Chapter

Treatment Approach in Patients with Decompensated Liver Cirrhosis

Anıl Delik and Yakup Ülger

Abstract

Chronic liver disease and decompensated cirrhosis are the major causes of morbidity and mortality in the world. According to current data, deaths due to liver cirrhosis constitute 2.4% of the total deaths worldwide. Cirrhosis is characterized by hepatocellular damage that leads to fibrosis and regenerative nodules in the liver. The most common causes of cirrhosis include alcohol consumption, hepatitis C, hepatitis B, and non-alcoholic fatty liver disease. Dysbiosis and intestinal bacterial overgrowth play a role in the development of complications of cirrhosis through translocation. In liver cirrhosis, ascites, gastrointestinal variceal bleeding, spontaneous bacterial peritonitis infection, hepatic encephalopathy, hepatorenal syndrome, hepatocelluler carcinoma are the most common complications. In addition, there are refractory ascites, hyponatremia, acute on-chronic liver failure, relative adrenal insufficiency, cirrhotic cardiomyopathy, hepatopulmonary syndrome and portopulmonary hypertension. In the primary prophylaxis of variceal bleeding, non-selective beta blockers or endoscopic variceal ligation are recommended for medium and large variceal veins. In current medical treatment, vasoactive agents, antibiotics, blood transfusion, endoscopic band ligation are the standard approach in the treatment of acute variceal bleeding. Sodium-restricted diet, diuretics and large-volume paracentesis are recommended in the management of ascites. In the treatment of hepatic encephalopathy, lactulose, branched chain amino acids, rifaximin and L-ornithine L-aspartate can be used. New therapeutic approaches such as ornithine phenyl acetate spherical carbon and fecal microbiota transplantation have shown beneficial effects on hepatic encephalopathy symptoms. In addition to their antioxidative, anti-proliferative and anti-inflammatory properties, statins have been shown to reduce the risk of decompensation and death by reducing portal pressure in compensated cirrhosis. In the treatment of liver failure, some artificial liver devices such as molecular adsorbent recirculating system, the single albumin dialysis system, fractionated plasma separation and adsorption are used until transplantation or regeneration. The purpose of this chapter is to review the most up-to-date information on liver cirrhosis and to explain the complications assessment, current management and potential treatment strategies in decompensated cirrhosis.

Keywords: advanced liver disease, ascites, gastrointestinal bleeding, hepatic encephelopathy, acute on chronic liver failure, therapy

1. Introduction

Decompensated cirrhosis is characterized by the development of complications related to portal hypertension (PHT) such as variceal bleeding, ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), hepatorenal syndrome (HRS), or hepatopulmunary syndrome (HPS) in the presence of cirrhosis [1]. The mortality rate in patients with decompensated cirrhosis is 10 times higher than in the normal population. In cirrhosis, PHT occurs due to increased plasma volume, cardiac output and imbalance of biochemical parameters (such as vasoconstrictors, vasodilators, vascular endothelial growth factor, and nitric oxide) [2]. The incidence of cirrhosis is 26 per 100,000 in Europe, and the incidence in Asia ranges from 16.5 per 100,000 in East Asia to 23.6 per 100,000 in Southeast Asia [3]. It causes 1.2 million deaths due to complications of cirrhosis and 790.000 deaths due to liver cancer, accounting for 3.5% of all deaths worldwide [4]. Chronic liver disease epidemiology, hepatitis B (HBV) incidence and complications decrease with HBV vaccination and antiviral treatment programs. In addition, chronic hepatitis C (HCV) infection reduces the risk of cirrhosis and HCC development with direct-acting antiviral (DAA) treatment. Non-alcoholic fatty liver disease (NAFLD) increases due to obesity and metabolic syndrome. Similarly, alcohol consumption accounts for approximately 27% of liver-related death causes in the world. NAFLD has the highest mortality rate in western countries [5]. Asymptomatic cirrhotic patients develop decompensated cirrhosis at a rate of 5–7% each year [6]. The development of decompensation causes dysfunction in multiple organs and systems, leading to systemic disease [7]. Although many factors play a role in the background of cirrhosis pathophysiology, mainly according to the peripheral vasodilation hypothesis, arterial vasodilation in the splanchnic circulatory system in cirrhosis leads to the activation of compensatory vasoconstrictor systems (such as renal angiotensin aldosterone axis, sympathetic nervous system and activation of water retention systems). Changes in saliva and intestinal microbiome in cirrhosis have been found to be associated with the development of intestinal bacterial overgrowth, dysbiosis, increased intestinal permeability, and decompensating complications from portal tract intestinal translocation [8]. Treatment strategy in decompensated cirrhosis patients should be aimed at preventing the progression of cirrhosis before complications occur. The ultimate treatment for decompensated cirrhosis should be aimed at regressing fibrosis by suppressing inflammation, normalizing liver cell number and function by regulating portal and arterial circulation, and restoring liver integrity [9].

2. Treatment of complications in decompensated cirrhosis

2.1 Ascites

Ascites is the abnormal accumulation of fluid in the abdominal cavity and is the most common cause of decompensation in cirrhosis. The basis for the formation of ascites is renal sodium uptake due to activation of sodium-sparing systems such as the renin angiotensin aldosterone system (RAAS) and the sympathetic nervous system [10]. Extra cellular volume increase and decreased effective volume secondary to splanchnic arterial vasodilation are the main determinants of these changes. There are 5 different phases of the ascites development process. The first phase pre-ascites does not cause a decrease in effective blood volume due to hyperdynamic circulation accompanying splanchnic arterial vasodilation, cardiac output and increase in plasma volume. Blood pressure, kidney function, renin

activity, noradrenaline and anti-diuretic hormone (ADH) levels remain normal. In the second phase, there is a moderate decrease in sodium excretion unrelated to the sympathetic nervous system and RAAS activation [11]. In the third phase, RAAS and activation of the sympathetic nervous system cause sodium retention as a result of an increase in splanchnic arterial vasodilation. In the fourth phase, plasma renin activity, noradrenaline and ADH levels increase significantly, decreasing the renal perfusion and glomerular filtration rate (GFR) and decreasing the osmotic free water excretion ability of the kidneys leads to dilutional hyponatremia. In the fifth phase, severe systemic vasodilation and a decrease in cardiac output cause left ventricular systolic dysfunction in cirrhosis patients and type 2 hepatorenal syndrome develops [12, 13].

2.1.1 Classification of ascites

It is classified as uncomplicated ascites and refractory ascites according to the recommendation of the international ascites club (IAC). Ascites is considered uncomplicated if not associated with infection or hepatorenal syndrome (**Table 1**).

Refractory ascites are defined as non-regressing at least one degree of regression with diuretic therapy and dietary sodium restriction, or early recurrence after large-volume paracentesis. There are two subtypes, diuretic resistance and diuretic intractable. Type 1 subtype has resistance to optimal dose diuretics. The second subtype is due to insufficient diuretic dose [14].

2.1.2 Ascites treatment in cirrhosis patients

2.1.2.1 Uncomplicated ascites treatment

The management of uncomplicated acids according to the European association for the study of the liver (EASL) guidelines depends on the degree of clinical symptoms. Diuretics and low sodium diet are not needed in patients with grade 1 ascite. Grade 2 ascite patients can be treated on an outpatient basis using sodium restriction and diuretics. Daily sodium intake should be determined as 80–120 mmol/d. A very low sodium restrictive diet should be avoided (<40 mmol/d). Bed rest is not required due to the lack of data on the activation of sodium-sparing systems and the negative effect of vertical posture on renal perfusion. It can lead to the progression of muscle atrophy [15]. The diuretic agents preferred in the treatment of ascites are aldosterone antagonists (spironolactone, carnenone, potassium canrenoate etc). They not only inhibit sodium and water retention, but also suppress potassium excretion and reduce the synthesis of permeases in the collecting tubules and distal tubules of the aldosterone-sensitive kidney. In addition, loop diuretics are used. It inhibits sodium reabsorption along the emerging branch of the henle ring. Loop diuretics are not recommended as monotherapy because of their lower efficacy and higher number of complications compared to aldosterone antagonists [16].

Grading of ascites	**Findings**
Grade 1	A small amount of acid that can only be demonstrated by ultrasonography
Grade 2	Moderate acid in the abdomen
Grade 3	Massive, common acid

Table 1.
Grading ascites according to the amount of intraabdominal ascites.

Sequential administration of aldosterone antagonists and loop diuretics in the first phase of acid therapy and a combination of these drugs if recurrence occurs. Initial treatment starts with 100–200 mg/d spironolactone administration, then 20–40 mg furosemide is added within two weeks in case of no effect. In the follow-up, daily doses can be increased to 400 mg and 160 mg, respectively. The second recommended method is the combination of diuretic agents and it is recommended to increase the dose of spironolactone and furosemide gradually to 400 mg and 160 mg/d [17]. Daily diuresis and weight monitoring is required to prevent hypovolemia, hyponatremia and acute kidney damage. The reduction in body weight should not exceed 500 g/day in patients without peripheral edema and 1000 g/day in patients with this [18]. In cirrhosis patients with second degree uncomplicated acid, it is possible to achieve 90% success with a combination of diuretic therapy and low sodium diet. Even if a small amount of fluid remains in the abdomen, the effect is considered sufficient, but peripheral edema should not be. It is recommended that the dose of diuretic be reduced to the lowest effective dose after the treatment goal is reached [19]. Diuretic-related side effects may occur during the first weeks of treatment. It often causes fluid electrolyte imbalance such as dehydration, hypovolemic hypoosmolar hyponatremia, hypokalemia or hyperkalemia. It can also cause possible complications such as HE, gynecomastia, muscle cramps, and acute kidney damage. Aldosterone antagonists may cause hypovolemic hypoosmolar hyponatremia, especially with the use of thiazide group diuretics in elderly patients with cirrhotic acid. This group of agents inhibit reabsorption of sodium and chlorine in distal folded tubules. Hypovolemic hypoosmolar hyponatremia is characterized by a serum sodium level below 130 mmol/L, low plasma osmolarity and simultaneous reduction in extracellular fluid volume. It can lead to weakness, apathy, irritability, dizziness, hypotension, nausea and vomiting in the clinic [20]. The development of severe hyponatremia (serum sodium level < 125 mmol/L), the presence of signs of HE worsening, muscle cramps, and acute kidney damage necessitate discontinuation of the drug. Loop diuretics can cause hypokalemia (serum potassium level less than 3 mmol/L), aldosterone antagonists can cause hyperkalemia (more than 6 mmol/L). In this case, diuretics should be discontinued.

Large volume paracentesis (LVP) is the preferred method in patients with third degree ascites. Removal of more than 5–6 L of acid fluid with LVP (albumin infusion 8 g/L acites removed), diuretic agents and a low sodium diet are recommended. Paracentesis with plasma support should be performed under sterile conditions using disposable material to prevent effective blood volume reduction after paracentesis circulatory impairment (PPCD). The procedure may cause very low local complications, especially bleeding. Clinical symptoms of PPCD are renal failure, dilutional hyponatremia, HE and decreased survival. Artificial plasma expanders such as dextran-70 (8 g/L ascites removed) or polygeline (150 ml/L), saline solution (170 ml/L) to prevent these complications (if less than 5 L ascites are discharged) only 20% albumin-like effect. Polygeline prions are not used in many countries due to the potential risk of contamination. Dextran carries the risk of severe allergic reactions and kidney failure.

According to recent studies, a reduction in short-term mortality has been reported in patients who underwent LVP. According to a meta-analysis, PPCD due to large volume paracentesis has been shown to be associated with acid recurrence, dilutional hyponatremia, development of hepatorenal syndrome, and high mortality [21]. The diagnosis of PPCD is made 5 days after LVP when the plasma renin concentration is 50% higher or 4 ng/ml compared to the basal value. Albumin infusion can prevent this complication with its increased oncotic pressure, anti-inflammatory and antioxidant properties. Alternative concentrated

ascites reinfussion therapy (CART) is in the form of intravenous and reinfusion of proteins collected by concentrating and filtering acid fluid to maintain serum albumin level [22].

Since nonsteroidal anti-inflammatory drug (NSAIDs) inhibit prostaglandin synthesis and cause sodium retention, hyponatremia and acute kidney damage, they should not be used in acidic patients. Angiotensin converting enzyme inhibitors, angiotensin 2 antagonists or alpha 1 adrenergic receptor blockers are not used in patients with ascites due to an increased risk of renal failure [13].

2.1.2.2 Refractory ascites

The definition of refractory ascites is in the form of refractory ascites that cannot be mobilized with medical treatment or early recurrence (after LVP) according to the criteria of the IAC. Refractory ascites is associated with a poor prognosis. Average survival is about 6 months. These patients should be referred to transplant centers for transplantation. Diuretic resistant ascites: an acid that does not respond to sodium restriction and diuretic therapy or whose early recurrence cannot be prevented. Diuretic intractable ascites: Ascites that prevent the use of diuretics at effective doses and cannot be mobilized or early recurrence cannot be prevented due to the development of diuretic-related complications.

The duration of treatment should be salt restricted diet (less than 90 mmol/d) and at least one week of intensive diuretic therapy spirinolactone 400 mg/d, furosemide 160 mg/d. Lack of responce weight loss of less than 0.8 kg in 4 days and urine sodium should be less than the sodium intake.

Early acid development: Reappearance of Grade 2 or 3 acid within 4 weeks is the development of drug-induced HE in the absence of other predisposing factors, diuretic-induced renal failure, in patients with ascites serum creatinine level increases above 2 mg/dl. Diuretic-induced encephalopathy: The development of hepatic encephalopathy in the absence of any other precipitating factors.

Diuretic induced renal failure: an increase in serum creatinine level to >2 mg/dl (177 lmol/L) in patients with ascites. It is defined as a serum sodium level falling below 125 mmol/L. Diuretic-induced hypo or hyperkalemia is defined as serum potassium <3 mmol/L or > 6 mmol/L [23, 24].

First-line therapy combined with albumin infusion (8 g/L ascites removed) should be repeated every 2–3 weeks for LVP, and diuretics are only recommended when sodium concentration in urine is >30 mmol/d. Clonidine (alpha 2 presynaptic receptor agonist) may be considered to increase the effectiveness of the diuretic response and reduce the need for diuretics. Midodrine (alpha 1 receptor agonist) increases sodium excretion by decreasing plasma renin activity in patients with refractory ascites without azotemia. According to the meta-analysis results, it was shown that midodrine is effective therapeutically but does not have a statistically significant effect on survival [25]. The addition of clonidine or midodrine to diuretic therapy in resistant acids is not recommended according to current guidelines [13]. Despite controversial data on the use of non-selective beta-blockers (NSBBs) refractory ascites, high doses of NSBBs should be avoided in refractory ascites or circulatory dysfunction. (systolic blood pressure < 90 mmol Hg, serum sodium <130 mEq/L, sepsis, bleeding, AKI, SBP) (such as; propranolol >80 mg/d). Followed by an attempt at re-introduction of beta-blocker therapy after recovery. According to EASL, carvedilol is not recommended in this case. Terlipressin stimulates specific V1 receptors in arterial muscle cells, causing the arteries to contract. Reduced splanchnic vasodilation decreases the portal pressure and increases the effective blood volume and renal

No.	Factors
1.	MELD score > 25 and portasystemic pressure gradient <8 mm Hg
2.	INR value >2
3.	Ttotal serum bilirubin value >3 mg/dl and platelet count <75.000
4.	Serum creatinine >1.9 mg/dl
5.	GFR <90 ml/min and platelet count <125.000
6.	Recurrent HE (stage 2 and above)
7.	Diastolic diysfunction (E/A ratio ≤ 1)

MELD Model for End-Stage Liver disease, INR international normalized ratio, GFR glomerular filtration rate, HE hepatic encephelopathy, E/A: Echocardiographic E wave velocity, A wave velocity.

Table 2.
Factors negatively affecting the result in transjugular intrahepatic portosystemic shunt (TIPS).

perfusion pressure with a positive effect on hyperdynamic circulation, decreases plasma renin activity and noradrenaline level, and increases renal glomerular filtration rate and sodium excretion.

It has been shown that resistant acids can be successfully treated with transjugular intrahepatic portosystemic shunt (TIPS) [26]. TIPS improves cardiovascular function by causing a decrease in portal pressure, increased renal blood flow and glomerular filtration rate. According to current guidelines, cases where LVP is contraindicated (uncooperative patient, skin infection at the puncture site, pregnancy, severe abdominal distension, severe coagulopathy) and TIPS is recommended only when LVP is not effective. Diuretic and salt restriction after TIPS, close clinical monitoring is recommended until the acid regresses. The reason for this is the high mortality in decompensated cirrhotic patients and the development of HE associated with TIPS [27]. Patients undergoing TIPS should be selected carefully. TIPS is not recommended for patients with CTP C [23, 28] (**Table 2**).

The use of polytetrafluoroethylene (PTFE) stents is recommended for patients with TIPS dysfunction and high risk of HE. If the patient has contraindications for TIPS, implantation of a permanent peritoneal catheter may be an alternative. In addition, although the automatic low flow pump (alfa pump system) can reduce the need for paracentesis in patients with cirrhosis and refractory ascites, it remains unclear whether it has a significant advantage over LVP in improving survival. It is currently not considered a standard of medical care, but theoretically TIPS can serve as a bridge for liver transplantation in patients with contraindications [29].

2.2 Gastrointestinal bleeding

Gastrointestinal varices develop as a result of the dilation of abnormally enlarged submucosal veins in the digestive system as a result of PHT. The most important complication of PHT causing morbidity and mortality is gastrointestinal variceal bleeding. The most common gastrointestinal variceal type is esophageal varices 42.7% in CTP A, 70.7% in CTP B, and 75.5% in CTP C [30]. The prevalence of variceal veins increases with the severity of liver disease. Variceal veins can be in the form of esophagus, stomach or ectopic variceal (**Table 3**). Esophageal variceal incidence in cirrhosis patients is 5% in the first year and 28% in the third year. Small esophageal varices can progress to large varices at a rate of 10–12% annually. The risk of variceal bleeding is 5% annually in small variceal and 15% in large variceal veins (**Table 4**). Early mortality (6 weeks) rate after esophageal variceal bleeding is approximately 20%.

Esophageal varices		Stomach varices	
Grade	**Class of modified paquet**	**No**	**By anatomical location**
1	Lying on top of the mucosa	1	GOV-1 (most common type)
2	Covering 1/3 of a lumen	2	GOV-2
3	Covering 50% of the lumen	3	İsolated gastric varise- type 1
		4	Isolated gastric varise-type 2

GOV: gastroesophageal varices.

Table 3.
Esophageal varices according to the modified Paquet classification and gastric varices according to anatomical classification.

No of risk	Factors of risk
1	Hepatic venous pressure gradient>12 mm Hg
2	Medium and Large varices (varices veins>5 mm)
3	Increased varices wall tension and enlarged capillaries in the varices wall (red wale sign)
4	Small varices veins in patients with CTP C
5	Other factors (Coagulopathy, infection, presence of DS)

CTP: child turcotte pugh, DS: decompansated cirrhosis.

Table 4.
Risk factors for varices bleeding.

Endoscopy is the gold standard in the diagnosis of gastrointestinal variceal veins. Endoscopic ultrasonography (EUS) can be used to detect gastric varices, to evaluate the anatomical structure, and to evaluate the response to treatment with endoscopic variceal ligation [31]. Temporary elastography to predict PHT clinically, platelet count, spleen size, MR elastography, splenic stiffness are the most commonly used non-invasive parameters in cirrhotic patients. If the liver stiffness measured by transient elastography is <20 kPa and the thrombocyte count is>150.000 uL, the probability of high risk variceal is less than 5% [32]. Esophageal varices are the most common gastrointestinal varices. Endoscopy is recommended for all newly diagnosed cirrhosis patients. Endoscopy is recommended every 3 years in compensated cirrhotic patients without variceal veins, but if the patient has other predisposing factors such as HCV, alcohol use, obesity, endoscopic screening should be repeated every 2 years.

2.2.1 Non-bleeding variceal treatment

NSBBs (propranolol, nodolol), carvedilol, or endoscopic band ligation are recommended for patients with moderate or large variceal veins for primary prophylaxis. Primary prophylaxis should be initiated after the detection of small variceal veins with red sign, medium and large variceal veins, small variceal veins in patients with CTP C. NSBBs are recommended for patients with small variceal or CTP C with red wale marks. Patients with moderate to large variceal veins should be treated with NSBBs or endoscopic band ligations. Although there is no contraindication for ascites NSBBs, caution should be exercised in severe or refractory ascites cases and high dose NSBBs should be avoided. The EASL guideline does not recommend the use of carvedilol. NSBBs should be discontinued in patients with

progressive hypotension (systolic blood pressure < 90 mm Hg), bleeding, sepsis, SBP and acute kidney injury. Endoscopic band ligation is recommended if the patient has NSBBs intolerance or contraindications. The NSBBs + EBL combination is recommended as it reduces the risk of bleeding compared to monotherapy [23, 32]. Primary prophylaxis of gastric varices NSBBs can be used in primary prophylaxis in the prevention of cardiofundal varices.

2.2.2 Treatment in acute variceal bleeding

Endoscopy should be performed within 12 hours after admission and when the patient is hemodynamically stable. Initially, the patient should be evaluated hemodynamically. Early TIPS should be considered in cases of resuscitation, vasoactive drugs, antibiotic therapy, early endoscopic evaluation, and endoscopic treatment (such as endoscopic band ligation) insufficiency.

Hemoglobin target should be kept between 7–9 g/dl. Antibiotic therapy (ceftriaxone 1 g/24 h, max. 7 days) has been associated with decreased mortality, reduced re-bleeding, and reduced hospital stay. Vasoactive drugs reduce portal blood flow. The use of agents such as octreotide, somatostatin and terlipressin is recommended in all main guidelines. When variceal bleeding is suspected, it should be started early and should be continued for 2–5 days. NSBBs should be initiated after stopping vasoactive drugs. Octireotide (somatostatin analogue) initially 50 microgram IV bolus, then 50 micrograms/hr. infusion 2–5 days. Somatostatin initially 250 microgram IV bolus, then 250 microgram/hr. 2–5 days.

Terlipressin (an analogue of vasopressin) initially 2 mg IV every 4 fours untill control of bleeding, maintenance therapy 1 mg IV every hours to prevent re-bleeding 2–5 days. Among the vasoactive agents, terlipressin was only associated with reduced mortality [33]. Endoscopic intervention (such as, endoscopic band ligation) constitutes the basis of treatment in variceal bleeding. Endoscopy should be performed within 24 hours after resuscitation.

Combination of NSBBs and endoscopic band ligation is first choice for preventing re-bleeding. In patients with high failure of endoscopic treatment or risk of re-bleeding (CTP C or endoscopic active bleeding CTP B, if bleeding recurs despite vasoactive drugs), an early TIPS within 72 hours may be beneficial in selected patients. TIPS is the recommended salvage therapy for recurrent bleeding despite NSBB and endoscopic band ligation treatment. Propranolol 20-40 mg orally, 2 times/day, the treatment goal should not be below the resting heart rate 55–60/min and systolic blood pressure < 90 mm Hg. Nadolol 20–40 mg/day oral, once/day. Endoscopic band ligation should be done at intervals of 1–4 weeks until variceal veins are eradicated. Endoscopy is recommended every 6 to 12 months after eradication [31].

Treatment of gastric varices endoscopic band ligation, cyanoacrylate injection, endoscopic ultrasound guided coil placement, TIPS and BRTO treatments require a multi-disciplinary approach. Patients with acute gastric variceal bleeding are initially performed similarly to esophageal varices (a restrictive transfusion policy, vasoactive drug infusion, and antibiotic prophylaxis). NSBBs can be used in primary prophylaxis to prevent cardio fundal varices. In the endoscopic treatment of gastric varices, mainly cyanoacrylate adhesives, fibrin and thrombin therapy, use of sclerosing agents such as endoscopic band ligation and alcohol are among the treatment options [34].

Endoscopic band ligation or cyanoacrylate glue injection are recommended treatments for bleeding GOV2 varices. In the secondary prophylaxis of GOV1 variceal bleeding, the combination of NSBBs and endoscopic variceal treatment (endoscopic band ligation or cyanoacrylate injection) is the first-line treatment to prevent re-bleeding. High dose NSBBs (propranolol>160 mg/d, nadolol>80 mg/d)

should be avoided in patients with refractory ascites SBP. With refractory ascites and systolic blood pressure < 90 mm Hg, serum sodium level < 130 meq/L or hepatorenal syndrome (HRS) dose should be reduced [35].

It is an adhesive hemostatic powder. It forms a mechanical barrier that covers the bleeding area by contacting with blood or tissue. Its effect lasts about 24 hours [36]. There are case reports of the use of hemospray as a salvage therapy in the failure of cyanoacrylate injection [37]. There is little evidence to support its current use in active varices bleeding.

Balloon tamponade is a short-term measure. Sengstaken Blakemore (SB) tube, Minnesota tube, Linton-Nachlas tube. Because of the high risk of re-bleeding when the balloon is lowered and its complications, it should be considered as a temporary measure until definitive control of bleeding is achieved [38]. While the success rate with the use of balloon tamponade in gastric varices is 88%, the complication rate has been reported as 10% [39]. Complications include esophageal ulcers, necrosis, esophageal rupture, and aspiration pneumonia. Consequently, it is recommended that its use be limited to temporary control until a more precise method is applied [34].

TIPS is a shunt created by placing a stent between the portal vein and hepatic vein to reduce portal pressure. If variceal bleeding of the patient cannot be controlled due to medical and endoscopic treatment, early TIPS (24 hours) should be considered [31, 40]. Complications caused by TIPS include HE, heart failure and stent stenosis. Heart failure, severe pulmonary hypertension, severe tricuspid valve insufficiency, sepsis, unresolved bile duct obstruction are among the absolute contraindications for TIPS. Relative contraindications are portal vein thrombosis, hepatoma, uncorrected coagulopathy, and severe thrombocytopenia (<20,000 uL). Cardio fundal is increasingly used as a first-line treatment for the control of bleeding from varices (GOV2, IGV1) [41].

Balloon occluded retrograde transvenous obliteration (BRTO): It is an interventional radiology technique performed by accessing gastric varices through a gastrorenal shunt and injecting the variceal sclerosing agent. The current recommendation for BRTO can be applied as a salvage therapy in cases where TIPS such as advanced liver failure or HE is contraindicated. The main side effect of BRTO can be stated as causing vascular damage due to sclerosing substance and progression of esophageal varices in case of accidental displacement of the balloon. TIPS or BRTO is not recommended for primary prophylaxis in fundal varices without bleeding. However, fundal variceal veins are the first step treatments to prevent re-bleeding. Cyanoacrylate injection is recommended instead of TIPS in patients at high risk of advanced liver dysfunction and HE [42].

2.3 Hepatic encephalopathy

HE is a complication of liver failure characterized by reversible neuropsychiatric symptoms and signs ranging from disorientation to coma. High portosystemic shunting is an important cause of morbidity in acute and chronic liver diseases. It is the second most common complication of decompensated cirrhosis after acid. In addition, HE is the most common cause of hospitalization in decompensated cirrhosis patients. The incidence of symptomatic HE ranges from 30–40% and minimal encephalopathy from 20–80% [43, 44]. Although the pathogenesis of HE is not fully understood, ammonia toxicity is an important factor in its development, but inflammation (proinflammatory cytokines, TNF alpha, ınterleukin 1, ınterleukin 6) oxidative stress, changes in intestinal microbiota play a role [45, 46]. Intestinal flora changes play an important role in the development of HE. Ammonia, which is a product of intestinal metabolism in liver cirrhosis, cannot be effectively converted into urea in the liver. Serum ammonia level rises due to the passage of portal blood

to the systemic circulation and the blood passes to the brain barrier. Astrocytes are neuroglial cells responsible for protecting the blood brain barrier and detoxifying it by converting ammonia to glutamine. Glutamine increase leads to astrocyte swelling, morphological changes and cell dysfunction [47]. Increased production of ammonia during HE triggers in the clinic (GIS bleeding, hypovolemia, hypokalemia, acidosis, diabetes, excessive diuresis, excessive protein intake), impaired ammonia excretion (constipation, renal failure, sarcopenia, portosystemic shunt, zinc deficiency, branched chain amino acid deficiency) and Increased neurotoxicity (infection, drug/substance abuse, hyponatremia, hyperglycemia).

Studies have shown a decrease in bile acid production in advanced stage liver disease, an increase in more pathogenic bacteria such as enterobacteia, and a decrease in protective bacteria such as lachnospiraceae [48]. Regarding the importance of gut-liver-brain axis in HE, it has been shown that patients with HE have more systemic inflammation, dysbiosis, hyperammonemia and neuronal/astrocytic dysfunction compared to controls and patients with cirrhosis without HE [49]. According to a recent meta-analysis, it has been reported that a decrease in serum ammonia and endotoxin levels can improve and prevent HE [50]. It has been shown that HE patients who underwent fecal microbiota transplantation (FMT) had fewer HE attacks and hospitalizations. In addition, albumin infusion can reduce the frequency and severity of HE in liver cirrhosis [51].

Current guidelines for the clinical management of HE suggest lactulosis and rifaximine as first-line therapy [44]. In HE patients, care needs to be initiated for a change in consciousness, which includes securing the airway, hemodynamic stabilization, and ensuring patient safety to prevent physical injury. Intubation is recommended in patients with HE 3 or above, Glasgow score (GCS) < 8, but this is not possible in many hospitals. Protection of the airway and close monitoring is recommended. CT scan is recommended to evaluate the causes of mental changes. Infection bleeding, constipation, dehydration, sedative drugs, alcohol intoxication, or electrolyte disturbances should be identified and corrected. The goal of many treatments is to reduce ammonia levels.

In the treatment of hepatic encephalopathy, lactulose, branched chain amino acids, rifaximine, and L-ornithine L-aspartate can be used. The current treatment in HE as the first step is lactulose 20 g/30 ml-30 g/45 ml orally 3–4 times a day, if not oral, similar dose nasogastric or 300 ml enema can be given 3–4 times a day. As a side effect, diarrhea is seen as abdominal swelling and taste disturbance. In the second step treatment, rifaximine 400–500 mg can be taken orally twice a day. An important side effect is the road. It is reported that percutaneous endoscopic gastrostomy, which has not yet been approved by food and drug administration (FDA), can be used in the third step.

Lactulose and rifaximine are recommended as primary care in the prevention of recurrent HE (**Figure 1**). Probiotics and fecal microbiota transplantation are included. There is no evidence yet for the use of probiotics in acute HE [52]. L ornithine L-Aspartate (LOLA) is a substrate for the urea cycle. It can be used in HE and other hyperammonemia conditions. According to a recent meta-analysis, it is reported that HE LOLA has a positive effect on decompensation and mortality.

The american association for the study of liver diseases (AASLD) and EASL guidelines suggest that LOLA oral therapy is not effective. The potential beneficial effect of LOLA remains unclear [53]. Osmotic laxatives, non-absorbable disaccharides lactulose and lactitol are recommended as first-line therapy. Lactulose is likely to increase intestinal transit, acidifying the intestinal environment, reducing ammonia production in the intestine, increasing fecal excretion and decreasing ammonia absorption. As an antimicrobial agent, Rifaximine is a semi-synthetic non-aminoglycoside substance effective against gram-positive, negative aerobic,

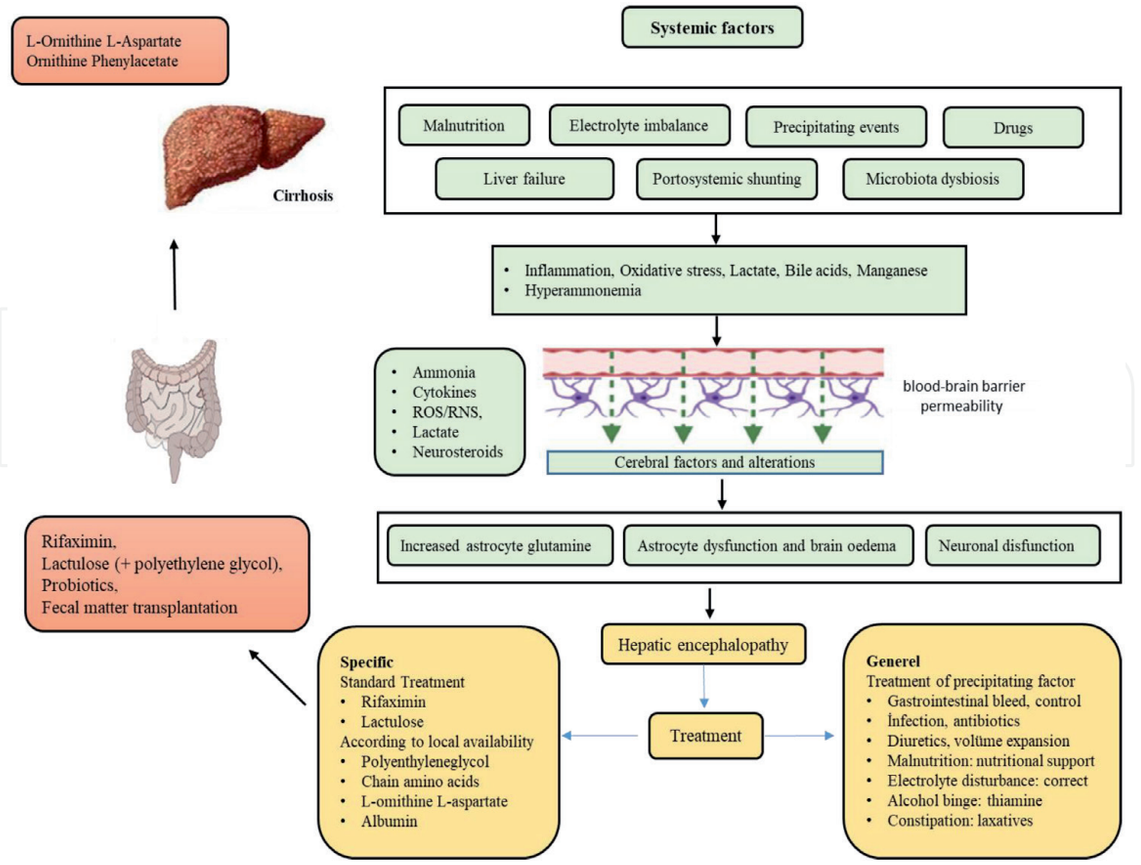

Figure 1.
Hepatic encephalopathy (HE) pathogenesis and treatment approaches.

anerobic enteric bacteria. It inhibits bacterial RNA synthesis. Rifaximine + lactulose has been shown to increase recovery in HE and decrease mortality.

In patients with recurrent HE, an improvement in FMT coordination has been shown to result in an improvement in the fecal microbiome profile with a decrease in the incidence of HE [54]. Other new treatments are changed to brain gamma-aminobutyric acid (GABA) receptors. Therapies focusing on *E. coli* are some of the new methods that are actively researched in HE but not currently close to clinical use.

2.4 Hepatorenal syndrome

Hepatorenal syndrome (HRS) is one of the most important complications in cirrhosis patients. In patients with cirrhotic portal hypertension in the pathophysiology of HRS, systemic and splanchnic vasodilation, bacterial translocation, inflammation, nitric oxide, increased prostacyclin, decrease in effective arterial blood volume (GIS bleeding, diuretics, lactulose, non-steroids, radiocontrast agent, oral intake failure) may cause hypovolemia. It causes vasoconstriction in renal artery tracts with RAAS and activation of sympathetic nervous system to decrease renal blood flow and HRS develops. It is evaluated in two groups in cirrhotic patients. (HRS AKI and non-HRS AKI) (**Table 5**). HRS AKI, decompensated cirrhosis is characterized by prerenal azotemia in patients with severe portal hypertension, nephrotoxicity, and worsening of renal functions in the absence of intrinsic renal disease. Non-HRS AKI may result from prerenal hypoperfusion bile acid nephropathy, nephrotoxicity, or acute parenchymal injury [55]. Although the best treatment option for HRS is liver transplantation, the basis of medical therapy is vasoconstrictor agents, such as terlipressin noradrenaline and dopamine in combination with albumin [56].

HRS subtypes according to the new classification	Criteria
HRS AKI	sCr ≥ 0.3 mg/dl increase up to 48 hours and/or
	Urine amount ≤ 0.5 ml/kg B.W. ≥6 h or
	sCr ≥ 50% according to basal value, increase within 3 months
HRS NAKI	eGFR <60 ml/min 1.73 m^2 in the absence of other structural causes
	<50% increase in sCr basal value within 3 months in outpatients

HRS AKI Hepatorenal sendrom acute kidney injury, NRS NAKI hepatorenal sendrom non acute kidney injury sCr, serum creatinine, eGFR estimated glomerular filtration rate.

Table 5.
Classification of Hepatorenal syndrome subtypes in cirrhosis.

In patients followed up with HRS in the intensive care unit, initial treatment is recommended as a combination of norepinephrine and albumin. (norepinephrine intravenously continuous infusion 0.5–3 mg/hr, albumin intravenous bolus 1 g/kg per day for at least two days). Terlipressin albumin combination is recommended as the initial therapy in HRS patients outside the intensive care unit. Terlipressin 1–2 mg is recommended as an intravenous bolus every 4 to 6 hours. Albumin is given for 2 days as intravenous bolus (1 gr/kg per day). During follow-up, terlipressin treatment is recommended as 25–50 g/day until discontinuation. TIPS therapy until liver transplantation can sometimes be successful in specially selected patients who are unresponsive to medical therapy [57–59].

2.5 Hepatopulmonary syndrome

Hepatopulmonary syndrome (HPS) is the most common cause of respiratory failure in patients with chronic liver disease. It is characterized by a gas exchange abnormality caused by intrapulmonary vascular dilatations (IPVD) in liver patients. Its incidence ranges from 4–47%. The pathogenesis of HPS includes a complex pathogenetic mechanism such as increased nitric oxide production, angiogenesis, intrapulmonary shunt and ventilation perfusion mismatch. Clinical consequences of hypoxemia can be seen together with progressive dyspnea, cyanosis, clubbing, platypnea and orthodoxy, and chronic pulmonary comorbidity (COPD, asthma bronchiale, idiopathic pulmonary fibrosis, restrictive lung disease).

Hepatopulmonary syndrome diagnostic criteria are partial oxygen pressure < 80 mmHg or alveolar-arterial oxygen gradient ≥15 mmHg (PO2 gradient) (or > 20 mmHg over 65 years of age). Detection of intrapulmonary vascular dilatation (Contrasted ECO cardıography or lung perfusion scan with radioactive albumin). Liver transplantation is the only successful treatment that alters the natural history of HPS and improves arterial hypoxemia. There is no effective treatment support for HPS other than long-term oxygen support [60–62].

2.6 Acute on chronic liver failure

Acute on chronic liver failure (ACLF) is a clinical sudden hepatic decompensation syndrome associated with one or more extra hepatic organ failure, increased mortality, observed in patients with pre-existing chronic liver disease. Hepatic causes include alcohol-related liver damage, drug-induced hepatic damage, viral hepatitis (A, B, C, D, and E), hypoxic damage or liver surgeries, including TIPS, in the etiology of pre-existing liver disease precipitating events. Extrahepatic causes are

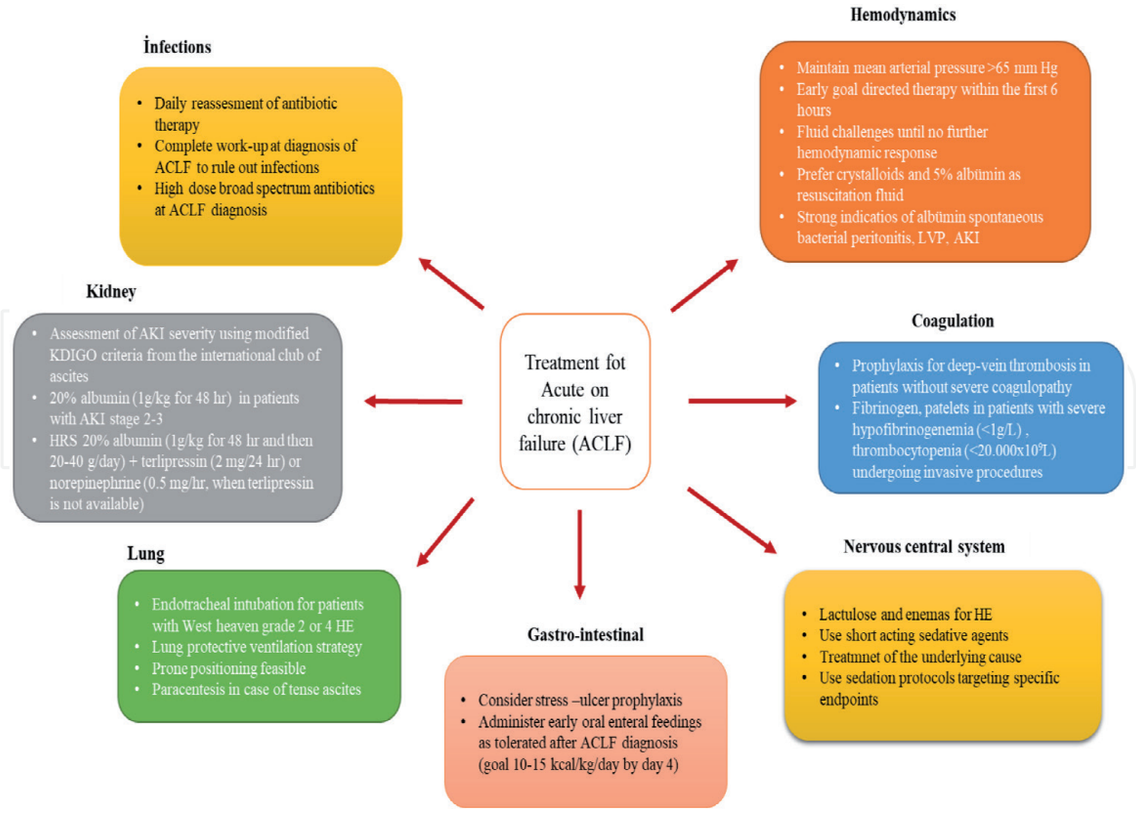

Figure 2.
Treatment approaches in organ failure due to acute on chronic liver failure (ACLF), AKI: Acute kidney injury, KDIGO: kidney disease improving globai outcomes, HE: Hepatic encephalopathy, HRS: Hepatorenal syndrome, LVP: large volume paracentesis.

bacterial infection and major surgical interventions. In patients with chronic liver disease, acute triggering agents trigger inflammatory cytokine cascade by causing hepatocyte damage, leading to further liver damage decompensation, multi-organ failure and death in the presence of insufficient hepatocyte regeneration [63, 64].

It consists of prevention of triggering factors that lead to acute decompensation, supportive therapy, early initiation of specific therapy and management of complications (**Figure 2**). All patients should be followed, preferably in a center with liver transplant facilities.

The essence of ACLF treatment is based on supportive treatment of organ failure in intensive care conditions. Liver transplantation is a good long-term effective treatment for selected patients. Potential treatment alternatives that will improve patient survival are highly awaited. There is currently no specific effective treatment for their patients. Therefore, treatment is based on organ support and treatment of associated complications.

2.7 Gut microbiota relationship in decompensated cirrhosis

Cirrhosis is associated with an altered immune response in the stool, potentially due to dysbiosis in the intestinal mucosa. Patients with cirrhosis have an altered gut-liver axis associated with changes in gut microbiota composition and function, associated with liver disease severity, intestinal barrier disorder, and changes in intestinal and systemic inflammation. Microbiota is one of the organs most exposed to intestinal toxins through the liver portal system. The gut microbiota is the first line of defense against toxic bacterial products in protecting the host's mucosal barrier integrity. Firmicutes, bacteroidetes, actinobacteria, proteobacteria, verrucomicrobia and

fusobacteria are the main intestinal bacteria in the gastrointestinal flora. Firmicutes and bacteroidetes make up 90% of all bacteria [65]. Gastrointestinal system microbiota plays an important role in providing intestinal epithelial permeability and barrier function in NAFLD/NASH. Toxic bacterial products such as lipopolysaccharides bind to the CD14 receptor with Toll-like receptors (TLR), and stress-activated protein kinase, JNK, P38, interferon regulatory factor 3, nuclear factor JB play a role in the NASH process by initiating inflammatory cascade [66, 67]. In animal models, it has been shown that feeding mice with impaired intestinal barrier function with a diet containing high saturated fat, fructose and cholesterol leads to more severe steatohepatitis development compared to the control group [68]. Nutrition with a high fat diet; Atrophy in epithelial cell microvilli, disruption in the tight junction between cells, bacterial overgrowth in the small intestine (SIBO) is more severe in NASH than in NAFLD. Change in intestinal barrier function; Lipopolysaccharide and toxic bacterial products (other organic compounds such as ethanol, acetone, butanoic acid) cause the liver to be exposed to higher levels of inflammatory bacterial metabolites [69].

2.8 Artificial liver support systems

Artificial liver support systems (ALSS) are used to provide recovery in patients with acute liver failure (ALF) and acute-chronic liver failure and to act as a bridge until transplantation. There are two main types of devices, artificial and bio-artificial. Artificial liver devices are detoxification of blood or plasma, removal of physical and chemical gradients, removal of toxic and metabolic wastes by means of albumin. There are artificial liver support systems used today, such as Molecular adsorbent recirculating system (MARS), single - pass albumin dialysis (SPAD), Prometheus, selective plasma filtration therapy and hemodiafiltration. There was no difference between Prometheus and standard medical treatment in terms of survival. The role of TPE2 in patients with ALF plasmapheresis ACLF is not known. Prospective studies are needed on this issue. Its effectiveness in hemodialysis patients with ALF and ACLF remains unclear. The effect of MARS therapy on ACLF and ALF survival has not been demonstrated [70, 71].

3. Conclusions

Portal hypertension has an important place in complications and deaths related to cirrhosis. Non-selective beta blockers occupy an important place in the medical treatment of portal hypertension, but their potential side effects limit their use. New agents that suppress fibrosis, tissue damage and angiogenesis are needed in cirrhosis. Statins and PPARα/y agonists may be an alternative in this regard. Intestinal microbiota (systemic inflammation, dysbiosis, increased intestinal permeability, endotoxemia, impaired intestinal motility, bacterial overgrowth, increased production of short-chain fatty acids and changes in metabolism) play an important role in the pathogenesis of liver diseases. Dysbiosis plays a key role in the development of cirrhosis-related complications. Moreover, modulation of the microbiome with current and future therapeutic strategies is thought to be the cornerstone of cirrhosis management. It is predicted that the microbiota will play an important role in developing new prognostic and therapeutic strategies in cirrhotic patients.

Conflict of interest

The authors declare no conflict of interest.

DOI: http://dx.doi.org/10.5772/intechopen.96155

Author details

Anıl Delik* and Yakup Ülger
Department of Gastroenterology, Faculty of Medicine, Çukurova University, Adana, Turkey

*Address all correspondence to: anildelik@gmail.com

References

[1] Long, Brit, and Alex Koyfman. "The emergency medicine evaluation and management of the patient with cirrhosis." The American Journal of Emergency Medicine 2018:36.4: 689-698.

[2] P. Ichai, D. Samuel Epidemiology of liver failure Clin Res Hepatol Gastroenterol.2011:35(1), pp. 610-617. DOI: 10.1016/j.clinre.2011.03.010

[3] Wong MCS, Huang JLW, George J, et al. The changing epidemiology of liver diseases in the Asia-Pacific region. Nat Rev Gastroenterol Hepatol 2019;16:57-73. DOI: 10.1038/s41575-018-0055-0

[4] Asrani SK, Devarbhavi H, Eaton J, et al. Burden of liver diseases in the world. J Hepatol 2019;70:151-171. DOI: 10.1016/j.jhep.2018.09.014

[5] Hofmeister MG, Rosenthal EM, Barker LK, et al. Estimating prevalence of hepatitis C virus infection in the United States,2013-2016. Hepatology 2019;69:1020-1031. DOI: 10.1002/hep.30297

[6] 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;44:217-231. DOI: 10.1016/j.jhep.2005.10.013

[7] Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: From peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol 2015;63:1272-1284. DOI: 10.1016/j.jhep.2015.07.004

[8] Hotchkiss, RS. et al. Sepsis and septic shock. Nat. Rev. Dis. Primers. 2016:2, 16045. DOI: 10.1038/nrdp.2016.45

[9] Trautwein C, Friedman SL, Schuppan D, Pinzani M. Hepatic fibrosis: Concept to treatment. J Hepatol 2015;62:S15–S24. DOI: 10.1016/j.jhep.2015.02.039

[10] Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodes J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988;8:1151-1157. DOI: 10.1002/hep.1840080532

[11] Arroyo V, Fernandez J. Relationship Between Systemic Hemodynamics, Renal Dysfunction, and Fluid Retention in Cirrhosis. Clin Liver Dis 2013; 2: 120-122 [DOI: 10.1002/cld.185]

[12] Arroyo V, Terra C, Ginès P. Advances in the pathogenesis and treatment of type-1 and type-2 hepatorenal syndrome. J Hepatol 2007; 46: 935-946 [PMID: 17391801 DOI: 10.1016/j.jhep.2007.02.001]

[13] Garbuzenko, Dmitry Victorovich, and Nikolay Olegovich Arefyev. "Current approaches to the management of patients with cirrhotic ascites." World Journal of Gastroenterology 25.28 2019: 3738. DOI: 10.3748/wjg.v25.i28.3738

[14] Arroyo V, Ginès P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, Reynolds TB, Ring-Larsen H, Schölmerich J. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology 1996; 23: 164-176 [PMID: 8550036 DOI: 10.1002/hep.510230122]

[15] Haberl J, Zollner G, Fickert P, Stadlbauer V. To salt or not to salt?-That is the question in cirrhosis. Liver Int 2018; 38: 1148-1159 [PMID: 29608812 DOI: 10.1111/liv.13750]

[16] Lenz K, Buder R, Kapun L, Voglmayr M. Treatment and management of ascites and

hepatorenal syndrome: an update. Therap Adv Gastroenterol 2015; 8: 83-100 [PMID: 25729433 DOI: 10.1177/1756283X14564673]

[17] Angeli P, Fasolato S, Mazza E, Okolicsanyi L, Maresio G, Velo E, etal. Combined versus sequential diuretic treatment of ascites in non-azotaemic patients with cirrhosis: results of an open randomised clinical trial. Gut 2010; 59: 98-104 [PMID: 19570764 DOI: 10.1136/gut.2008.176495]

[18] Piano S, Tonon M, Angeli P. Management of ascites and hepatorenal syndrome. Hepatol Int 2018; 12: 122-134 [PMID: 28836115 DOI: 10.1007/s12072-017-9815-0]

[19] Biecker E. Diagnosis and therapy of ascites in liver cirrhosis. World J Gastroenterol 2011; 17: 1237-1248 [PMID: 21455322 DOI: 10.3748/wjg.v17.i10.1237]

[20] Sahay M, Sahay R. Hyponatremia: A practical approach. Indian J Endocrinol Metab 2014; 18: 760-771 [PMID: 25364669 DOI: 10.4103/2230-8210.141320]

[21] Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing largevolume paracentesis: a meta-analysis of randomized trials. Hepatology 2012; 55: 1172-1181 [PMID: 22095893 DOI: 10.1002/hep.24786]

[22] Kozaki K, IInuma M, Takagi T, Fukuda T, Sanpei T, etal. Cell-Free and Concentrated Ascites Reinfusion Therapy for Decompensated Liver Cirrhosis. Ther Apher Dial 2016; 20: 376-382 [PMID: 27523078 DOI: 10.1111/1744-9987.12469]

[23] European Association for the Study of the Liver. "EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis." Journal of hepatology 69.2 2018: 406-460. DOİ: 10.1016/j.jhep.2018.03.024.

[24] Runyon, Bruce A. "Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012." Hepatology 57.4 2013: 1651-1653. DOI: 10.1002/hep.26359

[25] Guo TT, Yang Y, Song Y, Ren Y, Liu ZX, Cheng G. Effects of midodrine in patients with ascites due to cirrhosis: Systematic review and meta-analysis. J Dig Dis 2016; 17: 11-19 [PMID: 26630543 DOI: 10.1111/1751-2980.12304]

[26] Bai M, Qi XS, Yang ZP, Yang M, Fan DM, Han GH. TIPS improves liver transplantation-free survival in cirrhotic patients with refractory ascites: an updated meta-analysis. World J Gastroenterol 2014; 20: 2704-2714 [PMID: 24627607 DOI: 10.3748/wjg.v20.i10.2704]

[27] Allegretti AS, Ortiz G, Cui J, Wenger J, etal. Changes in Kidney Function After Transjugular Intrahepatic Portosystemic Shunts Versus Large-Volume Paracentesis in Cirrhosis: A Matched Cohort Analysis. Am J Kidney Dis 2016; 68: 381-391 [PMID: 26994685 DOI: 10.1053/j.ajkd.2016.02.041]

[28] Hamel B, Guillaud O, Roman S, Vallin M, Pilleul F, Valette PJ, etal Prognostic factors in patients with refractory ascites treated by transjugular intrahepatic porto-systemic shunt: From the liver to the kidney. Dig Liver Dis 2014; 46: 1001-1007 [PMID: 25096966 DOI: 10.1016/j.dld.2014.06.013]

[29] Solà E, Sanchez-Cabús S, Rodriguez E, Elia C, Cela R, Moreira R, etal. Effects of alfapump™ system on kidney and circulatory function in patients with cirrhosis and refractory ascites. Liver Transpl 2017; 23: 583-593 [PMID: 28318147 DOI: 10.1002/lt.24763]

[30] Kovalak M, Lake J, Mattek N, Eisen G, Lieberman D, Zaman A. Endoscopic screening for varices in cirrhotic patients: data from a national endoscopic database. Gastrointest Endosc. 2007;65:82-88. DOI: 10.1016/j.gie.2006.08.023

[31] Lesmana, CRA, Raharjo, M, Gani, RA. Managing liver cirrhotic complications: Overview of esophageal and gastric varices. Clinical and molecular hepatology. 2020;26(4): 444. DOI:https://doi.org/10.3350/cmh.2020.0022

[32] Garcia-Tsao, Guadalupe, et al. "Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases." Hepatology 65.1 :2017: 310-335. DOI: 10.1002/hep.28906

[33] Zhou X, Tripathi D, Song T, Shao L, Han B, Zhu J, Han D, Liu F, Qi X. Terlipressin for the treatment of acute variceal bleeding: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2018; 97: e13437 [PMID: 30508958 DOI: 10.1097/MD.0000000000013437]

[34] Tripathi D, Stanley AJ, Hayes PC, Patch D, Millson C, Mehrzad H, etal Clinical Services and Standards Committee of the British Society of Gastroenterology. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut 2015; 64: 1680-1704 [PMID: 25887380 DOI: 10.1136/gutjnl-2015-309262]

[35] McAvoy NC, Plevris JN, Hayes PC. Human thrombin for the treatment of gastric and ectopic varices. World J Gastroenterol 2012; 18: 5912-5917 [PMID: 23139607 DOI: 10.3748/wjg.v18.i41.5912]

[36] Ibrahim M, El-Mikkawy A, Abdel Hamid M, Abdalla H, Lemmers A, Mostafa I, Devière J. Early application of haemostatic powder added to standard management for oesophagogastric variceal bleeding: a randomised trial. Gut 2018 [PMID: 29730601 DOI: 10.1136/gutjnl-2017-314653]

[37] Holster IL, Poley JW, Kuipers EJ, Tjwa ET. Controlling gastric variceal bleeding with endoscopically applied hemostatic powder (Hemospray™). J Hepatol 2012; 57: 1397-1398 [PMID: 22864337 DOI: 10.1016/j.jhep.2012.07.024]

[38] Carbonell N, Pauwels A, Serfaty L, Fourdan O, Lévy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. Hepatology 2004; 40: 652-659 [PMID: 15349904 DOI: 10.1002/hep.20339]

[39] Panés J, Terés J, Bosch J, Rodés J. Efficacy of balloon tamponade in treatment of bleeding gastric and esophageal varices. Results in 151 consecutive episodes. Dig Dis Sci 1988; 33: 454-459 [PMID: 3280273] DOI: 10.1097/MD.0000000000013437

[40] 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. DOI: 10.1016/j.jhep.2015.05.022

[41] Vine, Louisa J., Mohsan Subhani, and Juan G. Acevedo. "Update on management of gastric varices." World Journal of Hepatology 11.3 :2019: 250. DOI: 10.4254/wjh.v11.i3.250

[42] Kim SK, Lee KA, Sauk S, Korenblat K. Comparison of Transjugular Intrahepatic Portosystemic Shunt with Covered Stent and Balloon-Occluded Retrograde Transvenous Obliteration in Managing Isolated Gastric Varices. Korean J Radiol 2017; 18: 345-354 [PMID: 28246514 DOI: 10.3348/kjr.2017.18.2.345].

[43] Dharel N, Bajaj JS. Definition and nomenclature of hepatic encephalopathy. J Clin Exp Hepatol. 2015;5:S37-S41. DOI: 10.1016/j.jceh.2014.10.001

[44] Vilstrup H., Amodio P., Bajaj J., Cordoba J., Ferenci P., Mullen K. D., Wong P. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology, 2014:60(2), 715-735. doi:10.1016/j.jhep.2014.05.042

[45] Tranah T., Paolino A., Shawcross D. Pathophysiological mechanisms of hepatic encephalopathy: Pathophysiological mechanisms. Clinical Liver Disease, 2015:5(3), 59-63. doi:10.1002/cld.445

[46] Butt Z., Jadoon N., Salaria O., Mushtaq K., Riaz I., Shahzad A., Sarwar S. Diabetes mellitus and decompensated cirrhosis: Risk of hepatic encephalopathy in different age groups. Journal of Diabetes, 2013:5(4), 449-455. doi:10.1111/1753-0407.12067

[47] Iwasa M., Takei Y. Pathophysiology and management of hepatic encephalopathy 2014 update: Ammonia toxicity and hyponatremia: Management of hepatic encephalopathy. Hepatology Research, 2015:45(12), 1155-1162. doi:10.1111/hepr.12495

[48] 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. DOİ.org/10.1002/hep.20194

[49] Ahluwalia V, Betrapally NS, Hylemon PB. Impaired gut-liver-brain axis in patients with cirrhosis. Sci Rep 2016;6:26800. DOI: 10.1038/srep26800

[50] Cao Q, Yu CB, ang SG, et al. Effect of probiotic treatment on cirrhotic patients with minimal hepatic encephalopathy: a meta-analysis. HepatobiliaryPancreat Dis Int 2018;17(1):9-16. DOI: 10.1016/j.hbpd.2018.01.005

[51] Bai Z., Bernardi M., Yoshida EM., Li, H., Guo, X., Méndez-Sánchez, N. et al. Albumin infusion may decrease the incidence and severity of overt hepatic encephalopathy in liver cirrhosis. Aging (Albany NY), 2019:11(19), 8502. DOI: 10.18632/aging.102335.

[52] Dalal R, McGee RG, Riordan SM, et al. Probiotics for people with hepatic encephalopathy. Cochrane Database Syst Rev. 2017;2:CD008716. DOI: 10.1002/14651858.CD008716.pub3

[53] Rose CF, Amodio P, Bajaj JS, Dhiman RK, Montagnese S, taylor-Robinson SD, et al. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology . 2020;73:1526-1547. DOI:https://doi.org/10.1016/j.jhep.2020.07.013

[54] Bajaj JS, Kassam Z, Fagan A, et al. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: a randomized clinical trial. Hepatology. 2017;66:1727-1738. DOI: 10.1002/hep.29306

[55] Amin AA, Alabsawy EI, Jalan R, davenport A. Epidemiology, Pathophysiology, and Management of Hepatorenal Syndrome. Seminars in Nephrology. 2019;39:1:17-30. DOI: 10.1016/j.semnephrol.2018.10.002.

[56] Zhang, J., Rössle, M., Zhou, X., Deng, J., Liu, L., Qi, X. Terlipressin for the treatment of hepatorenal syndrome: an overview of current evidence. Current medical research and opinion. 2019;35(5): 859-868. DOI: 10.1080/03007995.2018.1552575

[57] Rajesh, S., George, T., Philips, C. A., Ahamed, R., Kumbar, S., Mohan, N. et al. Transjugular intrahepatic

portosystemic shunt in cirrhosis: An exhaustive critical update. World Journal of Gastroenterology. 2020:26(37); 5561. DOİ: 10.3748/wjg.v26.i37.556.

[58] Bruce AR. Hepatorenal syndrome. UpToDate. 2020. www.uptodate.com/contents/hepatorenal-syndrome

[59] Angeli P, Garcia-Tsao G, Nadim MK, Parikh CR. News in pathophysiology, definition and classification of hepatorenal syndrome: A step beyond the ınternatıonal club of ascites (ıCA) consensus document. 2019;71:811-822. DOI: 10.1016/j.jhep.2019.07.002

[60] Krowka MJ, Fallon MB, Kawut SM, et al. International Liver Transplant Society Practice Guidelines: Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Hypertension. Transplantation 2016; 100:1440. DOI: 10.1097/TP.0000000000001229

[61] Nayyar D, Man HS, Granton J, et al. Proposed management algorithm for severe hypoxemia after liver transplantation in the hepatopulmonary syndrome. Am J Transplant 2015; 15:903. DOI: 10.1111/ajt.13177

[62] Zhao H, Liu F, Yue Z, et al. Clinical efficacy of transjugular intrahepatic portosystemic shunt in the treatment of hepatopulmonary syndrome. Medicine (Baltimore) 2017; 96:e9080. DOİ: 10.1097/MD.0000000000009080

[63] Arroyo V, Moreau R, Jalan R. Acute-on-Chronic Liver Failure. New England journal of Medicine. 2020;382:2137-2145. DOI: 10.1056/NEJMra1914900

[64] Zaccherini G, Weiss E, Moreau R. Acute-on-Chronic liver failure: Definitions pathophysiology and principles of treatment. JHEP Reports. 2020;100176. DOI: 10.1016/j.jhepr.2020.100176

[65] Zhou D, Fan JG. Gut microbiota and energy balance: role in obesity. Proc Nutr Soc. 2015;74:227-234. DOİ: 10.1017/S0029665114001700.

[66] Bajaj JS. Altered Microbiota in Cirrhosis and its relationship to the Development of infection. Clinical Liver Disease, 2019:14(3), 107. DOI: 10.1002/cld.827.

[67] Zheng, R., Wang, G., Pang, Z., Ran, N., Gu, Y., Guan, X. et al. Liver cirrhosis contributes to the disorder of gut microbiota in patients with hepatocellular carcinoma. Cancer Medicine. 2020. Jun;9(12):4232-4250. DOİ: 10.1002/cam4.3045.

[68] Rahman K, Desai C, Iyer SS, et al. Loss of junctional adhesion molecule A promotes severe steatohepatitis in mice on a diet high in saturated fat, fructose, and cholesterol. Gastroenterology. 2016;151:733-746 e712. DOİ: 10.1053/j.gastro.2016.06.022

[69] Mao JW, Tang HY, Zhao T, et al. Intestinal mucosal barrier dysfunction participates in the progress of nonalcoholic fatty liver disease. Int J Clin Exp Pathol. 2015;8:3648-3658. PMID: 26097546

[70] Larsen, FS. Artificial liver support in acute and acute-on-chronic liver failure. Current opinion in critical care, 2019;25(2):187-191. DOI: 10.1097/MCC.0000000000000584

[71] Tandon, R., and Froghi, S. Artificial liver support systems. Journal of Gastroenterology and Hepatology. 2020. DOİ: 10.1111/jgh.15255.