DOI: 10.5212/Publ.Biologicas.v.30.24502

O MANEJO TERAPÊUTICO DE PACIENTES COM ENCEFALOPATIA HEPÁTICA: UMA REVISÃO INTEGRATIVA
MANEJO TERAPEUTICO DA ENCEFALOPATIA HEPATICA

THERAPEUTIC MANAGEMENT OF PATIENTS WITH HEPATIC ENCEPHALOPATHY: AN INTEGRATIVE REVIEW
THERAPEUTIC MANAGEMENT OF HEPATIC ENCEPHALOPATHY

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RESUMO

A encefalopatia hepática configura-se como a consequência neurológica mais relevante nos pacientes cirróticos. O objetivo desta revisão é elencar os principais métodos utilizados para o manejo da encefalopatia hepática, sejam estes farmacológicos ou não. Para elaborar essa revisão integrativa de literatura foi realizada uma pesquisa bibliográfica. Utilizando-se do fluxograma PRISMA, foram identificados 1214 artigos nas bases de dados, triados 324 e elegidos 890 para a análise por resumo e título. Os textos analisados integralmente totalizaram 127, destes foram selecionados 30 artigos publicados entre 2015 e 2021, estes com abordagens quantitativas, revisões de literatura e estudos de coorte. A partir desta revisão observou-se que, atualmente, os fármacos mais utilizados no tratamento incluem a lactulose e a rifaximina, sendo que outros, como albumina, fenilacetato de ornitina, zinco, polietilenoglicol, flumazenil, etc., também vêm sendo aplicados no manejo. Ademais, tratamentos como transplante de microbiota fecal, embolização de shunt-portossistêmico, obliteração transvenosa retrógrada e transplante hepático também são utilizados na prática clínica. Conclui-se, porém, que ainda faltam terapias capazes de ocasionar a cura dessa patologia, sendo as disponíveis eficazes apenas para melhora sintomática e da qualidade de vida do paciente.

Palavras-chave: encefalopatia hepática; manejo terapêutico, cirrose, ensino na saúde.

ABSTRACT

Hepatic encephalopathy is the most significant neurological consequence in cirrhotic patients. The aim of this review is to list the main methods used to manage hepatic encephalopathy, including both pharmacological and non-pharmacological approaches. This integrative literature review was carried out using a bibliographic search. Utilizing the PRISMA flowchart, a total of 1214 articles were identified from the databases, 324 were screened and 890 were selected for analysis based on their title and abstract. Finally, 127 full texts were analyzed and 33 articles published between 2015 and 2025 were selected, which included quantitative studies, literature reviews, and cohort studies. This review revealed that the most commonly used pharmacological approach includes lactulose and rifaximin, while others drugs (such as albumin, ornithine phenylacetate, zinc,

polyethylene glycol, flumazenil, etc.) have also been used in the management of this condition. In addition, treatments such as fecal microbiota transplantation, portosystemic shunt embolization, retrograde transvenous obliteration, and liver transplantation are also used in clinical practice. However, therapies capable of curing this pathology are still lacking, and those available are only effective in improving symptoms and the patient's life quality.

Keywords: hepatic encephalopathy; therapeutic management, cirrhosis, health education.

INTRODUCTION

Hepatic encephalopathy (HE) is one of the most serious complications of cirrhosis and is responsible for a wide range of neurological abnormalities[1]. This disease is defined by the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) as a brain dysfunction caused by liver failure associated or not with portosystemic shunt, related with a wide range of cognitive, psychomotor, and psychiatric disorders. These findings can result from severe acute or severe chronic liver disease[2]. The etiological classification of HE is divided as follows: type A occurs due to acute liver failure; type B due to portosystemic shunt without significant associated liver disease; and type C is caused by cirrhosis with or without portosystemic shunt[3-4].

The available treatments for HE management aim to ensure clinical improvement. Some of the therapeutic options include rifaximin, lactulose, L-ornithine-L-aspartate, zinc, flumazenil, ornithine phenylacetate, probiotics, fecal transplantation, and even liver transplantation. With the exception of liver transplantation, the other approaches do not reduce the morbidity and mortality of the disease[5-6].

Therefore, in an attempt to help expand knowledge in this area, this study aims to analyze and review the therapeutic measures applied in the management of patients with hepatic encephalopathy.

METHODS

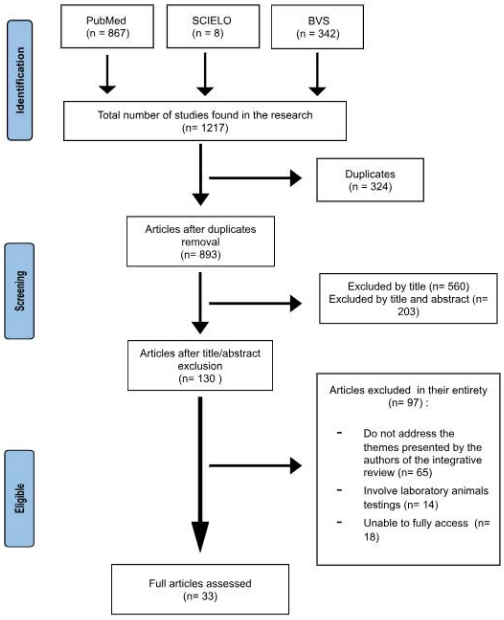
This work is an integrative literature review, in which the information was based on a bibliographical search with up-to-date data applied in clinical practice. In order to develop the theory, the following steps were taken: establishing the guiding question; selecting articles, by inclusion and exclusion criteria; eliminating articles that did not fulfill the established criteria; evaluating the included studies, and then drawing up the review. The research was guided by the question: "How does therapeutic management affect the clinical condition of a patient with hepatic encephalopathy?". The question was established through the use of the PIO strategy, where P = population; I = intervention; O = outcomes. Thus, when the model is applied to the question, "P" is determined as patients with hepatic encephalopathy; "I" as therapeutic management; and "O" as clinical improvement of the clinical condition. The strategic search system used was: "Hepatic Encephalopathy AND Treatment"; and "Hepatic Encephalopathy AND pathophysiology", based on MeSH (Medical Subject Headings). The bibliographic databases used were: PUBMED, SCIELO, and BVS. The inclusion criteria were articles published between 2015 and 2025, in English and Portuguese, which addressed the topic of hepatic encephalopathy. Exclusion criteria included articles that only addressed the topic of encephalopathy, not specifying the hepatic background; duplicate articles; articles about animal experiments; and

those in which it was not possible to obtain full access to its content. The eligibility criteria were used according to the PRISMA flowchart (figure 1).

RESULTS

After searching the databases according to the predefined inclusion criteria, 1,217 articles were found and identified – of which 324 were recognized as duplicates and excluded. Of the 893 studies resulting from this exclusion, 560 were eliminated by its title and 203 by its abstract. Of the 130 articles remaining from the selection, 97 were excluded due to their low relevance in the context of therapeutic management, totaling 33 articles. The distribution of articles was made by year of publication, with the highest concentration observed between 2015 to 2025.

Figure 1. PRISMA Flowchart.



Source: the authors

DISCUSSION

Hepatic encephalopathy occurs in 30% to 45% of patients with cirrhosis, with annual incidence of 20%, and reaches up to 50% after transjugular intrahepatic portosystemic shunt. Its prevalence is difficult to be determined due to the lack of a standardized diagnostic method. However, estimates suggest that more than two-thirds of patients with cirrhosis are affected, with some studies indicating a prevalence rate up to 85%. The onset of HE is one of the main risk factors for poor outcomes, as the occurrence of the first episode of overt HE is associated with increased mortality. The 1- and 3-year cumulative survival rates following an initial episode are approximately 42% and 23%, respectively. In addition to its impact on mortality, HE is associated with a negative effect on life quality and impaired driving. Given the availability of the effective treatments, screening all cirrhotic patients for HE seems to be a reasonable approach[7].

There are four main pillars for the treatment of hepatic encephalopathy: (I) treatment of the underlying cause; (II) severity of the disease; (III) duration of the disease; and (IV) recurrence of the disease[8]. Regarding underlying pathologies, any condition that can lead to hepatocellular failure is associated with the onset of this neurological condition[9]. As for the main pathophysiological mechanism of the disease, it is believed that an increase in ammonia serum levels is responsible for the clinical picture of hepatic encephalopathy - given that, in healthy individuals, ammonia is metabolized through the urea and glutamine synthetase cycle, which takes place in the liver, and is excreted by the kidneys[3]. Since the liver is compromised in patients with this condition, serum ammonia accumulates, directly affecting brain metabolism by its excess levels[2].

Hyperammonemia inhibits the TCA cycle, a metabolic pathway involved in maintaining the brain's energy demands[2]. In addition to hepatocyte dysfunction and hyperammonemia, chronic liver disease leads to complications such as portal hypertension, portal systemic shunt, altered gut microbiota, bacterial translocation, malnutrition, sarcopenia, electrolyte imbalance, constipation and gastrointestinal bleeding. In chronic liver disease, urea and glutamine metabolism is altered. Hepatocytes reduce their ability to eliminate ammonia through the urea cycle, leading to hyperammonemia. This stimulates glutamine synthesis in extrahepatic tissues such as muscle, brain, heart, and lungs. Glutamine is then degraded into ammonia in the intestine and kidneys, only allowing a partial excretion. At brain level, excess ammonia conditions an increase in glutamine synthetase activity. Once the metabolic capacity of astrocytes is exceeded, intracellular osmolarity is altered, leading to edema, cytolysis, and proinflammatory cytokine release. These cellular changes inhibit glutamine synthesis and glutamate receptor expression, reducing its neuronal uptake and triggering an imbalance in the glutamate-glutamine cycle, contributing to increased cerebral blood flow, brain edema, and intracranial pressure. These factors lead to neuropsychiatric and neurologic clinical manifestations of HE[10].

The gut microbiome also plays a direct role in brain function. A study has shown that pathogenic bacteria were associated with hyperammonemia-induced astrocytic changes and diffuse white matter interstitial edema, which can happen in HE. These studies underscore the critical role of the gut microbiome in the disease progression11.

Some precipitating factors are conditions that exacerbate the liver's chronic metabolic status, triggering encephalopathies. This, in turn, can lead to upper gastrointestinal bleeding, metabolic and respiratory alkalosis, hypokalemia, infections, and intestinal constipation[5].

Concerning non-pharmacological treatment, several studies emphasize that regular calorie intake is essential to prevent gluconeogenesis and to maintain the visceral glucose production in a constant level. This measure is especially important for patients with HE because the transformation of amino acids to produce glucose depletes protein storages in the tissues, producing ammonia. It is therefore important that patients avoid fasting for more than 5 hours and are encouraged to eat small, frequent meals[9].

Regarding the drugs used to control and treat this condition, osmotic laxatives such as lactulose and lactitol are effective in 70 to 80 percent of cases. These non-absorbable disaccharides and prebiotics can be used as first-line treatment for HE[5,12]. These drugs are not metabolized until they reach the gastrointestinal colon where they become short-chain fatty acids (lactic and acetic acid) and acidify the environment[7]. In the acidic environment, ammonia is converted into ammonium, which cannot be absorbed and ends up being excreted[5]. In addition, it disrupts the intestinal microbiota,

favoring non-urease producers' bacteria. Moreover, osmotic laxatives also increase the number of peristaltic movements and help eliminate nitrogenous compounds from the human organism[8]. As they are also prebiotics, these drugs stimulate the growth of beneficial bacteria in the colon[9]. Another positive point favoring the use of these drugs in the management of this disease is their low cost and few side effects. Among the possible repercussions, the most common are diarrhea and abdominal discomfort[3].

Regarding antibiotics, Rifaximin, mainly used alongside lactulose, is approved for secondary prophylaxis of HE as an important measure to reduce the risk of recurrence in patients recovering from a prior episode. It primarily alters the gut microbiota by replacing pathogenic bacteria and reducing the number of ammonia-producing microorganisms[13]. A meta-analysis found that rifaximin significantly benefits secondary prevention of HE by increasing recovery rates and decreasing mortality in patients with HE. However, these results should be interpreted with caution due to a number of reasons, including variations in study populations (overt or minimal HE), different doses and treatment duration, and evolving changes in treatment and definitions of HE over time[14]. Compared to lactulose alone, combining these two drugs can improve clinical outcomes and reduce mortality in patients with HE, especially for those at sepsis risk and prone to inflammation[15].

L-Ornithine-L-aspartate (LOLA), a salt composed of two amino acids, improves ammonia metabolism by enhancing its conversion into glutamine, consequently lowering plasma concentrations of ammonia[12]. It also stimulates glutamine synthesis in skeletal muscle, further decreasing ammonia levels[13]. A recent meta-analysis found that LOLA improves all forms of hepatic encephalopathy when compared to placebo, whether in oral or intravenous formulations of this amino acid[16].

Zinc (Zn) is considered a non-standard therapy for HE, but it can be helpful for patients unresponsive to initial standardized therapy. Zinc supplementation primarily optimizes urea formation from ammonia and amino acids[6]. Studies show that zinc improved 54% of outcomes in grade I and II patients previously refractory to standard therapy, usually at a dose of 600 mg of Zinc Sulfate[17].

Glycerol phenylbutyrate (GPB), an aromatic fatty acid salt, is used to manage pathologies involving the urea cycle and other conditions that may lead to hyperammonemia. It is hydrolyzed by pancreatic lipases and subsequently undergoes beta-oxidation in the liver. Some studies report that GPB can reduce ammonia levels up to 75% in HE patients[18].

Polyethylene glycol (PEG), an osmotic laxative polymer, can be used as a monotherapy or in combination with lactulose to improve acute symptoms and to prevent exacerbating forms of HE[19].

Another therapy reported therapy that targets glutamine synthesis is ornithine phenylacetate (OP). OP is responsible for enhancing NH_3 excretion by binding phenylacetate to excess glutamine, removing nitrogen through urine. Research suggests that the use of OP shows very promising results for decreasing ammonia levels[4].

Symbiotics, such as probiotics and fermentable fibers, play a positive role in reducing ammonia absorption, oxidative stress, and inflammation. Therefore, probiotic therapy has been considered beneficial to the human body due to its role in gut microbiota modulation[20].

Sodium benzoate, an inorganic salt, serves as a safe and effective alternative for patients with acute HE crisis. It lowers serum ammonia levels due to its mechanism of binding to glycine and glutamine to form hippurate, which is then excreted in the urine. As a third or fourth-line treatment option, sodium benzoate can be used in patients with good kidney function who are unable to tolerate

standard therapy or have persistent or recurrent HE. Studies suggest that sodium benzoate is as effective as lactulose in reducing ammonia levels in cirrhotic patients[21]. However, because it may lead to an increase in sodium levels as well as cause gastrointestinal symptoms, it requires caution during administration[19].

Bromocriptine, a dopaminergic agonist mostly used for Parkinson's disease, decreases dopaminergic neurotransmission and has managed to improve mental state, especially memory and concentration in patients with HE. However, its efficacy is limited for patients refractory to first-line treatments, being only considered as an alternative option in the treatment of HE[22].

BCAAs are associated with a positive effect by maintaining muscle mass in hepatic encephalopathy patients, as muscles aid ammonia clearance[23] It is therefore recommended that BCAAs be administered for patients with severe protein intolerance, as they help gain muscle mass. If prescribed, oral administration is preferred over intravenous, as the latter may result in a reduction of intestinal glutaminase activity[24]

Flumazenil, a benzodiazepine receptor antagonist, decreases GABAergic signaling in the brain of patients with hepatic encephalopathy. Thus, it leads to positive results in rapid improvement of the clinical condition during an acute episode of HE[25].

Thiamine (vitamin B1) deficiency is common in people with liver disease. As this vitamin has an important role preventing oxidative stress and also acts as a cofactor in glucose metabolism - two factors that may precipitate an episode of HE - this vitamin intravenous supplementation is promising in HE prophylaxis[26].

L-arginine, an amino acid, serves as a substrate in the urea cycle, indirectly enhancing ammonia excretion. Early studies revealed that intravenous L-Arginine administration can potentially reduce serum ammonia levels.

Albumin, a protein synthesized in the liver, binds to various toxic substances capable of inflammation. Albumin infusion has been studied as a protective effect for symptomatic manifestations of HE in patients with decompensated cirrhosis[27,28]. Therefore, extracorporeal albumin dialysis has also been used as a treatment strategy. Using the Molecular Adsorbent Recirculating System (MARS), this dialysis has proved to be very effective in improving quality of life in patients with refractory HE and even in some acute episodes[29]. MARS works by removing toxins from the body that bind to albumin, such as bilirubin, bile acids, nitric oxide, endogenous benzodiazepines, and ammonia[13].

New potential treatments for HE have been reported in the literature, being under investigation:

The use of ethylenediaminetetraacetic acid (EDTA) and para-aminosalicylic acid (PAS), magnesium chelating agents, may help by preventing dopaminergic cells death associated with HE, due to the accumulation of this latter element in the brain[30].

Urea transport protein cloning is underway aiming the reduction of NH3 gut production and enhancing ammonia elimination[31].

FSK-1 enzyme inhibitors are undergoing studies as they may prevent episodes of HE, by regulating glycolysis and lactate production.

Follistatin, a glycoprotein from the TGF-Beta family, is a new option for the HE treatment due to its potential for increasing muscle growth in patients[6].

Liposome-supported peritoneal dialysis (LSPD) is being researched as a strategy for early detoxification of various molecules possibly related to HE, such as ammonia, even before clinical symptoms appear[23].

Other new techniques for the hepatic encephalopathy treatment include retrograde transvenous obliteration (PARTO) and plug/coil-assisted retrograde transvenous obliteration (CARTO)[9].

However, to this day liver transplantation remains the only effective and definitive treatment for cirrhosis. Liver transplantation can fully reverse encephalopathy, provided that the brain damage is not irreversible yet. Transplant priority is based on the Model for End-Stage Liver Disease (MELD), which includes creatinine and bilirubin levels, and prothrombin activity time. However, this score might underestimate the mortality and hospitalization risk in encephalopathic patients. Research has shown that the greater the clinical manifestations before liver transplantation the least likely is the post-transplant remission of HE[32,33].

CONCLUSION

Hepatic encephalopathy is a common and frequent complication in patients with cirrhosis. Therapeutic approach for this clinical condition aims to alleviate the neurological symptoms provoked by HE through inhibiting its pathogenic factors. It is important to emphasize that the therapies currently prescribed can result in substantial improvement in patients' life quality without necessarily affecting the underlying disease or having the potential to cure it.

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Submissão: 21/01/2025 / Aceite: 10/02/2025