NEUROCRITICAL CARE MANAGEMENT OF HEPATIC ENCEPHALOPATHY AND COMA IN LIVER FAILURE

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ABSTRACT

Hepatic encephalopathy (HE) is a severe complication of liver disease, describing a spectrum of neurological and psychiatric abnormalities ranging from subclinical alterations to coma. HE is the leading cause for hospital readmission, intensive care treatment and mortality in patients with chronic liver disease. The complex and multifaceted pathogenesis is not yet fully understood, but hypotheses focus on ammonia and systemic inflammation, which are the main targets for currently available therapies in clinical practice. Nevertheless, the remaining high clinical relevance and healthcare burden of this syndrome underlines the emergence for further unraveling the full spectrum of pathomechanisms as this provides the basis for the development of novel, highly targeted therapies.

In this review, the most recent literature about current and future therapies for HE, relevant for intensive care management, will be discussed.

KEYWORDS: hepatic encephalopathy; pathogenesis; classification; diagnosing; treatment

INTRODUCTION

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome caused by acute or chronic liver disease and/ or portosystemic shunting. It describes a spectrum of neurological and psychiatric manifestations ranging from subclinical alterations to coma [1]. HE is associated with a substantial burden among caregivers and on the overall health care system and severely impacts on the patients' health-related quality of life [2, 3]. Recent data show that HE remains a leading cause for readmission and mortality in patients with chronic liver disease (CLD) and intensive care management is often required in patients with higher grades of HE [4-8]. The persisting high clinical relevance underlines the emergence of improving its current management. However, the development of novel treatment options has been hampered because of the fact that the complex pathogenesis of HE is not yet fully understood. Traditionally, hyperammonemia secondary to liver dysfunction is considered central in the pathogenesis, but also systemic inflammation seems to play a major role. Currently available therapies are therefore based on reducing gut-derived ammonia using non-absorbable disaccharides and reducing bacterial translocation with poorly absorbed antibiotics [1]. However, recent advances in the understanding of this complex syndrome revealed potential novel therapeutic targets. In this article, we will discuss the most current management strategies for HE, thereby focusing on neurocritical care in the intensive care unit (ICU). In addition, novel therapeutic opportunities will be highlighted.

CLINICAL FEATURES AND CLASSIFICATION

Clinical presentation

HE manifests as a wide spectrum of (non-specific) neurological and psychiatric symptoms [9]. In lower grades of HE, symptoms as euphoria, anxiety and a trivial lack of awareness occur, whereas higher HE grades are associated with disorientation, flapping tremor (asterixis), lethargy and eventually coma (**table 1**) [10-13]. Alterations of the motor system, such as hypertonia, hyperreflexia and a positive Babinski sign may be present. Transient focal neurological signs are rare, but may be observed [14]. In contrast, signs of extrapyramidal dysfunction such as muscular rigidity, brady-, hypo-, and dyskinesia are common findings [15]. It was generally believed that manifestations of HE are completely reversible. However, more recent research in liver transplant patients and in patients with recurrent HE episodes showed that cognitive abnormalities may persist [16, 17]. Rarely, persistent HE may present with irreversible (extra-)pyramidal signs.

Epidemiology

Incidence and prevalence of HE are highly related to the severity and type of the liver disease [18-20].

In CLD, the overall prevalence of fully symptomatic HE at time of diagnosis of cirrhosis is 10-14% [21-23] and 16-21% in the subgroup of patients with decompensated cirrhosis [5, 24]. In 30-40% of patients with cirrhosis, HE will develop at some point during the clinical course [25]. In 5-25% of patients, the first episode of fully symptomatic HE develops within 5 years after diagnosis of cirrhosis, depending on the presence of risk factors, such as subclinical HE,

infections, variceal bleeding or ascites [26-30]. Patients with a previous episode of HE, have a cumulative risk of recurrence of 40% within 1 year [31]. Recently, a large, prospective study assessing the natural history of patients admitted for acute decompensation of liver cirrhosis (AD), showed that the incidence of HE in these patients was 34% [32]. In the subgroup of patients with acute-on-chronic liver failure (ACLF), which was found to be a distinct entity from AD and associated with (multi-) organ failure and high short-term mortality, survival was significantly lower in patients with as compared to those without HE. This indicates that the presence of HE significantly adds to the risk of death, independently from other organ failures [33].

Acute liver failure (ALF) is characterized by severe acute liver injury with impaired synthetic function (International Normalized Ratio>1.5) and the development of HE in a patient without prior liver disease [34]. Unlike CLD, ALF can lead to cerebral edema with increased intracranial pressure (ICP), potentially leading to cerebral herniation and death [35, 36]. Over the last decades, a considerable decline in the incidence of cerebral edema in ALF has been observed and is now seen in less than 25% of patients [16, 17]. This may be due to the implementation of emergency liver transplantation as well as practical improvements in critical care management. When present, however, cerebral edema in ALF is still associated with very poor survival [37-39].

Classification

The disease classification and grading are of high importance as it guides patients' treatment strategies. Whereas subclinical stages can be often managed in an outpatient setting does

clinically apparent HE require hospital admission, imminent treatment and intensive care management in higher grades.

Considering the intra- and inter-individual variability of symptoms, reliable diagnostic tools to define and grade HE are of high importance. In order to optimize the diagnostic accuracy, the current European Association for the Study of the Liver (EASL)/ American Association for the study of liver diseases (AASLD) guideline [1] implemented a multiaxial classification system, categorizing HE into: 1) the underlying disease (type A: acute liver failure, type B: portosystemic bypass or shunting, type C: cirrhosis), 2) the severity of the manifestations, 3) time course (episodic, recurrent, persistent), 4) the existence of precipitating factors (**figure 1**). An additional category has been proposed according to the presence of ACLF [33], as it is a distinct entitiy from CLD and ALF in terms of pathophysiology, prognostic impact and management strategy. However, this classification is still subject of research.

The West Haven Criteria (WHC) remains the gold standard for grading the severity of HE (**table 1**) [1, 9]. Based on clinical criteria, this tool categorizes HE into 4 stages. Whereas it reliably distinguishes between patients with low vs. high grade HE, it has its weakness in discriminating between patients with grade I HE and those with no HE or minimal HE (mHE). Therefore, this is to date the domain of psychometric tests. The International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) additionally introduced the terms covert HE (CHE; i.e., $\leq$ grade 1) and overt HE (OHE; i.e., $\geq$ grade 2) [40]. Considering the scope of this article, we will focus on the subgroup of patients with OHE.

Diagnosis

The diagnosis of OHE is primarily based on clinical signs and context [1]. As described previously, WHC is the gold standard to diagnose and grade the severity of OHE [1, 9]. A limitation of the WHC is that it is a subjective tool, resulting in inter-observer variability. In contrast, the presence of disorientation and asterixis has been found to have a good inter-rater reliability and are therefore considered key symptoms of OHE [41]. The Glasgow Coma Scale is widely implemented for patients with a markedly altered level of consciousness and supplies an accurate description of the disease severity. Blood ammonia levels may be useful as the absence of hyperammonemia makes the diagnosis of OHE unlikely. In contrast, a high blood ammonia level alone in patients with CLD has no diagnostic or prognostic value [42]. Therefore, ammonia measurements in clinical practice in CLD remain controversial. In ALF, however, there is a good correlation between blood ammonia and disease severity and prognosis [43]. In patients with ALF and brain edema, it has been shown that persistent elevation of arterial ammonia (>124 umol/L) following initial therapeutic interventions, is associated with an increased risk of intracranial hypertension [44-46]. Ammonia measurements comprise some logistic obstacles that should be taken into consideration. First of all, arterial blood should be preferred over venous blood as it gives more reliable results [47, 48]. However, this advantage is limited and is therefore considered acceptable [49]. When venous blood is used, it should preferably be drawn when the patient is fasting, stored and transported on ice and analyzed immediately.

Even when clinical signs are clear, it does not absolve from the necessity to search for precipitating events on the one hand and to be alert on alternative causes for an altered mental state on the other hand, as both require either additional or alternative treatments.

Especially in (end-stage) CLD, OHE is considered a 'diagnosis of exclusion' as this patient population is prone to other causes of mental state abnormalities, such as several types of metabolic encephalopathy as well as non-metabolic causes (i.e., alcohol abuse, drug use, psychiatric disorders, cerebrovascular disease). Therefore, laboratory or radiological diagnostics may be needed to exclude these alternative causes. Cerebral imaging is recommended in case of non-specific clinical presentation or when cerebrovascular disease is suspected. However, it does not add any diagnostic or grading information [1]. Moreover, other complications of advanced liver disease, such as infections and hyponatremia may either lead to mental states mimicking OHE (i.e., delirium) or be the precipitating factor for HE. All of the aforementioned factors may of course co-exist with OHE, which makes the diagnosis of exclusion-process' a complex one [50].

Based on the most recent guideline and literature, we have summarized practice recommendations for diagnosing OHE in **table 2**.

PATHOGENESIS

Although the complex pathogenesis of HE remains not fully elucidated, hyperammonemia is still thought to be the key mediator. However, other distinct pathophysiological mechanisms are involved, including impaired energy metabolism [47], oxidative stress [48], systemic inflammation [49, 51], cerebral haemodynamic dysregulation and impaired blood-brain-barrier (BBB) permeability [52]. Especially the role of inflammation has gained more and more importance in both acute and chronic liver disease in the past decades. Moreover, there appears to be a synergistic relationship between hyperammonemia and inflammation in the progression of HE in CLD, ACLF and ALF [52-56]. Another important factor in the pathogenesis of HE is an altered cerebral blood flow (CBF), which seems to be directly linked to

hyperammonemia and inflammation [57, 58]. Therefore, hyperammonemia, systemic inflammation and CBF seem to be critical in the current paradigm for the pathophysiology of HE and will be discussed in further detail below.

Hyperammonemia and its consequences

Ammonia is a nitrogen-containing compound that is neurotoxic at elevated concentrations. The intestine is the major supplier of plasma ammonia levels (responsible for about 50% of the plasma load). Intestinal ammonia is produced by bacterial metabolism of urea from consumed proteins and by glutamine deamination by glutaminase [59]. Another main source of ammonia is its production by the kidney, which is responsible for about 40% of plasma ammonia levels. Ammonia is mainly metabolized by the periportal hepatocytes through the urea cycle and is subsequently cleared by the kidneys and (to a lesser extent) by the muscles [60]. Liver dysfunction is therefore associated with impaired detoxification of ammonia and portal hypertension leads to shunting of ammonia-containing blood to the systemic circulation. Ammonia c rosses the BBB and is metabolized by astrocytes by converting glutamate and ammonia into glutamine by the enzyme glutamine synthetase. At elevated plasma ammonia concentrations, accumulation of glutamine creates an osmotic gradient resulting in astrocyte swelling and astrocyte dysfunction [61].

Another ammonia-related contributor to neurotoxicity in HE is the activation of N-methyl-D-aspartate (NMDA) receptors by astrocytes stimulated by ammonia. This results in a decrease in antioxidant enzyme activity and increases the production of reactive oxygen species (ROS) [62, 63]. In addition, mitochondrial dysfunction caused by exposure to high amounts of

glutamine may lead to enhanced oxidative stress in astrocytes [64]. Also systemic inflammation, a common and significant feature in HE, contributes to the generationcer of oxidative stress by neutrophil activation and enhanced ROS production [52]. An excess of these oxidative agents may lead to oxidization of RNA, resulting in impaired protein synthesis and molecular damage [65, 66]. Animal and human studies have shown beneficial effects of treatment with antioxidants in the setting of fulminant liver failure and HE, thereby supporting a role for (ammonia-induced) oxidative stress as a relevant pathomechanism and potential therapeutic target [67-71].

Other actions of ammonia on the brain include the effects on excitatory and inhibitory neurotransmission, inhibition of glucose oxidation and stimulation of glycolysis [72, 73].

The systemic inflammation hypothesis

Although there is a large amount of evidence showing that ammonia plays a key role in the pathogenesis of HE, the correlation between blood ammonia levels and HE severity in CLD is poor [49, 74], meaning that other mechanisms are involved. In cirrhotic patients, infection is a well-known precipitating factor for HE. The presence of infections, especially pneumonia and sepsis, significantly impact on the mortality risk in these patients [75]. In addition, multiple studies revealed that an elevated blood level of the pro-inflammatory cytokine TNF-a positively correlates with the severity of HE [49, 76, 77]. Also in ALF, the presence of a systemic inflammatory response syndrome (SIRS) is involved in the progression of HE and therefore negatively impacts on prognosis [78, 79]. In ACLF, sepsis was found to be an important precipitating factor for HE in previously stable CLD [80]. Based on these observations, it was hypothesized that systemic inflammation is directly involved in the pathogenesis of HE.

It has indeed been shown that the peripheral immune system communicates with the brain in the setting of systemic inflammation in liver disease, although the underlying mechanisms are not fully understood. During infection, the systemic inflammatory response leads to a cytokine storm and release of inflammatory modulators that may impact on the permeability and signaling pathways through the BBB [81]. This may in turn lead to microglia activation and local production of pro-inflammatory cytokines (i.e., TNF-a, IL-1B and IL-6), a phenomenon referred to as 'neuroinflammation' [78]. This has especially been shown in advanced stages of HE in ALF, while the degree of neuroinflammation in CLD seems less pronounced and relies on the characteristic of the precipitating factor [82]. Multiple studies have shown that neuroinflammation can lead to neuronal cell death [83, 84].

Endotoxemia secondary to bacterial infections plays an important role in the development of a systemic inflammatory response and thus in the development of neuroinflammation in liver disease. Besides infections, endotoxemia can result from intestinal bacterial translocation due to impairment of the intestinal barrier integrity in cirrhosis and directly from the liver dysfunction [85, 86]. Many studies have shown that bacterial antigens, such as lipopolysaccharide (LPS) are involved in HE development. In several ALF animal models, LPS administration has been shown to increase BBB permeability and lead to coma [87]. Also in a CLD model, as induced by bile duct ligation (BDL) in rats, the administration of LPS was found to induce coma [56]. Moreover, LPS administration in BDL rats has been found to exacerbate brain edema through a synergistic effect of hyperammonemia and endotoxemia [81].

Synergy between hyperammonemia and systemic inflammation

Data of recent animal studies suggest that hyperammonemia and systemic inflammation are not isolated pathomechanisms, but act synergistically in producing the clinical manifestations of HE in both acute and chronic liver disease [52, 53, 55, 56]. In a CLD rat model for example, it was shown that administration of LPS resulted in hyperammonemia, brain swelling and coma [56]. Moreover, another study showed that a reduction in blood ammonia level protected the brain from a subsequent injection with LPS, suggesting that ammonia makes the brain more susceptible for a secondary inflammatory hit [56]. This was confirmed in a human study, in which significant deterioration in neuropsychometric tests was shown following induced hyperammonemia during the inflammatory state, but not after resolution of the infection [55]. Interestingly, administration of ammonia to healthy rats activates the microglial cells, which modulate neuroinflammation [88]. The exact mechanism behind this synergistic relationship is still subject of research, but it potentially provides interesting therapeutic targets for HE, such as endotoxin receptors, which will be discussed in the next section.

Brain edema and the role of cerebral hemodynamics

Altered CBF is a crucial factor in the pathogenesis of HE. While CLD is known to be associated with progressive reduction in CBF (i.e., cerebral oligaemia), is ALF characterized by significant increases in CBF (i.e., cerebral hyperaemia) [58]. Cerebral hyperaemia may lead to an increase in brain blood volume and promotes the movement of water through the BBB and is therefore relevant to the pathogenesis of increased intracranial pressure. Multiple mechanisms are involved in inducing alterations in cerebral haemodynamics in ALF, among which

inflammation and hyperammonemia, acting synergistically, seem once again important mediators [57, 58].

Unlike ALF, mild brain edema has been shown in patients with CLD and HE using advanced magnetic resonance imaging techniques [89]. Nevertheless, lower grade edema appeared to be a significant feature in these patients as improvement of HE was found to be associated with a decrease in brain edema [90]. In ACLF, severity of brain edema and intracranial hypertension have not been studied extensively yet, but a significant increase in ICP has been previously described in small studies [53, 91]. A more recent study reports a relatively low incidence of high grade cerebral edema in ACLF patients of about 5% [92].

In summary, the current paradigm for the pathogenesis of HE in both acute and chronic liver disease involves the interaction between hyperammonemia, systemic inflammation and CBF and these pathomechanisms are therefore clear therapeutic targets for HE.

TREATMENT

General management

The management of patients with HE has two primary goals: 1) to prevent HE related complications (e.g. brain herniation, aspiration, asphyxia) and 2) to restore patients' individual cognitive function and consciousness. All patients with OHE must be evaluated for intensive care monitoring and treatment. Whereas patients with preserved synthetic liver function and mild to moderate HE (i.e., WHC grade 1-2) can be safely managed on the normal ward, HE in association with ALF or ACLF is an indication for transfer to ICU in order to protect

the airway, provide full organ support including mechanical ventilation, vasopressor support and renal replacement therapy.

The management strategy depends on the underlying liver disease. In ALF, HE development is a direct consequence of the acute deterioration of liver function and subsequent hyperammonemia and inflammation, which may result in cerebral oedema and increase in ICP [87, 93]. Therefore, treatment strategies in ALF focus on reducing the ICP and identifying patients eligible for high urgency liver transplantation. This is in contrast to ACLF, in which HE is dominated by a pro-inflammatory reaction and less strongly associated with hyperammonemia. Moreover, in ACLF, HE is triggered in more than 60% of patients by precipitating events such as alcohol binge, infection, electrolyte disbalance, gastrointestinal bleeding and treatment with diuretic agents [33, 94]. Therefore, the initial management of HE in ACLF involves the identification and treatment of precipitating events, e.g. restoring fluid balance and electrolyte disturbances, identification of infections and administration of appropriate and early antibiotics and to treat gastrointestinal bleedings. In addition, administration of specific therapeutics targeting ammonia and inflammation play a central role. In this section, treatment strategies for both ALF and ACLF will be outlined and are summarized in table 3 and 4 and in figure 2.

Nutrition

Patients with liver cirrhosis are generally prone to be in a catabolic state characterized by protein degradation and reduced gluconeogenesis [95]. Dietary recommendations aim at maintaining patients' energy and protein intake independently on the presence of HE. The ESPEN guidelines suggest a caloric intake of about 35-40 kcal/Kg, in order to avoid protein

catabolism. Ideally, this should be distributed between multiple meals throughout the day including a high caloric meal at bedtime [93]. A protein intake of about 1.2-1.5 gram protein/kg body weight is recommended in order to maintain the nitrogen balance. There is no reliable data supporting a strict dietary restriction in patients with HE, unless the HE bout can be clearly allocated to an excessive protein intake [93]. This is in contrast to the widespread belief that protein restriction fastens the recovery after hepatic encephalopathy. Long-term energy and protein restriction must be avoided, also in obese patients with cirrhosis, as it leads to protein depletion and exacerbation of HE [93]. In this situation endogenous amino acids are utilized to maintain the blood sugar levels. This leads to protein break down and production of ammonia [96]. In stressful situations such as intensive care stays the energy and protein requirement might be even higher [93].

Hyperammonemia is considered the main cause of reduced levels of branched chain amino acids (BCAAs) [97]. Its oral supplementation has been reported to enhance ammonia detoxification [98, 99], to stimulate the secretion of hepatocyte growth factor [100] which stimulates liver regeneration, to induce muscle protein synthesis [101] and insulin secretion [102]. A recent Cochrane meta-analysis confirmed the clinical efficacy on the development of HE by analyzing 16 studies, although the survival endpoint was not met [97]. However, BCAA supplementation is not effective in patients with overt HE [94].

Patient with liver cirrhosis, notably with alcoholic liver cirrhosis, are prone to be thiamine deficient [93] and are therefore at risk of developing a Wernicke's encephalopathy. Although there are disease specific symptoms such as nystagmus and ptosis, clinical presentation of Wernicke's encephalopathy may overlap with HE (e.g. ataxia, confusion, memory loss),

making the diagnostic process challenging. As thiamine substitution is cheap and safe, thiamine should be given in all patients with HE associated with alcoholic liver disease.

Current specific treatments

Therapies targeting the gut

Nonabsorbable disaccharides, notably lactulose, is traditionally used as the initial treatment in HE associated with CLD. Lactulose has a restoring effect on the intestinal dysbiosis, as it reduces the amount of ammonia-producing bacteria. In addition, its laxative effect results in removal of nitrogen-containing substances from the gastrointestinal tract. Its benefit regarding the resolution of the HE bout [RR 0.63], liver related complications (e.g. variceal bleedings, SBP and hepatorenal syndrome) [RR 0.42] and mortality [RR 0.36] was shown in a meta-analysis, which updated a 2004 published Cochrane Review [103, 104]. Furthermore, the low costs, its ease of use and the small spectrum of side effects still speak for its widespread use as a first line treatment in cirrhosis associated HE. Initially, lactulose is given to achieve two to three loose bowel movements daily. The dose can be increased if there is no treatment response, or alternatively administered as enema [94]. However, at higher doses, side effects such as hyponatremia, dehydration, meteorism and skin irritation occur more frequently and may limit its applicability. Polyethylene glycol, which is commonly used as laxative, might be an alternative to lactulose, as shown in a small study with 50 patients. Administration of polyethylene glycol resulted in a significantly quicker resolution of the HE episode [105]. However, further validation is needed before polyethylene glycol could be implemented as a first line treatment.

In ALF, the evidence for the efficacy of lactulose is limited and the oral administration may cause gastrointestinal side effects such as bowel distension, worsening of paralytic ileus, which ultimately jeopardizes liver transplantation [106]. If necessary, the rectal administration should be preferred over the oral approach, as it less likely causes treatment related complications.

Rifaximin (550mg BD) is a non-absorbable antibiotic agent, which inhibits bacterial RNA synthesis by binding to the DNA-dependent RNA-polymerase. It targets the intestinal dysbiosis, the bacterial translocation and reduces the production of neurotoxin (ammonia) and the amount of circulating endotoxins [107]. In most European and North American countries Rifaximin is approved and tested to prevent the development of HE episodes [108-110] as secondary prophylaxis [94]. Data about its benefit in the acute HE is sparse. A positive effect on resolution of OHE and survival has been shown in a study with 120 patients comparing lactulose vs. rifaximin plus lactulose [111]. However, according to the approval status and its limited evidence, the use of rifaximin for the acute HE bout in association with ACLF is limited to treatment of non-responders.

Rifaximin was not evaluated for HE associated with ALF and can therefore not be recommended in this setting.

Ammonia targeting therapies

L-ornithine L-aspartate (LOLA) is known to lower ammonia levels by interacting with the glutamine synthetase and urea cycle enzyme system [112]. Whilst the oral effect especially in

the acute situation is questionable, the intravenous administration (25-40 g/day, max 5g/hour) was shown to reduce ammonia levels and improve the performance of psychometric tests [112]. This was confirmed by a published meta-analysis [113]. However, a recently released Cochrane meta-analysis emphasized, that the quality of evidence is poor. Further trials are required [114] and its use is restricted to countries in which it is approved for the treatment of HE. The potential ammonia regeneration from glutamine breakdown may lead to a rebound effect and a certain number of non-responder [115].

In ALF LOLA was not effective in improving the HE severity [116], although its ammonia lowering effect had been shown previously [117].

Albumin

Albumin plays a prominent role among all plasma proteins. Its effect goes far beyond the maintenance of the systemic oncotic pressure. It comprises numerous additional functions, including detoxification, modulating inflammation and stabilizing endothelial function [118]. However, at this time point there is no credible data showing a true benefit in HE, which adds to the plasma expanding effect of albumin [119], although a survival benefit in the setting of cirrhosis associated HE has been shown [120]. HE is therefore, not an indication for albumin administration. However, albumin is crucial component in most extracorporeal liver assist devices, as discussed below, and might through this channel gain importance in the treatment of HE.

Management of intracranial hypertension

<u>Measurement and monitoring</u>

Under normal conditions the ICP approximately equals the central venous pressure. However, in the setting of intracranial hypertension, the ICP increases above 20 mmHg. Increased ICP can reduce the cerebral perfusion pressure (CPP), thereby increasing the risk of ischemic brain damage on the one hand and herniation of the brain on the other hand [121]. As previously discussed, intracranial hypertension and cerebral oedema is more prominent in ALF than in ACLF. Therefore, management strategies are primarily developed for patients with ALF. Nevertheless, its principals do also apply to patients with ACLF.

If there is evidence of intracranial hypertension, adequate monitoring is essential. Given the fact that patients with liver failure have a coagulopathy and are therefore at risk of bleeding complications, invasive measurement of intracranial pressure should be carefully considered. There is no agreement on the localization of the pressure probe, ranging from epidural over subdural and intraparenchymal to intraventricular [121]. Whereas the epidural approach bears the lowest risk for complications does the intraparenchymal and intraventricular probes provide the most accurate results [121]. Ultimately, the access path strongly depends on the confidence of the neurosurgeon and individual patients factors such as the severity of coagulopathy. Unfortunately, there are no randomized controlled trials proving the general efficacy of this measure. Some data from uncontrolled trials suggest that invasive pressure measurement might reduce the frequency of HE related endpoints with a low risk of complications [122, 123]. In a case series of 37 patients with ALF and HE grade 4, intraparenchymal probes were inserted after sufficient substitution with recombinant factor VIIa and desmopressin, elevating the platelet count to > 50,000/mm3 and the fibrinogen level to >100 mg/dL. [122]. In this study, one patient developed an intracranial bleed but required evacuation of the haematoma. Four patients died due to brain herniation und thus

uncontrolled intracranial hypertension. Although this study has several limitations, of which the missing control group is certainly the most important one, it shows that under certain conditions invasive ICP measurement is feasible with an acceptable risk of complications. However, data from other studies underline the conflicting discussion regarding this measure. A large case-control study in 629 patients with ALF and HE grade 3/4 matched 140 patients with invasive ICP measurements with 489 non-invasively monitored patients. Bleeding complications were rare (4/56, 7%). Nevertheless, in non-paracetamol induced ALF, invasive ICP measurement was associated with an increased risk of death with a hazard ratio of 3 [124]. In this study the cause of inferiority of invasive ICP monitoring could not be clarified. It might be related to a more aggressive ICP treatment or selection of sicker patients [124, 125]. In conclusion, the benefit of invasive ICP monitoring needs to be proven weighing up the risk of bleeding versus benefit.

The high costs and the potential complications of invasive ICP management emphasize the need for the development of non-invasive assessment strategies. There are numerous studies evaluating transcranial Doppler ultrasound techniques to assess the intracranial pressure. However only a few reported the correlation with invasive methods and showed a wide range of sensitivity (25%-100%) [126, 127] and specificity (69%-99%) [128, 129]. In addition, the reliability of this method is highly investigator-dependent and data in adult liver disease patients do still not exist.

Treatment of increased ICP

Treatment strategies for intracranial hypertension focus on the reduction of the cerebral oedema and the maintenance of the CPP. Therapies of intracranial hypertension correspond

to the principals of the general neurological and neurointensive care management. Intravenous sedation with barbiturates, an elevated head position and controlled sodium levels (aim 145-150 mmol/l) should be achieved. If necessary, continuous hypertonic saline infusion are useful to maintain the high sodium level [130]. Pressure peaks might be controlled by bolus injections of mannitol and hypertonic saline [106]. Metabolic alkalosis and hypokalemia increases ammonia production and need to be corrected. Although short term hyperventilation leads to reduced CO2 levels thereby causing cerebral vasoconstriction and decreased intracranial pressure, this measure should be avoided beyond short term application for pressure peaks [121] as it may lead to cerebral ischemia and rebound oedema [131]. However, as hypercapnia worsens the cerebral oedema a target PaO2 level of about 32-34 mmHg followed by normocapnia (35-40mmHg) is of benefit to control intracranial pressure [121, 132] (figure 2b, table 4).

Results from a systematic review published in 2010 suggested that hypothermia in ALF with intracranial hypertension is effective, feasible and safe in the treatment of uncontrolled intracranial hypertension [123]. However, a recently published randomized controlled trial investigated 46 patients with ALF, high-grade HE and intracranial pressure measurement into groups with moderate hypothermia (33-34°C) and normothermia. The aim of this study was to evaluate whether hypothermia could prevent sustained ICP-elevation. The data did not confirm the benefit of moderate hypothermia in this setting but the study was thought to be underpowered to detect a difference.[133].

Extracorporeal devices

The use of renal replacement, notably continuous veno-venous hemofiltration (CVVH), reduces circulating ammonia levels [134]. Therefore, early initiation of CVVH is widely recommended in ALF [135]. Other extracorporeal devices focus on the removal of inflammatory mediators and toxins. Of them, high volume plasmapheresis has been recently evaluated for the treatment of ALF in comparison with standard of care [136]. In 182 patients, plasmapheresis achieved a survival improvement from 47.8% to 58.7% [136]. A reduced vasopressor requirement and a decrease of markers for inflammation and cell damage were the most compelling results [136]. Therefore, plasma exchange is an important measure in the early phase of ALF, independently of the presence of HE or intracranial hypertension. However, if not indicated per se, its utilization might be considered in patients with refractory circulatory insufficiency and HE. Although Larsen et al. [136] could not show an effect of high volume plasmapheresis on the intracranial pressure, the stabilization of the circulation can increase the cerebral perfusion pressure and thereby lower the risk for ischemic cerebral damage.

In ACLF, there are two single-center, non-controlled observational studies [137, 138] and two randomized controlled trials evaluating the plasma-exchange either against the molecular adsorbent system (non-MARS)[139] or standard of care [140]. Results suggest its feasibility and a positive effect on the survival. However, it remains unclear whether there is an independent effect on HE.

Other extracorporeal devices such as the molecular adsorbent recirculating system (MARS) use albumin as a scavenger molecule to clear the circulation from toxins. However, neither

MARS nor other albumin-based systems have been shown to have a positive effect on ACLF or ALF. Two multicenter randomized trials, the RELIEF trial [141] and the FULMAR study [142], evaluated MARS in both disease entities and reported additional results about HE development. The FULMAR study could not show an improvement of HE in ALF. This was most likely due to the fact, that the median time from randomization to liver transplantation was too short to unfold a potential effect. In ACLF the RELIEF trial reported a diminished severity of HE during the MARS treatment period [141].

A novel extracorporeal assist device, called DIALIVE, combines albumin exchange with endotoxin adsorption. The first study in patients is currently ongoing. This randomized controlled trial is designed as a proof of concept trial in patients with ACLF (NCT03065699).

Overall, there are currently two systems that play a role in management of HE associated with ALF or ACLF; high volume plasmapheresis and MARS. Plasma exchange may have its indication in both entities, especially if the circulatory insufficiency is predominating, in order to stabilize the systemic blood pressure and intracranial perfusion pressure. Patients with HE but without circulatory failure might benefit from MARS, especially as a bridge to transplantation or spontaneous recovery.

Liver transplantation

HE is traditionally regarded as being fully reversible if treated adequately. Liver transplantation, by restoring liver function, should therefore allow patients to fully recover from their neuropsychological impairment. However, there is evidence suggesting that HE, even after liver transplantation, leaves some cognitive sequelae [143]. A two-component

model has been proposed, consisting of a reversible delirium-like state and a irreversible dementia-like state [143]. The delirium-like state relates majorly to the cerebral oedema, whereas the dementia-like state includes degenerative cerebellar and ganglia alterations [144]. As to whether this significantly impacts the selection of liver transplant candidates is unclear, notably because neuropsychological disorders after liver transplantation are most often multifactorial (e.g. dementia, immunosuppression, depression etc.). HE is therefore perceived as an indication instead of a contraindication for liver transplantation.

The role of HE in the organ allocation system for liver transplant candidates depends on the underlying liver disease. In ALF HE defines the condition [145, 146]. In ACLF, the presence of HE is an independent risk factor for mortality [32]. Though, liver transplantation is a potentially life saving intervention in this specific group of patients [147]. HE is not a criterion for priorisation on the waiting list in most countries with MELD score based organ allocation and standard exceptions for this type of complications do not exist. It is therefore essential to clarify the type of underlying liver disease, as it determines how liver transplantation fits into individual patient management strategies.

TIPSS- and portosystemic shunt related HE

In patients with refractory HE associated with ACLF, the presence of portosystemic shunts should be excluded. If large shunts are present, their occlusion may improve HE especially if the liver function is preserved (MELD 11 or below) [148-150]. After transjugular intrahepatic shunt insertion (TIPS), HE may occur in up to 50% of patients and is associated with hyperammonemia, endotoxemia and cerebral oedema [151-153]. As the efficacy of medical

treatment is limited, stent reduction or occlusion remains the gold standard especially in those with refractory or recurrent TIPS-related HE [154, 155]

Novel therapeutic opportunities

Targeting ammonia

Ornithine is a component of LOLA and acts by stimulating the glutamine synthetase, which eliminates ammonia to glutamine. LOLA bears the risk of an ammonia rebound phenomenon as glutamine can be recycled to ammonia [115]. New drug formulations combine ornithine with phenylacetate (ornithine phenylacetate, OP) or its prodrug phenylbutyrate, which increases glutamine excretion by binding to phenylacetate [156, 157]. Although these treatments were proven to be safe and effective in reducing ammonia [156, 157] results need to be confirmed in phase 3 study.

Targeting the intestinal microbiome

Probiotics, which correct dysbiosis and intestinal bacterial translocation, were tested in prospective trials assessing its capacity to prevent the occurrence of HE bouts. Overall it failed to prove a significant benefit over the standard treatment with lactulose [158-161]. Besides, a randomized controlled study in acute HE does not exist so that this type of treatment cannot be recommended.

Fecal microbiota transplantation is a novel approach to restore dysbiosis [162] and seems to be an attractive target for patients with liver cirrhosis and HE. In fact, its ammonia-lowering effect has been proven in animal studies [163, 164] and there are currently three human

studies actively recruiting patients (NCT03014505, NCT02862249) or completed (NCT02636647).

However, in the setting of acute HE and intensive care, this treatment that requires specific resources and logistics, might be difficult to implement as first line therapy.

Targeting (neuro-)inflammation

There are a few approaches that target altered neuro-(inflammatory) pathways. Sildenafil is a phosphodiesterase inhibitor, which improves the function of glutamate-NO-cGMP pathway and restores extracellular cGMP levels. It has been shown to improve learning abilities in rats with porto-caval anastomosis and hyperammonemia [165]. Moreover, a reduction of neuroinflammation along with an improvement of cognitive functions was reported in other studies [166, 167].

Indomethacin is a cyclooxygenase inhibitor, which reduces the intracranial pressure in a porcine model and might play a role in humans [168]. Although further studies need to confirm the results, it may be considered in treatment of refractory cases of severe intracranial hypertension in patients with ALF [106].

CONCLUSION

HE is a devastating complication of liver failure and an independent predictor of mortality both in patients with ALF and those with ACLF. Although the mechanisms of HE are still being investigated, ammonia and inflammation are pathogenically important. Therapeutic option for management of patients with severe HE are limited. Newer strategies based on

the better understanding of interorgan metabolism of ammonia are in late stages of development. With improvements in treatment of HE, it is likely that the survival of patients with ALF and ACLF will improve.

TABLES

Table 1. West-Haven criteria and ISHEN classification (modified according to Vilstrup H et al. [1]).

WHC grade	**ISHEN**	**Clinical features**
Unimpaired		No encephalopathy at all, no history of HE
Minimal	Covert	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change
Grade I		• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm
Grade II	Overt	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis
Grade III		• Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior
Grade IV		Coma

WHC, West Haven criteria; ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism.

Table 2. Practice recommendation for the diagnostic work-up of OHE in patients with confirmed hepatic failure and/ or portosystemic shunting (modified according to Romero-Gómez M et al. [169]).

Steps in diagnostic work-up of OHE in the setting of confirmed hepatic failure and/ or portosystemic shunting	
1. History taking	• precipitating factors for HE • list of medication • previous HE episodes (requiring hospitalization) • time course and pre-morbid functioning
2. Neuropsychiatric assessment	• focusing on disorientation in place and time • use of GCS in patients with significantly altered consciousness
3. Clinical examination	• including neurological examination • asterixis
4. Laboratory testing	• full blood count, liver and kidney function, electrolytes, ammonia, CRP, TSH, glucose, vitamin B12 • ammonia: preferably arterial blood. If venous: preferably when patient is fasting, refrigerated on ice, immediate analyzation
5. Imaging	cerebral imaging should be performed in case of non-specific clinical presentation or when cerebrovascular disease is suspected

HE, hepatic encephalopathy; GCS, Glasgow coma scale; CRP, C-reactive protein; TSH, thyroid stimulating hormone

Table 3. Dosage guideline for different specific treatment options in patient with hepatic encephalopathy.

Therapeutic agent	**Dose**
Lactulose	Initially 25ml BD orally, increase of necessary to achieve two to three loose bowel movements daily
Rifaximin	550 mg BD orally
L-Ornithine-L-Aspartate	25-40g continuous i.v. infusion per day
High caloric nutrition	35-40kcal/Kg
Thiamine	100mg/day i.v.
Indomethacin	0.5mg/kg i.v.
Ornithine phenylacetate	Up to 20g/day i.v.
Glycerol phenylbutyrate	6ml BD orally

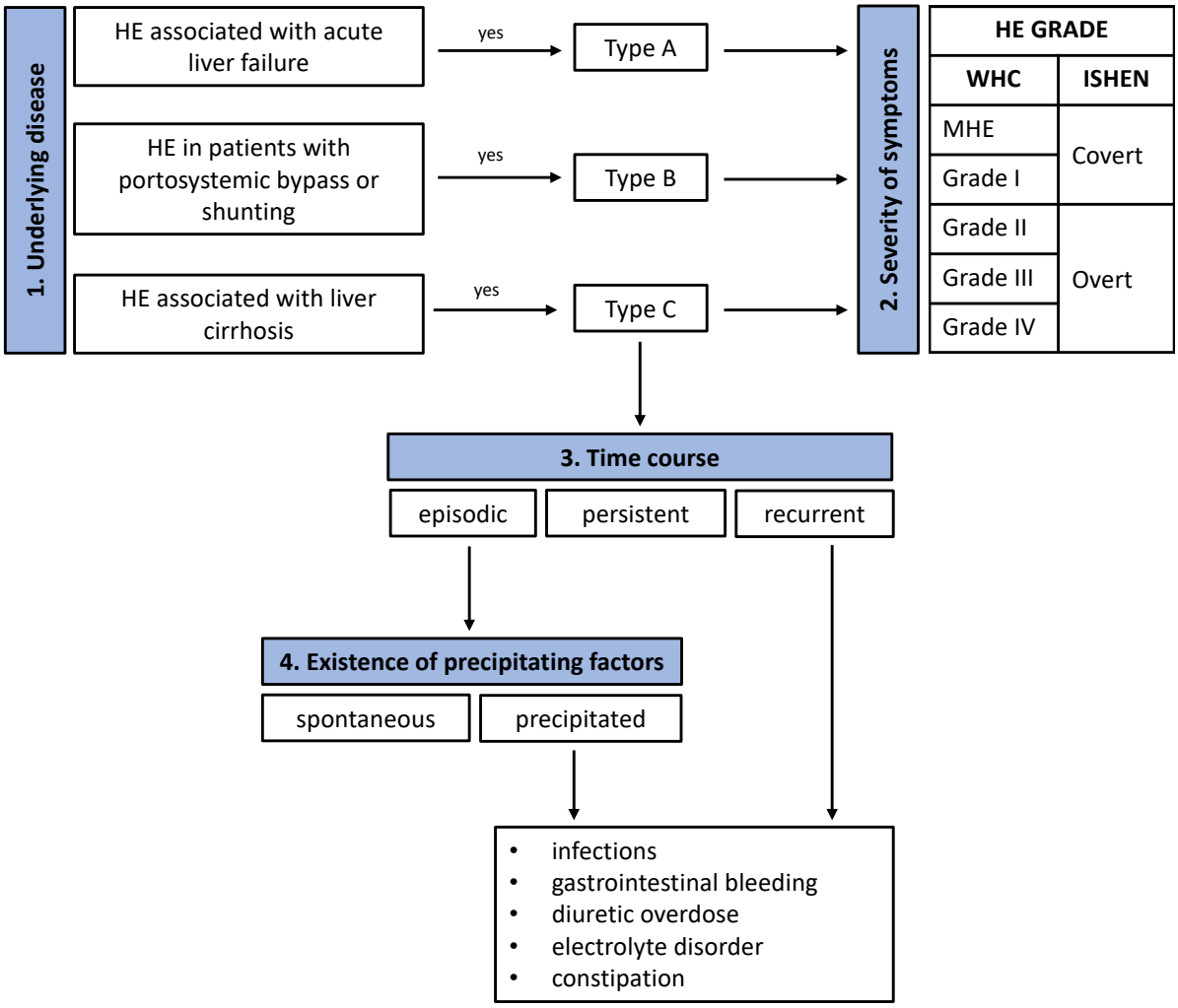
i.v. - intravenously

Table 4. Specific measures to treat cerebral oedema and intracranial hypertension (modified according to Kandiah PA et al [106]).

Neuroprotective strategies	
Increase sodium level	Continuous infusion: 30% NaCL infusion titrated between 5 and 20 ml/h or 3% titrated between 30 and 100 ml/h
	Intermittent bolus injection: 200ml 3% NaCL
Mannitol infusion	20% mannitol 0.5-1g/kg bolus, avoid plasma osmolarity >320 mOsm/L

FIGURES

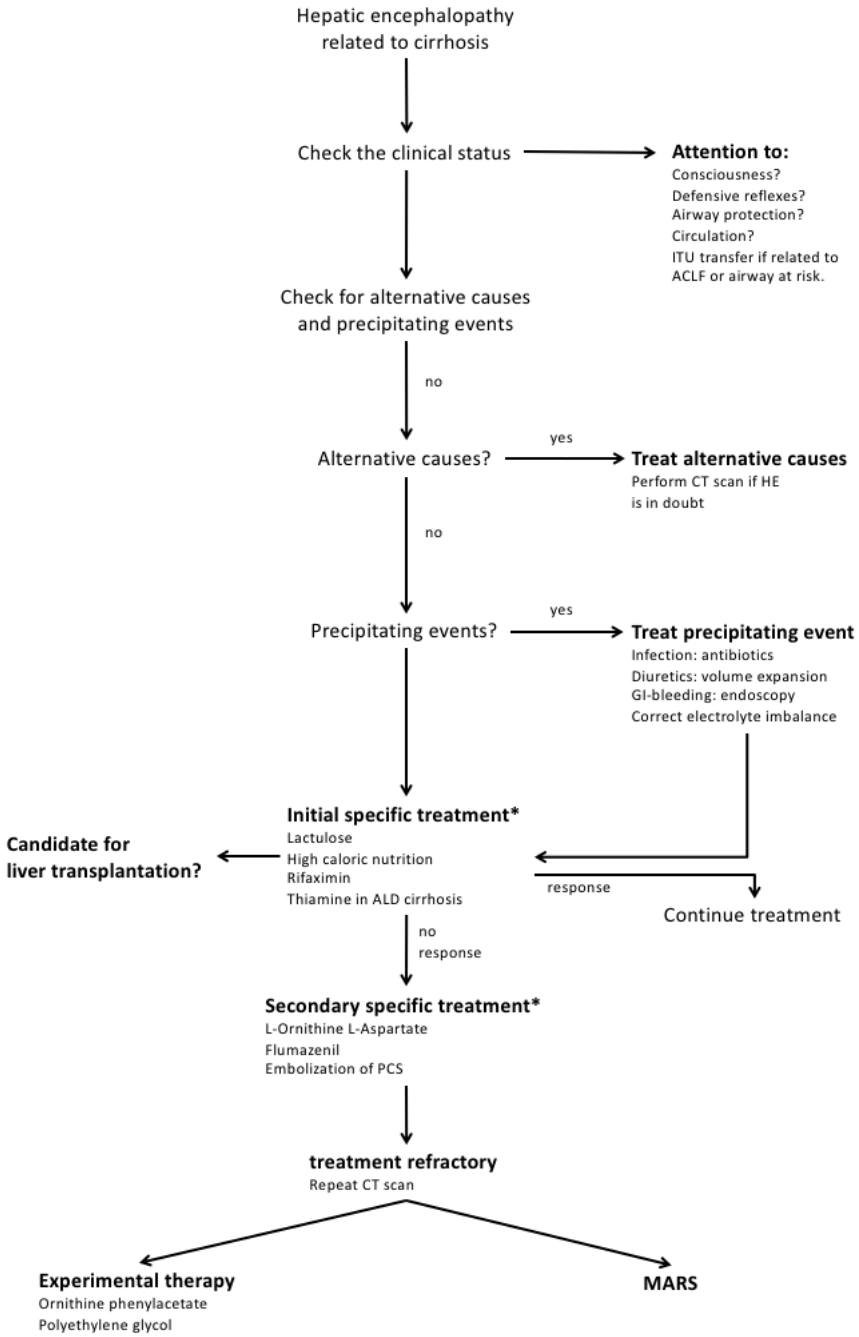
Figure 1. Classification of HE according to the multiaxial system as recommended by the current practice guideline of HE in CLD by the EASL/ AASLD (modified according to Prakash R and Mullen KD [80])



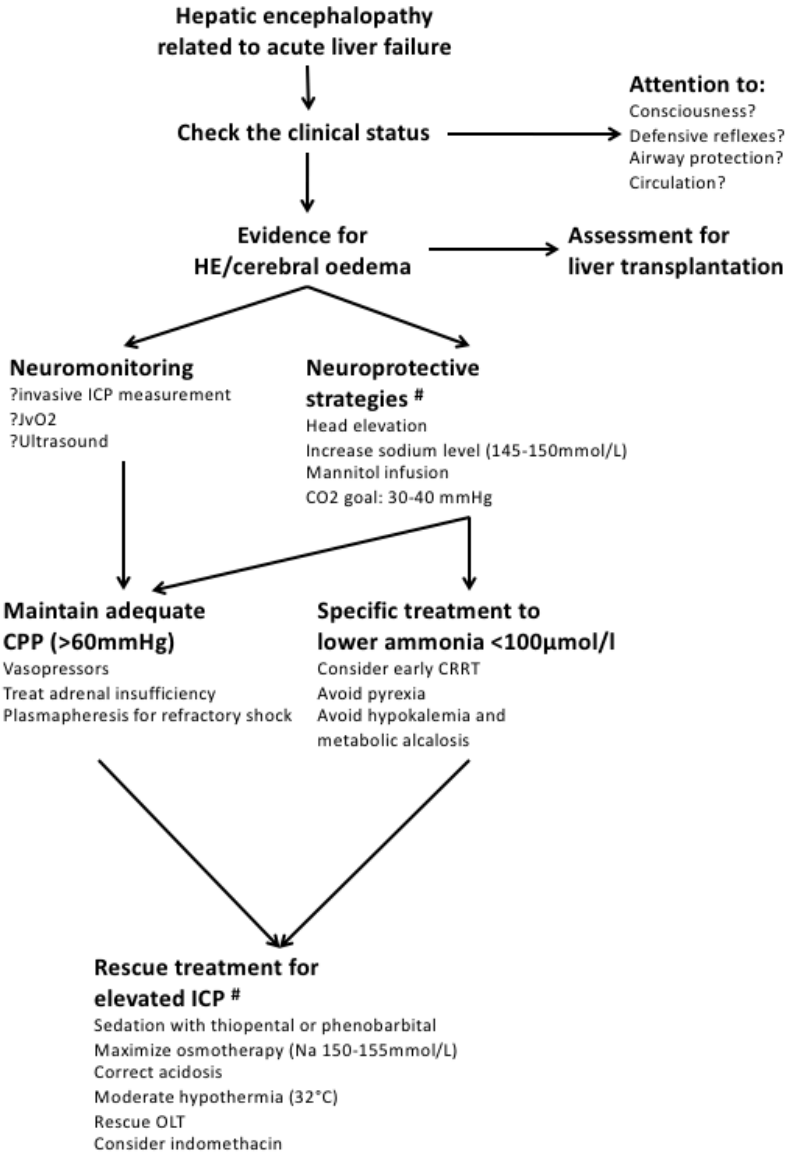
HE, hepatic encephalopathy; WHC, West Haven criteria; ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism; MHE, minimal HE.

Figure 2. Management algorithm for hepatic encephalopathy divided by patients with acute-on-chronic liver failure (2A, modified according to Kandiah PA et al. [106]) and acute liver failure (2B; modified according to Romero-Gomez M et al. [169])

A



B



*Treatment doses are displayed in table 3
#measures are explained in detail in table 4
ITU – intensive therapy unit
JvO2 – jugular venous oxygen saturation
MARS - molecular adsorbent recirculating system
PCS – portocaval shunt
ICP – intracranial pressure
CPP – cerebral perfusion pressure
CRRT – continuous renal replacement therapy
Na – sodium level
ALD – alcoholic liver disease
GI-bleeding – gastrointestinal bleeding
ACLF – acute-on-chronic liver failure
OLT – orthotopic liver transplantation

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