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TOPIC HIGHLIGHT

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Hepatic encephalopathy therapy: An overview

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Abstract

Type-C hepatic encephalopathy (HE) is a severe complication of cirrhosis, which seriously affects quality of life and is strongly related to patient survival. Treatment based on a classical pharmacological approach that is aimed at reducing the production of gut-derived toxins, such as ammonia, is still under debate. Currently, results obtained from clinical trials do not support any specific treatment for HE and our competence in testing old and new treatment modalities by randomized controlled trials with appropriate clinically relevant end-points urgently needs to be improved. On the other hand, patients who are at risk for HE are now identifiable, based on studies on the natural history of the disease. Today, very few studies that are specifically aimed at establishing whether HE may be prevented are available or in progress. Recent studies have looked at non absorbable disaccharides or antibiotics and other treatment modalities, such as the modulation of intestinal flora. In the treatment of severe stage HE, artificial liver supports have been tested with initial positive results but more studies are needed.

Key words: Complications of cirrhosis; Porto-systemic shunts; Ammonia; Nitrogen metabolism; Transjugular intrahepatic portosystemic shunt

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INTRODUCTION

Hepatic encephalopathy (HE) is a neurological syndrome that occurs as a consequence of severe liver damage and portal hypertension. HE is divided into three types: (1) encephalopathy associated with acute liver failure [type-A (= acute) HE], occurring in patients with fulminant hepatitis; (2) encephalopathy associated with portal-systemic bypass [type-B (= bypass) HE], observed in patients with portal-systemic bypass and no intrinsic hepato-cellular disease; and (3) [type-C (= cirrhosis) HE][1] most frequently observed in patients with cirrhosis and portal hypertension. This review is on the treatment of the latter type of HE only.

In cirrhotic patients, HE may be clinically overt or minimal. The term minimal HE (MHE) includes a number of cognitive deficits such as alterations of psychomotor speed and executive functions[2], detectable in patients with liver cirrhosis only by psychometric[3-5] or electrophysiological techniques[6,7]. Clinically, overt HE (OHE) may be further divided into episodic (developing over a short period of time and fluctuating in severity), or persistent (with continuous neurological symptoms negatively affecting the patient's self-sufficiency). Both episodic and persistent HE may be induced by a precipitating event or may occur apparently

spontaneously[1]. Some HE precipitating events are: constipation, hypo- or hyperkalemia, alkalosis, hyponatremia, dietary indiscretion, hypovolemia, gastrointestinal bleeding, dehydration, infections, surgery, renal failure, anaemia, diuretics and psychoactive medications. Defining type-C HE into minimal or overt, episodic or persistent and precipitated or spontaneously occurring is clinically relevant since the management of each category is very different. Moreover, in planning clinical trials on HE treatment, including patients that are homogeneous according to the above classifications is of crucial importance.

Type-C HE represents a major clinical problem. In cirrhotic patients who were followed from a time when the disease was compensated, HE represents, in fact, the second most frequent cause of decompensation after ascites and before variceal bleeding[8]. HE is particularly frequent in patients undergoing portal-systemic shunt[9-11], and is considered an important prognostic factor for survival[12-15]. Both overt and MHE have a detrimental effect on the overall quality of life[15], since even MHE impairs the execution of simple and complex tasks, such as driving[16-18]. For these reasons, research searching for a better treatment is ongoing.

At present, many aspects of HE remain a matter of debate and are seen as "beyond treatment". The current recommendations are based on the generic hypothesis that the symptoms are caused by the loss of a "protective" mechanism exerted by the liver on brain functions. As an effect of liver failure and porto-systemic shunting, substances arising from the gut are able to reach the systemic circulation and the central nervous system, where they can exert a "toxic effect" on brain function. This concept goes back to the beginning of the last century and is supported by: (1) the high incidence of HE after surgical, radiological or spontaneous porto-systemic shunting[9,10,19-22]; (2) the improvement of HE after bowel cleansing by enema[23] or gut irrigation[24]; (3) the improvement of HE by decreasing the stent diameter of transjugular intrahepatic porto-systemic shunts (TIPS)[22,25], and consequently, increasing the amount of intestinal blood shunted into the systemic circulation; and (4) the improvement of HE by closing large spontaneous porto-systemic shunts[26]. Any attempt to clarify the nature of the substances involved in the pathogenesis of HE, as well as the exact mechanism affecting brain function, have been unsatisfactory until now. Ammonia is still incriminated more often, but several other compounds, such as mercaptans, short-chain fatty acids amines, γ-aminobutyric acid (GABA), endorphins, glutamate, endogenous benzodiazepine agonists, tryptophan and several of its metabolites have also been investigated.

However, the role of these factors is still a matter of debate. As far as the mechanism involved in the central nervous system is concerned, in the last few years, astrocyte swelling has been identified as an important process negatively influencing neuronal neurotransmission as well as the brain energy production rate. Moreover, astrocyte swelling may affect the function of important brain proteins by causing oxidative and nitrosative stress with evidence of protein tyrosine nitration and, more recently, ribonucleic acid (RNA) oxidation[27]. The astrocyte swelling hypothesis is able to explain one of the key features of HE, namely that the syndrome is precipitated by heterogeneous factors. Many of these factors have been shown to induce the swelling of astrocytes by different mechanisms[28]. The infection may, for example, induce astrocyte swelling by endotoxins and pro-inflammatory cytokines[29]. Moreover, it has been recently proposed that neutrophils, in addition to ammonia, may be involved in the pathogenesis of HE. Thus, neutrophils can be a target for future anti-inflammatory therapeutic strategies in addition to ammonia lowering therapies[30].

Uncertainties on the pathogenesis of HE limit the development of specific pharmacological therapies. Nevertheless, treatments such non-absorbable disaccharides or antibiotics, gut cleansing by enemas or nasogastric tubes, general measures such as nutritional supports, correction of the precipitating events and of electrolyte imbalance have been used empirically for a long time and are considered standard treatments[31] in patients with HE. Unfortunately, their efficacy cannot be considered as "evidence-based". In fact, most studies were performed before the era of rigorous randomized controlled trials (RCTs) and well-designed therapeutic trials on HE are warranted. It can be difficult to objectively stage HE's severity and to appropriately select clinically relevant end-points[32].

PREVENTION OF HE

A number of observational studies on the natural history of HE and on risk factors for its development are in the literature. These studies allow the identification of patients at risk for developing this complication of liver cirrhosis with sufficient confidence. Therefore, prevention of HE is possible. Preventive treatments are above all needed by patients at high risk of HE, such as those with more advanced liver disease (Child C or ascites)[33], those undergoing radiological[9,11,19-22] or surgical porto-systemic shunts, as well as those bearing large spontaneous shunts in whom episodes of HE are very frequent or persistent[21]. Other patients likely to be selected for preventive measures are those who have already had at least one episode of HE in the past[34] and those with MHE at their first observation[4,35,36]. These two conditions are in fact associated with bouts of HE at follow up.

Given the large prevalence of patients at risk of HE, the possible advantages of a life- long preventive treatment should be balanced against possible adverse events and costs and should be tested by appropriate RCTs. These studies should be specifically aimed at establishing whether HE can be prevented. Their design should be different from that used in HE treatment studies. In fact, the ideal preventive study should include patients without HE at entry, and the main end-point should be the occurrence of any overt episode of HE during follow-up. This end point is very objective and easily identifiable. Each study should include patients with a given risk factor for HE. For exam-

Table 1 RCTs on the prevention of episodes of overt hepatic encephalopathy

Ref.	Type and NO. of patients included	Aim of the study	Tested treatment (s)	Control treatment	Results
Riggio *et al*[38] 2005	Patients submitted to TIPS (75)	Prevention of post TIPS HE	Lactitol (60 g/d) rifaximin (1200 mg/d)	No treatment (25)	No difference between treatment and control groups
Sharma *et al*[39] 2009	Patients who recovered from HE (140)	Prevention of recurrence of HE (secondary prophylaxis)	Lactulose (30-60 mL in 2 or 3 divided doses)	No treatment (70)	Lactulose effective
Kanematsu *et al*[42] 1988	Patients submitted to surgery (56)	Prevention of HE precipitated by surgery	BCAA enriched solution, (29)	Conventional AA solution (27)	No difference between treatment and control groups
Rolachon *et al*[24] 1994	Patients bleeding from varices	Prevention of HE precipitated by bleeding	Gut cleansing using mannitol by naso-gastric tube	No treatment	Gut cleansing effective
Bass *et al*[53] 2009	History of HE	Prevention of recurrence of HE (secondary prophylaxis)	Rifaximin 550 mg twice daily for 6 mo	Placebo	Rifaximin effective

TIPS: Transjugular intrahepatic portosystemic shunt; HE: Hepatic encephalopathy; BCAA: Branched-chain amino acid.

ple, all patients who survived a first episode of HE or, as another example, all patients submitted to a transjugular intrahepatic portosystemic shunt (TIPS) The sample size for the study could be estimated from the incidence of HE in the population at risk (for example, from the incidence of HE occurring in patients submitted to a TIPS). The inclusion of a "no-treatment" or a "placebo" group is mandatory. Cost/benefit ratios, as well as data on tolerability and safety, should be considered. Survival should be a secondary end point of the study. Since a prophylactic treatment should be prolonged life-long, the ideal therapy should be extremely safe and well tolerated.

In clinical practice, measures to reduce the nitrogenous load from the gut, such as long-term administration of non-absorbable disaccharides, are commonly applied in patients with advanced cirrhosis[37]. However, their efficacy in preventing HE has been specifically tested only very recently; one RCT report is now available on patients submitted to a TIPS and another has been reported on patients who recovered from an episode of OHE (secondary prophylaxis) (Table 1).

In post-TIPS patients, a recent RCT demonstrated that there was no difference in the incidence of OHE during the first month after TIPS placement, regardless of whether the patients received a prophylaxis with lactitol, rifaximin or no treatment[38]. On the contrary, lactulose has been shown to be able to significantly prevent the occurrence of a second episode of HE in patients who recovered from the first episode[39]. In both studies, a control group receiving no treatment was included. Therefore, low-absorbable disaccharides (lactitol or lactulose) resulted in effective prevention of recurrence of HE after a first episode but not in the prevention of HE after a TIPS. These different results underline the need for including homogeneous patients with specific risk factors in studies aimed at HE prophylaxis. In fact, HE in the first month after TIPS placement may be particularly difficult to prevent. Further compromise of first-pass hepatic clearance of ammonia is to be expected after TIPS placement. Additionally, splanchnic blood flow increases when there is a major reduction of the porto-systemic pressure gradient. Thus, delivery of ammonia to the systemic circulation may increase. Another factor to consider is upregulation of intestinal glutaminase activity, which has been reported to increase after porto-systemic shunt procedures[40]. This enzyme is responsible for the large amount of ammonia generated by the small intestine. Accordingly, one might anticipate that in the immediate aftermath of a TIPS procedure, more "intense" HE therapy might be needed to prevent overt episodes of HE.

Another RCT aimed at studying the effect of a probiotic yoghurt on the psychometric performance of cirrhotic patients with MHE showed that the episodes of OHE at follow up were significantly lower that those observed in the no-treatment arm of the study[41].

Concerning the prevention of precipitant induced HE, a series of specific treatments may be adopted, such as blood aspiration by a nasogastric tube, gut cleansing (by means of gut lavage, oral laxatives or enemas), parenteral/enteral nutrition (in case of bleedings or infections that may lead to a negative energy balance), diet (e.g. no proteins, low proteins, vegetable proteins) and specific drugs [e.g. branched-chain amino acids (BCAAs), ornithine aspartate, non-absorbable disaccharides, antibiotics]. However, until now, RCTs specifically aimed at testing these prophylactic approaches are very few. The only examples are a RCT showing that gut cleansing by means of a solution of mannitol can reduce the incidence of post-hemorrhagic HE[24] and another study on post-operative parenteral nutrition that showed no differences in the rate of occurrence of HE between patients treated with BCAAs-enriched and conventional amino acid solutions[42] (Table 1).

TREATMENT OF HE

MHE

The diagnosis and treatment of MHE are still active matters of discussion[43]. Computerized tests have been recently proposed (and validated) in patients with MHE[44,45] and may represent an amelioration of our diagnostic capacity. Most studies available in the literature have shown that several pharmacological approaches seemed to ameliorate patient psychometric performances. However, MHE affects quality of life and is a risk factor for the development of episodes of OHE[4,35,36]. In the last few years, it has been repeatedly suggested that it may seri-

Table 2 RCTs on the treatment of MHE

Ref.	Type of study	Type of HE/ patients (*n*)	Tested treatment	Control treatment	Results
Prasad *et al*[46] 2007	RCT	MHE (61)	Lactulose (30-60 mL of lactulose in 2 or 3 divided doses)	No treatment	Lactulose improved the quality of life
Bajaj *et al*[41] 2008	Prospective randomized trial	MHE (25)	Probiotic yoghurt	No treatment	Probiotic improved the psychometric performance
Liu *et al*[73] 2004	Double blind, randomized study	MHE (55)	Bioactive, fermentable fibers and lactic acid bacteria	Placebo	Synbiotic treatment improved the psychometric performance and the Child-Turcotte-Pugh class
Malaguarnera *et al*[74] 2009	Randomized study	MHE (125)	Bioactive, fermentable fibers Bifidobacterium + fructo-oligosaccharides	Lactulose	Both treatments improve blood ammonia and psychometric performance

MHE: Minimal hepatic encephalopathy.

ously impair the driving capacity of cirrhotic patients[16,18], which can be evaluated by driving simulators[17].

The recent demonstration that lactulose in patients with MHE is able to induce an amelioration in the quality of life[46] raised a new prospective in the therapeutic approach of this clinical condition (Table 2). In fact, the demonstration that a given treatment can ameliorate patient psychometric performances, although obtained in RCTs (Table 2), is meaningless because MHE is by definition a subclinical condition. Future studies on the treatment of MHE should be aimed a ameliorating the clinical consequences of this alteration. In addition to quality of life, possible end-points in these studies could be the prevention of overt episodes of HE, which are particularly frequent in patients with MHE, and the improvement of skills such as driving capacity. Nevertheless, the modification of psychometric tests should not be chosen as the main end-point of the study, but as criteria to include comparable patients. Since a treatment of MHE should be prolonged life-long, the ideal therapy should be extremely safe and well tolerated. The modulation of intestinal bacterial flora can be a valid therapeutic approach for MHE.

Precipitant-induced episodic HE

The cornerstones of treatment for precipitant-induced episodic HE are the identification and treatment of the precipitating events and the general support of patients. In fact, the prevention of falls or body injuries in disorientated patients, the care of bladder and bowel functions, the care of intravenous lines, the monitoring of fluid balance, the monitoring of blood glycaemia and electrolytes (such as of arterial blood gases), the correction of acid/base disorders, blood pressure monitoring and the avoidance of aspiration pneumonia are the strategies commonly applied to support patients with episodic HE. The nutritional status of the patient is also considered to be useful. An energy intake of 35/40 kcal/kg body weight per day and a protein intake of 1.2/1.5 g/kg body weight per day are recommended. Energy should be provided by glucose and fat in a ratio of 50%-65%/35%-50% of non-protein calories, according to the european society of parenteral and enteral nutrition guidelines for nutrition in liver disease[47].

Moreover, in patients with severe HE (grades Ⅲ to Ⅳ), solutions with an increased content of BCAAs and a reduced amount of aromatic amino acids can ameliorate neurological symptoms by ensuring, at the same time, an adequate protein intake.

The action of a well-recognized precipitating factor acts as a trigger in precipitant-induced HE. Multiple precipitating events may coexist in the same patient. Although not specifically evaluated, the identification and correction of the precipitating event is considered the first-line effort in patients with this type of HE. If the symptoms do not ameliorate once the identified precipitating event is resolved, a well-known clinical rule is to search for a second complication, for example, a superimposed infection in a patient who has recently bled. Some strategies that are commonly applied to stop precipitating events are the following: (1) in patients with HE induced by gastrointestinal hemorrhage, stop the bleeding with vasoactive drugs, an endoscopic therapy or an angiographic shunt (TIPS), correct the anemia with a blood transfusion and use a nasogastric tube to facilitate upper gastrointestinal cleansing; (2) infections (e.g. pulmonary, of the urinary tract, spontaneous bacterial peritonitis) should be promptly treated with appropriate antibiotic therapies; (3) constipation should be resolved by cathartic and/or bowel enema, electrolyte abnormalities by discontinuing diuretics and correcting hypo- or hyperkalemia; (4) deterioration of renal function should be corrected, if possible, by stopping diuretics, treating dehydration and discontinuing nephrotoxic drugs; and (5) if HE is precipitated by the administration of exogenous sedatives, benzodiazepines should be discontinued and flumazenil, the competitive benzodiazepine antagonist that binds with the benzodiazepine receptor with a high affinity, should be initiated, thus inhibiting the action of these drugs[48] (Table 3).

Recurrent/persistent HE

Searching for possible identifiable and correctable precipitating events is important also in recurrent/persistent HE. The presence of large spontaneous porto-systemic shunts is demonstrable in some patients with persistent HE[21]. In selected cases, the diameter of such large shunts have been reduced by surgical or radiological techniques, resulting in an amelioration in HE[49-52]. Since

Table 3 Treatment strategies in patients with precipitant-induced episodic HE

General supportive care	
	Prevention of falls or body harm in disorientated patients
	Care of bladder and bowel function
	Care of i.v. lines
	Monitor fluid balance
	Monitor glycaemia and electrolytes
	Monitor arterial blood gases
	Correct acid/base disturbances
	Monitor blood pressure
	Avoid aspiration pneumonia
	Prevent causes of sepsis
Support nutritional needs	An energy intake of 35-40 kcal /kg BW/d and a protein intake of 1.2-1.5 g/kg BW/d are recommended. Energy should be provided by glucose and fat in a ratio of 65-50: 35%-50% of non protein calories according to the ESPEN guidelines for nutrition in liver disease (31)
	In patients with severe hepatic encephalopathy (Grade Ⅲ-Ⅳ), solutions with an increase content of BCAAs and reduced amount of aromatic amino acid can ameliorate neurological symptoms ensuring adequate protein intake
Treatment of the precipitating event	
GI bleeding	Stop bleeding with vasoactive drugs, endoscopic therapy or angiographic shunt (TIPS)
	Correct anaemia with blood transfusion
	Nasogastric tube to facilitate upper GI cleansing
Infection (pulmonary, urinary tract, spontaneous bacterial peritonitis)	Appropriate antibiotic terapie
Exogenous sedatives	Discontinue benzodiazepines
Electrolyte abnormalities	Discontinue diuretics
	Correct hypo or hyperkalemia
Constipation	Cathartic
	Bowel enema
Deterioration of renal function	Discontinue diuretics
	Correct dehydration
	Discontinue nephrotoxic antibiotics

large spontaneous shunts are similar to a well-functioning surgical or radiological anastomosis, this approach must be balanced against the possibility of a significant increase in portal hypertension and liver transplantation should always be considered as the first option in these patients. Refractory post-TIPS HE may also be successfully treated by reducing the stent diameter[22,25]. Since the treatment should be prolonged life-long, the ideal therapy should be extremely safe and well tolerated.

PHARMACOLOGICAL APPROACHES TO THE TREATMENT OF HE

The following pharmacological approaches have been used in the treatment of HE (Table 4).

Low-absorbable antibiotics

One of the first strategies applied in patients with HE aimed to suppress bacteria involved in colonic ammonia genesis. In fact, more than 25 trials evaluated the use of a large series of antibiotics (i.e. neomycin, paromomycin, metronidazole, vancomycin, rifaximin) in patients with minimal, persistent and episodic HE. Currently, however, the use of antibiotics is only recommended for short periods of time. However, a recent study suggested that rifaximine may be given for prolonged periods safely and this drug may be able to prevent HE recurrence in patients with previous episodes of OHE[53].

Non-absorbable disaccharides

Lactulose and lactitol administered per os, reaching the colon unmodified, act by reducing the production and absorption of ammonia through several mechanisms. A recent systematic review concluded that "there is insufficient evidence to determine whether non-absorbable disaccharides are of benefit in patients with HE"[54]. Although this analysis can be criticized on several aspects[55], it has raised the issue of non-absorbable disaccharide efficacy and, more generally, the need for placebo-controlled trials in the therapy of HE[56]. An open label RCT that was recently published concluded that lactulose is effective for secondary prophylaxis of HE; i.e in patients who recovered after a first episode[39].

Interestingly, in the group of patients treated with lactulose, significantly fewer patients developed an overt episode of HE precipitated by infections. Non-absorbable disaccharides were able to reduce bacterial translocation in cirrhotic patients, thus reducing the occurrence of spontaneous bacterial peritonitis and other infections. By the same mechanism, these drugs were able to reduce the inflammation, which had been proposed as a pathogenetic mechanism for astrocyte swelling in the brain.

Association between intestinal antibiotics and non-absorbable disaccharides

From a pathophysiological point of view, the association between intestinal antibiotics and non-absorbable disaccharides should not provide additive benefits because

Table 4 Some of the RCTs available on the treatment of hepatic encephalopathy

Ref.	Type of study	Type of HE/ patients (*n*)	Tested treatment	Control treatment	Results
Uribe *et al*[23] 1987	Double-blind, controlled trial	Episodic overt HE (20)	Lactitol and lactose enemas	Nonacidifying enemas	Acidifying agents like lactose and lactitol are effective and superior to tap-water enemas for the treatment of HE
Hassanein *et al*[31] 2007	Prospective, randomized, controlled, multicenter trial	Severe episodic overt HE (70)	Molecular adsorbent recirculating system (MARS) and standard medical therapy	Standard medical therapy	MARS is associated with an earlier and more frequent improvement of HE
Kircheis *et al*[57] 1997	Randomized, double-blind, placebo-controlled, multicenter trial	MHE (53) and mild overt HE (grade Ⅰ-Ⅱ, 53)	L-ornithine-L-aspartate, 20 g/d i.v.	Placebo	Therapy improves psychometric performance and is safe and effective in HE treatment
Stauch *et al*[58] 1998	Randomized, double-blind, placebo-controlled clinical trial	MHE (23) and mild overt HE (43)	L-ornithine-L-aspartate, 9 g/d orally	Placebo	Therapy improves psychometric performance, blood ammonia levels and is safe and effective in HE treatment
Ahmad *et al*[59] 2008	RCT	Overt HE (80)	L-ornithine-L-aspartate, 20 g/d i.v.	Placebo	Treatment improves blood ammonia and mental state
Sushma *et al*[62] 1992	Prospective randomized double-blind study	Overt HE (74)	Sodium Benzoate, 5 g	Lactulose	Improvement in portal-systemic encephalopathy parameters occurred in both treatment groups and was similar
Reding *et al*[66] 1984	Double-blind randomised trial	Chronic HE (22)	Zinc acetate 600 mg/d	Placebo	Treatment improves psychometric performance
Riggio *et al*[67] 1991	Double-blind, crossover trial	Chronic HE (15)	Zinc sulfate 600 mg/d and lactitol	Lactitol	Zinc was significantly raised after oral administration, but no modification in the parameters included in Conn's index were observed
Loguercio *et al*[72] 1995	Double blind parallel trial	HE (40)	SF-68	Lactulose	SF-68 improves blood ammonia and psychometric performance
Gentile[75] 2005	Randomized, double-blind, crossover study	HE (107)	Acarbose 300 mg/d	Placebo	Acarbose improves blood ammonia levels and HE clinical parameters

the former are supposed to act against the intestinal flora, which are responsible for the efficacy of the latter. Nonetheless, some clinical observations support a role for this association in the sub-group of patients with a scarce response to each agent separately. The efficacy of the association can be monitored through the measurement of faecal pH, which should be maintained as lower than 6.

Ornithine aspartate

L-ornithine-L-aspartate (LOLA) is a stable salt composed of two natural amino acids, both important substrates in the metabolic conversion of ammonia to urea and glutamine. LOLA induces an increase of liver and muscle ammonia metabolism, leading to a decrease in blood levels, and is able to cross the blood-brain barrier, increasing the cerebral ammonia disposal. The drug can be administrated both intravenously and orally[57-60]. According to the results of published studies, LOLA is more effective than placebo in reducing blood ammonia and in ameliorating patient mental status and psychometric performance. It should be noted that additional studies have been completed but the publication of results was not allowed by the company producing the drug[55]. Moreover, LOLA is not available in several countries. Recently LOLA showed similar results to placebo in patients with acute liver failure and HE[61].

Drugs favoring alternative pathways of nitrogen metabolism

Sodium benzoate (SB) is able to bind ammonia to form hippurate, a non-toxic substance that can be eliminated in urine and is widely used in patients with a congenital deficit in the urea cycle. SB has the advantage of being particularly inexpensive (1/30 of the cost of lactulose). SB showed an efficacy similar to lactulose in patients with episodic precipitant-induced HE[62], but a note of caution in the use of SB in cirrhotic patients derives from the observation that its administration (10 g/d) induced an increase in both basal blood ammonia and glutamine-induced ammonia levels[63]. Moreover, the prolonged use of SB can interfere with the management of ascites because it induces a significant sodium load. Sodium phenylacetate and SB (Ammonul) is the only drug approved by the Food and Drug Administration for the treatment of acute hyperammonemia and associated encephalopathy in patients with urea cycle disorders[64]. Ammonul *via* intravenous injections is able to promote the synthesis of non-urea nitrogen-containing metabolites, which can be excreted in the urine. A RCT on cirrhotic patients with severe (grade Ⅲ-Ⅳ) HE is currently ongoing. HPN-100 is a pro-drug of phenylbutyrate and a pre-pro-drug of phenylacetic acid (dosed orally in a liquid form). HPN-100 provides an alternative pathway to the urea cycle for the disposal of waste nitrogen through renal excretion of phenylacetylglutamine. The drug is under investigation in patients with urea cycle diseases but has never been used in patients with liver failure.

Zinc

Zinc deficiency has been reported in patients with liver cirrhosis and related neurologic dysfunction. Moreover, reduced zinc concentrations inversely correlate with blood

Table 5 Possible future approaches to HE treatment

Objectives	Approaches currently used	Proposed approaches under evaluation
To reduce the production of Gut-derived toxins	Disaccharides	Probiotics
	Low-absorbable antibiotics	Fermentable fibers, acarbose
		Spherical adsorptive carbon (AST 120)
To favor nitrogen metabolism	Liver transplantation	Artificial liver support
	Reduction of TIPS diameter	Sodium benzoate + phenylacetate (Ammonul)
	Closure of a spontaneous portal systemic shunt	L-ornithine phenylacetate
	Ornithine Aspartate	HPN-100 (Phenylbutyrate + phenylacetic acid)
	Zinc	
	Sodium benzoate	
To correct the alterations in neurotransmission	BCAA	
	Flumazenil	

ammonia and experimental studies showed that zinc supplementation improves ammonia detoxification through urea genesis by increasing liver ornithine transcarbamylase activity[65]. Existing RCTs on oral zinc supplementation to cirrhotic patients, however, have shown conflicting results[66,67].

Benzodiazepine antagonists

Endogenous benzodiazepine (BZD)-like substances have been involved in HE pathogenesis. Flumazenil is a competitive BZD antagonist. One meta-analysis of six RCTs[68] showed that flumazenil induced a clinical improvement in 27% of the patients versus 3% of the placebo group, and an improvement of the EEG tracing (19% *vs* 2%). Another meta-analysis, including 12 trials for a total of 756 patients, led to the conclusion that flumazenil had no significant effect on recovery or survival from HE[69]. No side effects were observed during flumazenil treatment.

BCAAs

Several RCTs and reviews have assessed the effects of BCAAs in patients with HE. In fact, solutions with an increased content of BCAAs and a reduced amount of aromatic amino acids can ameliorate neurological symptoms by ensuring an adequate protein intake at the same time. One meta-analysis[70] concluded that BCAA increased recovery rates from episodic HE without definite effects on mortality, and a more recent review[71], based on 11 RCTs, where BCAAs were either parenterally or orally administered and given alone or as part of solutions containing other amino acids, confirmed that BCAAs significantly increased the number of patients improving from HE as compared with control treatments, without any convincing evidence of any effect on survival. The authors remarked that most trials were small, with a short follow-up, and were of low methodological quality.

Modulators of intestinal bacterial flora

Probiotics, synbiotics (when combined with fermentable fibres), and prebiotics can reduce ammonia production by modifying the gut bacterial flora. The effect of these products in the treatment of HE are currently under investigation: two RCTs have been reported on the effect of probiotics on minimal[41] and OHE[72]; two on synbiotics in MHE[73,74] and one on prebiotic acarbose in patients with OHE[75]. Table 5 shows an overview of the new therapeutic approaches for HE treatment.

FURTHER APPROACHES

Artificial devices

Artificial devices have been shown to improve HE symptoms in patients with decompensated cirrhosis, probably by favoring the disposal of toxins accumulated as the result of a failing liver. Extra-corporeal albumin dialysis (ECAD), using the molecular adsorbent re-circulating system (MARS), has been recently tested by a RCT. Seventy patients with grade-Ⅲ or grade-Ⅳ HE were randomised to receive ECAD plus standard medical therapy (SMT) or SMT alone. The improvement of HE was significantly more frequent and faster in the ECAD group as compared with the SMT group[31].

Correction of electrolyte disturbances

Hyponatremia, commonly found in patients with cirrhosis and ascites, may increase brain edema, a typical condition in case of acute liver failure. A "low-grade brain edema" leading to astrocyte swelling has been also hypothetically thought to be involved in the pathogenesis of type-C HE[29,76]. In rats with a portacaval shunt, chronic hyponatremia exacerbated ammonia-induced brain edema[77]. Hyponatremia was related, in patients with cirrhosis, to the comparison of electroencephalographic abnormalities, known as a risk factor for the development of OHE[22] and a well-known precipitating factor for the development of episodic HE. In this direction, Aquaretic drugs have been proposed in the treatment of hyponatremia in cirrhotic patients[78]. Unfortunately, their use in the prevention of HE in cirrhotic patients with low sodium levels or in the treatment of episodic HE precipitated by hyponatremia can be only hypothesized, since it was never tested until recently. No data are available on the evolution of HE in patients treated with aquaretic drugs.

CONCLUSION

The efficacy of most pharmacological approaches tradi-

tionally used in the treatment of HE is still a matter of intense debate. The empirically developed strategies for the treatment of HE, such as the identification and treatment of the precipitating event and the general support of the patients with episodic HE or the reduction of the blood flow thought a large portal-systemic shunt in the patients with recurrent/persistent HE, make this complication treatable in the majority of patients.

Therapy for HE remains strongly based on the pathophysiological assumption that nitrogen substances coming from the gut are not cleared by the failing liver and are relevant for the modifications occurring in the central nervous system. Improvement in our knowledge of the pathogenesis of HE suggests that several new therapies for HE will emerge (Table 5). These new approaches are likely to be derived from: (1) a better understanding of the cause of astrocyte swelling in the brain as well as the role of inflammation in the pathogenesis of HE; and (2) new knowledge on ammonia trafficking and on the role of intestine and kidney in nitrogen handling. At the same time, our competence in testing old and new treatment modalities should be enhanced urgently. Novel, well designed studies are needed. In particular, RCTs of the new era should have the following characteristics: (1) Homogeneous patients should be included. For example, the inclusion of patient groups with both minimal and OHE in the same study is to be avoided, as it is now clear that these two types of patients are not comparable and the methodology used to stage their symptoms is completely different; (2) Appropriate end points for the study need to be chosen, such as improvement in quality of life or the prevention of future OHE manifestations; and (3) It is necessary to standardize and objectively stage the severity of OHE. In fact, the development of a simple and clinically applicable standardized grading scale, useful for both diagnosing and staging, is essential to obtain a diagnostic tool that is easily applied in practice and sufficiently accurate to offer precise end-points for controlled therapeutic trials.

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