Hepatic encephalopathy (HE) is a complex condition with multiple causes each with varying degrees of severity. HE negatively impacts patients' quality of life, and it is associated with significant burdens to patients and their caregivers. The prevalence of cirrhosis, the most common risk factor for HE, has steadily increased during recent years. In turn, an upsurge in the clinical and health care burdens related to HE is expected in the upcoming years. This article provides a comprehensive review of the epidemiology of HE.

Hepatic encephalopathy (HE) is one of the major clinical decompensations of cirrhosis, with a high impact on health care resource utilization and cost. For an effective and comprehensive management of HE, the clinicians need to understand the pathophysiologic mechanisms of HE. This review describes the multiorgan processes involved in HE and how several HE precipitants and treatment strategies act on ammonia production, excretion, and neurotoxicity, including the impact of diabetes and use of cannabinoids. The authors also discuss the current and future role of gut microbiome, systemic/central inflammation, and various neurotransmitters for the pathogenesis and treatment of HE.

Hepatic encephalopathy (HE) occurs in patients with acute-on-chronic liver disease. It has a wide progression of symptoms, with its initial presentation being subtle. The symptoms of HE mainly affect mental status, the musculoskeletal system, and mood/behavior. Its severity ranges from minor disturbances in sleep-wake cycle to the patient being comatose. HE is categorized based on 4 main features: the underlying disease, the severity of manifestations, the time course, and whether precipitating factors are present. The severity of the manifestations is classically identified using the West Haven Criteria. There are several other clinical tests, but they require further validation.

Currently, there is no gold standard serologic or imaging modality to detect hepatic encephalopathy (HE). It is a clinical diagnosis gathered from the
history and physical. Imaging is nonspecific; however, PET and MRI have shown areas of utility, but are not widely available, cost-efficient, or necessary for diagnosis. Electroencephalogram has shown promise as it can be used in conjunction with the Portal Systemic Hepatic Encephalopathy Score test to diagnose minimal HE. Further research on these techniques would need to be performed to identify strict criteria and cutoffs for diagnosing HE as well as associated sensitivities and specificities.

Minimal Hepatic Encephalopathy
Briette Verken Karanfilian, Taeyang Park, Frank Senatore, and Vinod K. Rustgi

Minimal hepatic encephalopathy, previously called subclinical hepatic encephalopathy, represents the earliest and mildest form of hepatic encephalopathy. It is the most under-recognized and underdiagnosed form of hepatic encephalopathy. Although there is no diagnostic gold standard, validated testing modalities have been devised to detect this neurocognitive complication. The newest developments include medically related apps for smartphones or tablets that can be easily used to diagnose and monitor minimal hepatic encephalopathy. Although recognition of this neurocognitive impairment can be challenging, early detection is paramount with the discovery of an association with worse clinical outcomes in patients diagnosed with minimal hepatic encephalopathy.

Prognosis of Hepatic Encephalopathy
Anita Krishnarao and Fredric D. Gordon

The presence of hepatic encephalopathy is often associated with worse clinical outcomes and increased mortality. Even subclinical hepatic encephalopathy has clinical impacts on daily life and has been linked to increased falls, motor vehicle accidents, and hospitalizations. The presence and degree of hepatic encephalopathy can also affect survival outcomes in cirrhosis, acute liver failure, and liver transplant recipients. Patients may have improved clinical outcomes after treatment of hepatic encephalopathy, but the long-term impact of treatment on prognosis is unclear.

Pharmacologic Management of Hepatic Encephalopathy
Noah Y. Mahpour, Lauren Pioppo-Phelan, Mishal Reja, Augustine Tawadros, and Vinod K. Rustgi

Pharmacologic management of hepatic encephalopathy includes a broad range of therapies. This article covers the specific mainstays of therapies, such as antimicrobials and laxatives, with an established evidence base. This article also covers newer modalities of therapies, such as fecal microbiota transplant, probiotics, bioartificial support systems, small molecular therapies such as L-ornithine L-aspartate, branched chain amino acids, L-carnitine, zinc, and other forms of therapy currently under review.

Nonpharmacologic Management of Hepatic Encephalopathy: An Update
Vanessa Weir and K. Rajender Reddy

Research increasingly shows that the gut-liver-brain axis is a crucial component in the pathophysiology of hepatic encephalopathy (HE). Due
to the limitations of current standard-of-care medications, non-pharmacological treatments that target gut dysbiosis, including probiotics, nutritional management, and fecal microbiota transplants, are being considered as alternative and adjunct therapies. Meta-analyses note that probiotics could offer benefits in HE treatment, but have not shown superiority over lactulose. Emerging literature suggests that fecal microbiota transplants could offer a novel strategy to treat gut dysbiosis and favorably impact HE. Finally, liver support devices and liver transplantation could offer a last-resort treatment option for persistent HE.

The Health Care Burden of Hepatic Encephalopathy

Mohamed I. Elsaid, Tina John, You Li, Sri Ram Pentakota, and Vinod K. Rustgi

Hepatic encephalopathy is a major neuropsychiatric complication of liver disease that affects 30% to 40% of cirrhotic patients. Hepatic encephalopathy is characterized by a brain dysfunction that is associated with neurologic complications. Those complications are associated with cognitive impairments, which negatively impacts patients' physical and mental health. In turn, hepatic encephalopathy poses a substantial economic and use burdens to the health care system. This article reviews the multi-dimensional aspects of the health care burden posed by hepatic encephalopathy.

Long-Term Management: Modern Measures to Prevent Readmission in Patients with Hepatic Encephalopathy

Russell Rosenblatt, Johnathan Yeh, and Paul J. Gaglio

Hepatic encephalopathy (HE) is a frequent indication for hospitalization and represents a common manifestation of portal hypertension and de-compensated liver disease that contributes to hospital readmissions. Multiple new techniques are being evaluated to assist in preventing readmissions in these high-risk patients. Techniques to improve medication adherence are paramount. The use of telemedicine and on-demand patient assessment is likely to diminish hospitalizations for HE. Wearable technology has the potential to assist in HE diagnosis and prevent HE progression, with an anticipated diminution in hospital readmissions. This article discusses current and potential future techniques to improve outcomes in these vulnerable patients.

Social Impact of Hepatic Encephalopathy

Mishal Reja, Lauren Pioppo Phelan, Frank Senatore, and Vinod K. Rustgi

Hepatic encephalopathy (HE) is a multifaceted disorder, with effects stretching far beyond office visits and hospitalizations. Patients with HE suffer from varying degrees of altered consciousness, intellectual disability, and personality changes. A large social impact exists for patients with HE. Quality of life and activities of daily living, such as work capacity, driving ability, and sleep quality, have been shown to be affected. Additionally, caregiver and financial burdens are highly prevalent. Multiple tools exist to assess quality of life, including the CLD-Q questionnaire. Common treatments for HE, including rifaximin and lactulose, have been shown to improve overall quality of life.
Novel Therapies in Hepatic Encephalopathy

Maryam Alimirah, Omar Sadiq, and Stuart C. Gordon

Despite widespread use of lactulose and rifaximin for the treatment of hepatic encephalopathy, this complication of advanced liver disease remains a major burden on the health care system in the United States and continues to predispose to high morbidity and mortality. Several agents have surfaced over recent years with promise to treat hepatic encephalopathy and mitigate the cognitive impairment associated with this disease process. The purpose of this article is to highlight the leading emerging therapies in hepatic encephalopathy as well as their therapeutic targets.