MANAGEMENT OF DECOMPENSATED LIVER CIRRHOSIS I

Ndububa D.A.[1], Obuekwe C.A[2], Adegoke K.J.[2]

[1]*Consultant Gastroenterologist & Professor, Department of Medicine, Obafemi Awolowo University & Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Osun State, Nigeria*
[2]*Clinical 1, Faculty of Clinical Sciences, College of Health Sciences, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria*

ABSTRACT

The natural history of liver cirrhosis begins with an asymptomatic phase of compensation. This is followed by a rapidly progressive phase of decompensation marked by clinical evidence of the complications of portal hypertension and/or impairment of liver function. The clinical prognosis of this decompensated phase is poor with reduced survival time. As a result, liver cirrhosis remains a leading cause of disability and mortality globally. To this end, the management of decompensated liver cirrhosis has evolved with the rationale of improving care and survival of the patient by managing individually the complications as they arise. This review discusses the stages of liver cirrhosis and details on interventions and improved therapeutic options for the complications of the decompensation phase —ascites, varices and variceal haemorrhage, hepatic encephalopathy, hyponatremia, hepato-renal syndrome, and infections in cirrhosis— while briefly discussing the pathogenesis of these complications and highlighting the pieces of evidence and rationale behind management options. However, the discussion at hand is an extensive one, and we have taken the liberty of splitting it into two parts for the sake of brevity without compromising on relevant information. In this first part, we discuss the importance of therapeutic albumin, the management of hepatic encephalopathy and varices/variceal haemorrhage. The second part of this review will focus on the management of ascites, hyponatraemia, hepatorenal syndrome and infections in the cirrhotic patient. This review also recognizes the gap in the prevention of these complications.

Keywords: Ascites; variceal haemorrhage; encephalopathy; hyponatremia; hepato-renal syndrome; spontaneous bacterial peritonitis

INTRODUCTION

Hepatic cirrhosis remains a leading cause of disability and mortality globally and many patients suffer from complications, such as ascites, gastrointestinal bleeding, hepatic encephalopathy, immunosuppression, and jaundice all acting as a harbinger of decompensation, the final stage of the disease [1]. Despite its significant burden on health-care costs and repeated hospital admissions, liver cirrhosis still retains a poor prognosis and median survival time is just about 2 years [1,2].

In the current approach to the management of patients with decompensated liver cirrhosis, proper management of each complication is emphasised. While this may seem logically beneficial, there remains a strategic gap in the prevention of complications. Cost-effective therapeutic interventions aimed at limiting development and treating this condition will be most beneficial in reducing hospitalisations while improving quality of life and survival [3].

The Patient in Decompensated Liver Cirrhosis

Liver cirrhosis is the result of tissue healing in response to chronic liver injury. It represents the architectural distortion of the liver parenchyma with consequent fibrosis, nodule formation, as well as modification in tissue perfusion [4]. Liver cirrhosis typically begins with a protracted relatively asymptomatic phase of "compensation", this is closely followed by a rapidly progressive phase of "decompensation". Decompensated liver cirrhosis is characterised by clinical evidence of complications of portal hypertension and impairment of liver function featured by ascites, variceal bleeding, encephalopathy, coagulopathy and jaundice [5]. The clinical prognosis for patients with decompensated cirrhosis is bleak. The median survival for decompensated liver cirrhosis is two years compared to over 12 years for the compensated patient [1].

The prognosis is made even worse by the onset of hepatorenal syndrome, refractory ascites, hepatopulmonary syndrome, or spontaneous bacterial peritonitis [1]. There is

also the ever-present possibility of hepatocellular carcinoma (HCC) which can develop at any stage of cirrhosis.
Cirrhotic patients display marked heterogeneity in aetiology and disease stage. The clinical presentation and management of liver cirrhosis are primarily dictated by the stage of disease [6]. With regards to the stage of the disease, patients can conveniently be grouped into stable/early cirrhosis (Child-Pugh class A), end-stage liver disease (ESLD), and acute decompensation (AD) [6]. Acute decompensation carries significant morbidity risk, including increased susceptibility to infection (probably reflecting underlying immune dysfunction) amongst others [6].

Cirrhotic patients in decompensation typically present with any or all of the following: ascites with or without oedema, variceal bleeding, hepatic encephalopathy, coagulopathy, hyponatraemia, and hyperbilirubinaemia 6. The term Acute Decompensation is used to describe patients presenting either for the first time or with acute on chronic liver failure [6]. It is also worthy to note that Acute-on-Chronic Liver Failure (ACLF) refers to the acute deterioration of pre-existing, chronic liver disease; the deterioration is often related to a precipitating event and associated with increased mortality at three months due to multisystem organ failure [7]. It is a highly prevalent syndrome characterized by acute decompensation, organ/system failure(s), and high 28- day mortality rate (32%) [8].

The Systemic Inflammation Hypothesis[9] describes acute-on-chronic liver failure as resulting from aggravation of the systemic inflammation and associated systemic circulatory dysfunction already present in acute decompensation. This leads to organ failure secondary to hypoperfusion and injurious damage of inflammatory mediators on the organ microcirculation and cellular homeostasis [9,10]. According to the hypothesis, acute decompensation would occur on a foundation of systemic inflammation due to translocation of pro-inflammatory cytokines from the gut to the systemic circulation and the release of Damage Associated Molecular Patterns (DAMPs) from the diseased liver or other organs [9,10]. It follows that acute-on-chronic liver failure is the consequence of an additional increase in systemic inflammation in the context of precipitating events such as active alcoholism, viral hepatitis, or bacterial infections [10].

STAGING OF LIVER CIRRHOSIS

Several prognostic models and staging systems have been developed to guide the management of patients with liver cirrhosis.
The Child-Pugh score aids in predicting the prognosis after surgery for portal hypertension in patients with liver cirrhosis[11].The original score has since been modified and currently utilises five variables for scoring. However useful, some have criticised the Child-Pugh score for its use of empirical cut-off values of laboratory parameters and the inclusion of clinical variables such as encephalopathy and ascites which require subjective assessment [12].
Originally designed to assess patient outcome after transjugular portosystemic intrahepatic shunt implantation for liver cirrhosis, the Model for End-Stage Liver Disease (MELD) score currently has a modified version and has been prospectively evaluated for its ability to estimate 3-month mortality in liver transplant candidates with chronic liver disease [13]. The MELD score utilises three variables for this purpose; serum bilirubin, creatinine, and INR, and requires a logarithmic formula for calculation of the final score [13]. The current recommendation is a MELD score of ≥15 for listing patients with end-stage liver disease [14]. The 1-year survival rate for patients with MELD score <15 is lower for patients who receive liver transplantation compared to those who do not [15].

The MELD scoring system provides an advantage of objective variables for its calculation, and the lack of an upper limit for disease severity features unavailable with the Child-Pugh system [5]. However, its drawbacks include the need for computation and the absence of well-defined stratifications for the assessment of individual mortality risk, thus making the Child-Pugh score more ubiquitous in daily clinical practice [12]. Several modifications of the MELD score have been proposed and are underway.
Patients with compensated and decompensated liver cirrhosis have a distinct prognosis, and the very low probability of death (14%) before decompensation for compensated patients supports the course of cirrhosis [16]. Considering the disparity in the prognosis of patients with compensated and decompensated liver cirrhosis, a four-stage clinical classification was proposed. It was later modified into a five-stage system (table 2):

Table 1: Child-Pugh Scoring system

	Points		
Variable	**1**	**2**	**3**
Encephalopathy	None	Stage I-II	Stage III-IV
Ascites	Absent	Controlled	Refractory
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/L)	>35	28-35	<28
Prothrombin time (seconds)	<4	4-6	>6
Sum of Points	5-6	7-9	10-15

Stage	A	B	C
1-year survival rate (%)	95	80	44

Adapted from Pugh et al. (1973)[17]. Sometimes prothrombin index or international normalised ratio (INR) is used instead of prothrombin time.[12]

Table 2: Clinical Stages of Liver Cirrhosis

Stage	Definition	5-year mortality rate (%)
Compensated stages		
1	Varices absent	1.5
2	Varices present	10
Decompensated stages		
3	Bleeding	
No other decompensating event	20	
4	Ascites, Jaundice or Encephalopathy	30
5	More than one decompensating event	88

Adapted from D'Amico et al. 2010[18]

MANAGEMENT OPTIONS

ALBUMIN

The administration of long-term human albumin to patients with ascites, the most characteristic feature of decompensation[19], has been a subject of debate for decades. The rational assumption is that some improvement in hypoalbuminaemia following albumin administration would ameliorate ascites by increasing plasma oncotic pressure. It is worthy to note however that hypoalbuminaemia per se has not been explicitly demonstrated to have a pre-eminent role in ascites formation because the colloid-osmotic pressure gradient which regulates fluid partition between plasma and the interstitial space, is not reduced in cirrhosis with ascites [20].

Reduced intravascular fluid volume secondary to peripheral arterial vasodilation is a cardinal feature of decompensated cirrhosis. This results in renal sodium and water retention that favours ascites formation[21]. One beneficial effect of human albumin could be an increase in intravascular volume, which would inhibit activated sodium-retaining, taper vasoconstriction, thus improving renal perfusion.

Its non-oncotic properties manifest another relevant feature of human albumin in decompensated cirrhosis. Sustained systemic inflammation along with a pro-oxidant state contributes to circulatory and extrahepatic organ dysfunction in advanced cirrhosis. Human albumin appears to mitigate these effects via antioxidant and scavenging activities, binding and transport of exogenous and endogenous substances, and regulation of endothelial function and inflammatory or immune responses [22].

Initial studies reporting the use of albumin treatment in cirrhosis from the 1980s consisted of several randomized clinical trials which demonstrated that paracentesis was an effective and safe therapy of ascites if performed with intravenous (IV) albumin administration [23].

Subsequent studies further showed that the treatment of spontaneous bacterial peritonitis with a therapeutic regimen of antibiotics plus albumin was associated with a 60% reduction in the prevalence of type-1 hepatorenal syndrome and hospital mortality [24]. It was later demonstrated that in approximately 50% of patients with hepatorenal syndrome, simultaneous administration of terlipressin and albumin helped normalize serum creatinine concentration [25]. Recently, the ANSWER study, an investigator-initiated multicentre randomised, parallel, open-label, pragmatic Italian trial showed that long-term (18 months) prophylactic administration of albumin (40 g every week) to patients with prior history of ascites was effective in preventing new episodes of ascites, refractory ascites, hepatorenal syndrome, hepatic encephalopathy, and bacterial infections while reducing hospital admissions and improving survival[3].

The ANSWER Study was the first prospective study providing robust evidence of clinical advantage conferred by the addition of long-term human administration to the standard-of-care in a large cohort of patients with cirrhosis and uncomplicated ascites. In this study, it was found that the administration of human albumin significantly improved 18-month survival and reduced overall mortality rate. Results from the ANSWER study also showed significant reductions in the incidence of refractory ascites and diuretic-related side-effects, such as renal dysfunction, hyponatraemia, and hyperkalaemia, in the group receiving standard medical treatment plus human albumin[3]. It was also found that the incidence of spontaneous bacterial peritonitis and other related bacterial infections along with type 1 hepatorenal syndrome, and severe hepatic encephalopathy, were reduced to a significant extent [3].

Previous anecdotal literature reported that intravascular volume expansion following prolonged administration of high does human albumin (up to 100 g/day) caused bleeding from oesophageal varices [26 27 28]. However, the ANSWER study revealed that the dose of human albumin given did not increase oesophageal variceal bleeding. Indeed long-term albumin administration was generally very well tolerated, and only three mild allergic reactions and two severe side-effects (septic events; one likely due to venepuncture and the other with concomitant previously unrecognised pneumonia as a likely focus) were reported[3]. Findings from the study also proved the cost-effectiveness of long-term administration of human albumin in hospitalised patients. In the human albumin treatment group, the cost-effectiveness of such an expensive treatment was demonstrated by a significant reduction in the number of hospital admissions and total days spent in the hospital, fewer paracenteses, and reduction in complications.

Albumin and Immuno-modulation

Recent investigations suggest that systemic inflammation plays a significant role in the pathogenesis of acute decompensation and acute on chronic liver failure in cirrhosis[10]. The Pilot-PRECIOSA study, a proof of concept, open-label, multicentre, nonrandomized (single-group) prospective phase 4 (safety and dosage-exploratory) investigation revealed a marked suppression of the plasma levels of interleukin-6 (IL-6) during long term albumin treatment (1 year)[29]. This finding suggests an immunomodulatory effect of albumin treatment.

Albumin binds to pro-inflammatory cytokines, including pathogen-associated molecular patterns (PAMPs), prostaglandins, nitric oxide, and reactive oxygen and nitrogen species[6 30 31]. These cytokines play a vital role in the pathogenesis of the systemic inflammation, circulatory dysfunction, and organ failure seen in decompensated cirrhosis as well as acute on chronic liver failure[32].

Fernandez and colleagues [29] described the pathophysiology and long term benefits of albumin treatment of decompensated cirrhosis. They found that high doses (but not low doses) of albumin had a significant immunomodulatory effect and prevented "bursts" of circulatory dysfunction while improving left ventricular function and correcting serum albumin levels without inducing albumin overdose" in patients with decompensated cirrhosis. Since albumin is capable of binding and inactivating many inflammatory promoters such as PAMPs, bioactive lipid metabolites, reactive oxygen species, and nitric oxide, the immunomodulatory effect of albumin could be related to this scavenging function.

The results of the study by Fernandez [29] indicate that a dose of 1g/kg, which is higher than the MATCH study dose (40g every two weeks) and only slightly lower than the ANSWER study dose (40g of albumin every week), was insufficient to normalize serum albumin concentration in seven out of the eight patients with hypoalbuminemia included in the Low albumin dose treatment group of their 2019 study. Also, a second albumin dosage (1.5 g/kg per week) rapidly normalized serum albumin concentration in all patients with hypoalbuminemia included in the High albumin dose group. The rapid and maximal initial increase in serum albumin concentration following treatment is likely the result of a combination of increased albumin synthesis by the liver secondary to hypoalbuminemia and the effect of the exogenous albumin administration [29]. It is worthy to note that after the normalization of serum albumin, the inhibitory effect of normo-albuminemia upon albumin synthesis precluded any further increase in serum albumin concentration despite continuous albumin treatment. Also, it was found that a high dosage of either long-term and short-term albumin treatment was associated with significant immunomodulatory effects in decompensated cirrhosis.

Furthermore, it was shown that normalization of serum albumin concentration with long-term high albumin was associated with a significant improvement in left ventricular function[29]. Likely, the beneficial effect of albumin treatment in the management of organ dysfunction/failure in cirrhosis is the result of its immunomodulatory effect and direct mitigation of systemic inflammation which would otherwise have a deleterious effect on cardiac function. Indeed earlier studies involving rodent models of carbon tetrachloride-induced cirrhosis showed reversal of systemic inflammation and left ventricular contractile dysfunction following albumin treatment [33].

Cyclooxygenase (COX)-derived lipid mediators have broad immunosuppressive effects that could explain the aetiology of infection susceptibility in cirrhosis patients [34 35]. In one anecdotal study which investigated the primary cause of immunosuppression in acutely decompensated and end-stage liver disease patients, it was found that elevated circulating PGE2 concentration, in combination with hypoalbuminaemia, drives innate immune dysfunction and increases vulnerability to infection. This finding was observed in all acutely decompensated patients from the second day of hospital admission and lasted for up to 60 days following hospital discharge. It was demonstrated that a serum albumin concentration <30mg/dl was predictive of immunosuppression and 20% Human Albumin infusion at a concentration >30mg/dl reversed immunosuppression in both human plasma ex-vivo and in vivo rodent models. The results of this study suggest that all acutely decompensated patients should receive stratified human albumin therapy; the goal is to maintain plasma albumin concentration at >3.0g/dl throughout their admission. Patients with end-stage liver disease may also benefit from this treatment as human albumin has been shown to represent an effective immune restorative strategy in this cohort of patients. In addition to immunomodulation and restoration of immune competency, human albumin therapy will also contribute to a reduction in mortality and length of hospital stay while acting as adjuvant treatment of infection. Large volume paracentesis (LVP) is a treatment modality that is often used in conjunction with salt-poor albumin infusion. It is discussed in a later section of this article.

MANAGEMENT OF HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy refers to a decline in cognitive function that develops in patients with significant liver function impairment or with portosystemic shunting[36]. It is a complex neuropsychiatric syndrome, which may complicate acute or chronic liver failure[37] characterised by changes in mental state including a wide range of neuropsychiatric symptoms ranging from minor not readily discernible signs of altered brain function to deep coma[38]. The diagnosis and staging of hepatic encephalopathy can be a challenge to the clinician, and several attempts have been made at scoring systems for ease of staging and assessment of the severity of hepatic encephalopathy. Indeed the myriad of neurological signs including altered consciou sness, impairment in intellectual and motor function as well as in patient autonomy and derangements in behaviour and the sleep-wake cy-

cle impede the development of a simple staging system [39 40]. The West-Haven criteria were met with difficulties in assessing the impaired consciousness[40 41]. The Clinical Hepatic Encephalopathy Staging Scale (CHESS) was developed in 2007 as a scoring system for diagnosed cases that could be valid for all grades of hepatic encephalopathy, interpreted as a continuum[40]. It is important to note that the CHESS criteria was developed to monitor the severity of but not diagnose hepatic encephalopathy. This is why some objective parameters, such as asterixis was excluded from the CHESS criteria. Asterixis, although a frequent manifestation and a pointer to the diagnosis of hepatic encephalopathy has the disadvantage of disappearing in a coma, thus making it a poor indicator of the severity of hepatic encephalopathy. The CHESS provides a consistent, reproducible, valid, and sensitive system for monitoring the severity of hepatic encephalopathy to guide treatment. Its validity and sensitivity are supported by the high correlation between the global scores of the CHESS and those of two other hepatic encephalopathy indexes, the adapted-West-Haven Criteria and Glasgow Coma Scale[40].

THE ROLE FOR NON-ABSORBABLE DISACCHARIDES IN HEPATIC ENCEPHALOPATHY

The goal of treatment of hepatic encephalopathy is the achievement of modest to a significant reduction in the production and absorption of ammonia, which is involved in its pathogenesis[42]. Initial therapeutic strategies aimed at alleviating hepatic encephalopathy targeted colonic bacteria which are the primary source of ammonia. This included the use of poorly absorbed antibiotics, especially neomycin [43,44]. However, this was met with undesirable side effects of neomycin, including ototoxicity, nephrotoxicity, malabsorption, and deterioration of the intestinal microbiota [43]. In 1966, Lactulose, a synthetic a non-absorbable disaccharide, was introduced as a safer alternative [45]. Early reports stated that lactulose (1-4 galactoside fructose) had the advantage of reducing the production and absorption of ammonia [42,45] without the harmful side effects of neomycin. It is interesting to note that although only a few, small randomised trials assessing the efficacy of lactulose versus placebo [46,47,48] or neomycin [43,44] in acute or chronic hepatic encephalopathy had been conducted, lactulose has been considered the treatment of choice for hepatic encephalopathy since the 1980s [49]. Even though lactulose is without any significant adverse effects, it may be poorly tolerated as a result of its overly sweet taste and gastrointestinal reactions experienced by some patients, which may be unresponsive to dose reductions [36]. In 1982, another synthetic nonabsorbable disaccharide, Lactitol (b-galactosido-sorbitol), was suggested as a more sustainable alternative to Lactulose [45]. Since then, several isolated randomised trials have compared lactulose versus lactilol. In one systematic review which attempted to estimate and compare the efficacy and tolerance of lactulose or lactitol for acute and chronic (including subclinical) hepatic encephalopathy, sufficient evidence was not found to confirm or exclude the significant beneficial effect of nonabsorbable disaccharides (lactulose and lactitol) on patients with hepatic encephalopathy[36].

Additionally, although the authors [36] found in their overall analysis that nonabsorbable disaccharides appeared to improve encephalopathy, this effect was not seen when only trials of high quality were included. However, far too few patients have been randomised to exclude a potentially beneficial effect reliably. It is important to note that even though low-quality trials on minimal hepatic encephalopathy found that lactulose had a beneficial effect, this was assessed by various non-validated psychometric tests that have questionable and uncertain clinical relevance[42]. It is likely that the beneficial effects of nonabsorbable disaccharides on patients with hepatic encephalopathy, if any, could be due to the cathartic effects of nonabsorbable disaccharides. Whether nonabsorbable disaccharides are superior to other laxatives in this regard remains uncertain.

Upon the introduction of lactulose, few trials were conducted comparing lactulose against placebo[47, 48], none of which found a beneficial effect of lactulose. Notwithstanding, lactulose was implemented in clinical practice because two trials found it equally useful to neomycin [43,44], which had been the prior standard for the treatment of hepatic encephalopathy. When one considers the adverse drug events of neomycin, it seems plausible that any equally effective intervention, albeit not superior, is desirable. However, there are two major pitfalls in this reasoning. First, the efficacy of neomycin on hepatic encephalopathy has never been shown. In one randomised trial for acute hepatic encephalopathy which attempted to compare the efficacy neomycin versus placebo[50] and another trial comparing neomycin plus lactulose versus placebo[51], a statistically significant beneficial effect of neomycin was never found. Secondly, it appears that lactulose was considered equally valid to neomycin only due to the absence of a statistically significant difference in event outcomes in the two intervention groups. However, it is well known that a lack of statistical significance does not imply that treatments have similar effects[52].

A systematic review by Als-Nielsen and colleagues[36] showed that antibiotics were statistically superior to nonabsorbable disaccharides in improving hepatic encephalopathy and lowering blood ammonia. Nevertheless, it remains unclear whether the effects are clinically

meaningful. It was concluded that there is insufficient evidence to recommend antibiotics for hepatic encephalopathy given the evidence from placebo-controlled trials[50,51], the risk of multi-resistance, and the potential risk of more severe adverse events of antibiotics[43]. When comparing lactulose with lactitol, it was found that there was no statistically significant difference in treatment efficacy between lactulose and lactitol; however, comparable efficacy could not be confirmed or excluded due to insufficient evidence. Although lactitol appeared to cause fewer adverse events than lactulose, there was insufficient evidence to confirm a significant difference.

Interestingly, some studies[53,54] highlighted the uncertain efficacy of nonabsorbable disaccharides when given orally, but one clinical trial demonstrated the efficacy of lactulose and lactitol enemas. It is, however, essential to note that this was a single small three-arm trial comparing lactitol enemas, lactose enemas, and tap water enemas[55]. Als-Nielsen and colleagues[36] in their systematic review later concluded based on the available evidence from that single trial that lactose and lactitol enemas are equally effective and superior to tap water enemas in the treatment of acute hepatic encephalopathy. In a meta-analysis[56] comparing the clinical efficacy of Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy, it was discovered that rifaximin was not superior to nonabsorbable disaccharides for acute or chronic hepatic encephalopathy in the long or short term. However, nonabsorbed oral antibiotic rifamixin did show higher tolerability and safety when compared to nonabsorbable disaccharides and was considered an alternative for patients who were intolerant to nonabsorbable disaccharides[56].

Although it may seem that patients with hepatic encephalopathy appear to benefit from treatment with nonabsorbable disaccharides, front-line clinicians must be reminded that in the assessment of intervention effects for hepatic encephalopathy, it is expedient to consider the fluctuating course as well as the impact of treating precipitating factors in acute hepatic encephalopathy[36]. It may very well be that the seemingly beneficial effect of nonabsorbable disaccharides is the result of spontaneous improvement and successful treatment of precipitants of acute encephalopathy.

PROBIOTIC YOGURT FOR MINIMAL HEPATIC ENCEPHALOPATHY

Minimal Hepatic Encephalopathy (mHE) is the preclinical stage of Overt Hepatic Encephalopathy. Patients affected with minimal hepatic encephalopathy usually suffer from limited work performance, a decrease in quality of life, and an increased risk of progression to overt hepatic encephalopathy[57]. Although some have advocated lactulose as first-line therapy for minimal hepatic encephalopathy due to improvements in psychometric testing and quality of life observed in patients following lactulose therapy for minimal hepatic encephalopathy, the frequency of gastrointestinal side effects such as bloating and diarrhoea associated with lactulose deter long-term adherence[58].

Probiotics have emerged as a therapeutic option for hepatic encephalopathy. These live microbiological dietary supplements act by manipulation of intestinal flora thus alleviating the production of ammonia and benzodiazepine-like compounds, providing therapeutic benefit without the adverse effects associated with non-absorbable disaccharides such as lactulose[59]. Earlier studies have recorded a significant reversal of minimal hepatic encephalopathy and improvement of Child score with a symbiotic (fibre and a probiotic) and fibre alone. Compared to other probiotics, yoghurts provide probiotics in the form of a nonpharmacological food item to enhance patient acceptance and adherence[60].

In one randomized, controlled, single tertiary centre trial aimed at determining the effect of a probiotic yoghurt treatment on the reversal of minimal hepatic encephalopathy and long-term adherence in nonalcoholic cirrhotics, it was found that probiotic yoghurt supplementation over 60 days caused the reversal of minimal hepatic encephalopathy in patients with nonalcoholic cirrhosis while demonstrating good adherence to treatment. Furthermore, the rate of minimal hepatic encephalopathy reversal was significantly higher in yoghurt-treated patients compared to patients who were not treated on both the intention-to-treat and per-protocol analysis. Psychometric battery employed in this trial tested for several aspects of cognition, including attention, visuomotor tracking, visuospatial orientation, and mental speed[60].

The results of this trial have some interesting therapeutic implications. Foremost, it identifies probiotic yoghurt as an effective dietary intervention for minimal hepatic encephalopathy in addition to already established therapies such as lactulose and antibiotics. When treating minimal hepatic encephalopathy, the goal must be to improve quality of life, work, and to limit progression to overt hepatic encephalopathy. The reversal of minimal hepatic encephalopathy following yoghurt supplementation suggests an improvement in cognition comparable to healthy controls[60].

Also, minimal hepatic encephalopathy is a condition that requires treatment that could last for months to multiple years. As such, ideal strategies for treatment should

aim at long term efficacy and reduction or complete elimination of adverse effects that may deter patient adherence. The 2008 trial by Bajaj and colleagues[60] demonstrated good overall adherence to treatment (only 12% of patients who were given the yoghurt discontinued it). In contrast, earlier trials involving lactulose for minimal hepatic encephalopathy showed short-term lactulose adherence of approximately 80%. Indeed, despite improvement in psychometric tests and quality of life in a few trials, long-term adherence to lactulose is affected by the accompanying side effects such as bloating, diarrhoea, and nausea 58. Probiotic yoghurt cultures lack these side effects while providing comparable benefits. However, this trial was not without limitations; including small sample size, early termination of the trial, lack of blinding in the yoghurt treatment arm (for obvious reasons) as well as a lack of placebo (non-availability of yoghurt without active cultures). Nonetheless, some of these limitations (such as the lack of blinding) were corrected for in the final analysis of results.

The therapeutic benefit of probiotics is probably the result of substrate deprivation from potentially pathogenic bacteria and the provision of fermentation end products as a substrate for potentially beneficial ones[61].

VARICES AND VARICEAL HEMORRHAGE

Cirrhosis is by far the most common cause of portal hypertension. The portosystemic gradient in cirrhosis is assessed by measuring hepatic venous pressure gradient (HVPG). The typical values range from 1-5mmHg. While pre-clinical portal hypertension ranges from 5-9mmHg, diagnosis of the clinically significant portal hypertension (CSPH) is made only when there are manifestations of the disease or when the HVPG exceeds a defined threshold of 10mmHg[62].

Varices are abnormally dilated vessels with a tortuous course which appear when HVPG increases above 10 mm Hg. Gastro-oesophagal varices are a direct consequence of portal hypertension. They are the most common and dangerous complication associated with cirrhosis present in approximately 50% of patients with cirrhosis at the time of diagnosis[63]. It has been reported that cirrhotic patients without varices develop them at a rate of 8% per year and a HPVG value above 10mmHg is said to contribute significantly to this at the time of initial endoscopic screening[64]. Once varices develop, they progressively dilate until they finally rupture, resulting in haemorrhage[62].

The management of varices and variceal haemorrhage are stratified based on the clinical stages in the natural history of portal hypertension into:

Patients with compensated cirrhosis without clinically significant portal hypertension

These cirrhotic patients have HVPG greater than 5 mmHg but lower than 10 mmHg but do not have CSPH. The aim of therapy in these patients is to prevent the development of clinically significant portal hypertension. Treatment modalities are directed against the aetiologies of cirrhosis and fibrogenesis.

Patient with compensated cirrhosis with clinically significant portal hypertension who has not yet developed varices

Clinically significant portal hypertension is defined as hepatic venous pressure gradient ≥10 mmHg. The patients are at risk of developing varices and variceal haemorrhage. The goal of treatment is to prevent the development of varices. To achieve this, the patients are screened early at the time of diagnosis using oesophago-gastro-duodenal endoscopy to assess for the presence and size of varices. Endoscopy may be avoided in patients with liver stiffness < 20 kPa and with a platelet count > 150,000, as their risk of having varices that require treatment is very low. Albeit, these patients are followed up yearly. If their liver stiffness increases or platelet count reduces, endoscopic screening is required [65]. If a patient does not have varices after the initial endoscopic screening, follow-ups are repeated at intervals based on whether the patient has an ongoing liver injury or if the etiologic factor has been controlled; 2-year intervals were suggested for the former and three-year intervals for the latter [66].

Compensated patients with gastroesophageal varices

If a patient has low-risk, small varices, after the initial screening, such patient is scheduled for follow-up endoscopy every 1-2 years if beta-blockers are not initiated [62]. This interval is, however, subject to adjustment if the HVPG exceeds 10mmHg.

Patients with high-risk varices include those with medium or large varices, small varices with red signs, and Class-Pugh Class C patients [67]. The current guidelines advise initiating non-selective beta-blockers in this group of patients.

Patients with medium or large varices should be treated with a non-selective beta-blockers provided there are no contraindications. If there are contraindications to beta-blockers, they should be offered Endoscopic Variceal Ligation (EVL) [62]. If no haemorrhage occurs, this treatment can be maintained for life for every 2-4 weeks until the liver disease improves, and there is no significant portal hypertension [62].

It is essential to state that nitrates (whether in combina-

tion with beta-blockers or alone), shunt therapy or sclerotherapy should not be used in the primary prophylaxis of variceal haemorrhage [68].

Patient with an acute variceal hemorrhagic episode

Variceal haemorrhage is a medical emergency with a high incidence of complications and high mortality and thus, requires intensive care. Variceal haemorrhage accounts for 70% of upper GI bleeding in patients with portal hypertension 69. Due to this, acute variceal haemorrhage (AVH) must be suspected as soon as the bleeding is confirmed clinically and treatment should start as soon as possible regardless of confirmation by upper endoscopy 68.

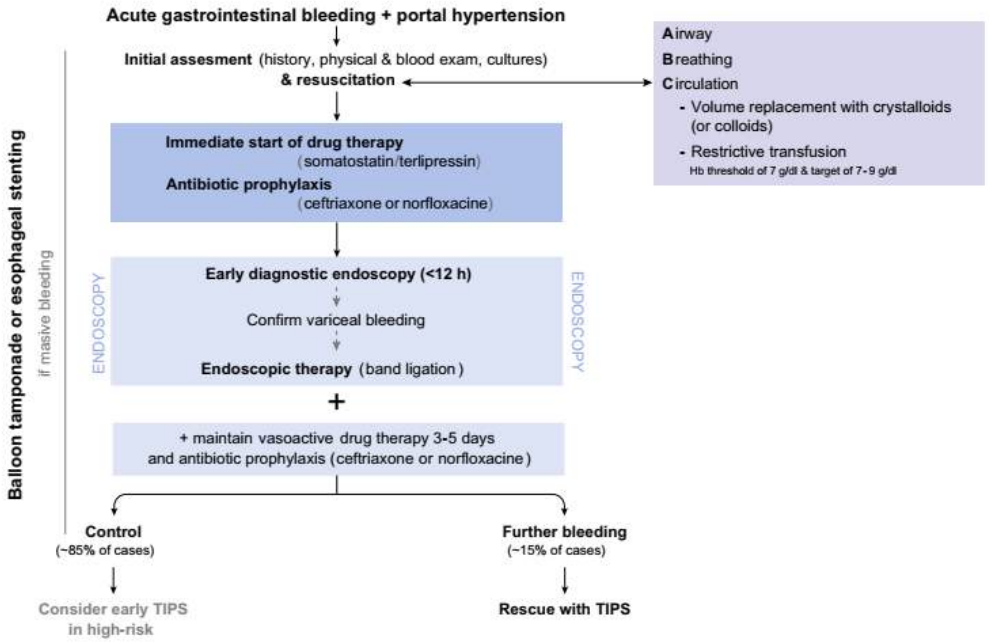

Figure 1. Algorithm for the management of acute gastrointestinal bleeding in patients with cirrhosis (adapted from Ref 65)

The goal of therapy is to prevent the early reoccurrence of bleeding (within five days) and death. Based on the most recent Baveno convention, the primary outcome is six-week mortality that can be predicted using prognostic scales [65].

Initial therapy directed at volume resuscitation, followed by vasoactive therapy and antibiotic prophylaxis should be engaged.

Volume resuscitation is done using plasma expanders such as colloids and crystalloids and aimed at restoring and maintaining hemodynamic stability and haemoglobin of 7-8g/dL. It is achieved based on the underlying medical principles of airway, breathing and circulation to preserve tissue perfusion and oxygen delivery [66]. A restrictive blood transfusion strategy, against a liberal one, is conservatively engaged in maintaining the haemoglobin level between 7-8g/dL. Notwithstanding, the restricted threshold may be higher in patients with massive haemorrhage [70]. It is also essential to consider other prognostic factors such as age, cardiovascular disorders, ongoing haemorrhage, and hemodynamic status [66].

Patients with upper gastrointestinal bleeding are at a higher risk of developing severe bacterial infections (spontaneous bacterial peritonitis and other infections) that are associated with early recurrence of variceal haemorrhage and greater mortality which can be reduced by antibiotic prophylaxis [71]. According to the Baveno conference, antibiotic prophylaxis should be initiated in all patients from admission [66].

Prior to diagnostic endoscopy, safe vasoactive drugs (such as somatostatin, octreotide, terlipressin) are administered with antibiotics as soon as possible. These vasoactive drugs significantly control haemorrhage and reduce mortality and are administered by intravenous infusion (Table 3). Vasoactive therapy can be on for five days once acute variceal haemorrhage is confirmed, to avoid early rebleeding [65].

Table 3: Most commonly used vasoactive agents used in the management of acute hemorrhage.

Drug	Standard Dosing	Duration	Mechanism of action
Somatostatin	• Initial IV bolus 250 mcg (can be repeated in the first hour if ongoing bleeding) • Continuous IV infusion of 250 to 500 mcg/hr	Up to 5 days	Inhibits vasodilator hormones like glucagon causing splanchnic vasoconstriction and reduces portal blood flow. Facilitates adrenergic vasoconstriction.
Octreotide	• Initial IV bolus 250 mcg (can be repeated in the first hour if ongoing bleeding) • Continuous IV infusion of 250 to 500 mcg/hr	Up to 5 days	Inhibits vasodilator hormones like glucagon causing splanchnic vasoconstriction and reduces portal blood flow. Facilitates adrenergic vasoconstriction.
Terlipressin (Vasopressin analogue)	Initial 48 hours: 2 mg IV every 4 hours until control of bleeding. Maintenance: 1 mg IV every 4 hours to prevent re-bleeding.	Up to 5 days	Splanchnic vasoconstriction. The active metabolite lysine-vasopressin is gradually released over several hours in tissue thus decreasing typical systemic vasopressin side effects.

Adapted from Garcia-Tsao & Bosch, (2015) [68]

Endoscopy is done after the initial therapy of volume resuscitation, vasoactive drugs and antibiotic prophylaxis. It should be conducted not more than 12 hours after the presentation to detect the cause of bleeding [66]. Once the source of bleeding is confirmed, endoscopic therapy is deployed. Both sclerotherapy and Endoscopic Variceal Ligation (EVL) are useful in the control of this acute variceal haemorrhage of oesophagal origin. However, by consensus, EVL is better in the initial control of bleeding and has less adverse events and reduced mortality [72].

It has been reported that the combination of endoscopic therapy and vasoactive therapy is more effective than the use of either alone [73]. Despite this combination, about 10-15% of patients persist with acute variceal haemorrhage or early rebleeding [63,68]. In such instances, rescue therapy is deployed. Transjugular Intrahepatic Porto-systemic Shunt (TIPS) is considered as the rescue therapy of choice in patients with a high risk of failure on standard therapy [65]. If rebleeding is modest, the second session of endoscopic therapy should be attempted [66]. Balloon tamponade is used in refractory or massive oesophagal bleeding for a maximum of 24 hours as a temporary 'bridge' with intensive monitoring and intubation till a definitive treatment is instituted [66]. Removable, covered, and self-expanding oesophagal stents are an alternative to balloon tamponade and are safer [74].

Patients who have recovered from an episode of acute variceal haemorrhage (secondary prophylaxis)
The risk of rebleeding is of great concern in patients who have earlier survived an episode of acute variceal hae-

morrhage. Thus, prevention of rebleeding is a vital part of the management of patients with controlled bleeding [66]. This can be managed using pharmacological therapy (such as nadolol/propranolol and 5-isosorbide mononitrate) [75], endoscopic therapy, TIPS and surgical shunting. It has been noted that the combination of both the best pharmacological therapy and endoscopic therapy (EVL) is the most rational approach in the prevention of rebleeding [63,67]. EVL should be repeated every 1-2 weeks until obliteration with the first surveillance endoscopy performed 1-3 months after obliteration and then every 6-12 months to check for variceal recurrence [63].

Table 4: Combination of one non-selective beta-blocker (NSBB) and EVL in the management of patients who have recovered from an episode of acute variceal heamorrahge.

Therapy	Starting Dose	Therapy goals	Maintenance/ Followup
Propanolol	• 20 mg orally twice a day • Adjust every 2-3 days until treatment goal is achieved. • Maximal daily dose should not excmmeed 320 mg.	• Maximum tolerated dose • Aim for resting heart rate of 50-55 beats per minute.	• At every outpatient visit make sure that patient is appropriately beta-blocked. • Continue indefinitely. • In patiens with refractory ascites, reduce dose or dscontinue if SBP <90 mmHg, serum sodium <130 or with acute kidney injury
Nadolol	• 40 mg orally twice a day • Adjust every 2-3 days until treatment goal is achieved. • Maximal daily dose should not exceed 160 mg.	• Maximum tolerated dose • Aim for resting heart rate of 50-55 beats per minute.	• At every outpatient visit make sure that patient is appropriately beta-blocked. • Continue indefinitely. • In patiens with refractory ascites, reduce dose or dscontinue if SBP <90 mmHg, serum sodium <130 or with acute kidney injury
Endoscopic variceal ligation (EVL)	Every 2–4 weeks until the obliteration of varice	Obliteration varices Eradication of new varices following initial obliteration	First EGD performed 1 – 3 months after obliteration and every 6 – 12 months thereafter

Adapted from Garcia-Tsao & Bosch, (2015)[68]

Despite this combination therapy, some patients still rebleed. These patients should undergo percutaneous placement of a TIPS or surgical creation of a shunt [68]. Because both are similar in rebleeding, encephalopathy occurrence, and mortality, the choice between these two is dependent on the local expertise and patient's preference [68].

REFERENCES

1. *D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006; 44:217–31.*
2. *Stepanova M, De Avila L, Afendy M, et al. Direct and indirect economic burden of chronic liver disease in the United States. Clin Gastroenterol Hepatol2017; 15:759–66.*
3. *Caraceni P, Riggio O, Angeli P, et al. ANSWER Study investigators. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet. 2018; 391:2417-2429.*
4. *Jiao J, Friedman SL, Aloman C. Hepatic fibrosis. Curr Opin Gastroenterol 2009; 25:223–9.*
5. *Pinter M, Trauner M, Peck-Radosavljevic M, et al. Cancer and liver cirrhosis: implications on prognosis and management. ESMO Open 2016;1: e000042. doi:10.1136/esmoopen-2016- 000042*
6. *O'Brien AJ, Fullerton JN, Massey KA, et al. Prostaglandin E2 Mediates Immunosuppression in Acutely Decompensated Cirrhosis. Nature Medicine. 2014: 20; 518-523*
7. *Laleman W, et al. Acute-on-chronic liver failure: current concepts on definition pathogenesis, clinical manifestations and potential therapeutic interventions. Expert Rev Gastroenterol Hepatol. 2011; 5:523–537. quiz 537. [PubMed: 21780899]*
8. *Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on- chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013; 144:1426-1437.*
9. *Bernardi J, Moreau R, Angeli P, Schnable B, Arroyo V. Mechanism of decompensation and organ failure in cirrhosis. From peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol 2015; 63:1272-1284.*
10. *Clària J, Stauber RE, Coenraad MJ, et al. Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liverfailure. Hepatology 2016; 64:1249-64.*
11. *Child CG. Surgery and portal hypertension. In: Child CG, ed. The liver and portal hypertension. Philadelphia, PA: WB Saunders, 1964:50–72*
12. *Durand F, Valla D. Assessment of prognosis of cirrhosis. Semin Liver Dis 2008; 28:110–22.*
13. *Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003; 124:91–6.*
14. *European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol 2016; 64:433–85.*
15. *Merion RM, Schaubel DE, Dykstra DM, et al. The survival benefit of liver transplantation. Am J Transplant 2005;5:307–13*
16. *D'Amico G, Pasta L, Morabito A, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther 2014;39:1180–93*
17. *Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60:646–9.*
18. *D'Amico G, Villanueva C, Burroughs AK, et al. Clinical stages of cirrhosis a multicenter study of 1858 patients. Hepatology 2010;52 (S1):329A.*
19. *Gines P, Quintero E, Arroyo V, et al. Compensated cirrhosis: natural history and prognostic factors. Hepatology 1987; 7: 122–28.*
20. *Henriksen JH, Stage JG, Schlichting P, Winkler K. Intraperitoneal pressure: ascitic fluid and splanchnic vascular pressures, and their role in prevention and formation of ascites. Scand J Clin Lab Invest 1980; 40: 493–501.*
21. *Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology1988; 8:1151–57.*
22. *Garcia-Martinez R, Caraceni P, Bernardi M, Ginés P, Arroyo V, Jalan R. Albumin: pathophysiologic basis of its role in the treatment of cirrhosis and its complications. Hepatology2013; 58:1836–46.*
23. *Arroyo V, García-Martínez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. J Hepatol 2014; 61:396-407.*
24. *Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999;341:403-409.*
25. *Ortega R, Ginès P, Uriz J, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome; results of a prospective non-randomized study. Hepatology 2002; 36:941-948.*
26. *Kunkel HG, Labby DH, Ahrens EH Jr, Shank RE, Hoagland CL. The use of concentrated human serum albumin in the treatment of cirrhosis of the liver. J Clin Invest 1948; 27: 305–19.*
27. *Faloon WW, Eckhardt RD, Murphy TL, Cooper AM, Davidson CS. An evaluation of human serum albumin in the treatment of cirrhosis of the liver. J Clin Invest 1949; 28: 583–94.*
28. *Wilkinson P, Sherlock S. The effect of repeated albumin infusions in patients with cirrhosis. Lancet 1962; 2: 1125–29.*
29. *Fernández J, Clària J, Amorós A, Aguilar F, Castro*

M, Casulleras M, Acevedo J, Duran-Güell M, Nuñez L, Costa M, Torres M, Horrillo R, Ruiz-del-Árbol L, Villanueva C, Prado V, Arteaga M, Trebicka J, Angeli P, Merli M, Alessandria C, Aagaard NK, Soriano G, Durand F, Gerbes A, Gustot T, Welzel TM, Salerno F, Bañares R, Vargas V, Albillos A, Silva A, Morales-Ruiz M, Pavesi M, Jalan R, Bernardi M, Moreau R, Páez A, Arroyo V, Effects of Albumin Treatment on Systemic and Portal Hemodynamics and Systemic Inflammation in Patients With Decompensated Cirrhosis, Gastroenterology 2019; 157;149-152.

30. Gioannini TL, Zhang D, Teghanemt A, et al. An essential role for albumin in the interaction of endotoxin with lipopolysaccharide-binding protein and sCD14 and resultant cell activation. J Biol Chem 2002; 277:47818-47825.

31. Anraku M, Chuang VT, Maruyama T, et al. Redox properties of serum albumin. Biochim Byophys Acta 2013;1830:5465-5472

32. Gentilini P, Casini-Raggi V, Di Fiore G, et al. Albumin improves the response to diuretics in patients with cirrhosis and ascites: results of a randomized, controlled trial. J Hepatol 1999; 30:639-645.

33. Bortoluzzi A, Ceolotto G, Gola E, et al. Positive cardiac inotropic effect of albumin infusion in rodents with cirrhosis and ascites: molecular mechanisms. Hepatology 2013; 57:266-276.

34. Scher JU, Pillinger MH. The anti-inflammatory effects of prostaglandins. J Investig Med. 2009; 57:703–708.

35. Kalinski P. Regulation of immune responses by prostaglandin E2. Journal of immunology. 2012; 188:21–28.

36. Als-Nielsen_B, Gluud_LL, Gluud_C. Nonabsorbable disaccharides for hepatic encephalopathy. Cochrane Database of Systematic Reviews 2004, Issue 2. Art. No.: CD003044. DOI: 10.1002/14651858.CD003044.pub2.

37. Gitlin N. Hepatic encephalopathy. In: Zakim D, Boyer TD editor(s). Hepatology. A textbook of liver disease. 3rd Edition. Vol. 1, Philidelphia: WB Saunders, 1996:605-17

38. Conn HO, Lieberthal MM. Lactulose in the management of chronic portal-systemic encephalopathy. The hepatic coma syndromes and lactulose. Baltimore: The Williams & Wilkins Company, 1979:323-39

39. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy – definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002; 35: 716–21.

40. Ortiz M, Cordoba J, Doval E, et al. Development of a clinical hepatic encephalopathy staging scale. Aliment Pharmacol Ther. 2007; 26: 859-867.

41. Teasdale G, Knill-Jones R, Van der SJ. Observer variability in assessing impaired consciousness and coma. J Neurol Neurosurg Psychiatry 1978; 41: 603–10

42. Weissenborn K. Recent developments in the pathophysiology and treatment of hepatic encephalopathy. Bailliere's Clinical Gastroenterology 1992;6(3):609-30. [MEDLINE: 1993043643]

43. Conn_HO, Leevy_CM, Vlacevic_ZR, Rodgers_JB, Maddrey_WC, Seef_L, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. Gastroenterology 1977;72(4 Pt 1):573-83. [MEDLINE: 1977116769]

44. Atterbury_CE, Maddrey_WC, Conn_HO. Neomycin-sorbitol and lactulose in the treatment of acute portal-systemic encephalopathy. A controlled, double-blind clinical trial. American Journal of Digestive Diseases 1978;23(5):398-406. [MEDLINE: 78232593]

45. Bircher_J, Muller_J, Guggenheim_P, Hammerli_UP. Treatment of chronic portal-systemic encephalopathy with lactulose. Lancet 1966;1(7443):890-2. [MEDLINE: 1966097157]

46. Elkington_SG, Floch_MH, Conn_HO. Lactulose in the treatment of chronic portal-systemic encephalopathy. A doubleblind clinical trial. The New England Journal of Medicine 1969;281(8):408-12. [MEDLINE: 69242833]

47. Simmons_F, Goldstein_H, Boyle_JD. A controlled clinical trial of lactulose in hepatic encephalopathy. Gastroenterology. 59 1970; Vol. 59, issue 6:827-32. [MEDLINE: 71054874]

48. Germain_L, Frexinos_J, Louis_A, Ribet_A. Double blind study of lactulose in 18 patients with chronic hepatic encephalopathy after portocaval shunt [Étude en double aveugle du lactulose chez 18 malades atteints d'encéphalopathie hépatique chronique après shunt porto-cave]. Archives Francaises des Maladies de L'appareil Digestif 1973;62(4):293-302. [MEDLINE: 74133808]

49. Morgan_MY. Nutritional aspects of liver and biliary disease. In: Bircher J, Benhamou JP, McIntyre N, Rizzetto M, Rodes J. editor(s). Oxford textbook of clinical hepatology. 1981. Oxford, UK: Oxford University Press, 1999:1923-81.

50. Strauss_E, Tramote_R, Silva_EP, Caly_WR, Honain_NZ, MaKei_RA, et al. Double-blind randomized clinical trial comparing neomycin and placebo in the treatment of exogenous hepatic encephalopathy. Hepatogastroenterology 1992;39(6):542-5. [MEDLINE: PMID: 1483668]

51. Blanc_P, Daures_JP, Liautard_J, Buttigieg_R, Desprez_D, Pageaux_G, et al. Lactulose-neomycin combination versus placebo in the treatment of acute hepatic encephalopathy. Results of a randomized controlled trial [Association lactulose-neomycine versus placebo dans le traitement de l'encephalopathie hepatique aigue. Resultats d'un essai controlé randomisé]. Gastroenterologie Clinique et Biologique 1994;18(12):1063-8. [MEDLINE: 1992137897]

52. Pocock_SJ. The size of a clinical trial. Clinical trials: a practical approach. Chichester: John Wiley & Sons Ltd, 1983:123-42.

53. Ferenci_P, Müller_C. Hepatic encephalopathy: treatment. In: McDonald J, Burroughs A, Feagan B editor(s). Evidence based gastroenterology and hepatology. London: BMJ Books, 1999:443-55.

54. Kircheis_G, Haussinger_D. Management of hepatic encephalopathy. Journal of Gastroenterology and Hepatology 2002;17 Suppl 3:260-7. [MEDLINE: PMID: 12472947]

55. Uribe_M, Campollo_O, Vargas_F, Ravelli_GP, Mundo_F, Zapata_L, et al. Acidifying enemas (lactitol and lactose) vs. nonacidifying enemas (tap water) to treat acute portal-systemic encephalopathy: a double-blind, randomized clinical trial. Hepatology 1987;7(4):639-43.

56. Jiang Q, Jiang XH, Zheng MH, Jiang LM, Chen YP, Wang L. Rifamixin versus nonabsorbable dissacharides in the management of hepatic encephalopathy: a meta-analysis. Eur J Gastroenterol Hepatol. 2008; 20: 1064-1070

57. Ortiz M, Jacas C., and Cordoba J. Minimal Hepatic Encephalopathy: diagnosis, clinical significance and recommendations. Journal of Hepatology 2005l 42 Suppl (1): S45-53.

58. Bajaj JS, Etemadian A, Hafeezullah M, et al. Testing for minimal hepatic encephalopathy in the United States: An AASLD survey. Hepatology 2007; 45:833–4.

59. Liu Q, Duan ZP, Ha DK, et al. Synbiotic modulation of gut flora: Effect on minimal hepatic encephalopathy in patients with cirrhosis. Hepatology 2004; 39:1441–9.

60. Bajaj JS, Saeian K, Christensen KM. Probiotic yogurt for the treatment of minimal hepatic encephalopathy. Am J Gastroenterol. 2008; 103: 1707-1715.

61. Solga SF. Probiotics can treat hepatic encephalopathy. Med Hypotheses 2003; 61:307–13.

62. Jaime Bosch, Annalisa Berzigotti, Juan Carlos Garcia-Pagan, and Juan G. Abraldes 2008. The management of portal hypertension: Rational basis. available treatments and future options Journal of Hepatology 48 (2008) S68–S92

63. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W Practice Guidelines Committee of the American Association for the Study of Liver Diseases Practice Parameters Committee of the American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal haemorrhage in cirrhosis. Hepatology 2007; 46:922–938

64. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. for the Portal Hypertension Collaborative Group. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med 2005; 353:2254-2261

65. de Franchis R Baveno VI faculty. Expanding consensus in portal hypertension: report of the BAVENO VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015; 63:743–752

66. Guadalupe Garcia-Tsao and Jaime Bosch 2015. Varices and Variceal Hemorrhage in Cirrhosis. A new view of an old problem Clin Gastroenterol Hepatol. 2015 November; 13(12): 2109–2117. doi: 10.1016/j.cgh.2015.07.012

67. de Franchis R. Evolving consensus in portal hypertension report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2005; 43:167–176

68. Garcia-Tsao G and Bosch J. Management of varices and variceal haemorrhage in cirrhosis. N Engl J Med 2010; 362:823–832