The burden of hepatic encephalopathy and the use of albumin as a potential treatment

Jasmohan S. Bajaj[a,*], Enrico Pompili[b,c], Paolo Caraceni[b,c]

[a] Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and Central Virginia Healthcare System, Richmond, Virginia, USA
[b] Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy
[c] Unit of Semeiotics, Liver and Alcohol-Related Diseases, IRCCS Azienda Ospedaliero-Universitaria Di Bologna, Bologna, Italy

ARTICLE INFO

ABSTRACT

As a potential sequela of cirrhosis, hepatic encephalopathy (HE) significantly impacts the lives of patients and caregivers and places a substantial burden on the healthcare system. With an increasing incidence over time and a cumulative effect on cognition, HE adversely effects quality of life, morbidity and mortality in patients with cirrhosis. HE can range from minimal or covert (MHE/CHE) to overt and symptomatic (OHE). HE has profound impacts on the health and wellbeing of patients and their families and caregivers. Effective treatments could improve the quality of life for all those affected. In this article, we discuss the existing treatments for HE and focus on the potential role of albumin in the treatment of HE. Currently approved therapies for HE (lactulose and rifaximin) are focused on decreasing the formation of ammonia in the gastrointestinal tract. Among the many agents with alternative mechanisms being investigated for treatment of HE, albumin has been studied in clinical trials with acute (≤ 3 days), short-term (up to 2 weeks) prolonged (> 2 weeks) and long-term administration (months). Current studies indicate that acute or short-term administration of albumin does not provide significant benefit for patients with OHE. However, there is increasing evidence that prolonged or long-term albumin therapy can help improve cognition in OHE and prevent recurrence. Additional studies are needed to substantiate these positive findings for longer term administration of albumin in HE and to increase our comprehension of the pharmacologic basis of the effects of albumin.

1. Introduction

Hepatic encephalopathy (HE) is a complication of cirrhosis that produces substantial health and quality of life deterioration not only for the patients, but also for their caregivers. HE is a neurological condition precipitated by decompensated liver insufficiency and/or portosystemic shunting and can range in severity from mild, undetected cognitive impairment to coma [1−3]. HE is associated with falls, accidents (especially in motor vehicles), an increased risk of hospitalization and increased mortality. The spectrum of HE ranges from the subclinical, minimal/covert (MHE/CHE) stage to the overt, clinically apparent stage (OHE). Moreover, MHE/CHE can predispose patients

to OHE episodes and even after recovery from OHE; recurrences are common.

1.1. Prevalence and progression of HE

The incidence of HE in patients with cirrhosis has not been widely studied, but a study of US Medicare patients with cirrhosis (20 % random sample, n = 166,192) found an incidence of 11.6 per 100 patient years for HE. Thirty-one percent of the patients with HE had alcohol-related cirrhosis and 49 % had cirrhosis due to fatty liver disease [4]. A longitudinal study (January 1, 2005 − December 31, 2010) of patients with cirrhosis and without HE at baseline (n = 1,979) showed these patients had a 43.7 % chance of developing HE within five years. This study also showed that higher bilirubin and use of non-selective beta blockers were risk factors for developing HE, while higher albumin levels and statin use were protective against HE [5].

Some studies have suggested that HE may have a chronic and cumulative effect on cognitive function. A cross-sectional study in cirrhosis patients compared patients with or without prior HE and a prospective study compared cirrhosis patients before and after a first episode of HE. These studies demonstrated that the cognitive

* Corresponding author.

E-mail address: Jasmohan.bajaj@vcuhealth.org (J.S. Bajaj).

impairment seen with overt HE (assessed by psychometric testing) does not completely reverse despite resolution of impaired overall mental status. The prospective study found that the patients who developed HE had significant deterioration of cognitive performance while those without HE did not [6]. Residual cognitive impairment may persist in patients that had overt HE even after liver transplantation [7].

1.2. Impact of HE

HE has been associated with poorer quality of life in patients and caregivers [8−10]. In a study of 152 cirrhosis patients in Germany, HE and continued alcohol consumption were identified as factors that correlated with a lower quality of life [8]. HE has been found to decrease the patient's ability to carry out the activities of daily life [11]. This includes an impairment in the ability of patients with HE to drive safely, alteration of sleep patterns, decreased mobility, and decreased work capability [11−16].

Impaired driving ability has been verified in road driving tests with an instructor [14,16], driving simulators [17,18] and in epidemiologic studies. A real-world epidemiologic study found an increase in traffic accidents and citations in cirrhosis patients with HE (n= 42) compared to cirrhosis patients without MHE (n= 26) [19].

In a study of 110 cirrhosis patients examining work capability, those with unskilled or skilled labor or craftsperson jobs (blue collar workers) were more likely to be considered unable to earn a living than patients with civil service, academic or entrepreneurial (white collar) employment. The authors attributed this difference to greater deficits in psychomotor functioning than in verbal and intellectual skills [20].

As a result of the factors cited above, HE has been shown to have profound effects on psychological and social wellbeing of patients. Impaired cognition and decreased driving ability can lead to loss of employment and economic hardship. A study on the extent of the burden imposed by HE found that cirrhosis patients with a history of HE had worse unemployment rates and worse financial status than cirrhosis patients who had not had an episode of HE [21].

Cognitive impairment, loss of independence and lowered socioeconomic status can all contribute to deterioration in the patient's quality of life [21−23]. Altered socioeconomic status can compound the health and quality of life problems for patients and their families by decreasing their access to adequate housing, medical care, and food [11]. Quality of life was degraded to a similar extent in caregivers as in patients [24]. Persistent alcohol consumption and HE correlated with a lower quality of life and a higher psychosocial burden for caregivers [8].

Perhaps most importantly, HE has also been associated with an increased risk of mortality. A retrospective study in Spain looked at the medical records of 111 patients with cirrhosis who had suffered an initial episode of HE. The mortality rate was 58 % (42 % survival) at one year and 77 % at three years (23 % survival) [25]. A similar study was conducted with 466 Danish patients with cirrhosis. In this study, one-year mortality was 64 % and five-year mortality was 85 % in patients with HE [26]. In these studies conducted a decade apart in different countries, the estimates of mortality range similar and quite high (58-64 % at one year and 77-85 % at five years) [25,26].

HE imposes additional burdens on health care systems which have been increasing in recent years. Emergency department visits, hospitalizations, and the associated charges have all increased [9,27]. A study using the US National Inpatient Sample showed that hospitalizations that included HE increased by 24.4 % over the period 2010-2014. The inpatient charges for patients with HE increased by 46.0 % (to $11.9 billion) over the same period [27].

Another study utilizing the Healthcare Cost and Utilization Project database (US data) showed that emergency department visits related to HE increased by 35.0 % over the period 2006-2014. HE-related emergency department charges increased by 110.6 % over the same period. Hospital discharges related to HE increased by 117.7 % over the period 2000 to 2014. Cirrhosis patients with HE had longer hospital stays and more frequent readmissions than cirrhosis patients without HE [9]. These studies clearly demonstrate that, at least in the US, the magnitude of the impact of HE is growing.

Patients with MHE were 3.7 times more likely to develop OHE over three years than cirrhosis patients without MHE [28]. MHE is also associated with a higher rate of hospitalization and increased mortality compared to patients with cirrhosis and no MHE [2,29]. Estimates of the prevalence of MHE in cirrhosis patients vary from 20-54 % depending on the psychometric test(s) administered [30 −32]. Due to the less obvious nature of MHE, diagnosis can be difficult and resource intensive. Frequently, multiple testing strategies are required to make an accurate diagnosis of MHE [2] and many practitioners who see cirrhosis patients do not test for it [33]. Even in this milder form, MHE can affect numerous measures of psychosocial function including attention, alertness, response inhibition and executive functions [34−38].

It is clear from these studies that HE has profound effects on the health and wellbeing of patients with cirrhosis and continued investigation into new or improved treatments for HE is warranted. Effective treatments could help improve the health of cirrhosis patients with HE and improve the quality of life for patients and their caregivers. The remainder of this article will focus on the existing treatments, and particularly the role of albumin in the prevention and treatment of HE.

2. Results

2.1. Current and investigational treatment options for HE

2.1.1. Lactulose

The first line treatment for MHE or overt HE is generally lactulose [1]. It is a non-absorbable disaccharide that suppresses the growth of ammonia-producing bacteria in the gut [2]. This treatment has been shown to improve cognitive function and health-related quality of life in patients with MHE [39]. and can help prevent recurrence of HE [40]. However, due to its gastrointestinal side effects, lactulose is difficult to tolerate for many patients especially those from Western countries, [41] and a large proportion of patients experience recurrence or occurrence of HE due to non-adherence [42].

2.1.2. Rifaximin

Rifaximin has been found to be useful add-on therapy to lactulose in the treatment of HE [1]. It is an antibiotic with little systemic absorption that also acts to decrease ammonia-producing bacteria in the digestive tract. Rifaximin added to lactulose therapy was found to be superior to lactulose alone in preventing a recurrence of HE [43]. Clinical trials have also shown that rifaximin can improve cognitive performance in patients with MHE [44,45]. However, rifaximin is an expensive medication in some countries, which could be a barrier preventing its wider use [46].

2.1.3. Investigation treatments

Given the gravity of the condition and its impact on the lives of patients and their caregivers, it is not surprising that many new approaches have been investigated for the treatment of HE (Fig. 1) [47]. These approaches include modulation of neurotransmitters, increased urea production, decrease production and absorption of ammonia in the gut, alteration of gut microbiota, increased urinary excretion of phenylacetyl glutamine, increased glutamine synthesis and reduction of oxidative stress. Moreover, medications with actions outside the gut that focus on removal of ammonia and inflammatory mediators in the systemic circulation are needed. Unfortunately, further development of ammonia scavengers is not currently being
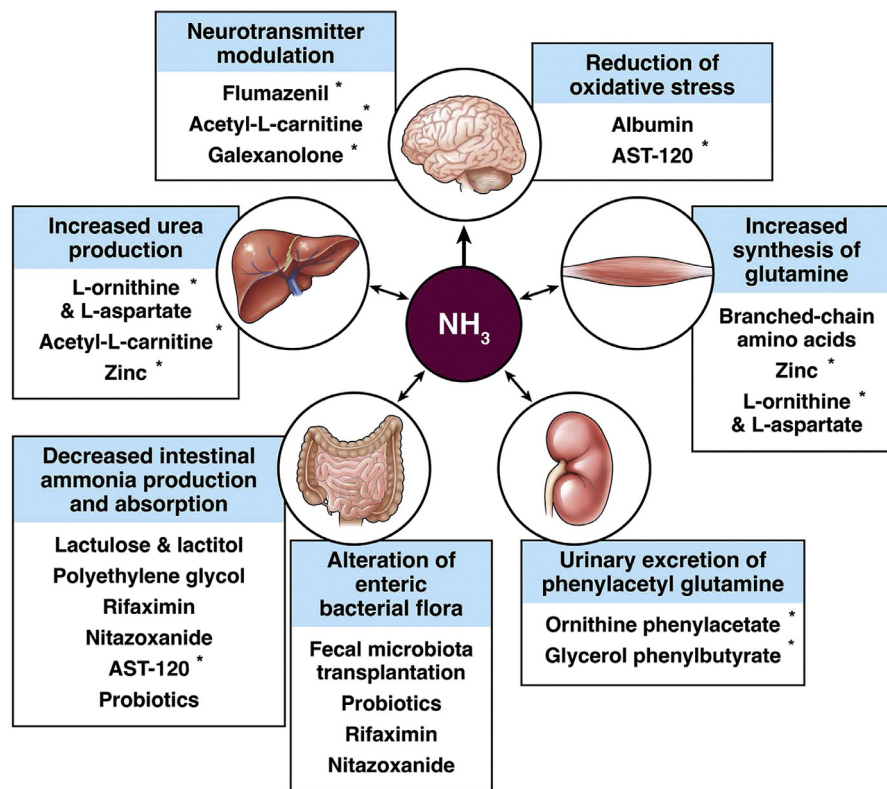
Fig. 1. Established and emerging treatments for hepatic encephalopathy (HE). *These therapies were not being actively investigated for HE as of March 23, 2022 per clinicaltrails.gov [47].

pursued. Therefore, agents that enhance or improve the removal of inflammatory cytokines and ammonia from the circulation are needed to complement the gut-based action of the current HE medications.

Although the medications noted in Fig. 1 have been studied for their effects in treating HE, data supporting their use is limited [1]. Guidelines from the American Association for the Study of Liver Diseases, published in 2014, stated that the use of albumin lacked sufficient data to support its use as a therapy for HE [1]. However, since that time, several clinical trials studying albumin as a treatment for MHE and HE have been published. These studies on albumin treatment of HE will be the focus of this review. Studies on the treatment of MHE or HE with albumin and the efficacy of different administration strategies will be considered.

2.2. Albumin treatment of HE

The evidentiary basis for the use of human albumin (HA) in treating HE and the potential therapeutic gaps in that could be filled by this medication are the subject of the studies discussed below (as a primary or secondary endpoint) and a driving force for future studies. Besides its well-known oncotic activity, which makes HA the main regulator of fluid distribution among the different body compartments, the albumin molecule has multiple other biological functions grouped under the term non-oncotic properties. It binds a long series of exogenous and endogenous compounds through specific and non-specific molecular sites, thus exerting an essential activity of solubilization, transport and detoxification. HA is the main circulating antioxidant in our body and is also able to stabilize endothelia, contributing to a normal capillary permeability. In the last decade, several studies have attributed to HA an important role in modulating inflammatory and immunological responses. It can be speculated that the antioxidant and anti-inflammatory are the most relevant non-oncotic properties that can potentially improve HE [48].

Clinical and translational data on the effects of HA administration have been generated from a few recent randomized clinical trials (RCTs) addressing different phases of HE: MHE/CHE [49], OHE requiring hospitalization [50−52] and recurrent OHE [53−55].

Based on the length of HA treatment, we have divided these studies in acute HA administration (up to three days) [50,51], short-term (up to two weeks) [52], prolonged (weeks) [49], and long-term (months) of albumin. [53−55] (Fig. 2). In three of them, the primary endpoint was focused on the management of HE, while, in the others, HE was included among the secondary endpoints.

2.2.1. Acute albumin administration (≤ 3 days)

Two RCTs performed in Spain have investigated the effects of acute administration of HA in patients admitted to hospital with at least grade 2 HE according to West-Haven criteria [47,48].

In the first double-blind RCT [51], published in 2013, 56 patients admitted to hospital with at least grade 2 HE according to the West-Haven criteria were randomly assigned to receive albumin 20 % at a dose of 1.5 g/kg body weight at diagnosis and 1.0 g/kg on day 3 (the same dose and schedule used to prevent renal failure in spontaneous bacterial peritonitis) or isotonic saline solution on top of standard medical treatment (SMT). Patients were stratified according to the grade of OHE (grade II-III vs grade IV). Unfortunately, HA administration was not associated with any benefit on OHE. Indeed, the prevalence of clinical resolution of HE at day 4, which was the primary endpoint of the study, and the improvement of the neuropsychometric tests were similar between the two groups Moreover, no differences were found in the circulating levels of ammonium, inflammatory cytokines, or markers of oxidative stress. However, the study found a significant increase of the 90-day survival rate in patients who were treated with HA, as compared to those who received saline (96 % vs 40 %).

This latter result prompt the same investigators to perform a second RCT assessing the effect of HA at the same schedule and dose in
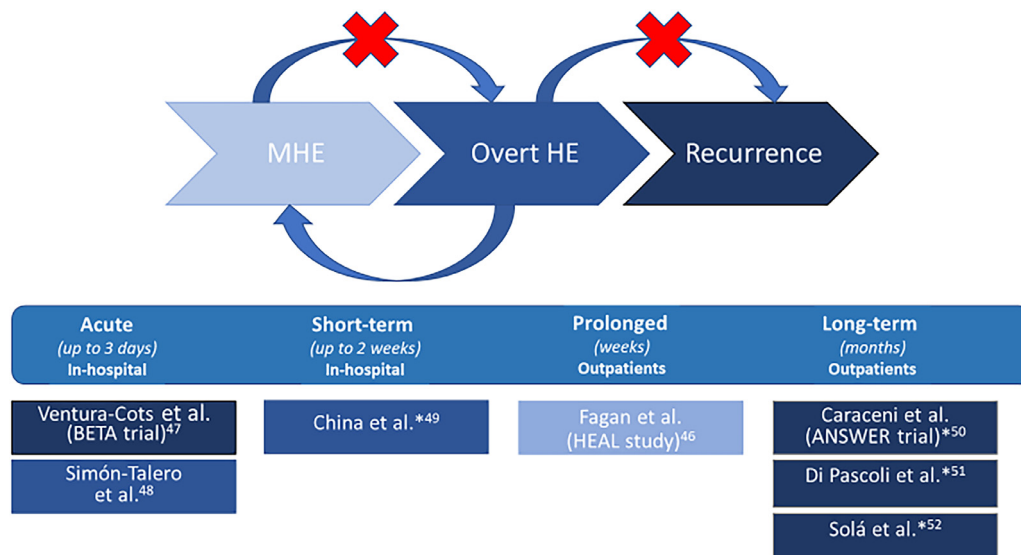
Fig. 2. Studies of albumin therapy on hepatic encephalopathy (HE) in cirrhosis patients have covered different phases of the disease. They include blocking progression from minimal HE (MHE) to overt HE, blocking recurrence or progression in patients with a history of HE or active HE and resolving overt episodes of HE. Studies have varied in the length of administration from a few days to months. *Studies which did not have HE as a primary inclusion criterion.

the same population, but with a more ambitious primary end-point, which was the 90-day transplant-free survival [50].

The study enrolled 82 patients admitted to hospital for at least grade 2 overt HE, who were randomized to receive HA (1.5 g/kg body weight at diagnosis and 1.0 g/kg body weight on day 3) (n=42) or placebo (n=40). The study was interrupted due to low enrolment and excessive duration when 64 % of the estimated sample size was recruited. Again, the primary endpoint was not met since no statistically significant differences between the two groups were found in the 90-day transplant-free survival (HA: 87 % vs placebo: 80 %). Also, no benefit of HA administration was observed on the incidence of new OHE episodes, infections, and hospitalizations, which were all secondary endpoints.

Finally, the authors performed a meta-analysis combining the data from both RCTs. With the increase of sample size, a significantly better transplant-free survival rate was observed in patients who received HA compared to those who received saline [51,50].

Despite this latter promising data, there is currently no solid evidence supporting the acute administration (up to 3 days) of high doses of HA for treating acute episodes of OHE.

2.2.2. Short-term albumin administration (up to 2 weeks)

A pragmatic example of short-term HA treatment is the ATTIRE study, a large, multicenter, randomized, open-label trial performed in UK [52], which investigated the efficacy and safety of HA in patients admitted to the hospital for acute onset or worsening of complications of cirrhosis and moderate to severe hypoalbuminemia. Albumin was infused daily until discharge or a maximum of 15 days, following an individualized dosing protocol designed to achieve and maintain a target level of 3 g/dL.

The primary endpoint was a composite of infection from any cause, kidney dysfunction and death from day 3 to 15 or up to discharge, and the main secondary end-points were death at 28 days, 3 months and 6 months and the incidence of each of the three components of the primary end-point.

The results of the ATTIRE study were comprehensively negative. No differences between the two groups were observed for both the primary endpoint and all the secondary endpoints. Unfortunately, the data regarding HE are limited in this study, even if the episodes of brain dysfunction reported among the adverse events appear to be similar between the two groups.

Therefore, based on the available evidence, there is no indication for daily HA short-term administration (up to a maximum of 2 weeks) for treating and/or preventing OHE in hospitalized patients admitted for acute decompensation of cirrhosis.

2.2.3. Prolonged albumin administration (> 2 weeks)

In contrast to the results of acute and short-term administration of albumin, prolonged and long-term administration showed positive effects in decreasing the incidence of HE and other complications of cirrhosis. Even after recovery from OHE, cirrhosis patients can have persistent cognitive impairment or minimal HE [1] despite optimal treatment with lactulose and/or rifaximin [6,56]. As previously stated, even minimal HE can adversely affect quality of life for patients and caregivers.

Prolonged inflammation and endothelial dysfunction have been implicated in the mechanisms of HE [57−59]. Due to the anti-inflammatory and endothelium stabilizing effects of albumin, a prolonged albumin treatment regimen was investigated in the HEAL study (5 weeks at 1.5 g/kg weekly albumin administration) in outpatients with minimal HE. Patients were randomly assigned to receive albumin or saline weekly. Pre-infusion serum albumin was checked and if over 4.0 g/dL, patients in the albumin group received a saline infusion [49].

Treatment of the covert/minimal stage of HE in the HEAL trial is a departure from the more advanced disease treated in other trials, i.e., inpatients [51,52] and patients with recurrent disease [50,53]. This stage of HE is the focus of this trial because even covert HE can have detrimental effects on quality of life and survival. Patients with covert HE can have persistent cognitive impairment despite continued treatment with lactulose and/or rifaximin.

Patients included in the HEAL trial were > 18 years old with cirrhosis who had been on treatment with lactulose and/or rifaximin for at least two months. Their serum albumin was < 4 g/dL and they had cognitive impairment at screening based on at least one of three tests: critical flicker frequency (CFF) < 39 Hz [60]; psychomotor hepatic encephalopathy score (PHES) < - 4SD [35] or minimal HE on EncephalApp Stroop [32].

Patients were excluded if they had no prior history of HE or if in the past three months they required an albumin infusion, had a history of alcohol or illegal drug use, or had an infection. Patients were also excluded if they had congestive heart failure, were unable to
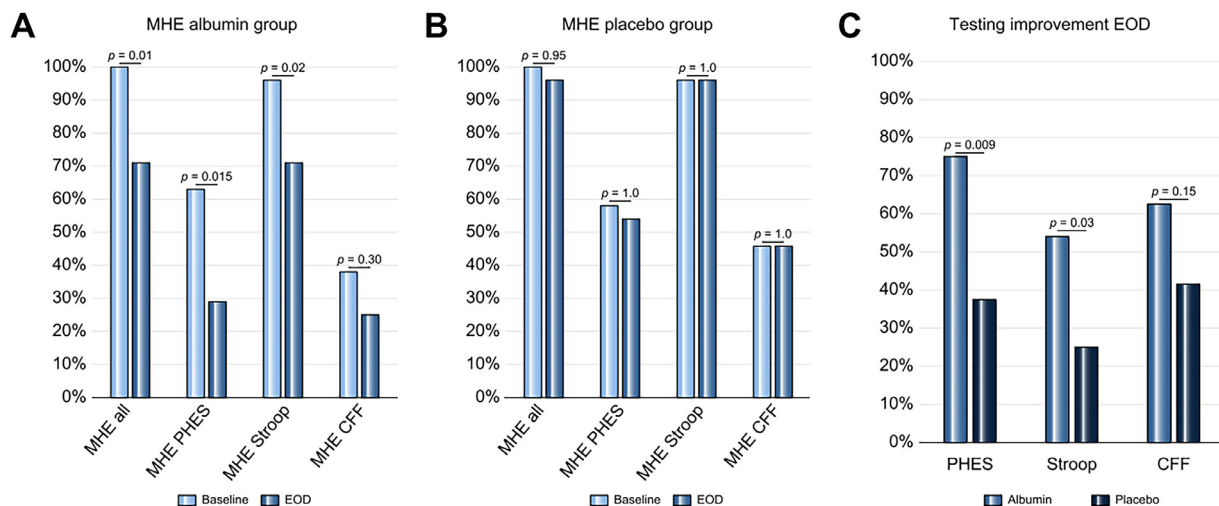
Fig. 3. Percentage of patients with minimal HE (MHE) at baseline and end of drug treatment (EOD) and improvement in test scores from baseline to EOD. PHES = psychomotor hepatic encephalopathy score; Stroop = EncephalApp Stroop; CFF = critical flicker frequency [49].

provide informed consent, unable to commit to attend follow-up visits for six weeks or were overtly confused (West-Haven grade ≥ 2) at enrolment.

Demographic and cognitive testing as baseline showed no significant differences between the treatment groups. Significant decreases were seen in the percentage of patients with minimal HE based on PHES (63 % at baseline to 29 % at the end of treatment and 38 % at the end of study) and EncephalApp (96 % at baseline to 71 % at the end of treatment and 79 % at the end of study) (Fig. 3). The changes seen in the albumin group on CFF were not significant. When all minimal HE measures were combined albumin treatment decreased the percentage of patients with minimal HE from 100 % at baseline to 71 % at the end of treatment and 79 % at the end of study (p = 0.05).

When health-related quality of life was assessed using the sickness impact profile (SIP) [61], total score and psychosocial domain scores were improved by albumin treatment (p = 0.008 and p = 0.004, respectively) (Fig. 4, 5). The physical domain of the SIP score was decreased but the change was not statistically significant (p = 0.08)

To help assess the potential mechanism of the effect of albumin, several inflammatory and anti-inflammatory blood markers were measured: interleukin (IL)-1β, IL-6, IL-10, tumor necrosis factor (TNF)α, lipopolysaccharide binding protein (LBP), intercellular adhesion molecule (ICAM)-1, and asymmetric dimethyl arginine (ADMA) (Table 1) [49]. No significant differences were seen between the treatment groups in the values of these markers at baseline.

In general, the pro-inflammatory markers increased over the course of the study in the placebo group. Statistically significant increases were observed in the pro-inflammatory markers ICAM-1 and ADMA in the placebo group at the end-of-treatment and end-of-study measurements. Overall, in the albumin group there was a decrease in these markers. Significant decreases were seen in IL-1β, ICAM-1 , and ADMA and the end of treatment and IL-1β and ADMA at the end of study. Conversely, there was a decrease in the anti-inflammatory cytokine, IL-10 in the placebo group, but no significant change in the albumin group. The specific markers that were changed in this study suggested that endothelial dysfunction may be an important factor in HE [49].

Serum albumin levels increased in the albumin treatment group from baseline (3.38±0.36) to end of drug treatment (EOD: 3.81±0.33; p < 0.0001) and were unchanged in the placebo group (3.20±0.38 baseline and 3.19±0.49 EOD; p = 0.94). Ischemia-modified albumin (IMA), a less functional form of the protein, was increased over the study period in the placebo group but decreased in the albumin

treatment group (Table 1). Overall, the improvements in cognitive and health-related quality of life measures were correlated with blood markers indicating an improvement in endothelial function, a decrease in inflammatory mediators and an increase in functional albumin [49].

In summary, the HEAL study demonstrated that a 5-week course of albumin improved cognitive performance and health-related quality of life compared to placebo in patients with cirrhosis and prior HE who had cognitive impairment despite being on lactulose and rifaximin [49]. Additional, larger, multi-center trials will be necessary to confirm these results, refine the best albumin administration schedule and determine the duration of the positive effects of albumin. The same team is now studying how long the effect of albumin lasts in patients with prior OHE and current MHE who are on lactulose and rifaximin [62]. It is still an open question whether HA could be efficacious in patients with cirrhosis and MHE/CHE without prior HE and lactulose/rifaximin use.

2.2.4. Long-term albumin administration (months)

A benefit of HA in the prevention of recurrent OHE emerged from the results of clinical trials evaluating long-term administration in patients with cirrhosis and ascites.

The ANSWER study is a no-profit, open-label, multi-center, randomized clinical trial in 33 Italian centers that enrolled 431 patients with at least grade 2 uncomplicated ascites requiring diuretic therapy (anti-aldosterone agents ≥ 200 mg/day and furosemide ≥ 25 mg/day) [53]. Patients were randomized to receive either SMT or SMT plus HA (40 g twice weekly for 2 weeks, then 40 g weekly) for up to 18 months. At enrolment, approximately 10 % of patients had grade I or II HE and approximately one-quarter had a history of previous overt HE.

HA treatment induced a significant improvement of the 18-month overall survival, which was the primary endpoint of the study, eased the management of ascites by reducing more than 50 % the number of large-volume paracenteses, significantly reduced the incidence rate of many severe complications with the exception of gastrointestinal bleedings which were similar between the two groups. Thus, not surprisingly, HA was associated with a significant reduction on liver-related hospital admissions and length of hospitalization. Finally, patients receiving albumin also presented a better quality of life as compared to those receiving only standard medical treatment.

When looking specifically at HE, the 18-month cumulative incidence of the first episode of grade III/IV HE was significantly lower in patients receiving SMT+HA than in those treated with only SMT
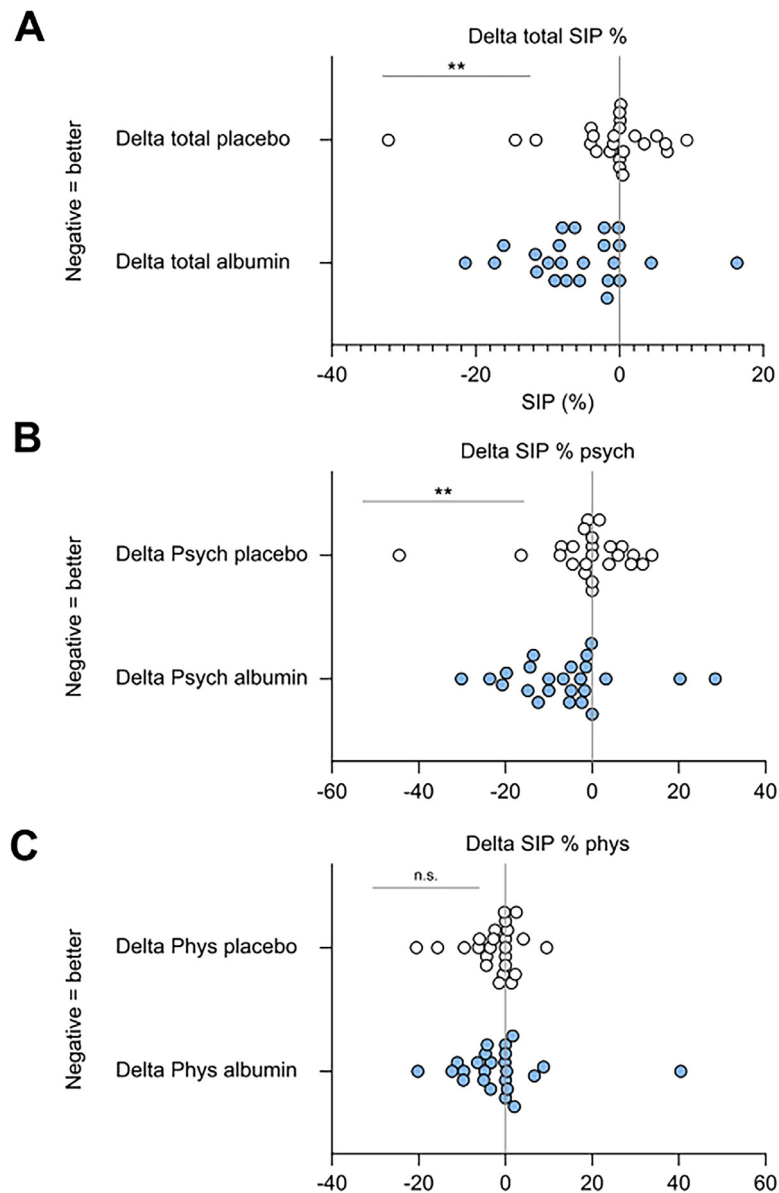
Fig. 4. Effects of treatment on changes in A) total, B) psychosocial, and C) physical scores using the sickness impact profile (SIP) to assess quality of life. ** p < 0.01 comparing baseline and end of drug treatment (EOD) [49].

(Fig. 3), as well as the incidence rate of grade III/IV HE during follow-up was reduced by almost 50 % [53].

In the same year, a monocentric, non-randomized clinical trial was conducted in Padua, Italy, to explore the efficacy of long-term albumin treatment in the management of patients with refractory ascites [54]. The study enrolled 70 patients, 45 of whom received 20 grams of HA twice a week up to a maximum of 24 months in addition to SMT, while the remaining 35 were treated with SMT only. The allocation to one of the two arms was based on the willingness of patients to have biweekly albumin infusions.

As in the ANSWER trial, besides the significantly lower cumulative incidence of 24-months mortality, the probability of being admitted to hospital for complications of cirrhosis, except for gastrointestinal bleeding, was significantly reduced by HA administration. Specifically, the incidence of hospitalization due to HE during follow-up was significantly lower in patients receiving HA than in those treated with SMT alone (27 % vs 65 %).

In contrast with the above two studies, the MACHT trial, a double-blind, Spanish multi-center, randomized clinical trial, produced completely different results [55]. One hundred ninety-six patients

with cirrhosis and ascites awaiting LT were randomized to receive HA albumin (40 g twice every 15 days) plus midodrine (15-30 mg/day) and or placebo until LT, removal from the waiting list or up to a maximum of 12 months [55]. No significant differences were observed between the two groups in the probability of developing cirrhosis complications (including HE), which was the primary endpoint of the study, or in the probability of 1-year mortality. These variant results, however, may be explained by two main differences between the ANSWER and MACHT studies: first, the length of treatment in the MACHT trial was only 2 months due to high transplantation rate in Spain, while in the ANSWER trial was longer than a year; second, the weekly amount of HA infused in the MACHT patients was half of the amount received by the ANSWER patients, so that serum albumin concentration was not increased by administration of exogenous HA [55]. Thus, it appears that to unveil the benefit of treatment, HA should be given for at least weeks and at a dose able to at least normalize serum albumin concentration ("enough albumin for enough time") [63].

In conclusion, consistent evidence indicates that long-term HA administration represents a potential effective approach for
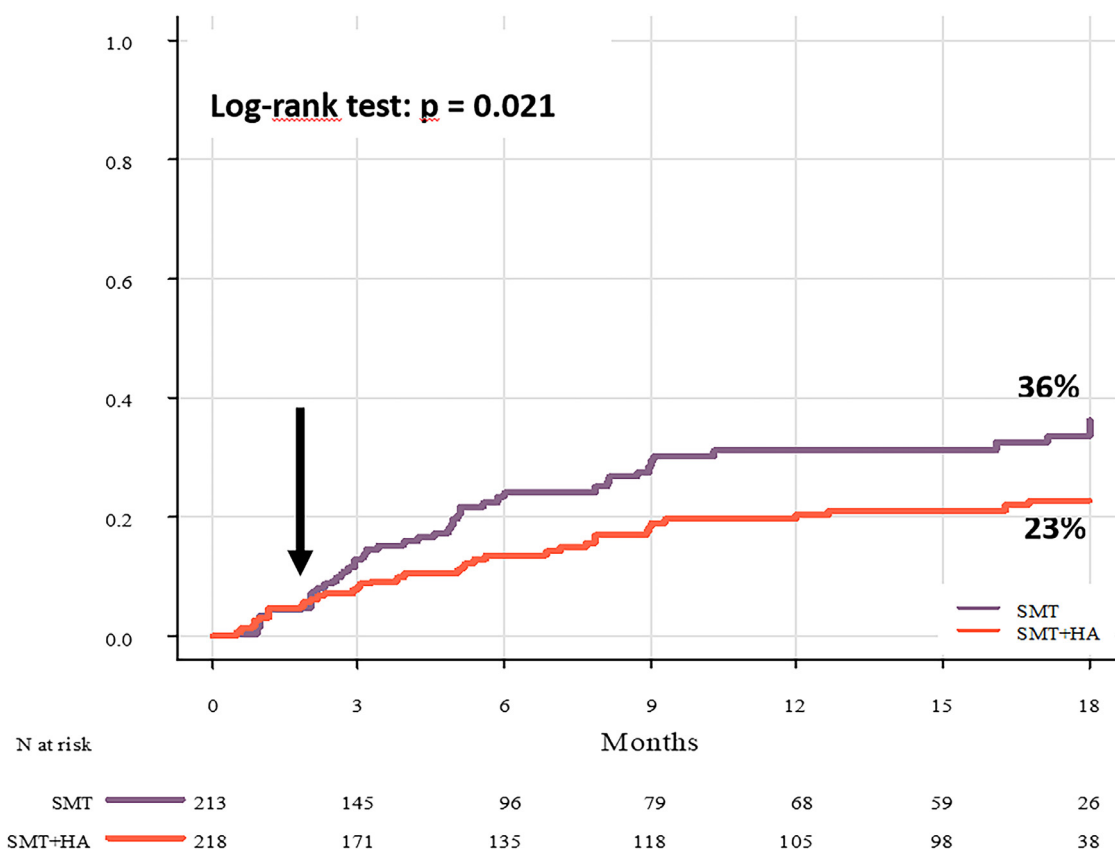
Fig. 5. Cumulative incidence of the first episode of hepatic encephalopathy in the ANSWER trial. SMT = standard medical treatment; SMT + HA = standard medical treatment plus human albumin. Arrow indicates where the curves for the treatments separate at approximately two months. Unpublished data from the ANSWER trial Caraceni et al.

Table 1
Changes in blood markers over the course of the HEAL study.

	Placebo Baseline	Placebo EOD	Placebo EOS	Albumin Baseline	Albumin EOD	Albumin EOS
IL-1β (pg/mL)	0.53±0.57	0.50±0.47	0.47±0.50	0.42±0.39	0.37±0.29*	0.35±0.37*
IL-6 (pg/mL)	3.61±2.67	3.80±2.23	4.94±7.52	3.71±2.56	3.91±2.61	3.18±1.73
TNFα (pg/mL)	15.55±8.34	15.09±6.23	16.88±7.32	16.34±14.46	14.46±7.06	15.06±7.94
IL-10 (pg/mL)	3.69±3.09	2.93±3.17*	3.08±3.02*	4.01±4.07	3.83±2.96	3.28±1.81
LBP (ng/mL)	1784.9±1557.3	1714.8±1255.5	1931.2±316.7	1651.1±952.1	1669.8±1010.4	1659.7±931.6
ICAM-1 (ng/mL)	298.1±97.1	341.6±118.8*	343.6±125.9*	316.7±140.3	271.1±134.1*,†	313.1±125.6
ADMA (μM)	0.65±0.12	0.72±0.13*	0.65±0.14	0.69±0.13	0.63±0.09*,†	0.63±0.10*
IMA (IU/mL)	831.7±1335.6	997.2±1529.3*	1604.9±3082.3*	1491.5±3125.9	1144.1±2812.6*	1042.9±2753.9*

EOD = end of drug treatment; EOS = end of study; IL = interleukin; TNF = tumor necrosis factor; LBP = lipopolysaccharide binding protein; ICAM = intercellular adhesion molecule; ADMA = asymmetric dimethyl arginine; IMA = ischemia-modified albumin [49].
* $p < 0.05$ compared to baseline (Wilcoxon signed rank test and paired t-tests).
† $p , 0.05$ compared to placebo (Kruskal-Wallis test).

preventing bouts of overt HE. However, before a conclusive recommendation could be made, confirmatory new randomized clinical trials, primarily focused on HE, are warranted.

At the same time, further investigation is necessary to determine the mechanisms underlying the protective effect of long-term HA administration. First, the non-oncotic properties of the molecule, particularly the antioxidant and anti-inflammatory activities, could antagonize key mechanisms involved in the pathophysiology of HE, thus supporting a direct protective effect of HA against HE. Alternatively, it could be hypothesized that prevention of new episode of overt HE is the indirect consequence of the effective treatment achieved by long-term HA on other complications of the disease, such as ascites, infections, renal failure, and electrolyte disturbances [53]. At this regard, a complication frequently linked to HE is hyponatremia [64]. Interestingly, as shown in a post-hoc analysis of the ANSWER trial, serum sodium concentration was significantly higher

and correction of hyponatremia faster in patients receiving HA [65]. Finally, it cannot be excluded that both direct and indirect effects concur to the benefits of long-term HA on HE.

3. Conclusions

In summary, the current scientific evidence does not support the use of acute/short-term HA administration for the treatment of overt HE. In contrast, data are accumulating that prolonged or long-term HA administration improves cognitive function and contributes to prevent new episodes of HE. The key for unveiling the clinical benefits appears to be "giving enough HA for enough time". However, additional randomized clinical trials and translational studies that primarily focus on HE are needed to confirm these positive findings and to advance our understanding of the underlying pathophysiological mechanisms of protection.

Declaration of interests

Data availability statement

Data for the studies discussed in this review are available as described in the original publications.

Funding

Accessible materials

Permission was obtained to reproduce previously published material included in this review.

Acknowledgements

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(2):715–35. https://doi.org/10.1002/hep.27210.
[2] Badal BD, Bajaj JS. Hepatic encephalopathy: diagnostic tools and management strategies. Med Clin North Am 2023;107(3):517–31. https://doi.org/10.1016/j.mcna.2023.01.003.
[3] Poordad FF. Review article: the burden of hepatic encephalopathy. Aliment Pharmacol Ther 2007;25(Suppl 1):3–9. https://doi.org/10.1111/j.1746-6342.2006.03215.x.
[4] 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(11):1510–9. https://doi.org/10.1002/hep4.1425.
[5] Tapper EB, Parikh ND, Sengupta N, Mellinger J, Ratz D, Lok ASF, et al. A risk score to predict the development of hepatic encephalopathy in a population-based cohort of patients with cirrhosis. Hepatology 2018;68(4):1498–507. https://doi.org/10.1002/hep.29628.
[6] 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(7):2332–40. https://doi.org/10.1053/j.gastro.2010.02.015.
[7] 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(8):977–86. https://doi.org/10.1002/lt.23909.
[8] Nagel M, Weidner V, Schulz S, Marquardt JU, Galle PR, Schattenberg JM, et al. Continued alcohol consumption and hepatic encephalopathy determine quality of life and psychosocial burden of caregivers in patients with liver cirrhosis. Health Qual Life Outcomes 2022;20(1):23. https://doi.org/10.1186/s12955-022-01923-z.
[9] Elsaid MI, John T, Li Y, Pentakota SR, Rustgi VK. The health care burden of hepatic encephalopathy. Clin Liver Dis 2020;24(2):263–75. https://doi.org/10.1016/j.cld.2020.01.006.
[10] Montagnese S, Bajaj JS. Impact of hepatic encephalopathy in cirrhosis on quality-of-life issues. Drugs 2019;79(Suppl 1):11–6. https://doi.org/10.1007/s40265-018-1019-y.
[11] Kappus MR, Bajaj JS. Covert hepatic encephalopathy: not as minimal as you might think. Clin Gastroenterol Hepatol 2012;10(11):1208–19. https://doi.org/10.1016/j.cgh.2012.05.026.
[12] Reja M, Phelan LP, Senatore F, Rustgi VK. Social iImpact of hepatic encephalopathy. Clin Liver Dis 2020;24(2):291–301. https://doi.org/10.1016/j.cld.2020.01.008.
[13] Schomerus H, Hamster W, Blunck H, Reinhard U, Mayer K, Dölle W. Latent portasystemic encephalopathy. I. Nature of cerebral functional defects and their effect on fitness to drive. Dig Dis Sci 1981;26(7):622–30. https://doi.org/10.1007/bf01367675.
[14] Wein C, Koch H, Popp B, Oehler G, Schauder P. Minimal hepatic encephalopathy impairs fitness to drive. Hepatology 2004;39(3):739–45. https://doi.org/10.1002/hep.20095.
[15] Watanabe A, Tuchida T, Yata Y, Kuwabara Y. Evaluation of neuropsychological function in patients with liver cirrhosis with special reference to their driving ability. Metab Brain Dis 1995;10(3):239–48. https://doi.org/10.1007/bf02081029.
[16] Kircheis G, Knoche A, Hilger N, Manhart F, Schnitzler A, Schulze H, et al. Hepatic encephalopathy and fitness to drive. Gastroenterology 2009;137(5):1706–15 e1-9. https://doi.org/10.1053/j.gastro.2009.08.003.
[17] Felipo V, Urios A, Valero P, Sánchez M, Serra MA, Pareja I, et al. Serum nitrotyrosine and psychometric tests as indicators of impaired fitness to drive in cirrhotic patients with minimal hepatic encephalopathy. Liver Int 2013;33(10):1478–89. https://doi.org/10.1111/liv.12206.
[18] Lauridsen MM, Thacker LR, White MB, Unser A, Sterling RK, Stravitz RT, et al. In Patients with cirrhosis, driving simulator performance is associated with real-life driving. Clin Gastroenterol Hepatol 2016;14(5):747–52. https://doi.org/10.1016/j.cgh.2015.11.007.
[19] Bajaj JS, Hafeezullah M, Hoffmann RG, Saeian K. Minimal hepatic encephalopathy: a vehicle for accidents and traffic violations. Am J Gastroenterol 2007;102(9):1903–9. https://doi.org/10.1111/j.1572-0241.2007.01424.x.
[20] Schomerus H, Hamster W. Quality of life in cirrhotics with minimal hepatic encephalopathy. Metab Brain Dis 2001;16(1-2):37–41. https://doi.org/10.1023/a:1011610427843.
[21] Bajaj JS, Wade JB, Gibson DP, Heuman DM, Thacker LR, Sterling RK, et al. The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. Am J Gastroenterol 2011;106(9):1646–53. https://doi.org/10.1038/ajg.2011.157.
[22] Bajaj JS, Lauridsen M, Tapper EB, Duarte-Rojo A, Rahimi RS, Tandon P, et al. Important unresolved questions in the management of hepatic encephalopathy: An ISHEN consensus. Am J Gastroenterol 2020;115(7):989–1002. https://doi.org/10.14309/ajg.0000000000000603.
[23] Bajaj JS. The three villages of hepatic encephalopathy. Am J Gastroenterol Jun 1 2021;116(6):1184–6. https://doi.org/10.14309/ajg.0000000000001212.
[24] Fabrellas N, Moreira R, Carol M, Cervera M, de Prada G, Perez M, et al. Psychological burden of hepatic encephalopathy on patients and caregivers. Clin Transl Gastroenterol 2020;11(4):e00159. https://doi.org/10.14309/ctg.0000000000000159.
[25] Bustamante J, Rimola A, Ventura PJ, Navasa M, Cirera I, Reggiardo V, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hepatol 1999;30(5):890–5. https://doi.org/10.1016/s0168-8278(99)80144-5.
[26] Jepsen P, Ott P, Andersen PK, Sorensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology 2010;51(5):1675–82. https://doi.org/10.1002/hep.23500.
[27] 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(6):1448–57. https://doi.org/10.1007/s10620-019-05576-9.
[28] Hartmann IJ, Groeneweg M, Quero JC, Beijeman SJ, de Man RA, Hop WC, et al. The prognostic significance of subclinical hepatic encephalopathy. Am J Gastroenterol 2000;95(8):2029–34. https://doi.org/10.1111/j.1572-0241.2000.02265.x.
[29] Patidar KR, Thacker LR, Wade JB, Sterling RK, Sanyal AJ, Siddiqui MS, et al. Covert hepatic encephalopathy is independently associated with poor survival and increased risk of hospitalization. Am J Gastroenterol 2014;109(11):1757–63. https://doi.org/10.1038/ajg.2014.264.
[30] Ampuero J, Montoliu C, Simon-Talero M, Aguilera V, Millan R, Marquez C, et al. Minimal hepatic encephalopathy identifies patients at risk of faster cirrhosis progression. J Gastroenterol Hepatol 2018;33(3):718–25. https://doi.org/10.1111/jgh.13917.
[31] Labenz C, Toenges G, Schattenberg JM, Nagel M, Huber Y, Marquardt JU, et al. Outcome prediction of covert hepatic encephalopathy in liver cirrhosis: Comparison of four testing strategies. Clin Transl Gastroenterol 2020;11(6):e00172. https://doi.org/10.14309/ctg.0000000000000172.
[32] 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(1):78–86. https://doi.org/10.1038/ajg.2015.377.
[33] Bajaj JS, Etemadian A, Hafeezullah M, Saeian K. Testing for minimal hepatic encephalopathy in the United States: An AASLD survey. Hepatology 2007;45(3):833–4. https://doi.org/10.1002/hep.21515.
[34] Bajaj JS, Duarte-Rojo A, Xie JJ, Acharya C, Wade JB, Robles C, et al. Minimal hepatic encephalopathy and mild cognitive impairment worsen quality of life in elderly patients with cirrhosis. Clin Gastroenterol Hepatol 2020;18(13):3008–16 e2. https://doi.org/10.1016/j.cgh.2020.03.033.
[35] Weissenborn K, Ennen JC, Schomerus H, Rückert N, Hecker H. Neuropsychological characterization of hepatic encephalopathy. J Hepatol 2001;34(5):768–73. https://doi.org/10.1016/s0168-8278(01)00026-5.
[36] Schiff S, Vallesi A, Mapelli D, Orsato R, Pellegrini A, Umilta C, et al. Impairment of response inhibition precedes motor alteration in the early stage of liver cirrhosis: a behavioral and electrophysiological study. Metab Brain Dis 2005;20(4):381–92. https://doi.org/10.1007/s11011-005-7922-4.
[37] Bajaj JS, Saeian K, Verber MD, Hischke D, Hoffmann RG, Franco J, et al. Inhibitory control test is a simple method to diagnose minimal hepatic encephalopathy and

predict development of overt hepatic encephalopathy. Am J Gastroenterol 2007;102(4):754–60. https://doi.org/10.1111/j.1572-0241.2007.01048.x.

[38] Ridola L, Cardinale V, Riggio O. The burden of minimal hepatic encephalopathy: from diagnosis to therapeutic strategies. Ann Gastroenterol 2018;31(2):151–64. https://doi.org/10.20524/aog.2018.0232.

[39] 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(3):549–59. https://doi.org/10.1002/hep.21533.

[40] Sharma BC, Sharma P, Agrawal A, Sarin SK. Secondary prophylaxis of hepatic encephalopathy: an open-label randomized controlled trial of lactulose versus placebo. Gastroenterology 2009;137(3):885–91 891 e1. https://doi.org/10.1053/j.gastro.2009.05.056.

[41] Rathi S, Fagan A, Wade JB, Chopra M, White MB, Ganapathy D, et al. Patient Acceptance of lactulose varies between Indian and American cohorts: Implications for comparing and designing global hepatic encephalopathy trials. J Clin Exp Hepatol 2018;8(2):109–15. https://doi.org/10.1016/j.jceh.2017.11.010.

[42] Bajaj JS, Sanyal AJ, Bell D, Gilles H, Heuman DM. Predictors of the recurrence of hepatic encephalopathy in lactulose-treated patients. Aliment Pharmacol Ther 2010;31(9):1012–7. https://doi.org/10.1111/j.1365-2036.2010.04257.x.

[43] Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010;362(12):1071–81. https://doi.org/10.1056/NEJMoa0907893.

[44] 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(4):e60042. https://doi.org/10.1371/journal.pone.0060042.

[45] Sidhu SS, Goyal O, Mishra BP, Sood A, Chhina RS, Soni RK. Rifaximin improves psychometric performance and health-related quality of life in patients with minimal hepatic encephalopathy (the RIME Trial). Am J Gastroenterol 2011;106(2):307–16. https://doi.org/10.1038/ajg.2010.455.

[46] Tapper EB, Essien UR, Zhao Z, Ufere NN, Parikh ND. Racial and ethnic disparities in rifaximin use and subspecialty referrals for patients with hepatic encephalopathy in the United States. J Hepatol 2022;77(2):377–82. https://doi.org/10.1016/j.jhep.2022.02.010.

[47] Fallahzadeh MA, Rahimi RS. Hepatic encephalopathy: Current and emerging treatment modalities. Clin Gastroenterol Hepatol 2022;20(8S):S9–S19. https://doi.org/10.1016/j.cgh.2022.04.034.

[48] Garcia-Martinez R, Caraceni P, Bernardi M, Gines P, Arroyo V, Jalan R. Albumin: pathophysiologic basis of its role in the treatment of cirrhosis and its complications. Hepatology 2013;58(5):1836–46. https://doi.org/10.1002/hep.26338.

[49] Fagan A, Gavis EA, Gallagher ML, Mousel T, Davis B, Puri P, et al. A double-blind randomized placebo-controlled trial of albumin in outpatients with hepatic encephalopathy: HEAL study. J Hepatol 2023;78(2):312–21. https://doi.org/10.1016/j.jhep.2022.09.009.

[50] Ventura-Cots M, Simon-Talero M, Poca M, Ariza X, Masnou H, Sanchez J, et al. Effects of albumin on survival after a hepatic encephalopathy episode: Randomized double-blind trial and meta-analysis. J Clin Med 2021;10(21) 23. https://doi.org/10.3390/jcm10214885.

[51] Simon-Talero M, Garcia-Martinez R, Torrens M, Augustin S, Gomez 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(6):1184–92. https://doi.org/10.1016/j.jhep.2013.07.020.

[52] China L, Freemantle N, Forrest E, Kallis Y, Ryder SD, Wright G, et al. A randomized trial of albumin infusions in hospitalized patients with cirrhosis. N Engl J Med 2021;384(9):808–17. https://doi.org/10.1056/NEJMoa2022166.

[53] 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(10138):2417–29. https://doi.org/10.1016/s0140-6736(18)30840-7.

[54] Di Pascoli M, Fasolato S, Piano S, Bolognesi M, Angeli P. Long-term administration of human albumin improves survival in patients with cirrhosis and refractory ascites. Liver Int 2019;39(1):98–105. https://doi.org/10.1111/liv.13968.

[55] Sola E, Sole C, Simon-Talero M, Martin-Llahi M, Castellote J, Garcia-Martinez R, et al. Midodrine and albumin for prevention of complications in patients with cirrhosis awaiting liver transplantation. A randomized placebo-controlled trial. J Hepatol 2018;69(6):1250–9. https://doi.org/10.1016/j.jhep.2018.08.006.

[56] 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(2):181–3. https://doi.org/10.1016/j.cgh.2010.10.002.

[57] Shawcross DL, Davies NA, Williams R, Jalan R. Systemic inflammatory response exacerbates the neuropsychological effects of induced hyperammonemia in cirrhosis. J Hepatol 2004;40(2):247–54. https://doi.org/10.1016/j.jhep.2003.10.016.

[58] Bajaj JS, Ahluwalia V, Wade JB, Sanyal AJ, White MB, Noble NA, et al. Asymmetric dimethylarginine is strongly associated with cognitive dysfunction and brain MR spectroscopic abnormalities in cirrhosis. J Hepatol 2013;58(1):38–44. https://doi.org/10.1016/j.jhep.2012.08.005.

[59] Shawcross DL, Wright G, Olde Damink SW, Jalan R. Role of ammonia and inflammation in minimal hepatic encephalopathy. Metab Brain Dis 2007;22(1):125–38. https://doi.org/10.1007/s11011-006-9042-1.

[60] Ampuero J, Simon M, Montoliu C, Jover R, Serra MA, Cordoba J, et al. Minimal hepatic encephalopathy and critical flicker frequency are associated with survival of patients with cirrhosis. Gastroenterology 2015;149(6):1483–9. https://doi.org/10.1053/j.gastro.2015.07.067.

[61] Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care 1981;19(8):787–805. https://doi.org/10.1097/00005650-198108000-00001.

[62] clinicaltrails.gov. Hepatic encephalopathy and albumin lasting cognitive improvement (HEAL-LAST). https://classic.clinicaltrials.gov/ct2/show/NCT06052176 Updated 03 January 2024. [accessed 26 February 2024]

[63] Caraceni P, O'Brien A, Gines P. Long-term albumin treatment in patients with cirrhosis and ascites. J Hepatol 2022;76(6):1306–17. https://doi.org/10.1016/j.jhep.2022.03.005.

[64] Younas A, Riaz J, Chughtai T, Maqsood H, Saim M, Qazi S, et al. Hyponatremia and its correlation with hepatic encephalopathy and severity of liver disease. Cureus 2021;13(2):e13175. https://doi.org/10.7759/cureus.13175.

[65] Zaccherini G, Baldassarre M, Tufoni M, Nardelli S, Piano S, Alessandria C, et al. Correction and prevention of hyponatremia in patients with cirrhosis and ascites: post hoc analysis of the ANSWER study database. Am J Gastroenterol 2023;118(1):168–73. https://doi.org/10.14309/ajg.0000000000001995.