a venue, that reaches the global critical care community.

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***See also p. e247.**

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