Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

HEPATIC ENCEPHALOPATHY: NOVEL INSIGHTS INTO CLASSIFICATION, PATHOPHYSIOLOGY AND THERAPY.

[1]Christopher F. Rose, [2]Piero Amodio, [3]Jasmohan S. Bajaj, [4]Radha Krishan Dhiman, [2]Sara Montagnese, [5]Simon D. Taylor-Robinson , [6]Hendrik Vilstrup, [7,8]Rajiv Jalan

Affiliations

1 Hepato-Neuro Laboratory, CRCHUM, Université de Montréal, Montreal, Canada
2 Department of Medicine, University of Padova, Padova, Italy
3 Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, Virginia, USA
4 Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
5 Department of Surgery and Cancer, St. Mary's Hospital Campus, Imperial College London, London, United Kingdom
6 Aarhus University Hospital, Dept. of Hepatology and Gastroenterology, Denmark
7 Liver Failure Group, Institute for Liver and Digestive Health, University College London, Royal Free Campus, London, United Kingdom
8 European Foundation for the Study of Chronic Liver Failure, Barcelona, Spain

Correspondence

Rajiv Jalan : Liver Failure Group, Institute for Liver and Digestive Health, University College London, Royal Free Campus, London, United Kingdom

Christopher F. Rose: Hepato-Neuro Laboratory, CRCHUM, Université de Montréal, Montreal, Canada

ABSTRACT

Hepatic encephalopathy (HE) is a frequent and serious complication of both chronic liver disease and acute liver failure. HE manifests as a wide spectrum of neuropsychiatric abnormalities, from subclinical changes (mild cognitive impairment) to marked disorientation, confusion and coma. The clinical and economic burden of HE is considerable, and it contributes greatly to impaired quality of life, morbidity and mortality. This review will critically discuss the latest classification of HE, as well as the pathogenesis and pathophysiological pathways underlying the neurological decline in patients with end-stage liver disease. In addition, management strategies, diagnostic approaches, currently available therapeutic options and novel treatment strategies are discussed.

KEYWORDS

Hepatic encephalopathy, Treatments, Pathogenesis, Pathophysiology, Ammonia, Management, Diagnosis

ABBREVIATIONS

ACLF, acute-on-chronic liver failure; ALF, acute liver failure; ATP, adenosine triphosphate; BBB, blood-brain barrier; BCAA, branched-chain amino acids; BOLD, blood oxygenation level dependent; CLDs, chronic liver diseases; CRP, C-reactive protein; CSF, cerebrospinal fluid; ECAD, extracorporeal liver assist device; FMT, faecal microbiota

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

transplantation; GS, glutamine synthetase; HE, hepatic encephalopathy; GABA, gamma-aminobutyric acid; GAMSA, ABAA receptor-modulating steroid antagonists; GCS, Glasgow Coma Score; Gln, glutamine; LOLA, L-ornithine L-aspartate; LSPD, liposome-supported peritoneal dialysis; LT, liver transplantation; mHE, minimal hepatic encephalopathy; MELD, model for end-stage liver disease; MR, magnetic resonance; NAFLD, non-alcoholic fatty liver disease; NMDA, N-methyl-D-aspartate; OP, ornithine phenylacetate; PEG, polyethylene glycol; TIPS, transjugular intrahepatic portosystemic shunt; TSH, thyroid-stimulating hormone; TSPO, translocator protein.

KEY POINTS

Hepatic encephalopathy is an important complication and cause of death in patients with cirrhosis.

Even the minimal form of hepatic encephalopathy, which is not clinically detectable, is associated with driving difficulties, poor quality of life and independently associated with mortality.

Ammonia is central in the pathogenesis of hepatic encephalopathy; its levels define prognosis and it is an important therapeutic target.

Inflammation-derived from liver injury, hyperammonaemia or infection is a frequent precipitating factor.

Hepatic encephalopathy is not always reversible and multiple episodes are associated with poor neurological outcomes even after liver transplantation.

Mainstay treatment for episodes of hepatic encephalopathy is lactulose and rifaximin with many new approaches under development and in clinical trials.

INTRODUCTION

Hepatic encephalopathy (HE) is broadly defined as brain dysfunction caused by liver insufficiency and/or portal-systemic shunting, which manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.[1] This definition of HE does not consider the underlying cause of the liver disease. However, the aetiological factors leading to chronic liver diseases (CLDs), such as alcohol-related liver disease, non-alcoholic fatty liver disease, viral hepatitis and primary biliary cholangitis can all affect the brain through mechanisms independent from those triggered by liver failure/dysfunction.[2, 3, 4, 5] Defined as a metabolic disorder, HE is widely considered to be reversible following liver transplantation (LT). However, this notion is changing as numerous studies have demonstrated that neuroinflammation and neuronal cell death are features of HE and episodes of overt HE can lead to irreversibility. These manifest as persisting neurological complications post-LT.[6,7] This fundamentally changes our understanding of HE as a reversible syndrome.

From the epidemiological perspective, it has become clear that HE is probably the most frequent complication of cirrhosis that leads to hospitalisations and repeated re-admissions.[8] Therefore, the healthcare burden and costs associated with the management of HE are extensive and increasing.[9] More

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

importantly, it has been demonstrated that HE is associated with high rates of mortality, irrespective of the severity of liver disease, indicating that HE is not merely a symptom of liver failure, but that it may have independent pathophysiological and prognostic implications.[10]

From the pathophysiologic perspective, data from recent studies indicate that ammonia remains the central player in the pathogenesis of HE. However, systemic and neuroinflammation, as well as oxidative stress and cellular senescence, are known to be implicated. In addition, blood-brain barrier (BBB) permeability/function, cerebrospinal fluid composition, glymphatic flow, cerebral energy metabolism, neurotransmission and cell-cell communication are all deranged, causing neurological impairment and providing potential therapeutic targets.[11, 12, 13, 14, 15, 16, 17]

The AASLD-EASL clinical guidelines for HE, published in 2014, were an important initiative.[1] However, since this publication, there have been many advances in the classification of HE, as well as our understanding of its pathophysiology, diagnosis and treatment. For instance, 'covert' HE, a term which was first introduced in 2014, has been studied further. In addition, acute-on-chronic liver failure (ACLF) has recently been defined and needs to be considered. Furthermore, based on a better understanding of the pathophysiology of HE and a clearer view of inter-organ ammonia metabolism, many new therapeutic agents are being developed.

The purpose of this review is to provide a detailed and critical insight into the current state-of-the-art and discuss each of the issues described above, as well as point out avenues for future research. This review will focus on discussing HE in association with CLD (Type C HE). Where relevant, reference to HE in association with acute liver failure (ALF) (referred to as Type A HE) and HE that occurs in patients with large portosystemic shunts without underlying liver disease (referred to as Type B HE) will be made.[1]

EPIDEMIOLOGY AND COST ASSOCIATED WITH HEPATIC ENCEPHALOPATHY

HE results in utilisation of more healthcare resources compared to other complications of liver disease.[9] The incidence of HE is 11.6 per 100 person years which increases to 40% by 5 years.[18] The prevalence of overt HE at the time of diagnosis of cirrhosis is 10–14%,[19,20] 16–21% in decompensated cirrhosis[21] and 10–50% in patients who have had a transjugular intrahepatic portosystemic shunt (TIPS) inserted.[22,23] Estimates of the prevalence of minimal hepatic encephalopathy (mHE) in patients with cirrhosis range from 20% to 80%.[24, 25, 26] This variability reflects the definition of what constitutes mHE as discussed later in the review. The risk of developing the first episode of overt HE is about 25% within 5 years after the diagnosis of cirrhosis, depending on the presence of risk factors such as mHE, grade 1 HE, diabetes, hyponatremia, and hepatitis C.[27, 28, 29] Patients with a previous episode of overt HE have a 42% risk of recurrence at 1 year, and those with recurrent overt HE have a 46% risk of another episode within 6 months, despite receiving standard care.[30,31] Even patients with cirrhosis and mild cognitive dysfunction or slight electroencephalogram slowing have a 1-year risk of developing an episode of overt HE of about 33%.[30,32]

As HE is a manifestation of serious liver impairment, its outcome depends on the severity of underlying liver disease, its clinical course, and its treatment. Population-based cohorts of patients with

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

cirrhosis presenting with overt HE have a median survival time of just a few months and a 2-fold increased risk of mortality over 1-year compared to cirrhotic patients without HE.[10,20]

The healthcare resource requirements of patients with HE are relevant from a public health perspective. In the USA, from 2010–2014, there was a 30% increase in HE-related hospitalisations.[8] Such numbers are not available for the European Union but are expected to be similar. Furthermore, the burden of CLD and cirrhosis is increasing in most countries, primarily due to a rise in non-alcoholic steatohepatitis-related cirrhosis[33]; therefore, more cases with HE will likely emerge in the future. Patients hospitalized with HE in the US generated charges of about US $11.9 billion per year, a 46% increase from 2010–2014[8] Recent data confirm this estimate, but also provide evidence that readmission rates with HE at 90 days are about 27% and cost an additional USD $200M.[34] Such costs will increase because of changes in the cirrhosis case-mix towards more advanced liver disease and correspondingly more complex healthcare efforts. There are no direct EU cost data, but the epidemiology suggests comparable costs, supported by inference from regional patient sampling,[35] also showing that the yearly cost of patients with HE is 50% higher than of patients with heart failure or chronic obstructive pulmonary disease.[36] These figures are a gross underestimate of total HE costs, because costs associated with primary healthcare, disability and lost productivity as well as the negative impact on the patient's family or support network are not included.[37]

CLASSIFICATION OF HEPATIC ENCEPHALOPATHY

HE occurs in the setting of ALF, portal-systemic shunting without liver disease and most commonly in cirrhosis.[1] However, the categorisation of disease severity across the spectrum of HE in cirrhosis is challenging. HE has traditionally been graded into overt (clinically manifest neurological-psychiatric abnormalities) and mHE (abnormalities on neuropsychological or electrophysiological tests without clinically detectable neurological-psychiatric abnormalities).[38] As the clinical diagnosis of mild forms of overt HE is heavily operator-dependent, it has been suggested[1] that HE is qualified as overt when at least temporal disorientation and/or asterixis are detected (≥grade II according to the West Haven criteria). However, the grades of HE, defined according to these criteria are not reproducible across observers and are thought to be inappropriate for clinical trials.[1,39] Hence, newer classifications have been developed, which are more accurate in the assessment of overt HE. (i) The hepatic encephalopathy scoring algorithm (HESA),[40] (ii) the clinical hepatic encephalopathy staging scale (CHESS),[41] (iii) the hepatic encephalopathy staging tool (HEST) and (iv) the hepatic encephalopathy grading instrument (HEGI)[42] have been developed, validated and are being used in ongoing clinical trials.

The estimation of the condition in its milder stages is also fraught with inter-observer issues.[39] At the heart of this is the semi-quantitative nature of the West Haven criteria, which have not defined grade I HE well. The term ‘covert HE’ was suggested because of its sound (opposite to overt).[43] Therefore, in patients with deranged psychometric or neuropsychological tests but with no grade 2 HE, the umbrella term of ‘covert HE’ was introduced.[43] Covert HE requires testing for its detection and quantification, and the diagnosis cannot be made clinically[1] and its validity has been determined using standardized patient testing modalities (Table 1).[39,42] However, it has been shown that covert HE is a heterogeneous entity,[44] and that grade I HE abnormalities have additional prognostic[44,45] and possibly also therapeutic

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

implications compared to abnormalities on testing for mHE alone. In addition, since patients with grade I alterations are symptomatic, albeit mildly, there is no reason not to treat them like any patient with a symptomatic medical condition. Thus, in clinical practice, particularly where neuropsychological and/or neurophysiological tests are not performed systematically,[46] grade I abnormalities should not be neglected if accurately diagnosed and should contribute to both treatment- and prognosis-related decisions. Importantly, regulatory agencies such as the FDA, have moved away from grade I HE and require at least grade 2 or higher to define HE events for multicentre clinical trials.[42] Even more controversial is the division between mHE and normal, given the multiple testing strategies that are available.[47]

Table 1. Neuropsychological tests used for the diagnosis of minimal hepatic encephalopathy.

Test	Test type	Test description
Psychometric hepatic encephalopathy score (PHES)	Neuropsychological, paper & pencil	The PHES consists of 5 paper-pencil tests evaluating cognitive/psychomotor processing speed and visuomotor coordination. They are relatively easy to administer, have good external validity and have been translated/validated into several languages and countries.[251]
Animal naming test (ANT)	Neuropsychological, bed-side	The ANT (***i.e.*** the number of animals listed in 60 seconds, no equipment required except a stopwatch) has recently been shown to compare favourably with more established mHE measures and to predict overt HE.[186]
Continuous reaction time (CRT)	Neuropsychological, computerised	The 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.[245]
The inhibitory control test (ICT)	Neuropsychological, computerised	ICT is a computerised 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.[246]
Stroop test	Neuropsychological, computerised	The Stroop test evaluates psychomotor speed and cognitive flexibility by the interference between recognition reaction time to a coloured field and a written colour name; also available in app form.[26]
SCAN test	Neuropsychological, computerised	The SCAN test is a computerised test that measures speed and accuracy to perform a digit recognition memory task of increasing complexity. It has been shown to have prognostic value.[247]
Electroencephalogram (EEG)	Neurophysiological	The EEG can detect changes in cortical cerebral activity across the spectrum of HE and its reliability increases with quantitative analysis. More recently, a cheap gaming device has been shown to produce similar results compared to a standard EEG machine across the HE spectrum.[248]
Critical flicker frequency (CFF)	Psychophysical	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. It requires specialized equipment.[249]

mHE, minimal hepatic encephalopathy.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

The operative criteria proposed for the diagnosis of grade 1 HE by the AASLD/EASL clinical practice guideline[1] ("despite being oriented in time and space, the patient appears to have some cognitive/behavioural decay with respect to his/her standard on clinical examination or to the *caregivers*") aims to overcome some of the difficulties that were inherent in the original description, which comprised a list of vague signs and symptoms.[48] If one follows the proposed definition, the problem of diagnosing grade 1 HE becomes particularly problematic in patients who do not have a caregiver. In these patients, careful observation and clinical examination are the only tools available to diagnose grade 1 HE and how these patients are classified will be based on Consensus statements. This current dilemma in the definitions and the lack of specific tests to diagnose and grade covert/low grade HE makes this a very challenging condition for which to define endpoints and develop new therapies; its pathophysiologic basis is therefore also undefined. Furthermore, how liver disease aetiology is implicated in these subtle neurologic abnormalities remains unclear.

HEPATIC ENCEPHALOPATHY ASSOCIATED WITH ACUTE-ON-CHRONIC LIVER FAILURE

Patients with 'overt HE' are not homogeneous and the clinical, prognostic and pathophysiological characteristics of HE that are observed in patients with and without ACLF are likely to be different.[10,49,50] ACLF is a newly defined syndrome that occurs in hospitalised patients with cirrhosis and is characterised by organ failures, systemic inflammation and high mortality rates.[51, 52, 53] Increased intracranial pressure implies cerebral oedema and is a characteristic feature of ALF. In CLD, numerous studies have demonstrated HE is associated with an increase in brain water[54, 55, 56, 57] without intracranial hypertension. However, a retrospective study comparing patients with CLD and ACLF with high grade HE (3/4) showed that cerebral oedema was evident in less than 5% patients, although this study relied on CT scans which are an insensitive measure of brain swelling.[58] In a prospective study, Sawhney *et al.* observed that higher ammonia levels, more marked systemic inflammation and reduced jugulo-venous oxygen saturation distinguished ACLF patients with HE from those without.[49] The most convincing argument that ACLF is associated with distinct changes in the brain comes from studies in animal models. Data from the ACLF models clearly demonstrate evidence of astrocytic swelling and vasoconstriction of cerebral microvessels on electron microscopy with increased expression of inducible nitric oxide synthase. Moreover, these pathophysiological changes are therapeutically relevant as strategies to reduce ammonia or inflammation abrogate these changes and are potential therapeutic targets.[59, 60, 61] The most convincing clinical argument suggesting that patients with HE and ACLF are clinically and prognostically different to those without ACLF are provided by Cordoba *et al.* where they analysed the data from the CANONIC study and demonstrated that the presence of ACLF in patients with HE increased both short- and long-term mortality.[10] More recently, these data have been confirmed by a large study from the NACSELD group and a further smaller prospective study from the UK.[49,62] Taken together, the data argue that these syndromes are clinically and pathophysiologically distinct. However, more studies are needed to better understand the pathophysiological basis and clinical characteristics of HE in patients with ACLF.

DISEASE-RELATED MENTAL DYSFUNCTION AND ROLE OF COMORBIDITIES

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

It is clear that liver failure is associated with HE, but the causes underlying the development of liver disease such as alcohol abuse, obesity and viral hepatitis (particularly hepatitis C), as well as extrahepatic conditions such as diabetes and ageing, may impact on the manifestations of HE (Fig.1). At present, it is not clear whether the neurologic dysfunction observed in the different aetiologies of cirrhosis or in association with diabetes or ageing are different.

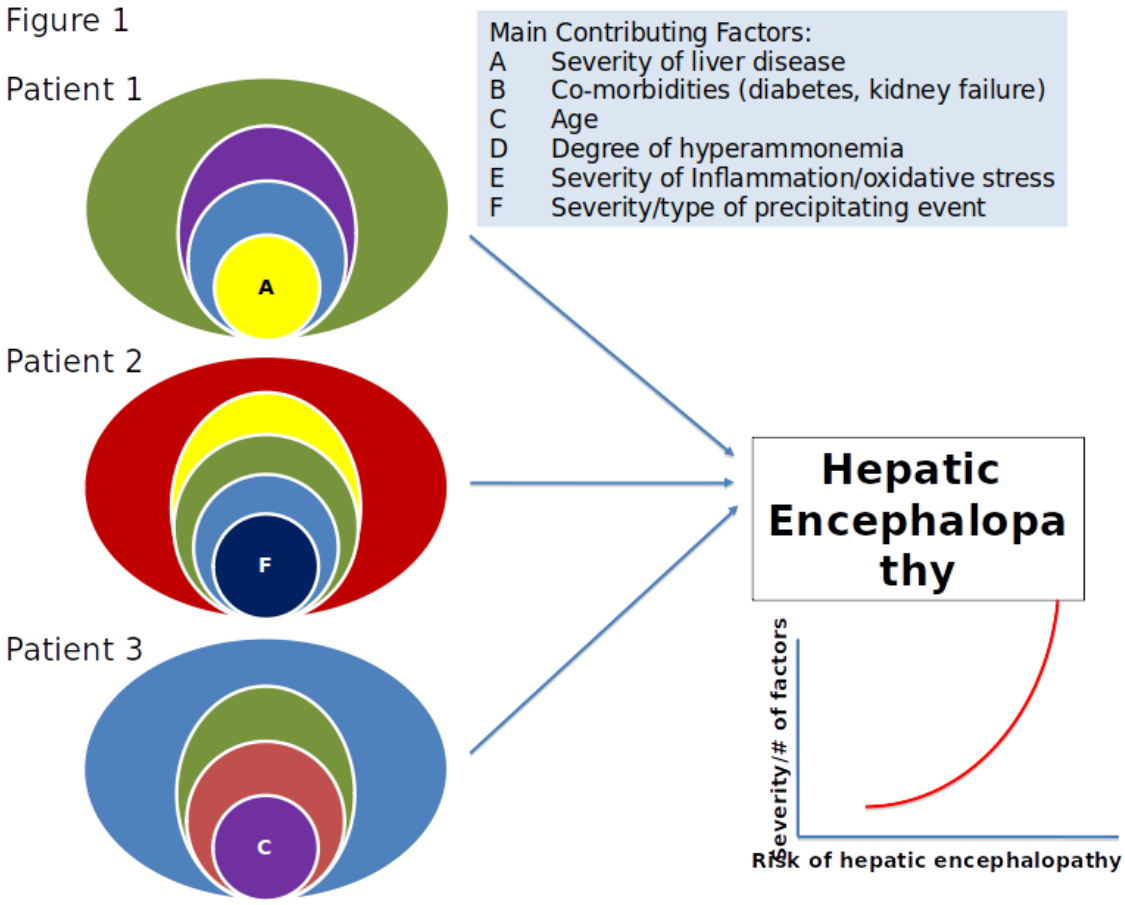

Fig. 1. Brain dysfunction increases with cumulative pathogenic factors.
Severity of liver disease, comorbidities (diabetes, kidney failure), age, degree of hyperammonaemia, severity of inflammation/oxidative stress and severity/type of precipitating event can independently affect and sensitise the brain. Simultaneous pathogenetic factors can synergistically cause a greater impact on brain function and an increased risk of hepatic encephalopathy.

ALCOHOL ABUSE

As alcohol is a common cause of cirrhosis and a direct neurotoxin, difficulties in diagnosis may arise in distinguishing what element is directly related to alcohol and what component results from liver injury. This problem is particularly evident in the context of LT, where incomplete recovery of

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

neuropsychometric function and MRI abnormalities were observed in patients with alcohol-related liver disease.[6,7] Post-mortem studies from brain banks have revealed greater evidence of structural brain injury in those dying from alcohol-related cirrhosis, compared with other aetiologies.[63] These changes may impact on the assessment of these patients when using neuropsychometric tests to diagnose mHE and grade 1 HE. In the acute situation, where patients appear clinically confused, withdrawal from alcohol and the Wernicke-Korsakoff syndrome may make the diagnosis of HE difficult.[64] However, loss of orientation in space and time is rarely a feature of alcohol withdrawal syndrome but is a characteristic of overt HE.

NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease (NAFLD) is fast becoming the most common cause of cirrhosis. More recently, studies have demonstrated that psychometric function in obese children is impaired[65,66] and data also indicate lower brain volume in patients with NAFLD.[67, 68, 69] Recently published studies have started to indicate that even in the non-cirrhotic stages of NAFLD, urea cycle enzyme function is impaired, which results in hyperammonaemia that is reversible with resolution of NAFLD.[70] In such patients, astrocytic and microglial activation have been observed.[2] Taken together, it is probable that NAFLD has serious negative functional impact on the brain that results from hyperammonaemia and neuroinflammation. Even in patients without cirrhosis, changes in the brain are observed in association with NAFLD.[67,71,72] These data need to be confirmed in carefully characterised groups of patients to dissect the associated mechanisms and define whether there are specific features related to NAFLD and how these impact on the diagnosis of early stages of HE in this patient population.

HEPATITIS C

Many studies over the past 2 decades have confirmed a clear association between hepatitis C virus infection and neuropsychiatric symptoms.[3] The reported symptoms vary widely, manifesting as fatigue, depression and loss of attention. It has become clear that these symptoms are independent of severity of liver disease and characterised by abnormalities on brain imaging and neuroinflammation that are distinct from patients with cirrhosis. Indeed, they resemble the changes observed in patients with HIV. Further proof for the role of hepatitis C in producing neuropsychiatric disturbances comes from the demonstration of the virus in the post-mortem brains and the observation that the virus can replicate in many cell types including the endothelial cells, astroglia and microglia.[73] This possibly explains the neuroinflammation observed in these patients. It is important to note that eradication of the virus results in substantial improvement in neuropsychiatric function.

OBESITY, DIABETES AND AGE

Ageing, obesity and diabetes are emerging as important contributors to the development of HE. Diabetes is frequently associated with cirrhosis and clinical studies suggest that the risk of developing HE is significantly greater in these patients.[28,74] Likewise, the risk of HE is greater with ageing and the insertion of TIPS in older patients is a relative contraindication because of the risk of HE development.[75] Concomitant medications can modulate the cognitive function and course of HE as

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

well.[76, 77, 78, 79] The mechanisms underlying the increased risk of HE in these populations is not clear, but likely result from worsening cerebrovascular disease, systemic inflammation, the effect of senescence and oxidative stress.[80] Further elucidation of the relevant pathogenic pathways would enable the development of new therapeutic strategies to prevent HE in these patients.

PATHOPHYSIOLOGY (FIG. 2)

SYSTEMIC PATHOGENIC FACTORS

Neurological impairment and cognitive decline provoked by liver dysfunction are the result of blood-derived factors influencing the permeability and/or altering the integrity of the BBB. In cirrhosis, factors which are normally prevented from crossing the BBB enter the brain and other molecules (such as ammonia), which naturally cross the BBB, flood the brain and stimulate pathophysiological pathways, causing deleterious effects.

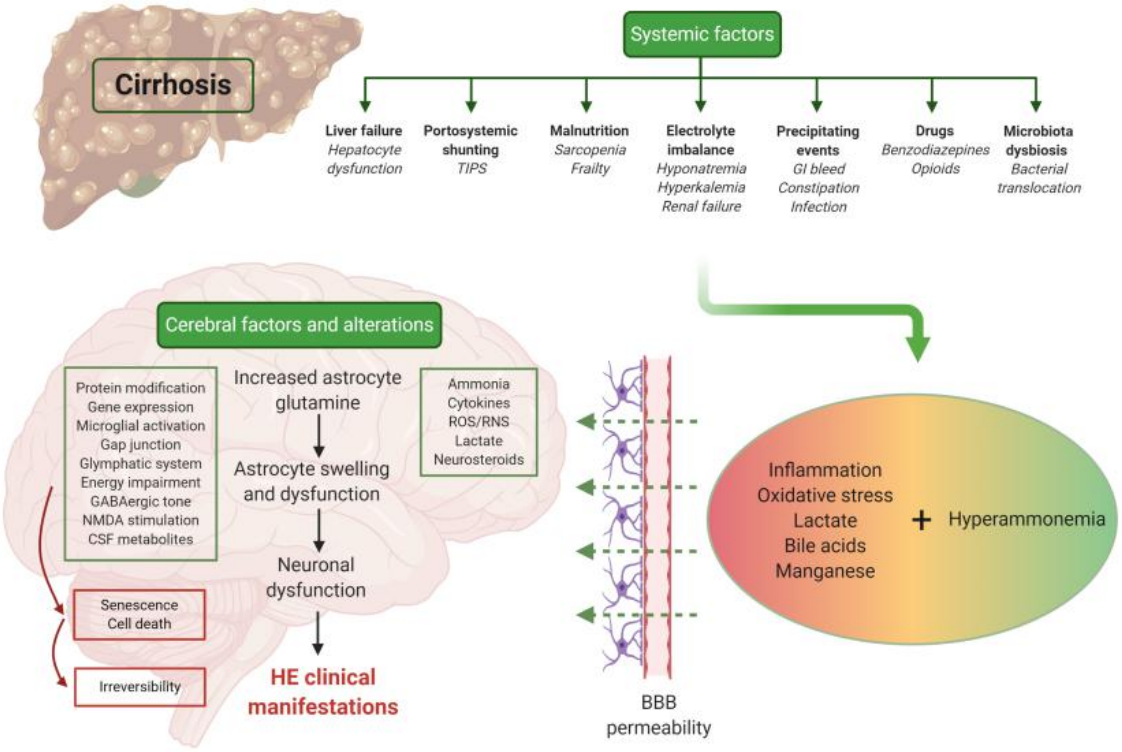

Fig. 2. Pathogenesis and pathophysiology of hepatic encephalopathy.
BBB, blood-brain barrier; CSF, cerebrospinal fluid; HE, hepatic encephalopathy; NMDA, N-methyl-D-aspartate; TIPS, transjugular intrahepatic portosystemic shunt.

Chronic liver disease leads to hepatocyte dysfunction, portal hypertension, portal-systemic shunting, altered microbiota, bacterial translocation, malnutrition, sarcopenia, electrolyte imbalance as well as

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

constipation and gastrointestinal bleeding. Consequently, pathogenic factors are generated including hyperammonemia, systemic inflammation/oxidative stress as well as increased blood manganese, circulating bile acids and lactate. These systemic factors influence the blood-brain barrier (BBB) by increasing its permeability (increased signaling across the BBB, physical breakdown of the BBB which allows for an increased influx of molecules which normally do and do not cross the BBB). Independent of BBB status, ammonia passes freely into the brain which is exclusively removed by astrocytes via glutamine synthetase. The generation of glutamine renders the astrocyte hypertonic resulting in swelling and impaired function and brain oedema. Astrocyte swelling leads to compromised neuronal communication leading to neuronal dysfunction. Alterations of cerebrospinal fluid (CSF) metabolites are observed, as well as alterations in neurotransmission such as increased GABergic tone potentiated with neurosteroids and glutamate-induced N-methyl-D-aspartate (NMDA) stimulation. Blood derived increase in brain ammonia is central in the pathophysiological mechanisms underlying the development of HE. Neuroinflammation and microglia activation are significant modulators in the onset of neurological decline. Astrocyte senescence as well as neuronal cell death may be key features in the irreversibility of HE. However, the extent and underlying causes of neuronal cell death remain to be defined.

Ammonia

Although the pathophysiology of HE remains incompletely understood, neurotoxic levels of ammonia in the brain are a feature.[81] Ammonia is primarily produced in the gut, as an end product of protein digestion, amino acid deamination and bacterial urease activity. Subsequently, a healthy liver, with an intact urea cycle, regulates the concentration of ammonia in the systemic circulation, thus maintaining blood ammonia levels in the low 35–50 μM range. However, ammonia is also generated and utilised in a number of biochemical reactions, (*i.e* amidation of glutamate and deamidation of glutamine via glutamine synthetase [GS] and glutaminase, respectively), which are active in multiple organs (including the brain, muscle and kidney). In the setting of liver disease, inter-organ ammonia metabolism is altered.[82] In aqueous solutions, ammonia is present as a dissolved gas (NH_3) and an ion (NH_4^+), with the former freely diffusing across plasma membranes. NH_4^+ is transported into cells through aquaporins, ammonia transporters, K^+ channels and co-transporters. Ammonia exerts its deleterious effects through multiple pathways including cellular swelling, inflammation, oxidative stress, mitochondrial dysfunction, disruption of cellular bioenergetics, changes in pH and alterations in membrane potential.[83] A direct correlation between the degree of hyperammonaemia and the severity (grade) of HE has not been confirmed but it is clear the diagnosis of HE is incompatible with normal ammonia levels. This lack of correlation may reflect the idea that different patients have different sensitivities to the same levels of ammonia. The deleterious effects of high ammonia extend to organs such as the liver, immune system and muscles.[84,85]

Inflammation and oxidative stress

The inflamed liver, together with gut bacterial translocation and superimposed infection,[86] aggravates systemic inflammation, which in turn produces BBB dysfunction and drives neuroinflammation. Oxidative stress, a systemic phenomenon that is frequently observed in cirrhosis, can compromise BBB permeability as reactive oxygen (and nitrogen) species are highly reactive with lipids, proteins and

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

DNA.[87] Signs of cerebral oxidative stress have been documented in patients with overt HE[88] but a disconnect between systemic and cerebral oxidative stress has been revealed.[89] Underlying hyperammonaemia has been shown to induce neutrophil dysfunction and release reactive oxygen species, triggering systemic oxidative stress and inflammation which exacerbate the deleterious effects of hyperammonaemia on the brain.[90, 91, 92, 93]

Bile acids

Bile acids are a metabolic product of cholesterol metabolism and are synthesised in the liver via cytochrome p450 activity in hepatocytes. Bile acids are elevated in the blood of patients with end-stage liver disease due to disrupted enterohepatic circulation. Bile acids have been detected in the brains of rats with HE induced by bile-duct ligation,[94] which consequently induces neuroinflammation.[95]

Metals

Metals play an important role as co-factors for numerous enzymatic reactions. Manganese is a co-factor for the ammonia-removing enzymatic reaction of GS. Manganese is normally excreted via a biliary route, but this is impaired in end-stage liver disease, leading to manganese deposition within the basal ganglia, which is believed to explain the psychomotor impairment associated with HE.[96,97] However, the reason for the accumulation of manganese in specific brain regions and the mechanisms underlying manganese neurotoxicity in the context of cirrhosis remain unresolved. Zinc is a cofactor for the antioxidant enzyme superoxide dismutase. Zinc deficiency has been observed in patients with HE[253] and oral zinc supplementation been demonstrated to improve neurocognitive function in patients with HE.[254]

ELECTROLYTE IMBALANCE

Patients with cirrhosis often present with dilutional hyponatremia, which interferes with the other suspected pathogenic mechanisms of HE, particularly those centred around the osmotic effects of ammonia. There is linear risk relation between low plasma sodium concentrations over a wide range and the risk for HE.[98] Resolution of hyponatremia in patients with cirrhosis without HE leads to improved complex information processing.[99] Treatment with vasopressin receptor antagonists does not reduce the frequency of HE but tolvaptan led to improvements in cognition and health-related quality of life in a small study.[100,101] Improved management of and research on hyponatremia in patients with HE remains relevant.

NEUROPATHOPHYSIOLOGY

It is important to note that the blood and brain compartments are separate entities, ammonia aside, what occurs in the blood does not necessarily occur in the brain. It has been shown that cerebrospinal fluid composition is significantly different in cirrhotic patients with HE compared to those without. In addition, in patients with overt HE, cerebrospinal fluid metabolomics highlighted alterations of metabolites that were not observed in plasma samples.[15] Recent evidence describes a defective

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

glymphatic system (which facilitates clearance of various substances that accumulate in the brain) that may contribute to the development of HE.[12] Significant increases in concentrations of neurosteroids have been reported in autopsied brain tissue from cirrhotic patients with HE, which increase GABAergic tone by positively modulating the $GABA_A$ receptor complex.[102]

Cerebral energy and lactate metabolism

In HE, an increase in brain water is observed primarily due to swelling of the astrocytes with the underlying causes pointing primarily to the hypertonic accumulation of intracellular glutamine and/or lactate as a result of hyperammonaemia.[103,104] A swollen astrocyte can independently impact on astrocyte function disconnecting astrocyte-neuronal cell communication, altering cell metabolism and neurotransmission.[105] Elevated levels of lactate in the brain during HE may depict energy impairment, which is thought to be a result of reduced oxidative metabolism in neurons, as astrocytes appear unaffected.[106] Recently, analysis of plasma samples showed that alterations in the concentration of metabolites linked to energy metabolism were specifically and significantly increased in cerebrospinal fluid samples of patients with HE.[15] Furthermore, this may denote disturbances in lactate homeostasis as a result of dysregulation of lactate transport and metabolism, possibly depleting neuronal energy supply.[104,107]

Neuronal cell death

Neuronal cell death has been largely disregarded in HE, but with increasing cases and evidence of "untreatable HE", along with neurological complications arising post-LT, permanent brain injury needs to be included in the pathogenesis of HE.[7,108, 109, 110, 111, 112] There is increasing evidence that recurrent episodes of overt HE prior to LT are associated with persistent neurocognitive abnormalities post-LT.[113, 114, 115] Neurodegeneration is probably the operative mechanism, as seen in a rodent model of episodic HE.[116] Moreover, ammonia neurotoxicity has been shown to induce astrocyte senescence,[14] which leads to neuronal cell death. The mechanisms of neuronal cell death remain unresolved and will be an important line of research in the years to come.

THE GUT-LIVER AXIS AND THE ROLE OF THE MICROBIOME

The gut milieu has a major impact on brain function in patients with HE.[117] This is borne out by extensive clinical experience with drugs that modify the gut, which can in turn improve brain function.[1] The constituents of the gut microbiome include bacteria, fungi and viruses, particularly bacteriophages.[118,119] These interact with each other, the host as well as with the food and medications to which the host is exposed. With the advent of culture-independent techniques, improved understanding of the gut microbiome has[119] led to new thinking in terms of disease pathogenesis, progression and the mechanism of action of some commonly used medications for HE. Importantly, both the structure (which taxa are present) and the function (what are they producing/consuming) are relevant in the study of the microbiome in HE.[117] Specific bacterial families belonging to phylum Proteobacteria (Enterobacteriaceae, which includes *E. coli, K. pneumoniae* etc.) are potentially harmful since they produce very damaging endotoxins. On the other hand, certain families belonging to gram-

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

positive Clostridia (Lachnospiraceae, Ruminococcaceae) are thought to be autochthonous and potentially beneficial, as they produce short-chain fatty acids and possess capabilities to convert bile acids.[120]

In cirrhosis, the aetiology of the disease modulates the capacity of diseased and inflamed liver to produce bile acids, while the ability to clear bacterial antigens arriving from the gut is impaired. This leads to an increase in potentially pathogenic Proteobacteria. Toxins such as ammonia and inflammatory cytokines produced by this impaired intestinal milieu access the circulation and exacerbate or precipitate HE.[121]

Bacterial taxa in cirrhosis show impaired composition (higher potentially pathogenic and lower autochthonous taxa) in the stool, large and small intestinal mucosa, ascites and the liver itself.[122, 123, 124, 125] However, similar microbial changes are also found in locations distant from the gut-liver axis such as the saliva and the serum, likely due to an underlying immuno-suppressed state.[126, 127, 128] Microbial functionality is also impaired with changes in bile acid profile and endotoxin production, which mirror cirrhosis severity.[129] Bacterial profiles can predict hospitalisations, death and organ failure in cirrhosis and may be of clinical relevance.[124,130,131] Recent evidence shows that fungal dysbiosis may also play a role in cirrhosis progression.[132] Thus, the composition and functionality of microbiota in HE may modulate the clinical disease course, brain function and effect therapeutic interventions.

MALNUTRITION

Malnutrition is a common occurrence in CLD. The underlying reasons for the onset of malnutrition include inadequate dietary intake, increased energy expenditure, impaired digestion and malabsorption.[133] Consequently, an increased metabolic rate leads to the catabolism of muscle proteins, which is compounded by depletion of glycogen stores and impairment in glycogenolysis. In addition, elevated ammonia levels can impact on the muscle, causing deleterious effects (including impairing muscle protein synthesis) setting up a detrimental vicious cycle.[85] In patients with cirrhosis, nutritional supplements are indicated to achieve a target of 35–45 kcal/kg and 1.2–1.5 g/kg protein per day, as well as late night snacks.[134] Low-protein diets do not add any beneficial effect.[135]

SARCOPENIA

Sarcopenia (muscle mass depletion) is nearly universal in patients with cirrhosis. Characterised by a deterioration in muscle quantity and quality, sarcopenia is also associated with decreased functional capacity[136,137] and has been shown to be an independent prognostic factor for survival in patients with cirrhosis.[138] Moreover, muscle mass loss has a significant impact on the risk of developing HE.[139] Muscle, due to the fact it houses GS (an important ammonia removing enzyme), plays a vital compensatory role in ammonia detoxification during liver disease. Indeed, cirrhotic patients with sarcopenia have higher ammonia levels and increased risk of developing HE.[140, 141, 142, 143] In addition, muscle catabolism during muscle wasting promotes increased glutamine release which can generate ammonia via glutaminase, contributing to hyperammonaemia. Results from recent pre-clinical studies

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

suggest that ammonia-lowering treatments should be tested to prevent and treat sarcopenia, which would reduce the risk of HE.[144]

Sarcopenia can also manifest as frailty, which is an independent predictor of mortality in patients with cirrhosis.[145,146] The relationship between frailty and sarcopenia is stronger in men than in women.[145] The direct impact of frailty on the risk of HE is unknown.

IMPACT OF HEPATIC ENCEPHALOPATHY ON NEUROLOGICAL OUTCOME FOLLOWING LIVER TRANSPLANTATION

HE, defined as a metabolic disorder, is presumed to completely resolve following LT. However, persisting neurological complications remain problematic following LT, affecting as many as 47% (8–47%) of LT recipients.[147,148] Consequently, these enduring neurological complications following LT (not defined as HE since the diseased liver has been replaced with a healthy liver) not only severely weigh on the patients' health-related quality of life but also lead to longer hospitalisations. Numerous studies have documented patients with cirrhosis and a history of HE display impaired neurological recovery, suggesting that repeated episodes of HE lead to permanent cell damage.[7,108, 109, 110, 111, 112] Therefore, irreversible brain damage may not be resolved with LT, leading to continued neurological disturbances. It is thought that patients with cirrhosis and no history of HE pre-LT rarely develop neurological complications following LT. However, post-LT immunosuppression induced neurotoxicity, particularly from calcineurin inhibitors, should not be disregarded as a causal factor.[149] In addition, perioperative conditions, including seemingly innocuous hypotensive insults, may be detrimental for a compromised brain. Whether neurological complications observed in LT recipients are residual symptoms from a history of HE (pre-LT) or newly developed perioperatively (HE-influenced) or related to a comorbidity is difficult to define accurately. Having said this, a recent study reported a recovery of brain function in patients followed-up long-term (>5 years) post-LT.[150]

INSIGHTS FROM NEUROIMAGING STUDIES

The diverse neurological manifestations of CLD present a diagnostic challenge for modern hepatologists, with magnetic resonance techniques representing a highly profitable avenue to investigate structural and functional aspects of brain dysfunction in an objective way (Table 2).[151,152] While there is widespread acceptance of its importance, there is little consensus on how best to diagnose and monitor HE. Of note, modern clinical MRI scanners with multinuclear MR spectroscopy capabilities and brain mapping software can objectively demonstrate structural and functional cellular changes (such as brain size and astrocyte swelling) using volumetric MRI, magnetization transfer MRI, diffusion-weighting MRI, functional MRI with oxygenation measurements and *in vivo* ^{1}H and ^{31}P MR spectroscopy, with the option of performing many sequences at a single sitting to maximise information gathering and cohort characterisation.[153, 154, 155, 156, 157, 158] PET studies have provided clear evidence of increased ammonia uptake in the brain and alterations in regional cerebral blood flow, as well as evidence of neuroinflammation, microglial activation and altered benzodiazepine receptors, confirming the role of these putative mechanisms in the pathogenesis of HE.[152,156]

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

Table 2. Information provided by different imaging techniques.

Imaging technique	Information
Volumetric T_1-weighted MR imaging	Regional or global changes in brain size. A reduction in brain volume is observed in patients with HE.[153]
Magnetisation-transfer MR imaging	Measures shifts in bound and free water content, which have been associated with intracellular and extracellular oedema and with alterations in cell membrane fluidity. In patients with HE there is evidence of reduced magnetisation transfer, indicating increased brain water.[154]
Diffusion-weighted MR imaging	Measures ADCs of water molecules. Associated with structural damage to white matter tracts. Changes in ADCs have been observed in patients with HE.[252]
Functional MR imaging (fMRI)	Measures changes in blood flow in metabolically active areas of the brain, related to oxygenation and de-oxygenation of haemoglobin (BOLD response). Resting state or responses to cognitive tasks can be assessed in imaging paradigms. In patients with HE, changes in fMRI have been shown to occur.[155]
^{31}P MR spectroscopy	Measures high energy metabolites, such as ATP and phosphocreatine, together with cell membrane precursors (phosphomonoesters) and cell membrane degradation products (phosphodiesters). Widespread changes in ^{31}P metabolites have been shown to occur in patients with HE.[158]
^{1}H MR spectroscopy	Measures lactate, choline, glutamine and glutamate levels and fluxes in osmolytes such as myo-inositol and taurine. Neuronal integrity reflected by N-acetyl aspartate measurements. Cannot measure ammonia levels directly, but increased glutamine represents amidation by glutamine synthetase. This is the best validated imaging test that may be useful for the diagnosis of HE as the severity of HE has been shown to correlate with changes in metabolites.[157]
Positron emission tomography (PET)	Depending on the radioligand used, information can be obtained on a wide variety of brain activity including neurotransmitter binding (such as dopamine or GABA receptors), TSPO activity (as a measure of neuroinflammation) and glucose utilisation. Several studies using PET have revealed alterations in cerebral blood flow, perfusion, glucose utilisation, oxygenation, ammonia metabolism, benzodiazepine receptor expression and neuroinflammation in patients with HE.[250]

ADCs, apparent diffusion coefficients; ATP, adenosine triphosphate; BOLD, Blood oxygenation level dependent; GABA, gamma-aminobutyric acid; HE, hepatic encephalopathy; MR, magnetic resonance; TSPO, translocator protein.

Investigations using MRI have shown evidence of hyperintensity of the basal ganglia, possibly related to the deposition of manganese, which correlated with the severity of extrapyramidal symptoms.[154] Other studies showed altered magnetization transfer ratio suggesting regional brain swelling, which in the early stages was also evident in the white matter.[153] In patients with ACLF, MRI studies have shown clear evidence of brain oedema.[151] In general, the MRI studies have suggested that there is a loss of brain volume, which continues even after LT, particularly in those with alcohol-related cirrhosis.[155] Proton MR spectroscopy has clearly shown evidence of osmolyte shifts in patients with cirrhosis, which manifest as increased glutamine and reduced myoinositol, the severity of which seem to correlate with the severity of HE.[157] Disturbances in choline metabolism and possible neuronal loss have also been suggested.[151] Phosphorus MR spectroscopy has confirmed disturbances of lipid metabolism in the brain and also corroborated other studies suggesting disturbances of cerebral bioenergetics.[158] Recent studies using quantitative CT scanning with Brainview have provided evidence of altered blood-cerebrospinal fluid barrier permeability in patients with acute decompensation of cirrhosis even in the absence of overt HE, suggesting a generalised defect in brain homeostasis in patients with advanced cirrhosis.[159]

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

However, these imaging techniques have so far yielded disappointing performance in diagnostic paradigms and therefore remain largely the preserve of research studies.[73,159, 160, 161, 162] Nevertheless, there is the possibility that imaging may be useful for monitoring in trials.[163,164] More importantly, the suggestion that the abnormalities detected using imaging techniques are evident even in patients without manifest HE suggests that imaging may well be useful to identify patients at risk of HE so that appropriate prophylactic measures can be put in place. In support of this hypothesis, a study using proton MR spectroscopy suggested that the glutamine/myoinositol ratio in the brain may help define patients at risk of developing ammonia-induced neuropsychometric abnormalities.[160] In clinical practice, at present, brain imaging is largely used to exclude other causes of brain dysfunction rather than to diagnose HE.

MANAGEMENT OF HEPATIC ENCEPHALOPATHY

DIAGNOSIS OF OVERT HEPATIC ENCEPHALOPATHY

As mentioned, the diagnosis of HE is challenging, particularly in the covert/minimal forms. Diagnosis of overt HE is relatively straightforward and usually a diagnosis of exclusion. In complex situations, particularly when there are no obvious precipitating events leading to HE, the diagnosis may be more difficult. In alcoholics, it may be difficult to distinguish HE from withdrawal. Cross-sectional imaging of the brain should be performed in patients in whom the diagnosis is not clear and is absolutely necessary in patients that present with localising signs. A 2-step approach to the differential diagnosis has been suggested[64] (Fig. 3). Response to treatment may be a powerful tool for diagnosis and differential diagnosis. A disease that responds to ammonia-lowering treatment is likely to be HE; thus, when the syndrome is mild and diagnostic tools limited, treatment may help confirm the diagnosis. However, the time needed to decipher whether a patient responds to a treatment or not is critical time, as episodes lasting longer than 48 hours lead to higher mortality.[165]

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

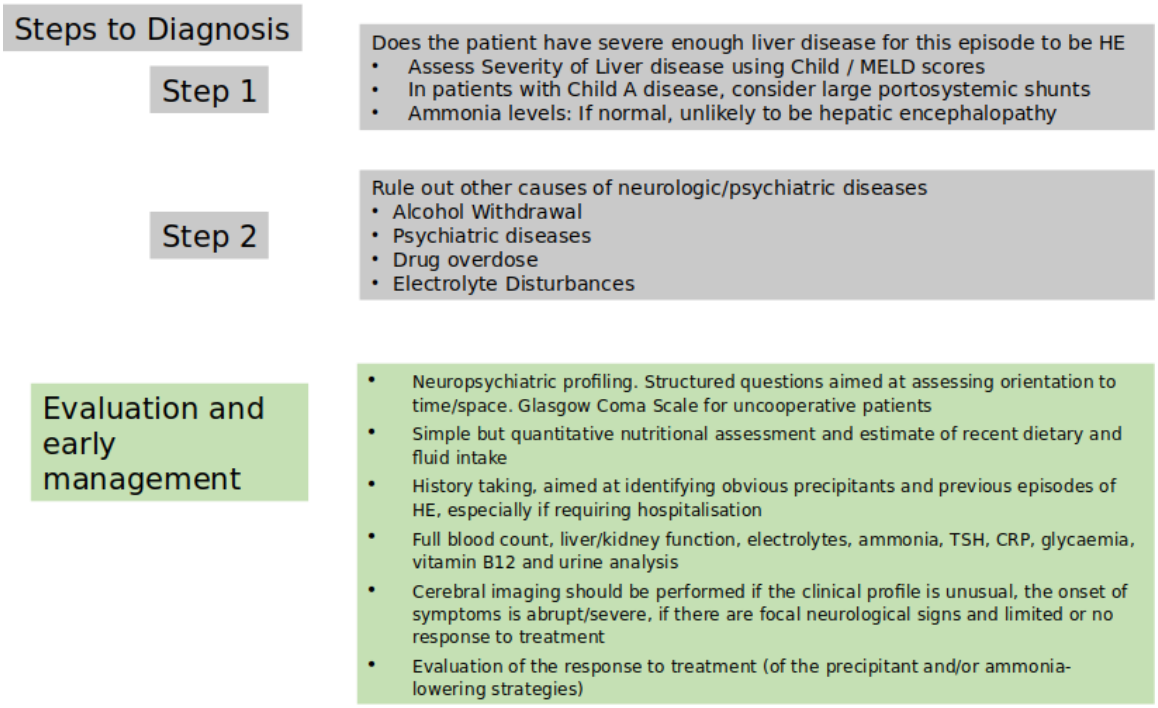

Fig. 3. Two step approach for the diagnosis and evaluation of a patient presenting with a possible hepatic encephalopathy.
CRP, C-reactive protein; MELD, model for end-stage liver disease; TSH, thyroid-stimulating hormone.
(Modified from Romero-Gomez *et al.* J Hepatol 2015).[244]

ROLE OF AMMONIA MEASUREMENT

The EASL-AASLD guidelines[1] are not clear on the role of ammonia measurement in HE. In patients suspected of overt HE, a normal ammonia concentration can be used to rule out the diagnosis of HE because the negative predictive value of a normal ammonia concentration is high (0.81).[166] The best evidence for the prognostic role of ammonia and its relationship with severity of HE is observed in patients with ALF. It is clear that ammonia level of >120 μmol/L seems to identify a group of patients at a high risk of developing intracranial hypertension and cerebral oedema.[167, 168, 169] In patients with cirrhosis, recent data have demonstrated the important prognostic role of elevated blood ammonia. Although the level of ammonia does not follow the severity of HE, more severe HE is associated with higher ammonia levels.[49,166,170, 171, 172, 173, 174] It is interesting to note that advanced degrees of HE are associated with relatively low ammonia levels in cirrhosis compared with ALF, suggesting other factors in addition to ammonia may be pathophysiologically important in cirrhosis-induced HE.[49,173,174] In any case, elevated ammonia levels have been shown to be associated with reduced transplant-free survival in acutely decompensated cirrhosis.[173, 174, 175] Importantly, a response to intervention that is associated with a reduction in ammonia concentrations is associated with good outcomes,[41,176] while the reverse is true if ammonia increases further.[49,177] This observation is supported by studies of various

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

interventions such as lactulose, rifaximin or extracorporeal albumin dialysis where reduction in ammonia was indeed associated with improvement in the severity of HE.[31,178,179] In a prospective study, an ammonia cut-off of 80 μmol/L was shown to be associated with a high risk of death, irrespective of the severity of HE.[174] This suggests that ammonia is more than just a neurotoxin and can serve as a biomarker of outcome in patients with cirrhosis and acute decompensation. Therefore, increasing evidence that ammonia can exert its toxic effects on extracerebral organs and tissues strongly support its management, not only to reduce the risk of HE, but also to prevent multiple organ injury and mortality.[84] It is important to note that ammonia measurement is not easy and requires careful sample handling and rapid measurement using a reliable analyser to obtain accurate results.[180,181] This is especially important in multicentre studies that rely on ammonia levels to guide entry into trials or to determine success because of the variations within and between individuals and clinical centres.[180,182]

TREATMENT OF AN EPISODE OF OVERT HEPATIC ENCEPHALOPATHY

General measures

The main aims of treatment are managing bouts of overt HE efficiently; reducing its duration, limiting its consequences, preventing recurrence and hospital readmissions, limiting effects on patients' quality of life, social and professional functioning and, limiting its impact on patients' families and caregivers.

Treatment of an episode of overt HE in a patient with CLD includes:

(i) Initiation of care for altered consciousness, which includes securing the airway, haemodynamic stabilisation, and ensuring patient safety to prevent physical injury. Patients with HE III or higher or Glasgow Coma Score (GCS) ≤8 should be intubated in order to prevent aspiration, but this is not possible in many hospitals. In these environments, careful attention to airway protection and close monitoring should be instituted.

(ii) Evaluation of alternative causes of altered mental status, including a CT scan of the head for first time presentation of HE and if there is a history of seizures, headache, fall, or neurological evaluation reveals a focal deficit.

(iii) Identification and correction of precipitating events, such as, infection, gastrointestinal bleed, constipation, dehydration, sedatives, alcohol intoxication or electrolyte disturbances.

(iv) (iv)Treatment of HE.

Once a patient recovers from an episode of HE, the risk of relapse is high; therefore, approaches to prevent the recurrence of HE and the associated hospitalisations are of paramount importance.
At present, no strategies have been specifically tested but approaches for home monitoring of biochemical, inflammatory and neurological strategies are becoming available. As ammonia is a major neurotoxin, further development of strategies to measure capillary ammonia would be desirable. Indeed such tests now exist.[183] Changes in heart rate variability reflect inflammation and have been shown to be associated with HE.[184] This type of device can be worn and the patient can be monitored remotely; one such device was shown to be useful in patients with cirrhosis.[185] Finally, neurological monitoring

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

at home can be undertaken using the animal naming test[186] or a wearable electroencephalogram.[187] These approaches warrant evaluation in clinical trials.

Specific treatment

Most of the therapies for HE target ammonia[188] (Fig. 4). These therapies are based on the knowledge gained from better understanding of inter-organ ammonia metabolism and the gut-liver-brain axis. The majority of ammonia is produced in the gut and in cirrhosis, the liver is not efficiently able to detoxify ammonia into urea. Secondarily, the muscle begins to play an increasingly important role in ammonia metabolism. In cirrhosis, apart from the urea cycle, 2 other enzymes are crucially important in maintaining ammonia homeostasis: glutamine synthase (predominantly expressed in the liver, muscle and kidneys) and glutaminase (predominantly expressed in the gut, liver and kidneys). Therefore, reducing ammonia production and preventing ammonia absorption from the gut, in addition to manipulating GS and glutaminase are all potential targets that could reduce circulating ammonia levels.

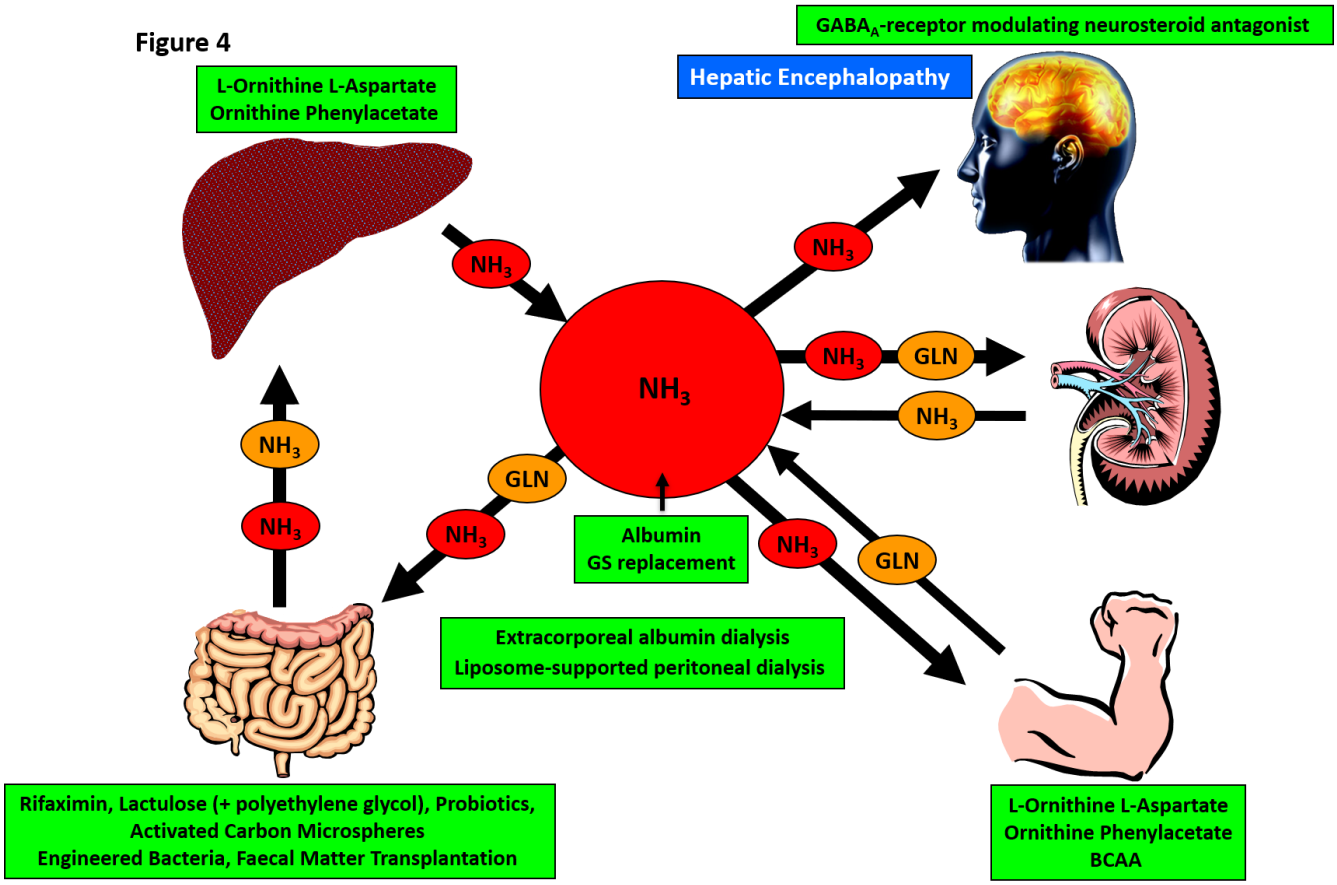

Fig. 4. Therapeutic targets for hepatic encephalopathy.
Ammonia-lowering strategies primarily involve reducing the production or increasing the removal of ammonia. Since a large amount of ammonia is produced within the gut, many therapeutics target the gut to reduce the production and

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

absorption of ammonia including rifaximin (non-absorbable antibiotic), lactulose (osmotic laxative), probiotics, activated carbon microspheres, engineered bacteria and faecal matter transplantation. Alternatively, stimulating ammonia clearance can be targeted via residual hepatocytes (ureagenesis and glutamine synthesis) and/or muscle (glutamine synthesis) with L-Ornithine L-Aspartate and Ornithine Phenylacetate. Branched chain amino acids (BCAA) benefit the muscle in clearing ammonia. The binding properties of albumin remove toxic molecules in circulation via infusion or with extracorporeal albumin dialysis. Liposome-supported peritoneal dialysis or glutamine synthetase (GS) replacement can also benefit in eliminating ammonia. $GABA_A$-receptor modulating steroid antagonists are centrally acting. NH_3= ammonia-derived from the gut, NH_3= ammonia derived from glutamine, GLN= glutamine generated from muscle. BCAA, branched chain amino acids; Gln, glutamine.

Osmotic laxatives: Non-absorbable disaccharides, lactulose and lactitol, are recommended as first-line treatment for HE. Lactulose is a laxative which has negligible impact on gut microbiota composition or function and likely works through increasing intestinal transit as well as acidification of the bowel milieu.[189] Subsequently, ammonia production is reduced in the gut, faecal excretion is increased and ammonia absorption is reduced. Lactulose is the agent most extensively studied in patients with an episode of HE. A large number of randomized clinical trials as well as observational studies have shown the benefit of lactulose over no therapy, although there are no true double-blinded studies as it is extremely difficult to blind for the laxative effect and the typical sweet taste of lactulose. A recent Cochrane review demonstrated the beneficial effect of non-absorbable disaccharides on HE severity (number needed to treat 4), prevention of HE (number needed to treat 6), mortality (relative risk 0.36; 95% CI 0.14–0.94; 172 participants; 6 randomized clinical trials) and on serious adverse events such as liver failure, variceal bleeding, serious infections, spontaneous bacterial peritonitis and hepatorenal syndrome in randomised clinical trials evaluating episodic HE.[178] Lactulose therapy is not without risks, and potential side effects include diarrhoea, nausea and bloating. Diarrhoea and vomiting may lead to electrolyte disturbances, and even exacerbate HE. The dosing of lactulose can be started at 15–20 ml every 12 hours until 2 soft stools are passed, followed by titration to 2–3 semi-soft stools/day. In a randomized controlled trial in hospitalized patients with episodic overt HE compared with lactulose therapy, a single dose of polyethylene glycol (PEG) significantly improved the overall grade of HE after 24 hours, reduced days to HE resolution, and led to shorter length of hospital stay.[190] Before widespread usage, these data need to be confirmed in larger multicentre studies.

Antimicrobial agents: Rifaximin is a semi-synthetic, non-aminoglycoside which acts against gram+, gram-, aerobic and anaerobic enteric bacteria. It binds to the beta subunit of bacterial DNA-dependent RNA polymerase, inhibiting bacterial RNA synthesis. It is administered orally and is minimally absorbed (>4%), lowering the risk of bacterial resistance. Rifaximin also has negligible impact on microbial composition but supposedly has beneficial effects on functionality, reducing secondary bile acid production; its effects on bacterial translocation are controversial.[191, 192, 193] No dose adjustments are necessary in patients with liver dysfunction or renal insufficiency. The most solid evidence for the utility of rifaximin is use of the drug as an add-on to lactulose to prevent recurrence of HE.[31] Quality evidence is lacking for the use of rifaximin as a monotherapy for the treatment of episodic HE. Large-scale head-to-head comparisons of lactulose and rifaximin are not available, but in randomised controlled trials, rifaximin was as effective as non-absorbable disaccharides or other oral antibiotics in the treatment of episodic HE, but with a better safety profile.[194, 195, 196, 197, 198, 199] Treatment with rifaximin has been shown to increase the proportion of patients who recover from HE, as well as reducing mortality.[163] A combination of lactulose plus rifaximin was more effective than lactulose

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

alone for improvement of HE and reduction in mortality, which was due to a decrease in sepsis-related deaths. Patients who received lactulose plus rifaximin also had shorter hospital stays.[200] However, further trials of rifaximin plus lactulose are needed before this approach can be considered standard of care.

Probiotics: Probiotics are live bacteria which are believed to improve gut dysbiosis and negatively impact ammonia production. A Cochrane systematic review concluded that probiotic treatment may lead to improvements in the development of overt HE, quality of life, and lower plasma ammonia but with little effect on mortality. However, most clinical trials to date are of low quality and therefore the evidence remains unconvincing.[201]

Branched-chain amino acids (BCAA): A recent Cochrane systematic review indicated that BCAA therapy improved the manifestation of overt HE, while it had no effect on mortality (high quality of evidence).[202] BCAA have been documented to promote muscle protein synthesis and improve muscle mass loss, however adequately powered multicentre clinical trials with appropriate control groups (comparing with standard interventions) are still required.[202]

L-ornithine L-aspartate (LOLA): A preliminary meta-analysis of 8 randomised controlled trials comparing LOLA with placebo/no-intervention control, suggested that intravenous LOLA improved overt HE.[203] The efficacy of oral LOLA has been a subject of debate, as the AASLD-EASL clinical guidelines suggested that oral supplementation with LOLA is not effective.[1] Recent meta-analyses[204, 205, 206] suggest that LOLA has beneficial effects on HE, decompensation, and mortality, but the number of clinical trials analysed was dissimilar in the reports, with one stating that the quality of evidence was very low.[206] Thus, the potential beneficial effect of LOLA remain uncertain.

Embolisation of portosystemic shunts: In some patients with cirrhosis and HE who are difficult to treat or have recurrent episodes, particularly when the liver function is not severely compromised, the possibility of a spontaneous large portosystemic shunt should be considered. Although clinical trial data in this patient group are limited, many case reports and a large case series from Europe have suggested that embolising these shunts can alleviate HE, particularly in patients with a model for end-stage liver disease score of <11.[207] More recently, a single centre study suggested that although there was significant improvement in the severity of HE in the immediate post-embolisation period, most patients developed complications of portal hypertension or died during the following 12 months.[208] The currently available data suggest that shunt embolisation is a useful treatment modality for patients with cirrhosis and HE, but that it should be considered a bridge to transplantation in most cases.

Albumin and extracorporeal albumin dialysis (ECAD): Albumin is a multifunctional protein synthesized in the liver, the quantity and quality of which is significantly reduced in patients with cirrhosis. Until recently, albumin was thought of as a plasma volume expander. It is now clear that albumin has many additional functions including anti-inflammatory properties and the ability to bind and clear many toxic substances that accumulate during liver failure. An early uncontrolled non-randomised study suggested its potential role in the treatment of HE,[209] but this was not confirmed in a randomised controlled clinical trial. The combination of lactulose with albumin was, however, more effective than lactulose alone for the complete reversal of HE.[210] These binding properties of albumin

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

have been exploited in the ECAD. In 2 randomised, controlled clinical trials of ECAD in patients with cirrhosis and HE, ECAD was associated with significantly faster reduction in the severity of HE but no survival improvement.[179,211]

Alternative strategies: Volume expansion (administering 1 L of 0.9% saline to patients intravenously over 1 hour) has been shown to reduce plasma ammonia concentrations by increasing ammonia excretion and reducing ammoniagenesis in patients with cirrhosis.[212] In addition, the use of haemofiltration to reduce hyperammonaemia is very effective.[213] However, high-quality randomised clinical trials with standardised outcome collection and data reporting are needed to further clarify the true efficacy of these simple alternative strategies.

Management algorithm for overt hepatic encephalopathy (Fig. 5)

An episode of overt HE must be actively treated. Precipitating factors must be diligently looked for and controlled. Lactulose is the first-line therapy. Quality data is lacking for rifaximin in this setting, either as add-on or monotherapy. In patients with episodic HE and ACLF who are difficult to control, ECAD should be considered where available. Other agents such as PEG, LOLA, BCAA and albumin should be considered safe and potentially useful but cannot be recommended for routine use

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

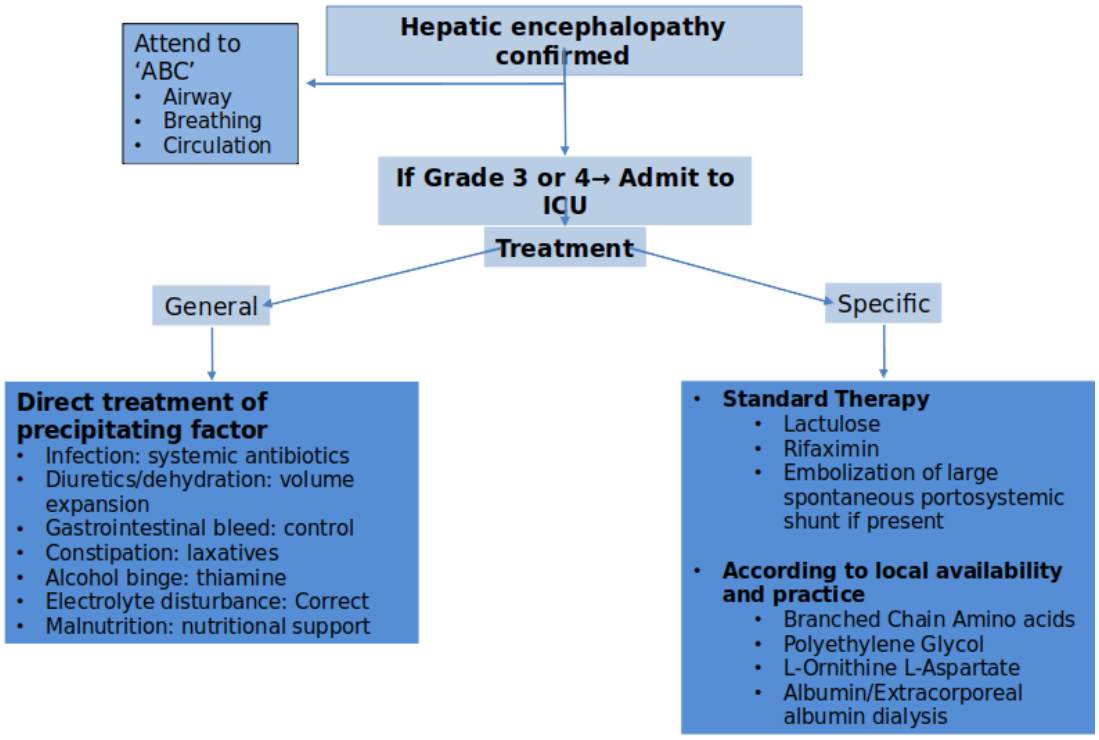

Fig. 5. Algorithm for the management of a hospitalised patient with overt hepatic encephalopathy.
Once overt hepatic encephalopathy is confirmed, attend to "ABC" management. If hepatic encephalopathy is severe, admit to ICU. Management involves identifying correcting the precipitating factor. If patient has hyperammonaemia, ammonia-lowering strategies are initiated. ICU, intensive care unit.

PREVENTION OF OVERT HEPATIC ENCEPHALOPATHY

Primary prophylaxis

Two recent clinical trials evaluated the efficacy of lactulose or VSL#3, a probiotic preparation, for primary prophylaxis of overt HE compared with no treatment in patients with cirrhosis.[214,215] Child-Pugh class B/C and presence of mHE at baseline were predictors of development of overt HE. Both trials, though from the same centre, have demonstrated that lactulose and VSL#3 are effective in preventing the first episode of overt HE. There is also evidence that lactulose treatment reverses mHE, prevents overt HE and improves health-related quality of life in patients with liver cirrhosis.[216] Therefore, although it seems logical to give primary prophylaxis with lactulose to patients with cirrhosis at high risk of overt HE, further multicentre clinical trials are needed to confirm these early clinical trial data, considering that lactulose treatment may be difficult to tolerate and is not completely without side effects.

Secondary prophylaxis

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

Patients with cirrhosis who have recovered from an episode of HE are at higher risk of developing recurrent episodes of overt HE. Lactulose is effective at preventing the subsequent episode of overt HE in patients with cirrhosis but there is no effect on hospitalisation rate or mortality.[30,217] Rifaximin as add-on to lactulose is more effective than lactulose alone in preventing a third breakthrough episode of HE and in reducing the risk of hospitalisations involving overt HE.[31] Long-term treatment with rifaximin, as add-on to lactulose, does not increase the rates of adverse events and appears to provide a continued reduction in the rate of HE-related and all-cause hospitalisation.[218] VSL#3, a probiotic preparation has also been shown to effectively prevent subsequent episodes of overt HE and reduce hospitalisations, but further appropriately powered multicentre studies are required before it can be recommended for routine use.[219] More recently, in a randomised controlled clinical trial, long-term albumin administration to patients with decompensated cirrhosis was associated with a reduction in the occurrence of most of the major complications of cirrhosis (including HE) as well as in mortality.[220]

EMERGING THERAPIES FOR HEPATIC ENCEPHALOPATHY

There are exciting, innovative, emerging therapies for HE that are currently being developed at the pre-clinical phase, as well as options currently being tested in clinical trials (Fig. 4).

CLINICAL STAGE

Ornithine phenylacetate (OP): The combination of ornithine and phenylacetate was designed to increase muscle ammonia detoxification via the stimulation of the enzyme GS. This results in the production of glutamine, which is converted to phenylacetylglutamine – to avoid glutamine metabolism – via glutaminase and ammonia regeneration.[221] In addition, it has been demonstrated that OP also chelates glycine, another ammoniagenic amino acid.[222] OP significantly lowers blood ammonia in a number of different animal models of liver disease/failure.[59,223,224] In a preliminary communication, the results of a phase 2b study were described, which showed that OP reduced ammonia concentrations in patients with overt HE in a dose-dependent manner but did not meet its primary end-point of time to improvement in HE.[225] A phase III study is being planned.

Glycerol/sodium phenylbutyrate: Sodium phenylbutyrate is a treatment of choice for patients with genetic urea cycle disorders. In a small study, it was recently demonstrated to improve neurological outcome in association with lowering blood ammonia in patients with cirrhosis treated in an intensive care unit setting.[226] Even though this study did not include a control arm, the associations between neurological improvement and change in blood ammonia are important. In a randomized, double-blind, controlled study, glycerol phenylbutyrate was demonstrated to lower ammonia and significantly reduce the proportion of patients who experienced a HE event, as well as reducing HE hospitalisations.[41] Whether glycerol phenylbutyrate will continue to develop as a treatment for HE is not clear.

Faecal microbiota transplantation: Faecal microbiota transplantation (FMT) from healthy donors has been given to patients with cirrhosis to ameliorate the gut's microbial dysbiosis. Recent secondary results from a safety protocol suggest a beneficial effect on cognition in patients with HE receiving an FMT.[227, 228, 229] These encouraging results have been associated with enrichment of supposedly

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

beneficial taxa. However, the understanding of how and why certain taxa are beneficial remains unknown.

PRE-CLINICAL STAGE

Liposome-supported peritoneal dialysis (LSPD): Dialysis fluids supplemented with micrometre-sized, transmembrane pH-gradient liposomes were developed as a detoxification strategy for the removal of small ionizable molecules such as ammonia. LSPD was able to sequester ammonia in a rat model of cirrhosis, lowering plasmatic ammonia levels and attenuating brain oedema compared to conventional peritoneal dialysis.[230]

Engineered bacteria: Genetically modified *E. coli nissle* have been programmed to metabolise ammonia. Orally administered, they have been shown to lower blood ammonia in an animal model of liver injury (thioacetamide-induced) as well as in animals with ornithine transcarbamylase-deficiency (model of urea cycle disorder).[231] However, the clinical study in patients with cirrhosis did not meet the endpoint for ammonia reduction.[232]

Activated carbon microspheres: Designed to adsorb ammonia and other organic compounds in the gut, AST-120 demonstrated promising results by lowering blood ammonia in an animal model of liver disease.[233] However, AST-120 did not meet the primary endpoint in a phase II clinical study (ASTUTE trial). This may to some extent be related to the trial design and activated carbon microspheres merit further development.

$GABA_A$ receptor-modulating steroid antagonists (GAMSA): Patients with HE have increased GABA-ergic tone, potentiated by neurosteroids which contribute to their neuroinhibition. A new drug of 3-beta-hydroxysteroid conformation is shown to effectively antagonise this mechanism and restore brain function in rats with experimental hyperammonaemia and HE and to counteract the effects of administered neurosteroids in healthy individuals.[234,235] The drug is presently under clinical investigation and has recently been identified as a therapeutic target for HE.[236]

Glutamine synthetase (GS) replacement: Glutamine is an important intermediate in ammonia metabolism, particularly when the urea cycle is dysfunctional, as it is in patients with liver disease. The main site for the localisation of GS is in the liver and muscle. In ALF and CLD models, GS has been shown to be upregulated in the muscle.[237, 238, 239] Knocking out GS selectively in the liver[240] and/or the muscle[241] resulted in hyperammonaemia. Reconstitution of GS in an animal model of hyperammonaemia was effective in reducing ammonia levels.[242] These data provided the rationale for the development of a strategy for GS enzyme induction or replacement therapy. Preliminary data from a study showed that AM-535, which is a recombinant GS, reduced ammonia effectively in an animal model of cirrhosis and urea cycle enzyme disorder.[243]

CONTROVERSIES, FUTURE RESEARCH AND CONCLUSIONS

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

Although there has been a considerable increase in our understanding of the pathophysiology of the syndrome, targeting ammonia and inflammation remains the cornerstone of treatment. The main controversies relate to classification of HE and the role of ammonia measurements in the management of patients. It is clear that the diagnosis of Grade 1 HE is difficult – whether this term should be dropped altogether is under intense discussion. Although there are arguments for ammonia measurement as an aid to patient management, doing this accurately in clinical practice remains challenging. Future research should be directed at understanding the impact of comorbidities on outcomes, testing strategies that target systemic- and neuroinflammation and providing guidance to drug developers and regulators on clear endpoints. With the improvements in MR technology, research needs to further develop MR-based methodology to personalise prophylactic and therapeutic approaches for patients with HE. Finally, the increasing understanding of the terrible quality of life endured by patients with HE and their relatives highlights the need for new tools to better monitor and manage patients in their homes. In conclusion, it is clear that HE remains one of the most important complications of cirrhosis, contributing both to the morbidity and mortality of patients with cirrhosis, while considerable advances in our understanding are now being translated into improving clinical outcomes.

FINANCIAL SUPPORT

The authors received no financial support to produce this manuscript.

AUTHORS' CONTRIBUTIONS

All authors contributed equally. However, C. Rose and R. Jalan initiated the format, edited the content and finalized the review.

CONFLICTS OF INTEREST

Christopher Rose has research collaborations with Mallinckrodt and Neuractas and is an advisor for Axcella, Horizon Therapeutics, Lupin Pharma Canada, Morphocell Technologies, Neuractas, Sana Biotechnologies and Thoeris.

Jasmohan Bajaj has research collaborations with Grifols, Valeant and Mallinckrodt.

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

Simon Taylor-Robinson has had previous research collaborations with Merz GmbH (Frankfurt, Germany) and has spoken at Merz and Norgine-sponsored symposia.

Rajiv Jalan has research collaborations with Yaqrit and Takeda. Rajiv Jalan is the inventor of OPA, which has been patented by UCL and licensed to Mallinckrodt. He is also the founder of Yaqrit Ltd, a

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

spin out company from University College London. He is also a Founder of Thoeris Ltd. Other authors have no conflicts to declare.

ACKNOWLEDGEMENTS

SDTR is supported by a United Kingdom NIHR Biomedical Facility grant at Imperial College London.

REFERENCES

[1] 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;60:715–35. https://doi.org/10.1002/hep.27210.

[2] Balzano T, Forteza J, Borreda I, Molina P, Giner J, Leone P, et al. Histological Features of Cerebellar Neuropathology in Patients With Alcoholic and Nonalcoholic Steatohepatitis. J Neuropathol Exp Neurol 2018;77:837–45. https://doi.org/10.1093/jnen/nly061.

[3] Forton DM, Allsop JM, Main J, Foster GR, Thomas HC, Taylor-Robinson SD. Evidence for a cerebral effect of the hepatitis C virus. Lancet 2001;358:38–9. https://doi.org/10.1016/S0140-6736(00)05270-3.

[4] Mosher VAL, Swain MG, Pang JXQ, Kaplan GG, Sharkey KA, MacQueen GM, et al. Magnetic resonance imaging evidence of hippocampal structural changes in patients with primary biliary cholangitis. Clin Transl Gastroenterol 2018;9:169. https://doi.org/10.1038/s41424-018-0038-z.

[5] Grover VPB, Southern L, Dyson JK, Kim JU, Crossey MME, Wylezinska-Arridge M, et al. Early primary biliary cholangitis is characterised by brain abnormalities on cerebral magnetic resonance imaging. Alimentary Pharmacology & Therapeutics 2016;44:936–45. https://doi.org/10.1111/apt.13797.

[6] Garcia-Martinez R, Rovira A, Alonso J, Jacas C, Simón-Talero M, Chavarria L, et al. Hepatic encephalopathy is associated with posttransplant cognitive function and brain volume. Liver Transpl 2011;17:38–46. https://doi.org/10.1002/lt.22197.

[7] Sotil EU, Gottstein J, Ayala E, Randolph C, Blei AT. Impact of preoperative overt hepatic encephalopathy on neurocognitive function after liver transplantation. Liver Transplant 2009;15:184–192. https://doi.org/10.1002/lt.21593.

[8] Hirode G, Vittinghoff E, Wong RJ. Increasing Burden of Hepatic Encephalopathy Among Hospitalized Adults: An Analysis of the 2010-2014 National Inpatient Sample. Dig Dis Sci 2019;64:1448–57. https://doi.org/10.1007/s10620-019-05576-9.

[9] Tapper EB, Finkelstein D, Mittleman MA, Piatkowski G, Chang M, Lai M. A Quality Improvement Initiative Reduces 30-Day Rate of Readmission for Patients With Cirrhosis. Clin Gastroenterol Hepatol 2016;14:753–9. https://doi.org/10.1016/j.cgh.2015.08.041.

[10] Cordoba J, Ventura-Cots M, Simón-Talero M, Amorós À, 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;60:275–81. https://doi.org/10.1016/j.jhep.2013.10.004.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[11] Butterworth RF. Neurotransmitter dysfunction in hepatic encephalopathy: new approaches and new findings. Metab Brain Dis 2001;16:55–65.

[12] Hadjihambi A, Harrison IF, Costas-Rodríguez M, Vanhaecke F, Arias N, Gallego-Durán R, et al. Impaired brain glymphatic flow in experimental hepatic encephalopathy. J Hepatol 2019;70:40–9. https://doi.org/10.1016/j.jhep.2018.08.021.

[13] Bjerring PN, Gluud LL, Larsen FS. Cerebral Blood Flow and Metabolism in Hepatic Encephalopathy-A Meta-Analysis. J Clin Exp Hepatol 2018;8:286–93. https://doi.org/10.1016/j.jceh.2018.06.002.

[14] Görg B, Karababa A, Häussinger D. Hepatic Encephalopathy and Astrocyte Senescence. J Clin Exp Hepatol 2018;8:294–300. https://doi.org/10.1016/j.jceh.2018.05.003.

[15] 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;65:1120–30. https://doi.org/10.1016/j.jhep.2016.07.046.

[16] Dam G, Keiding S, Munk OL, Ott P, Vilstrup H, Bak LK, et al. Hepatic encephalopathy is associated with decreased cerebral oxygen metabolism and blood flow, not increased ammonia uptake. Hepatology 2013;57:258–265. https://doi.org/10.1002/hep.25995.

[17] Lu K, Zimmermann M, Görg B, Bidmon H-J, Biermann B, Klöcker N, et al. Hepatic encephalopathy is linked to alterations of autophagic flux in astrocytes. EBioMedicine 2019. https://doi.org/10.1016/j.ebiom.2019.09.058.

[18] Tapper EB, Henderson JB, Parikh ND, Ioannou GN, Lok AS. Incidence of and Risk Factors for Hepatic Encephalopathy in a Population-Based Cohort of Americans With Cirrhosis. Hepatol Commun 2019;3:1510–9. https://doi.org/10.1002/hep4.1425.

[19] Saunders JB, Walters JR, Davies AP, Paton A. A 20-year prospective study of cirrhosis. Br Med J (Clin Res Ed) 1981;282:263–6. https://doi.org/10.1136/bmj.282.6260.263.

[20] Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology 2010;51:1675–82. https://doi.org/10.1002/hep.23500.

[21] D'amico G, Morabito A, Pagliaro L, Marubini E. Survival and prognostic indicators in compensated and decompensated cirrhosis. Digestive Diseases and Sciences 1986;31:468–75. https://doi.org/10.1007/bf01320309.

[22] Nolte W, Wiltfang J, Schindler C, Münke H, Unterberg K, Zumhasch U, et al. Portosystemic hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in patients with cirrhosis: Clinical, laboratory, psychometric, and electroencephalographic investigations. Hepatology 1998;28:1215–25. https://doi.org/10.1002/hep.510280508.

[23] Fonio P, Discalzi A, Calandri M, Doriguzzi Breatta A, Bergamasco L, Martini S, et al. Incidence of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt (TIPS) according to its severity and temporal grading classification. Radiol Med 2017;122:713–21. https://doi.org/10.1007/s11547-017-0770-6.

[24] Lauridsen MM, Jepsen P, Vilstrup H. Critical flicker frequency and continuous reaction times for the diagnosis of minimal hepatic encephalopathy: a comparative study of 154 patients with liver disease. Metab Brain Dis 2011;26:135–9. https://doi.org/10.1007/s11011-011-9242-1.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[25] Romero-Gómez M, Córdoba J, Jover R, del Olmo JA, Ramírez M, Rey R, et al. Value of the critical flicker frequency in patients with minimal hepatic encephalopathy. Hepatology 2007;45:879–85. https://doi.org/10.1002/hep.21586.

[26] Allampati S, Duarte-Rojo A, Thacker LR, Patidar KR, White MB, Klair JS, et al. Diagnosis of Minimal Hepatic Encephalopathy Using Stroop EncephalApp: A Multicenter US-Based, Norm-Based Study. Am J Gastroenterol 2016;111:78–86. https://doi.org/10.1038/ajg.2015.377.

[27] Guevara M, Baccaro ME, Torre A, Gómez-Ansón B, Ríos J, Torres F, et al. Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: a prospective study with time-dependent analysis. Am J Gastroenterol 2009;104:1382–9. https://doi.org/10.1038/ajg.2009.293.

[28] Jepsen P, Watson H, Andersen PK, Vilstrup H. Diabetes as a risk factor for hepatic encephalopathy in cirrhosis patients. J Hepatol 2015;63:1133–8. https://doi.org/10.1016/j.jhep.2015.07.007.

[29] Duarte-Rojo A, Allampati S, Thacker LR, Flud CR, Patidar KR, White MB, et al. Diagnosis of covert hepatic encephalopathy: a multi-center study testing the utility of single versus combined testing. Metab Brain Dis 2018;34:289–95. https://doi.org/10.1007/s11011-018-0350-z.

[30] 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;137:885–91, 891.e1. https://doi.org/10.1053/j.gastro.2009.05.056.

[31] Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010;362:1071–81. https://doi.org/10.1056/NEJMoa0907893.

[32] Prasad S, Dhiman RK, Duseja A, Chawla YK, Sharma A, Agarwal R. Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy. Hepatology 2007;45:549–59. https://doi.org/10.1002/hep.21533.

[33] Younossi ZM, Tampi R, Priyadarshini M, Nader F, Younossi IM, Racila A. Burden of Illness and Economic Model for Patients With Nonalcoholic Steatohepatitis in the United States. Hepatology 2019;69:564–72. https://doi.org/10.1002/hep.30254.

[34] Shaheen A-A, Nguyen HH, Congly SE, Kaplan GG, Swain MG. Nationwide estimates and risk factors of hospital readmission in patients with cirrhosis in the United States. Liver Int 2019;39:878–84. https://doi.org/10.1111/liv.14054.

[35] Roggeri A, Roggeri DP, Rossi E, Cinconze E, Gasbarrini A, Preti PM, et al. Overt hepatic encephalopathy in Italy: clinical outcomes and healthcare costs. Hepatic Medicine: Evidence and Research 2015:37. https://doi.org/10.2147/hmer.s87594.

[36] Pascoli MD, Ceranto E, Nardi PD, 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. Digestive Diseases 2017;35:433–8. https://doi.org/10.1159/000458722.

[37] 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;106:1646–53. https://doi.org/10.1038/ajg.2011.157.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[38] 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;35:716–721. https://doi.org/10.1053/jhep.2002.31250.

[39] 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;24:587–94. https://doi.org/10.1002/lt.25032.

[40] Hassanein T, Blei AT, Perry W, Hilsabeck R, Stange J, Larsen FS, et al. Performance of the hepatic encephalopathy scoring algorithm in a clinical trial of patients with cirrhosis and severe hepatic encephalopathy. Am J Gastroenterol 2009;104:1392–400. https://doi.org/10.1038/ajg.2009.160.

[41] Rockey DC, Vierling JM, Mantry P, Ghabril M, Brown RS, Alexeeva O, et al. Randomized, double-blind, controlled study of glycerol phenylbutyrate in hepatic encephalopathy. Hepatology 2014;59:1073–1083. https://doi.org/10.1002/hep.26611.

[42] Bajaj JS, Frederick RT, Bass NM, Ghabril M, Coyne K, Margolis MK, et al. Overt hepatic encephalopathy: development of a novel clinician reported outcome tool and electronic caregiver diary. Metab Brain Dis 2016;31:1081–93. https://doi.org/10.1007/s11011-016-9851-9.

[43] 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;33:739–47. https://doi.org/10.1111/j.1365-2036.2011.04590.x.

[44] 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;20:15756–62. https://doi.org/10.3748/wjg.v20.i42.15756.

[45] Thomsen KL, Macnaughtan J, Tritto G, Mookerjee RP, Jalan R. Clinical and Pathophysiological Characteristics of Cirrhotic Patients with Grade 1 and Minimal Hepatic Encephalopathy. PLOS ONE 2016;11:e0146076. https://doi.org/10.1371/journal.pone.0146076.

[46] Bajaj JS, Etemadian A, Hafeezullah M, Saeian K. Testing for minimal hepatic encephalopathy in the United States: An AASLD survey. Hepatology 2007;45:833–834. https://doi.org/10.1002/hep.21515.

[47] Montagnese S, De Rui M, Angeli P, Amodio P. Neuropsychiatric performance in patients with cirrhosis: Who is “normal”? J Hepatol 2017;66:825–35. https://doi.org/10.1016/j.jhep.2016.11.021.

[48] 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;72:573–83. https://doi.org/10.1016/S0016-5085(77)80135-2.

[49] 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;22:732–42. https://doi.org/10.1002/lt.24443.

[50] Verma A, Saraswat VA, Radha Krishna Y, Nath K, Thomas MA, Gupta RK. In vivo 1H magnetic resonance spectroscopy-derived metabolite variations between acute-on-chronic liver failure and acute liver failure. Liver Int 2008;28:1095–103. https://doi.org/10.1111/j.1478-3231.2007.01648.x.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[51] Jalan R, Stadlbauer V, Sen S, Cheshire L, Chang Y-M, Mookerjee RP. Role of predisposition, injury, response and organ failure in the prognosis of patients with acute-on-chronic liver failure: a prospective cohort study. Critical Care 2012;16:R227.

[52] Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426–37, 1437.e1-9. https://doi.org/10.1053/j.gastro.2013.02.042.

[53] Arroyo V, Moreau R, Jalan R. Acute-on-Chronic Liver Failure. New England Journal of Medicine 2020;382:2137–45. https://doi.org/10.1056/NEJMra1914900.

[54] Shah NJ, Neeb H, Kircheis G, Engels P, Häussinger D, Zilles K. Quantitative cerebral water content mapping in hepatic encephalopathy. Neuroimage 2008;41:706–717. https://doi.org/10.1016/j.neuroimage.2008.02.057.

[55] Chavarria L, Alonso J, García-Martínez R, Simón-Talero M, Ventura-Cots M, Ramírez C, et al. Brain magnetic resonance spectroscopy in episodic hepatic encephalopathy. J Cereb Blood Flow Metab 2013;33:272–277. https://doi.org/10.1038/jcbfm.2012.173.

[56] Poveda M-J, Bernabeu A, Concepción L, Roa E, de Madaria E, Zapater P, et al. Brain edema dynamics in patients with overt hepatic encephalopathy A magnetic resonance imaging study. NeuroImage 2010;52:481–7. https://doi.org/10.1016/j.neuroimage.2010.04.260.

[57] Winterdahl M, Abbas Z, Noer O, Thomsen KL, Gras V, Nahimi A, et al. Cerebral water content mapping in cirrhosis patients with and without manifest HE. Metab Brain Dis 2019. https://doi.org/10.1007/s11011-019-00427-y.

[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;34:362–6. https://doi.org/10.1111/liv.12257.

[59] Wright G, Vairappan B, Stadlbauer V, Mookerjee RP, Davies NA, Jalan R. Reduction in hyperammonaemia by ornithine phenylacetate prevents lipopolysaccharide-induced brain edema and coma in cirrhotic rats. Liver Int 2012;32:410–9. https://doi.org/10.1111/j.1478-3231.2011.02698.x.

[60] 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;45:1517–26. https://doi.org/10.1002/hep.21599.

[61] Balasubramaniyan V, Wright G, Sharma V, Davies N a, Sharifi Y, Habtesion A, et al. Ammonia reduction with ornithine phenylacetate restores brain eNOS activity via the DDAH-ADMA pathway in bile duct-ligated cirrhotic rats. Am J Physiol Gastrointest Liver Physiol 2012;302:G145–52. https://doi.org/10.1152/ajpgi.00097.2011.

[62] O'Leary JG, Reddy KR, Garcia-Tsao G, Biggins SW, Wong F, Fallon MB, et al. NACSELD acute-on-chronic liver failure (NACSELD-ACLF) score predicts 30-day survival in hospitalized patients with cirrhosis. Hepatology 2018;67:2367–74. https://doi.org/10.1002/hep.29773.

[63] Kril JJ, Butterworth RF. Diencephalic and cerebellar pathology in alcoholic and nonalcoholic patients with end-stage liver disease. Hepatology 1997;26:837–41. https://doi.org/10.1002/hep.510260405.

[64] Weissenborn K. Minimal/Covert Hepatic Encephalopathy - Impact of Comorbid Conditions. J Clin Exp Hepatol 2019;9:109–11. https://doi.org/10.1016/j.jceh.2018.08.010.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[65] Kamijo K, Pontifex MB, Khan NA, Raine LB, Scudder MR, Drollette ES, et al. The negative association of childhood obesity to cognitive control of action monitoring. Cereb Cortex 2014;24:654–62. https://doi.org/10.1093/cercor/bhs349.

[66] Reinert KRS, Po'e EK, Barkin SL. The relationship between executive function and obesity in children and adolescents: a systematic literature review. J Obes 2013;2013:820956. https://doi.org/10.1155/2013/820956.

[67] Weinstein G, Zelber-Sagi S, Preis SR, Beiser AS, DeCarli C, Speliotes EK, et al. Association of Nonalcoholic Fatty Liver Disease With Lower Brain Volume in Healthy Middle-aged Adults in the Framingham Study. JAMA Neurol 2018;75:97–104. https://doi.org/10.1001/jamaneurol.2017.3229.

[68] Filipović B, Marković O, Đurić V, Filipović B. Cognitive Changes and Brain Volume Reduction in Patients with Nonalcoholic Fatty Liver Disease. Can J Gastroenterol Hepatol 2018;2018:9638797. https://doi.org/10.1155/2018/9638797.

[69] VanWagner LB, Terry JG, Chow LS, Alman AC, Kang H, Ingram KH, et al. Nonalcoholic fatty liver disease and measures of early brain health in middle-aged adults: The CARDIA study. Obesity (Silver Spring) 2017;25:642–51. https://doi.org/10.1002/oby.21767.

[70] De Chiara F, Heebøll S, Marrone G, Montoliu C, Hamilton-Dutoit S, Ferrandez A, et al. Urea cycle dysregulation in non-alcoholic fatty liver disease. J Hepatol 2018;69:905–15. https://doi.org/10.1016/j.jhep.2018.06.023.

[71] Seo SW, Gottesman RF, Clark JM, Hernaez R, Chang Y, Kim C, et al. Nonalcoholic fatty liver disease is associated with cognitive function in adults. Neurology 2016;86:1136–42. https://doi.org/10.1212/WNL.0000000000002498.

[72] Weinstein G, Davis-Plourde K, Himali JJ, Zelber-Sagi S, Beiser AS, Seshadri S. Non-alcoholic fatty liver disease, liver fibrosis score and cognitive function in middle-aged adults: The Framingham Study. Liver Int 2019;39:1713–21. https://doi.org/10.1111/liv.14161.

[73] Grover VPB, Pavese N, Koh S-B, Wylezinska M, Saxby BK, Gerhard A, et al. Cerebral microglial activation in patients with hepatitis C: in vivo evidence of neuroinflammation. J Viral Hepat 2012;19:e89-96. https://doi.org/10.1111/j.1365-2893.2011.01510.x.

[74] Kalaitzakis E, Olsson R, Henfridsson P, Hugosson I, Bengtsson M, Jalan R, et al. Malnutrition and diabetes mellitus are related to hepatic encephalopathy in patients with liver cirrhosis. Liver Int 2007;27:1194–201. https://doi.org/10.1111/j.1478-3231.2007.01562.x.

[75] Jalan R, Elton RA, Redhead DN, Finlayson ND, Hayes PC. Analysis of prognostic variables in the prediction of mortality, shunt failure, variceal rebleeding and encephalopathy following the transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage. J Hepatol 1995;23:123–8.

[76] Bajaj JS, Thacker LR, Heuman DM, Sterling RK, Stravitz RT, Sanyal AJ, et al. Cognitive performance as a predictor of hepatic encephalopathy in pretransplant patients with cirrhosis receiving psychoactive medications: A prospective study. Liver Transpl 2012;18:1179–1187. https://doi.org/10.1002/lt.23484.

[77] Bajaj JS, O'Leary JG, Tandon P, Wong F, Kamath PS, Biggins SW, et al. Targets to improve quality of care for patients with hepatic encephalopathy: data from a multi-centre cohort. Aliment Pharmacol Ther 2019. https://doi.org/10.1111/apt.15265.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[78] Tapper EB, Parikh ND, Sengupta N, Mellinger J, Ratz D, Lok AS-F, et al. A risk score to predict the development of hepatic encephalopathy in a population-based cohort of patients with cirrhosis. Hepatology 2018;68:1498–507. https://doi.org/10.1002/hep.29628.

[79] Grønbæk L, Watson H, Vilstrup H, Jepsen P. Benzodiazepines and risk for hepatic encephalopathy in patients with cirrhosis and ascites. United European Gastroenterol J 2018;6:407–12. https://doi.org/10.1177/2050640617727179.

[80] Görg B, Karababa A, Shafigullina A, Bidmon HJ, Häussinger D. Ammonia-induced senescence in cultured rat astrocytes and in human cerebral cortex in hepatic encephalopathy. Glia 2015;63:37–50. https://doi.org/10.1002/glia.22731.

[81] Keiding S, Sørensen M, Bender D, Munk OL, Ott P, Vilstrup H. Brain metabolism of 13N-ammonia during acute hepatic encephalopathy in cirrhosis measured by positron emission tomography. Hepatology 2006;43:42–50. https://doi.org/10.1002/hep.21001.

[82] Wright G, Noiret L, Damink SWMO, Jalan R. Interorgan ammonia metabolism in liver failure: the basis of current and future therapies. Liver Int 2011;31:163–75. https://doi.org/10.1111/j.1478-3231.2010.02302.x.

[83] Bosoi CR, Rose CF. Identifying the direct effects of ammonia on the brain. Metab Brain Dis 2009;24:95–102. https://doi.org/10.1007/s11011-008-9112-7.

[84] Dasarathy S, Mookerjee RP, Rackayova V, Rangroo Thrane V, Vairappan B, Ott P, et al. Ammonia toxicity: from head to toe? Metab Brain Dis 2017;32:529–38. https://doi.org/10.1007/s11011-016-9938-3.

[85] Davuluri G, Allawy A, Thapaliya S, Rennison JH, Singh D, Kumar A, et al. Hyperammonaemia-induced skeletal muscle mitochondrial dysfunction results in cataplerosis and oxidative stress. J Physiol (Lond) 2016;594:7341–60. https://doi.org/10.1113/JP272796.

[86] Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol 2014;60:1310–24. https://doi.org/10.1016/j.jhep.2014.01.024.

[87] Dröge W. Free radicals in the physiological control of cell function. Physiol Rev 2002;82:47–95. https://doi.org/10.1152/physrev.00018.2001.

[88] Görg B, Qvartskhava N, Bidmon H-J, Palomero-Gallagher N, Kircheis G, Zilles K, et al. Oxidative stress markers in the brain of patients with cirrhosis and hepatic encephalopathy. Hepatology 2010;52:256–265. https://doi.org/10.1002/hep.23656.

[89] Bosoi CR, Yang X, Huynh J, Parent-Robitaille C, Jiang W, Tremblay M, et al. Systemic oxidative stress is implicated in the pathogenesis of brain edema in rats with chronic liver failure. Free Radic Biol Med 2012;52:1228–35. https://doi.org/10.1016/j.freeradbiomed.2012.01.006.

[90] Shawcross DL, Davies NA, Williams R, Jalan R. Systemic inflammatory response exacerbates the neuropsychological effects of induced hyperammonemia in cirrhosis. J Hepatol 2004;40:247–54. https://doi.org/10.1016/j.jhep.2003.10.016.

[91] Shawcross DL, Sharifi Y, Canavan JB, Yeoman AD, Abeles RD, Taylor NJ, et al. Infection and systemic inflammation, not ammonia, are associated with Grade 3/4 hepatic encephalopathy, but not mortality in cirrhosis. J Hepatol 2011;54:640–649.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[92] Montoliu C, Cauli O, Urios A, ElMlili N, Serra MA, Giner-Duran R, et al. 3-Nitro-Tyrosine as a Peripheral Biomarker of Minimal Hepatic Encephalopathy in Patients With Liver Cirrhosis. Am J Gastroenterol 2011;106:1629–37. https://doi.org/10.1038/ajg.2011.123.

[93] Bosoi CR, Tremblay M, Rose CF. Induction of systemic oxidative stress leads to brain oedema in portacaval shunted rats. Liver Int 2014;34:1322–9. https://doi.org/10.1111/liv.12414.

[94] Tripodi V, Contin M, Fernández MA, Lemberg A. Bile acids content in brain of common duct ligated rats . Annals of Hepatology : Official Journal of the Mexican Association of Hepatology 2012;11:930–934.

[95] McMillin M, Frampton G, Grant S, Khan S, Diocares J, Petrescu A, et al. Bile Acid-Mediated Sphingosine-1-Phosphate Receptor 2 Signaling Promotes Neuroinflammation during Hepatic Encephalopathy in Mice. Front Cell Neurosci 2017;11:191. https://doi.org/10.3389/fncel.2017.00191.

[96] 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;117:640–644. https://doi.org/10.1016/S0016-5085(99)70457-9.

[97] Rovira A, Alonso J, Córdoba J. MR imaging findings in hepatic encephalopathy. AJNR Am J Neuroradiol 2008;29:1612–21. https://doi.org/10.3174/ajnr.A1139.

[98] Bossen L, Ginès P, Vilstrup H, Watson H, Jepsen P. Serum sodium as a risk factor for hepatic encephalopathy in patients with cirrhosis and ascites. J Gastroenterol Hepatol 2019;34:914–20. https://doi.org/10.1111/jgh.14558.

[99] Watson H, Guevara M, Vilstrup H, Ginès P. Improvement of hyponatremia in cirrhosis is associated with improved complex information processing. J Gastroenterol Hepatol 2019;34:1999–2003. https://doi.org/10.1111/jgh.14683.

[100] Watson H, Jepsen P, Wong F, Ginès P, Córdoba J, Vilstrup H. Satavaptan treatment for ascites in patients with cirrhosis: a meta-analysis of effect on hepatic encephalopathy development. Metab Brain Dis 2013;28:301–5. https://doi.org/10.1007/s11011-013-9384-4.

[101] Ahluwalia V, Heuman DM, Feldman G, Wade JB, Thacker LR, Gavis E, et al. Correction of hyponatraemia improves cognition, quality of life, and brain oedema in cirrhosis. J Hepatol 2015;62:75–82. https://doi.org/10.1016/j.jhep.2014.07.033.

[102] Butterworth RF. Neurosteroids in hepatic encephalopathy: Novel insights and new therapeutic opportunities. J Steroid Biochem Mol Biol 2016;160:94–7. https://doi.org/10.1016/j.jsbmb.2015.11.006.

[103] Dabrowska K, Skowronska K, Popek M, Obara-Michlewska M, Albrecht J, Zielinska M. Roles of Glutamate and Glutamine Transport in Ammonia Neurotoxicity: State of the Art and Question Marks. Endocr Metab Immune Disord Drug Targets 2018;18:306–15. https://doi.org/10.2174/1871520618666171219124427.

[104] Bosoi CR, Zwingmann C, Marin H, Parent-Robitaille C, Huynh J, Tremblay M, et al. Increased brain lactate is central to the development of brain edema in rats with chronic liver disease. J Hepatol 2014;60:554–60. https://doi.org/10.1016/j.jhep.2013.10.011.

[105] Llansola M, Montoliu C, Agusti A, Hernandez-Rabaza V, Cabrera-Pastor A, Gomez-Gimenez B, et al. Interplay between glutamatergic and GABAergic neurotransmission alterations in cognitive and motor impairment in minimal hepatic encephalopathy. Neurochem Int 2015;88:15–9. https://doi.org/10.1016/j.neuint.2014.10.011.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[106] Iversen P, Mouridsen K, Hansen MB, Jensen SB, Sørensen M, Bak LK, et al. Oxidative metabolism of astrocytes is not reduced in hepatic encephalopathy: a PET study with [(11)C]acetate in humans. Front Neurosci 2014;8:353. https://doi.org/10.3389/fnins.2014.00353.

[107] Hadjihambi A, Rose CF, Jalan R. Novel insights into ammonia-mediated neurotoxicity pointing to potential new therapeutic strategies. Hepatology 2014;60:1101–3. https://doi.org/10.1002/hep.27282.

[108] Aceto P, Perilli V, Lai C, Ciocchetti P, Vitale F, Sollazzi L. Postoperative cognitive dysfunction after liver transplantation. Gen Hosp Psychiatry 2015;37:109–15. https://doi.org/10.1016/j.genhosppsych.2014.12.001.

[109] Campagna F, Montagnese S, Schiff S, Biancardi A, Mapelli D, Angeli P, et al. Cognitive impairment and electroencephalographic alterations before and after liver transplantation: What is reversible? Liver Transpl 2014;20:977–86. https://doi.org/10.1002/lt.23909.

[110] Atluri DK, Asgeri M, Mullen KD. Reversibility of hepatic encephalopathy after liver transplantation. Metab Brain Dis 2010;25:111–3. https://doi.org/10.1007/s11011-010-9178-x.

[111] Amodio P, Biancardi A, Montagnese S, Angeli P, Iannizzi P, Cillo U, et al. Neurological complications after orthotopic liver transplantation. Dig Liver Dis 2007;39:740–7. https://doi.org/10.1016/j.dld.2007.05.004.

[112] Guarino M, Benito-Leon J, Decruyenaere J, Schmutzhard E, Weissenborn K, Stracciari A. EFNS guidelines on management of neurological problems in liver transplantation. Eur J Neurol 2006;13:2–9. https://doi.org/10.1111/j.1468-1331.2006.01353.x.

[113] Bajaj JS, Schubert CM, Heuman DM, Wade JB, Gibson DP, Topaz A, et al. Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. Gastroenterology 2010;138:2332–40. https://doi.org/10.1053/j.gastro.2010.02.015.

[114] Riggio O, Ridola L, Pasquale C, Nardelli S, Pentassuglio I, Moscucci F, et al. Evidence of persistent cognitive impairment after resolution of overt hepatic encephalopathy. Clin Gastroenterol Hepatol 2011;9:181–183. https://doi.org/10.1016/j.cgh.2010.10.002.

[115] Rai R, Ahuja CK, Agrawal S, Kalra N, Duseja A, Khandelwal N, et al. Reversal of Low-Grade Cerebral Edema After Lactulose/Rifaximin Therapy in Patients with Cirrhosis and Minimal Hepatic Encephalopathy. Clin Trans Gastroenterol 2015;6:e111. https://doi.org/10.1038/ctg.2015.38.

[116] García-Lezana T, Oria M, Romero-Giménez J, Bové J, Vila M, Genescà J, et al. Cerebellar neurodegeneration in a new rat model of episodic hepatic encephalopathy. J Cereb Blood Flow Metab 2017;37:927–37. https://doi.org/10.1177/0271678X16649196.

[117] Davis B, Bajaj J. The Human Gut Microbiome in Liver Diseases. Seminars in Liver Disease 2017;37:128–40. https://doi.org/10.1055/s-0037-1602763.

[118] Dinan TG, Cryan JF. The Microbiome-Gut-Brain Axis in Health and Disease. Gastroenterology Clinics of North America 2017;46:77–89. https://doi.org/10.1016/j.gtc.2016.09.007.

[119] Peterson J, Garges S, Giovanni M, McInnes P, Wang L, Schloss JA, et al. The NIH Human Microbiome Project. Genome Research 2009;19:2317–23. https://doi.org/10.1101/gr.096651.109.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[120] Nava GM, Stappenbeck TS. Diversity of the autochthonous colonic microbiota. Gut Microbes 2011;2:99–104. https://doi.org/10.4161/gmic.2.2.15416.

[121] Tranah TH, Vijay GKM, Ryan JM, Shawcross DL. Systemic inflammation and ammonia in hepatic encephalopathy. Metab Brain Dis 2013;28:1–5. https://doi.org/10.1007/s11011-012-9370-2.

[122] Chen Y, Yang F, Lu H, Wang B, Chen Y, Lei D, et al. Characterization of fecal microbial communities in patients with liver cirrhosis. Hepatology 2011;54:562–72. https://doi.org/10.1002/hep.24423.

[123] Qin N, Yang F, Li A, Prifti E, Chen Y, Shao L, et al. Alterations of the human gut microbiome in liver cirrhosis. Nature 2014;513:59–64. https://doi.org/10.1038/nature13568.

[124] Bajaj JS, Heuman DM, Hylemon PB, Sanyal AJ, White MB, Monteith P, et al. Altered profile of human gut microbiome is associated with cirrhosis and its complications. J Hepatol 2014;60:940–7. https://doi.org/10.1016/j.jhep.2013.12.019.

[125] Chen Y, Ji F, Guo J, Shi D, Fang D, Li L. Dysbiosis of small intestinal microbiota in liver cirrhosis and its association with etiology. Scientific Reports 2016;6. https://doi.org/10.1038/srep34055.

[126] Bajaj JS, Betrapally NS, Hylemon PB, Heuman DM, Daita K, White MB, et al. Salivary microbiota reflects changes in gut microbiota in cirrhosis with hepatic encephalopathy. Hepatology 2015;62:1260–71. https://doi.org/10.1002/hep.27819.

[127] Santiago A, Pozuelo M, Poca M, Gely C, Nieto JC, Torras X, et al. Alteration of the serum microbiome composition in cirrhotic patients with ascites. Scientific Reports 2016;6. https://doi.org/10.1038/srep25001.

[128] Jensen A, Ladegaard Grønkjær L, Holmstrup P, Vilstrup H, Kilian M. Unique subgingival microbiota associated with periodontitis in cirrhosis patients. Sci Rep 2018;8:10718. https://doi.org/10.1038/s41598-018-28905-w.

[129] Kakiyama G, Pandak WM, Gillevet PM, Hylemon PB, Heuman DM, Daita K, et al. Modulation of the fecal bile acid profile by gut microbiota in cirrhosis. Journal of Hepatology 2013;58:949–55. https://doi.org/10.1016/j.jhep.2013.01.003.

[130] Chen Y, Guo J, Qian G, Fang D, Shi D, Guo L, et al. Gut dysbiosis in acute-on-chronic liver failure and its predictive value for mortality. Journal of Gastroenterology and Hepatology 2015;30:1429–37. https://doi.org/10.1111/jgh.12932.

[131] Bajaj JS, Betrapally NS, Hylemon PB, Thacker LR, Daita K, Kang DJ, et al. Gut Microbiota Alterations can predict Hospitalizations in Cirrhosis Independent of Diabetes Mellitus. Sci Rep 2015;5:18559. https://doi.org/10.1038/srep18559.

[132] Bajaj JS, Liu EJ, Kheradman R, Fagan A, Heuman DM, White M, et al. Fungal dysbiosis in cirrhosis. Gut 2017;67:1146–54. https://doi.org/10.1136/gutjnl-2016-313170.

[133] 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;58:325–336. https://doi.org/10.1002/hep.26370.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[134] Plank LD, Gane EJ, Peng S, Muthu C, Mathur S, Gillanders L, et al. Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: A randomized 12-month trial. Hepatology 2008;48:557–566. https://doi.org/10.1002/hep.22367.

[135] Córdoba J, López-Hellín J, Planas M, Sabín P, Sanpedro F, Castro F, et al. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. J Hepatol 2004;41:38–43. https://doi.org/10.1016/j.jhep.2004.03.023.

[136] Tandon P, Ney M, Irwin I, Ma MM, Gramlich L, Bain VG, et al. Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. Liver Transpl 2012;18:1209–16. https://doi.org/10.1002/lt.23495.

[137] Andersen H, Borre M, Jakobsen J, Andersen PH, Vilstrup H. Decreased muscle strength in patients with alcoholic liver cirrhosis in relation to nutritional status, alcohol abstinence, liver function, and neuropathy. Hepatology 1998;27:1200–6. https://doi.org/10.1002/hep.510270503.

[138] Montano-Loza AJ, Meza-Junco J, Prado CMM, Lieffers JR, Baracos VE, Bain VG, et al. Muscle wasting is associated with mortality in patients with cirrhosis. Clin Gastroenterol Hepatol 2012;10:166–73. https://doi.org/10.1016/j.cgh.2011.08.028.

[139] 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;15:934–6. https://doi.org/10.1016/j.cgh.2016.10.028.

[140] Gioia S, Merli M, Nardelli S, Lattanzi B, Pitocchi F, Ridola L, et al. The modification of quantity and quality of muscle mass improves the cognitive impairment after TIPS. Liver Int 2019;39:871–7. https://doi.org/10.1111/liv.14050.

[141] Bhanji RA, Moctezuma-Velazquez C, Duarte-Rojo A, Ebadi M, Ghosh S, Rose C, et al. Myosteatosis and sarcopenia are associated with hepatic encephalopathy in patients with cirrhosis. Hepatol Int 2018;12:377–86. https://doi.org/10.1007/s12072-018-9875-9.

[142] Hanai T, Shiraki M, Watanabe S, Kochi T, Imai K, Suetsugu A, et al. Sarcopenia predicts minimal hepatic encephalopathy in patients with liver cirrhosis. Hepatol Res 2017;47:1359–67. https://doi.org/10.1111/hepr.12873.

[143] 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;28:281–284. https://doi.org/10.1007/s11011-012-9365-z.

[144] Kumar A, Davuluri G, Silva RNE, Engelen MPKJ, Ten Have GAM, Prayson R, et al. Ammonia lowering reverses sarcopenia of cirrhosis by restoring skeletal muscle proteostasis. Hepatology 2017;65:2045–58. https://doi.org/10.1002/hep.29107.

[145] Fozouni L, Wang CW, Lai JC. Sex Differences in the Association Between Frailty and Sarcopenia in Patients With Cirrhosis. Clin Transl Gastroenterol 2019;10:e00102. https://doi.org/10.14309/ctg.0000000000000102.

[146] Haugen CE, McAdams-DeMarco M, Holscher CM, Ying H, Gurakar AO, Garonzik-Wang J, et al. Multicenter Study of Age, Frailty, and Waitlist Mortality Among Liver Transplant Candidates. Ann Surg 2019. https://doi.org/10.1097/SLA.0000000000003207.

[147] Stracciari A, Guarino M. Neuropsychiatric complications of liver transplantation. Metab Brain Dis 2001;16:3–11.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[148] Weiss N, Thabut D. Neurological Complications Occurring After Liver Transplantation: Role of Risk Factors, Hepatic Encephalopathy, and Acute (on Chronic) Brain Injury. Liver Transpl 2019;25:469–87. https://doi.org/10.1002/lt.25420.

[149] Lué A, Martinez E, Navarro M, Laredo V, Lorente S, Araiz JJ, et al. Donor age predicts calcineurin inhibitor induced neurotoxicity after liver transplantation. Transplantation 2019. https://doi.org/10.1097/TP.0000000000002750.

[150] Hopp A-E, Dirks M, Petrusch C, Goldbecker A, Tryc AB, Barg-Hock H, et al. Hepatic Encephalopathy Is Reversible in the Long Term After Liver Transplantation. Liver Transpl 2019;25:1661–72. https://doi.org/10.1002/lt.25626.

[151] Grover V-PB, Dresner M-A, Forton D-M, Counsell S, Larkman D-J, Patel N, et al. Current and future applications of magnetic resonance imaging and spectroscopy of the brain in hepatic encephalopathy. World J Gastroenterol 2006;12:2969–78.

[152] Baker L, Lanz B, Andreola F, Ampuero J, Wijeyesekera A, Holmes E, et al. New technologies – new insights into the pathogenesis of hepatic encephalopathy. Metab Brain Dis 2016;31:1259–67. https://doi.org/10.1007/s11011-016-9906-y.

[153] Patel N, White S, Dhanjal NS, Oatridge A, Taylor-Robinson SD. Changes in Brain Size in Hepatic Encephalopathy: A Coregistered MRI Study. Metab Brain Dis 2004;19:431–45. https://doi.org/10.1023/b:mebr.0000043987.09022.e3.

[154] Taylor-Robinson SD, Oatridge A, Hajnal JV, Burroughs AK, McIntyre N, deSouza NM. MR imaging of the basal ganglia in chronic liver disease: correlation of T1-weighted and magnetisation transfer contrast measurements with liver dysfunction and neuropsychiatric status. Metab Brain Dis 1995;10:175–88. https://doi.org/10.1007/bf01991864.

[155] Miese F, Kircheis G, Wittsack HJ, Wenserski F, Hemker J, Mödder U, et al. 1H-MR spectroscopy, magnetization transfer, and diffusion-weighted imaging in alcoholic and nonalcoholic patients with cirrhosis with hepatic encephalopathy. AJNR Am J Neuroradiol 2006;27:1019–26.

[156] McPhail MJW, Leech R, Grover VPB, Fitzpatrick JA, Dhanjal NS, Crossey MME, et al. Modulation of neural activation following treatment of hepatic encephalopathy. Neurology 2013;80:1041–7. https://doi.org/10.1212/wnl.0b013e31828726e1.

[157] Haseler LJ, Sibbitt WL, Mojtahedzadeh HN, Reddy S, Agarwal VP, McCarthy DM. Proton MR spectroscopic measurement of neurometabolites in hepatic encephalopathy during oral lactulose therapy. AJNR American Journal of Neuroradiology 1998;19:1681–1686.

[158] Taylor-Robinson SD, Sargentoni J, Mallalieu RJ, Bell JD, Bryant DJ, Coutts GA, et al. Cerebral phosphorus-31 magnetic resonance spectroscopy in patients with chronic hepatic encephalopathy. Hepatology 1994;20:1173–8.

[159] Bémeur C, Cudalbu C, Dam G, Thrane AS, Cooper AJL, Rose CF. Brain edema: a valid endpoint for measuring hepatic encephalopathy? Metab Brain Dis 2016;31:1249–58. https://doi.org/10.1007/s11011-016-9843-9.

[160] Chavarria L, Cordoba J. Magnetic resonance imaging and spectroscopy in hepatic encephalopathy. J Clin Exp Hepatol 2015;5:S69–74. https://doi.org/10.1016/j.jceh.2013.10.001.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[161] Jackson CD, Gram M, Halliday E, Olesen SS, Sandberg TH, Drewes AM, et al. New spectral thresholds improve the utility of the electroencephalogram for the diagnosis of hepatic encephalopathy. Clinical Neurophysiology 2016;127:2933–41. https://doi.org/10.1016/j.clinph.2016.03.027.

[162] Jalan R, Turjanski N, Taylor-Robinson SD, Koepp MJ, Richardson MP, Wilson JA, et al. Increased availability of central benzodiazepine receptors in patients with chronic hepatic encephalopathy and alcohol related cirrhosis. Gut 2000;46:546–52. https://doi.org/10.1136/gut.46.4.546.

[163] Kimer N, Krag A, Møller S, Bendtsen F, Gluud LL. Systematic review with meta-analysis: the effects of rifaximin in hepatic encephalopathy. Aliment Pharmacol Ther 2014;40:123–32. https://doi.org/10.1111/apt.12803.

[164] Berding G, Banati RB, Buchert R, Chierichetti F, Grover VPB, Kato A, et al. Radiotracer imaging studies in hepatic encephalopathy: ISHEN practice guidelines. Liver International 2009;29:621–8. https://doi.org/10.1111/j.1478-3231.2009.02008.x.

[165] Ventura-Cots M, Carmona I, Moreno C, Ampuero J, Simón-Talero M, Sanpedro F, et al. Duration of the acute hepatic encephalopathy episode determines survival in cirrhotic patients. Therap Adv Gastroenterol 2018;11:1756283X17743419. https://doi.org/10.1177/1756283X17743419.

[166] Drolz A, Jäger B, Wewalka M, Saxa R, Horvatits T, Roedl K, et al. Clinical impact of arterial ammonia levels in ICU patients with different liver diseases. Intensive Care Med 2013;39:1227–37. https://doi.org/10.1007/s00134-013-2926-8.

[167] 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;29:648–653. https://doi.org/10.1002/hep.510290309.

[168] Bhatia V, Singh R, Acharya SK. Predictive value of arterial ammonia for complications and outcome in acute liver failure. Gut 2006;55:98–104. https://doi.org/10.1136/gut.2004.061754.

[169] Bernal W, Hall C, Karvellas CJ, Auzinger G, Sizer E, Wendon J. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. Hepatology 2007;46:1844–52. https://doi.org/10.1002/hep.21838.

[170] Ong JP, Aggarwal A, Krieger D, Easley KA, Karafa MT, Lente FV, et al. Correlation between ammonia levels and the severity of hepatic encephalopathy. Am J Med 2003;114:188–193. https://doi.org/10.1016/S0002-9343(02)01477-8.

[171] Kumar R, Shalimar, Sharma H, Prakash S, Panda SK, Khanal S, et al. Persistent hyperammonemia is associated with complications and poor outcomes in patients with acute liver failure. Clin Gastroenterol Hepatol 2012;10:925–931. https://doi.org/10.1016/j.cgh.2012.04.011.

[172] Nicolao F, Efrati C, Masini A, Merli M, Attili AF, Riggio O. Role of determination of partial pressure of ammonia in cirrhotic patients with and without hepatic encephalopathy. J Hepatol 2003;38:441–6. https://doi.org/10.1016/S0168-8278(02)00436-1.

[173] Patwardhan VR, Jiang ZG, Risech-Neiman Y, Piatkowski G, Afdhal NH, Mukamal K, et al. Serum Ammonia in Associated With Transplant-free Survival in Hospitalized Patients With Acutely Decompensated Cirrhosis. J Clin Gastroenterol 2016;50:345–50. https://doi.org/10.1097/MCG.0000000000000443.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[174] Shalimar, Sheikh MF, Mookerjee RP, Agarwal B, Acharya SK, Jalan R. Prognostic Role of Ammonia in Patients With Cirrhosis. Hepatology 2019;70:982–94. https://doi.org/10.1002/hep.30534.

[175] Vierling JM, Mokhtarani M, Brown RS, Mantry P, Rockey DC, Ghabril M, et al. Fasting Blood Ammonia Predicts Risk and Frequency of Hepatic Encephalopathy Episodes in Patients With Cirrhosis. Clin Gastroenterol Hepatol 2016;14:903-906.e1. https://doi.org/10.1016/j.cgh.2015.11.018.

[176] Zacharias HD, Zacharias AP, Gluud LL, Morgan MY. Pharmacotherapies that specifically target ammonia for the prevention and treatment of hepatic encephalopathy in adults with cirrhosis. Cochrane Database Syst Rev 2019;6:CD012334. https://doi.org/10.1002/14651858.CD012334.pub2.

[177] Ampuero J, Gil A, Viloria MDM, Rico MC, Millán R, Camacho I, et al. Oral glutamine challenge is a marker of altered ammonia metabolism and predicts the risk of hepatic encephalopathy. Liver Int 2019. https://doi.org/10.1111/liv.14297.

[178] 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:CD003044. https://doi.org/10.1002/14651858.CD003044.pub4.

[179] Hassanein TI, Tofteng F, Brown RS, McGuire B, Lynch P, Mehta R, et al. Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. Hepatology 2007;46:1853–62. https://doi.org/10.1002/hep.21930.

[180] Bajaj JS, Bloom PP, Chung RT, Hassanein TI, Padilla-Martinez M, Kayali Z, et al. Variability and Lability of Ammonia Levels in Healthy Volunteers and Patients With Cirrhosis: Implications for Trial Design and Clinical Practice. Am J Gastroenterol 2019. https://doi.org/10.14309/ajg.0000000000000384.

[181] Hashim IA, Cuthbert JA. Elevated ammonia concentrations: Potential for pre-analytical and analytical contributing factors. Clin Biochem 2014;47:233–6. https://doi.org/10.1016/j.clinbiochem.2014.08.013.

[182] Rahimi RS, Safadi R, Thabut D, Bajaj JS, Bhamidimarri KR, Pyrsopoulos NT, et al. STOP-HE: A Randomized, Double-blind, Placebo-controlled Study of OCR-002 in Patients with Hepatic Encephalopathy. Hepatology 2017;66:276A-276A.

[183] Ditisheim S, Giostra E, Burkhard PR, Goossens N, Mentha G, Hadengue A, et al. A capillary blood ammonia bedside test following glutamine load to improve the diagnosis of hepatic encephalopathy in cirrhosis. BMC Gastroenterol 2011;11:134. https://doi.org/10.1186/1471-230X-11-134.

[184] Mani AR, Montagnese S, Jackson CD, Jenkins CW, Head IM, Stephens RC, et al. Decreased heart rate variability in patients with cirrhosis relates to the presence and degree of hepatic encephalopathy. Am J Physiol Gastrointest Liver Physiol 2009;296:G330-338. https://doi.org/10.1152/ajpgi.90488.2008.

[185] Jansen C, Chatterjee DA, Thomsen KL, Al- Kassou B, Sawhney R, Jones H, et al. Significant reduction in heart rate variability is a feature of acute decompensation of cirrhosis and predicts 90-day mortality. Alimentary Pharmacology & Therapeutics 2019;50:568–79. https://doi.org/10.1111/apt.15365.

[186] Campagna F, Montagnese S, Ridola L, Senzolo M, Schiff S, Rui MD, et al. The animal naming test: An easy tool for the assessment of hepatic encephalopathy. Hepatology 2017;66:198–208. https://doi.org/10.1002/hep.29146.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[187] Neumann T, Baum AK, Baum U, Deike R, Feistner H, Scholz M, et al. Assessment of the technical usability and efficacy of a new portable dry-electrode EEG recorder: First results of the HOMEONE study. Clin Neurophysiol 2019;130:2076–87. https://doi.org/10.1016/j.clinph.2019.08.012.

[188] Rose CF. Ammonia-Lowering Strategies for the Treatment of Hepatic Encephalopathy. Clin Pharmacol Ther 2012;92:321–31. https://doi.org/10.1038/clpt.2012.112.

[189] Bajaj JS, Gillevet PM, Patel NR, Ahluwalia V, Ridlon JM, Kettenmann B, et al. A longitudinal systems biology analysis of lactulose withdrawal in hepatic encephalopathy. Metab Brain Dis 2012;27:205–15. https://doi.org/10.1007/s11011-012-9303-0.

[190] 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;174:1727–33. https://doi.org/10.1001/jamainternmed.2014.4746.

[191] Bajaj JS, Heuman DM, Sanyal AJ, Hylemon PB, Sterling RK, Stravitz RT, et al. Modulation of the Metabiome by Rifaximin in Patients with Cirrhosis and Minimal Hepatic Encephalopathy. PLoS ONE 2013;8:e60042. https://doi.org/10.1371/journal.pone.0060042.

[192] DuPont HL. Review article: the antimicrobial effects of rifaximin on the gut microbiota. Alimentary Pharmacology & Therapeutics 2015;43:3–10. https://doi.org/10.1111/apt.13434.

[193] Kimer N, Pedersen JS, Tavenier J, Christensen JE, Busk TM, Hobolth L, et al. Rifaximin has minor effects on bacterial composition, inflammation, and bacterial translocation in cirrhosis: A randomized trial. J Gastroenterol Hepatol 2018;33:307–14. https://doi.org/10.1111/jgh.13852.

[194] Mas A, Rodés J, Sunyer L, Rodrigo L, Planas R, Vargas V, et al. Comparison of rifaximin and lactitol in the treatment of acute hepatic encephalopathy: results of a randomized, double-blind, double-dummy, controlled clinical trial. J Hepatol 2003;38:51–8.

[195] Miglio F, Valpiani D, Rossellini SR, Ferrieri A. Rifaximin, a non-absorbable rifamycin, for the treatment of hepatic encephalopathy. A double-blind, randomised trial. Curr Med Res Opin 1997;13:593–601. https://doi.org/10.1185/03007999709113333.

[196] Paik Y-H, Lee KS, Han K-H, Song KH, Kim MH, Moon BS, et al. Comparison of rifaximin and lactulose for the treatment of hepatic encephalopathy: a prospective randomized study. Yonsei Medical Journal 2005;46:399–407. https://doi.org/10.3349/ymj.2005.46.3.399.

[197] Jiang Q, Jiang X-H, Zheng M-H, Jiang L-M, Chen Y-P, Wang L. Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy: a meta-analysis. European Journal of Gastroenterology & Hepatology 2008;20:1064–1070. https://doi.org/10.1097/MEG.0b013e328302f470.

[198] Eltawil KM, Laryea M, Peltekian K, Molinari M. Rifaximin vs conventional oral therapy for hepatic encephalopathy: A meta-analysis. World Journal of Gastroenterology : WJG 2012;18:767–777. https://doi.org/10.3748/wjg.v18.i8.767.

[199] Bucci L, Palmieri GC. Double-blind, double-dummy comparison between treatment with rifaximin and lactulose in patients with medium to severe degree hepatic encephalopathy. Curr Med Res Opin 1993;13:109–18. https://doi.org/10.1185/03007999309111539.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[200] Sharma BC, Sharma P, Lunia MK, Srivastava S, Goyal R, Sarin SK. A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. Am J Gastroenterol 2013;108:1458–63. https://doi.org/10.1038/ajg.2013.219.

[201] Dalal R, McGee RG, Riordan SM, Webster AC. Probiotics for people with hepatic encephalopathy. Cochrane Database Syst Rev 2017;2:CD008716. https://doi.org/10.1002/14651858.CD008716.pub3.

[202] 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. https://doi.org/10.1002/14651858.CD001939.pub4.

[203] 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;28:783–792. https://doi.org/10.1111/jgh.12142.

[204] Butterworth RF, Kircheis G, Hilger N, McPhail MJW. Efficacy of l-Ornithine l-Aspartate for the Treatment of Hepatic Encephalopathy and Hyperammonemia in Cirrhosis: Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Clin Exp Hepatol 2018;8:301–13. https://doi.org/10.1016/j.jceh.2018.05.004.

[205] Butterworth RF, McPhail MJW. L-Ornithine L-Aspartate (LOLA) for Hepatic Encephalopathy in Cirrhosis: Results of Randomized Controlled Trials and Meta-Analyses. Drugs 2019;79:31–7. https://doi.org/10.1007/s40265-018-1024-1.

[206] 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. https://doi.org/10.1002/14651858.CD012410.pub2.

[207] 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;57:2448–57. https://doi.org/10.1002/hep.26314.

[208] Privitera G, Figorilli F, Jalan R, Mehta G. Portosystemic Shunt Embolization and Recurrent Ascites: A Single-Center Case Series. Gastroenterology 2018;155:1649–50. https://doi.org/10.1053/j.gastro.2018.06.092.

[209] Simón-Talero M, García-Martínez R, Torrens M, Augustin S, Gómez S, Pereira G, et al. Effects of intravenous albumin in patients with cirrhosis and episodic hepatic encephalopathy: A randomized double-blind study. J Hepatol 2013;59:1184–92. https://doi.org/10.1016/j.jhep.2013.07.020.

[210] Sharma BC, Singh J, Srivastava S, Sangam A, Mantri AK, Trehanpati N, et al. Randomized controlled trial comparing lactulose plus albumin versus lactulose alone for treatment of hepatic encephalopathy. J Gastroenterol Hepatol 2017;32:1234–9. https://doi.org/10.1111/jgh.13666.

[211] Bañares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M, et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatology 2013;57:1153–62. https://doi.org/10.1002/hep.26185.

[212] Jalan R, Kapoor D. Enhanced renal ammonia excretion following volume expansion in patients with well compensated cirrhosis of the liver. Gut 2003;52:1041–5. https://doi.org/10.1136/gut.52.7.1041.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[213] Slack AJ, Auzinger G, Willars C, Dew T, Musto R, Corsilli D, et al. Ammonia clearance with haemofiltration in adults with liver disease. Liver Int 2014;34:42–8. https://doi.org/10.1111/liv.12221.

[214] Sharma P, Sharma BC, Agrawal A, Sarin SK. Primary prophylaxis of overt hepatic encephalopathy in patients with cirrhosis: an open labeled randomized controlled trial of lactulose versus no lactulose. Journal of Gastroenterology and Hepatology 2012;27:1329–1335. https://doi.org/10.1111/j.1440-1746.2012.07186.x.

[215] Lunia MK, Sharma BC, Sharma P, Sachdeva S, Srivastava S. Probiotics prevent hepatic encephalopathy in patients with cirrhosis: a randomized controlled trial. Clin Gastroenterol Hepatol 2014;12:1003-1008.e1. https://doi.org/10.1016/j.cgh.2013.11.006.

[216] Dhiman RK, Thumburu KK, Chopra M, Dutta U, Duseja A, Chawla YK. Comparative effectiveness of different pharmacological interventions for the treatment of minimal hepatic encephalopathy: a systematic review with network meta-analysis. Hepatology 2016;64:711A.

[217] 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. The American Journal of Gastroenterology 2012;107:1043–1050. https://doi.org/10.1038/ajg.2012.113.

[218] 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;12:1390-1397.e2. https://doi.org/10.1016/j.cgh.2013.12.021.

[219] Dhiman RK, Rana B, Agrawal S, Garg A, Chopra M, Thumburu KK, et al. Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: a randomized, controlled trial. Gastroenterology 2014;147:1327-1337.e3. https://doi.org/10.1053/j.gastro.2014.08.031.

[220] Caraceni P, Riggio O, Angeli P, Alessandria C, Neri S, Foschi FG, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet 2018;391:2417–29. https://doi.org/10.1016/S0140-6736(18)30840-7.

[221] Jalan R, Wright G, Davies NA, Hodges SJ. L-Ornithine phenylacetate (OP): a novel treatment for hyperammonemia and hepatic encephalopathy. Med Hypotheses 2007;69:1064–9. https://doi.org/10.1016/j.mehy.2006.12.061.

[222] Kristiansen RG, Rose CF, Fuskevåg O-M, Mæhre H, Revhaug A, Jalan R, et al. L-Ornithine phenylacetate reduces ammonia in pigs with acute liver failure through phenylacetylglycine formation: a novel ammonia-lowering pathway. Am J Physiol Gastrointest Liver Physiol 2014;307:G1024-1031. https://doi.org/10.1152/ajpgi.00244.2014.

[223] Ytrebø LM, Kristiansen RG, Maehre H, Fuskevåg OM, Kalstad T, Revhaug A, et al. L-ornithine phenylacetate attenuates increased arterial and extracellular brain ammonia and prevents intracranial hypertension in pigs with acute liver failure. Hepatology 2009;50:165–174. https://doi.org/10.1002/hep.22917.

[224] Oria M, Romero-Giménez J, Arranz JA, Riudor E, Raguer N, Córdoba J. Ornithine phenylacetate prevents disturbances of motor-evoked potentials induced by intestinal blood in rats with portacaval anastomosis. J Hepatol 2012;56:109–14. https://doi.org/10.1016/j.jhep.2011.06.026.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[225] Safadi R, Rahimi RS, DiLiberti CE, Wang L, Pyrsopoulos NT, Potthoff A, et al. OCR-002 (ornithine phenylacetate) is a potent ammonia scavenger as demonstrated in phase 2b STOP-HE study. Hepatology 2017;66:126A-126A.

[226] 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;32:209–15. https://doi.org/10.1111/fcp.12340.

[227] 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;63:339–40. https://doi.org/10.1002/hep.28121.

[228] 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;66:1727–38. https://doi.org/10.1002/hep.29306.

[229] Mullish BH, McDonald JAK, Thursz MR, Marchesi JR. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. Hepatology 2017;66:1354–5. https://doi.org/10.1002/hep.29369.

[230] Agostoni V, Lee SH, Forster V, Kabbaj M, Bosoi CR, Tremblay M, et al. Liposome-Supported Peritoneal Dialysis for the Treatment of Hyperammonemia-Associated Encephalopathy. Adv Funct Mater 2016;26:8382–9. https://doi.org/10.1002/adfm.201603519.

[231] Kurtz CB, Millet YA, Puurunen MK, Perreault M, Charbonneau MR, Isabella VM, et al. An engineered E. coli Nissle improves hyperammonemia and survival in mice and shows dose-dependent exposure in healthy humans. Sci Transl Med 2019;11:eaau7975. https://doi.org/10.1126/scitranslmed.aau7975.

[232] Synlogic Discontinues Development of SYNB1020 to Treat Hyperammonemia. Synlogic n.d. https://investor.synlogictx.com/news-releases/news-release-details/synlogic-discontinues-development-synb1020-treat-hyperammonemia (accessed October 23, 2019).

[233] 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;53:1995–2002. https://doi.org/10.1002/hep.24273.

[234] Johansson M, Agusti A, Llansola M, Montoliu C, Strömberg J, Malinina E, et al. GR3027 antagonizes GABAA receptor-potentiating neurosteroids and restores spatial learning and motor coordination in rats with chronic hyperammonemia and hepatic encephalopathy. Am J Physiol Gastrointest Liver Physiol 2015;309:G400–9. https://doi.org/10.1152/ajpgi.00073.2015.

[235] Johansson M, Strömberg J, Ragagnin G, Doverskog M, Bäckström T. GABAA receptor modulating steroid antagonists (GAMSA) are functional in vivo. J Steroid Biochem Mol Biol 2016;160:98–105. https://doi.org/10.1016/j.jsbmb.2015.10.019.

[236] Agusti A, Llansola M, Hernández-Rabaza V, Cabrera-Pastor A, Montoliu C, Felipo V. Modulation of GABAA receptors by neurosteroids. A new concept to improve cognitive and motor alterations in hepatic encephalopathy. J Steroid Biochem Mol Biol 2016;160:88–93. https://doi.org/10.1016/j.jsbmb.2015.08.020.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[237] Desjardins P, Rao KV, Michalak A, Rose C, Butterworth RF. Effect of portacaval anastomosis on glutamine synthetase protein and gene expression in brain, liver and skeletal muscle. Metab Brain Dis 1999;14:273–280. https://doi.org/10.1023/A:1020741226752.

[238] Jover-Cobos M, Noiret L, Lee K, Sharma V, Habtesion A, Romero-Gomez M, et al. Ornithine phenylacetate targets alterations in the expression and activity of glutamine synthase and glutaminase to reduce ammonia levels in bile duct ligated rats. J Hepatol 2014;60:545–53. https://doi.org/10.1016/j.jhep.2013.10.012.

[239] Chatauret N, Desjardins P, Zwingmann C, Rose C, Rao KVR, Butterworth RF. Direct molecular and spectroscopic evidence for increased ammonia removal capacity of skeletal muscle in acute liver failure. J Hepatol 2006;44:1083–8. https://doi.org/10.1016/j.jhep.2005.11.048.

[240] Qvartskhava N, Lang PA, Görg B, Pozdeev VI, Ortiz MP, Lang KS, et al. Hyperammonemia in gene-targeted mice lacking functional hepatic glutamine synthetase. PNAS 2015;112:5521–6. https://doi.org/10.1073/pnas.1423968112.

[241] Hakvoort TBM, He Y, Kulik W, Vermeulen JLM, Duijst S, Ruijter JM, et al. Pivotal role of glutamine synthetase in ammonia detoxification. Hepatology 2017;65:281–93. https://doi.org/10.1002/hep.28852.

[242] Torres-Vega MA, Vargas-Jerónimo RY, Montiel-Martínez AG, Muñoz-Fuentes RM, Zamorano-Carrillo A, Pastor AR, et al. Delivery of glutamine synthetase gene by baculovirus vectors: a proof of concept for the treatment of acute hyperammonemia. Gene Ther 2015;22:58–64. https://doi.org/10.1038/gt.2014.89.

[243] Song G, Kerbert A, Jones H, Davies N, Andreola F, Nicolson T, et al. Recombinant glutamine synthetase: A novel strategy for the treatment of hyperammonemia and consequent hepatic encephalopathy in rodent model of cirrhosis and urea cycle enzyme deficiency. Journal of Hepatology 2019;70:e93–4.

[244] Romero-Gómez M, Montagnese S, Jalan R. Hepatic encephalopathy in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure. J Hepatol 2015;62:437–47. https://doi.org/10.1016/j.jhep.2014.09.005.

[245] Lauridsen MM, Mikkelsen S, Svensson T, Holm J, Klüver C, Gram J, et al. The continuous reaction time test for minimal hepatic encephalopathy validated by a randomized controlled multi-modal intervention-A pilot study. PLoS ONE 2017;12:e0185412. https://doi.org/10.1371/journal.pone.0185412.

[246] 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;135:1591-1600.e1. https://doi.org/10.1053/j.gastro.2008.07.021.

[247] Montagnese S, Schiff S, Turco M, Bonato CA, Ridola L, Gatta A, et al. Simple tools for complex syndromes: A three-level difficulty test for hepatic encephalopathy. Dig Liver Dis 2012;44:957–960. https://doi.org/10.1016/j.dld.2012.06.010.

[248] Marchetti P, D'Avanzo C, Orsato R, Montagnese S, Schiff S, Kaplan PW, et al. Electroencephalography in patients with cirrhosis. Gastroenterology 2011;141:1680-1689.e1-2. https://doi.org/10.1053/j.gastro.2011.06.085.

[249] Kircheis G, Hilger N, Häussinger D. Value of Critical Flicker Frequency and Psychometric Hepatic Encephalopathy Score in Diagnosis of Low-Grade Hepatic Encephalopathy. Gastroenterology 2014;146:961-969.e11. https://doi.org/10.1053/j.gastro.2013.12.026.

Rose, C. F.; Amodio, P.; Bajaj, J. S.; Dhiman, R. K.; Montagnese, S.; Taylor-Robinson, S. D.; Vilstrup, H. & Jalan, R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology, 2020 published in final form at doi.org/10.1016/j.jhep.2020.07.013.

[250] Keiding S, Pavese N. Brain metabolism in patients with hepatic encephalopathy studied by PET and MR. Archives of Biochemistry and Biophysics 2013;536:131–42. https://doi.org/10.1016/j.abb.2013.05.006.

[251] Gabriel MM, Kircheis G, Hardtke S, Markwardt D, Buggisch P, Mix H, et al.Risk of recurrent hepatic encephalopathy in patients with liver cirrhosis:a German registry study. Eur J Gastroenterol Hepatol 2020.https://doi.org/10.1097/MEG.0000000000001822.

[252]Grover VPB, Crossey MME, Fitzpatrick JA, Saxby BK, Shaw R,Waldman AD, et al. Quantitative magnetic resonance imaging in patientswith cirrhosis: a cross-sectional study. Metab Brain Dis 2016;31:1315–1325.

[253]Poo JL, Rosas-Romero R, Rodríguez F, Silencio JL, Muñoz R, Bourges H,et al. Serum zinc concentrations in two cohorts of 153 healthy subjectsand 100 cirrhotic patients from Mexico City. Dig Dis 1995;13:136–142.

[254]Takuma Y, Nouso K, Makino Y, Hayashi M, Takahashi H. Clinical trial: oral zinc in hepatic encephalopathy. Aliment Pharmacol Ther 2010;32:1080–1090.