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PRACTICE GUIDELINES

Hepatic Encephalopathy

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PREAMBLE

Guidelines for clinical practice are intended to suggest preferable approaches to particular medical problems as established by interpretation and collation of scientifically valid research, derived from extensive review of the published literature. When data are not available that will withstand objective scrutiny, a recommendation may be made based on a consensus of experts. Guidelines are intended to apply to the clinical situation for all physicians without regard to specialty. Guidelines are intended to be flexible, not necessarily indicating the only acceptable approach, and should be distinguished from standards of care that are inflexible and rarely violated. Given the wide range of choices in any health care problem, the physician should select the course best suited to the individual patient and the clinical situation presented. These guidelines are developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee. These guidelines are also approved by the governing board of the American Gastroenterological Association. Expert opinion is solicited from the outset for the document. Guidelines are reviewed in depth by the committee, with participation from experienced clinicians and others in related fields. The final recommendations are based on the data available at the time of the production of the document and may be updated with pertinent scientific developments at a later time. The following guidelines are intended for adults and not for pediatric patients. (Am J Gastroenterol 2001;96:1968–1976. © 2001 by Am. Coll. of Gastroenterology)

INTRODUCTION

Hepatic encephalopathy (HE) may be defined as a disturbance in central nervous system function because of hepatic insufficiency. This broad definition reflects the existence of a spectrum of neuropsychiatric manifestations related to a range of pathophysiological mechanisms. Present in both acute and chronic liver failure, these neuropsychiatric manifestations are potentially reversible.

Multiple treatments have been used for HE. However, their efficacy has been infrequently assessed by well-designed randomized clinical trials. This handicap reflects the difficulty in evaluating the wide range of neuropsychiatric symptomatology. Alteration of consciousness—its most relevant manifestation—undergoes spontaneous fluctuations and will be influenced by concurrent clinical factors, such as infection, hypoxemia, GI hemorrhage, or electrolyte disturbances. Despite these limitations, a critical appraisal of available data renders it possible to delineate a rational approach to the treatment of HE.

CLINICAL CONSIDERATIONS

Pathophysiology

The main tenet of all theories of the pathogenesis of HE is firmly accepted: nitrogenous substances derived from the gut adversely affect brain function. These compounds gain access to the systemic circulation as a result of decreased hepatic function or portal-systemic shunts. Once in brain tissue, they produce alterations of neurotransmission that affect consciousness and behavior. Abnormalities in glutamatergic, serotoninergic, γ-aminobutyric acid–ergic (GABA-ergic), and catecholamine pathways, among others, have been described in experimental HE (1). The research challenge lies in the dissection of each of these systems and their possible pharmacological manipulation to improve treatment.

A large body of work points at ammonia as a key factor in the pathogenesis of HE (2, 3). Ammonia is released from several tissues (kidney, muscle), but its highest levels can be found in the portal vein. Portal ammonia is derived from both the urease activity of colonic bacteria and the deamidation of glutamine in the small bowel, and is a key substrate for the synthesis of urea and glutamine in the liver. The hepatic process is efficient, with a first pass extraction of ammonia of approximately 0.8 (4). In acute and chronic liver disease, increased arterial levels of ammonia are commonly seen. In fulminant hepatic failure (FHF), elevated arterial levels (>200 μg/dl) have been associated with an increased risk of cerebral herniation (5). However, correlation of blood levels with mental state in cirrhosis is inaccurate. The blood-brain barrier permeability to ammonia is increased in patients with HE (6); as a result, blood levels will correlate weakly with brain values, though recent studies indicate an improvement of this correlation by correcting the ammonia value to the blood pH (7). Furthermore, the alterations in neurotransmission induced by ammonia also occur after the metabolism of this toxin into astrocytes (3),

resulting in a series of neurochemical events caused by the functioning alteration of this cell (8).

Other gut-derived toxins have been proposed. Benzodiazepinelike substances (9) have been postulated to arise from a specific bacterial population in the colon (10). Other products of colonic bacterial metabolism (11), such as neurotoxic short- and medium-chain fatty acids, phenols, and mercaptans, have received less attention in recent years. Manganese may deposit in basal ganglia and induce extrapyramidal symptomatology (12). All of these compounds may interact with ammonia and result in additional neurochemical changes. For example, ammonia activates peripheral-type benzodiazepine receptors with subsequent stimulation of the GABA-ergic system, an effect also induced directly by ammonia (13).

Clinical Subtypes

Under the auspices of the World Congress of Gastroenterology, a consensus terminology has been proposed to normalize the designation of the different clinical presentations of HE (14). The most distinctive presentation is the development of an acute confusional state that can evolve into coma (acute encephalopathy). Patients with FHF and subjects with cirrhosis can present with acute encephalopathy. In patients with cirrhosis, acute encephalopathy is most commonly associated with a precipitating factor that triggers the change in mental state.

In cirrhosis, recurrent episodes of an altered mental state may occur in the absence of precipitating factors (recurrent encephalopathy) or neurological deficits may not completely reverse (persistent encephalopathy). The most frequent neurological disturbance is not evident on clinical examination: mild cognitive abnormalities only recognizable with psychometric or neurophysiologic tests (minimal or subclinical encephalopathy).

The therapeutic imperative in the first three subtypes is clear. Considerable controversy still exists regarding the definition and clinical implications of a diagnosis of minimal encephalopathy (15, 16).

Diagnosis

Hepatic encephalopathy is a diagnosis of exclusion.

Other metabolic disorders, infectious diseases, intracranial vascular events, and intracranial space–occupying lesions can present with neuropsychiatric symptomatology. Knowledge of the existence of acute or chronic liver disease, the existence of a precipitating factor, and/or a prior history of HE are clinical elements needed for diagnosis.

Intrinsically linked to the diagnosis of HE is an evaluation of the degree of liver dysfunction and possible alterations of the hepatic circulation (thrombosis, large spontaneous portal-systemic shunt, transjugular intrahepatic portal-systemic shunt [TIPS]). The detection of asterixis, fetor hepaticus, and fluctuating long-tract signs are helpful clues, albeit nonspecific. The absence of such clinical signs does not exclude the diagnosis of HE.

Measurement of venous ammonia blood levels may be helpful in the initial evaluation when there is doubt about the presence of significant liver disease or of other causes for an abnormality in consciousness. Follow-up with repeated ammonia levels is unnecessary and does not replace the evaluation of the patient's mental state. A relation between ammonia levels and the risk of cerebral edema in cirrhosis (17) has not been examined. Ammonia levels should be promptly assayed in an experienced laboratory to avoid pitfalls in its determination (18).

Tools to exclude other causes of an abnormal mental state include automated electroencephalogram analysis (19), brain imaging (especially in patients in stupor and coma), and lumbar puncture (for patients with unexplained fever, leukocytosis, or other symptoms suggestive of meningeal irritation). Alterations of the electroencephalogram are not specific for HE and are subject to variability in interpretation; automated analysis of the tracings simplifies the diagnosis (19).

Neuropsychological testing can range from an extensive battery to a single test office-based screening approach. The Number Connection Test, parts A and B; the Digit Symbol Test; and the Block Design Test have been the tests most frequently employed (15, 16).

Staging

In patients with cirrhosis and overt encephalopathy, two staging classifications have been used for patients with HE.

1. The West Haven criteria of altered mental state in HE (20) (numerous studies have employed variations of these criteria).

   Stage 0. Lack of detectable changes in personality or behavior. Asterixis absent.

   Stage 1. Trivial lack of awareness. Shortened attention span. Impaired addition or subtraction. Hypersomnia, insomnia, or inversion of sleep pattern. Euphoria or depression. Asterixis can be detected.

   Stage 2. Lethargy or apathy. Disorientation. Inappropriate behavior. Slurred speech. Obvious asterixis.

   Stage 3. Gross disorientation. Bizarre behavior. Semistupor to stupor. Asterixis generally absent.

   Stage 4. Coma.

2. Evaluation of the level of consciousness with the Glasgow Scale (21) (Table 1): although the Glasgow coma scale has not been rigorously evaluated in patients with HE, its widespread use in structural and metabolic disorders of brain function justifies its application in acute and chronic liver disease.

Table 1. Level of Consciousness With the Glasgow Scale

Eyes Open		Best Motor Response		Best Verbal Response	
Spontaneously	4	Obeys verbal orders	6	Oriented, conversant	5
To command	3	Localizes painful stimuli	5	Disoriented, conversant	4
To pain	2	Painful stimulus, flexion	3	Inappropriate words	3
No response	1	Painful stimulus, extension	2	Inappropriate sounds	2
		No response	1	No response	1

To obtain the score, the best ocular, verbal, and motor responses are summed. The best score is 15 and the worst 3. Severe encephalopathy is defined as a score of <12.

TREATMENT GOALS

1. Provision of Supportive Care

Adequate supportive care is critical during all stages of HE and may involve other professionals in the provision of patient care.

Standard measures for hospitalized patients are applicable to subjects with HE. Special considerations include a critical role for the nursing staff in the management of these individuals. The mental state can change rapidly, and disorientation can result in bodily harm. Prevention of falls in disoriented patients at earlier stages of HE may require special measures. In deeper stages of HE, the need for prophylactic tracheal intubations needs to be considered. Adequate nutrition should be provided during the period of altered mental state (see Treatment Options).

2. Identification and Removal of Precipitating Factors

A vigorous search to identify and eliminate a precipitating factor or factors should be immediately instituted.

In most cases of cirrhosis with acute or chronic HE, a precipitating factor is found, such as the following:

GI hemorrhage. Exploration requires stool analysis and/or placement of a nasogastric tube.

Infections. This factor requires culture of all appropriate body fluids, especially ascites when present. Spontaneous bacterial peritonitis and pneumonia may present with HE.

Renal and electrolyte disturbances. These include renal failure, metabolic alkalosis, hypokalemia, dehydration, and diuretic effects.

Use of psychoactive medication. This factor may require a urine screen for benzodiazepines, narcotics, and other sedatives.

Constipation

Excessive dietary protein. In many cases, an adequate clinical history can be best provided by the patient's relatives.

Acute deterioration of liver function in cirrhosis. In contrast to the situation in FHF, HE in cirrhosis seldom reflects the acute impact of liver failure. Exceptions include the presence of superimposed alcoholic hepatitis, the development of an acute circulatory disturbance (*e.g.*, portal vein thrombosis), and the impairment of liver function seen after surgery in cirrhosis. Precipitating events should also be sought with the development of encephalopathy after placement of a TIPS for control of portal hypertension (22).

Spontaneous encephalopathy (no precipitant factor identified) should raise the suspicion of an abnormal collateral circulation (see Manipulation of the Splanchnic Circulation).

3. Reduction of Nitrogenous Load From the Gut

Measures to reduce the nitrogenous load from the gut should be implemented.

These include catharsis and the use of nonabsorbable disaccharides and/or antibiotics. Treatment options are discussed in detail in Drugs That Affect Neurotransmission. Surgical exclusion of the colon (23), via ileorectal anastomosis, is rarely performed in a nontransplant candidate.

4. Assessment of the Need for Long Term Therapy

Patients with cirrhosis are at risk of developing new episodes of encephalopathy. At discharge, three factors need to be considered:

Control of potential precipitating factors. These include avoidance of constipation; prophylaxis of bleeding from gastroesophageal varices, when indicated; prophylaxis of spontaneous bacterial peritonitis, when indicated; judicious use of diuretics; and avoidance of psychoactive medication.

Higher likelihood of recurrent encephalopathy. The development of HE in the absence of a precipitating factor or the development of HE in patients with poor liver function (Child B/C) is such a situation. Prevention of a first episode of HE in subjects who have undergone a TIPS procedure is done in some centers, though no controlled data are available.

Assessment of the need for liver transplantation. The development of overt HE carries a poor prognosis (24), with a 1-yr survival of 40%. Appropriate candidates should be referred to transplant centers after the first episode of overt encephalopathy of any type.

TREATMENT OPTIONS

Treatment of HE is based on several, non–mutually exclusive options.

1. Nutritional Management

Patients with HE should avoid prolonged periods of dietary protein restriction and receive the maximum tolerable protein intake, aiming at 1.2 g of protein/kg/day (range 1–1.5).

BACKGROUND. Restriction of dietary protein at the time of acute encephalopathy with subsequent increments to assess clinical tolerance is a classic cornerstone of therapy. Protracted nitrogen restriction may contribute to malnutrition and aggravate the prognosis (25). On the other hand, a positive nitrogen balance will have positive effects on encephalopathy by promoting hepatic regeneration and increasing the capacity of muscle to detoxify ammonia. Thus, nutritional management includes intrinsic effects of dietary components as well as long term effects on organs whose dysfunctions contribute to the pathogenesis of HE.

The increased catabolic rate of cirrhosis leads to a recommendation of 1–1.5 g protein/kg/day (26). Provision of an adequate nitrogen intake is difficult. Vegetable and dairy sources are preferable to animal protein (27), as they provide a higher calorie to nitrogen ratio and, in the case of vegetable protein, provide nonabsorbable fiber, a substrate for colonic bacteria and subsequent colonic acidification.

Zinc, a cofactor of urea cycle enzymes, may be deficient in cirrhotic patients, especially if associated with malnutrition. Zinc supplementation improves the activity of the urea cycle in experimental models of cirrhosis (28). One trial has evaluated the effects of zinc over a short period (up to a week), without major improvement (29). A positive study administered zinc for 3 months, though the study was not randomized (30). Zinc deficiency precipitated encephalopathy in a well-described patient (31). Patients with zinc deficiency should receive oral zinc supplements.

IMPLEMENTATION

Acute encephalopathy. Protein feeding can be withdrawn for the first day. Short term (4 days) enteral nutrition has not been shown to benefit hospitalized cirrhotic patients (32).

Chronic management. An increase in protein tolerance can be achieved by increasing protein intake in combination with other therapeutic measures, such as nonabsorbable disaccharides. Substitution of animal protein with vegetable and/or dairy protein should be reviewed, a process facilitated by a consultation with a nutritional expert. Oral formulation of branched chain amino acids may provide a better tolerated source of protein in patients with chronic encephalopathy and dietary protein intolerance (33). Zinc acetate can be administered as 220 mg *b.i.d.* It may reduce the absorption of other divalent cations (*e.g.,* copper).

2. Reduction in the Nitrogenous Load Arising From the Gut

A. BOWEL CLEANSING. *Bowel cleansing is a standard therapeutic measure in HE.*

Background. Because the toxins responsible for HE arise from the gut, bowel cleansing is a mainstay of therapy. In addition, HE itself may result in a slow transit time (34). Colonic cleansing reduces the luminal content of ammonia, decreases colonic bacterial counts, and lowers blood ammonia in cirrhotic patients (35).

Implementation. Various laxatives may be used, but nonabsorbable disaccharides are preferred, as they result in additional effects that potentiate the elimination or reduce the formation of nitrogenous compounds (see below). Administration of enemas may be necessary in the patient with a severe impairment of consciousness. Alternatively, bowel cleansing can also be achieved after irrigation of the gut via a *p.o.* tube. Irrigation with a 5-L isotonic solution of mannitol, 1 g/kg, has been shown in a controlled trial to prevent encephalopathy after a GI hemorrhage (36).

B. NONABSORBABLE DISACCHARIDES. *Lactulose is a first-line pharmacological treatment of HE.*

Background. Careful scrutiny of the clinical trials that are the basis for the use of lactulose (galactosido-fructose) can lead to the conclusion that current standards of evidence-based medicine are not met (37, 38). Pooled analysis of the results of controlled studies is not possible because of methodological differences between trials. A summary of controlled studies is provided in the Appendix. In fact, a critical reappraisal of the use of lactulose, especially in the management of acute encephalopathy in cirrhosis, would require a new clinical trial. This would be of interest, as in one double-blind study the combination of lactulose and neomycin was not better than a placebo in the management of acute encephalopathy when the precipitant factor was simultaneously corrected (39). On the other hand, extensive data point at the potential mechanism of action of lactulose (40). Lactulose is not broken down by intestinal disaccharidases and thus reaches the colon, where bacteria will metabolize the sugar to acetic acid and lactic acid. The acidification of the colon may underlie its cathartic effect. Passage of ammonia into the colonic lumen results in its incorporation into bacteria with the resulting decrease of portal blood ammonia. As a result, peripheral levels of ammonia are reduced and the total body pool of urea decreases. An excessively sweet taste, flatulence, and abdominal cramping are the most frequent subjective complaints with this drug. If diarrhea develops, the drug should be stopped and reinstituted at a lower dose. Protracted diarrhea may result in hypertonic dehydration with hypernatremia (41); the resulting hyperosmolarity may aggravate the patient's mental state.

Implementation. For acute encephalopathy, lactulose (ingested or via nasogastric tube), 45 ml *p.o.,* is followed by dosing every hour until evacuation occurs. Then

dosing is adjusted to an objective of two to three soft bowel movements per day (generally 15–45 ml every 8–12 h). Only one study examined in a controlled fashion the effectiveness of Lactitol enemas (42). Lactulose by enema (300 ml in 1 L of water) is retained for 1 h, with the patient in the Trendelenburg position (to increase the possibility of access to the right colon). For chronic encephalopathy, oral dosing of lactulose does not require the hourly initial administration. Lactose can be used in patients with lactase deficiency. Lactitol, more palatable, is available in Europe but not the United States.

C. ANTIBIOTICS. *Antibiotics are a therapeutic alternative to nonabsorbable disaccharides for treatment in acute and chronic encephalopathy and cirrhosis.*

Background. Benefits from neomycin, the most widely used drug, are attributed to effects on colonic bacteria. However, neomycin will also affect the small bowel mucosa and may impair the activity of glutaminase in intestinal villi (43). Metronidazole, affecting a different bacterial population than neomycin, will also improve encephalopathy (44). Infection with *Helicobacter pylori* was proposed as a mechanism responsible for encephalopathy, in view of the generation of ammonia by this urease-containing organism (45). A careful assessment of its eradication failed to show a distinct impact on mental states or blood ammonia levels in patients with minimal encephalopathy (46). At this time, eradication of *H. pylori* cannot be recommended as a therapeutic strategy. Associated toxicity may hamper the use of antibiotics for a prolonged period. Despite its poor absorption, chronic neomycin, as other aminoglycosides, can cause auditory loss and renal failure. Patients require annual auditory testing if maintained on chronic neomycin. Intestinal malabsorption can result in a spruelike diarrhea. Staphylococcal superinfection can also supervene. Metronidazole neurotoxicity can be severe in patients with cirrhosis, where impaired clearance of the drug may be present (47).

Implementation. For acute encephalopathy, neomycin (3–6 g/day *p.o.*) should be given for a period of 1–2 wk. For chronic encephalopathy, neomycin (1–2 g/day *p.o.*) should be given, with periodic renal and annual auditory monitoring. Neomycin can be combined with oral lactulose in problematic cases. Metronidazole should be started at a dose of 250 mg *b.i.d.*

D. OTHER THERAPIES. Ornithine aspartate drug is not available in the United States. It provides substrates for the urea cycle (ornithine) as well as for the synthesis of glutamine (aspartate, via transamination to glutamate). It is available in oral and *i.v.* formulations. Preliminary experience in both acute (48) and chronic (49) encephalopathy has been encouraging.

3. Drugs That Affect Neurotransmission

Flumazenil and bromocriptine administration may have a therapeutic role in selected patients.

BACKGROUND. Flumazenil and bromocriptine exert their effects directly on the brain. An enhanced GABA-ergic tone was postulated to contribute to the development of encephalopathy (50). It has been proposed that "endogenous benzodiazepines" may be present in patients with HE and exert neuroinhibitory effects via binding to the $GABA_A$ receptor (51). Antagonism of their effect with flumazenil has been tested in patients with acute encephalopathy and severe changes in mental state. In a large clinical trial of 560 patients, an *i.v.* bolus of flumazenil improved mental state in approximately 15% of patients, as compared to 3% of placebo-treated controls (52). Although these results are not striking, flumazenil may be administered to patients with HE and suspected benzodiazepine ingestion. An oral preparation is unfortunately not available for chronic long term administration.

Alterations of dopaminergic neurotransmission were initially postulated 2 decades ago as the basis for the "false neurotransmitter" hypothesis (53). The tenets of this theory, where the imbalance between aromatic and branched-chain amino acids favored the entry into the brain of the former, were subsequently challenged by the unconvincing results with branched-chain amino acids for the therapy of HE (54, 55). The recent observation of manganese accumulation in basal ganglia of patients with cirrhosis has rekindled the possible alteration of dopamine neurotransmission (56). These changes may underlie the frequent finding of extrapyramidal symptomatology in patients with liver disease. Improvements of extrapyramidal signs have been reported when bromocriptine was added to conventional therapy (57).

IMPLEMENTATION. At this time, a formal recommendation on the use of these drugs cannot be made on the basis of evidence-based data. Flumazenil (1 mg bolus *i.v.*) is indicated for patients with HE and suspected benzodiazepine intake. Although flumazenil has been reported to occasionally cause seizures, such findings have not been described in patients with HE. Bromocriptine (30 mg *p.o. b.i.d.*) is indicated for the treatment of chronic encephalopathy in patients unresponsive to other therapy. Bromocriptine may result in elevation of prolactin levels.

4. Manipulation of the Splanchnic Circulation

The presence of large spontaneous portal-systemic shunts should be sought in selected patients with recurrent episodes of encephalopathy despite medical therapy, where a precipitating factor is not found.

BACKGROUND. Large splenorenal or gastrorenal communications have been associated with episodes of "spontaneous" encephalopathy (absence of a precipitating factor) (58). Visualization of the collaterals can be obtained with

ultrasound techniques and confirmed with visceral angiography. These shunts may be amenable to occlusion via radiological techniques, including placement of occlusive coils (59). Access to the portal circulation is best obtained through the transhepatic route. In this limited experience, no increased risk of variceal hemorrhage was observed after occlusion of the shunt.

IMPLEMENTATION. Occlusion of portal-systemic collaterals should be undertaken only in centers with experienced interventional radiologists and after all other medical measures have failed.

SUMMARY

1. Acute Encephalopathy in Cirrhosis

A. GENERAL MEASURES. Tracheal intubation in patients with deep encephalopathy should be considered. A nasogastric tube is placed for patients in deep encephalopathy. Avoid sedatives whenever possible. Correction of the precipitating factor is the most important measure.

B. SPECIFIC MEASURES

i. *Nutrition.* In case of deep encephalopathy, oral intake is withheld for 24–48 h and *i.v.* glucose is provided until improvement. Enteral nutrition can be started if the patient appears unable to eat after this period. Protein intake begins at a dose of 0.5 g/kg/day, with progressive increase to 1–1.5 g/kg/day.

ii. *Lactulose* is administered via enema or nasogastric tube in deep encephalopathy. The oral route is optimized by dosing every hour until stool evacuation appears. Lactulose can be replaced by oral neomycin.

iii. *Flumazenil* may be used in selected cases of suspected benzodiazepine use.

2. Chronic Encephalopathy in Cirrhosis

i. Avoidance and prevention of precipitating factors, including the institution of prophylactic measures.

ii. *Nutrition.* Improve protein intake by feeding dairy products and vegetable-based diets. Oral branched-chain amino acids can be considered for individuals intolerant of all protein.

iii. *Lactulose.* Dosing aims at two to three soft bowel movements per day. Antibiotics are reserved for patients who respond poorly to disaccharides or who do not exhibit diarrhea or acidification of the stool. Chronic antibiotic use (neomycin, metronidazole) requires careful renal, neurological, and/or otological monitoring.

iv. Refer for liver transplantation in appropriate candidates.

For problematic encephalopathy (nonresponsive to therapy), consider imaging of splanchnic vessels to identify large spontaneous portal-systemic shunts potentially amenable to radiological occlusion. In addition, consider the combination of lactulose and neomycin, addition of oral zinc, and invasive approaches, such as occlusion of TIPS or surgical shunts, if present.

Minimal or Subclinical Encephalopathy

Treatment can be instituted in selected cases. The most characteristic neuropsychological deficits in patients with cirrhosis are in motor and attentional skills (60). Although these may impact the ability to perform daily activities, many subjects can compensate for these defects. Recent studies suggest a small but significant impact of these abnormalities on patients' quality of life (61), including difficulties with sleep (62). In patients with significant deficits or complaints, a therapeutic program based on dietary manipulations and/or nonabsorbable disaccharides may be tried. Benzodiazepines should not be used for patients with sleep difficulties.

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REFERENCES

1. Blei AT. Hepatic encephalopathy. In: Bircher J, Benhamou JP, McIntyre N, et al, eds. Oxford textbook of hepatology. Oxford, UK: Oxford University Press, 1999:765–86.
2. Butterworth RF. The neurobiology of hepatic encephalopathy. Semin Liver Dis 1996;16:235–44.
3. Norenberg MD. Astrocytic-ammonia interactions in hepatic encephalopathy. Semin Liver Dis 1996;16:245–53.
4. Nomura F, Ohnishi K, Terabayashi H, et al. Effect of intrahepatic portal-systemic shunting on hepatic ammonia extraction in patients with cirrhosis. Hepatology 1994;20:1478–81.
5. Clemmesen JO, Larsen FS, Kondrup J, et al. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology 1999;29:648–53.
6. Lockwood AH, Yap EW, Wong WH. Cerebral ammonia metabolism in patients with severe liver disease and minimal hepatic encephalopathy. J Cereb Blood Flow Metab 1991;11:337–41.
7. Kramer L, Tribl B, Gebdo A, et al. Partial pressure of ammonia versus ammonia in hepatic encephalopathy. Hepatology 2000;31:30–4.
8. Haussinger D, Kircheis G, Fischer R, et al. Hepatic encephalopathy in chronic liver disease: A clinical manifestation of astrocyte swelling and low grade cerebral edema? J Hepatol 2000;32:1035–8.
9. Mullen KD, Jones EA. Natural benzodiazepines and hepatic encephalopathy. Semin Liver Dis 1996;16:255–64.
10. Yurdaydin C, Walsh TJ, Engler HD, et al. Gut bacteria provide precursors of benzodiazepine receptor ligands in a rat model of hepatic encephalopathy. Brain Res 1995;679:42–8.
11. Zieve L, Doizaki WM, Zieve J. Synergism between mercaptans and ammonia or fatty acids in the production of coma: a

possible role for mercaptans in the pathogenesis of hepatic coma. J Lab Clin Med 1974;83:16–28.
12. Rose C, Butterworth RF, Zayed J, et al. Manganese deposition in basal ganglia structures results from both portal-systemic shunting and liver dysfunction. Gastroenterology 1999;117: 640–4.
13. Jones EA, Basile AS. Does ammonia contribute to increased GABA-ergic neurotransmission in liver failure? Metab Brain Dis 1998;13:351–60.
14. Mullen KD, Ferenci P, Tartar R, et al. Clinical research in hepatic encephalopathy. Submitted for publication.
15. Gitlin N, Lewis DC, Hinkley L. The diagnosis and prevalence of subclinical hepatic encephalopathy in apparently healthy, ambulant, non-shunted patients with cirrhosis. J Hepatol 1986; 3:75–82.
16. Weissenborn K, Ennen JC, Schomerus H, et al. Neuropsychological characterization of hepatic encephalopathy. J Hepatol (in press).
17. Donovan JP, Schafer DF, Shaw BW Jr, Sorrell MF. Cerebral oedema and increased intracranial pressure in chronic liver disease. Lancet 1998;351:719–21.
18. Stahl J. Studies of blood ammonia in liver disease. Ann Intern Med 1963;58:1–23.
19. Van der Rijt CCD, Schalm SW, De Groot GH, De Vlieger M. Objective measurements of hepatic encephalopathy by means of automated EEG analysis. Electroencephalogr Clin Neurophysiol 1984;57:423–6.
20. Atterbury CE, Maddrey WC, Conn HO. Neomycin-sorbitol and lactulose in the treatment of acute portal-systemic encephalopathy. A controlled, double-blind clinical trial. Am J Dig Dis 1978;23:398–406.
21. Teasdale G, Jennett B. Assessment and prognosis of coma after head injury. Acta Neurochir 1976;34:45–55.
22. Blei AT. Hepatic encephalopathy in the age of TIPS. Hepatology 1994;20:249–52.
23. Resnick RH, Ishihara A, Chalmers TC, Schimmel EM. A controlled trial of colon bypass in chronic hepatic encephalopathy. Gastroenterology 1968;54:1057–69.
24. Bustamante J, Rimola A, Ventura PJ, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hepatol 1999;30:890–5.
25. Merli M, Riggio O, Dally L, PINC (Policentrica Italiana Nutrizione Cirrosi). Does malnutrition affect survival in cirrhosis? Hepatology 1996;23:1041–6.
26. Plauth M, Merli M, Kondrup J, et al. ESPEN guidelines for nutrition in liver disease and transplantation. Clin Nutr 1997; 16:43–55.
27. Bianchi GP, Marchesini G, Fabbri A, et al. Vegetable versus animal protein diet in cirrhotic patients with chronic encephalopathy. A randomized cross-over comparison. J Intern Med 1993;233:385–92.
28. Riggio O, Merli M, Capocaccia L, et al. Zinc supplementation reduces blood ammonia and increases liver ornithine transcarbamylase activity in experimental cirrhosis. Hepatology 1992; 16:785–9.
29. Riggio O, Ariosto F, Merli M, et al. Short-term oral zinc supplementation does not improve chronic hepatic encephalopathy. Results of a double-blind crossover trial. Dig Dis Sci 1991;36:1204–8.
30. Marchesini G, Fabbri A, Bianchi G, et al. Zinc supplementation and amino acid-nitrogen metabolism in patients with advanced cirrhosis. Hepatology 1996;23:1084–92.
31. Van der Rijt CC, Schalm SW, Schat H, et al. Overt hepatic encephalopathy precipitated by zinc deficiency. Gastroenterology 1991;100:1114–8.
32. de Ledinghen V, Beau P, Mannant PR, et al. Early feeding or enteral nutrition in patients with cirrhosis after bleeding from esophageal varices? A randomized controlled study. Dig Dis Sci 1997;42:536–41.
33. Horst D, Grace NE, Conn HO, et al. Comparison of dietary protein with an oral, branched-chain enriched amino acid supplement in chronic portal-systemic encephalopathy. Hepatology 1984;2:279–87.
34. Van Thiel DH, Fagiuoli S, Wright HI, et al. Gastrointestinal transit in cirrhotic patients: Effect of hepatic encephalopathy and its treatment. Hepatology 1994;19:67–71.
35. Wolpert E, Phillips SF, Summerskill WH. Ammonia production in the human colon. Effects of cleansing, neomycin and acetohydroxamic acid. N Engl J Med 1970;283:159–64.
36. Rolachon A, Zarski JP, Lutz JM, et al. [Is the intestinal lavage with a solution of mannitol effective in the prevention of post-hemorrhagic hepatic encephalopathy in patients with liver cirrhosis? Results of a randomized prospective study]. Gastroenterol Clin Biol 1994;18:1057–62.
37. Cordoba J, Blei AT. Treatment of hepatic encephalopathy. Am J Gastroenterol 1997;92:1429–39.
38. Riordan SM, Williams R. Treatment of hepatic encephalopathy. N Engl J Med 1997;337:473–9.
39. Blanc P, Daures JP, Liautard J, et al. [Lactulose-neomycin combination versus placebo in the treatment of acute hepatic encephalopathy. Results of a randomized controlled trial]. Gastroenterol Clin Biol 1994;18:1063–8.
40. Clausen MR, Mortensen PB. Lactulose, disaccharides and colonic flora. Clinical consequences. Drugs 1997;53:930–42.
41. Warren SE, Mitas JA 2d, Swerdlin AH. Hypernatremia in hepatic failure. JAMA 1980;243:1257–60.
42. Uribe M, Campollo A, Vargas F, et al. Acidifying enemas (Lactitol and lactose) vs. non-acidifying enemas (tap water) to treat acute portal-systemic encephalopathy: A double-blind randomized clinical trial. Hepatology 1987;7:639–43.
43. Hawkins RA, Jessy J, Mans AM, et al. Neomycin reduces the intestinal production of ammonia from glutamine. Adv Exp Med Biol 1994;368:125–34.
44. Morgan MH, Read AE, Speller DC. Treatment of hepatic encephalopathy with metronidazole. Gut 1982;23:1–7.
45. Gubbins GP, Moritz TE, Marsano LS, et al. Helicobacter pylori is a risk factor for hepatic encephalopathy in acute alcoholic hepatitis: The ammonia hypothesis revisited. The Veterans Administration Cooperative Study Group No. 275. Am J Gastroenterol 1993;88:1906–10.
46. Vasconez C, Elizalde JI, Llach J, et al. Helicobacter pylori, hyperammonemia and subclinical portosystemic encephalopathy: Effects of eradication. J Hepatol 1999;30:260–4.
47. Loft S, Sonne J, Dossing M, Andreasen PB. Metronidazole pharmacokinetics in patients with hepatic encephalopathy. Scand J Gastroenterol 1987;22:117–23.
48. Kircheis G, Nilius R, Held C, et al. Therapeutic efficacy of L-ornithine-L-aspartate infusions in patients with cirrhosis and hepatic encephalopathy: Results of a placebo-controlled, double-blind study. Hepatology 1997;25:1351–60.
49. Stauch S, Kircheis G, Adler G, et al. Oral L-ornithine-L-aspartate therapy of chronic hepaticencephalopathy. Results of a placebo-controlled double-blind study. J Hepatol 1998;28: 856–64.
50. Schafer DF, Jones EA. Hepatic encephalopathy and the gamma-amino-butyric acid system. Lancet 1982;1:18–20.
51. Basile AS, Hughes RD, Harrison PM, et al. Elevated brain concentrations of 1,4-benzodiazepines in fulminant hepatic failure. N Engl J Med 1991;325:473–8.
52. Barbaro G, Di Lorenzo G, Soldini M, et al. Flumazenil for hepatic encephalopathy grade III and Iva in patients with cirrhosis: An Italian multicenter double-blind, placebo-controlled, cross-over study. Hepatology 1998;28:374–8.
53. James JH, Ziparo V, Jeppsson B, Fischer JE. Hyperammon-

aemia, plasma aminoacid imbalance, and blood-brain amino-acid transport: A unified theory of portal-systemic encephalopathy. Lancet 1979;2:772–5.
54. Morgan MY. Branched chain amino acids in the management of chronic liver disease. Facts and fantasies. J Hepatol 1990; 11:133–41.
55. Fabbri A, Magrini N, Bianchi G, et al. Overview of randomized clinical trials of oral branched-chain amino acid treatment in chronic hepatic encephalopathy. JPEN J Parenter Enteral Nutr 1996;20:159–64.
56. Pomier-Layrargues G, Rose C, Spahr L, et al. Role of manganese in the pathogenesis of portal-systemic encephalopathy. Metab Brain Dis 1998;13:311–7.
57. Uribe M, Farca A, Marquez MA, et al. Treatment of chronic portal systemic encephalopathy with bromocriptine: A double-blind controlled trial. Gastroenterology 1979;76:1347–51.
58. Takashi M, Igarashi M, Hino S, et al. Portal hemodynamics in chronic portal-systemic encephalopathy. Angiographic study in seven cases. J Hepatol 1985;1:467–76.
59. Sakurabayashi S, Sezai S, Yamamoto Y, et al. Embolization of portal-systemic shunts in cirrhotic patients with chronic recurrent hepatic encephalopathy. Cardiovasc Intervent Radiol 1997;20:120–4.
60. McCrea M, Cordoba J, Vessey G, et al. Neuropsychological characterization and detection of subclinical hepatic encephalopathy. Arch Neurol 1996;53:758–63.
61. Groeneweg M, Quero JC, De Bruijn I, et al. Subclinical hepatic encephalopathy impairs daily functioning. Hepatology 1998;28:45–9.
62. Cordoba J, Cabrera J, Lataif L, et al. High prevalence of sleep disturbance in cirrhosis. Hepatology 1998;27:339–45.
63. Simmons F, Goldstein H, Boyle JD. A controlled clinical trial of lactulose in hepatic encephalopathy. Gastroenterology 1970;59:827–32.
64. Morgan MY, Hawley KE. Lactitol vs. lactulose in the treatment of acute hepatic encephalopathy in cirrhotic patients: A double-blind, randomized trial. Hepatology 1987;7:1278–84.
65. Heredia D, Caballeria J, Arroyo V, et al. Lactitol versus lactulose in the treatment of acute portal systemic encephalopathy (PSE). A controlled trial. J Hepatol 1987;4:293–8.
66. Uribe M, Berthier JM, Lewis H, et al. Lactose enemas plus placebo tablets vs. neomycin tablets plus starch enemas in acute portal systemic encephalopathy. A double-blind randomized controlled study. Gastroenterology 1981;81:101–6.
67. Strauss E, Tramote R, Silva EP, et al. Double-blind randomized clinical trial comparing neomycin and placebo in the treatment of exogenous hepatic encephalopathy. Hepatogastroenterology 1992;39:542–5.
68. Sushma S, Dasarathy S, Tandon RK, et al. Sodium benzoate in the treatment of acute hepatic encephalopathy: A double-blind randomized trial. Hepatology 1992;16:138–44.
69. Pomier-Layrargues G, Giguere JF, Lavoie J, et al. Flumazenil in cirrhotic patients in hepatic coma: A randomized double-blind placebo-controlled crossover trial. Hepatology 1994;19: 32–7.
70. Cadranel JF, el Younsi M, Pidoux B, et al. Flumazenil therapy for hepatic encephalopathy in cirrhotic patients: A double-blind pragmatic randomized, placebo study. Eur J Gastroenterol Hepatol 1995;7:325–9.
71. Gyr K, Meier R, Haussler J, et al. Evaluation of the efficacy and safety of flumazenil in the treatment of portal systemic encephalopathy: A double blind, randomised, placebo controlled multicentre study. Gut 1996;39:319–24.
72. Elkington SG, Floch MH, Conn HO. Lactulose in the treatment of chronic portal-systemic encephalopathy. A double-blind clinical trial. N Engl J Med 1969;281:408–12.
73. Germain L, Frexinos J, Louis A, Ribet A. [Double blind study of lactulose in 8 patients with chronic hepatic encephalopathy after portocaval shunt]. Arch Fr Mal App Dig 1973;62:293–302.
74. Blanc P, Daures JP, Rouillon JM, et al. Lactitol or lactulose in the treatment of chronic hepatic encephalopathy: Results of a meta-analysis. Hepatology 1992;15:222–8.
75. Camma C, Fiorello F, Tine F, et al. Lactitol in treatment of chronic hepatic encephalopathy. A meta-analysis. Dig Dis Sci 1993;38:916–22.
76. Conn HO, Leevy CM, Vlahcevic ZR, 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.
77. Orlandi F, Freddara U, Candelaresi MT, et al. Comparison between neomycin and lactulose in 173 patients with hepatic encephalopathy: A randomized clinical study. Dig Dis Sci 1981;26:498–506.
78. Bresci G, Parisi G, Banti S. Management of hepatic encephalopathy with oral zinc supplementation: A long-term treatment. Eur J Med 1993;2:414–6.
79. Reding P, Duchateau J, Bataille C. Oral zinc supplementation improves hepatic encephalopathy. Results of a randomised controlled trial. Lancet 1984;2(8401):493–5.
80. Morgan MY, Jakobovits AW, James IM, Sherlock S. Successful use of bromocriptine in the treatment of chronic hepatic encephalopathy. Gastroenterology 1980;78:663–70.
81. Orlandi F, et al. Clinical trials of nonabsorbable disaccharide therapy in hepatic encephalopathy. In: Conn HO, Bircher J, eds. Hepatic encephalopathy: Syndromes and therapies. Bloomington, IL: Medi-Ed Press, 1994:209–17.

Appendix. Controlled Trials in Cirrhotic Patients

Treatment	Comparison	Trial	No. of Patients	Time*	Design	Effect
Acute encephalopathy†						
Lactulose	Placebo (glucose)	Simmons *et al.* (63)	21‡	10 days		+
Lactitol	Lactulose	Morgan *et al.* (64)	28‡	5 days		=
Lactitol	Lactulose	Heredia *et al.* (65)	40‡	5 days		=
Lactitol/lactulose enemas	Cleansing enemas	Uribe *et al.* (42)§	20‡	To clinical improvement		+
Lactitol enemas	Lactose enemas	Uribe *et al.* (42)	40‡	4 days		=
Lactose enemas + placebo	Neomycin + starch enemas	Uribe *et al.* (66)	18‡	5 days		=
Neomycin	Placebo	Strauss *et al.* (67)	39‡	To maximal improvement		=
Neomycin + sorbitol	Lactulose	Atterbury *et al.* (20)	45‡	To maximal improvement		=
Neomycin + lactulose	Placebo	Blanc *et al.* (39)	80‡	5 days		=
Sodium benzoate	Lactulose	Sushma *et al.* (68)	74‡	To maximal improvement		=
Flumazenil	Placebo	Pomier-Layrargues *et al.* (69)‖	21‡	1 h		+
Flumazenil	Placebo	Cadrenel *et al.* (70)	14‡	10 min		+
Flumazenil	Placebo	Gyr *et al.* (71)¶	49‡	8 h		=
Flumazenil	Placebo	Barbaro *et al.* (52)	527‡	24 h		+
Omithine-aspartate	Placebo	Kircheis *et al.* (48)	126‡	7 days		+
Chronic encephalopathy#						
Lactulose	Placebo (sorbitol)	Elkington *et al.* (72)	7		Crossover	+**
Lactulose	Placebo (saccarose)	Germain *et al.* (73)	18		Parallel	±**
Lactitol	Lactulose	Blanc *et al.* (74)	77		Meta-analysis	=**
Lactitol	Lactulose	Camma *et al.* (75)	72		Meta-analysis	=**
Neomycin + sorbitol	Lactulose	Conn *et al.* (76)	33		Crossover	=**
Neomycin + $MgSO_4$	Lactulose	Orlandi *et al.* (77)	173		Parallel	=**
Zinc + lactulose	Lactulose	Bresci *et al.* (78)	90		Parallel	=**
Zinc + lactulose	Placebo + lactulose	Reding *et al.* (79)	22		Parallel	±**
Zinc + lactulose	Placebo + lactulose	Riggio *et al.* (29)	15		Crossover	=**
Bromocriptine	Placebo	Uribe *et al.* (57)	7		Crossover	=**
Bromocriptine + lactulose	Placebo + lactulose	Morgan *et al.* (80)	6		Crossover	+**

Adapted from Riggio *et al.* (28).

* Period of time from initiation of treatment to measurement of outcome.

† Branched-chain amino acids not included.

‡ Total number of patients included in the study.

§ Analysis of the first 20 patients of the study.

‖All patients received only lactulose.

¶Only patients with encephalopathy grades I–III included. Additional treatment with lactulose was permitted. Twenty-four patients were excluded from the analysis. For patients with clinically relevant improvement (n = 5), flumazenil was associated with a better response.

Branched-chain amino acids not included. Four additional controlled trials, including less than 10 patients, compared neomycin and lactulose (81).

** Effect on encephalophathy: +, clinical improvement with treatment; ±, treatment associated with improvement in psychometric tests; =, no differences between treatment and control.