Hepatic encephalopathy: from pathophysiology to therapeutic management
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Hepatic encephalopathy is a complex and potentially reversible neuropsychiatric syndrome complicating acute or chronic liver disease. Clinical manifestations are multiple and varied, ranging from minimal neurological changes to coma. Ammonia is the main toxic substance involved in the pathogenesis of hepatic encephalopathy, although other mechanisms, such as modifications of the blood–brain barrier, disruptions in neurotransmission and abnormalities in GABAergic and benzodiazepine pathways may also play a role. The identification and treatment of precipitating factors is crucial in the management of patients with hepatic encephalopathy. Current treatments are based on reducing intestinal ammonia load by agents such as antibiotics or disaccharides, although their efficacy is yet to be clearly established. Eur J Gastroenterol Hepatol

Introduction
Hepatic encephalopathy (HE) is a complex and potentially reversible neuropsychiatric syndrome characterized by symptoms such as somnolence, confusion, asterixis, extrapyramidal hypertonia, convulsions and coma. HE, which can be either acute or chronic, may complicate one of three major clinical situations: severe acute liver failure in the absence of pre-existing liver disease (e.g. fulminant hepatitis), portocaval anastomosis in a patient without pre-existing chronic liver disease and finally cirrhosis with or without portocaval anastomosis.

HE involves the coexistence of two predisposing factors: liver dysfunction and portocaval anastomoses. Liver dysfunction plays an essential role in HE triggered by fulminant hepatitis or portocaval shunts in cirrhotics. Clinical manifestations of HE are multiple and varied, ranging from discreet neuropsychiatric symptoms to coma. Common manifestations include an altered state of consciousness and neuromuscular abnormalities [1].

The occurrence of the first episode of HE in a cirrhotic patient is a pejorative prognostic factor, and constitutes a turning point in the evolution of liver disease. Estimated survival rates are 42% at 1 year, and 23% at 3 years [2]. In subfulminant or fulminant hepatitis, HE plays a predominant role in deciding whether the patient is a candidate for superurgent liver transplantation.

Pathophysiological concepts
Pathophysiology of HE is complex and probably involves the association of several different factors [3–10]. Ammonia, which is produced in the colon by intestinal bacteria, is the principal toxic substance involved in the pathogenesis of HE. Enteric flora generates the production of additional neurotoxic molecules, such as phenols, mercaptans, and short-chain fatty acids, which potentize the toxic effects of ammonia. Additional mechanisms involved in HE include modifications of the blood–brain barrier, disruptions in neurotransmission and abnormalities in GABAergic and benzodiazepine pathways. Normal brain function requires anatomical neuron integrity, production of sufficient energy and efficient synapse neurotransmission, all of which can be affected in HE.

Anatomical lesions
Anatomical lesions of the central nervous system cannot be held responsible for the clinical manifestations of HE [11]. However, microscopic structural abnormalities have been found in glial cells of patients with HE, namely astrocytes. Astrocytes are the only cells in the human brain equipped with the enzymes necessary for ammoniac metabolism (glutamine synthase). These cells undergo functional and structural alterations in patients with HE, increasing in size and number [12]. These morphological modifications predominate in the cortex, the cerebellum and in the brainstem nuclei, and are the equivalent of type II Alzheimer astrocytosis. The most serious anatomical lesion is brain oedema [13], which is mainly observed in fulminant hepatitis, and is a major prognostic factor [11]. Nevertheless, anatomical lesions in
HE are generally mild, thus allowing for complete and frequent reversibility of clinical symptoms in the majority of cases.

Imaging techniques, such as magnetic resonance imaging (MRI) allow for the detection of minimal cerebral oedema in cirrhotics with mild HE, with oedema becoming more pronounced in severe HE [14]. These MRI abnormalities have been shown to regress after liver transplantation [14] or after medical treatment of HE [15]. In addition to MRI, other noninvasive techniques, such as magnetic resonance spectroscopy and positron emission tomography have recently been used to study the effect of chronic liver disease on the central nervous system [16]. A detailed description of these techniques and their findings is found in the review of Butterworth [17]. These techniques have provided valuable insight on the modifications in brain chemistry and metabolism induced by liver disease. However, they are not currently used in clinical practice because of debate over scientific results and lack of consensus over the correct methods and implementation of these techniques. Additional multicentre studies with a high degree of consensus are needed to define the role of MRI and magnetic resonance spectroscopy in the diagnosis and monitoring of HE [18,19].

Impairment of cerebral energy metabolism

Impairment of cerebral energy metabolism has been suggested as one of the underlying mechanisms of HE. Studies evaluating glucose and oxygen consumption in HE have shown a marked reduction in cerebral energy metabolism [20]. This metabolic disturbance may be because of excess quantities of neurotoxic substances, such as ammonia, short-chain fatty acids and mercaptans.

The presence of abnormally high levels of ammonia is the oldest theory used to explain the pathogenesis of HE [3,8]. Ammonia is a product of protein catabolism and has two origins:

1. Exogenous ammonia is produced in the intestine from alimentary proteins, and in blood from the oxidative deamination of amino acids, which arises from putrefying bacteria in the caecum. Ammonia is also produced through hydrolysis of urea by ureases found in intestinal bacteria. Constipation and haemorrhage within the digestive tract thus increase ammonia production. Ammonia from the colon enters the portal venous circulation by passive diffusion, which is influenced by faecal pH levels. Hepatic venous inflow is therefore rich in ammonia, with levels 2–8 times higher in the portal vein compared with systemic venous circulation.

2. Endogenous ammonia is produced in muscle, brain and renal tissue and results from transamination and deamination of amino acids (mainly glutamine, and asparagine, alanine and histidine).

Both exogenous and endogenous ammonia is detoxified by the liver into urea through the Krebs–Henseleit urea cycle. In cirrhotics, the elevation of portal venous pressure and the presence of collateral circulation lead to diversion of portal blood flow directly into systemic circulation. In addition, decreased liver function leads to decreased ammonia detoxification. In the event of decreased liver function or portosystemic shunt, non-detoxified ammonia enters the systemic circulation and crosses the blood–brain barrier, and thus may induce HE.

Ammonia toxicity can be explained by three underlying mechanisms, as shown in Fig. 1 [3,21]:

1. Depletion of cerebral alphaketoglutaric acid levels. This acid is consumed to produce glutamine and detoxify ammonia by two chemical reactions:
   (a) alphaketoglutaric acid + NH₃ → glutamic acid; and
   (b) glutamic acid + NH₃ → glutamine. Reduced levels of alphaketoglutaric acid in the brain are impossible to compensate, as both this molecule and its precursor, oxaloacetate, are incapable of crossing the blood–brain barrier. The consumption of glutamic acid further depletes reserves of alphaketoglutaric acid, which is a substrate of the Krebs cycle.

2. Impairment of oxidative decarboxylation of pyruvic acid, which is a crucial step of the Krebs cycle.

Fig. 1

![Mechanisms of ammonia toxicity according to Blanc et al. [3].](image-url)
The role of ammonia in the pathophysiology of HE remains widely debated, even controversial. Certain arguments seem convincing: ingestion of proteins and gastrointestinal bleeding both induce HE, ammonia levels are elevated in over 90% of patients with HE, and levels of glutamine in cerebrospinal fluid, which is the end by-product of ammonia detoxification, are correlated with the severity of HE [24]. Moreover, recent studies in rats with portocaval shunts have shed light on the correlation between the effects of ammonia on the molecular level and clinical aspects of HE. For example, it has been shown that ammonia impairs the glutamate–nitric oxide (NO)–cyclic guanosine monophosphate pathway, which is involved in cognitive function and learning ability. This impairment results from a decrease in activation of soluble guanylate cyclase by NO [25,26] and reduction of the activation of neuronal NO synthase [27], which has been shown in the cerebellum in both in-vivo animal models of chronic HE and in brain autopsies of patients deceased with HE [28]. A study in rats with chronic HE showed that increasing brain cyclic guanosine monophosphate levels restored learning ability [29].

However, several doubts have been cast on the role of ammonia in the pathophysiology of HE. The ingestion or intravenous injection of ammonium salts automatically induces arterial hyperammonaemia in cirrhotics; however, this increase in ammonia levels leads to neuropsychiatric perturbations and electroencephalographic abnormalities in only a very small number of cases [30]. Furthermore, ammonia levels in the blood are neither correlated with ammonia levels in the brain and in cerebrospinal fluid nor with the severity of clinical symptoms. Finally, hyperammonaemia observed in certain enzyme deficiencies (e.g. Krebs–Henseleit urogenesis cycle) is never associated with coma [31].

Therefore, alterations in ammonia metabolism cannot be deemed solely responsible for HE [32]. The existence of additional toxic substances acting in synergy with ammonia has been suggested. This hypothesis would correct certain inconsistencies in the ammonia theory. According to Zieve et al. [33], the toxic effects of ammonia would act in synergy with those of mercaptans and short-chain fatty acids. Mercaptans are by-products of the transformation of methionine by bacteria in the colon, and are eliminated by the liver. Levels of mercaptans in the blood may rise in patients with liver failure or portocaval anastomoses. However, no correlation exists between mercaptan serum levels and severity of HE. Short-chain fatty acids are synthesised by bacteria in the colon and are metabolised by the liver. The combined administration of ammonia, mercaptans and short-chain fatty acids in rats can induce coma and perturbations in evoked potentials similar to those observed in HE [34].

Abnormalities in synapse transmission
Abnormalities in synapse transmission are a possible underlying mechanism of HE [3,8,35], for which four different theories have been suggested.

False neurotransmitter theory
This theory was put forward in 1971 by Fischer and Baldessarini [36], who for the first time described HE as a disease of the central nervous system. In cirrhosis and liver failure, the plasma concentrations of amino acids are altered due to perturbations of their metabolism. Ammonia also plays a role in this theory [37], as hyperammonaemia induces excess glucagon secretion, which in turn stimulates glycogenesis [38]. To maintain normoglycaemia, reactionary hyperinsulinaemia occurs. This in turn provokes the capture of branched amino acids by muscle tissue, which leads to a decrease in serum concentrations of valine, leucine and isoleucine. In contrast, an increase in serum concentrations of aromatic amino acids (tryptophan, phenylalanine, tyrosine, precursors of dopamine and norepinephrine [39]) is observed. Both aromatic and branched amino acids use the same transport system at the blood–brain barrier, where large quantities of aromatic amino acids reach the central nervous system. High cerebral phenylalanine levels inhibit tyrosine 3 hydroxylase, which is a key enzyme in catecholamine synthesis. Aromatic amino acids are precursors of neurotransmitters, and are preferentially β-hydroxylsed into false neurotransmitters, such as tyramine, octopamine, serotonin and β-phenylethanolamine. These false neurotransmitters replace actual neurotransmitters, such as dopamine and norepinephrine, within synapses. This phenomenon thus leads to a decrease in catecholaminergic neurotransmission [40].

Although this theory explains extrapyramidal manifestations in HE, it is also the target of numerous criticisms:

(1) In animals, the intraventricular injection of octopamine induces a marked depletion in cerebral catecholamine levels, but does not lead to alteration of consciousness [41].

(2) Norepinephrine and dopamine concentrations in the brains of deceased cirrhotics who had HE are normal [42].

(3) Imbalances in plasma amino acid levels are also observed in cirrhotics without HE, and are a consequence of liver failure and portocaval anastomoses [43].

(4) Treatment of HE by bromocriptine is ineffective [44].
GABAergic theory
This theory was put forward following the false neurotransmitter theory [8,45–50]. Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in humans, and induces the opening of a chloride channel. GABA is a product of the metabolism of intestinal bacteria, and is produced from amino acids. GABA is normally catabolized in the liver by a GABA transaminase, and cannot cross the blood–brain barrier [51]. In liver failure or in the presence of portocaval shunts GABA is not completely catabolized by the liver, leading to a rise in plasmatic GABA levels. GABA is thus able to cross the blood–brain barrier and enter the central nervous system, binding to its synaptic receptors. GABA receptors are macromolecular complexes associated with benzodiazepine receptors and chloride channels. When GABA binds to its receptor, it provokes an inflow of chloride ions into the postsynaptic neuron, inducing a hyperpolarization and therefore decreasing excitability of the postsynaptic neuron. This results in inhibition of neurotransmission and a decrease in vigilance.

The GABAergic hypothesis, based on the sensitivity of certain experimental models to GABA agonists (muscimol) [52], and on the improvement of neurological status and visual evoked potentials induced in rabbits by administration of antagonists of GABA-benzodiazepine receptors [53], is yet to be confirmed. In other animal models, modifications of blood–brain barrier GABA permeability, GABA receptor density and cerebral GABA concentrations have not yet been demonstrated [54]. Finally, no increase in cerebral GABA levels or GABA receptor density has been found in cirrhotics deceased with HE [55,56].

Benzodiazepine theory
The benzodiazepine theory was the next theory to be established [8,45–60]. Benzodiazepine receptors are present in close proximity to GABA receptors. Activation of this receptor by endogenous or exogenous benzodiazepines results in an inhibition of neurotransmission. Thus, the administration of benzodiazepines in large quantities induces neuropsychic alterations comparable with those of HE. Early studies have shown that cirrhotics are particularly sensitive to the administration of benzodiazepines [57]. These clinical observations were initially explained by an increase in the density of benzodiazepine receptors, as shown in an animal model of HE [58]. This increase in density of benzodiazepine receptors has not been confirmed in humans [56]. However, a natural ‘benzodiazepine-like’ substance has been isolated in the blood, cerebrospinal fluid and brain tissue of cirrhotics with HE [59,60]. The exact nature of this ‘benzodiazepine-like’ substance is yet to be determined. By binding with the benzodiazepine receptor, this substance would potentimize GABAergic neurotransmission and would induce HE [61]. However, this ‘benzodiazepine-like’ substance is not always present in all cirrhotics with HE [62].

Updated ammonia theory
None of the earlier theories is able to explain why digestive bleeding and high protein diet precipitate HE. The current trend is a return towards a ‘revised’ ammonia theory. Ammonia, which floods the central nervous system, is detoxified into glutamine, leading to a decrease in glutamate levels [63]. Glutamine is the principal excitatory neurotransmitter and low glutamine levels in the central nervous system could explain the inhibition of neurotransmission seen in HE [64].

Other pathophysiological concepts
Hyponatremia
HE and Hyponatremia are two frequent conditions in cirrhotosis and are responsible for metabolic encephalopathy. These two conditions may coexist in the same patient, with an increase in the frequency of HE in patients with Hyponatremia. Similarities between the two conditions are multiple, concerning clinical (abnormalities in neuropsychological tests, confusion and possibly coma), microscopic (astrocyte injury with sparing of neurons and oligodendrocytes), imaging (brain oedema recognizable with MRI) and biological findings (symptoms imperfectly correlated with plasma sodium or plasma ammonia). However, differences exist between HE and Hyponatremia, both clinical (headaches and seizure in Hyponatremia; disturbances in motor function such as asterixis in HE) and on MRI (decrease in apparent diffusion coefficient and brain atrophy after recurrent episodes of HE). The main pathophysiological factor linking HE with Hyponatremia is the hypertrophic and hyperplastic character of astrocyte modifications (swelling). It has been shown that chronic Hyponatremia aggravates cerebral oedema induced by hyperammonemia, as differences in osmolality between the intra-astrocytic and extracellular compartments are exacerbated [65].

Neurosteroids
Synthesis of neurosteroids, such as allopregnanolone and tetrahydradeoxycorticosterone by astrocytes and neurons in the brain could play a role in HE. The accumulation of inhibitory neurosteroids, of either central or peripheral origin, has been described in experimental and clinical HE. Neurosteroids bind and modulate several types of membrane receptors, notably GABA_A receptors, which are the most extensively studied. Studies have shown that allopregnanolone levels in patients with HE are physiopathologically relevant, and are capable of modulating GABA_A receptors, thus accounting for the phenomenon of ‘increased GABAergic’ tone in HE [66,67]. Neurosteroids may also interact with intracellular receptors, thus
altering gene expression within astrocytes and neurons [68,69]. They may also contribute to brain oedema and astrocyte swelling [70] observed in HE.

Oxidative stress
The direct role of oxidative stress in the pathophysiology of HE has been shown in experimental models of acute or chronic liver failure. One recently published study showed an increase in markers of oxidative stress in patients deceased in HE, which may indicate that oxidative stress plays a role in the pathogenesis of HE in cirrhotics [71]. Several reports suggest that oxidative/nitrosative stress participates in the pathophysiological cascade responsible for HE [72]. Ammonia leads to astrocyte swelling, and also alters mitochondrial function and neurotransmission, inducing oxidative stress. Astrocyte alterations and oxidative stress are closely linked and result in an ‘auto-amplifying loop’, contributing to the pathogenesis of HE [73].

Inflammation
Studies in patients with acute liver failure have shown that patients with a systemic inflammatory response progress more rapidly towards severe HE, suggesting a possible link between inflammation and HE [74,75]. This is further supported by observations in patients with acetaminophen-induced acute liver failure, where infection and/or the resulting systemic inflammatory response have been shown to be important factors in contributing to deterioration in the severity of HE [76]. In advanced stages of liver failure, the brain produces a number of proinflammatory cytokines, such as tumour necrosis factor-α, interleukins 1 and 6 [77,78]. During infection, endothelial cells are activated and release various mediators into the brain. These mediators in turn activate microglia, which may release inflammatory molecules affecting neuron function [79]. Studies have shown that treatment with an anti-inflammatory (ibuprofen) restores motor and cognitive function in rats with HE [80,81].

Inflammation seems to have a synergistic effect with ammonia, with hyperammonaemia increasing sensitivity to inflammation [82], whereas inflammation exacerbates the effects of ammonia on the brain, in particular brain oedema [83].

The exact mechanisms of HE are still unclear despite the various pathophysiological theories elaborated earlier. None of these hypotheses alone is able to explain the occurrence of HE. It is probable that the appearance of HE is linked to several mechanisms. Ammonia seems to play a central role, but cannot be considered solely responsible for the development of HE, and seems to act synergistically with several additional factors. Recent studies have revealed the emerging role of inflammation and oxidative stress in HE, but the large variety of possible mechanisms implicated in HE means that there is much potential for future research.

Classification of hepatic encephalopathy: nomenclature
The diagnosis of HE and the evaluation of its severity can be difficult because of the variability and heterogeneity of clinical symptoms. This led to a consensus statement concerning both diagnosis and staging of HE, for both clinical and research purposes. This consensus was elaborated by hepatologists, neurologists and researchers over several international congresses (working party at the 11th World Congress of Gastroenterology in 1998 in Vienna, 10th International Symposium on Ammonia at Istanbul in 1999, meetings of the American Association of the Study of Liver Diseases in 1999 and 2000 in Dallas), and published in a final report by Ferenci et al. [84].

Thus, a new nomenclature of HE was proposed, defining three types (Table 1) [84]:

1. Type A, corresponding to HE in acute liver failure.
2. Type B, corresponding to portosystemic shunts without intrinsic liver dysfunction.
3. Type C, corresponding to HE in cirrhotics, with or without surgical or radiological [transjugular intrahepatic portosystemic shunt (TIPS)] portocaval shunt.

Type B and C HE can be episodic, persistent or minimal, depending on the persistence of clinical manifestations and precipitating factors (Table 2). Episodic HE is considered to be secondary to a precipitating factor, but can also be spontaneous or repetitive. Systematic detection of one or several precipitating factors is necessary as their correction plays a crucial role in the management of HE. The main precipitating factors of HE are shown in Table 2 [85,86].

| Type | Description | Subcategory (according to duration and characteristics) | Subdivision (according to duration and characteristics) |
|------|-------------|----------------------------------------------------------|----------------------------------------------------------|
| A    | HE associated with acute liver failure | Episodic HE | Precipitated* | Persistent HE | Mid | Severe Treatment dependent |
| B    | HE associated with portal-systemic shunts and/or porto-systemic shunts | | | | | |
| C    | HE associated with cirrhosis and portal hypertension and/or portal systemic shunts | | | | | |

HE, hepatic encephalopathy.
*Presence of a recognized precipitating factor.
**Without recognized precipitating factors.
Clinical features, clinical forms and differential diagnoses

Principal clinical features and classification criteria for neuropsychiatric abnormalities are shown in Table 3.

The diagnosis of HE in a cirrhotic is dependent on the presence of a depressed level of consciousness (at varying degrees) associated with personality changes and neurological abnormalities without focal signs. Owing to the absence of pathognomonic features and the variable nature of symptoms, a thorough physical examination is necessary to distinguish HE from other causes of altered mental status. All cirrhotics presenting with an altered mental status should be checked for focal neurological signs, which are rare, but may be present in HE [87].

This type of neurological finding is regressive and does not influence prognosis. If organic disease cannot be completely ruled out, imaging studies (computed tomography scan or cerebral MRI) and/or lumbar puncture should be performed. Metabolic abnormalities, such as hypoglycaemia, hypophosphataemia, hypoxaemia, hypercapnia or ischaemic stroke may be responsible for symptoms resembling those of HE. Certain pathologies, such as acute alcoholic intoxication, alcohol withdrawal syndrome or Gayet–Wernicke syndrome (ophthalmoplegia, nystagmus) can easily be identified on physical examination.

The main differential diagnoses for HE are shown in Table 4 [88].

### Table 2 Main precipitating factors of hepatic encephalopathy according to their possible mechanism

| Increase in nitrogen load | Gastrointestinal bleeding | Excessive dietary protein intake | Hyperazotaemia | Constipation | Renal failure |
|---------------------------|---------------------------|-------------------------------|----------------|-------------|--------------|
| Metabolic disorders       |                           |                               |                |             |              |
| Hyponatraemia (astrocyte swelling) |                   |                               |                |             |              |
| Hypokalaemia (increase in renal NH₃) |                   |                               |                |             |              |
| Metabolic alkalosis (increase in NH₃ diffusion across the blood–brain barrier) |                   |                               |                |             |              |
| Hypoxaemia                |                           |                               |                |             |              |
| Hypovolaemia              |                           |                               |                |             |              |
| Dehydration (diuretics, diarrhoea) |                   |                               |                |             |              |
| Medication                |                           |                               |                |             |              |
| Narcotics                 |                           |                               |                |             |              |
| Benzodiazepines           |                           |                               |                |             |              |
| Sedatives                 |                           |                               |                |             |              |
| Diuretics (protein catabolism) |                   |                               |                |             |              |
| Miscellaneous             |                           |                               |                |             |              |
| Bacterial infection       |                           |                               |                |             |              |
| Surgery (protein catabolism) |                   |                               |                |             |              |
| Additional concomitant acute liver dysfunction (viral, drug-induced, acute alcoholic hepatitis) |                   |                               |                |             |              |
| Progressively worsening liver disease |                   |                               |                |             |              |
| Transjugular intrahepatic portosystemic shunt |                   |                               |                |             |              |

Adapted with permission from [85,86].

NH₃, ammonia.

### Table 3 Stages of hepatic encephalopathy

| Stage | Level of consciousness | Personality and mental status | Neurological manifestations | Electroencephalography abnormalities |
|-------|------------------------|------------------------------|----------------------------|-------------------------------------|
| I     | Normal                 | Normal                       | Abnormalities in psychometric tests only | None |
|       | Inversion of sleep–wake rhythms | Impaired coordination | Impaired coordination | Triphasic waves with slow wave activity (5–6 cycles/s) |
|       | Altered state of consciousness | Mild confusion | Finger tremor (difficulty in writing) | |
|       | Personality changes | Irritability | | |
|       | Fatigue | | | |
| II    | Lethargy               | Disorientation | Flapping tremor | Triphasic waves with slow wave activity (5 cycles/s) |
|       | Inappropriate behaviour | Amnesia | Hyporeflexia | |
|       | Confusion | Agressivity | Dysarthria | |
|       | Confusion | | | |
| III   | Somnolence             | Disorientation | Flapping tremor | Triphasic waves with slow wave activity (5 cycles/s) |
|       | Confusion | Agressivity | Hyperreflexia | |
|       | Confusion | | Babinski sign | |
|       | Confusion | | Muscular rigidity | |
| IV    | Coma                   | None | Decerebration | Delta activity, very slow wave activity (2–3 cycles/s) |
|       | Awakening impossible | | Rigidy | |

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CT, computed tomography; HSV, Herpes simplex virus; MRI, magnetic resonance imaging.
Minimal hepatic encephalopathy

The creation of a new nomenclature, established in the final report of a multidisciplinary working party [84,85], has allowed for a more precise description of minimal HE (earlier referred to as subclinical HE). This term concerns patients with neuropsychometric abnormalities, and was initially used to describe cirrhotics presenting no clinical manifestations or electroencephalographic perturbations. Diagnosis can be obtained by the use of several psychometric tests, of which the most well-known is the Number Connection Test (NCT). The 1998 working party [84,85] recommended that in clinical trials at least two of the following tests should be used to quantify minimal HE: NCT-A, NCT-B, block design test, digit-symbol test. A combined standardized test, the Psychometric Score of HE, includes the NCT A and B, the line-tracing test, the serial-dotting test and the digit-symbol test, and is particularly recommended for the diagnosis of minimal HE.

The detection of minimal HE is clinically significant as it is present in 30–80% of cirrhotics [89]. In a prospective study including 63 cirrhotics, minimal HE was diagnosed in 34 patients (53%) [89]. Over the course of follow-up, 19 patients developed classical HE.

Hepatic encephalopathy after transjugular intrahepatic portosystemic shunt

HE is one of the most frequent complications of TIPS placement [4]. In a prospective study including 30 patients, HE appeared in the first months after TIPS placement, but generally improved over time (6 month follow-up) [90]. The occurrence of HE was directly correlated with the diameter of the shunt placed. The risk of developing HE was lower when the diameter of the TIPS was less than 8 mm.

Other risk factors concerning HE occurrence have been identified and described in several reviews [5]: age over 65 years, past history of HE before TIPS placement, ongoing alcohol consumption, female sex. A retrospective study including 430 cirrhotics treated by TIPS has shown that cirrhosis of alcoholic origin and presence of diabetes were predictive factors of HE in later years [91].

A large number of studies have shown that TIPS placement is often responsible for the precipitation or aggravation of HE (Table 5). After creation of a surgical portocaval anastomosis, the frequency of HE varies depending on the technique used: 50% after truncular portocaval anastomosis, 10–15% after splenorenal anastomosis [4]. Minimal HE is often observed after TIPS placement [92]. The mechanism of post-TIPS HE is close to that of the persistent HE observed in patients with large spontaneous portosystemic shunts.

Clinical management of hepatic encephalopathy and treatment principles

In 2001, the American College of Gastroenterology (ACG) published clinical practice guidelines for HE [93]. Appropriate supportive care should be initiated, in particular in an intensive-care environment for comatose patients with severe HE. Specific measures, such as tracheal intubation and assisted ventilation may be necessary. The systematic detection and removal of precipitating factors is of the utmost importance. If one or several precipitating factors are identified, they should immediately be targeted by appropriate therapeutic measures.

Identification and correction of precipitating factors

Bacterial infection

According to the 2001 ACG practice guidelines [93], the identification of bacterial infection as a precipitating factor of HE requires a thorough physical examination, and the culture of all appropriate body fluids, especially ascites when present. Spontaneous bacterial peritonitis and pneumonia are often associated with HE. If pneumonia is suspected, a thoracic computed tomography scan may be performed. Bacterial infections are a frequent precipitating factor of HE, regardless of their site. Pathophysiology may involve systemic inflammatory response [7]. Systematic identification and treatment of patent or latent infection is necessary in all cirrhotics presenting with HE.

Metabolic disturbances

According to the 2001 ACG practice guidelines [93], metabolic disturbances include metabolic alkalosis, renal

Table 5 Incidence of hepatic encephalopathy following TIPS placement

| Studies          | Number of patients | A | B | C | Onset or aggravation of HE (%) | Chronic HE (%) |
|------------------|--------------------|---|---|---|-------------------------------|----------------|
| Somberg et al.   | 77                 | 16| 55| 29| 23                            | 5              |
| Sanyal et al.    | 30                 | 20| 33| 47| 33                            | 3              |
| Dagenais et al.  | 45                 | 2 | 51| 47| 25                            | 18             |
| Coldwell et al.  | 96                 | 25| 40| 35| 29                            | 7              |
| Roissle et al.   | 10                 | 27| 52| 22| 16                            | 7              |
| Martin et al.    | 45                 | 22| 58| 20| 43                            | 20             |
| Ochs et al.      | 50                 | – | 36| 64| 44                            | 16             |
| Jalan et al.     | 68                 | 25| 4 | 31| 13                            | NI             |

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HE, hepatic encephalopathy; NI, not indicated; TIPS, transjugular intrahepatic portosystemic shunt.
insufficiency, hypokalaemia, dehydration and/or diuretic effects. A recent Spanish study [94] showed that renal insufficiency and hyponatraemia are responsible for aggravation of liver dysfunction and HE in cirrhotics. Hyponatraemia may act through its effects on astrocytes (ballonisation), whereas renal insufficiency is accompanied by an increase in renal ammonia production.

The use of certain diuretics, and hypokalaemia and dehydration, may cause metabolic alkalosis. Diuretics (spironolactone, furosemide) are potential precipitating factors of HE, as they are capable of inducing renal insufficiency.

**Gastrointestinal bleeding**

According to the 2001 ACG practice guidelines [93], stool analysis and/or placement of a nasogastric tube are necessary for the identification of latent gastrointestinal bleeding.

Gastrointestinal bleeding is a well-established precipitating factor of HE. Diagnosis is easy in the majority of cases as bleeding is often patent. However, bleeding may be occult and digital rectal examination and upper gastrointestinal endoscopy may be necessary.

**Use of psychoactive medication**

According to the 2001 ACG practice guidelines [93], urine screening for benzodiazepines, narcotics and other sedatives may be necessary to detect the use of psychoactive medication.

All psychoactive substances, especially benzodiazepines, morphine derivatives, H1 antihistamines, hypnotics and sedatives, may be responsible for the appearance or aggravation of HE. The use of psychoactive medication should systematically be sought after, by questioning the patient (if possible) and/or his or her family. In case of doubt concerning the consumption of benzodiazepines, a flumazenil test may be performed.

**Constipation and decreased bowel movement**

Constipation is a potential precipitating factor of HE. Patients should be systematically screened for stool impaction by digital rectal examination. However, constipation alone is rarely responsible for HE, and the presence of additional precipitating factors should be verified.

The study of Bouin et al. [95] showed that the orocaecal transit time was increased in alcoholic cirrhotics with HE compared with those who did not have HE. This dysautonomic manifestation may be responsible for bacterial overgrowth and translocation, which may justify antibiotic therapy in certain cases.

**Deterioration of liver function in cirrhosis**

According to the 2001 ACG practice guidelines [93], the acute deterioration of liver function is rarely the sole factor responsible for HE, contrary to fulminant hepatitis. However, acute deterioration of liver function may be directly responsible for HE in the case of acute alcoholic hepatitis or surgical treatment of acute portal thrombosis.

**Excess dietary protein**

According to the 2001 ACG practice guidelines [93], the patient or his or her family should be questioned concerning excessive protein intake.

An episode of HE is deemed spontaneous if no precipitating factor is found. If this is the case, the presence of portosystemic shunts or an abnormal collateral circulation should be suspected.

**Prevention of recurrence of hepatic encephalopathy in cirrhotic patients**

Specific preventative measures should be aimed at the cirrhotic population, such as prevention of constipation, prophylactic treatment of oesophageal variceal haemorrhage if indicated, prophylaxis of spontaneous bacterial peritonitis, and caution concerning administration of diuretics and psychoactive medications. In case of disturbed sleep patterns or insomnia, hydroxyzine (Atarax) may be used, which has a lower risk of precipitating HE compared with other hypnotic drugs [96]. Precipitating factors of HE are often absent in patients at high risk of HE, or in those having undergone TIPS. Medication aiming to reduce blood ammonia levels may be required. Results concerning this treatment goal are lacking in current literature.

**Treatment principles**

**Treatment to decrease intestinal ammonia production**

**Dietary protein intake and amino acids:** according to the 2001 ACG guidelines [93], prolonged restriction of dietary protein intake should be avoided because of the risk of denutrition and malnutrition in particular (recommended dietary protein intake 1–1.5 g/kg/day). In the case of chronic HE, a high-protein diet including dietary protein from vegetable and dairy sources is preferred.

Restriction of dietary protein intake aims at reducing hyperammonaemia. However, Cordoba et al. [97] have demonstrated that the systematic introduction of a low-protein diet is not always necessary for patients with HE. Such a diet may even be deleterious as it may worsen a poor nutritional status. A review of the literature [93] recently reported the results of a randomized study including 20 patients with HE, which showed that a balanced protein intake (1.2 kg/day) did not alter the course of HE. Moreover, a positive nitrogen balance may have a positive effect on HE, allowing for an increase in muscle capacity, thus increasing the transformation of ammonia into glutamine by muscle tissue [93].

Chronic liver disease is often associated with an amino acid imbalance with an increase in the ratio between aromatic/branched amino acids. This observation led to
Numerous studies whose aim was to treat HE by correcting amino acid imbalance. Various studies concerning amino acids were included in a meta-analysis by Als-Nielsen *et al.* [45]. No convincing argument in favour of the administration of branched amino acids in patients with acute and chronic HE was found. However, these studies included only a small number of patients, with short follow-up duration and questionable methodology. The authors of this meta-analysis concluded that it was not possible to affirm the noneffectiveness of branched amino acids, and that additional high-quality randomized trials versus placebo including patients in sufficient numbers are necessary.

**Nonabsorbable disaccharides:** according to the 2001 ACG guidelines [93], bowel cleansing reduces luminal ammonia content, decreases colonic bacterial counts and lowers blood ammonia levels in certain patients. This is more important as there is a reduction in intestinal transit time in patients with HE, and HE in itself may contribute to this reduction [95]. Various types of laxatives may be used, but nonabsorbable disaccharides are preferred as they also induce a decrease in the production of nitrogenous compounds. Bowel cleansing may require the administration of enemas in patients with severely impaired consciousness. Another option is irrigation of the digestive tract through a nasogastric tube, but the risk of inhalation should be taken into account, particularly if alterations of consciousness are present, and orotracheal intubation may be required.

Lactulose is the preferred pharmacological treatment for patients presenting with HE, according to the 2001 ACG guidelines [93]. Nonabsorbable synthetic disaccharides, such as lactose (β-galactosidofructose) and lactitol (β-galactosidosorbitol) have long since been considered as first-line treatment of HE. They possess both a laxative effect and an effect on ammonia metabolism. Lactulose is not broken down by intestinal disaccharidases, and reaches the colon where it is metabolized by bacteria into acetic, butyric, propionic and lactic acids. These molecules are responsible for:

1. A reduction of pH in the colonic lumen, which in turn reduces the intestinal absorption of ionized ammonia. The laxative effect of lactulose may thus be secondary to colonic acidification;
2. Inhibition of ammonia synthesis by colonic bacteria;
3. Stimulation of incorporation of ammonia within bacterial proteins;
4. Reduction of transit time, leading to a reduction in ammonia release; and
5. Increase in faecal excretion of nitrogenous compounds.

All these mechanisms induce a reduction of ammonia levels in portal and systemic circulation. Sufficient doses of lactulose result in 2–3 soft stools per day, with a faecal pH below 6. Generally, daily doses of 40–60 g of lactulose are required, or 30–50 g of lactitol. The use of disaccharides in excessive quantities may lead to dehydration, which can aggravate HE. No significant statistical difference in efficacy has been shown between lactulose and lactitol, although the meta-analysis of Blanc *et al.* [98] suggested that lactitol should be preferred because of less frequent digestive side effects, in particular reduced flatulence and bloating. The results of previous randomized controlled studies on the patient are shown in Table 6, as reported by a 2005 review [10].

A recent meta-analysis by Als-Nielsen *et al.* [99] revealed that the superiority of lactulose over placebo has not been shown, and that lactitol is not yet been proved equally effective as lactulose. Antibiotics were found to be more effective, but clinical parameters were not significantly improved. The vast majority of studies considered for this meta-analysis were subject to methodological biases, such as incorrect randomization, lack of intention-to-treat analysis and insufficient follow-up duration. Consequently, only 44 studies out of a potential 444 were included in the meta-analysis. The authors concluded that there is insufficient scientific evidence in favour of the use of disaccharides, and that antibiotics seem to be the superior treatment. They also suggest that disaccharides should not be used as the gold standard treatment in trials evaluating the efficacy of new molecules.

The absence of efficacy of nonabsorbable disaccharides has been shown in less recent studies. The double-blinded trial of Blanc *et al.* [100] published in 1994 did not show any significant therapeutic benefit when combination lactulose–neomycin treatment was administered in 80 patients with acute HE compared with placebo.

Table 6  Randomized controlled trials comparing disaccharides with placebo or absence of treatment in hepatic encephalopathy in cirrhotic patients

| Trials                  | Trial type | N | HE                        | Treatment                | Results (treated patients/controls) | End of trial (treated patients/controls) |
|-------------------------|------------|---|--------------------------|--------------------------|------------------------------------|----------------------------------------|
| Elkingston et al. [140] | Crossover  | 7 | Chronic                  | Lactulose/sorbitol        | Equivalence*                        | Nil                                    |
| Simmons et al. [141]   | Comparative| 26| Acute and chronic        | Lactulose/glucose         | 4/14/5/12                           | 3/14/2/12                              |
| Rodgers et al. [142]   | Crossover  | 6 | Chronic                  | Lactulose/sorbitol        | Equivalence*                        | 3/6                                    |
| Germain et al. [143]   | Comparative| 18| Chronic                  | Lactulose/saccharose      | 4/9/3/9                             | 0/0                                    |

*Reproduced with permission from [10].

HE, type of hepatic encephalopathy; *N*, number of patients randomized; *NI*, not indicated.

*Exact numbers not available.*
Additional large randomized controlled double-blinded trials are therefore necessary to draw conclusions on the therapeutic benefit of these molecules. Further studies should stratify treatment groups according to the type of HE.

**Antibiotics:** according to the 2001 ACG guidelines [93], antibiotics are an alternative to nonabsorbable disaccharides for the treatment of acute or chronic HE in cirrhotics. Numerous studies have confirmed the beneficial effect of antibiotics in the treatment of HE [3,6,101–104]. A meta-analysis by Als-Nielsen et al. [99] showed the superiority of antibiotics compared with nonabsorbable disaccharides. Antibiotics act by reducing intestinal ammonia production through their bacterioidal properties on proteolytic urease-rich bacteria.

Neomycin was one of the first antibiotics to be used in this indication. Despite weak systemic absorption, it may put patients with renal insufficiency at risk of adverse renal and aural events [105]. The efficacy of neomycin for the treatment of HE has not been formally established. It has been suggested to be equally effective as lactulose for the treatment of acute and chronic HE [3]. One trial compared neomycin with placebo in acute HE and did not show any difference between the two groups [106].

Various other nonabsorbable antibiotics have been studied (paromomycin, vancomycin), and seem to be useful for patients presenting chronic HE nonresponsive to lactulose [107]. Metronidazole seems to be equally effective as neomycin for the treatment of chronic HE [3]. This molecule is absorbed by the digestive tract with a strong hepatic first-pass effect, and may induce neurological toxicity. Use of this molecule is not recommended for cirrhosis.

Rifaximin is a derivative of rifamycin, and has a low bioavailability (less than 0.5%), which means that most of an orally administered dose is eliminated unchanged in the faeces. Consequently, dose adjustments are not required in patients with liver or kidney dysfunction, and significant drug interactions have not been reported. This drug has been approved for the treatment of hyperamnonaemia in certain European countries. Two recent reviews [108,109] have evaluated the effectiveness and safety of rifamixin in the treatment of HE. Nine open-label studies, four double-blind studies and one dose-finding study have been published, comparing rifamixin with nonabsorbable disaccharides or antibiotics. Response rates ranged from 80 to 90%, and rifamixin was found to be of superior efficacy compared with lactulose, of similar efficacy to paromomycin and of similar or greater efficacy than neomycin. Rifaximin was found to improve clinical signs or symptoms of HE more rapidly (by up to 3 days) and was better tolerated than other pharmacological treatments. A retrospective study found that patients treated with rifamixin had fewer hospitalizations, fewer days of hospitalization and lower hospitalization charges compared with patients treated with lactulose. A recently published randomized double-blind placebo-controlled study [110] suggests that rifamixin may have a role in preventing HE. However, the majority of rifamixin trials were limited by study design (open-label), patient heterogeneity and lack of clearly defined criteria for defining the efficacy of treatment. Nonetheless, rifamixin seems to be an effective and safe treatment option for HE, although additional well-designed studies are needed to better characterize its efficacy.

**Probiotics:** it is possible to modify digestive flora by administering high doses of probiotics, and in particular urease negative bacteria such as *Lactobacillus acidophilus* or *Enterococcus faecium* SF 68. The study of Liu et al. [111] showed that the administration of probiotics in patients with minimal HE led to a significant increase in nonurease-producing species, and a significant decrease in ammonaemia accompanied by an improvement in mental state in 50% of patients. This relatively innovative therapeutic concept needs to be supported by controlled studies on a larger scale [111].

**Acarbose:** acarbose is an oral antidiabetic treatment that inhibits the absorption of glucose in the gut, thus promoting intestinal saccharolytic flora at the expense of proteolytic flora, leading to a decrease in ammonia production. In the study by Gentile et al. [112], 107 cirrhotics with grade 1–2 HE and type 2 diabetes were randomized into two groups versus placebo. Patients on acarbose had significantly decreased ammonia levels and mental status and psychometric tests were superior to patients in the placebo group. Adverse events, such as flatulence and abdominal pain were observed. The authors concluded that acarbose used at 150–300 mg/day is a safe and effective treatment in cirrhosis presenting with mild HE and type 2 diabetes. However, further studies are necessary to confirm the relevance of this treatment in HE.

**Treatment to increase ammonia clearance**

1-Ornithine-1-Aspartate (LOLA): 1-Ornithine-1-Aspartate (LOLA) is an ammonia-reducing substance that acts by providing substrates for the metabolism of ammonia into urea and glutamine. This product is not currently available in France. Several studies [113,114] have suggested that LOLA is safe and effective. A randomized double-blind study including 126 cirrhotics with hyperammonaemia and chronic HE compared patients treated with 20 mg of LOLA over 5 days with patients on placebo. A significant improvement in psychometric tests was observed, as well as a decrease in hyperammonaemia.

**Zinc deficiency:** zinc is a co-factor of the urea cycle, and promotes an increase in urea production leading to a loss of ammonia ions. Zinc deficiency is common in poorly
nourished cirrhotics. According to the 2001 ACG recommendations [93], all patients should be screened for zinc deficiency, which should be supplemented if present (200 mg twice a day). Results of published studies concerning zinc supplementation are contradictory (certain studies show that zinc improves the evolution of HE, whereas no difference is shown in other studies). Zinc can potentially block the absorption of other divalent cations.

L-carnitine: L-carnitine may reduce ammonia levels by increasing energy metabolism. Studies evaluating L-carnitine in HE are scarce. In a study [115] including 150 cirrhosis (alcoholic cirrhosis n = 10, viral B cirrhosis n = 41, viral C cirrhosis n = 78, cryptogenic cirrhosis n = 21), L-carnitine (dose 2 g/day) was compared with placebo. A significant reduction in fasting ammonia levels and improvement in psychometric tests were observed in the group of patients treated by L-carnitine [116].

Sodium benzoate: sodium benzoate is a compound, which reduces ammonaemia by increasing urinary secretion of ammonia in the form of hippurate. It has been successfully used in the treatment of congenital hyperammonaemia [117]. Published data concerning sodium benzoate are scarce. In a controlled randomized study [118], 38 patients were treated with sodium benzoate, whereas 36 were treated with lactose. The cost of sodium benzoate therapy was 30 times lower than that of lactulose. Despite the fact that this study was not designed to demonstrate equivalence between the two treatments, the authors concluded that sodium benzoate is an effective and safe alternative to lactulose for the treatment of HE.

Molecules affecting neurotransmission
According to the 2001 ACG guidelines [93], the administration of flumazenil and bromocriptine may have a favourable effect in selected patients. Bromocriptine or L-DOPA has been tested in patients presenting HE with extrapyramidal symptoms. A recent meta-analysis by Als-Nielsen et al. [40] was unable to confirm or refute the beneficial effect of dopaminergic agonists for the treatment of HE. These molecules are currently not used in this indication.

Flumanezil, commonly used in benzodiazepine overdose, has been evaluated in HE by numerous high-quality studies [119]. The largest controlled double-blind crossover trial [119] included 527 patients with grade 3 or 4 HE hospitalized in intensive care units for over 5 years. Two hundred and sixty-five patients received flumanezil, whereas 262 received a placebo. Treatment was initiated 15 min after randomization. Improvement in neurological status was observed in 17% of patients treated by flumanezil with grade 3 HE, and in 14.7% with grade 4 HE, compared with 3.8 and 2.7% respectively in the placebo group. Electroencephalogram abnormalities were also improved in patients in the flumanezil group (improvements observed in 27.8% of grade 3 patients, and in 21.5% of grade 4 patients) compared with the placebo group (improvements in 5% of grade 3 patients and 3.3% of grade 4 patients). Benzodiazepines were detected in only 10 patients (four patients with grade 3 HE and six patients with grade 4 HE). Two subsequent meta-analyses confirmed the results of this study [40,120].

Clinical improvement after flumanezil administration is not always marked, and this treatment is only available in intravenous form. However, the administration of fluman- nezil (current dose 1 mg, intravenous) may be recommended in particular for cirrhotics with HE likely to have consumed benzodiazepines.

Other treatments
Eradication of Helicobacter pylori
The results of the latest research evaluating the role of Helicobacter pylori as a causal pathogen responsible for HE are contradictory. The first studies published between 1999 and 2001 [121–123] did not confirm the presence H. pylori as an independent risk factor of HE. In these studies, the presence of H. pylori did not increase ammonaemia and its eradication did not improve psychometric and electrophysiological tests, in particular in cases of infraclinical HE. A recent Chinese study published in 2008 [124] including 457 cirrhotics revealed that H. pylori infection has a deleterious effect on the onset of hyperammonaemia and HE. HE was more frequently observed in patients infected with H. pylori (58.5 vs. 30.6%, P < 0.01). The eradication of this bacterium allowed to significantly reduce the number of episodes of HE. At present, there is no consensus on the management of H. pylori in the context of HE or hyperammonaemia. Additional trials with large numbers of patients or the performance of a meta-analysis would be necessary to reach a conclusion.

Manipulation of splanchnic circulation
According to the 2001 ACG guidelines [93], the eventual presence of a large portosystemic shunt should be ascertained in certain patients with recurring episodes of HE despite appropriate medical treatment, or when no precipitating factor has been identified. Large splenorenal and spleno-gastro-renal shunts may be associated with severe post-TIPS HE. In this situation, partial occlusion using interventional radiology techniques, such as the use of vascular endoprostheses, has been proposed in several different publications [125–128]. These techniques should only be performed by experienced interventional radiologists. However, one of the drawbacks of these techniques is the theoretical risk of redeveloping portal hypertension, with recurrence of oesophageal varices, and ultimately a risk of digestive tract bleeding.
Bioartificial liver and MARS liver support therapy

Bioartificial livers and the MARS system may be effective for the treatment of HE in certain situations (results of noncontrolled studies [6]). These procedures have proven to be useful in HE secondary to acute liver failure, and in patients with permanent HE [129].

Liver transplantation

In patients with fulminant or subfulminant hepatitis, the onset of HE is an adverse prognostic factor reflecting the severity of liver failure. The presence of HE associated with factor V levels less than 20% is an indication for liver transplantation [130]. Neurological complications, in particular cerebral oedema, may be extremely serious, with a mortality of 30% after liver transplantation [131]. In cirrhotics, the presence of chronic HE or recurring episodes of HE are a consequence of severe liver failure for which liver transplantation is the only therapeutic option [132].

Conclusion

HE is a serious complication of acute or chronic liver disease. The pathophysiology of HE is yet to be fully elucidated. Current treatments are based on reducing intestinal ammonia load by agents, such as antibiotics or disaccharides. However, their efficacy is yet to be clearly established. The mainstream of therapeutic management remains the correction and treatment of an eventual precipitating factor.

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