

# Treatment Guidelines for Hepatic Encephalopathy

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Practice guidelines for hepatic encephalopathy were developed and published in 2001 for overall management in adults. Hepatic encephalopathy is caused by nitrogenous substances from the gastrointestinal tract that adversely affect brain function. Hepatic encephalopathy is a diagnosis of exclusion. The West Haven criteria are recommended for staging the disease. Treatment goals are providing supportive care, identifying and removing precipitating factors, reducing nitrogenous load, and assessing long-term therapy needs. Data from some trials published before 2001 are not included in the guidelines. In addition, since the publication of the guidelines, new data have become available regarding treatment interventions and outcomes. Newer, nonabsorbed agents, such as rifaximin, alone or in conjunction with lactulose, may enhance compliance and adherence with therapy, and provide better treatment outcomes. New updated practice guidelines need to be developed for hepatic encephalopathy, along with treatment algorithms for patients with both minimal hepatic encephalopathy and overt hepatic encephalopathy.

**Key Words:** hepatic encephalopathy, practice guidelines, lactulose, rifaximin. (Pharmacotherapy 2010;30(5 Pt 2):4S–9S)

Hepatic encephalopathy is a diagnosis that has seen little change in management until the March 2010 approval of rifaximin by the United States Food and Drug Administration (FDA). The practice guidelines for hepatic encephalopathy were developed and published in 2001 as a collaborative effort between the American College of Gastroenterology Practice Parameters Committee, Northwestern University College of Medicine, and the University of Barcelona (Barcelona, Spain).<sup>1</sup> These practice guidelines were established by interpreting and collating scientifically valid research, performing a review of the published literature, and providing opinions

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based on the consensus of experts.

Most practice guidelines for other disorders, such as hypertension, hypercholesterolemia, and asthma, are reviewed and revised on a continual basis, approximately every 5 years, or sooner if significant new data become available. This has not yet occurred, however, with the practice guidelines for hepatic encephalopathy. In fact, data from European, double-blind, randomized clinical trials that had been published before 2001 were not included in these guidelines. For example, the data from four trials of rifaximin published before 2001<sup>2–5</sup> were not included in the analysis for reasons unknown. In addition, the practice guidelines were for the overall management of adults with hepatic encephalopathy, not of pediatric patients. The major topics addressed in the hepatic encephalopathy practice guidelines are clinical considerations, treatment goals, and treatment options.

The objective of this article is to review the current hepatic encephalopathy treatment guidelines and make recommendations for improvement based on additional information accrued since these guidelines were first published.

## Clinical Considerations

Clinical considerations for hepatic encephalopathy are subdivided into four areas: an understanding of the pathophysiology of the disease, the various subtypes of hepatic encephalopathy, diagnosis of hepatic encephalopathy, and staging of the disease.

## Pathophysiology

It is generally believed that hepatic encephalopathy is caused by nitrogenous substances from the gastrointestinal tract that adversely affect brain function. Although several different theories have been proposed about the manner in which this effect occurs mechanistically, it is generally accepted that nitrogenous substances gain access to the systemic circulation as a result of decreased hepatic function or portal-systemic shunts.

The pathophysiologic problem in the brain appears to be multimodal, with a number of different neurotransmitter systems being affected. In the practice guidelines, the data support roles for glutamine and serotonin, for interference with  $\gamma$ -aminobutyric acid and its role in the brain, and for catecholamine pathways.

Ammonia also appears to be a key factor in the disease.<sup>6,7</sup> However, ammonia is a nonspecific indicator. Other potential gastrointestinal tract-derived toxins, such as benzodiazepine-like substances,<sup>8,9</sup> neurotoxic short- and medium-chain fatty acids, phenols, mercaptans,<sup>10</sup> and manganese,<sup>11</sup> may also be involved. All of these toxins may interact with ammonia, causing additional neurochemical changes.

## Hepatic Encephalopathy Subtypes

The 2001 practice guidelines delineate four specific subtypes of hepatic encephalopathy: acute, recurrent, persistent, and minimal. Today, hepatic encephalopathy is often categorized as either minimal or overt, and as being in acute or maintenance phases. Acute hepatic encephalopathy is manifested generally because of one or more precipitating factors such as gastrointestinal hemorrhage, infection, renal and electrolyte disturbances, use of psychoactive drugs, constipation, excessive dietary protein, acute deterioration of liver function in cirrhosis, and abnormal collateral circulation.

Managing a patient with minimal hepatic encephalopathy (MHE) presents a challenge and often requires psychometric testing to make a

**Table 1. Glasgow Coma Scale for Measuring Level of Consciousness**

Category	Response	Score
Ocular (eyes open)	Spontaneously	4
	To command	3
	To pain	2
	No response	1
Motor	Obeys verbal orders	6
	Localizes painful stimuli	5
	Painful stimulus, flexion	3
	Painful stimulus extension	2
	No response	1
Verbal	Oriented, conversant	5
	Disoriented, conversant	4
	Inappropriate words	3
	Inappropriate sounds	2
	No response	1

The Glasgow Coma Scale score is a total of the best response of each category; scores range from 3 (worst) to 15 (best). Severe encephalopathy is defined as a score below 12.

Adapted from references 1 and 13.

definitive diagnosis. Although sometimes difficult to recognize and diagnose, this form of hepatic encephalopathy is by far the most common form of the disease and may have significantly more impact than previously appreciated, as evidenced recently by the association of the disease with driving impairment.

## Diagnosis

Hepatic encephalopathy is a diagnosis of exclusion. The elements that provide an accurate diagnosis include the presence of acute or chronic liver disease, presence of an identifiable precipitating factor, and/or history of hepatic encephalopathy.

An evaluation of liver dysfunction or circulation, along with clinical signs and symptoms of disease, will aid in the diagnosis. Measurement of venous ammonia level, brain imaging, lumbar puncture to evaluate central nervous system activity, and neuropsychologic testing to identify less prominent clinical forms of hepatic encephalopathy are also recommended.<sup>12</sup>

## Staging

The West Haven criteria are recommended for staging hepatic encephalopathy. The Glasgow Coma Scale, which the guidelines state has not been specifically studied and used for hepatic encephalopathy staging, is also recommended because of its use for other forms of coma. The Glasgow Coma Scale is a scoring system based on the best response in three categories: ocular

response, motor response, and verbal response (Table 1).<sup>13</sup> Scores range from 3 (worst) to 15 (best); a score below 12 is equivalent to overt (severe) hepatic encephalopathy.

### Treatment Goals

The 2001 practice guidelines identify four treatment goals, which continue to be recognized as clinically relevant. These goals are providing supportive care, identifying and removing precipitating factors, reducing the nitrogenous load from the gastrointestinal tract, and assessing the need for long-term therapy.<sup>1</sup>

Whereas all regular hospital standards that apply to critically ill patients should be employed, particular emphasis should be placed on nursing management. Appropriate nursing management can prevent falls in patients with residual confusion. It is also important to perform prophylactic tracheal intubation in more severely staged patients, and provide nutritional interventions, where needed.

Identifying and removing precipitating factors that contribute to clinical symptomatology is important, as is reducing nitrogenous load from the gastrointestinal tract. Four recommendations for reducing nitrogenous load are catharsis, use of nonabsorbable disaccharides, administration of antibiotics, and, rarely, in patients without liver transplants, ileorectal anastomosis.

As patients improve and are discharged from the hospital and return to outpatient care, considerations for long-term therapy must be addressed. An assessment of control of potential precipitating factors, the likelihood of recurrent encephalopathy, the degree of compromised liver function, and possible need for future liver transplantation should all be taken into account.

### Treatment Options

Treatment options include instituting nutritional management, reducing nitrogenous load from the gastrointestinal tract, administering drugs that affect neurotransmission, and manipulating the splanchnic circulation.<sup>1</sup>

#### Instituting Nutritional Management

In acute hepatic encephalopathy, protein restriction may be necessary. However, long periods of protein restriction should be avoided. In some instances, protein intake should be withdrawn or reduced on the first day and restarted as the encephalopathy improves. No

benefit has been reported for instituting short-term (< 4 days) enteral nutrition.

For long-term management, protein intake should be increased to the maximum tolerated, aiming for 1.2 g/kg (range 1–1.5 g/kg) of body weight per day. Vegetable and dairy protein are preferred over animal protein. Supplementation with oral zinc acetate 220 mg twice/day is recommended due to its enzymatic function in the urea cycle.

#### Reducing Nitrogenous Load

Bowel cleansing was considered the mainstay of therapy in 2001 since it reduces luminal ammonia, decreases colonic bacterial counts, and lowers blood ammonia levels in patients with cirrhosis. Lactulose was recommended as the first-line nonabsorbable disaccharide for treatment, which is consistent with standard of care in most institutions today. The guideline experts in 2001 recognized that whereas the data on lactulose were sparse, they believed that the mechanisms of delivering lactulose to the gastrointestinal tract and its subsequent breakdown into lactic acid and acetic acid in the acidification process, in addition to its effects on ammonia, are basically sound. Unpleasant taste, flatulence, and cramping are adverse effects of lactulose use and should be taken into consideration. In addition, protracted use may lead to hypertonic dehydration with hypernatremia and aggravate the patient's mental state.

The practice guidelines recommend lactulose 45 ml/hour until evacuation occurs,<sup>1</sup> titrating the dose to two or three soft-stool bowel movements/day, using 15–45 ml every 8–12 hours, and if needed, a lactulose enema of 300 ml in one liter of water retained for an hour. These dosages are higher than what is standard practice in most liver transplant and treatment centers today.

Neomycin or, alternatively, metronidazole was recommended as a therapeutic alternative to nonabsorbable disaccharides, combined with oral lactulose if needed. Most centers today do not routinely use these agents, however, in patients with hepatic encephalopathy.

Curiously, the 2001 guidelines make no mention of rifaximin therapy, despite the use of the agent in several European, double-blind, randomized trials that had been previously published.<sup>2–5</sup> From the available data, this nonabsorbed antibiotic appears to be at least as effective as the other antibiotics recommended in the guidelines and has fewer adverse effects.<sup>14</sup>

**Table 2. Levels of Strength of Evidence in the Literature Review Process**

Level	Definition
1	Well-designed RCTs, meta-analyses, and systematic reviews of RCTs
2	Prospective studies, retrospective studies, and cross-sectional studies
3	Evidence from expert committee reports, opinions, and clinical experiences of highly respected authorities

RCTs = randomized controlled trials.

Adapted from reference 25.

Eradication of *Helicobacter pylori* is not recommended, as it was recognized in the guidelines that toxicity issues may hamper prolonged antibiotic use. Ornithine aspartate, which is not approved in the United States but is used in Europe, is often beneficial because of its role in the urea cycle and glutamine synthesis.

#### Administering Drugs That Affect Neurotransmission

The practice guidelines state that flumazenil and bromocriptine, both of which affect neurotransmission, may have a therapeutic role in select patients, although no formal recommendation could be made because no published evidence existed at that time.<sup>1</sup> In today's practice, these agents have a limited role, reserved mostly for patients unresponsive to other therapies.

#### Manipulating the Splanchnic Circulation

Manipulation of splanchnic circulation should be undertaken only in centers with interventional radiology departments.<sup>15</sup> Only patients with recurrent episodes of encephalopathy, despite appropriate medical therapy and no precipitating factors, who have large spontaneous portal-systemic shunts should be candidates. Visualization should be done with ultrasound and confirmed with visceral angiography.

#### Treating Minimal Hepatic Encephalopathy

Most of the deficits in patients with MHE involve motor and attentional skills,<sup>16</sup> significantly impacting quality of life and sleep patterns.<sup>17, 18</sup> In select patients, therapy should be based on dietary manipulation, use of nonabsorbable disaccharides to reduce nitrogenous load, and avoidance of benzodiazepines for sleep disorders.

### Developing New Practice Guidelines

Clinical practice guideline development has vastly improved over the past decade, since the 2001 guidelines for hepatic encephalopathy were developed. The trend today is a movement from largely consensus forums to those that apply vigorous evidenced-based data.<sup>19</sup> Whereas clinical practice guidelines offer concise instructions to improve health care services<sup>20</sup> and are beneficial in improving the process of care and patient health outcomes,<sup>21, 22</sup> they must be methodologically rigorous, incorporate the best evidence available, and demonstrate successful acceptance and implementation.<sup>23, 24</sup>

New guidelines need to be developed for treating patients with hepatic encephalopathy. This process should be undertaken by an organization representing hepatologists and gastroenterologists in collaboration with other expert groups, including pharmacists. Some of the information presented in the 2001 guidelines is still valid and should be included. However, a complete and thorough analysis of all of the available data since the original guidelines were developed must be undertaken. The development of new evidenced-based guidelines for diagnosing and treating hepatic encephalopathy requires a systematic and structured process. An extensive time frame for all activities should be established to provide a timely outcome.

#### Conducting an Extensive Literature Review

A systematic review and appraisal of the published literature must be among the first activities in the development of new evidenced-based guidelines. Levels for assessing the strength of evidence should be implemented in the literature review process (Table 2).<sup>25</sup>

A full-time project director or codirectors should be appointed to oversee this time-consuming process, using the assistance of researchers experienced in implementing evidence-based practice guidelines. An evaluation team, composed of university researchers, specialty clinicians, pharmacists, and others with vast knowledge and experience in hepatic encephalopathy, should be established to serve as an expert resource and sounding board for the core development committee.

#### Writing the Practice Guidelines

Once this is accomplished, committee members should agree on specific language for

each section of the guidelines: pathophysiology of hepatic encephalopathy, subtypes of the disorder, diagnostic criteria, staging of the disease, treatment considerations, treatment options, and other areas of importance.

A process should be implemented to systematically search and evaluate new data on a continuing basis (every 6 mo or yearly), and a commitment should be made to reevaluate and possibly update the guidelines, if necessary, within a certain time frame (2–5 yrs being the norm).

#### Soliciting Feedback, Approval, Consensus, and Implementation

Once guidelines are established and approved by the full committee, they should be sent to the full membership of the sponsoring organizations or posted on a specially designed Web site to solicit feedback, approval, consensus (support), and other comments for a specified length of time (3–6 mo). After evaluating the responses, the full guidelines should be approved. Meetings should be organized to present the guidelines to clinicians, and articles should be published to inform all constituents.

Treatment algorithms for both MHE and overt hepatic encephalopathy in outpatient, inpatient, and intensive care settings should be developed in concert with the practice guidelines, following the same procedures.

#### Conclusion

The practice guidelines for patients with hepatic encephalopathy, published in 2001, do not reflect significant new data that have become available regarding treatment interventions and outcomes. The clinical data for lactulose are weak and its adverse effects may be dose limiting. Newer, nonabsorbed agents, such as rifaximin, used alone or in conjunction with lactulose, may enhance compliance and adherence with therapy and provide better treatment outcomes. In light of newer well-designed, well-controlled clinical trial data and the recent FDA approval of rifaximin for treating overt hepatic encephalopathy, complete reassessment and reprioritization of treatment approaches are warranted. New practice guidelines for hepatic encephalopathy should be established along with appropriate treatment algorithms for both MHE and overt hepatic encephalopathy in outpatient, inpatient, and intensive care settings.

#### Participants' Discussion

After the live presentation that was the basis for this article, pharmacists participated in a panel discussion.

##### 1. Do you restrict protein in your patients with cirrhosis?

Although several pharmacists in attendance acknowledged that vegetable and dairy protein are preferred over animal protein, many stated that in their institutions, they rarely restrict protein. The major reason is that most of their patients with hepatic encephalopathy are also malnourished. Patients with cirrhosis already have significant muscle wasting, and dietary restrictions accentuate this. Many patients with hepatic encephalopathy and diabetes mellitus are usually reducing their carbohydrate intake and are actually starving. One participant stated that at his institution they actually increase protein intake in these patients. Another participant noted that at his institution there exists a universal application of protein, sodium, and acetaminophen restrictions for patients with cirrhosis. He reported it is challenging trying to “un-teach” patients what they have been previously taught.

##### 2. What dosing levels of lactulose are used at your institution?

Several pharmacists felt that the recommended dosages of lactulose in the guidelines are much more aggressive than those currently used in actual practice. One stated that there is really no reason to use more than 30 ml of lactulose at one time. Another pharmacist mentioned that his facility was able to obtain compassionate-use approval for ornithine aspartate for a patient with urea cycle problems (ammonia levels of 900–1000  $\mu\text{mol/L}$ ) stimulated by steroid use. Another pharmacist stated that his hospital uses sodium benzoate.

##### 3. Is manipulating shunts common practice?

In one pharmacist's experience, trying to manipulate shunts by interventional radiology is not very successful, and his institution has stopped doing it. Others had no opinion of the practice.

##### 4. What treatment guidelines are used in your institutions?

The expert panel of participants agreed that the 2001 guidelines for hepatic encephalopathy

are causing confusion in their institutions because they are outdated and do not contain good recent evidenced-based data. Most pharmacists stated that they do not have formalized guidelines at their facilities, nor do they have treatment algorithms. On follow-up feedback after the live presentation, one pharmacist reported that his institution uses the recent recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program (Garcia-Tsao G, Lim JK. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs hepatitis C resource center program and the national hepatitis C program. *Am J Gastroenterol* 2009;104:1802–29) when treating patients with hepatic encephalopathy.

All pharmacists endorsed the recommendation that the 2001 guidelines need to be updated to reflect current practices or, preferably, that entirely new formal evidence-based guidelines should be established, along with treatment algorithms for outpatient, inpatient, and intensive care settings.

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