Management of Hepatic Encephalopathy as an Inpatient

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This review is limited to the management of inpatients with clinically overt hepatic encephalopathy (HE) due to cirrhosis.¹ Type C overt HE should be divided into *episodic* HE (when the symptoms develop over a short period and fluctuate in severity), *recurrent* HE (characterized by bouts of HE within a time interval of 6 months or less), or *persistent* HE (with continuous behavioral or neurological symptoms). Another important distinction is between *spontaneous* and *precipitated* HE, the latter induced by a specific and clearly identifiable precipitating event, as those reported in Table 1.¹ The above taxonomy of overt HE (episodic versus recurrent versus persistent, precipitated versus spontaneously occurring) is clinically relevant because the diagnostic procedures and management of each category differ.

The four-pronged approach to management of HE, recommended in the 2014 EASL/AASLD Practice Guidelines for HE in chronic liver disease, is reported here with minor modifications:

1. Identify the cirrhotic patient with altered consciousness by using the confusion assessment method, shown in Table 1. In patients with significantly altered consciousness, the Glasgow Coma Scale is recommended (Table 2);
2. Exclude other causes of altered mental status according to the algorithm described in Table 3;
3. Identify precipitating factors according to the diagnostic workup shown in Table 4;
4. Start empiric treatment and correct the precipitating event (Table 5). Considering a broad differential diagnosis between overt HE and other neurological syndromes that may occur in a cirrhotic patient is very important because a specific diagnostic marker of HE does not exist. Venous ammonia, arterial ammonia, and the partial pressure of ammonia ($p\text{NH}_3$), which can be calculated from arterial ammonia and pH according to Manning's monogram, are

higher on average in cirrhotic patients than in controls and are usually related to the severity of HE. However, in an individual patient, ammonia may be unrelated to the presence and the evolution of HE, and thus, its diagnostic accuracy is far from satisfactory. The sensitivity and specificity of arterial ammonia or $p\text{NH}_3$ in correctly classifying patients as having or not having HE is similar to that of venous ammonia, which is simpler to determine.² The recent EASL/AASLD practice guidelines¹ state that *increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with CLD*. However, a normal ammonia value further stresses the need to consider an appropriate differential diagnosis. This is required in all cirrhotic patients with acute cognitive impairment, although more than 90% of such patients ultimately will be diagnosed as having overt HE.

Once the diagnosis of overt HE is made, every effort should be made to identify the precipitating cause. In fact, although not evaluated by specific randomized, controlled trials (RCTs), the rapid identification of the precipitant is considered the first line in managing patients with this type of HE, and its correction is essential for the resolution of symptoms. Multiple precipitating events frequently may coexist in the same patient. For example, a patient with HE precipitated by a gastrointestinal (GI) bleeding may also have severe anemia, hypovolemia, and functional renal failure. Moreover, infections such as a spontaneous bacterial peritonitis (SBP) may develop after GI bleeding, and this new event, if not promptly recognized, may contribute to the persistence of the neurological abnormalities. A well-known clinical rule is to search for any additional precipitant if the neurological symptoms do not ameliorate once the inciting precipitating event has resolved. The workup given in Table 3 may be useful and should be repeated

Abbreviations: GI, gastrointestinal; HE, hepatic encephalopathy; MARS, molecular absorbent recirculating system; RCT, randomized, controlled trial, SBP, spontaneous bacterial pericarditis; SMT, standard medical treatment.

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TABLE 1 Confusion Assessment Method (CAM) for the Diagnosis of Delirium*

Feature	Questions to Usually Ask a Family Member or Nurse
1. Acute onset and fluctuating course	"Is there evidence of an acute change in mental status from the patient's baseline?" "Did the abnormal behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?"
2. Inattention	"Did the patient have difficulty focusing attention, for example, being easily distractible or having difficulty keeping track of what was being said?"
3. Disorganized thinking	"Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?"
4. Altered level of consciousness	"Overall, how would you rate this patient's level of consciousness?" Normal = alert Hyperalert = vigilant Drowsy, easily aroused = lethargic Difficult to arouse = stupor Unarousable = coma

*The diagnosis of delirium requires the presence of features 1 AND 2 plus either 3 OR 4 and is shown by positive responses to the questions above.

TABLE 2 Glasgow Coma Scale

Glasgow Coma Scale						
	1	2	3	4	5	6
Eyes	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	n.a.	n.a.
Verbal	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	n.a.
Motor	Makes no movements	Extension to painful stimuli (decerebrate response)	Abnormal flexion to painful stimuli (decorticate response)	Flexion/withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

The scale comprises three tests: eyes, verbal, and motor responses. The three values separately as well as their sum are considered. The lowest possible Glasgow Coma Scale (the sum) is 3 (deep coma or death), whereas the highest is 15 (fully awake person). Abbreviation: n.a., not applicable.

TABLE 3 Algorithm to Exclude Neurological Diseases Other Than HE

1. Hypercapnic encephalopathy Is there any suspicion (based on prior history and physical examination) of a respiratory or neuromuscular diseases that may cause respiratory failure? Is $PCO_2 > 60$ mm Hg?	Yes: Assess PCO_2	No: go to 2
2. Hypoglycemic encephalopathy Is blood glucose < 50 mg/dL? Has the normalization of glycemia corrected the neurological manifestations?	Yes: diagnose hypercapnic encephalopathy and treat Yes: administer glucose and reassess the patient after glycemia is normal Yes: diagnose hypoglycemic encephalopathy and treat	No: go to 2 No: go to 3 No: go to 3
3. Hyperosmotic encephalopathy Is the calculated osmolality ($2 \times Na [mEq/L] + glucose/18 [mg/dL]$) > 320 ?	Yes: diagnose hyperosmotic encephalopathy and treat	No: go to 4
4. Intracranial structural injury Does the patient exhibit any of the following manifestations: hemiparesia, hemianopsia, aphasia, sudden headache, recent craniocephalic trauma? Does a neuroimaging study show structural damage of the brain?	Yes: perform a neuroimaging assessment (CT or MR of the brain) Yes: Referral and treatment of the patient according to the specific damage Yes: perform lumbar puncture	No: go to 5 No: go to 5 No: go to 5
Is there suspicion of subarachnoid hemorrhage (severe headache, meningeal signs) despite normal neuroimaging?	Yes: perform lumbar puncture (after CT or MR of the brain if intracranial hypertension cannot be excluded). Yes: perform EEG	No: go to 6 No: go to 7
5. Meningoencephalitis: Does the patient show meningeal signs or intense headache?		
6. Nonconvulsive status epilepticus Has the patient a history of seizures or shows myoclonies?	Yes: determine alcohol levels in blood or urine and if the values are toxic diagnose alcohol intoxication	No: go to 8
7. Alcohol intoxication Is there a history of recent alcohol intake or are the data suspicious for alcohol intake (odor, epidemiological background)?	Yes: Treat alcohol withdrawal syndrome	No: go to 9
8. Alcohol withdrawal syndrome Has the patient stopped regular alcohol intake > 80 g/day and shown psychomotor agitation or visual hallucinations?		
9. Intoxication by benzodiazepines Is there any possibility of benzodiazepine intake?	Yes: determine the level of benzodiazepines in blood or urine and administer flumazenil and decide based on the levels and the response to flumazenil. Yes: proceed to determine the existence of toxic levels if the drug can be measured in blood or other body fluids. Yes: proceed to determine the levels of thiamine.	No: go to 10 No: go to 11 No: go to 12
10. Pharmacological intoxication Is there any possibility of having had an intake of drugs that can depress the level of consciousness?		
11. Wernicke's encephalopathy Does the patient exhibit ophthalmoparesia, nystagmus, ataxia, confabulation or short-term memory loss?		
12. Hepatic encephalopathy

TABLE 4 Diagnostic Workup to Identify Precipitating Factors for Episodic or Recurrent Overt HE

Precipitating Factor	Definition:	Obligatory assessment:
1. Gastrointestinal bleeding	Any evidence of hemorrhage initiated in the gastrointestinal tract	<ul style="list-style-type: none"> • Ask for recent history of hematemesis, melena or hematochezia • Assess for the presence of blood in stools
2. Infection	According to standard clinical criteria <ul style="list-style-type: none"> • Pneumonia: compatible infiltrates in a chest X-ray • Urinary infection: increased number of leukocytes in urine or positive urinary culture • Spontaneous bacterial peritonitis: polymorphonuclear count in ascitic fluid > 250 cells/μL • Bacteremia: positive blood culture • Acute gastroenteritis: diarrhea + fever without alternative diagnosis or pathogen in stool • Other infections: microbiological demonstration 	<ul style="list-style-type: none"> • Assess the presence of anemia in the full blood count • Ask for recent history of fever, cough, or urinary symptoms • Assess body temperature, leukocyte count, chest x-ray, urinary cell count • If ascites: perform paracentesis • Perform blood and urinary culture
3. Constipation	More than 24 hours without passing stools or demonstration of significant fecal retention in the colon	<ul style="list-style-type: none"> • Ask for recent history of number of stools per day • Perform rectal exam
4. Excessive protein intake	More than 100 g of protein/day at least in 1 day of the previous 4 days	<ul style="list-style-type: none"> • Ask for recent dietary intake
5. Dehydration	Compatible clinical signs (dried oral mucosa, increase in sodium, hematocrit, creatinine) in the appropriate context (vomiting, diarrhea, diuretics)	<ul style="list-style-type: none"> • Ask for the presence of thirst, vomiting, diarrhea, use of diuretics • Assess hydration of oral mucosa • Perform laboratory tests (hematocrit, sodium, creatinine, urea)
6. Electrolyte abnormalities	<ul style="list-style-type: none"> • Renal insufficiency: creatinine > 1.5 mg/dL • Hyponatremia: Na < 130 mEq/L • Hypophosphatemia: <3 mEq/L • Hypokalemia: <3 mEq/L • Hypochloremia 	<ul style="list-style-type: none"> • Perform laboratory tests (pH, sodium, potassium, creatinine)
1. Diuretics	Development of HE in chronological association with the use of diuretics and cannot be attributed to dehydration or electrolyte abnormalities	<ul style="list-style-type: none"> • Ask for recent intake of diuretics

TABLE 5 Treatment Strategies in Patients With Precipitant-Induced Episodic HE

General supportive care	
	Prevent falls or body harm in disorientated patients Take care of bladder and bowel function Take care of intravenous lines Monitor fluid balance Monitor blood glucose and electrolytes Monitor arterial blood gases Correct acid/base disturbances Monitor blood pressure Avoid aspiration pneumonia Prevent causes of sepsis
Support nutritional needs	Energy intake of 35-40 kcal/kg body weight day and protein intake of 1.2-1.5 g / kg body weight/day are recommended. ⁷ In patients with severe hepatic encephalopathy (grades III-IV), solutions with an increased content of branched-chain amino acids and reduced amount of aromatic amino acids can ameliorate neurological symptoms, ensuring adequate protein intake.
Treatment of the precipitating event	
GI bleeding	Stop bleeding with vasoactive drugs, endoscopic therapy, or angiographic shunt (TIPS) Correct severe anemia with blood transfusion Nasogastric tube to facilitate upper GI cleansing: aspirating blood and administering osmotic laxative (lactulose, PEG) Appropriate antibiotic therapy
Infection (pulmonary, urinary tract, spontaneous bacterial peritonitis) Exogenous sedatives Electrolyte abnormalities	Discontinue benzodiazepines Discontinue diuretics Correct electrolyte disturbances
Constipation Deterioration of renal function	Cathartic; bowel enema Discontinue diuretics Correct dehydration Discontinue nephrotoxic antibiotics

when the resolution of HE does not follow the resolution of the initial precipitating event. Although the true prevalence of precipitants is not very well known, it is very likely that infections represent the most common precipitating event in the current series of patients.³ Therefore, in all patients with HE, it is mandatory to perform a careful search for a bacterial infection. Although most of the infectious episodes are clearly evident, others, such as SBP, require a specific diagnostic procedure to be detected (Table 2). The search for an occult infection is also mandatory in patients with recurrent HE and even in those with persistent HE. In patients with continuous or frequently recurrent HE symptoms, it is also important to search for the presence of large porto-systemic shunt,⁴ which may be suitable for occlusion.⁵ This therapeutic opportunity, as well as the possibility of reducing the diameter of a too-large stent in patients who have undergone transjugular intrahepatic portosystemic shunt placement,⁶ has to be considered, especially in patients with preserved liver function.

The general supportive care of a patient hospitalized because of overt HE is reported in Table 4, which also summarizes the main management of the precipitating events. The decision to maintain the patient in the general ward or in intensive care depends not only on the severity of HE, but also on the severity of and the number of precipitating events present at the same time and whether the patient is at risk or unable to protect his or her airway. The care of the patient's nutritional status is also considered useful. Energy intake of 35–40 kcal/kg body weight/day and protein intake of 1.2–1.5 g/kg body weight/day are

recommended.⁷ A recent RCT clearly showed that the reduction of protein intake in patients with overt HE is unnecessary for the resolution of symptoms and may further contribute to the patient's malnutrition.⁸

An RCT compared the use of the molecular absorbent recirculating system (MARS), a method of hemodiafiltration with standard medical treatment (SMT) in patients with severe (grades III–IV) HE. Seventy-two percent of the patients responded in the MARS group compared with 40% in the SMT group (not significant). None of the surviving patients whose HE improved by two stages returned to their prestudy HE grade during the 5-day study period, and mortality was not reduced by MARS. Thus, overall, there was no significant benefit of MARS in these patients.⁹ As 90% of patients hospitalized for episodic overt HE respond to the above general measures and to the treatment of the precipitating event, the use of drugs such nonabsorbable disaccharide, low-absorbable antibiotics, L-ornithine-L-aspartate, branched-chain amino acids, and benzodiazepine antagonists remain a matter of discussion.¹⁰ The clinical problem once HE is reversed is to determine how to prevent its recurrence. Recent RCTs showed that this goal could be obtained by the administration of lactulose,¹¹ rifaximin, or a combination of both.¹² ■

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