Clinical Practice Guidelines

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# Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases

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## Preamble

These recommendations provide a data-supported approach. They are based on the following: (1) formal review and analysis of the recently published world literature on the topic; (2) guideline policies covered by the American Association for the Study of Liver Diseases/European Association for the Study of the Liver (AASLD/EASL) Policy on the Joint Development and Use of Practice Guidelines; and (3) the experience of the authors in the specified topic.

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information.

To more fully characterize the available evidence supporting the recommendations, the AASLD/EASL Practice Guidelines Subcommittee has adopted the classification used by the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) workgroup, with minor modifications (Table 1). The classifications and recommendations are based on three categories: the source of evidence in levels I through III; the quality of evidence designated by high (A), moderate (B), or low quality (C); and the strength of recommendations classified as strong (1) or weak (2).

## Literature review and analysis

The literature databases and search strategies are outlined below. The resulting literature database was available to all members of the writing group (i.e., the authors). They selected references within their field of expertise and experience and graded the references according to the GRADE system [1]. The selection of references for the guideline was based on a validation of the appropriateness of the study design for the stated purpose, a relevant number of patients under study, and confidence in the participating centers and authors. References on original data were preferred and those that were found unsatisfactory in any of these respects were excluded from further evaluation. There may be limitations in this approach when recommendations are needed on rare problems or problems on which scant original data are available. In such cases, it may be necessary to rely on less-qualified references with a low grading. As a result of the important changes in the treatment of complications of cirrhosis (renal failure, infections, and variceal bleeding [VB]), studies performed more than 30 years ago have generally not been considered for these guidelines.

## Introduction

Hepatic encephalopathy (HE) is a frequent complication and one of the most debilitating manifestations of liver disease, severely affecting the lives of patients and their caregivers. Furthermore, cognitive impairment associated with cirrhosis results in utilization of more health care resources in adults than other

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*This guideline has been approved by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver and represents the position of both associations.*

These guidelines were developed by AASLD and EASL and are published simultaneously in *Hepatology* (volume 60, issue 2) and the *Journal of Hepatology* (volume 61, issue 3).

*Abbreviations:* AASLD, American Association for the Study of Liver Diseases; ACLF, acute-on-chronic liver failure; ALD, alcoholic liver disease; ALF, acute liver failure; BCAAs, branched-chain amino acids; CFF, Critical Flicker Frequency; CHE, covert HE; CLD, chronic liver disease; CRT, Continuous Reaction Time; CT, computed tomography; DM, diabetes mellitus; EASL, European Association for the Study of the Liver; EEG, electroencephalography; GI, gastrointestinal; GRADE, the Grading of Recommendation Assessment, Development, and Evaluation; GCS, Glasgow Coma Scale; GPB, glyceryl phenylbutyrate; HCV, hepatitis C virus; HE, hepatic encephalopathy; HM, hepatic myelopathy; ICT, Inhibitory Control Test; ISHEN, International Society for Hepatic Encephalopathies and Nitrogen Metabolism; IV, intravenous; LOLA, L-ornithine L-aspartate; LT, Liver transplantation; MHE, minimal HE; MR, magnetic resonance; OHE, overt HE; PH, portal hypertension; PHES, Psychometric Hepatic Encephalopathy Score; PP, portal pressure; PSE, portosystemic encephalopathy; PSS, portosystemic shunting; RCT, randomized, controlled trial; TIPS, transjugular intrahepatic portosystemic shunt; VB, variceal bleeding; WHC, West Haven Criteria; WM, working memory.

**Table 1. GRADE system for evidence.**

| Grade | Evidence | |
|---|---|---|
| I | Randomized, controlled trials | |
| II-1 | Controlled trials without randomization | |
| II-2 | Cohort or case-control analytic studies | |
| II-3 | Multiple time series, dramatic uncontrolled experiments | |
| III | Opinions of respected authorities, descriptive epidemiology | |
| **Evidence (quality)** | **Description** | |
| High | Further research is very unlikely to change our confidence in the estimated effect | **A** |
| Moderate | Further research is likely to have an important impact on our confidence in the estimate effect and may change the estimate | **B** |
| Low | Further research is likely to have an important impact on our confidence in the estimate effect and is likely to change the estimate. Any change of estimate is uncertain | **C** |
| **Recommendation** | | |
| Strong | Factors influencing the strength of recommendation included the quality of evidence, presumed patient-important outcomes, and costs | **1** |
| Weak | Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher costs, or resource consumption | **2** |

manifestations of liver disease [2]. Progress in the area has been hindered by the complex pathogenesis that is not yet fully elucidated. Apart from such biological factors, there remains the larger obstacle that there are no universally accepted standards for the definition, diagnosis, classification, or treatment of HE, mostly as a result of insufficient clinical studies and standardized definitions. Clinical management tends to be dependent on local standards and personal views. This is an unfavorable situation for patients and contrasts with the severity of the condition and the high level of standardization in other complications of cirrhosis. The lack of consistency in the nomenclature and general standards renders comparisons among studies and patient populations difficult, introduces bias, and hinders progress in clinical research for HE. The latest attempts to standardize the nomenclature were published in 2002 and suggestions for the design of HE trials in 2011. Because there is an unmet need for recommendations on the clinical management of HE, the EASL and the AASLD jointly agreed to create these practice guidelines. It is beyond the scope of these guidelines to elaborate on the theories of pathogenesis of HE, as well as the management of encephalopathy resulting from acute liver failure (ALF), which has been published as guidelines recently. Rather, its aim is to present standardized terminology and recommendations to all health care workers who have patients with HE, regardless of their medical discipline, and focus on adult patients with chronic liver disease (CLD), which is, by far, the most frequent scenario.

As these guidelines on HE were created, the authors found a limited amount of high-quality evidence to extract from the existing literature. There are many reasons for this; the elusive character of HE is among them, as well as the lack of generally accepted and utilized terms for description and categorization of HE. This makes a practice guideline all the more necessary for future improvement of clinical studies and, subsequently, the quality of management of patients with HE. With the existing body of evidence, these guidelines encompass the authors' best, carefully considered opinions. Although not all readers may necessarily agree with all aspects of the guidelines, their creation and adherence to them is the best way forward, with future adjustments when there is emergence of new evidence.

## Definition of the disease/condition

### *Overview*

Advanced liver disease and portosystemic shunting (PSS), far from being an isolated disorder of the liver, have well-known consequences on the body and, notably, on brain functioning. The alterations of brain functioning, which can produce behavioral, cognitive, and motor effects, were termed portosystemic encephalopathy (PSE) [3] and later included in the term HE [4].

Unless the underlying liver disease is successfully treated, HE is associated with poor survival and a high risk of recurrence [5,6]. Even in its mildest form, HE reduces health-related quality of life and is a risk factor for bouts of severe HE [7–9].

### *Definition of HE*

> **Hepatic encephalopathy** is a brain dysfunction caused by liver insufficiency and/or PSS; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma

This definition, in line with previous versions [10,11], is based on the concept that encephalopathies are "diffuse disturbances of brain function" [5] and that the adjective "hepatic" implies a causal connection to liver insufficiency and/or perihepatic vascular shunting [6].

### *Epidemiology*

The incidence and prevalence of HE are related to the severity of the underlying liver insufficiency and PSS [12–15]. In patients with cirrhosis, fully symptomatic overt HE (OHE) is an event that defines the decompensated phase of the disease, such as VB or