Digestive and Liver Disease xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Guidelines

Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF)

Sara Montagnese[a,*,1], Francesco Paolo Russo[b,2], Piero Amodio[a,3], Patrizia Burra[b,3], Antonio Gasbarrini[c,3], Carmela Loguercio[d,3], Giulio Marchesini[e,3], Manuela Merli[f,3], Francesca Romana Ponziani[c,3], Oliviero Riggio[f,3], Carmelo Scarpignato[g,3]

[a] Department of Medicine, University of Padova, Italy
[b] Department of Surgery, Oncology and Gastroenterology, University of Padova, Italy
[c] Division of Internal Medicine, Gastroenterology and Hepatology Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Catholic University of the Sacred Heart, Rome, Italy
[d] Department of Clinical and Experimental Medicine, University of Campania "L. Vanvitelli", Naples, Italy
[e] Unit of Metabolic Diseases & Clinical Dietetics, Department of Medical and Surgical Sciences, University of Bologna, Italy
[f] Division of Gastroenterology, Department of Clinical Medicine, La Sapienza University of Rome, Italy
[g] Clinical Pharmacology & Digestive Pathophysiology Unit, Department of Clinical & Experimental Medicine, University of Parma, Italy

ARTICLE INFO

Article history:
Received 29 October 2018
Accepted 28 November 2018
Available online xxx

Keywords:
AISF
Guideline
Hepatic encephalopathy

ABSTRACT

Hepatic encephalopathy (HE) is a common, worrisome and sometimes difficult to manage complication of end-stage liver disease. HE is often recurrent, requiring multiple hospital admissions. It can have serious implications in terms of a patient's ability to perform complex tasks (for example driving), their earning capacity, their social and family roles. This guideline reviews current knowledge on HE definition, pathophysiology, diagnosis and treatment, both by general principles and by way of a summary of available drugs and treatment strategies. The quality of the published, pertinent evidence is graded, and practical recommendations are made. Where possible, these are placed within the Italian health service context, with reference to local diagnosis and management experience.

1. Introduction

Hepatic encephalopathy (HE) remains one of the most severe and worrisome complications of end-stage liver disease. Despite a general improvement in the care of patients with liver failure and the availability of liver transplantation, HE remains a possible complication indicating either a stage of severe hepatocellular failure, the presence of large portal-systemic shunts or both.

The overall prevalence and cumulative incidence of HE is difficult to define, depending on symptom variability from mild neuropsychological dysfunction to deep coma, and on the tools used for detection and scoring; notably, HE may be largely underestimated in clinical practice [1]. A 2014 joint clinical practice guideline of the European Association for the Study of the Liver and the American Association for the Study of Liver Disease concluded that minimal HE (MHE) and covert HE (CHE) (*vide infra*) may be present at diagnosis, their prevalence increases to 20–80% in the course of follow-up, whereas overt HE (OHE) will occur in 30–40% of patients with cirrhosis during their overall clinical course [2]. A first bout of OHE is reported in 5–25% within 5 years of diagnosis, in relation to precipitants. After a first bout, the risk of additional episodes increases systematically and recurrence or the development of a persistent state of mild-to-severe cognitive impairment is not uncommon, and scarcely modified by treatment [2]. Prevalence rates may be much higher in the presence of transjugular intrahepatic portosystemic shunt (TIPS) [3], as well as spontaneous [4] or surgical shunting [5].

More recent data have largely confirmed the clinical severity of HE and its impact on National Health Systems. In a 5-year follow-up, 82% of patients with decompensated cirrhosis required hospitalization and 50% experienced an early readmission [6]. An early readmission to an acute care hospital – and OHE is a common cause [7] – is an independent predictor of mortality in patients with decompensated cirrhosis for at least 1 year following initial admission [1]. A large analysis of patients with cirrhosis hospitalized

* Corresponding author at: Dipartimento di Medicina, Via Giustiniani, 2, 35128 Padova, Italy.
E-mail address: sara.montagnese@unipd.it (S. Montagnese).
[1] Chair.
[2] AISF board representative.
[3] Panel Member.

https://doi.org/10.1016/j.dld.2018.11.035
1590-8658/

in tertiary-care centers showed that HE severity was significantly associated with in-hospital and 30-day mortality, independently of any extra-hepatic organ failure [8], as well as 90-day waitlist mortality, independently of Model for End-stage Liver Disease (MELD) scores [9]. HE improves the predictive ability of MELD within the transplant waiting list setting [10,11].

The total burden of HE goes well beyond morbidity and mortality. In the US the total charges of hospitalization for patients discharged with a diagnosis of HE, including resource utilization, number of inpatient procedures, and average length of stay, increased from 4.5 to over 7 billion dollars between 2004 and 2009 (approximately 110,000 hospitalizations) [12]. The overall costs should also include indirect cost for patients, families and caregivers [13]. Indirect costs for patients include inability to work and lost wages because of a higher rate of unemployment [14]; poor quality of life includes impairment in social functioning, mobility, sleep/rest, work and home management, and holidays [15], also associated with unfitness to drive [16]. Finally, the cost extends to families and caregivers, considering the need of continuous care, with absence to work and lost wages for family members, and anxiety/depression, which are present in nearly 20% of caregivers [14].

In order to produce this guideline, the panel established the most relevant questions to answer, considering relevance, urgency and completeness of the topics to be covered. These questions were: What are the definition, the pathophysiology and the classification of HE? How should HE be diagnosed and how relevant are differential diagnosis pathways? Does cerebral imaging have a role in HE diagnosis/management? What are the general principles of HE treatment? What are the drugs available for HE treatment and what are their mechanisms of action? Each expert took responsibility for a specific section of the guideline, including pertinent literature search and recommendations. The evidence and recommendations were graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [17]. The panel met twice during national meetings, while teleconferences were organised to discuss specific issues and vote the recommendations.

2. Definition

HE can be defined as '*brain dysfunction caused by liver failure and/or portal-systemic blood shunting that produces a spectrum of neurological/psychiatric abnormalities ranging from subclinical alterations to coma*'. The encephalopathies caused by isolated defects of liver metabolism (*i.e.*, urea cycle disorders, Reye syndrome), valproate-induced hyperammonaemia and urease containing organism infections are not covered by the term HE. Patients with severe liver disease may suffer from other types of delirium or coma that are not related to hepatic failure or portal-systemic shunting. These conditions are not covered by the term HE either, although overlapping clinical pictures may exist.

3. Pathophysiology

The pathophysiology of HE can be considered at both *organism* and *organ (brain) level* (Fig. 1).

3.1. Organism level

Both liver failure and portal-systemic shunting produce encephalopathy in humans, as well as in experimental models.

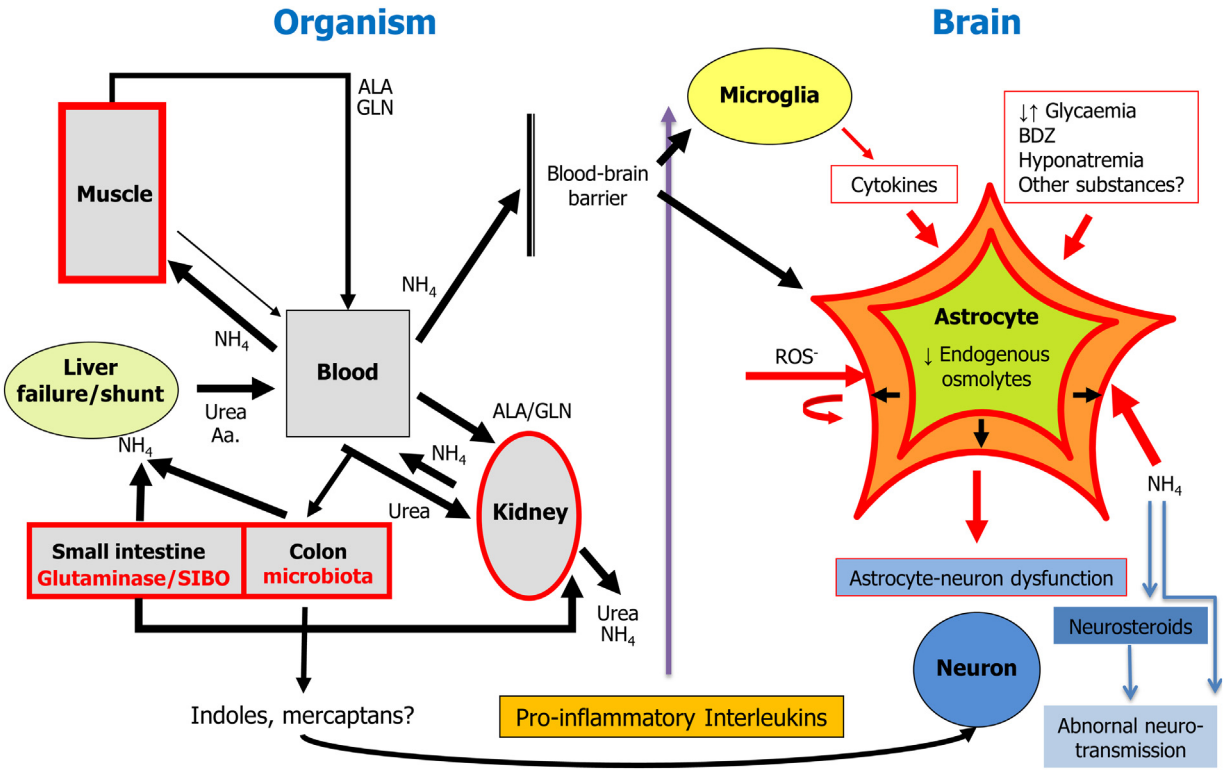

Fig. 1. The pathophysiology of HE. Several organs contribute to the development of hyperammonaemia and the increase in inflammatory cytokines. In addition, other toxic substances are produced by an altered gut microbiota (**left panel**). Peripheral cytokines and ammonia activate the brain microglia, which, in turn, amplifies the inflammatory reaction. This, together with ammonia and other substances, via different mechanisms, determines astrocyte swelling, causing oxidative and nitrosative stress, and determines astrocyte-neuron dysfunction. In addition, ammonia impinges on neurotransmission and oxidative metabolism directly, by promoting the production of inhibitory neurosteroids (**right panel**). The blood-brain barrier is also damaged, especially in patients with ALF and, less so, those with ACLF; ICH can also ensue (**right panel**). Adapted from Amodio et al. [197,198].

Please cite this article in press as: Montagnese S, et al. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.11.035

Table 1
Sites/conditions that play a role in determining plasma ammonia levels and/or sensitise to the action of ammonia.

Sites/conditions	Mechanisms
Kidneys	Ammoniogenic properties and regulation of serum levels of urea (a substrate used by the gut microbiota urease for the production of ammonia)
Urinary tract	Release of ammonia from urea by the action of urease-containing bacteria
Muscle	Utilization of ammonia for glutamine synthesis
Fasting	Protein breakdown and consequent amino acid oxidation
Increase of pro-inflammatory cytokines	Sensitization to the action of ammonia
Hyponatremia	Sensitization to the action of ammonia
Alkalaemia	Sensitization to the action of ammonia

Further, encephalopathy can be induced by the administration of ammonia salts in patients with cirrhosis [18], the administration of ammonia salts or urea precursors in dogs with surgical portal-systemic shunt, and meat feeding in dogs with surgical portal-systemic shunt [19]. Encephalopathy is reverted by oral non-absorbable disaccharides and antibiotics, both acting on gut bacteria [20–23], and by portal-systemic shunt reduction [24–26]. These findings support the view that HE may be specifically caused by liver failure and/or portal-systemic shunting, as well as by nitrogen metabolism and gut content, including the gut microbiota and its interaction with food. It is therefore reasonable to qualify this kind of encephalopathy as "hepatic encephalopathy".

Several gut-derived substances may have neurotoxic effects, including ammonia, mercaptans, benzodiazepine-like substances and indole, which is converted into the neurotoxic substance oxindole in the brain [27–33]. Plasma ammonia, in addition to its direct effect on the brain, is likely to be a marker of the presence of other toxic nitrogenous substances produced by the gut microbiota. For example, the levels of ammonia and indole are correlated, because the origin of these substances is similar. Other important sites that play a role in determining plasma ammonia levels are the kidneys, which have both ammoniogenic properties and regulate the serum level of urea, a substrate used by the gut microbiota urease for the production of ammonia [34], the urinary tract, where ammonia can be released from urea by the action of urease-containing bacteria hosted in the urinary tract [35], the muscles, which can utilize ammonia for glutamine synthesis, thus explaining why sarcopenia is a risk factor for HE [36–38]. Protein breakdown and the consequent amino acid oxidation in fasting conditions, which delivers nitrogen moieties, can also contribute to hyperammonaemia. Finally, any systemic condition increasing pro-inflammatory cytokines [39], causing hyponatremia [40] or determining alkalaemia [41] can sensitise to the action of ammonia (Table 1).

3.2. Organ level

An increase in cellular water content is observed in the brain in HE, and in extracellular water content in acute liver failure (ALF) [42,43] and acute on chronic liver failure (ACLF) [44], coupled with a reduction of myoinositol [45]. These findings are correlated with clinical findings to a varying extent. The oscillatory properties of neural networks are altered, thus the electroencephalogram (EEG) slows [46,47]. The transmission of stimuli in the white cortex is likely to be reduced, as documented by prolonged exogenous evoked potentials [48,49]. The increase in blood ammonia facilitates the entrance of ammonia in the brain with first order kinetics and can explain, at least in part, the neurological findings. Ammonia drives:

- An increased glutamine synthesis in astrocytes (cells containing glutamine synthetase), entrance of glutamine into the mitochondria with intra-mitochondrial ammonia release, oxidative and nitrosative stress, activation of mitochondrial permeability transition, mitochondrial dysfunction leading to astrocyte dysfunction. This process is favoured by the activation of pro-inflammatory cytokines and low sodium levels.
- The activation of microglia and induction of neuroinflammation, which favours astrocyte dysfunction.
- The impairment of brain energy metabolism via inhibition of ketoglutarate dehydrogenase and pyruvate dehydrogenase, with consequent tricarboxylic acid cycle dysfunction, increased glycolytic activity and lactate production.
- The interference with glutamatergic and GABAergic neurotransmission, the latter directly [50] or indirectly, via promotion of inhibitory neurosteroids synthesis [51].
- The interference with inhibitory and excitatory mechanisms of neurotransmission, due to the similarity in dimension and charge between the ammonium ion and potassium ion [52,53].

In addition, there is some evidence for alterations in serotoninergic, histaminergic and dopaminergic neurotransmission in HE [54,55]. Hyperintense globus pallidus and, to a lesser extent, globus striatum and substantia nigra reticulata on T1-weighted Magnetic Resonance Imaging (MRI) are frequently observed in patients with HE and are related to brain manganese deposition, which, in turn, is caused by reduced manganese clearance due to portal-systemic shunting and liver failure [56]. Manganese is neurotoxic and can impair dopaminergic neurotransmission, as well as cause astrocyte oxidative stress [57]. However, the hyperintensity of globus pallidus and basal ganglia is poorly related, if at all, to the cognitive symptoms of HE. In addition, after liver transplantation globus pallidus hyperintensity is maintained for much longer compared to HE-related symptoms, suggesting that their relationship is poor. Alterations of blood–brain barrier have been reported in ALF and severe ACLF. In these conditions, they may concur to the development of brain oedema and intracranial hypertension (ICH), with the risk of death caused by cerebellar tonsil herniation. This event is very rare in ACLF, while it is more common in ALF [58], and the risk increases for very high plasma ammonia levels [59].

4. Classification

Proper classification of HE is multiparametric and useful for patients' management. There is agreement [60] that HE should be classified on the basis of 4 items (Fig. 2):

1. The underlying condition leading to HE;
2. The severity of mental alteration;
3. The time-course of mental alteration;
4. The precipitating and facilitating events (the latter being spontaneous or surgical portal-systemic shunts, or TIPS);

1. The type of underlying disease is relevant in terms of pathophysiology and treatment options. In "type A" HE, ALF is recognized as the clinical setting for HE onset. Intracranial hemodynamic alterations, as well as brain barrier alterations and astrocyte swelling, cause ICH. This can lead to death because of cerebellar tonsils herniation [61].

Please cite this article in press as: Montagnese S, et al. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.11.035

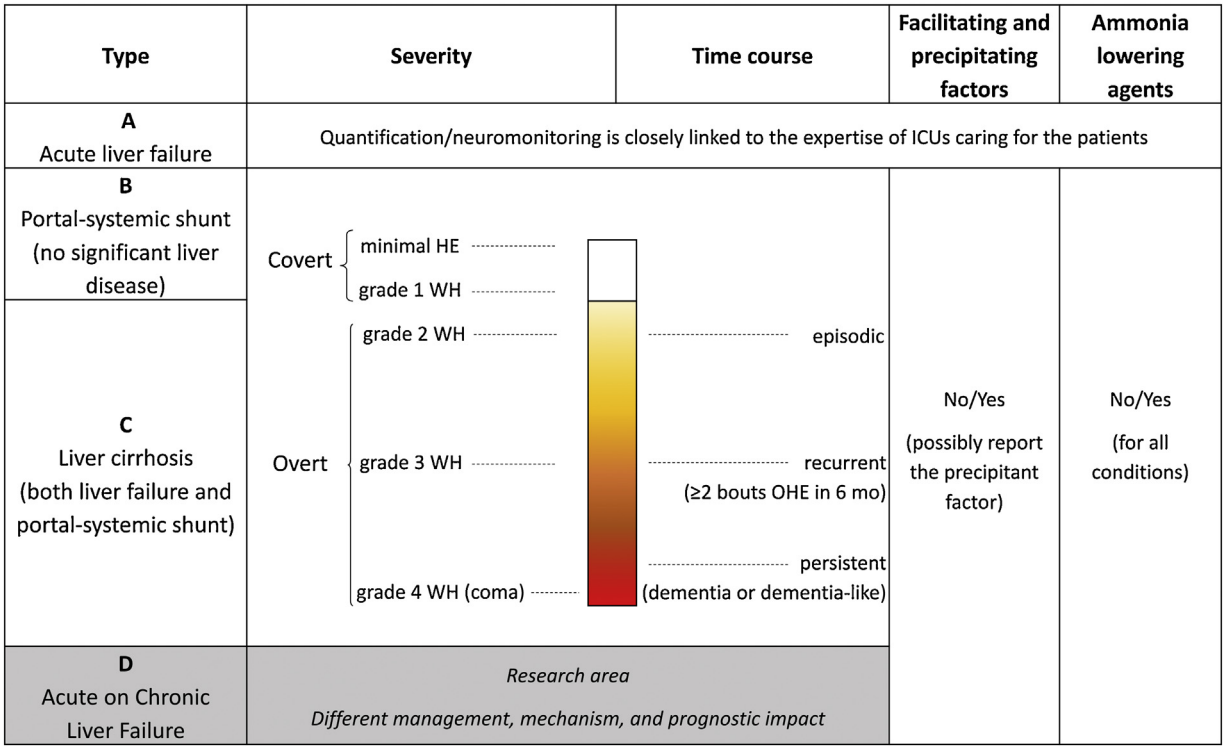

Fig. 2. The classification of HE, adapted from Amodio et al. [197].

In "type B" HE, portal-systemic shunting alone is the cause of HE development. Thus, if it is closed, the problem is solved.

In "type C" HE, both portal-systemic shunting and liver failure are at the basis of HE.

Recently, a distinction between patients with and without ACLF [62] has been suggested. HE in patients with ACLF has more severe prognostic value [63], intercellular brain oedema parallels the severity of symptoms [44], and ICH has been reported, albeit rarely [64]. In patients with ACLF, massive inflammation causing damage to the brain-blood barrier and injuries to the brain deriving by multiorgan failure and drug treatments [65–67] can be present. This may cause a mixed form of metabolic encephalopathy, for which personalized treatment might be preferable [68]. It has even been suggested that HE in patients with ACLF could be qualified as "type D" but the proposal remains debated and further research is needed to define the specifics of this entity, if any, in terms of mechanisms, management, and prognostic impact (shaded area of Fig. 2).

2. The severity of mental impairment has prognostic [63] and management implications. Comatose patients require airways protection and agitated patients require sedation. Despite the terms *overt* and *covert* being debated, they distinguish between undoubtedly symptomatic subjects, who may require hospitalization, and subjects who are scarcely symptomatic or asymptomatic, who do not require hospitalization. OHE can be graded according to the AASLD/EASL operative definitions [60] and other techniques; CHE does not have a universally accepted diagnosing tool. The animal naming test (ANT; *vide infra* for a complete description) [67] is a simple and costless approach to quantify mental function in non-disoriented subjects; further, it takes only 60 s. The ANT is related to patients' prognosis, and has good repeatability, so that its changes reflect changes in HE. Thus, the ANT can be recommended for everyday practice. For centers highly motivated in screening for the presence of MHE (*vide infra*), more accurate tools are the Psychometric Hepatic Encephalopathy Score (PHES), the critical flicker frequency (CFF) and the EEG, possibly quantified [69]. Computerized tests assessing attention [70,71], working memory [72] or inhibition [73,74] can also be used in highly skilled asymptomatic patients [75].

3. The time course and in particular the frequency of relapse has prognostic value in patients with HE, and is a guide for prophylactic treatment [23,76].

4. The precipitating (infection, gastro-intestinal bleeding, diuretic overdose, electrolyte disorder, constipation) [60,77] and facilitating events are relevant to support the diagnosis. Their prevention (*i.e.* bleeding prophylaxis, avoidance of constipation, diuretic treatment tapering, *etc.*) reduces the risk of bouts of HE. In all instances, information on the existence of surgical portal-systemic shunts, or TIPS should be acquired.

The response to treatment is useful to confirm the diagnosis and, if effective, to guide treatment choices in case of relapse. Thus, for purposes of hospital notes, discharge summaries *etc.*, an episode of HE should be described and reported as follows: first episode of OHE (grade III), precipitated by constipation and urinary tract infection, which resolved after two days of treatment with lactulose and ciprofloxacin.

Recommendation
HE should be defined according to the following criteria:
1. Underlying condition leading to HE (types A, B and C)
2. Severity of mental alteration (covert, overt)
3. Time course of mental alteration (episodic, recurrent, persistent)
4. Presence of precipitating and facilitating events [yes (and if so, which ones), no]
(Grade III, A, 1)

5. Diagnosis and differential diagnosis

HE is characterized by a wide spectrum of unspecific neurological and psychiatric abnormalities. In order for these to be qualified as HE one should: (1) confirm that the patient has significant liver failure and/or portal-systemic shunting, and (2) exclude other causes of neurological and psychiatric dysfunction, which may explain the entire set of abnormalities. This process is not necessar-

Please cite this article in press as: Montagnese S, et al. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.11.035

ily straightforward. In relation to point 1, measurement of fasting ammonia levels is a reasonable start, because normoammonaemia makes significant liver failure and/or shunting extremely unlikely, and thus equally unlikely that the observed abnormalities are due to HE. By contrast, as false positives are common in ammonia measurement (for example in relation to the length of time between sampling and assessment) high ammonia levels should not be used to stop the differential diagnosis procedure. Point 2 is also complicated by the fact that patients with end-stage liver disease are prone to several types of metabolic and non-metabolic neuropsychiatric dysfunction, which can co-exist with HE, thus compromising the 'exclusion diagnosis' process. Despite these difficulties, differential diagnosis is crucial to avoid mismanagement of hepatic failure, HE, and also other forms of neuropsychiatric dysfunction the symptoms of which have been wrongly attributed to HE.

5.1. Type A

Type A HE is included in the definition of ALF. It is characterized by a change in mental status, which may appear abruptly, fluctuate in severity and progress to deep coma. Due to the context of ALF, the diagnosis of type A HE needs the careful exclusion of other causes of mental impairment, which may need different therapeutic approaches. Differential diagnosis to be considered are severe hypercapnia, hypoglycaemia, hyponatremia, acidosis, bacterial or fungal infections with brain involvement [78], brain damage due to haemorrhage or ischaemia, sedation due to drugs or other toxic substances [68]. Glucose, electrolytes, arterial blood gases, including pH, and C reactive protein are helpful in this respect. Bacterial or fungal brain involvement, when suspected, needs appropriate imaging [either a cerebral Computerised Tomography (CT) or MRI], cerebrospinal fluid examination and microbiological tests to be confirmed or excluded. Sedation due to drugs or other toxic substances needs to be recognized through risk factors and accurate history taking from the patients' family, caregivers or friends.

Type A HE can be accompanied by the development of brain oedema and ICH. ICH has been reported in about one third of patients with severe HE (grades III–IV) [79]. On physical examination, these patients present with pupil dilatation, decrease response to light stimuli and arterial hypertension [80]. Monitoring ICH is not easy and the invasive measurement of intracranial pressure (ICP), the gold standard for diagnosis, is associated with an elevated clinical risk in patients with ALF due to impaired coagulation and potential intracranial bleeding. On the other hand, the reliability of measures derived from the non-invasive trans-cranial Doppler has been questioned [81]. Brain imaging may be of some help but the sensitivity of this exam has also been questioned, and in some instances moving patients with severe HE can even induce increases in ICP [82]. Finally, arterial angiography can help identify severe cerebral damage/death.

Neurological manifestations in acute liver failure, being essential for the diagnosis of ALF, represent an indicator of poor prognosis and require prompt hospitalization in a liver transplant centre for monitoring and evaluation. At the same time, irreversible brain damage needs to be promptly recognized, as this event may be a criterion to qualify transplantation as futile.

Recommendations
- The diagnosis of Type A HE requires the systematic and careful exclusion of other causes of mental impairment (**Grade II-3, A, 1**)
- Irreversible brain damage needs to be recognized, ideally by a combination of clinical and imaging criteria examined by a multidisciplinary expert team, in patients with severe coma, in order to avoid futile liver transplantation (**Grade III, B, 1**)

Table 2
List of disorders that could mimic or associate with HE, and should be considered for purposes of differential diagnosis.

Alcohol/opioids withdrawal syndromes
Electrolyte-related encephalopathy (*i.e.* hyponatremia, hyper/hypocalcemia *etc.*)
Encephalopathy of endocrine origin (*i.e.* hypothyroidism and hypocorticism)
Hypercapnic encephalopathy
Hyperosmotic encephalopathy
Hypo/hyperglycaemic encephalopathy
Intoxication with alcohol or other recreational drugs
Intoxication with benzodiazepines or other psychoactive drugs (*i.e.* anticonvulsants, sedative antidepressants, opioids, fluoroquinolones)
Intracranial structural injury (*i.e.* subarachnoid haemorrage, ischaemic or haemorragic stroke, brain neoplasms)
Meningoencephalitis
Non convulsive status epilepticus
Septic encephalopathy
Simulation
Uraemic encephalopathy
Vitamin deficiencies or complex malnutrition-related syndromes
Wernicke's encephalopathy

5.2. Type B

Type B HE results predominantly from portal-systemic shunting, either in the complete absence of liver disease or in association with portal hypertension not due to cirrhosis. The diagnostic criteria for both overt and covert type B HE are identical to those of overt and covert (*vide infra*) type C HE. However, type B HE is more often unsuspected or misdiagnosed, because of the absence of significant underlying liver disease. In order to direct diagnosis and to prompt the search for portosystemic shunts, which should be performed by angio-CT abdomen, venous blood ammonia should be part of the work up of all form of new onset unexplained delirium [83].

Recommendations
- Venous blood ammonia should be part of the work up of all forms of new onset unexplained delirium, as it may help identify unrecognized Type B HE (**Grade II-3, B, 1**)
- Should hyperammonaemia be documented in the absence of significant liver damage, an abdominal angio-CT is indicated (for both the identification of non-cirrhotic portal hypertension and portal-systemic shunt) (**Grade II-3, B, 1**)

5.3. Type C

None of the manifestations of type C OHE are specific and there are no clinical markers, which are truly useful in distinguishing between OHE and other neurological alterations of metabolic origin that may occur in patients with cirrhosis but are not causally related to liver disease. Ammonia levels within the normal range have a high negative predictive value and virtually no false negatives on measurement [84]. Thus, patients with overt neuropsychiatric abnormalities and normal ammonia levels should undergo a prompt and thorough differential diagnosis process, as they do not have a degree of liver failure and/or portal-systemic shunting that justifies a working diagnosis of HE [60,84,85]. Although the large majority of cirrhotic patients who develop delirium are eventually diagnosed with OHE, it is crucial to exclude other causes of altered mental status (Table 2) [85]. Once a diagnosis of OHE is made, every effort should be devoted to identify precipitating events (Table 3), as their correction is crucial. Multiple precipitating events may coexist in the same patient, together with co-morbid conditions [30], which should always be considered, especially if neuropsychiatric symptoms do not ameliorate once the initial precipitant has been managed appropriately. OHE may be graded according to the algorithm

Please cite this article in press as: Montagnese S, et al. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.11.035

Table 4
Algorithm for OHE grading.

1. Perform the Animal Naming Test (ANT)

Number of animals/min_____
If years of education < 8, please add 3 animals
If years of education < 8 and age > 80, please add 6 animals

> 15 animals (normal ANT) = No HE
< 15 animals (abnormal ANT), please go to 2

2. Orientation to time

	Incorrect	CORRECT
• What year is it?	☐	☐
• What season is it?	☐	☐
• What month is it?	☐	☐
• Which day of the month is it?	☐	☐
• Which day of the week is it?	☐	☐

At least 3 questions wrong = disoriented to time, please go to 3

3. Orientation to space

	Incorrect	CORRECT
• Which country are we in?	☐	☐
• Which region are we in?	☐	☐
• Which city are we in?	☐	☐
• Where are we? (church, park….)	☐	☐

At least 3 questions wrong = disoriented to space, please go to 4

4. Glasgow Coma Scale

Eye opening response

The patient does not open eyes (1 point)

The patient opens eyes in response to painful stimuli (2 points)

The patient opens eyes in response to voice (3 points)

The patient opens eyes spontaneously (4 points)

Verbal response

The patient makes no sounds (1 point)

The patient makes incomprehensible sounds (2 points)

The patient pronounces inappropriate words (3 points)

The conversation is confused, disoriented (4 points)

Motor response

The patient makes no movements (1 point)

Extension to painful stimuli (decerebrate response) (2 points)

Abnormal flexion to painful stimuli (decorticate response) (3 points)

Flexion/withdrawal to painful stimuli (4 points)

The patient localizes painful stimuli (5 points)

FINAL GRADING	
NO HE (grade 0)	ANT > 15 animals
Covert HE	Oriented to time Oriented to space ANT <15 animals
Overt HE grade II	Oriented to space Disoriented to time OR flapping tremor
Overt HE grade III	Disoriented to time Disoriented to space GCS = > 8
Overt HE grade IV (coma)	Disoriented to time Disoriented to space GCS < 8

Please cite this article in press as: Montagnese S, et al. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.11.035

Table 3
Precipitating factors of OHE, by decreasing frequency.

Episodic	Recurrent
Infections	Electrolyte disorder
GI bleeding	Infections
Diuretic overdose	Unidentified
Electrolyte disorder	Constipation
Constipation	Diuretic overdose
Unidentified	GI bleeding

Adapted from Strauss et al. [77] and Vilstrup et al. [60].

reported in Table 4, which is based on a combination of the West Haven criteria [72] and the Glasgow Coma Scale (GCS) [86].

Recommendations
- Once there is a working diagnosis of type C, OHE, every effort should be made to identify facilitating and precipitating events (**Grade III, A, 1**)
- Type C, OHE can be graded by use of a combination of the West Haven criteria, the presence/absence of flapping tremor and the GCS (**Grade III, A, 1**)

5.4. Minimal and covert HE

HE has been traditionally split into overt (clinically detectable neurological/psychiatric abnormalities) and minimal (abnormalities on neuropsychological, neurophysiological or psychophysic tests) [87]. As the clinical diagnosis of mild forms of OHE is heavily operator-dependent [88], it has been suggested [60,89] that HE is qualified as overt when at least temporal disorientation and/or flapping tremor are detected (≥ grade II according to the West Haven criteria [90]). In contrast, grade I HE [90] abnormalities, which are usually appreciated by caregivers or physicians who are well acquainted with the patient, are grouped with abnormalities on testing (MHE) and qualified as CHE. A diagnosis of CHE requires testing and cannot be solely clinical [89]. The term was suggested because of its sound (opposite to overt) rather than its meaning [60], and there are uncertainties as to how to translate it into Italian.

The diagnoses of MHE and CHE are relevant because overall these conditions are common (30–70% of patients, depending on tests/cut-offs), they can predict OHE, indicate poor quality of life and also reduced socio-economic potential. As a group, patients with MHE or CHE have been shown not to drive as well as unimpaired patients with cirrhosis. However, a diagnosis of MHE or CHE does not imply that the affected individual is a dangerous driver, and both *ad hoc* testing and decisions on the driving license should be delegated to the competent authority.

As MHE and CHE affect multiple components of mental functioning, which may or may not be impaired to the same degree at any given time, the International Society for Hepatic Encephalopathy and Nitrogen Metabolism suggests that the diagnosis is based on more than one test, to be chosen depending on available local norms/expertise [89]. There is virtually no information in the literature on how to combine different test strategies, and concordance between test results has generally been poor [91]. Tests can be *neuropsychological* (paper&pencil or computerized), *neurophysiological* and *psychophysic*. Neuropsychological tests have the advantage of being closer to the disability one is attempting to measure but they are prone to learning effects and can be manipulated by the patient; the existence of pertinent local norms is crucial, as age and educational attainment are major confounders and need to be adjusted for. Computerised neuropsychological tests have the advantage of being based on repeated trials, thus the obtained average is more stable than a single paper&pencil trial. On the other hand, they require familiarity with the device they are presented on. Neurophysiological tests like the EEG can be obtained across the HE spectrum (also in uncooperative patients) but they are further from the disability one is attempting to measure, and their recording/analysis requires an institutional set-up, equipment and expertise. A list of available tests, with short descriptions and placement within the Italian context, is provided here below:

5.4.1. Neuropsychological, paper&pencil or bed-side
- The PHES consists of five paper-pencil tests evaluating cognitive/psychomotor processing speed and visuomotor coordination [92]. They are relatively easy to administer, have good external validity and have been translated/validated into several languages/countries. Forms and pertinent Italian norms are available [93], also for purposes of on-line scoring (http://www.medicinadimed.unipd.it/servizi/tools/phes-and-z-scores-tests).
- The ANT (*i.e.* the number of animals listed in 60 s, no equipment required except for a stopwatch) has recently been shown to compare favorably with more established MHE/CHE measures and to predict OHE. Proposed and tested in Italy; Italian thresholds available [67].

5.4.2. Neuropsychological, computerised
- The Continuous Reaction Time (CRT) test relies on repeated registration of the motor reaction time (pressing a button) to auditory stimuli (through headphones). The most important test result is the CRT index, which measures the stability of the reaction times. Age and sex seem to exert limited influence and there are no learning/tiring effects either [94,95]; no Italian norms available.
- The Inhibitory Control Test (ICT) is a computerized test of response inhibition and working memory and is freely downloaded at www.hecme.tv. The ICT test has been judged to have good validity but requires highly functional patients [96]; tested in Italy [73]; no Italian norms available.
- The Stroop test evaluates psychomotor speed and cognitive flexibility by the interference between recognition reaction time to a colored field and a written color name; also available in app-form [71]. Tested in Italy [70] but not in app form; no Italian norms available.
- The SCAN test is a computerized test that measures speed and accuracy to perform a digit recognition memory task of increasing complexity. It has been shown to have prognostic value, has been proposed and tested in Italy; Italian norms available [72].

5.4.3. Neurophysiological
- The EEG can detect changes in cortical cerebral activity across the spectrum of HE and its reliability increases with quantitative analysis [97]. Recently, a cheap gaming device has been shown to produce similar results compared to a standard EEG machine across the HE spectrum [98].

5.4.4. Psychophysic
- CFF is defined as the frequency at which a flickering light (from 60 Hz downwards) appears to be flickering to the observer. Studies have shown its reduction with worsening cognition and improvement after therapy [99,100]. It requires specialized equipment. Tested in Italy [91,101]; no Italian norms available.

Recommendations
- The presence of CHE should be screened for in every patient with cirrhosis by the ANT (*i.e.* the number of animals listed in 60 s) **(GRADE II-3, B, 1)**
- The diagnosis of MHE should be made using combined neuropsychological and neurophysiological indices in patients whose job and life-style require high standards of functioning **(GRADE III, B, 1)**

Please cite this article in press as: Montagnese S, et al. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.11.035

5.5. Brain imaging

5.5.1. For purposes of differential diagnosis

Cirrhotic patients who are admitted into hospital with HE may need to be evaluated by imaging techniques when the diagnosis between different etiologies of neuropsychiatric impairment is uncertain. For example, the risk of intracerebral haemorrhage is considerably increased in patients with cirrhosis [102], and the symptoms can be very similar to those of HE. Imaging can also help to identify/rule out, amongst others, ischaemic brain injury, Wernicke's encephalopathy and meningo-encephalitis. Reasons to suspect alternative pathology often include abrupt onset of symptoms and lack of response to standard ammonia-lowering/management strategies over the first 12–24 h. Imaging does not contribute diagnostic or grading information on HE [60].

5.5.2. To evaluate brain injury in ALF

In patients with ALF, HE can be due to ICH and brain oedema. CT scans are relatively insensitive to actual ICH, and moving patients with severe HE can lead to surges for ICP. For this reason, scans are not recommended for monitoring brain oedema and are reserved for diagnosing intracranial bleeding or cerebral herniation with absent perfusion [103]. Arterial angiography can help identify severe cerebral damage/death.

5.5.3. To evaluate brain function in clinical research

Brain blood flow measurement represents an interesting tool to study HE in a clinical research more than a clinical practice context. It can be performed by simple methods such as the transcranial Doppler, or more complex methods such as Single-Photon Emission Computed Tomography (SPECT). A study performed several years ago [104] demonstrated how cerebral blood flow is significantly lower in patients with liver cirrhosis compared to controls, and particularly those with alcohol-related and viral aetiology. In patients with a history of alcohol misuse, cerebral blood flow was significantly more reduced in the frontal and temporal regions compared to that of patients with a negative history.

Recommendation
- Patients admitted into hospital for an episode of OHE can usually be managed on the basis of clinical and biochemical findings. Brain imaging is required to rule out alternative or co-existing causes of brain damage, only if: (i) the clinical profile is unusual, (ii) the onset of symptoms is abrupt/severe, (iii) there are focal neurological signs, or (iv) there is limited or no response to treatment of the precipitant and/or ammonia-lowering treatment over the first 12–24 h **(GRADE III, A, 1)**

6. Treatment

6.1. Type A

Patients with ALF and grade II HE should be managed in a quiet environment with slight head elevation (30°), and mental status should be periodically assessed (possibly by orientation in time and space, the presence/absence of flapping tremor, the West Haven criteria and the GCS) to recognize any signs of worsening. Patients with grades III–IV HE are generally managed in the Intensive Care Unit, and mechanical ventilation is started after intubation [105].

Any bacterial or fungal infection should be rapidly recognized and treated. Elevations in ICP are treated with intravenous mannitol or hypertonic saline. In uncontrolled ICH mild hypothermia and indomethacin can also be considered [103]. Antiepileptic drugs are utilized in the presence of seizures. Glucose and sodium levels need to be tightly controlled [105]. In this setting, the role of standard ammonia-lowering treatment (*i.e.* lactulose by mouth or by enema and rifaximin) is not evidence-based.

As toxins are involved in the development of HE and accumulate also in ALF, contributing to the development of severe HE, which is often resistant to standard medical therapy, extracorporeal devices have been utilized in these patients with the aim of toxins removal. *Extracorporeal albumin dialysis* (ECAD) aims to eliminate albumin-bound and water-soluble toxins and can represent a bridge therapy while waiting for liver transplantation. It includes various methods, among which the most used is *molecular adsorbent recirculating system* (MARS, Baxter Intl., Deerfield, IL, US), originally developed in 1993. MARS was granted approval by the Food and Drug Administration in January 2013 for the treatment of HE. In this system, blood is dialysed across an albumin-impregnated high-flux dialysis membrane, so it can remove ammonium, urea, inflammatory cytokines, endogenous benzodiazepines, bile acids, bilirubin and other albumin-bound toxins. A recent randomized controlled trial (RCT) compared the effect of MARS on ALF with that of another dialysis system called Single-Pass Albumin Dialysis (SPAD) and showed that both methods were safe and resulted in a reduction in bilirubin, but no significant improvement of HE, in contrast with previous studies. Another RCT demonstrated no difference in 6-month survival between MARS (85%) *versus* standard medical therapy (75%) [106]. A review dated 2015 [107] compared MARS with SPAD and the Prometheus system (which combines fractionated plasma separation, absorption and haemodialysis) predominantly in ACLF patients and showed, in all instances, an improvement in HE.

Recommendations
- In patients with grades III–IV HE intubation should be considered (**GRADE III, A, 1**)

[•]
- Signs of ICH should be sought for at regular intervals and intracranial pressure monitored and managed according to available, pertinent guidelines (**GRADE III, A, 1**)

[•]
- Liver support systems are not helpful for the treatment of HE type A in ALF and should be considered only in RCT (**GRADE II-1, B, 1**)

6.2. Type B

Recommendations
- Medically, type B HE should be treated as type C HE (*vide infra*) (**GRADE III, A, 1**)

- The feasibility, pros and cons of shunt obliteration should be vigorously investigated as this has the potential to cure the disease fully (*vide infra*) (**GRADE III, A, 1**)

6.3. Type C, general principles

The management of OHE is based on four general principles: (i) initiation of care of patients with altered consciousness; (ii) identification and treatment of alternative and co-existing causes of altered mental status; (iii) identification and correction of precipitating factors; (iv) commencement of empirical ammonia-lowering treatment. Patients with grades III and IV OHE according to the West Haven criteria [90] who are at risk or unable to protect their airways, should ideally be managed in an intensive care setting. This is not standard practice in Italy but the option should at least be considered, and the opinion of an intensivist with some hepatological experience sought for, where available. A naso-gastric tube can be used to administer drugs which are only available/known to work as by mouth formulations in patients who are unable to swallow or appear to be at risk of aspiration. The identification and control of precipitating factors (Table 3) is of paramount importance, as it can cure a significant proportion of patients with a bout of OHE [108].

Please cite this article in press as: Montagnese S, et al. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.11.035

The most commonly utilized drugs for the subsequent commencement of empirical treatment are non-absorbable disaccharides, such as lactulose, and non-absorbable antibiotics, such as rifaximin. Other agents, for which the available evidence is anecdotal, include intravenous branched-chain amino acids (BCAAs), intravenous L-ornithine L-aspartate (LOLA), probiotics, and other antibiotics (*vide infra*). Given that OHE is a predictor of death [63,109] and that its appearance generally marks a worsening in both hepatic function and prognosis [110], after a first bout of OHE the patient should be referred to a liver transplant center.

Primary prophylaxis of OHE is not generally recommended, with the exception of the rapid removal of blood from the gastrointestinal tract after an upper gastrointestinal bleed, for example with lactulose, which has been shown to be effective in preventing OHE over the subsequent 120 h [111]. Mannitol by mouth has also been shown to work in this context, also by comparison with paromomycine plus lactulose [112]. Finally, rifaximin has also been shown to have effects similar to those of lactulose in preventing OHE after an upper gastrointestinal bleed [113]. The mechanisms of action of rifaximin within this context remains unclear and at any rate, the administration of drugs by mouth should be cautious after an upper gastrointestinal bleed, especially if the patient appears at risk/unable to protect their airways.

By contrast, secondary prophylaxis is important, as once a patient has experienced a bout of OHE, the likelihood of further episodes is high and one of the main causes of re-admission into hospital and health-related expenses in patients with cirrhosis [7]. Secondary OHE prophylaxis should be commenced by a non-absorbable disaccharide (*i.e.* lactulose or lactitol) [23,114]. The laxative effect of non-absorbable disaccharides varies considerably in the population, so it is reasonable to start with 20 ml of syrup (or the equivalent in granules) twice daily, and then proceed by titrating the drug in order to obtain 2–3 soft stools per day. In the course of a few weeks, the patient generally adjusts and manages to avoid both constipation and diarrhoea. There is a danger for overuse of lactulose leading to complications, such as dehydration, which can even precipitate HE.

If OHE becomes recurrent (*i.e.* more than one bout within six months), the addition of the non-absorbable antibiotic rifaximin is useful in maintaining remission, as documented in a multicentre, multinational trial of rifaximin *versus* placebo in patients who had had previous bouts of OHE, and 91% of whom were already on lactulose [76].

Recommendations

- Where possible, avoidance of worsening/decompensation of the underlying liver disease contribute to the prevention of OHE (**GRADE II-3, A, 1**)
- Similarly, avoidance/rapid and effective management of precipitants such as infection, constipation, dehydration *etc.* also contribute to the prevention of OHE (**GRADE II-3, A, 1**)
- Patients with high grade OHE, who are at risk or unable to protect their airways, should ideally be managed in an intensive care setting (**GRADE III, A, 1**)
- Given that OHE is a predictor of death and its appearance generally marks a worsening in both hepatic function and prognosis, after a first bout of OHE the patient should be referred to a liver transplant center (**GRADE III, A, 1**)
- Primary prophylaxis for the prevention of OHE is not required, with the exception of rapid removal of blood from the gastrointestinal tract after an upper gastrointestinal bleed (**GRADE II-3, B, 2**)
- An episode of OHE, spontaneous or precipitated, should be actively treated (**GRADE II-3, A, 1**)
- The recurrence of HE needs to be addressed as it is frequent, costly and potentially preventable (**GRADE III, A, 1**)
- Non-absorbable disaccharides represent the first choice treatment for the secondary prophylaxis of OHE, at a dose that guarantees two/three soft stools per day (**GRADE I, A, 1**)
- Rifaximin may be used as first-line agent for the secondary prophylaxis of OHE (550 mg twice daily or, should this not be readily available and hyperammonaemia documented, 400 mg three times daily) in patients who are truly intolerant to non-absorbable disaccharides, after their tapering has been tested and shown not to be beneficial (**GRADE I, B, 1**)
- Rifaximin (550 mg twice daily or, should this not be readily available and hyperammonaemia documented, 400 mg three times daily) should be added to non-absorbable disaccharides in patients with recurrent OHE, *i.e.* those who have developed a second episode of OHE within 6 months of the first one (**GRADE I, A, 1**)

The management of patients with highly recurrent or persistent HE is extremely challenging. This form of HE is common in patients with large, spontaneous portal-systemic shunts, which should be always sought for [115], and those who have undergone TIPS [116–118].

Shunt embolization/closure can be considered in patients with demonstrated, accessible portal-systemic shunts. A recent retrospective study including 43 patients with OHE refractory to conventional therapy who underwent Coil-Assisted Retrograde Transvenous Obliteration (CARTO) [119] demonstrated significant improvement in 91% of cases, 67% with complete resolution during a median follow up of 755 days. Minor complications such as new or worsened ascites and oesophageal varices occurred in 39.6% of patients, while only 2.3% experienced a major complication (bleeding oesophageal varices requiring treatment). Another prospective study evaluated technical and clinical outcomes of PARTO (plug-assisted retrograde transvenous obliteration) for the treatment of HE [120]; none of the patients developed HE episodes during the follow-up, Child–Pugh score improved in 40% of them and worsening ascites or varices were observed in 23% and 26%, respectively. Similar positive experiences have been reported on other small retrospective series [25,121–123].

When related to TIPS, persistent/highly recurrent HE can be treated by reducing or occluding the stent [124,125]. TIPS should probably be revised when a causal relationship between the shunt and HE is suspected, when HE occurred within few weeks or months after TIPS, or when the procedure led to a significant reduction in portal-systemic gradient, supporting the hypothesis that the excessive portal blood diversion is responsible of HE. On the contrary, TIPS should not be revised in patients with persistent HE due to liver failure. At any rate, as the complications of portal hypertension (*i.e.* ascites or variceal bleeding) may recur as a consequence of shunt reduction, the decision to revise always requires a careful evaluation of risks and benefits.

Highly recurrent and persistent HE, together with those forms of HE with prominent motor dysfunction, also represent a clinical scenario where combination treatment is often necessary and can be probably tested on a case-by-case basis, even in the absence of hard evidence, together with modifications in the amount and sources of dietary protein (*vide infra*).

Liver transplantation is considered the ultimate therapeutic option for persistent/highly recurrent HE and for patients with prominent HE-related motor dysfunction (*i.e.* hepatic myelopathy) [126–128]. Prioritization of these patients is currently based on liver function and could therefore underestimate their risk of mortality and hospitalization. Therefore, it is important to adequately weight the prognostic impact of persistent/highly recurrent HE in patients on the waiting list for transplantation, possibly adding a quantitative or clinical HE parameter to the available scoring systems [10,11]. However, this issue is still under debate. Finally, it is

Please cite this article in press as: Montagnese S, et al. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.11.035

crucial that all significant shunts are closed during transplantation, to avoid post-transplant type B HE.

Recommendations

- In patients with persistent or highly recurrent HE spontaneous portal-systemic shunts should be sought for by Doppler ultrasound and, should this be negative, by angio-CT abdomen (**GRADE III, A, 1**)
- Persistent or highly recurrent OHE is an indication for spontaneous or surgical shunt reduction/obliteration (**GRADE II-3, A, 1**)
- Persistent or highly recurrent OHE and hepatic myelopathy are an indication for liver transplantation (**GRADE II-3, A, 1**)
- In patients with suboptimal response to lactulose and rifaximin, BCAAs, probiotics, LOLA, non ureic nitrogen scavengers (*i.e.* sodium benzoate, sodium phenylbutyrate, glycerol phenylbutyrate and ornithine phenylacetate) and albumin can all be considered as top-up therapies (**GRADE II-3, A, 1**)

6.4. Type C, drugs, mechanisms of action and available evidence

This section briefly reviews drugs and classes of drugs that have been used to treat and prevent HE. It should be noted that the available literature is extremely heterogeneous in terms of outcomes (*i.e.* length of an OHE episode, improvement of symptoms/signs/neuropsychological measures over a defined period of time, prevention of subsequent episodes *etc.*) and most meta-analyses are based on aggregated outcomes, making detailed conclusions on actual drug effects virtually impossible.

6.4.1. Non-absorbable disaccharides

Non-absorbable disaccharides efficacy in patients with HE relies on different mechanisms: (i) their laxative effect, which increases the elimination of ammonia, (ii) the acidification of the intestinal contents via the production of lactic and acetic acid by the gut microbiota, which reduces ammonia absorption, and (iii) their prebiotic action, as they favor the growth of saccharolytic bacteria such as *Bifidobacterium* and *Lactobacillus* instead of proteolytic ones, thus reducing ammoniagenesis and increasing ammonia clearance [129,130]. A recent, systematic review [131] evaluated the effects of lactulose and lactitol for the treatment and prevention of HE in patients with cirrhosis. Random-effects meta-analyses showed that, compared to placebo/no intervention, non-absorbable disaccharides have a beneficial effect on both HE and other serious liver-related adverse events such as liver failure, variceal bleeding, infections, spontaneous bacterial peritonitis, and hepato-renal syndrome. Treatment was also associated with a reduction in mortality. No difference between lactulose and lactitol was observed. Rectal route of administration by enema is also effective and can be considered in patients with difficulties swallowing [132]. Lactulose has been administered at various doses across studies. A starting dose of 30 ml (20 g of lactulose) twice daily could be a good compromise and should then be adapted with a view to obtain two to three bowel movements of soft stool per day. Lower doses (5 g) may also have beneficial effects via their prebiotic properties [130].

6.4.2. Non-absorbable antibiotics

Rifaximin is the most commonly used antibiotic for the treatment of HE. It is a poorly absorbed compound and has a very low, if any, potential for drug-to-drug interactions [133]. The mechanism of action is based on the modulation of both the composition and the function of the gut microbiota, and possibly also on its anti-inflammatory and eubiotic effects [134–137]. A meta-analysis has shown that rifaximin increases the proportion of patients who recover from HE and has a beneficial effect on its secondary prevention, as well as on mortality [138]. In Italy and several other countries, rifaximin is currently approved for the treatment of recurrent HE at the dose of 550 mg twice daily [76]. Compared to placebo, long-term therapy with rifaximin over 24 months for patients with OHE has demonstrated to maintain efficacy without increased rates of adverse events and has been associated with reduction in hospitalization and mortality [139–141]; in two of them, it was compared to non-absorbable disaccharides and in one to neomycin, showing equivalence in cognitive improvement and ammonia lowering. Several meta-analyses [138,142–146], including a network one [146], have confirmed the benefits of rifaximin treatment in patients with HE, including reduction in blood ammonia and improvement in neuropsychological performance.

Other antibiotics such as neomycin [90,108,147,148], metronidazole [149], and vancomycin [150] have been used but are currently not recommended, mainly because of their potential systemic toxicity. Paromomycin has also been utilized but the evidence for it is limited [151].

6.4.3. Polyethylene glycol (PEG)

PEG alone [152] or in association with lactulose [153] has been associated with a more rapid resolution (within 24 h) of a bout of OHE requiring hospitalization. Nasogastric tubes were used to administer PEG in patients with severe OHE and guarantee the administration of an adequate amount, thus PEG applicability may be limited to patients in whom tube placement is safe and successful.

6.4.4. L-ornithine and L-aspartate (LOLA)

LOLA represents a substrate for the urea cycle and can increase urea production in periportal hepatocytes. It also activates glutamine production by activating glutamine synthetase in perivenous hepatocytes and the skeletal muscle. In a recent meta-analysis, when compared to placebo/no-intervention [154], LOLA was significantly more effective on HE. Two studies comparing LOLA and lactulose showed similar efficacy [155,156]. Although LOLA initially lowers blood ammonia levels, even in end-stage liver disease, its effect appears to be temporary, as a rebound hyperammonemia is sometimes observed on treatment cessation [157]. Intravenous LOLA can be used as an additional agent to treat patients unresponsive to conventional therapy, but further research is required in determining amount, duration and dosage of this treatment. Its effect also seems to depend on HE severity, and in one study LOLA was shown to shorten a bout of OHE requiring hospitalization when added to non-absorbable disaccharides and ceftriaxone [158]. Despite an early network meta-analysis [146] suggested that – among the standard interventions for OHE – LOLA treatment showed a trend in superiority for clinical efficacy, a recent Cochrane review [159] scored as very low the available evidence and considered the possible beneficial effects of LOLA uncertain. Anyhow, neither of its available formulations (iv and oral granules) are currently available in Italy.

6.4.5. Probiotics

Probiotics are live bacteria that, when ingested, may confer a beneficial effect to the host. Their rationale for HE treatment relates to their capacity of modulating the gut microbiota composition and metabolic function, also reducing inflammation. A recent systematic review [160] compared the effect of probiotics or symbiotics (a combination of pre- and pro-biotics) with placebo or no intervention, or with any other treatment for people with a bout (any grade) of or persistent OHE. The trials used a variety of probiotics and symbiotics, and the duration of administration ranged from 3 weeks to 12 months. Compared with placebo or no intervention, probiotics and symbiotics could prevent OHE recurrence. However, this was not confirmed when probiotics were compared with lactulose, rifaximin or LOLA. According to a Cochrane review [161], the majority of trials suffered from a high risk of systematic error

Please cite this article in press as: Montagnese S, et al. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.11.035

and a high risk of random error, making the available evidence of low quality. A more recent meta-analysis [162], including 14 RCTs and 1132 patients, found that probiotics decreased serum ammonia and endotoxin levels, improved MHE, and prevented OHE. Of interest, fermentable fibre alone had effects which were comparable to those of a symbiotic preparation (fibre plus probiotics) on mental performance, ammonia levels and the gut flora in patients with MHE [163]. It should be noted that probiotics, just like antibiotics, are a class of drugs. Species, vitality and quantities utilized in HE studies have been extremely heterogeneous, making it difficult to draw reliable conclusions.

6.4.6. Non ureic nitrogen scavengers

- Sodium benzoate provides an alternative pathway for the disposal of waste nitrogen and has been used to treat patients with urea cycle defects and, to a lesser extent, patients with HE. While the results of one, available RCT were encouraging [164], sodium benzoate has also been associated with increased ammonia levels both at baseline and after a glutamine challenge [165]. Sodium benzoate is available in Italy as a Galenic, albeit with no indication for HE, and may be considered when HE and hyponatremia coexist [166].
- Pilot data suggest that sodium phenylbutyrate could be effective in reducing ammonia levels and improving neurological status and discharge survival in intensive care patients with OHE [167]
- Glycerol phenylbutyrate (GPB) is a drug used in urea cycle disorders, which favours nitrogen elimination by combining phenylacetic acid, a metabolite of phenylbutyric acid, with glutamine to form phenylacetyl-glutamine, which is excreted in the urine. In a randomized, double-blind Phase IIb study in cirrhotic patients who had experienced an episode of HE in the previous 6 months and were already on treatment with lactulose and rifaximin [168], 6 ml of GPB orally twice daily for 16 weeks significantly reduced ammonia levels as well as HE recurrence. GPB is not currently licensed in Italy.
- Ornithine phenylacetate (OP) is an ammonia scavenger. This therapy is based on the capacity of ornithine to stimulate glutamine synthetase activity in peripheral organs, hence incorporating ammonia into the 'nontoxic' molecule phenylacetylglutamine, which is eliminated in urine [169]. A randomized trial in 38 consecutive cirrhotic patients enrolled within 24 h of an upper gastrointestinal bleed [170] demonstrated that OP is well tolerated but does not significantly decrease plasma ammonia at a dose of 10 g/day. A subsequent phase IIb randomized trial [171] including 231 patients failed to demonstrate significant difference in the time to clinical improvement between OP and placebo. OP is not currently available in Italy.

6.4.7. Branched chain amino acids (BCAAs) and nutritional aspects

BCAAs – valine, leucine, and isoleucine – availability is reduced in patients with liver cirrhosis thus impairing the conversion of ammonia to glutamine in the skeletal muscle, and reducing its detoxification. A Cochrane review [172] of 16 RCTs comparing BCAA (oral/IV formulation) to placebo, no intervention, diet, neomycin or lactulose revealed that BCAAs had a beneficial effect on symptoms and signs of OHE when trials including lactulose or neomycin were excluded, and that there was no difference between those interventions when BCAAs and lactulose or neomycin were compared. No effect on mortality, quality of life, or nutritional parameters was observed.

Malnutrition is common in patients with cirrhosis and is associated with increased risk of sarcopenia and worsened survival [173]. Muscle tissue plays an important role in nitrogen metabolism and its loss is associated with increased risk of HE [37]. Thus, a low protein diet should be avoided in patients with HE [166,174,175]. The optimal daily energy intake for these patients is not different from that of patients with cirrhosis and no HE (*i.e.* 35–40 kcal/kg ideal body weight). Similarly, optimal daily protein intake should be 1.2–1.5 g/kg ideal body weight. Small meals, evenly distributed throughout the day, and a late evening snack with 20–40 g of protein and 50 g of complex carbohydrates [176] will minimize protein catabolism by breaking the long interval between dinner and breakfast, and should be encouraged. Physical exercise should also be encouraged and personalized according to patients' characteristics [177]. There is very limited evidence for the benefits of the replacement of meat with vegetable and dairy protein. This should be performed by experts, accompanied by close follow-up to avoid reduction in caloric and protein intake, and suggested to the few patients who are truly intolerant of meat protein [174].

Zinc is required for ammonia detoxification in the urea cycle, and low levels are commonly observed in patients with cirrhosis. A meta-analysis of four RCTs [178] showed that zinc supplementation improved some psychometric tests but did not reduce OHE recurrence.

Diagnosed of suspected deficits in vitamins and micronutrients should be treated, as they may worsen mental function and confound the diagnosis of HE [166,174].

Recommendations

- Zinc supplementation can be considered in cirrhotic patients with OHE and documented zinc deficiency (**GRADE III, B, 2**)
- Deficits in vitamins and micronutrients should be treated, as they may worsen mental function and confound the diagnosis of HE (**Grade III, A, 1**)
- A reduction in protein intake/administration is not recommended (**GRADE I, A, 1**)
- The replacement of meat with vegetable (pulses) and/or dairy protein is not recommended but in patients who are truly intolerant of meat protein (**GRADE III, A, 1**)

6.4.8. Other therapies

There is low quality evidence suggesting a short-term beneficial effect of *flumazenil* on HE in patients with cirrhosis, with no influence on all-cause mortality [179]. It is reasonable that this drug may play two roles: (i) produce a transient improvement in severe OHE, to allow the administration of treatment by mouth; (ii) revert an unrecognized intake of benzodiazepines.

Acetyl-L-carnitine is involved in ureagenesis. A meta-analysis of 7 RCTs [180], including 660 patients with minimal to grade III HE, concluded that acetyl-L-carnitine was effective in reducing ammonia levels and improving the paper&pencil number connection test. However, all 7 RCTs were performed at a single centres and were of small to moderate size. A recent network meta-analysis [181], comparing the efficacy of five drugs (*i.e.* lactulose, probiotics, rifaximin, acetyl-L-carnitine, and LOLA) in the treatment of MHE, revealed that – considering serum ammonia and serum albumin as end-points – acetyl-L-carnitine appeared the most effective.

Long-term and high dose *albumin* administration has been recently associated with a lower incidence of grade III and IV type C OHE compared to standard medical care in patients with cirrhosis and ascites [182].

The rationale of *Fecal transplantation* (FMT) for the treatment of HE is to modulate the gut microbiota composition and function. At present, there are only two published studies, one case report [183] and one small RCT [184], assessing the efficacy of FMT in patients with HE. In the study by Bajaj et al., a rational stool donor was used and this procedure was able to safely reduce hospitalizations, improve cognition and dysbiosis in patients with recurrent HE [184]. Despite promising, these are preliminary experiences on

Please cite this article in press as: Montagnese S, et al. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.11.035

a limited number of patients with issues relating to patients' and donors' selection, route and frequency of administration, duration of the follow-up and tolerability that need to be clarified.

There are a few treatments still in the experimental phase which hold promise for future treatment of HE, namely minocycline [185], ibuprofen [186], phosphodiesterase-5 inhibitors (*i.e.* sildenafil) [187], indomethacin [188], benzodiazepine inverse agonists (Ro15-4513) [189], and AST-120 [190], an orally administered microspherical carbon, which exhibits a selective adsorbent profile for small molecules such as ammonia. Finally, the direct modulation of vigilance (for example with caffeine) in combination with ammonia-lowering drugs [191] and educational strategies for the prevention of OHE recurrence [191] are also worthy of further study.

6.5. Minimal and covert HE

There are uncertainties in relation to the benefit of treatment of patients with MHE/CHE and not all centres have the ability, experience and tools to screen for and diagnose these milder forms of HE. Therefore, their routine treatment has not been generally recommended [60]. Of interest, a recent RCT showed that a nutritional intervention (30–35 kcal/kg BW/d, 1.0–1.5 g vegetable protein/kg BW/d for six months) was able to improve neuropsychiatric performance in patients with MHE and decrease their risk of developing OHE compared to no nutritional intervention [192]. Overall, the pathophysiology of MHE/CHE is identical to that of OHE, and several of the agents used to treat OHE have been tested also in patients with MHE/CHE. In particular, lactulose, rifaximin, probiotics and LOLA have all been shown to be beneficial, with documented improvement in psychometric performance after treatment [156,162,172,193–196]. It is therefore reasonable, even in the absence of a formal diagnosis, and especially if the patients or their family/caregivers report symptoms/signs compatible with mild HE (grade I, according to the original West Haven criteria), to institute treatment. This, if based on a combination of ammonia-lowering drugs and especially if instituted after documenting hyperammonaemia, may both confirm the diagnosis and cure the syndrome. This approach seems even more valuable in patients who are perceived to be at particular risk of the consequences of MHE/CHE, such as falls, reduced earning capacity, impaired driving ability *etc.*, because of their family/social/working context.

Recommendations

- Treatment of MHE is not routinely recommended but can be instituted on a case-by-case basis (**GRADE II-3, A, 1**)
- Treatment should be instituted in patients with CHE who appear marginally slowed, inadequate or irritable (grade I according to the West Haven criteria) to their habitual physician or their caregivers (**GRADE II-3, A, 1**)
- In both instances (MHE and CHE), the lack of response to treatment should prompt a differential diagnosis pathway, with particular attention for dementing disorders (**GRADE III, A, 1**)

7. Conclusions and future research

The past decade has been characterized by significantly more attention, research and funding being directed towards HE. The accepted definition of the syndrome has evolved and a number of new diagnostic tools have emerged. In addition, efforts have been made to identify and modify such diagnostic tools in order to make them practical, cheap and easily accessed by hepatogastroenterologists with no specific expertise in HE. In several instances, Italian research has been at the forefront of these efforts. A number of novel drugs and treatment strategies have also become available, and several additional drug trials are underway. This guideline has therefore been compiled at an exciting time for the field both in scientific and clinical terms. We have attempted to summarise current knowledge and to translate it into relevant, practical recommendations. Where solid evidence was lacking, recommendations were based on anecdotal but relevant reports, parallel clinical fields, standard practice, feasibility, costs and, ultimately, common sense. This document will hopefully serve as a basis for future studies, especially those addressing heavily recurrent and persistent OHE. These still pose a considerable treatment challenge and remain a significant burden on patients, their families, health services and society in general.

Conflict of interest

Sara Montagnese is an advisor for Umecrine, Meddey and Versantis, and her group has received research funds from Alfasigma, Ogilvie, Falk and Merz.

Francesco Paolo Russo: none to report.

Piero Amodio: none to report.

Patrizia Burra: none to report.

Antonio Gasbarrini is a member of the Advisory Boards of Alfasigma, MSD, Abbvie, Danone, Pileye, Actial.

Carmela Loguercio: none to report.

Giulio Marchesini is a member of the Advisory Boards of Sanofi, Astra-Zeneca, Gilead, Lilly.

Manuela Merli has received speakers fees from Kedrion.

Francesca Romana Ponziani: none to report.

Oliviero Riggio: none to report.

Carmelo Scarpignato is a member of the Advisory Boards and Speakers' Bureau of Alfasigma, Shionogi, Pfizer, Reckitt-Benkiser, Takeda.

References

[1] Labenz C, Worns MA, Schattenberg JM, Huber Y, Galle PR, Labenz J, et al. Epidemiology of hepatic encephalopathy in german hospitals — the EpHE study. Z Gastroenterol 2017;55(8):741–7.
[2] 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(3):642–59.
[3] Bai M, Qi X, Yang Z, Yin Z, Nie Y, Yuan S, et al. Predictors of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in cirrhotic patients: a systematic review. J Gastroenterol Hepatol 2011;26(6):943–51.
[4] Simon-Talero M, Roccarina D, Martinez J, Lampichler K, Baiges A, Low G, et al. Association between portosystemic shunts and increased complications and mortality in patients with cirrhosis. Gastroenterology 2018;154(6), 1694–1705.e4.
[5] Porcheron J, Balique JG. Physiopathology and surgical treatment of hepatic encephalopathy after porto-caval anastomosis. Ann Gastroenterol Hepatol (Paris) 1995;31(5):287–94.
[6] Scaglione SJ, Metcalfe L, Kliethermes S, Vasilyev I, Tsang R, Caines A, et al. Early hospital readmissions and mortality in patients with decompensated cirrhosis enrolled in a large national health insurance administrative database. J Clin Gastroenterol 2017;51(9):839–44.
[7] Di Pascoli M, Ceranto E, De Nardi P, Donato D, Gatta A, Angeli P, et al. Hospitalizations due to cirrhosis: clinical aspects in a large cohort of italian patients and cost analysis report. Dig Dis 2017;35(5):433–8.
[8] Bajaj JS, O'Leary JG, Tandon P, Wong F, Garcia-Tsao G, Kamath PS, et al. Hepatic encephalopathy is associated with mortality in patients with cirrhosis independent of other extrahepatic organ failures. Clin Gastroenterol Hepatol 2017;15(4), 565–574.e4.
[9] Gadiparthi C, Cholankeril G, Yoo ER, Hu M, Wong RJ, Ahmed A. Waitlist outcomes in liver transplant candidates with high MELD and severe hepatic encephalopathy. Dig Dis Sci 2018;63(6):1647–53.
[10] Montagnese S, De Rui M, Schiff S, Ceranto E, Valenti P, Angeli P, et al. Prognostic benefit of the addition of a quantitative index of hepatic encephalopathy to the MELD score: the MELD-EEG. Liver Int 2015;35(1):58–64.
[11] Lucidi C, Ginanni Corradini S, Abraldes JG, Merli M, Tandon P, Ferri F, et al. Hepatic encephalopathy expands the predictivity of model for end-stage liver disease in liver transplant setting: evidence by means of 2 independent cohorts. Liver Transpl 2016;22(10):1333–42.

Please cite this article in press as: Montagnese S, et al. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.11.035

[12] Stepanova M, Mishra A, Venkatesan C, Younossi ZM. In-hospital mortality and economic burden associated with hepatic encephalopathy in the United States from 2005 to 2009. Clin Gastroenterol Hepatol 2012;10(9), 1034–41.e1.
[13] Flamm SL. Considerations for the cost-effective management of hepatic encephalopathy. Am J Manag Care 2018;24(4 Suppl):S51–61.
[14] Bajaj JS, Wade JB, Gibson DP, Heuman DM, Thacker LR, Sterling RK, et al. The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. Am J Gastroenterol 2011;106(9):1646–53.
[15] Moscucci F, Nardelli S, Pentassuglio I, Pasquale C, Ridola L, Merli M, et al. Previous overt hepatic encephalopathy rather than minimal hepatic encephalopathy impairs health-related quality of life in cirrhotic patients. Liver Int 2011;31(10):1505–10.
[16] Poordad FF. Review article: the burden of hepatic encephalopathy. Aliment Pharmacol Ther 2007;25(Suppl 1):3–9.
[17] Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14: going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66(7):719–25.
[18] Van Caulert C, Deviller C, Halff M. Troubles provoques par l'ingestion de sels ammoniacaux chez l'homme atteint de cirrhose de Laennec. Comptes Rendus Soc Biol 1932;(111):739–40.
[19] Balo J, Korpassy K. The encephalitis of dogs with Eck fistula fed on meat. Arch Pathol 1932;13:80–7.
[20] Stormont JM, Mackie JE, Davidson CS. Observations on antibiotics in the treatment of hepatic coma and on factors contributing to prognosis. N Engl J Med 1958;259(24):1145–50.
[21] Bircher J, Haemmerli UP, Scollo-Lavizzari G, Hoffmann K. Treatment of chronic portal-systemic encephalopathy with lactulose. Report of six patients and review of the literature. Am J Med 1971;51(2):148–59.
[22] Watson H, Jepsen P, Wong F, Gines P, Cordoba J, Vilstrup H. Satavaptan treatment for ascites in patients with cirrhosis: a meta-analysis of effect on hepatic encephalopathy development. Metab Brain Dis 2013;28(2):301–5.
[23] Sharma BC, Sharma P, Agrawal A, Sarin SK. Secondary prophylaxis of hepatic encephalopathy: an open-label randomized controlled trial of lactulose versus placebo. Gastroenterology 2009;137(3), 885–91, 91.e1.
[24] Laleman W, Simon-Talero M, Maleux G, Perez M, Ameloot K, Soriano G, et al. Embolization of large spontaneous portosystemic shunts for refractory hepatic encephalopathy: a multicenter survey on safety and efficacy. Hepatology 2013;57(6):2448–57.
[25] Philips CA, Kumar L, Augustine P. Shunt occlusion for portosystemic shunt syndrome related refractory hepatic encephalopathy-A single-center experience in 21 patients from Kerala. Indian J Gastroenterol 2017;36(5):411–9.
[26] Maleux G, Heye S, Verslype C, Nevens F. Management of transjugular intrahepatic portosystemic shunt induced refractory hepatic encephalopathy with the parallel technique: results of a clinical follow-up study. J Vasc Interv Radiol 2007;18(8):986–92, quiz 93.
[27] Baraldi M, Avallone R, Corsi L, Venturini I, Baraldi C, Zeneroli ML. Natural endogenous ligands for benzodiazepine receptors in hepatic encephalopathy. Metab Brain Dis 2009;24(1):81–93.
[28] Felipo V, Urios A, Montesinos E, Molina I, Garcia-Torres ML, Civera M, et al. Contribution of hyperammonemia and inflammatory factors to cognitive impairment in minimal hepatic encephalopathy. Metab Brain Dis 2012;27(1):51–8.
[29] Mannaioni G, Carpenedo R, Corradetti R, Carla V, Venturini I, Baraldi M, et al. Tryptophan metabolism and hepatic encephalopathy: studies on the sedative properties of oxindole. Adv Exp Med Biol 1999;467:155–67.
[30] Montagnese S, Biancardi A, Schiff S, Carraro P, Carla V, Mannaioni G, et al. Different biochemical correlates for different neuropsychiatric abnormalities in patients with cirrhosis. Hepatology 2011;53(2):558–66.
[31] Odeh M. Pathogenesis of hepatic encephalopathy: the tumour necrosis factor-alpha theory. Eur J Clin Invest 2007;37(4):291–304.
[32] Riggio O, Mannaioni G, Ridola L, Angeloni S, Merli M, Carla V, et al. Peripheral and splanchnic indole and oxindole levels in cirrhotic patients: a study on the pathophysiology of hepatic encephalopathy. Am J Gastroenterol 2010;105(6):1374–81.
[33] Zieve L. The mechanism of hepatic coma. Hepatology 1981;1(4):360–5.
[34] Zhang Z, Zhai H, Geng J, Yu R, Ren H, Fan H, et al. Large-scale survey of gut microbiota associated with MHE Via 16S rRNA-based pyrosequencing. Am J Gastroenterol 2013;108(10):1601–11.
[35] Kenzaka T, Kato K, Kitao A, Kosami K, Minami K, Yahata S, et al. Hyperammonemia in urinary tract infections. PLoS One 2015;10(8):e0136220.
[36] Nardelli S, Lattanzi B, Torrisi S, Greco F, Farcomeni A, Gioia S, et al. Sarcopenia is risk factor for development of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt placement. Clin Gastroenterol Hepatol 2017;15(6):934–6.
[37] Merli M, Giusto M, Lucidi C, Giannelli V, Pentassuglio I, Di Gregorio V, et al. Muscle depletion increases the risk of overt and minimal hepatic encephalopathy: results of a prospective study. Metab Brain Dis 2013;28(2):281–4.
[38] Owen OE, Trapp VE, Reichard Jr GA, Mozzoli MA, Moctezuma J, Paul P, et al. Nature and quantity of fuels consumed in patients with alcoholic cirrhosis. J Clin Invest 1983;72(5):1821–32.
[39] Shawcross DL, Davies NA, Williams R, Jalan R. Systemic inflammatory response exacerbates the neuropsychological effects of induced hyperammonemia in cirrhosis. J Hepatol 2004;40(2):247–54.
[40] Amodio P, Del Piccolo F, Petteno E, Mapelli D, Angeli P, Iemmolo R, et al. Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients. J Hepatol 2001;35(1):37–45.
[41] Kramer L, Tribl B, Gendo A, Zauner C, Schneider B, Ferenci P, et al. Partial pressure of ammonia versus ammonia in hepatic encephalopathy. Hepatology 2000;31(1):30–4.
[42] Aggarwal S, Kramer D, Yonas H, Obrist W, Kang Y, Martin M, et al. Cerebral hemodynamic and metabolic changes in fulminant hepatic failure: a retrospective study. Hepatology 1994;19(1):80–7.
[43] Kato M, Hughes RD, Keays RT, Williams R. Electron microscopic study of brain capillaries in cerebral edema from fulminant hepatic failure. Hepatology 1992;15(6):1060–6.
[44] Gupta T, Dhiman RK, Ahuja CK, Agrawal S, Chopra M, Kalra N, et al. Characterization of cerebral edema in acute-on-chronic liver failure. J Clin Exp Hepatol 2017;7(3):190–7.
[45] Wright G, Davies NA, Shawcross DL, Hodges SJ, Zwingmann C, Brooks HF, et al. Endotoxemia produces coma and brain swelling in bile duct ligated rats. Hepatology 2007;45(6):1517–26.
[46] Marchetti P, D'Avanzo C, Orsato R, Montagnese S, Schiff S, Kaplan PW, et al. Electroencephalography in patients with cirrhosis. Gastroenterology 2011;141(5), 1680–9.e1–2.
[47] Montagnese S, Jackson C, Morgan MY. Spatio-temporal decomposition of the electroencephalogram in patients with cirrhosis. J Hepatol 2007;46(3):447–58.
[48] Zeneroli ML, Pinelli G, Gollini G, Penne A, Messori E, Zani G, et al. Visual evoked potential: a diagnostic tool for the assessment of hepatic encephalopathy. Gut 1984;25(3):291–9.
[49] Mehndiratta MM, Sood GK, Sarin SK, Gupta M. Comparative evaluation of visual, somatosensory, and auditory evoked potentials in the detection of subclinical hepatic encephalopathy in patients with nonalcoholic cirrhosis. Am J Gastroenterol 1990;85(7):799–803.
[50] Leke R, Bak LK, Iversen P, Sorensen M, Keiding S, Vilstrup H, et al. Synthesis of neurotransmitter GABA via the neuronal tricarboxylic acid cycle is elevated in rats with liver cirrhosis consistent with a high GABAergic tone in chronic hepatic encephalopathy. J Neurochem 2011;117(5):824–32.
[51] Norenberg MD, Huo Z, Neary JT, Roig-Cantesano A. The glial glutamate transporter in hyperammonemia and hepatic encephalopathy: relation to energy metabolism and glutamatergic neurotransmission. Glia 1997;21(1):124–33.
[52] Szerb JC, Butterworth RF. Effect of ammonium ions on synaptic transmission in the mammalian central nervous system. Prog Neurobiol 1992;39(2):135–53.
[53] Rodrigo R, Cauli O, Gomez-Pinedo U, Agusti A, Hernandez-Rabaza V, Garcia-Verdugo JM, et al. Hyperammonemia induces neuroinflammation that contributes to cognitive impairment in rats with hepatic encephalopathy. Gastroenterology 2010;139(2):675–84.
[54] Corenblum B, Shaffer EA. Hyperprolactinemia in hepatic encephalopathy may result from impaired central dopaminergic neurotransmission. Horm Metab Res 1989;21(12):675–7.
[55] Lozeva V, Montgomery JA, Tuomisto L, Rocheleau B, Pannunzio M, Huet PM, et al. Increased brain serotonin turnover correlates with the degree of shunting and hyperammonemia in rats following variable portal vein stenosis. J Hepatol 2004;40(5):742–8.
[56] Rose C, Butterworth RF, Zayed J, Normandin L, Todd K, Michalak A, et al. Manganese deposition in basal ganglia structures results from both portal-systemic shunting and liver dysfunction. Gastroenterology 1999;117(3):640–4.
[57] Rama Rao KV, Reddy PV, Hazell AS, Norenberg MD. Manganese induces cell swelling in cultured astrocytes. Neurotoxicology 2007;28(4):807–12.
[58] Joshi D, O'Grady J, Patel A, Shawcross D, Connor S, Deasy N, et al. Cerebral oedema is rare in acute-on-chronic liver failure patients presenting with high-grade hepatic encephalopathy. Liver Int 2014;34(3):362–6.
[59] Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, Ott P. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology 1999;29(3):648–53.
[60] Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology 2014;60(2):715–35.
[61] Bjerring PN, Eefsen M, Hansen BA, Larsen FS. The brain in acute liver failure: a tortuous path from hyperammonemia to cerebral edema. Metab Brain Dis 2009;24(1):5–14.
[62] Lee GH. Hepatic encephalopathy in acute-on-chronic liver failure. Hepatol Int 2015;9(4):520–6.
[63] Cordoba J, Ventura-Cots M, Simon-Talero M, Amoros A, Pavesi M, Vilstrup H, et al. Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF). J Hepatol 2014;60(2):275–81.
[64] Donovan JP, Schafer DF, Shaw Jr BW, Sorrell MF. Cerebral oedema and increased intracranial pressure in chronic liver disease. Lancet 1998;351(9104):719–21.
[65] Sawhney R, Holland-Fischer P, Rosselli M, Mookerjee RP, Agarwal B, Jalan R. Role of ammonia, inflammation, and cerebral oxygenation in brain dysfunction of acute-on-chronic liver failure patients. Liver Transpl 2016;22(6):732–42.
[66] Weiss N, Rosselli M, Mouri S, Galanaud D, Puybasset L, Agarwal B, et al. Modification in CSF specific gravity in acutely decompensated cirrhosis and

Please cite this article in press as: Montagnese S, et al. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.11.035

acute on chronic liver failure independent of encephalopathy, evidences for an early blood-CSF barrier dysfunction in cirrhosis. Metab Brain Dis 2017;32(2):369–76.
[67] Campagna F, Montagnese S, Ridola L, Senzolo M, Schiff S, De Rui M, et al. The animal naming test: an easy tool for the assessment of hepatic encephalopathy. Hepatology 2017;66(1):198–208.
[68] Weiss N, Barbier Saint Hilaire P, Colsch B, Isnard F, Attala S, Schaefer A, et al. Cerebrospinal fluid metabolomics highlights dysregulation of energy metabolism in overt hepatic encephalopathy. J Hepatol 2016;65(6):1120–30.
[69] Morgan MY, Amodio P, Cook NA, Jackson CD, Kircheis G, Lauridsen MM, et al. Qualifying and quantifying minimal hepatic encephalopathy. Metab Brain Dis 2016;31(6):1217–29.
[70] Amodio P, Gatta A. Neurophysiological investigation of hepatic encephalopathy. Metab Brain Dis 2005;20(4):369–79.
[71] Bajaj JS, Thacker LR, Heuman DM, Fuchs M, Sterling RK, Sanyal AJ, et al. The Stroop smartphone application is a short and valid method to screen for minimal hepatic encephalopathy. Hepatology 2013;58(3):1122–32.
[72] Amodio P, Del Piccolo F, Marchetti P, Angeli P, Iemmolo R, Caregaro L, et al. Clinical features and survivial of cirrhotic patients with subclinical cognitive alterations detected by the number connection test and computerized psychometric tests. Hepatology 1999;29(6):1662–7.
[73] Amodio P, Ridola L, Schiff S, Montagnese S, Pasquale C, Nardelli S, et al. Improving the inhibitory control task to detect minimal hepatic encephalopathy. Gastroenterology 2010;139(2), 510–8, 8 e1–2.
[74] Bajaj JS, Hafeezullah M, Franco J, Varma RR, Hoffmann RG, Knox JF, et al. Inhibitory control test for the diagnosis of minimal hepatic encephalopathy. Gastroenterology 2008;135(5), 1591–600.e1.
[75] Amodio P, Cordoba J. Smart applications for assessing minimal hepatic encephalopathy: novelty from the app revolution. Hepatology 2013;58(3):844–6.
[76] Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010;362(12):1071–81.
[77] Strauss E, da Costa MF. The importance of bacterial infections as precipating factors of chronic hepatic encephalopathy in cirrhosis. Hepatogastroenterology 1998;45(21):900–4.
[78] Rolando N, Philpott-Howard J, Williams R. Bacterial and fungal infection in acute liver failure. Semin Liver Dis 1996;16(4):389–402.
[79] Bernal W, Hyyrylainen A, Gera A, Audimoolam VK, McPhail MJ, Auzinger G, et al. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. J Hepatol 2013;59(1):74–80.
[80] Shawcross DL, Wendon JA. The neurological manifestations of acute liver failure. Neurochem Int 2012;60(7):662–71.
[81] Rajajee V, Williamson CA, Fontana RJ, Courey AJ, Patil PG. Noninvasive intracranial pressure assessment in acute liver failure. Neurocrit Care 2018;29(2):280–90.
[82] Karvellas CJ, Fix OK, Battenhouse H, Durkalski V, Sanders C, Lee WM, et al. Outcomes and complications of intracranial pressure monitoring in acute liver failure: a retrospective cohort study. Crit Care Med 2014;42(5):1157–67.
[83] Laish I, Ben Ari Z. Noncirrhotic hyperammonaemic encephalopathy. Liver Int 2011;31(9):1259–70.
[84] Romero-Gomez M, Montagnese S, Jalan R. Hepatic encephalopathy in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure. J Hepatol 2015;62(2):437–47.
[85] Nardelli S, Ridola L, Gioia S, Riggio O. Management of hepatic encephalopathy not responsive to first-line treatments. Curr Treat Options Gastroenterol 2018;16(2):253–9.
[86] Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2(7872):81–4.
[87] Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy — definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002;35(3):716–21.
[88] Reuter B, Walter K, Bissonnette J, Leise MD, Lai J, Tandon P, et al. Assessment of the spectrum of hepatic encephalopathy: a multicenter study. Liver Transpl 2018;24(5):587–94.
[89] Bajaj JS, Cordoba J, Mullen KD, Amodio P, Shawcross DL, Butterworth RF, 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(7):739–47.
[90] Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy: a double blind controlled trial. Gastroenterology 1977;72(4 Pt. 1):573–83.
[91] Montagnese S, Balistreri E, Schiff S, De Rui M, Angeli P, Zanus G, et al. Covert hepatic encephalopathy: agreement and predictive validity of different indices. World J Gastroenterol 2014;20(42):15756–62.
[92] Weissenborn K, Heidenreich S, Ennen J, Ruckert N, Hecker H. Attention deficits in minimal hepatic encephalopathy. Metab Brain Dis 2001;16(1–2):13–9.
[93] Amodio P, Campagna F, Olianas S, Iannizzi P, Mapelli D, Penzo M, et al. Detection of minimal hepatic encephalopathy: normalization and optimization of the psychometric hepatic encephalopathy score. A neuropsychological and quantified EEG study. J Hepatol 2008;49(3):346–53.
[94] Lauridsen MM, Gronbaek H, Naeser EB, Leth ST, Vilstrup H. Gender and age effects on the continuous reaction times method in volunteers and patients with cirrhosis. Metab Brain Dis 2012;27(4):559–65.
[95] Lauridsen MM, Thiele M, Kimer N, Vilstrup H. The continuous reaction times method for diagnosing, grading, and monitoring minimal/covert hepatic encephalopathy. Metab Brain Dis 2013;28(2):231–4.
[96] Bajaj JS, Saeian K, Verber MD, Hischke D, Hoffmann RG, Franco J, et al. Inhibitory control test is a simple method to diagnose minimal hepatic encephalopathy and predict development of overt hepatic encephalopathy. Am J Gastroenterol 2007;102(4):754–60.
[97] Amodio P, Marchetti P, Del Piccolo F, de Tourtchaninoff M, Varghese P, Zuliani C, et al. Spectral versus visual EEG analysis in mild hepatic encephalopathy. Clin Neurophysiol 1999;110(8):1334–44.
[98] Schiff S, Casa M, Di Caro V, Aprile D, Spinelli G, De Rui M, et al. A low-cost, user-friendly electroencephalographic recording system for the assessment of hepatic encephalopathy. Hepatology 2016;63(5):1651–9.
[99] Kircheis G, Wettstein M, Timmermann L, Schnitzler A, Haussinger D. Critical flicker frequency for quantification of low-grade hepatic encephalopathy. Hepatology 2002;35(2):357–66.
[100] Romero-Gomez M. Critical flicker frequency: it is time to break down barriers surrounding minimal hepatic encephalopathy. J Hepatol 2007;47(1):10–1.
[101] Barone M, Shahini E, Iannone A, Viggiani MT, Corvace V, Principi M, et al. Critical flicker frequency test predicts overt hepatic encephalopathy and survival in patients with liver cirrhosis. Dig Liver Dis 2018;50(5):496–500.
[102] Gronbaek H, Johnsen SP, Jepsen P, Gislum M, Vilstrup H, Tage-Jensen U, et al. Liver cirrhosis, other liver diseases, and risk of hospitalisation for intracerebral haemorrhage: a Danish population-based case-control study. BMC Gastroenterol 2008;8:16.
[103] Wendon J, Cordoba J, Dhawan A, Larsen FS, Manns M, Samuel D, et al. EASL clinical practical guidelines on the management of acute (fulminant) liver failure. J Hepatol 2017;66(5):1047–81.
[104] Burra P, Senzolo M, Pizzolato G, Ermani M, Chierichetti F, Bassanello M, et al. Does liver-disease aetiology have a role in cerebral blood-flow alterations in liver cirrhosis? Eur J Gastroenterol Hepatol 2004;16(9):885–90.
[105] Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. Lancet 2010;376(9736):190–201.
[106] Saliba F, Camus C, Durand F, Mathurin P, Letierce A, Delafosse B, et al. Albumin dialysis with a noncell artificial liver support device in patients with acute liver failure: a randomized, controlled trial. Ann Intern Med 2013;159(8):522–31.
[107] Tsipotis E, Shuja A, Jaber BL. Albumin dialysis for liver failure: a systematic review. Adv Chronic Kidney Dis 2015;22(5):382–90.
[108] Strauss E, Tramote R, Silva EP, Caly WR, Honain NZ, Maffei RA, et al. Double-blind randomized clinical trial comparing neomycin and placebo in the treatment of exogenous hepatic encephalopathy. Hepatogastroenterology 1992;39(6):542–5.
[109] Bustamante J, Rimola A, Ventura PJ, Navasa M, Cirera I, Reggiardo V, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hepatol 1999;30(5):890–5.
[110] D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44(1):217–31.
[111] Sharma P, Agrawal A, Sharma BC, Sarin SK. Prophylaxis of hepatic encephalopathy in acute variceal bleed: a randomized controlled trial of lactulose versus no lactulose. J Gastroenterol Hepatol 2011;26(6):996–1003.
[112] Tromm A, Griga T, Greving I, Hilden H, Huppe D, Schwegler U, et al. Orthograde whole gut irrigation with mannite versus paromomycine + lactulose as prophylaxis of hepatic encephalopathy in patients with cirrhosis and upper gastrointestinal bleeding: results of a controlled randomized trial. Hepatogastroenterology 2000;47(32):473–7.
[113] Maharshi S, Sharma BC, Srivastava S, Jindal A. Randomised controlled trial of lactulose versus rifaximin for prophylaxis of hepatic encephalopathy in patients with acute variceal bleed. Gut 2015;64(8):1341–2.
[114] Agrawal A, Sharma BC, Sharma P, Sarin SK. Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open-label, randomized controlled trial of lactulose, probiotics, and no therapy. Am J Gastroenterol 2012;107(7):1043–50.
[115] Riggio O, Efrati C, Catalano C, Pediconi F, Mecarelli O, Accornero N, et al. High prevalence of spontaneous portal-systemic shunts in persistent hepatic encephalopathy: a case-control study. Hepatology 2005;42(5):1158–65.
[116] Riggio O, Nardelli S, Moscucci F, Pasquale C, Ridola L, Merli M. Hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. Clin Liver Dis 2012;16(1):133–46.
[117] Rossle M. TIPS: 25 years later. J Hepatol 2013;59(5):1081–93.
[118] Bureau C, Garcia-Pagan JC, Otal P, Pomier-Layrargues G, Chabbert V, Cortez C, et al. Improved clinical outcome using polytetrafluoroethylene-coated stents for TIPS: results of a randomized study. Gastroenterology 2004;126(2):469–75.
[119] Lee EW, Saab S, Kaldas F, Fletcher S, Busuttil RW, Durazo F, et al. Coil-assisted retrograde transvenous obliteration (carto): an alternative treatment option for refractory hepatic encephalopathy. Am J Gastroenterol 2018;113(8):1187–96.
[120] Gwon DI, Kim YH, Ko GY, Kim JW, Ko HK, Kim JH, et al. Vascular plug-assisted retrograde transvenous obliteration for the treatment of gastric varices and hepatic encephalopathy: a prospective multicenter study. J Vasc Interv Radiol 2015;26(11):1589–95.
[121] Choudhary NS, Baijal SS, Saigal S, Agarwal A, Saraf N, Khandelwal R, et al. Results of portosystemic shunt embolization in selected patients

Please cite this article in press as: Montagnese S, et al. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.11.035

with cirrhosis and recurrent hepatic encephalopathy. J Clin Exp Hepatol 2017;7(4):300–4.
[122] Mukund A, Rajesh S, Arora A, Patidar Y, Jain D, Sarin SK. Efficacy of balloon-occluded retrograde transvenous obliteration of large spontaneous lienorenal shunt in patients with severe recurrent hepatic encephalopathy with foam sclerotherapy: initial experience. J Vasc Interv Radiol 2012;23(9):1200–6.
[123] Lynn AM, Singh S, Congly SE, Khemani D, Johnson DH, Wiesner RH, et al. Embolization of portosystemic shunts for treatment of medically refractory hepatic encephalopathy. Liver Transpl 2016;22(6):723–31.
[124] Kochar N, Tripathi D, Ireland H, Redhead DN, Hayes PC. Transjugular intrahepatic portosystemic stent shunt (TIPSS) modification in the management of post-TIPSS refractory hepatic encephalopathy. Gut 2006;55(11):1617–23.
[125] Riggio O, Angeloni S, Salvatori FM, De Santis A, Cerini F, Farcomeni A, 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(11):2738–46.
[126] Weissenborn K, Tietge UJ, Bokemeyer M, Mohammadi B, Bode U, Manns MP, et al. Liver transplantation improves hepatic myelopathy: evidence by three cases. Gastroenterology 2003;124(2):346–51.
[127] Caldwell C, Werdiger N, Jakab S, Schilsky M, Arvelakis A, Kulkarni S, et al. Use of model for end-stage liver disease exception points for early liver transplantation and successful reversal of hepatic myelopathy with a review of the literature. Liver Transpl 2010;16(7):818–26.
[128] Baccarani U, Zola E, Adani GL, Cavalletti M, Schiff S, Cagnin A, et al. Reversal of hepatic myelopathy after liver transplantation: fifteen plus one. Liver Transpl 2010;16(11):1336–7.
[129] Riggio O, Varriale M, Testore GP, Di Rosa R, Di Rosa E, Merli M, et al. Effect of lactitol and lactulose administration on the fecal flora in cirrhotic patients. J Clin Gastroenterol 1990;12(4):433–6.
[130] Bothe MK, Maathuis AJH, Bellmann S, van der Vossen J, Berressem D, Koehler A, et al. Dose-dependent prebiotic effect of lactulose in a computer-controlled in vitro model of the human large intestine. Nutrients 2017;9(7).
[131] Gluud LL, Vilstrup H, Morgan MY. Non-absorbable disaccharides versus placebo/no intervention and lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis. Cochrane Database Syst Rev 2016;5:CD003044.
[132] Uribe M, Campollo O, Vargas F, Ravelli GP, Mundo F, Zapata L, et al. Acidifying enemas (lactitol and lactose) vs. nonacidifying enemas (tap water) to treat acute portal-systemic encephalopathy: a double-blind, randomized clinical trial. Hepatology 1987;7(4):639–43.
[133] Scarpignato C, Pelosini I. Rifaximin, a poorly absorbed antibiotic: pharmacology and clinical potential. Chemotherapy 2005;51(Suppl. 1):36–66.
[134] Ponziani FR, Gerardi V, Pecere S, D'Aversa F, Lopetuso L, Zocco MA, et al. Effect of rifaximin on gut microbiota composition in advanced liver disease and its complications. World J Gastroenterol 2015;21(43):12322–33.
[135] Ponziani FR, Scaldaferri F, Petito V, Paroni Sterbini F, Pecere S, Lopetuso LR, et al. The role of antibiotics in gut microbiota modulation: the eubiotic effects of rifaximin. Dig Dis 2016;34(3):269–78.
[136] Ponziani FR, Zocco MA, D'Aversa F, Pompili M, Gasbarrini A. Eubiotic properties of rifaximin: disruption of the traditional concepts in gut microbiota modulation. World J Gastroenterol 2017;23(25):4491–9.
[137] Bajaj JS. Review article: potential mechanisms of action of rifaximin in the management of hepatic encephalopathy and other complications of cirrhosis. Aliment Pharmacol Ther 2016;43(Suppl. 1):11–26.
[138] Kimer N, Krag A, Moller S, Bendtsen F, Gluud LL. Systematic review with meta-analysis: the effects of rifaximin in hepatic encephalopathy. Aliment Pharmacol Ther 2014;40(2):123–32.
[139] Bannister CA, Orr JG, Reynolds AV, Hudson M, Conway P, Radwan A, et al. Natural history of patients taking rifaximin-alpha for recurrent hepatic encephalopathy and risk of future overt episodes and mortality: a post-hoc analysis of clinical trials data. Clin Ther 2016;38(5), 1081–1089.e4.
[140] Bajaj JS, Barrett AC, Bortey E, Paterson C, Forbes WP. Prolonged remission from hepatic encephalopathy with rifaximin: results of a placebo crossover analysis. Aliment Pharmacol Ther 2015;41(1):39–45.
[141] Mullen KD, Sanyal AJ, Bass NM, Poordad FF, Sheikh MY, Frederick RT, et al. Rifaximin is safe and well tolerated for long-term maintenance of remission from overt hepatic encephalopathy. Clin Gastroenterol Hepatol 2014;12(8), 1390–7.e2.
[142] Jiang Q, Jiang XH, Zheng MH, Jiang LM, Chen YP, Wang L. Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy: a meta-analysis. Eur J Gastroenterol Hepatol 2008;20(11):1064–70.
[143] Eltawil KM, Laryea M, Peltekian K, Molinari M. Rifaximin vs. conventional oral therapy for hepatic encephalopathy: a meta-analysis. World J Gastroenterol 2012;18(8):767–77.
[144] Gluud LL, Dam G, Borre M, Les I, Cordoba J, Marchesini G, et al. Lactulose, rifaximin or branched chain amino acids for hepatic encephalopathy: what is the evidence? Metab Brain Dis 2013;28(2):221–5.
[145] Wu D, Wu SM, Lu J, Zhou YQ, Xu L, Guo CY. Rifaximin versus nonabsorbable disaccharides for the treatment of hepatic encephalopathy: a meta-analysis. Gastroenterol Res Pract 2013;2013:236963.
[146] Zhu GQ, Shi KQ, Huang S, Wang LR, Lin YQ, Huang GQ, et al. Systematic review with network meta-analysis: the comparative effectiveness and safety of interventions in patients with overt hepatic encephalopathy. Aliment Pharmacol Ther 2015;41(7):624–35.
[147] Orlandi F, Freddara U, Candelaresi MT, Morettini A, Corazza GR, Di Simone A, et al. Comparison between neomycin and lactulose in 173 patients with hepatic encephalopathy: a randomized clinical study. Dig Dis Sci 1981;26(6):498–506.
[148] Atterbury CE, Maddrey WC, Conn HO. Neomycin-sorbitol and lactulose in the treatment of acute portal-systemic encephalopathy. A controlled, double-blind clinical trial. Am J Dig Dis 1978;23(5):398–406.
[149] Mekky MA, Riad AR, Gaber MA, Abdel-Malek MO, Swifee YM. Rifaximin versus metronidazole in management of acute episode of hepatic encephalopathy: an open labeled randomized clinical trial. Arab J Gastroenterol 2018;19(2):76–9.
[150] Tarao K, Ikeda T, Hayashi K, Sakurai A, Okada T, Ito T, et al. Successful use of vancomycin hydrochloride in the treatment of lactulose resistant chronic hepatic encephalopathy. Gut 1990;31(6):702–6.
[151] Berk DP, Chalmers T. Deafness complicating antibiotic therapy of hepatic encephalopathy. Ann Intern Med 1970;73(3):393–6.
[152] Rahimi RS, Singal AG, Cuthbert JA, Rockey DC. Lactulose vs polyethylene glycol 3350—electrolyte solution for treatment of overt hepatic encephalopathy: the HELP randomized clinical trial. JAMA Intern Med 2014;174(11):1727–33.
[153] Naderian M, Akbari H, Saeedi M, Sohrabpour AA. Polyethylene glycol and lactulose versus lactulose alone in the treatment of hepatic encephalopathy in patients with cirrhosis: a non-inferiority randomized controlled trial. Middle East J Dig Dis 2017;9(1):12–29.
[154] Bai M, Yang Z, Qi X, Fan D, Han G. l-ornithine-l-aspartate for hepatic encephalopathy in patients with cirrhosis: a meta-analysis of randomized controlled trials. J Gastroenterol Hepatol 2013;28(5):783–92.
[155] Poo JL, Gongora J, Sanchez-Avila F, Aguilar-Castillo S, Garcia-Ramos G, Fernandez-Zertuche M, et al. Efficacy of oral L-ornithine-L-aspartate in cirrhotic patients with hyperammonemic hepatic encephalopathy. Results of a randomized, lactulose-controlled study. Ann Hepatol 2006;5(4):281–8.
[156] Mittal VV, Sharma BC, Sharma P, Sarin SK. A randomized controlled trial comparing lactulose, probiotics, and L-ornithine L-aspartate in treatment of minimal hepatic encephalopathy. Eur J Gastroenterol Hepatol 2011;23(8):725–32.
[157] Hadjihambi A, Arias N, Sheikh M, Jalan R. Hepatic encephalopathy: a critical current review. Hepatol Int 2018;12(Suppl. 1):135–47.
[158] Sidhu SS, Sharma BC, Goyal O, Kishore H, Kaur N. L-ornithine L-aspartate in bouts of overt hepatic encephalopathy. Hepatology 2018;67(2):700–10.
[159] Goh ET, Stokes CS, Sidhu SS, Vilstrup H, Gluud LL, Morgan MY. L-ornithine L-aspartate for prevention and treatment of hepatic encephalopathy in people with cirrhosis. Cochrane Database Syst Rev 2018;5:CD012410.
[160] Viramontes Horner D, Avery A, Stow R. The effects of probiotics and symbiotics on risk factors for hepatic encephalopathy: a systematic review. J Clin Gastroenterol 2017;51(4):312–23.
[161] Dalal R, McGee RG, Riordan SM, Webster AC. Probiotics for people with hepatic encephalopathy. Cochrane Database Syst Rev 2017;2:CD008716.
[162] Cao Q, Yu CB, Yang SG, Cao HC, Chen P, Deng M, et al. Effect of probiotic treatment on cirrhotic patients with minimal hepatic encephalopathy: a meta-analysis. Hepatob Pancreat Dis Int 2018;17(1):9–16.
[163] Liu Q, Duan ZP, Ha DK, Bengmark S, Kurtovic J, Riordan SM. Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. Hepatology 2004;39(5):1441–9.
[164] Sushma S, Dasarathy S, Tandon RK, Jain S, Gupta S, Bhist MS. Sodium benzoate in the treatment of acute hepatic encephalopathy: a double-blind randomized trial. Hepatology 1992;16(1):138–44.
[165] Efrati C, Masini A, Merli M, Valeriano V, Riggio O. Effect of sodium benzoate on blood ammonia response to oral glutamine challenge in cirrhotic patients: a note of caution. Am J Gastroenterol 2000;95(12):3574–8.
[166] Amodio P, Bemeur C, Butterworth R, Cordoba J, Kato A, Montagnese S, et al. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus. Hepatology 2013;58(1):325–36.
[167] Weiss N, Tripon S, Lodey M, Guiller E, Junot H, Monneret D, et al. Treating hepatic encephalopathy in cirrhotic patients admitted to ICU with sodium phenylbutyrate: a preliminary study. Fundam Clin Pharmacol 2018;32(2):209–15.
[168] Rockey DC, Vierling JM, Mantry P, Ghabril M, Brown Jr RS, Alexeeva O, et al. Randomized, double-blind, controlled study of glycerol phenylbutyrate in hepatic encephalopathy. Hepatology 2014;59(3):1073–83.
[169] Jover-Cobos M, Noiret L, Sharifi Y, Jalan R. Ornithine phenylacetate revisited. Metab Brain Dis 2013;28(2):327–31.
[170] Ventura-Cots M, Concepcion M, Arranz JA, Simon-Talero M, Torrens M, Blanco-Grau A, et al. Impact of ornithine phenylacetate (OCR-002) in lowering plasma ammonia after upper gastrointestinal bleeding in cirrhotic patients. Therap Adv Gastroenterol 2016;9(6):823–35.
[171] https://clinicaltrials.gov/ct2/show/NCT01966419.
[172] Gluud LL, Dam G, Les I, Marchesini G, Borre M, Aagaard NK, et al. Branched-chain amino acids for people with hepatic encephalopathy. Cochrane Database Syst Rev 2017;5:CD001939.
[173] Merli M, Riggio O, Dally L. Does malnutrition affect survival in cirrhosis? PINC (Policentrica italiana nutrizione cirrosi). Hepatology 1996;23(5):1041–6.
[174] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol 2018, pii: S0168-8278(18)32177-9.
[175] Cordoba J, Lopez-Hellin J, Planas M, Sabin P, Sanpedro F, Castro F, et al. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. J Hepatol 2004;41(1):38–43.

Please cite this article in press as: Montagnese S, et al. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.11.035

[176] Tsien CD, McCullough AJ, Dasarathy S. Late evening snack: exploiting a period of anabolic opportunity in cirrhosis. J Gastroenterol Hepatol 2012;27(3):430–41.
[177] Tandon P, Ismond KP, Riess K, Duarte-Rojo A, Al-Judaibi B, Dunn MA, et al. Exercise in cirrhosis: translating evidence and experience to practice. J Hepatol 2018;69(5):1164–77.
[178] Chavez-Tapia NC, Cesar-Arce A, Barrientos-Gutierrez T, Villegas-Lopez FA, Mendez-Sanchez N, Uribe M. A systematic review and meta-analysis of the use of oral zinc in the treatment of hepatic encephalopathy. Nutr J 2013;12:74.
[179] Goh ET, Andersen ML, Morgan MY, Gluud LL. Flumazenil versus placebo or no intervention for people with cirrhosis and hepatic encephalopathy. Cochrane Database Syst Rev 2017;8:CD002798.
[180] Jiang Q, Jiang G, Shi KQ, Cai H, Wang YX, Zheng MH. Oral acetyl-L-carnitine treatment in hepatic encephalopathy: view of evidence-based medicine. Ann Hepatol 2013;12(5):803–9.
[181] Cai XJ, Wang L, Hu CM. Efficacy of different drugs in the treatment of minimal hepatic encephalopathy: a network meta-analysis involving 826 patients based on 10 randomized controlled trials. J Cell Biochem 2018;119(10):8336–45.
[182] Caraceni P, Pavesi M, Baldassarre M, Bernardi M, Arroyo V. The use of human albumin in patients with cirrhosis: a European survey. Expert Rev Gastroenterol Hepatol 2018;12(6):625–32.
[183] Kao D, Roach B, Park H, Hotte N, Madsen K, Bain V, et al. Fecal microbiota transplantation in the management of hepatic encephalopathy. Hepatology 2016;63(1):339–40.
[184] Bajaj JS, Kassam Z, Fagan A, Gavis EA, Liu E, Cox IJ, et al. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: a randomized clinical trial. Hepatology 2017;66(6):1727–38.
[185] Gamal M, Abdel Wahab Z, Eshra M, Rashed L, Sharawy N. Comparative Neuroprotective effects of dexamethasone and minocycline during hepatic encephalopathy. Neurol Res Int 2014;2014:254683.
[186] Cauli O, Rodrigo R, Piedrafita B, Boix J, Felipo V. Inflammation and hepatic encephalopathy: ibuprofen restores learning ability in rats with portacaval shunts. Hepatology 2007;46(2):514–9.
[187] Agusti A, Hernandez-Rabaza V, Balzano T, Taoro-Gonzalez L, Ibanez-Grau A, Cabrera-Pastor A, et al. Sildenafil reduces neuroinflammation in cerebellum, restores GABAergic tone, and improves motor in-coordination in rats with hepatic encephalopathy. CNS Neurosci Ther 2017;23(5):386–94.
[188] Ahboucha S, Jiang W, Chatauret N, Mamer O, Baker GB, Butterworth RF. Indomethacin improves locomotor deficit and reduces brain concentrations of neuroinhibitory steroids in rats following portacaval anastomosis. Neurogastroenterol Motil 2008;20(8):949–57.
[189] Steindl P, Puspok A, Druml W, Ferenci P. Beneficial effect of pharmacological modulation of the GABAA-benzodiazepine receptor on hepatic encephalopathy in the rat: comparison with uremic encephalopathy. Hepatology 1991;14(6):963–8.
[190] Bosoi CR, Parent-Robitaille C, Anderson K, Tremblay M, Rose CF. AST-120 (spherical carbon adsorbent) lowers ammonia levels and attenuates brain edema in bile duct-ligated rats. Hepatology 2011;53(6):1995–2002.
[191] Garrido M, Skorucak J, Raduazzo D, Turco M, Spinelli G, Angeli P, et al. Vigilance and wake EEG architecture in simulated hyperammonaemia: a pilot study on the effects of L-ornithine-L-aspartate (LOLA) and caffeine. Metab Brain Dis 2016;31(4):965–74.
[192] Maharshi S, Sharma BC, Sachdeva S, Srivastava S, Sharma P. Efficacy of nutritional therapy for patients with cirrhosis and minimal hepatic encephalopathy in a randomized trial. Clin Gastroenterol Hepatol 2016;14(3), 454–460.e3; quiz e33.
[193] Watanabe A, Sakai T, Sato S, Imai F, Ohto M, Arakawa Y, et al. Clinical efficacy of lactulose in cirrhotic patients with and without subclinical hepatic encephalopathy. Hepatology 1997;26(6):1410–4.
[194] Horsmans Y, Solbreux PM, Daenens C, Desager JP, Geubel AP. Lactulose improves psychometric testing in cirrhotic patients with subclinical encephalopathy. Aliment Pharmacol Ther 1997;11(1):165–70.
[195] Dhiman RK, Sawhney MS, Chawla YK, Das G, Ram S, Dilawari JB. Efficacy of lactulose in cirrhotic patients with subclinical hepatic encephalopathy. Dig Dis Sci 2000;45(8):1549–52.
[196] Sidhu SS, Goyal O, Mishra BP, Sood A, Chhina RS, Soni RK. Rifaximin improves psychometric performance and health-related quality of life in patients with minimal hepatic encephalopathy (the RIME Trial). Am J Gastroenterol 2011;106(2):307–16.
[197] Amodio P. Hepatic encephalopathy: diagnosis and management. Liver Int 2018;38(6):966–75.
[198] Amodio P. Hepatic encephalopathy. In: Lee SS, Moreau R, editors. Cirrhosis: a practical guide to management. 2015. p. 105–23.

Please cite this article in press as: Montagnese S, et al. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.11.035