

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Hepatic Encephalopathy

Eelco F.M. Wijdicks, M.D., Ph.D.

From the Division of Critical Care Neurology, Mayo Clinic, Rochester, MN. Address reprint requests to Dr. Wijdicks at the Division of Critical Care Neurology, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, or at wijde@mayo.edu.

N Engl J Med 2016;375:1660-70.

DOI: 10.1056/NEJMra1600561

Copyright © 2016 Massachusetts Medical Society.

WHEN THE LIVER FAILS, BRAIN FUNCTION CHANGES. ACUTE-ON-chronic liver failure is manifested initially as abnormal behavior and compromised cognition. In the absence of preexisting disease, acute, severe liver failure may cause the brain to swell, with patients becoming comatose and losing brain function altogether. Hepatic encephalopathy in patients with chronic liver disease is potentially reversible and manageable, but new, acute (fulminant) hepatic encephalopathy with rapidly rising blood ammonia levels is more difficult to control because of diffuse brain edema and structural brain-stem injury.

Although the onset of hepatic encephalopathy can rarely be pinpointed clinically, it is a clinical landmark in patients with advanced liver disease, invariably signaling a worsening medical condition. Severe hepatic encephalopathy in patients with cirrhosis is associated with a mortality of more than 50% in the first year alone.^{1,2} Hepatic encephalopathy in patients with cirrhosis does not decisively limit eligibility for liver transplantation, although patients often die while they are on the waiting list for a transplant.³ Similarly, among patients with fulminant hepatic failure, progression from acute hepatic encephalopathy to brain edema is associated with a high mortality. The rate of death is substantially lower for patients who receive a transplant. The survival rate is more than 70% in the first 5 years after transplantation,⁴ although only one of five patients with fulminant hepatic failure receives a transplant.⁵

Hepatic encephalopathy is not diagnosed and graded exclusively by specialists in chronic liver failure. Patients may first see a general practitioner, an emergency physician, or a hospitalist. These practitioners may consult the neurologist (or neurointensivist) for a detailed assessment of presumptive hepatic encephalopathy, to rule out treatable mimicking disorders, and in fulminant forms, to manage brain edema. This review addresses the manifestations, diagnosis, and in-hospital management of acute hepatic encephalopathy from the neurologist's perspective.

HEPATIC ENCEPHALOPATHY AND HYPERAMMONEMIA

The pathogenesis of hepatic encephalopathy has been incompletely understood since the first neuropathological descriptions of the disorder.⁶ Concepts explaining the pathophysiological features have been discussed elsewhere,^{7,8} and Figure 1 shows a potential pathway. Rapidly progressive hepatic encephalopathy in patients with fulminant hepatic failure is a clinical syndrome associated with cerebral edema.

Colonic bacteria and mucosal enzymes break down digested protein, releasing ammonia from the gut. Ammonia enters the portal circulation of the liver and is converted to urea through the urea cycle. In cases of hepatic failure, ammonia accumulates and is shunted into the systemic circulation. Hyperammonemia results in neuronal dysfunction, leading to hepatic encephalopathy. Brain edema

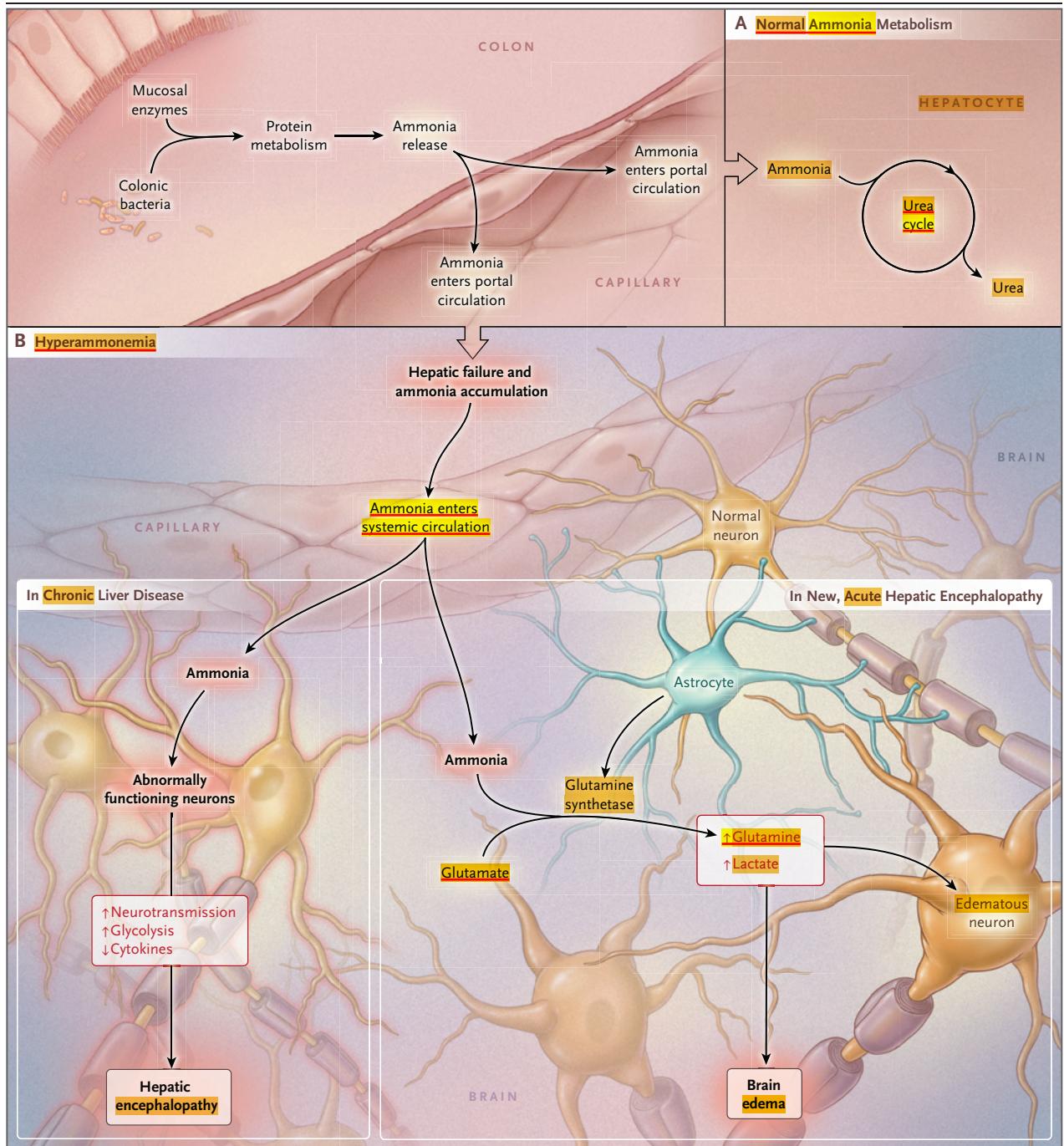


Figure 1. Putative Mechanisms Underlying Hepatic Encephalopathy and Brain Edema.

A potential pathway conceptualizes the pathophysiological features of hepatic encephalopathy and hyperammonemia.

may occur in conjunction with a rapid rise in ammonia levels, particularly in patients with no prior liver failure.⁹ At high levels, ammonia can cross the blood–brain barrier, where astrocytic glutamine synthetase converts ammonia and

glutamate into glutamine, which in turn acts as an osmolyte and increases cerebral volume.

Ammonia is one of many neurotoxic substances resulting in decreased excitatory neurotransmission.¹⁰ The role of benzodiazepine re-

ceptors in hepatic encephalopathy has been established. In a study of treatment with flumazenil, a γ -aminobutyric acid (GABA)-benzodiazepine receptor antagonist, patients had both clinical and electroencephalographic evidence of improvement, but the response rate was low and the responses were *unsustained*.¹¹ Moreover, the findings in some studies may have been confounded by prior administration of benzodiazepines.¹² The recent discovery that the neurosteroid allopregnanolone activates GABA type A (GABA_A) receptors, causing inhibition through a chloride-channel opening, has prompted efforts to develop agents that *antagonize GABA_A receptor-potentiating neurosteroids*.¹³ Another possible contributor to hepatic encephalopathy, particularly in patients with long-standing cirrhosis, is manganese toxicity, which appears on magnetic resonance imaging (MRI), especially on T₂-weighted imaging, as abnormalities in the globus pallidus.¹⁴ Mercaptans, short fatty acids, decreased glutaminergic synaptic function, lactate, and dopamine metabolites have also been implicated.¹³

Neuroinflammatory responses can play a role if an intercurrent infection or sepsis is responsible for hepatic encephalopathy in patients with *advanced liver disease*. Inflammatory cytokines may enhance ammonia-induced neurotoxicity through the blood-brain barrier.¹⁵ Microscopically, *hyperammonemia* may cause *enlarged, pale* (because of decreased chromatin) *astrocytes* (Alzheimer type II astrocytes) but *only after long-term exposure and not* in the context of *fulminant hepatic failure*.⁶

The increase in serum ammonia levels remains central to our understanding of hepatic encephalopathy, and therapies remain directed toward lowering ammonia levels in patients with signs of hepatic encephalopathy. The *correlation* between serum *ammonia levels* and the *severity* of hepatic *encephalopathy* in patients with cirrhosis is *monotonic* but is *not linear* or *exponential*.¹⁶ Long-term increases in serum ammonia levels may *not necessarily* lead to hepatic *encephalopathy*, and diuretic use or renal failure may play a role.¹⁷ The *correlation* appears to be *stronger* in patients with *fulminant hepatic failure*, and the *risk of cerebral edema* increases with arterial *ammonia* levels that *exceed 200 μ mol per liter* (340 μ g per deciliter).

Emerging or worsening hepatic encephalopa-

thy is a *complication* in *30 to 50%* of patients with *cirrhosis* who undergo transjugular, intrahepatic *portosystemic shunting*.¹⁸⁻²⁰ Minimal hepatic encephalopathy before the procedure may progress to marked hepatic encephalopathy afterward, with a documented *steep rise in venous ammonia levels*.²¹

DEFINITION AND GRADING OF HEPATIC ENCEPHALOPATHY

CLINICAL FEATURES

Initially, the terms “hepatic coma” and “hepatic encephalopathy” were used interchangeably.²²⁻²⁷ Sherlock and colleagues introduced the term “portal-systemic encephalopathy.”²⁸ Hepatic encephalopathy and disturbance of consciousness had been noted in von Frerichs’s classic work on liver disease.²⁹ Jaundice preceded the development of delirium, convulsions, and coma, as well as observed phases of “gloomy, irritable temper and restlessness,” “quiet, harmless wandering,” and “maniacal paroxysms.” One third of the patients had convulsions; most of these patients had delirium and “progressed to a deep coma from which no shouting or shaking could arouse [them].”

A landmark clinicopathological study by Adams and Foley further delineated clinical symptoms and pathological changes in the brain and also introduced *asterixis* as a *key observation*.⁶ The term “asterixis” (from the Greek *sterixis*, meaning “fixed position,” with the prefix *a*, meaning “without”) denoted an *inability to keep outstretched arms and hands in place* (see video, available with the full text of this article at NEJM.org).

Clinical features of hepatic encephalopathy can progress from mild to severe in patients with acute-on-chronic liver disease or acute liver disease. New-onset hepatic encephalopathy is syndromic but unpredictable in its manifestations. *Reduced awareness of surroundings* and stimuli, *yawning*, and *dozing off* are characteristic of the *earlier stages*, but *new irritability* and *maniacal excitement* have also been reported.^{6,28} Hepatologists have *graded the severity* of hepatic encephalopathy according to the *West Haven criteria*³⁰ (Table 1) and, more recently, have identified *covert hepatic encephalopathy* in patients with no particular symptoms beyond abnormal behavior on psychometric tests.^{32,33} Although *covert hepatic encephalopathy* is mild and occurs mostly in patients with cirrhosis, it is *associated* with



A video showing manifestations of hepatic encephalopathy is available at NEJM.org

frequent falls, incompetent driving, fatigue, disinterest, distraction, and serious socioeconomic consequences. Given its nonspecific nature, this low-grade encephalopathy may be indistinguishable from general malaise, frailty, and continual alcohol consumption, factors that potentially further compromise cognitive decline.³³

Impairment of consciousness characterizes progression to grade 3 or 4 hepatic encephalopathy. Fluctuating attention and slow responses to requests are typical. Patients are incapable of the three features of memory: registration, retention, and recall. The immediate memory span for digits is markedly reduced. Overactivity and unrest, delusions, repetitive picking movements, and disorientation with respect to place become evident in grade 3 hepatic encephalopathy. There is progression to stupor, with minimal verbal output, and a noxious stimulus (unfortunately, with easy bruising) is often required to obtain a sustained response. At this stage, patients have tachypnea, with loss of the usual chemical control of breathing, often leading to respiratory alkalosis.³⁴ Grading of hepatic encephalopathy categorizes it in clinical stages of stepwise worsening. The description of each grade varies somewhat in the literature, but differences between adjacent grades are clear enough to be helpful in clinical practice, although neurologic descriptors are sparse. One study showed that for patients who become comatose, the Full Outline of Unresponsiveness (FOUR) score is more discriminating than the West Haven grading system because it includes brain-stem and respiration assessment, which are not further differentiated in the West Haven system^{31,35} (Table 1).

In patients who have acute fulminant hepatic failure without chronic liver disease, the clinical development of hepatic encephalopathy is a more condensed process. Rigid extremities (and neck muscles) and resistance to passive movements (paratonia) are seen, as is worsening confusion. Extensor posturing, suggesting structural brain injury, characteristically occurs in grade 4 encephalopathy and may be completely reversible after correction of ammonemia. Grasp reflexes may be observed.⁶

The pupils of patients with early hepatic encephalopathy are normal, and the pupillary responses are preserved. In grade 3 or 4 encephalopathy, the pupillary reaction becomes sluggish and, because of diffuse cerebral edema, eventu-

Table 1. A Comparison of the West Haven and FOUR Scales: Criteria for Grading Hepatic Encephalopathy.*

Grade	West Haven		FOUR Score			
	Features	Score	Eye Response	Motor Response	Brain-Stem Reflex	Respiration
0	No abnormalities detected	4	Eyelids open or manually opened; tracking or blinking on command	Thumbs up, fist, or peace sign on command	Pupillary and corneal reflexes present	Not intubated, regular breathing
1	Unawareness (mild), euphoria or anxiety, shortened attention span, impairment of calculation ability, lethargy or apathy	3	Eyelids open but no tracking	Localized response to pain	One pupil wide and fixed	Not intubated, Cheyne–Stokes breathing
2	Disorientation to time, obvious personality change, inappropriate behavior	2	Eyelids closed but open to loud voice	Flexion response to pain	Pupillary or corneal responses absent	Not intubated, irregular breathing
3	Somnolence to stupor, responsiveness to stimuli, confusion, gross disorientation, bizarre behavior	1	Eyelids closed but open to pain	Extension response to pain	Pupillary and corneal responses absent	Breathing above ventilator rate
4	Coma	0	Eyelids remain closed to pain	No response to pain, or generalized myoclonus status	Pupillary, corneal, and cough reflexes absent	Breathing at ventilator rate or apnea

* Patients with minimal hepatic encephalopathy (grade 1 with the use of the West Haven criteria) would be classified as having covert hepatic encephalopathy. Patients with West Haven grade 2 or higher encephalopathy would be classified as having overt hepatic encephalopathy.^{30,31} The FOUR (Full Outline of Unresponsiveness) score clinical grading scale takes into account four components of neurologic function. Scores range from 0 to 16, with lower scores indicating a lower level of consciousness.

ally disappears as a consequence of progressive brain-stem injury. Pupil size is mostly unchanged in grade 1 or 2 encephalopathy, but the pupils enlarge and become midposition (3 to 5 mm) in grade 3 or 4 encephalopathy. Oculocephalic responses, although brisk, usually remain intact. Periodic lateral or dysconjugate gaze or a fixed dysconjugate gaze has been reported, which disappears after serum ammonia levels are reduced.

Jactitations (restless tossing and muscle or limb twitching) are common with progressive encephalopathy and may merge with multifocal myoclonus (see video). Abnormal movements such as dystonia, orofacial dyskinesias, and parkinsonian features may point to Wilson's disease, which in rare cases may be characterized by acute hepatic failure.³⁶

ELECTROPHYSIOLOGICAL FEATURES

Generally, worsening hepatic encephalopathy is associated with major changes in the electroencephalographic (EEG) pattern, such as dyssynchronization of fast activity, increased dysrhythmicity, and slower delta activity followed by mixtures of slow-with-fast frequencies, more frequent delta activity, and disorganization.^{24,37,38} Triphasic-wave patterns, defined as generalized, bilaterally synchronous, bifrontal periodic waves, are often associated with background slowing and appear in grade 2 or 3 hepatic encephalopathy but disappear in the comatose state.³⁹ These wave patterns are seen more often in patients with encephalopathy and subcortical brain atrophy than in patients with encephalopathy and no subcortical atrophy.⁴⁰ Once triphasic waves appear, the outcome worsens.⁴¹ A recent study emphasized increased fast beta activity in patients with alcoholic liver disease and suppressed variability in patients with hepatic encephalopathy.⁴² The role of evoked potentials in detecting covert hepatic encephalopathy for diagnosis or confirmation of hepatic encephalopathy has not been established, but brain-stem-evoked potentials are the most sensitive for detection of subclinical hepatic encephalopathy.⁴³⁻⁴⁵ There is renewed interest in using spectral EEG to diagnose hepatic encephalopathy.^{46,47}

It is unclear whether findings on EEG and evoked potentials help clinicians. The main practical use of EEG in assessing patients for hepatic encephalopathy is to rule out nonconvulsive status epilepticus.

MIMICKING DISORDERS

Wernicke–Korsakoff's syndrome, especially the amnestic state of Korsakoff's syndrome, may mimic hepatic encephalopathy. A global confusional state shares all the characteristics of early hepatic encephalopathy, including inattention, poor perceptual abilities, and irrational responses to questions, including a tendency to drift away from the topic. Confabulation (fabrication of answers or stories) is sometimes present early in Korsakoff's syndrome,⁴⁸ but an amnestic syndrome (anterograde amnesia) involving an inability to retain words, names, and tasks is invariably present. Wernicke's disease, known for ophthalmoplegia (lateral rectus paralysis and paralysis of horizontal or vertical conjugate gaze), gaze-evoked nystagmus, and ataxia, may be delayed. Patients with a history of alcohol abuse often receive intravenous thiamine soon after admission, which effectively treats the thiamine deficiency and makes Wernicke–Korsakoff's syndrome a less likely alternative explanation.

The features of acute alcohol-withdrawal delirium overlap those of worsening hepatic encephalopathy, but alcohol-withdrawal delirium, unlike hepatic encephalopathy, is characterized by coarse and rhythmic tremor, shouting, elided speech, and dysautonomia with cold sweats.⁴⁹ Neurologic findings are usually unremarkable.

New metabolic derangements reduce responsiveness and occur with dilutional hyponatremia, hypoglycemia, and metabolic alkalosis. The effect of these acute metabolic changes on clinical grading of hepatic encephalopathy is small because they are typically transient and rapidly corrected. Although hyponatremia can be severe, particularly in patients with acetaminophen toxicity, it is unlikely to confound the clinical examination in patients with chronically low sodium levels. However, sodium values have ranged from 110 to 147 mmol per liter in patients with hepatic encephalopathy.⁵⁰ A large reduction in sodium values is required to cause a change in responsiveness or a seizure. Conversely, aggressive correction (and overcorrection) of serum sodium levels (i.e., an increase of >8 mmol per liter in the first 12 hours) may lead to central pontine myelinolysis, particularly in patients with alcoholic hepatitis or cirrhosis.

Nonconvulsive status epilepticus has been described⁵¹ but is a challenging diagnosis to establish. It requires specialized expertise in the inter-

pretation of EEG findings because the triphasic-wave pattern that may be observed is somewhat similar to generalized periodic epileptiform discharges. This becomes particularly pertinent when triphasic waves are recorded in patients with hepatic encephalopathy who have altered consciousness and automatisms.

Chronic or acute subdural hematoma may mimic hepatic encephalopathy, except that focal signs are often present on neurologic examination. Alcohol addiction and chronic liver disease also increase the risk of subdural hematoma but not the risk of intracranial hemorrhage.^{52,53}

TREATMENT

INITIAL THERAPY

The goal of initial management of hepatic encephalopathy is to reduce ammonia absorption from the intestinal lumen with the use of lactulose or lactitol. These nonabsorbable disaccharides have laxative effects and change the gut microbiome to non-urease-producing bacteria, reducing intestinal ammonia production.⁵⁴ Protein restriction is ill advised, since normal protein intake does not appear to exacerbate hepatic encephalopathy.^{55,56} Guidelines recommend lactulose at a dose of 25 ml twice daily as a first-line agent, adjusted for the production of three bowel movements daily.⁵⁵ Intravenous L-ornithine-L-aspartate lowers ammonia levels by providing an alternative substrate for the urea cycle; its use is considered in patients who do not have a response to lactulose. For recurrent hepatic encephalopathy in patients with cirrhosis, rifaximin (550 mg twice a day), which alters gut microbiota, is added to lactulose; this combined treatment can reduce the frequency of hospitalization and prolong the time to a new bout of encephalopathy.⁵⁷ Probiotics (e.g., yogurts with lactobacillus or saccharomyces) have been shown to prevent or ameliorate hepatic encephalopathy in patients with cirrhosis.⁵⁸ Infection, which could precipitate gastrointestinal hemorrhage and dehydration, should be treated, and correction of hyponatremia and hypovolemia is warranted. Treatment may lead to impressive amelioration of symptoms; however, the clinical outcome often remains poor, with periods of worsening, partly because of poor adherence to medication regimens in cognitively incapacitated patients. Over time, the relationship between blood ammonia levels and the severity

of hepatic encephalopathy becomes less clear, and intercurrent infections or other causes may be implicated.

SECOND-LINE TREATMENTS

For patients with hepatic encephalopathy and cirrhosis who do not have a response to standard treatments, large portosystemic shunts are considered. End-stage liver disease can be an indication for liver transplantation, and in the past 5 years, the system for allocating transplants has been refined. The Model for End-Stage Liver Disease (MELD) is used to determine disease severity. The MELD score is calculated as follows: $3.78 \times \ln(\text{serum bilirubin in milligrams per deciliter}) + 11.2 \times \ln(\text{INR}) + 9.57 \times \ln(\text{serum creatinine in milligrams per deciliter}) + 6.43$, where \ln is the natural logarithm and INR is the international normalized ratio for prothrombin time. Scores range from 6 to 40, with higher scores indicating more severe disease.⁵⁹ Once a patient has had a major-index complication (e.g., ascites, hepatic encephalopathy, or variceal hemorrhage) or has a MELD score higher than 15, transplantation is considered.⁶⁰ The current allocation system uses the MELD score plus the sodium level.

INTENSIVE CARE

Measures to reduce hyperammonemia, the main driver of brain edema, are instituted in patients presenting with acute liver failure and in those presenting with acute-on-chronic liver failure. Acute fulminant hepatic failure requires intensive care to manage hypovolemic or distributive shock and renal failure, as well as severe coagulopathy and thrombocytopenia, which are equally worrisome.⁶¹ As soon as hepatic encephalopathy progresses to brain edema, management of increased intracranial pressure is urgent.⁶²⁻⁶⁵

A venous ammonia level of 150 to 200 μmol per liter (255 to 340 μg per deciliter) is a well-known risk factor for increased intracranial pressure in patients with fulminant hepatic failure. In one study, intracranial hypertension developed in 25% of patients with fulminant hepatic failure who had plasma ammonia levels of less than 250 μmol per liter (425 μg per deciliter).⁶⁶

Assessment of fulminant hepatic failure involves a neurologic evaluation and careful scrutiny of the computed tomographic (CT) scan. Disappearance of sylvian fissures and sulci characterizes early brain edema; narrowing or full

obliteration of the basal cisterns follows (Fig. 2). Diffuse brain edema causes coma with extensor posturing or no motor response to stimuli and, frequently, early brain-stem involvement with loss of pupillary responses and corneal reflexes. In patients with fulminant hepatic failure, abnormalities are clearly identifiable on the CT scan, but radiologic assessment can be difficult (Fig. 2). One study showed that half of patients with grade 4 or 5 hepatic encephalopathy had CT-scan abnormalities,⁶⁷ and in a study of acetaminophen toxicity with specific attention to

differentiation between gray and white matter, 40% of patients had cerebral edema.⁶⁸ The true incidence of brain edema, with or without increased intracranial pressure, remains unknown. In some situations, brain edema and tonsillar herniation are present on autopsy (Fig. 3).

Intracranial pressure-monitor placement has been considered in several studies for management of acute liver failure. An intracranial hemorrhage rate of 10% was reported in one prospective cohort of 92 patients with grade 3 or 4 encephalopathy in whom intracranial pressure

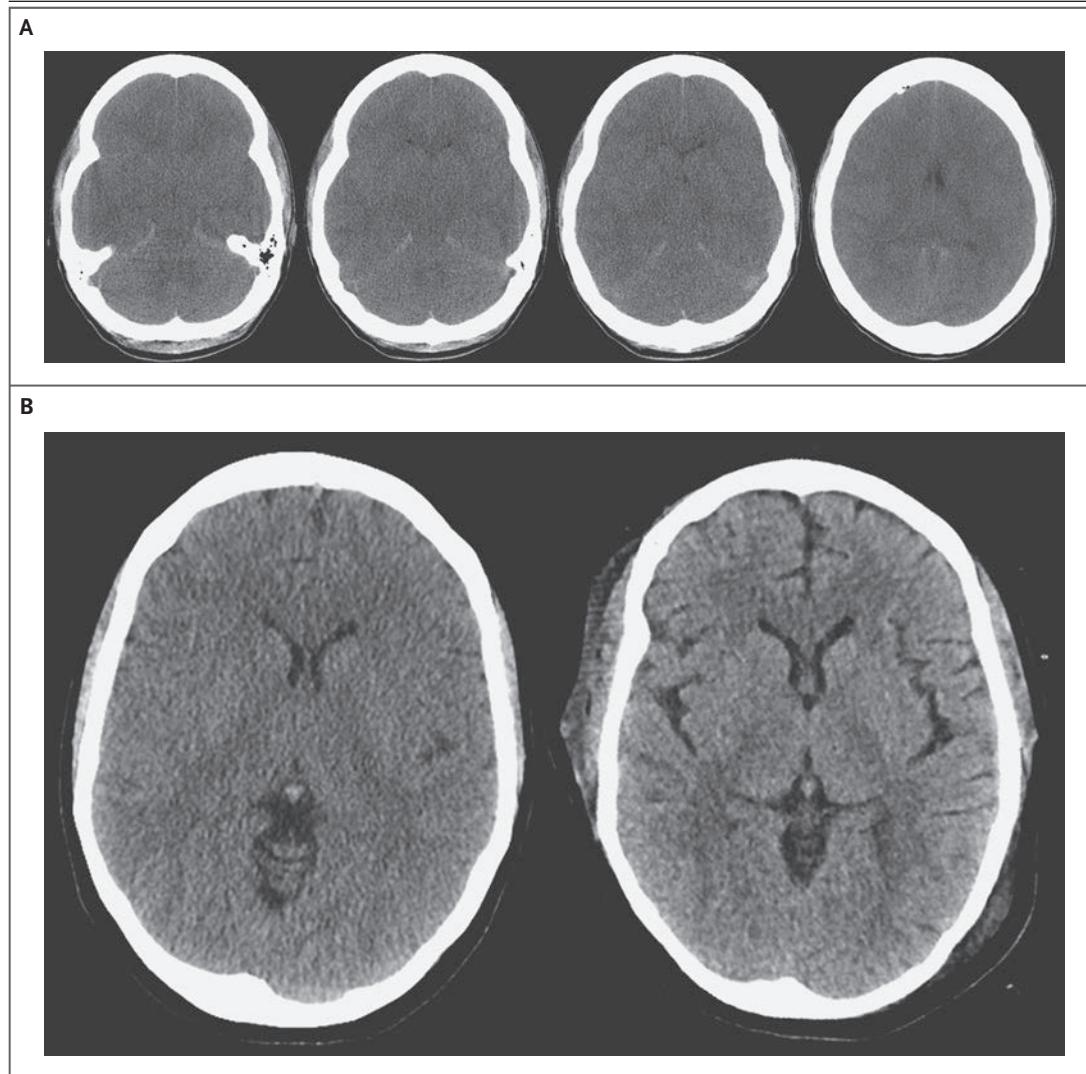


Figure 2. CT Findings in Fulminant Hepatic Failure.

In the CT scans shown in Panel A, in a patient with fulminant hepatic failure, the basal cisterns are absent, and there is loss of sulci and loss of differentiation between gray matter and white matter due to diffuse brain swelling. The CT scans in Panel B, obtained after mannitol administration in a young patient with acute hepatic failure and prior drug and alcohol use, are characterized by pseudonormal findings and show preexisting atrophy.

monitors were implanted, but half of the patients with hemorrhages were asymptomatic.⁶⁹ More recent studies showed a 7% hemorrhage rate among 56 patients with intracranial pressure monitors⁷⁰ and showed that the frequency of hemorrhage depends on postimplantation imaging.⁷¹ Correction of the INR with prothrombin-complex concentrate or recombinant activated factor VII can normalize the INR, but it may not fully correct the coagulopathy. Neurosurgeons recommend correction of the INR before monitor insertion, but prolonged control of the INR or thrombocytopenia is neither feasible nor necessary. Intracranial pressure monitoring is associated with a considerable risk of hemorrhage, and management without such monitoring has not been compared with management on the basis of CT-scan features and clinical examination. In fact, an intracranial pressure monitor is inserted in less than 15% of patients, and the proportion has declined in recent large cohorts.⁵ Placement of an intracranial pressure monitor in a comatose patient with CT-scan evidence of brain edema should be strongly considered.

The best approach to managing increased intracranial pressure in patients with fulminant hepatic failure is not known, but for most intensivists managing brain edema, the goal is to reduce intracranial pressure to less than 20 mm Hg. Cerebral perfusion pressures may be increased because of poor cerebral autoregulation and may need to be limited to a range of 50 to 70 mm Hg. There is insufficient experience with multimodal monitoring (e.g., a combination of tissue oxygenation, intracranial pressure, and electrophysiological monitoring), and it is unclear whether this approach could provide more precise information on ongoing neuronal injury and improve the outcome. Treatment may include elevating the head of the bed to 30 degrees and avoiding patient-ventilator dyssynchrony with the use of short-acting sedatives. Induced hypocapnia (a decrease of 15 mm Hg or more in the carbon dioxide level), resulting in alkalotic cerebrospinal fluid, constricts pH-dependent precapillary resistance vessels, reducing cerebral blood volume and thus intracranial pressure. Spontaneous hyperventilation is common in comatose patients with fulminant hepatic failure, and it is not known whether an additional lowering of the partial pressure of arterial carbon dioxide, to



Figure 3. Gross Photograph of Brain Edema and Tonsillar Herniation in a Patient with Fulminant Hepatic Failure.

20 to 25 mm Hg, may lead to critically reduced cerebral blood flow.

Therefore, in patients with evidence of cerebral edema on a CT scan, the best option is the administration of mannitol or a hypertonic saline bolus. A continuous hypertonic saline infusion lowers the osmotic gradient after the initial effect has passed, and it may be more difficult thereafter to change the gradient quickly with osmotic agents. One study used a prophylactic infusion of hypertonic saline (30%) in 15 patients, resulting in sodium levels of 145 to 155 mmol per liter and a sustained decrease in intracranial pressure, but this trial included patients receiving renal-replacement therapy, in whom the saline load depended on the hemofiltration rate.⁷² Repeated administration of a bolus of 10 or 23% hypertonic saline in response to increased intracranial pressure may be a reasonable option.

Most intensivists favor adjunctive fever control. A randomized, controlled trial of targeted temperature management (34°C) to prevent intracranial pressure and acute liver failure did not prevent increased intracranial pressure, and the mortality rate in the targeted-temperature group was the same as the rate in the control group.⁷³ The data were confounded because the number of patients who underwent transplantation was lower in the targeted-temperature group. In most patients, intracranial pressure at onset was less

than 27 mm Hg (up to 73% of patients with peak intracranial pressure in the mid-30s range).

Escalation to pentobarbital treatment before transplantation should probably be avoided because the neurologic examination will be confounded if a patient has no motor response and has possible involvement of brain-stem reflexes. If available, transcranial Doppler may indicate absent or reverberating flow, confirming increased intracranial pressure readings and avoiding transplantation in a brain-dead patient.

The molecular-adsorbent recirculating system (MARS), which dialyzes against a high-flux, albumin-coated polysulphone filter, is effective in preparing patients with fulminant hepatic failure for liver transplantation.^{74,75} However, MARS therapy can potentially worsen coagulopathy and was tentatively associated with intracranial hemorrhage in one study.⁷⁴

SUMMARY

Hepatic encephalopathy has Janus-faced characteristics, with clinical manifestations of chronically reduced neural metabolic function and acute cerebral edema. Hyperammonemia can be incriminated in both clinical scenarios, but other compounds contribute to them. Although cere-

bral edema in fulminant hepatic failure is largely cytotoxic, vasogenic components may play a role. Hyperemia as a result of increased cytokines may result in extracellular edema.^{76,77} It raises the question of whether extracellular cerebral edema may occur in worsening hepatic encephalopathy associated with cirrhosis.^{78,79} Increased apparent diffusion coefficient values on diffusion-weighted imaging in patients with varying degrees of cirrhosis indicate astrocyte swelling that correlates with venous ammonia levels.⁸⁰ Cerebral edema was seen on a CT scan in a patient with the terminal stage of cirrhosis.⁸¹ A recent experimental study could not confirm brain edema in earlier stages of hepatic encephalopathy.⁸²

Treatments for the two forms of acute encephalopathy also may differ. Lactulose or rifaximin can be beneficial for the treatment of gradual-onset encephalopathy in patients with prior cirrhosis, but additional, aggressive treatment of brain edema with osmotic diuretics is required in new, fulminant forms to prevent secondary, permanent brain-stem damage and to sustain patients through liver transplantation.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

I thank Michael D. Leise, M.D., for his insights.

REFERENCES

- Fichet J, Mercier E, Genée O, et al. Prognosis and 1-year mortality of intensive care unit patients with severe hepatic encephalopathy. *J Crit Care* 2009;24:364-70.
- García-Martínez R, Simón-Talero M, Córdoba J. Prognostic assessment in patients with hepatic encephalopathy. *Dis Markers* 2011;31:171-9.
- Wong RJ, Gish RG, Ahmed A. Hepatic encephalopathy is associated with significantly increased mortality among patients awaiting liver transplantation. *Liver Transpl* 2014;20:1454-61.
- Bernal W, Hyrylainen A, Gera A, et al. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. *J Hepatol* 2013;59:74-80.
- Reuben A, Tillman H, Fontana RJ, et al. Outcomes in adults with acute liver failure between 1998 and 2013: an observational cohort study. *Ann Intern Med* 2016;164:724-32.
- Adams RD, Foley JM. The neurologic changes in the more common types of severe liver disease. *Trans Am Neurol Assoc* 1949;74:217-9.
- Butterworth RF. Hepatic encephalopathy in alcoholic cirrhosis. *Handb Clin Neurol* 2014;125:589-602.
- Butterworth RF. Pathogenesis of hepatic encephalopathy and brain edema in acute liver failure. *J Clin Exp Hepatol* 2015;5:Suppl 1:S96-103.
- Bernal W, Wendon J. Acute liver failure. *N Engl J Med* 2013;369:2525-34.
- Butterworth RF, Giguère JF, Michaud J, Lavoie J, Layrargues GP. Ammonia: key factor in the pathogenesis of hepatic encephalopathy. *Neurochem Pathol* 1987;6:1-12.
- Barbaro G, Di Lorenzo G, Soldini M, et al. Flumazenil for hepatic encephalopathy grade III and IVa in patients with cirrhosis: an Italian multicenter double-blind, placebo-controlled, cross-over study. *Hepatology* 1998;28:374-8.
- Butterworth RF, Pomier Layrargues G. Benzodiazepine receptors and hepatic encephalopathy. *Hepatology* 1990;11:499-501.
- Butterworth RF. Neurosteroids in hepatic encephalopathy: novel insights and new therapeutic opportunities. *J Steroid Biochem Mol Biol* 2016;160:94-7.
- Butterworth RF, Spahr L, Fontaine S, Layrargues GP. Manganese toxicity, dopaminergic dysfunction and hepatic encephalopathy. *Metab Brain Dis* 1995;10:259-67.
- Odeh M. Pathogenesis of hepatic encephalopathy: the tumour necrosis factor-alpha theory. *Eur J Clin Invest* 2007;37:291-304.
- Ong JP, Aggarwal A, Krieger D, et al. Correlation between ammonia levels and the severity of hepatic encephalopathy. *Am J Med* 2003;114:188-93.
- Ge PS, Runyon BA. Serum ammonia level for the evaluation of hepatic encephalopathy. *JAMA* 2014;312:643-4.
- Riggio O, Angeloni S, Salvatori FM, et al. Incidence, natural history, and risk factors of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt with polytetrafluoroethylene-covered stent grafts. *Am J Gastroenterol* 2008;103:2738-46.
- Rössle M, Haag K, Ochs A, et al. The transjugular intrahepatic portosystemic stent-shunt procedure for variceal bleeding. *N Engl J Med* 1994;330:165-71.
- Saad WE. Portosystemic shunt syndrome and endovascular management of hepatic encephalopathy. *Semin Intervent Radiol* 2014;31:262-5.
- Nardelli S, Gioia S, Pasquale C, et al. Cognitive impairment predicts the occurrence of hepatic encephalopathy after trans-

- jugular intrahepatic portosystemic shunt. *Am J Gastroenterol* 2016;111:523-8.
22. Bessman SP, Fazekas JF, Bessman AN. Uptake of ammonia by the brain in hepatic coma. *Proc Soc Exp Biol Med* 1954; 85:66-7.
 23. Fazekas JF, Ticktin HE, Shea JG. Effect of L-glutamic acid on metabolism of patients with hepatic encephalopathy. *Am J Med Sci* 1957;234:145-9.
 24. Foley JM, Watson CW, Adams RD. Significance of the electroencephalographic changes in hepatic coma. *Trans Am Neurol Assoc* 1950;51:161-5.
 25. Murphy TL, Chalmers TC, Eckhardt RD, Davidson CS. Hepatic coma: clinical and laboratory observations on 40 patients. *N Engl J Med* 1948;239:605-12.
 26. Phillips GB, Schwartz R, Gabuzda GJ Jr, Davidson CS. The syndrome of impending hepatic coma in patients with cirrhosis of the liver given certain nitrogenous substances. *N Engl J Med* 1952;247: 239-46.
 27. Snell AM, Butt HR. Hepatic coma; observations bearing on its nature and treatment. *Tr A Am Physicians* 1941;56:321-9.
 28. Sherlock S, Summerskill WH, White LP, Phear EA. Portal-systemic encephalopathy: neurological complications of liver disease. *Lancet* 1954;267:454-7.
 29. Frerichs FT. A clinical treatise on diseases of the liver. London: The New Sydenham Society, 1860.
 30. Bajaj JS, Cordoba J, Mullen KD, et al. Review article: the design of clinical trials in hepatic encephalopathy — an International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus statement. *Aliment Pharmacol Ther* 2011;33:739-47.
 31. Wijdicks EF, Rabinstein AA, Bamlet WR, Mandrekar JN. FOUR score and Glasgow Coma Scale in predicting outcome of comatose patients: a pooled analysis. *Neurology* 2011;77:84-5.
 32. Bajaj JS. Current and future diagnosis of hepatic encephalopathy. *Metab Brain Dis* 2010;25:107-10.
 33. Kappas MR, Bajaj JS. Covert hepatic encephalopathy: not as minimal as you might think. *Clin Gastroenterol Hepatol* 2012;10:1208-19.
 34. Vanamee P, Poppell JW, Glicksman AS, Randall HT, Roberts KE. Respiratory alkalosis in hepatic coma. *AMA Arch Intern Med* 1956;97:762-7.
 35. Mouri S, Tripson S, Rudler M, et al. FOUR score, a reliable score for assessing overt hepatic encephalopathy in cirrhotic patients. *Neurocrit Care* 2015;22:251-7.
 36. Bandmann O, Weiss KH, Kaler SG. Wilson's disease and other neurological copper disorders. *Lancet Neurol* 2015;14: 103-13.
 37. Bickford RG, Butt HR. Hepatic coma: the electroencephalographic pattern. *J Clin Invest* 1955;34:790-9.
 38. Silverman D. Some observations on the EEG in hepatic coma. *Electroencephalogr Clin Neurophysiol* 1962;14:53-9.
 39. Marchetti P, D'Avanzo C, Orsato R, et al. Electroencephalography in patients with cirrhosis. *Gastroenterology* 2011; 141(5):1680-9.e1-2.
 40. Sutter R, Kaplan PW. Uncovering clinical and radiological associations of triphasic waves in acute encephalopathy: a case-control study. *Eur J Neurol* 2014; 21:660-6.
 41. Ficker DM, Westmoreland BF, Sharrbrough FW. Epileptiform abnormalities in hepatic encephalopathy. *J Clin Neurophysiol* 1997;14:230-4.
 42. Olesen SS, Gram M, Jackson CD, et al. Electroencephalogram variability in patients with cirrhosis associates with the presence and severity of hepatic encephalopathy. *J Hepatol* 2016;65:517-23.
 43. Sawhney IM, Verma PK, Dhiman RK, et al. Visual and auditory evoked responses in acute severe hepatitis. *J Gastroenterol Hepatol* 1997;12:554-9.
 44. Romero-Gómez M, Boza F, García-Valdecasas MS, García E, Aguilar-Reina J. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. *Am J Gastroenterol* 2001; 96:2718-23.
 45. Amodio P, Montagnese S. Clinical neurophysiology of hepatic encephalopathy. *J Clin Exp Hepatol* 2015;5:Suppl 1: S60-8.
 46. Schiff S, Casa M, Di Caro V, et al. A low-cost, user-friendly electroencephalographic recording system for the assessment of hepatic encephalopathy. *Hepatology* 2016;63:1651-9.
 47. Guerit JM, Amantini A, Fischer C, et al. Neurophysiological investigations of hepatic encephalopathy: ISHEN practice guidelines. *Liver Int* 2009;29:789-96.
 48. Victor M, Adams RD, Collins GH. The Wernicke-Korsakoff syndrome. Philadelphia: F.A. Davis, 1989.
 49. Davidson EA, Solomon P. The differentiation of delirium tremens from impending hepatic coma. *J Ment Sci* 1958; 104:326-33.
 50. Guevara M, Baccaro ME, Torre A, et al. Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: a prospective study with time-dependent analysis. *Am J Gastroenterol* 2009;104: 1382-9.
 51. Jhun P, Kim H. Nonconvulsive status epilepticus in hepatic encephalopathy. *West J Emerg Med* 2011;12:372-4.
 52. Schmidt L, Görtz S, Wohlfahrt J, Melbye M, Munch TN. Recurrence of subdural haematoma in a population-based cohort — risks and predictive factors. *PLoS One* 2015;10(10):e0140450.
 53. Donovan LM, Kress WL, Strnad LC, et al. Low likelihood of intracranial hemorrhage in patients with cirrhosis and altered mental status. *Clin Gastroenterol Hepatol* 2015;13:165-9.
 54. Nielsen K, Clemmesen JO, Vassiliadis E, Vainer B. Liver collagen in cirrhosis correlates with portal hypertension and liver dysfunction. *APMIS* 2014;122:1213-22.
 55. American Association for the Study of Liver Diseases, European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. *J Hepatol* 2014;61:642-59.
 56. Cabral CM, Burns DL. Low-protein diets for hepatic encephalopathy debunked: let them eat steak. *Nutr Clin Pract* 2011; 26:155-9.
 57. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010;362:1071-81.
 58. McGee RG, Bakens A, Wiley K, Riordan SM, Webster AC. Probiotics for patients with hepatic encephalopathy. *Cochrane Database Syst Rev* 2011;11:CD008716.
 59. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001;33:464-70.
 60. Martin P, DiMartini A, Feng S, Brown R Jr, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology* 2014;59:1144-65.
 61. Lee WM. Acute liver failure. *Semin Respir Crit Care Med* 2012;33:36-45.
 62. Qureshi AI, Suarez JJ. Use of hypertonic saline solutions in treatment of cerebral edema and intracranial hypertension. *Crit Care Med* 2000;28:3301-13.
 63. Rabinstein AA. Treatment of brain edema in acute liver failure. *Curr Treat Options Neurol* 2010;12:129-41.
 64. Tyagi R, Donaldson K, Loftus CM, Jallo J. Hypertonic saline: a clinical review. *Neurosurg Rev* 2007;30:277-90.
 65. Wijdicks EF, Nyberg SL. Propofol to control intracranial pressure in fulminant hepatic failure. *Transplant Proc* 2002;34: 1220-2.
 66. Kitzberger R, Funk GC, Holzinger U, et al. Severity of organ failure is an independent predictor of intracranial hypertension in acute liver failure. *Clin Gastroenterol Hepatol* 2009;7:1000-6.
 67. Karvellas CJ, Todd Stravitz R, Battenhouse H, Lee WM, Schilsky ML. Therapeutic hypothermia in acute liver failure: a multicenter retrospective cohort analysis. *Liver Transpl* 2015;21:4-12.
 68. Thayapararajah SW, Gulka I, Al-Amri A, Das S, Young GB. Acute fulminant hepatic failure, encephalopathy and early CT changes. *Can J Neurol Sci* 2013;40: 553-7.
 69. Vaquero J, Fontana RJ, Larson AM, et al. Complications and use of intracranial

- pressure monitoring in patients with acute liver failure and severe encephalopathy. *Liver Transpl* 2005;11:1581-9.
- 70.** Karvellas CJ, Fix OK, Battenhouse H, Durkalski V, Sanders C, Lee WM. Outcomes and complications of intracranial pressure monitoring in acute liver failure: a retrospective cohort study. *Crit Care Med* 2014;42:1157-67.
- 71.** Maloney PR, Mallory GW, Atkinson JL, Wijidicks EF, Rabinstein AA, Van Gompel JJ. Intracranial pressure monitoring in acute liver failure: institutional case series. *Neurocrit Care* 2016;25:86-93.
- 72.** Murphy N, Auzinger G, Bernal W, Wendon J. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. *Hepatology* 2004;39:464-70.
- 73.** Bernal W, Murphy N, Brown S, et al. A multicentre randomized controlled trial of moderate hypothermia to prevent intracranial hypertension in acute liver failure. *J Hepatol* 2016;65:273-9.
- 74.** Olin P, Hausken J, Foss A, Karlsten TH, Melum E, Haugaa H. Continuous molecular adsorbent recirculating system treatment in 69 patients listed for liver transplantation. *Scand J Gastroenterol* 2015;50:1127-34.
- 75.** Stutchfield BM, Simpson K, Wigmore SJ. Systematic review and meta-analysis of survival following extracorporeal liver support. *Br J Surg* 2011;98:623-31.
- 76.** Jalan R, Olde Damink SW, Hayes PC, Deutz NE, Lee A. Pathogenesis of intracranial hypertension in acute liver failure: inflammation, ammonia and cerebral blood flow. *J Hepatol* 2004;41:613-20.
- 77.** Aggarwal S, Obrist W, Yonas H, et al. Cerebral hemodynamic and metabolic profiles in fulminant hepatic failure: relationship to outcome. *Liver Transpl* 2005;11:1353-60.
- 78.** Häussinger D. Low grade cerebral edema and the pathogenesis of hepatic encephalopathy in cirrhosis. *Hepatology* 2006;43:1187-90.
- 79.** Keiding S, Pavese N. Brain metabolism in patients with hepatic encephalopathy studied by PET and MR. *Arch Biochem Biophys* 2013;536:131-42.
- 80.** Lodi R, Tonon C, Stracciari A, et al. Diffusion MRI shows increased water apparent diffusion coefficient in the brains of cirrhotics. *Neurology* 2004;62:762-6.
- 81.** Donovan JP, Schafer DF, Shaw BW Jr, Sorrell MF. Cerebral oedema and increased intracranial pressure in chronic liver disease. *Lancet* 1998;351:719-21.
- 82.** Cauli O, Llansola M, Agustí A, et al. Cerebral oedema is not responsible for motor or cognitive deficits in rats with hepatic encephalopathy. *Liver Int* 2014;34:379-87.

Copyright © 2016 Massachusetts Medical Society.