GI & LIVER FOUNDATION

GLF

(Myanmar)

Clinical Practice Guidance for Cirrhosis of Liver

GLF (Myanmar)

Diagnosis and Management of Cirrhosis of Liver: 2024 Myanmar Clinical Practice Guidance Recommendations by GI and Liver Foundation (Myanmar)

Preamble

GI and Liver Foundation (Myanmar) has produced clinical practice guidelines on Hepatitis B, Hepatitis C and Cirrhosis of the Liver to assist all the practicing doctors in the treatment of Liver Diseases.

However, AASLD has recently adopted a policy to differentiate between guidelines and guidance. AASLD published guidelines on some topics and guidance on some other diseases.

And therefore, it's time for GLF (Myanmar) to review the policy whether it should be clinical practice guidelines or guidance in future publications. For that purpose, GLF (Myanmar) decided to follow the AASLD policy.

According to the AASLD, practice guidelines use clinically relevant questions, which are then answered by systematic reviews of the literature and followed by data-supported recommendations. The guidelines are developed by a multidisciplinary panel of experts who rate the quality (level) of the evidence and the strength of each recommendation using the Grading of Recommendations Assessment, Development, and Evaluation system ("GRADE"). (AASLD Family of Websites:**AASLD.org**)

AASLD also publishes guidance on aspects of some topics. Practice guidances are based on a comprehensive review and analysis of relevant published data and put forward guidance statements to help clinicians understand and implement the most recent evidence. (AASLD Family of Websites:**AASLD.org**)

By AASLD policy mentioned above what GLF (Myanmar) has published are not practice guidelines but practice guidance. Therefore, future GLF (Myanmar) clinical practice publications will be labelled as "GLF (Myanmar) Clinical Practice Guidance".

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ABBREVIATIONS

AAA	Aromatic Amino Acid
ABG	Arterial Blood Gas
Abs	Antibodies
ACEi	Angiotensin-converting Enzyme Inhibitors
ACLF	Acute on Chronic Liver Failure
AD	Acute decompensation
AFP L3	Lens culinaris-agglutinin-reactive fraction of AFP
AFP	Alpha Feto Protein
AIH	Autoimmune Hepatitis
AKD	Acute Kidney Disease
AKI	Acute Kidney Injury
ALF	Acute Liver Failure
ALT	Alanine Aminotransferase
ANA	Anti-Nuclear Antibody
ANC	Absolute Neutrophil Count
APAP	Acetaminophen
APASL	Asian Pacific Association for the Study of the Liver
APRI	AST to Platelet Ratio Index
ARB	Angiotensin Receptor Blockers
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Transaminase
ATN	Acute Tubular Necrosis
AVB	Acute Variceal Bleeding
BCAAs	Brand-chain Amino Acids
BIA	Bioelectrical Impedance Analyzer
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
BUN	Blood Urea Nitrogen
cACLD	compensated Advanced Chronic Liver Disease

CARS	Compensatory Anti-inflammatory Response Syndrome
CCC	Cirrhotic Cardiomyopathy Consortium
CCM	Cirrhotic Cardiomyopathy
CCP	Cerebral Perfusion Pressure
CHE	Covert Hepatic Encephalopathy
CKD	Chronic Kidney Disease
CLD	Chronic Liver Disease
CLIF-OF	Chronic Liver Failure Consortium – Organ Failure
CMV	Cytomegalovirus
COL	Cirrhosis of Liver
CSPH	Clinically Significant Portal Hypertension
CT	Computed Tomography
CTP	Child-Turcotte-Pugh
DAAs	Direct-acting Antivirals
DCP	Das Gamma-carboxy Prothrombin
DD	Diastolic Dysfunction
DILI	Drug-induced Liver Injury
DNA	Deoxyribonucleic Acid
EASL-CLIF	European Association for the Study of the Liver-Chronic Liver Failure Consortium
EBV	Epstein Barr Virus
EGD	Esophagogastroduodenoscopy
eGFR	estimated Glomerular Filtration Rate
ELISA	Enzyme-Linked Immunosorbent Assay
EUS	Endoscopic Ultrasound
EV	Esophageal Varices
EVH	Esophageal Variceal Bleeding
EVL	Endoscopic Variceal Ligation
FDA	Food and Drug Administration
FIB-4	Fibrosis-4
GAVE	Gastric Antral Vascular Ectasia

GBD	Global Burden of Disease
GCS	Glasgow Coma Scale
GI	Gastrointestinal
GLS	Global Longitudinal Strain
GOV	Gastroesophageal Varices
HAV	Hepatitis A Virus
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HE	Hepatic Encephalopathy
HELLP	Hemolysis Elevated Liver Enzymes and Low Platelet count
HEV	Hepatitis E Virus
HH	Hepatic Hydrothorax
HPS	Hepatopulmonary Syndrome
HRS	Hepatorenal Syndrome
HSV	Herpes Simplex Virus
HVPG	Hepatic Venous Pressure Gradient
ICA	International Club of Ascites
ICU	Intensive Care Unit
IgM	Immunoglobin M
Igs	Immunoglobulins
INR	International Normalized Ratio
ISHEN	International Society for Hepatic Encephalopathy and Nitrogen Metabolism
KCC	King’s College Criteria
LSM	Liver Stiffness Measurement
LVEF	Left Ventricular Ejection Fraction
LVP	Large Volume Paracentesis
MAMC	Mid-arm Muscle Circumference
MAP	Mean Arterial Pressure

MASH	Metabolic Dysfunction-Associated Steatohepatitis
MASLD	Metabolic Dysfunction-Associated Steatotic Liver Disease
MDR	Multi-drug Resistance
MDRO	Multi-drug Resistance Organism
MELD	Model for End-stage Liver Disease
MHE	Minimal Hepatic Encephalopathy
MRE	Magnetic Resonance Elastography
MRI	Magnetic Resonance Imaging
MSG	Monosodium Glutamate
NACSELD	North American Consortium for the Study of End-stage Liver Disease
NAFLD	Non-alcoholic Fatty Liver Disease
NGAL	Neutrophil Gelatinase-associated Lipocalin
NO	Nitric Oxide
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
NSBBs	Non-selective Beta Blockers
OGD	OesophagoGastroDuodenoscopy
OHE	Over Hepatic Encephalopathy
PCR	Polymerase Chain Reaction
PEG	Polyethylene Glycol
PH	Portal Hypertension
PHG	Portal Hypertensive Gastropathy
PICD	Paracentesis-induced Circulatory Dysfunction
PIVKA II	Protein Induced by Vitamin K Absence/Antagonist
PPHTN	Portopulmonary Hypertension
PPI	Proton Pump Inhibitor
pSWE	point Shear Wave Elastography
PT	Prothrombin Time
PTFE	Polytetrafluoroethylene
RAAS	Renin-angiotensin-aldosterone System
RCT	Randomized Controlled Trial

RNA	Ribonucleic acid
RRT	Renal Replacement Therapy
SAAG	Serum Ascites Albumin Gradient
SBE	Spontaneous Bacterial empyema
SBP	Spontaneous Bacterial Peritonitis
SEMS	Self-expendable Metal Stent
SIRS	Systemic Inflammatory Response Syndrome
SMA	Smooth Muscle Antibodies
SSM	Spleen Stiffness Measurement
SVR	Sustained Virologic Response
T2DM	Type 2 Diabetes Mellitus
TB	Tuberculosis
TE	Transient Elastography
TIPS	Transjugular Intrahepatic Portosystemic Shunt
TPMT	Thiopurine methyltransferase
TR	Tricuspid Regurgitation
TSF	Triceps Skin Fold
VH	Variceal Hemorrhage
VNT	Varices Needing Treatment
VPTS	Video Assisted Thoracoscopic Surgery
VRE	Vancomycin-resistance Enterococci
VZV	Varicella Zoster Virus
WCG	World Congress of Gastroenterology
WHC	West Haven Criteria
WHO	World Health Organization

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Introduction

Cirrhosis of the liver is a chronic and progressive condition resulting from prolonged liver injury, characterized by significant fibrosis and the formation of regenerative nodules within the liver. This disease typically arises after years of ongoing liver damage due to factors such as chronic alcohol use, viral hepatitis, and Metabolic dysfunction-associated steatotic liver disease (MASLD, formerly termed NAFLD). Over time, continuous injury and scarring compromise liver function, leading to portal hypertension and increased risks of liver failure and liver cancer.

The stages of cirrhosis are divided into two clinical groups: the compensated and the decompensated. According to the recent Baveno VI consensus, these are also coined as compensated advanced chronic liver disease (cACLD) and decompensated advanced chronic liver disease (dACLD) respectively. Patients suffering from cACLD do not have significant damage to the liver and remain symptom-free. However, when the disease has progressed to dACLD, it is accompanied by significant complications such as ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepato-renal syndrome, variceal bleeding, and jaundice indicating liver dysfunction. These complications frequently cause impairment in the quality of life and raise risks of death.

Modern diagnostic methods, including non-invasive imaging and laboratory assessments, have facilitated the early identification of cirrhosis. Current treatment guidance emphasizes a comprehensive approach that addresses the underlying cause, monitors disease progression, and manages complications. Liver transplantation remains the definitive therapy for suitable patients with end-stage disease. Through preventive and therapeutic measures, this guidance aims to provide clinicians with effective, evidence-based strategies for managing cirrhosis both cACLD and dACLD, ultimately improving patient outcomes and quality of life.

1. Definition and Epidemiology of Cirrhosis of Liver

1.1 Definition of Cirrhosis of Liver

Cirrhosis is defined anatomically as a diffuse process with fibrosis and nodule formation. It is the end result of the fibrogenesis that occurs with chronic liver injury. [1]

Fibrosis is a reversible scarring response that occurs in almost all patients with chronic liver injury. Ultimately, hepatic fibrosis leads to cirrhosis, characterized by nodule formation and organ contraction. The exact moment when fibrosis becomes irreversible is not known, in terms of either a histologic marker or a specific change in the matrix composition or content.[2]

Dense cirrhosis, with nodule formation and portal hypertension, is generally considered irreversible. Irreversibility may be conferred by the density and cellularity of the septal scars, leading to the loss of sources of interstitial collagenases.[2]

1.2. Epidemiology of Cirrhosis of Liver

1.2.1 Prevalence of Cirrhosis of Liver

In the Global Burden of Disease (GBD) Study 2017, the estimated number of people with compensated cirrhosis was 112 million worldwide, corresponding to an age-standardized global prevalence of compensated cirrhosis of 1,395 cases per 100,000 populations. [3] COL is a leading cause of death worldwide; it was associated with 2.4% of global deaths in 2019. [4]

1.2.2 Etiologies of Cirrhosis of Liver

The major etiologies of cirrhosis are hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcohol-associated liver disease, and non-alcoholic fatty liver disease (NAFLD). [5] Internationally, within the cohort of individuals diagnosed with cirrhosis, 42% were afflicted with HBV infection, while 21% presented HCV infection. When examined through the lens of WHO regions, the prevalence of HBV infection among cirrhotic patients peaked in the Western Pacific region (59%), contrasting sharply with its nadir in the Americas (5%). Conversely, the highest incidence of HCV infection within this demographic was observed in the Eastern Mediterranean region (70%), whereas Africa and the Western Pacific displayed the lowest rates (both 13%). The incidence of cirrhosis attributed to heavy alcohol consumption was notably elevated in Europe (16–78%) and the Americas (17–52%), though comparatively subdued in Asia (0–41%). Data pertaining to the prevalence of NAFLD among cirrhotic patients were somewhat constrained yet estimates ranged from 2% in South Korea

and Brazil to 18% in Canada. [6] However, the past decade has seen major changes in the etiology and burden of liver disease. [7]

1.2.2.1 Trends in the Etiology of Cirrhosis of Liver

In the Americas, the etiology of cirrhosis is undergoing a transformation. Formerly dominated by active HBV and HCV infections, the landscape is now characterized by resolved or managed viral hepatitis, alcohol abuse, and NAFLD. These trends correlate with the escalating rates of obesity and alcohol intake observed across the region. [8]

Within the European context, there is a discernible upward trend in the prevalence of cirrhosis attributed to non-alcoholic fatty liver disease (NAFLD), juxtaposed with a concurrent decrease in cases linked to alcohol consumption. This decline in alcohol-associated cirrhosis may be attributed to the implementation of public health policies, including the enforcement of minimum pricing for alcohol and heightened taxation. Furthermore, the data indicate a diminishing prevalence of cirrhosis associated with hepatitis C virus (HCV) and hepatitis B virus (HBV) infections across Europe. [9]

Data concerning the Southeast Asia region are notably limited. In a study encompassing 4,413 cirrhotic patients across 11 hospitals in India, alcohol consumption emerged as the predominant etiology (34%), succeeded by other causative factors (29%), HBV infection (18%), HCV infection (17%), and NAFLD (2%). [10] Conversely, among 192 cirrhotic individuals subjected to endoscopic band ligation at a hospital in Pakistan, HCV infection accounted for 63% of cases, while HBV infection was implicated in 19%. [11]

Studies in the Western Pacific region have shown that NAFLD-associated and alcohol-associated cirrhosis are increasing in this region, but viral hepatitis remains the dominant cause of cirrhosis. [12]

1.2.2.2 Predictions for Etiology of Cirrhosis of Liver

HCV-associated Cirrhosis of Liver

The integration of a comprehensive literature review, a Delphi process, and Markov modeling facilitated the projection of the burden of incident decompensated cirrhosis associated with hepatitis C virus (HCV) for the year 2030. This collaborative approach yielded an estimated escalation from 148,000 cases in 2020 to 174,000 cases globally by 2030. [13]

HBV-associated Cirrhosis of Liver

Data on the projected global burden of HBV-associated cirrhosis are limited. Projections in one study suggest that the incidence of HBV infection will fall by 2030 but that HBV-related deaths will increase by 39% between 2015 and 2030. [14]

Despite the presence of vaccines and life-saving antiviral therapy, hepatitis B virus (HBV) infection continues to be significantly underdiagnosed. Consequently, only a minority of patients eligible for treatment receive antiviral therapy, further compounded by hindrances to HBV elimination efforts globally due to the COVID-19 pandemic. These observations underscore the persistence of HBV as a substantial public health menace in the forthcoming decade. [15]

Alcohol-associated Cirrhosis of Liver

A study conducted in the United States projected a notable surge of 77% in the age-standardized incidence of decompensated alcohol-associated cirrhosis, anticipated to rise from 9.9 cases per 100,000 patient-years in 2019 to 17.5 cases per 100,000 patient-years by 2040.[16]

MASLD-associated Cirrhosis of Liver

Projections indicate a substantial escalation in incident decompensated cirrhosis associated with Metabolic-Dysfunction associated Steatotic Liver Disease (MASLD) across several Asian regions. Between 2019 and 2030, forecasts anticipate a 65% increase in Hong Kong, an 85% increase in South Korea, and a 100% increase in Singapore and Taiwan. [17]

2. Diagnosis, and Prognosis of Cirrhosis of Liver

2.1 Diagnosis of Cirrhosis of Liver

2.1.1 Clinical

In clinical terms, cirrhosis is described as either ‘compensated’ or ‘decompensated’. This is an important clinical distinction. The natural history of cirrhosis is characterized by an asymptomatic compensated phase followed by a decompensated phase.

2.1.1.1 Compensated cirrhosis

Patients with compensated cirrhosis are typically asymptomatic and may be picked up as a result of abnormalities found on routine blood tests or signs found on clinical examination, for example, hepatomegaly, splenomegaly, vascular spiders, palmar erythema, and so on. Not

all compensated cirrhotic are the same. Decompensation may occur at a rate of 5–7% per year and may be precipitated by bacterial infection, surgery, trauma, or medication. [1]

2.1.1.2 Decompensated cirrhosis

Decompensated cirrhosis is marked by the development of overt clinical signs, the most frequent of which are ascites, bleeding, encephalopathy, and jaundice. Following the first appearance of any of these, the disease usually progresses more rapidly towards death or liver transplantation. [18]

2.1.2 Laboratory

2.1.2.1 FIB-4 score

FIB-4 = Age (years)×AST (U/L)/ [PLT (10^9/L) ×$ALT^{1/2}$ (U/L)].

The FIB-4 index is a simple non-invasive approach using selected laboratory measures (AST, ALT, platelet count) in combination with patient age. FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis. In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. [19]

2.1.2.2 APRI score

APRI score means AST to platelet ratio index.

APRI = [{AST (IU/L)/ AST_ULN (IU/L)} ×100]/platelet count (10^9/L)

Evidence of significant fibrosis (≥F2) should be based on an APRI score of >0.5 and cirrhosis (F4) should be based on an APRI score of >1.0. [25]

2.1.2.3 Platelet Count

Platelet count is a simple test. Unlike APRI and FIB-4, the platelet count has not been used alone to evaluate hepatic fibrosis. However, platelets have significant change in patients with liver fibrosis, and platelets as an indicator are involved in many conventional combination models of liver fibrosis. [20] Thrombocytopenia (platelet count < 150000/μL) is one of the most common abnormalities in patients with cirrhosis, seen in up to 78% of cirrhotic patients. [21]

2.1.3 Imaging

2.1.3.1 Ultrasound

USG is a useful technique to assess morphological and structural changes to the liver and is useful in evaluating cirrhosis. However, it is not sensitive for evaluating and staging

early fibrosis. D'Onofrio and colleagues reported conventional USG has a sensitivity of only 25% in identifying liver fibrosis in chronic liver disease. [22]

2.1.3.2 Computed tomography (CT)

CT is useful in assessing morphological features for the diagnosis of liver fibrosis and cirrhosis. However, CT is not considered to be sensitive enough for staging less advanced stages of liver fibrosis. [22]

2.1.3.3 MRI

MRI can evaluate morphologic and structural changes related to liver fibrosis. Imaging features include surface nodularity, widening of fissures, expanded gallbladder fosse sign, posterior hepatic notch sign, increased caudate to right lobe ratio, enlargement of the lateral segments of the left lobe and caudate lobe, regenerative nodules, splenomegaly, portosystemic varices, and ascites. However, in terms of diagnosis of early-stage liver fibrosis, the technique is less sensitive. [22]

2.1.3.4 Transient elastography

Liver fibrosis can be staged using 1-dimensional ultrasound TE, which measures the velocity of a low-frequency (50 Hz) elastic shear wave propagating through the liver. This velocity is directly related to tissue stiffness. The stiffer the tissue, the faster the shear wave propagates. The results are expressed in kilopascals (kPa) and range from 1.5 to 75 kPa with normal values around 5 kPa. (23,24). LSM > 12.5 kPa should be considered as cirrhosis. Transient elastography (FibroScan®) is no longer contraindicated in pregnancy. [25]

2.1.3.5 Liver biopsy

Liver histology remains the gold standard in all liver diseases for determining the pattern and severity of necro-inflammatory activity and fibrosis, including any remodeling of the parenchyma. However, liver biopsy can have multiple potential complications like pain and bleeding (including death) that may occur after liver biopsy and discuss these appropriately with their patients beforehand. [26] Therefore, liver biopsy is not recommended as a routine assessment for liver fibrosis in Myanmar.

2.2 Prognosis

When assessing the prognosis of cirrhosis of the liver, healthcare providers often use two scoring systems: the Child-Pugh score and the Model for End-Stage Liver Disease

(MELD) score. These scores help determine the severity of liver disease and predict patient outcomes. [27]

2.2.1 Child-Pugh Score

The Child-Pugh score is based on five clinical measures: total bilirubin levels, serum albumin levels, prothrombin time, presence of ascites, and presence of hepatic encephalopathy. Each measure is assigned a score from 1 to 3, with higher scores indicating more severe liver dysfunction. The total score is then used to classify patients into three categories: Class A (5-6 points), Class B (7-9 points), and Class C (10-15 points).

These classes correlate with one-year survival rates for patients with Child-Pugh class A, B, and C cirrhosis approximately 100, 80, and 45 percent, respectively. Treatment decisions for patients with cirrhosis are often guided by their Child-Pugh score. Patients with well-compensated cirrhosis (Child-Pugh Class A) may benefit from lifestyle modifications, surveillance for complications, and management of underlying liver disease. Patients with decompensated cirrhosis (Child-Pugh Class B or C) may require more intensive medical management, including medications to manage symptoms, procedures to address complications, and evaluation for liver transplantation.

Table (1) Child-Pugh Classification of Severity of Cirrhosis of Liver

Child-Pugh classification of severity of cirrhosis

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time (seconds over control) or	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

2.2.2 MELD Score

The MELD score is calculated based on the patient's serum creatinine, total bilirubin, and international normalized ratio (INR) levels. The formula for calculating the MELD score is: MELD = 3.78 x ln (serum bilirubin mg/dL) + 11.2 x ln (INR) + 9.57 x ln (serum creatinine mg/dL) + 6.43. The MELD score ranges from 6 to 40, with higher scores indicating a higher risk of mortality.

MELD scores below 10 are associated with a lower risk of mortality, while scores above 20 indicate a higher risk of mortality. MELD score is commonly used to prioritize patients for liver transplantation, with higher scores indicating greater urgency.

Patients with higher Child-Pugh scores (Class B and C) and higher MELD scores are at increased risk of complications such as variceal bleeding, hepatic encephalopathy, and hepatorenal syndrome.

2.2.3 MELD-Na Score

Adds sodium to the MELD model for liver cirrhosis.

MELD-Na = MELD + 1.32 x (137-Na) - [0.033 x MELD * (137-Na)]

In the MELD-Na equation, sodium values less than 125 mmol/L are set to 125, and values greater than 137 mmol/L are set to 137.

Hyponatremia is a common problem in patients with cirrhosis, and the severity of hyponatremia is a marker of the severity of the cirrhosis. Serum sodium reflects the vasodilatory state in cirrhosis and predicts waitlist mortality independent of the original MELD score. There is a linear increase in mortality by 5 percent for each mmol decrease in serum sodium between 125 and 140 mmol/L. Multiple studies have shown that the addition of serum sodium concentration improved the predictive accuracy of the original MELD score in hyponatremic patients with low MELD scores who were awaiting liver transplantation. Adding serum sodium to the MELD model elevated the transplant priority for about 12 percent of listed patients.

Limitations of the MELD-Na score included that serum sodium levels may be vulnerable to alterations by diuretic use and intravenous fluid administration and that variables of patient sex and serum albumin were not included.

2.3 Monitoring and Follow-Up

Patients with cirrhosis should undergo regular monitoring of their Child-Pugh and MELD scores to assess disease progression and response to treatment. Changes in these scores over time can indicate worsening or improvement of liver function and help guide adjustments in management. Close follow-up is essential for patients with cirrhosis to prevent complications and optimize outcomes.

In conclusion, the Child-Pugh and MELD scores are valuable tools in assessing the prognosis of cirrhosis of the liver and guiding clinical management. By understanding the

implications of these scoring systems and incorporating them into patient care, healthcare providers can optimize outcomes for patients with cirrhosis and provide individualized treatment plans based on their unique disease severity and prognosis.

Recommendation (Epidemiology, Diagnosis, and Prognosis of Cirrhosis of Liver)

1. In Myanmar, the major etiologies of cirrhosis are hepatitis B virus (HBV), hepatitis C virus (HCV) infection, and alcohol-associated liver disease.
2. The Trends in the etiology of cirrhosis may be changing in other countries. However, viral hepatitis still remains the major etiologies of cirrhosis in Myanmar.
3. For compensated cirrhosis, patients are usually asymptomatic and can be detected in routine medical check-ups. Diagnosis can be roughly made by US. However, its sensitivity is low and should be confirmed by non-invasive testing like FIB-4, APRI and transient elastography if possible. APRI > 1.0 and LSM > 12.5 kPa should be considered as cirrhosis.
4. For decompensated cirrhosis, diagnosis can be made by overt clinical signs.
5. CT and MRI are not routinely done for assessment of liver cirrhosis and are considered only in cases suspected of HCC.
6. Liver biopsy is not recommended as a routine assessment for liver fibrosis in Myanmar.
7. Child-Pugh score is a valuable tool in assessing the prognosis of cirrhosis of the liver and guiding clinical management. MELD and MELD-Na scores are more useful in patients who are awaiting liver transplantation.

3. Clinical Manifestations of Cirrhosis

Patients with compensated cirrhosis may be asymptomatic or may present with nonspecific symptoms, such as anorexia, weight loss, weakness, fatigue, and muscle wasting.[28] Patients with decompensated cirrhosis may present with jaundice, pruritus, signs of upper gastrointestinal bleeding (hematemesis, melena, hematochezia), abdominal distension from ascites, or confusion or sleep disturbances due to hepatic encephalopathy.

Patients with cirrhosis may present with diarrhea due to multifactorial causes (eg, alterations in small bowel motility, changes in intestinal permeability, and bile acid deficiency). Patients with cirrhosis may experience muscle cramps which may be related to a reduction in effective circulating plasma volume.

Cutaneous manifestations of cirrhosis include jaundice, spider angiomata, skin telangiectasias (termed "paper money skin" by Dame Sheila Sherlock), palmar erythema, white nails, disappearance of lunulae, and finger clubbing, especially in the setting of hepatopulmonary syndrome. [28] Patients with cirrhosis may experience gynecomastia and impotence, loss of axillary and pubic hair from increased conversion of androgenic steroids into estrogens. Spider angiomata and palmar erythema may also develop after hyperestrogenemia. [28] Major complications of cirrhosis will be discussed in separate chapters.

3.1 Hematologic Manifestations

Anemia may result from folate deficiency, hemolysis, or hypersplenism. Thrombocytopenia usually is secondary to hypersplenism and decreased levels of thrombopoietin. Coagulopathy results from decreased hepatic production of coagulation factors. If cholestasis is present, decreased micelle entry into the small intestine leads to decreased vitamin K absorption, resulting reduction in hepatic production of factors II, VII, IX, and X. Patients with cirrhosis also may experience fibrinolysis and disseminated intravascular coagulation. [28]

3.2 Pulmonary and Cardiac Manifestations

Patients with cirrhosis may have impaired pulmonary function. Pleural effusions and the diaphragmatic elevation caused by massive ascites may alter ventilation-perfusion relations. Interstitial edema or dilated precapillary pulmonary vessels may reduce pulmonary diffusing capacity. [28]

Patients also may have hepato-pulmonary syndrome (HPS). In this condition, pulmonary arteriovenous anastomoses result in arteriovenous shunting. HPS is a potentially progressive and life-threatening complication of cirrhosis. Classic HPS is marked by the symptom of platypnea (shortness of breath relieved when lying down and worsened when sitting or standing), and the finding of orthodeoxia (decrease in the arterial oxygen tension when the patient moves from a supine to an upright position), but the syndrome must be considered in any patient with cirrhosis who has evidence of oxygen desaturation. [28]

Porto-pulmonary hypertension (PPHTN) is observed in up to 6% of patients with cirrhosis. PPHTN is defined as the presence of a mean pulmonary artery pressure of greater than 25 mm Hg in the setting of a normal pulmonary capillary wedge pressure.

Cirrhotic cardiomyopathy refers to chronic cardiac dysfunction in a patient with established cirrhosis, characterized by a blunted contractile response to stress (pharmacological/surgical or inflammatory) and an altered diastolic relaxation, often associated with electrophysiological abnormalities such as prolongation of the QTc interval. These phenomena occur in the absence of any other cardiac disease. [28]

3.3. Clinical Cirrhosis

Clinically, cirrhosis presents in two main stages: compensated and decompensated. Decompensation most commonly occurs when portal pressure gradients are at or exceed 10 mmHg (measured by the hepatic venous pressure gradient or HVPG). This pressure gradient is defined as “clinically significant portal hypertension” or CSPH. [29]

Decompensation is defined by the development of clinically overt complications of portal hypertension, specifically overt ascites, variceal hemorrhage, or overt hepatic encephalopathy (HE). Although the median survival in the patient who is compensated exceeds 12 years, once a patient develops a decompensating event, median survival decreases to less than 1.5 years. [30]

Table (2) Stages of Cirrhosis of Liver

Stages of chronic liver disease	Compensated cirrhosis		Decompensated cirrhosis
	Lower risk of decompensation	Higher risk of decompensation	
Clinical features (ascites, VH, or HE)	None	None	One or more event
HVPG	5-10	>10 (CSPH)	> 20
Endoscopic features	No varices	± Varices	± Varices

3.3.1 Compensated Cirrhosis of Liver

Patients with compensated cirrhosis are typically asymptomatic and may be diagnosed as a result of abnormalities found on routine blood tests or clinical examination. Not all compensated cirrhotic patients are the same. The presence of esophageal or gastric varices, indicative of the presence of clinically significant portal hypertension is associated with a worse prognosis. [29]

Because of the strong association with clinical outcomes, patients with compensated cirrhosis should be subclassified into those without and with CSPH. Decompensation may occur at a rate of 5–7% per year and may be precipitated by bacterial infection, surgery, trauma, medication, or malignant change. Hepatocellular carcinoma occurs at a rate of 1–3% per year and screening with biannual ultrasound and AFP is recommended. [29]

3.3.2 Decompensated Cirrhosis of Liver

Decompensation most commonly occurs when portal pressure gradients are at or exceed 10 mmHg, measured by the hepatic venous pressure gradient. Among patients with decompensated cirrhosis, those who develop successive complications (i.e., recurrent variceal hemorrhage, refractory ascites, hepatorenal syndrome, spontaneous bacterial peritonitis, jaundice) exhibit much higher mortality rates; this stage has now been designated as “further decompensation”. [30]

3.3.3 Reversibility of Cirrhosis of Liver

Cirrhosis is usually believed to be irreversible. However, fibrosis may regress if the initiating insult is removed, for example, hepatitis C, biliary obstruction, obesity, or iron overload. In most cases repeat liver biopsies have shown a lesser degree of fibrosis rather than

a reversion to normal liver. Reversal of human cirrhosis is probably a slow process and may take several years. [29] Not all patients with cirrhosis have a reversible disease. Patients in the earlier stages of cirrhosis are more likely to witness the reversal of cirrhosis. Although the point at which cirrhosis is irreversible is not established, cirrhosis becomes irreversible once septal neovascularization happens and portal pressure increases significantly. [31]

Recommendation (Clinical Cirrhosis of Liver)

8. Clinically significant portal hypertension can be diagnosed by the presence of clinical decompensation or of gastroesophageal varices on endoscopy, or portosystemic collaterals or hepatofugal flow on Doppler USG as HVPG is not available in Myanmar.
9. Vibration-controlled transient elastography is widely available in Myanmar and liver stiffness measurement by TE can be used to noninvasively identify CSPH in combination with platelet count.
10. CSPH can also be diagnosed when LSM > 25KPa or LSM 20-24.9 with platelet count < 150 or LSM 15-19.9 with platelet count < 110.
11. According to Baveno VII criteria, CSPH can be ruled out if LSM < 15 kPa and platelet count > 150 K/mm3.
12. Endoscopy is recommended in patients with CSPH (LSM > 20 and platelet count <150).
13. Fibroscan assessment should be in an optimal setting (fasting > 3hr) and should be done by trained operator.

4. Management

4.1 General Management of Cirrhosis of Liver

The management of the compensated cirrhotic patient is directed towards the maintenance of an adequate balanced diet, avoidance of alcohol and obesity, early detection of hepatocellular carcinoma, fluid retention, and encephalopathy, maintenance of renal function, and prevention of variceal hemorrhage. Treatment in the decompensated cirrhotic patient is directed towards the specific form of decompensation, for example, hepatic encephalopathy, ascites, and variceal bleeding. In many cases, the episode of decompensation is precipitated by an event such as sepsis, hypotension, or injudicious medications. Identification and treatment of these precipitating causes may help to return the patient to a compensated state. [29]

Recommendation (General Management of Cirrhosis of Liver)

14. Lifestyle modification and treatment of underlying liver disease is recommended to prevent progression to CSPH and decompensation in all stages of cirrhosis.
15. In patients with compensated cirrhosis and CSPH, the goal of therapy is to prevent the development of clinical decompensation**.**
16. NSBBs (preferably carvedilol 12.5 mg/day) should be considered for patients with clinically advanced liver disease with CSPH to prevent decompensation.
17. NSBBs should not be administered to patients with asthma, advanced heart block, and bradyarrhythmia, and caution should be used in patients with chronic obstructive pulmonary disease and peripheral arterial diseases.

4.1.1 Pain Management

The general approach to chronic pain management for patients with cirrhosis can be divided into pharmacological and nonpharmacological approaches. The first step in addressing pain is to assess and treat reversible causes (e.g., tense ascites, local infection, and musculoskeletal injury). The chronicity of pain also determines the approach. For example, acute pain (≤12 weeks) is more responsive to short-term opioid therapy than chronic pain. Optimal chronic pain management often involves multimodal, nonpharmacological approaches, including behavioral management, physical therapy, and procedural approaches.[32]

Recommendation (Pain Management in Cirrhosis of Liver)
18. Assessment and treatment of reversible causes of pain should be addressed first.
19. Localized pain (e.g., knee osteoarthritis) should be addressed with local, rather than painkillers**.**
20. Acetaminophen, 500 mg every 6 h, up to a maximum dose of 2 g/d, is the preferred first-line pharmacotherapy for the management of pain in patients with cirrhosis.
21. Systemic NSAIDs should be avoided in patients with cirrhosis.
22. Opioids should be avoided, when possible, for chronic pain. When necessary, opioids should be used with caution with appropriate laxatives.

4.1.2 Muscle Cramps Management

Muscle cramps are common in cirrhosis and negatively impact health-related quality of life. Alterations in nerve function, energy metabolism, plasma volume, and electrolytes may contribute to the development of muscle cramps. Muscle cramping associated with cirrhosis is often spontaneous, intermittent, and nocturnal. [32]

Recommendation (Muscle Cramps Management in Cirrhosis of Liver)
23. Checking serum electrolyte levels and repleting potassium, magnesium, and zinc is the first step in the management of muscle cramps in patients with decompensated cirrhosis.
24. Taurine (2–3 g daily), vitamin E (200 mg three times a day), and baclofen (5–10 mg three times a day) can be considered in patients with cirrhosis and significant muscle cramps**.**

4.1.3 Pruritus Management in Cirrhosis of Liver

Pruritus is a common symptom in patients with cirrhosis of all etiologies, although it disproportionately affects patients with cholestatic liver diseases. [32]

Recommendation (Pruritus Management in Cirrhosis of Liver)
25. Pruritus should be approached starting with nonpharmacological options, including using moisturizing creams, avoiding hot baths and harsh soaps, and using loose-fitting clothes and cool humidified air.
26. Cholestyramine (4g/day with titration up to 16 g/day if needed) is recommended as first-line treatment for pruritus.
27. Low-dose naltrexone, Rifampicin (in anicteric patients), and sertraline can be considered as alternative agents, but these agents require careful titration in decompensated cirrhosis.

4.2 Specific Management of Cirrhosis of Liver

If the cause of cirrhosis is known, then specific treatment should be given. Antiviral treatment can eliminate the virus in hepatitis C and suppress it in hepatitis B. Liver function typically improves with antiviral treatment. Steroids and immunosuppressive drugs can be used in autoimmune hepatitis. Ursodeoxycholic acid should be given early in the course of primary biliary cirrhosis and continued long-term. Wilson's disease is treated with chelation therapy and hemochromatosis with venesection. In alcoholic cirrhosis, abstinence is essential. Weight loss may be beneficial in MASH cirrhosis.

4.2.1 Antiviral therapy for HBV-related Cirrhosis of Liver

Antiviral therapy can suppress HBV replication in patients with HBV-related cirrhosis. Patients with compensated or decompensated cirrhosis need treatment, with any detectable HBV DNA level regardless of ALT levels. The long-term administration of a potent nucleotid(s)e analogue with a high barrier to resistance is the treatment of choice. The main goal of therapy is to improve survival and quality of life by preventing disease progression, and consequently HCC development.

Recommendation (Antiviral therapy for HBV-related Cirrhosis of Liver)
28. The preferred antivirals are Entecavir, Tenofovir Disoproxil Fumarate, and Tenofovir Alafenamide as monotherapy.

4.2.2 Antiviral therapy for HCV-related Cirrhosis of Liver

Treatment with direct-acting antivirals (DAAs) regimens can achieve high sustained virological response (SVR) rates exceeding 90% without serious adverse reactions. SVR will provide significant reversion of the fibrosis and prevention of HCC.

Patients with decompensated cirrhosis without concomitant co-morbidities that could impact their survival should be treated urgently. Patients with decompensated cirrhosis without HCC can be treated prior to liver transplantation. Treatment should be initiated as soon as possible in order to complete a full treatment course before transplantation and assess the effect of viral clearance on liver function because significant improvement in liver function may lead to deferring liver transplant in selected cases. [33]

Ribavirin should be added in genotype 3 treatment naïve cirrhotic patients or treatment-experienced patients who have Y93H mutation and decompensated cirrhotic patients. More frequent monitoring with full blood count is recommended if Ribavirin is used. Ribavirin should not be used in women of childbearing potential and their partners during and 6 months prior to pregnancy. [34]

Recommendation (Antiviral therapy for HCV-related Cirrhosis of Liver)
29. Sofosbuvir 400mg + Velpatasvir 100mg for 12 weeks is the preferred regimen in compensated cirrhotic patients.
30. For decompensated cirrhotic patients -
- Sofosbuvir + Velpatasvir plus weight-based Ribavirin for 12 weeks or
- Sofosbuvir + Velpatasvir for 24 weeks in Ribavirin ineligible patients
- Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis of liver.

4.2.3 Therapy for Alcohol-related Cirrhosis of Liver

Patients with alcohol-related cirrhosis should be advised and encouraged to achieve complete abstinence from alcohol to reduce the risk of liver-related complications and mortality. [35]

Recommendation (Therapy for alcohol-related Cirrhosis of Liver)
31. Alcohol should be completely stopped. 32. Considering the potential risk of Wernicke's encephalopathy, supplementation with B-complex vitamins is recommended.

4.2.4 Therapy for MASLD-related Cirrhosis of Liver

The prevalence of MASLD and MASH is rising worldwide in parallel with increases in the prevalence of obesity and metabolic comorbid diseases (insulin resistance, dyslipidemia, central obesity, and hypertension). If not properly treated, the situation can progress to MASH and cirrhosis of liver and even HCC. [36]

MASH-related cirrhosis is already the leading indication for liver transplantation in women and those >65 years of age in the United States and is on par with alcohol as the leading indication overall. [36]

Recommendation (Therapy for MASLD-related Cirrhosis of Liver)

33. Dietary and behavioral therapy-induced weight loss is recommended in MASLD patients to improve liver injury.
34. For overweight/obese patients, weight reduction should be ≥ 5% to reduce liver fat, 7-10% to improve liver inflammation, and ≥ 10% to improve fibrosis.
35. Diet and exercise interventions are also recommended to reduce liver fat in normal-weight adults with MASLD.
36. Patients with MASLD who are overweight or obese should be prescribed a diet that leads to a caloric deficit. Diets with limited carbohydrates and saturated fat and enriched with high fiber and unsaturated fats (e.g., Mediterranean diet) should be encouraged due to their additional cardiovascular benefits.
37. Patients with MASLD should be strongly encouraged to increase their activity level to the extent possible.
38. Recently US FDA approved Resmetiron should be used whenever available in patients with non-cirrhotic MASH with significant liver fibrosis (stage ≥2).
39. Vitamin E can be considered in selected individuals as it improves MASH in some patients without diabetes after counseling potential risks of long-term use.
40. Semaglutide can be considered for its approved indications (T2DM/obesity) in patients with MASH, as it confers a cardiovascular benefit and improves MASH.
41. Pioglitazone improves MASH and can be considered for patients with MASH in patients with T2DM.

4.2.5 Therapy for Autoimmune Hepatitis (AIH) with Cirrhosis of Liver

Autoimmune Hepatitis is characterized by immune-mediated injury to hepatocytes. AIH can present at any age. Most patients with AIH present with chronic nonspecific symptoms (fatigue, malaise, arthralgias, or amenorrhea). Easy fatigability is present in 85% of patients, and jaundice may be present. Untreated autoimmune hepatitis can lead to cirrhosis and eventually to liver failure. [37]

The aim of treatment in AIH is to improve symptoms, control hepatic inflammation, achieve biochemical remission, prevent disease progression, and promote the regression of

fibrosis at the lowest risk of drug-induced complication. First-line treatment of AIH patients is prednisolone alone, 40-60 mg daily in adults, or a lower dose of prednisolone, 20-40 mg daily, in combination with Azathioprine. However, in patients with decompensated cirrhosis, Azathioprine is not recommended because the risk of hepatotoxicity of Azathioprine is increased in patients with advanced liver disease. In cirrhotic patients, budesonide should not be used as portosystemic shunting may reduce drug efficacy and promote steroid-specific side effects by allowing budesonide to bypass the liver. Portal vein thrombosis has also been reported in patients with cirrhosis taking budesonide. [37]

Recommendation (Therapy for Autoimmune Hepatitis (AIH) with Cirrhosis of Liver)
42. First-line treatment in AIH patients with compensated cirrhosis is steroid therapy followed by Azathioprine after checking the TPMT level if available. 43. Azathioprine should not be used in decompensated cirrhotic patients. 44. Budesonide should not be used in cirrhotic patients.

4.2.6 Elimination of Precipitating Factors

Table (3) Factors associated with decompensation of compensated liver cirrhosis

Risk factors for non-acute decompensation	Precipitating factors for acute decompensation
(a) Thick fibrous septa and micronodularity on liver biopsy (b) Persistent liver injury by etiological factor (c) High portal pressure (d) Systemic inflammation & hemodynamic changes (e) Metabolic risk factors: DM, obesity, and dyslipidemia (f) Genetic risk factors: PNPLA3 G/G genotype	(a) Bacterial infection (b) Active alcoholism (c) Gastrointestinal hemorrhage (d) Consumption of hepatotoxic drug/alternative medicine (e) Superinfection or flare of viral hepatitis (f) Major surgery and general anesthesia

Several precipitating events can lead to the abrupt worsening of the clinical condition of cirrhotic patients by causing ACLF. Thus, controlling such precipitating variables can thereby significantly reduce cirrhosis-related morbidity and mortality. Antibiotic prophylaxis and prompt, judicious antibiotic treatment can aid in the prevention of ACLF triggered by infection. Prophylactic antibiotics in conjunction with effective gastrointestinal bleeding management can prevent precipitating ACLF. [38]

Another important preventive strategy is vaccination for viral hepatitis. For all cirrhotic patients, hepatitis B vaccine is advised. However, compared to normal subjects, patients with cirrhosis achieve lower seroprotection rates following HBV vaccination (mean response rate of 47%). Hepatitis E virus (HEV) and hepatitis A virus (HAV) superinfection is another well-known cause of ACLF in endemic areas. While many nations recommend HAV immunization for CLD patients, routine vaccination is not advised in Myanmar, where most of the adults already have exposure to hepatitis A.

Recommendation (Elimination of Precipitating Factors)

45. Every cirrhotic patient who are not immune to HBV should receive hepatitis B vaccination.
46. Cirrhotic patients should avoid precipitating factors that can cause acute and non-acute liver injury like alcohol and hepatotoxic drugs.
47. Early recognition and management of bacterial infection and GI hemorrhage is recommended in cirrhotic patients.
48. Influenza and pneumococcal vaccines are recommended.

4.3 Nutrition therapy in Cirrhosis of Liver

Cirrhosis is a major predisposing condition for the development of malnutrition, frailty, and sarcopenia. The presence of malnutrition and sarcopenia worsens the prognosis of cirrhosis and leads to adverse health outcomes including hepatic decompensation, increased healthcare use, worse health-related quality of life, adverse post-transplant outcomes, and increased overall risk of death. [39] Malnutrition has been reported in 20% of patients with compensated cirrhosis and in more than 50% of patients with decompensated liver disease. [40]

Patients with cirrhosis frequently have either global malnutrition or alteration in specific aspects of nutritional status, such as micro-nutrients deficiency due to multiple mechanisms, including poor nutritional intake and poor absorption. [39]

4.3.1 Malnutrition

A nutrition-related disorder resulting from “an imbalance (deficiency or excess) of nutrients that leads to altered body composition and body cell mass, leading to diminished physical and mental function and impaired clinical outcome from disease. [39]

4.3.2 Frailty

Loss of functional, cognitive, and physiologic reserve leading to a vulnerable state. Frailty may be considered a form of nutrition-related disorder. [40]

4.3.3 Sarcopenia

A generalized reduction in muscle mass and function due to aging (primary sarcopenia), acute or chronic illness (secondary sarcopenia), including chronic liver disease. [40]

4.3.4 Sarcopenic Obesity

The combination of loss of skeletal muscle and gain of adipose tissue is termed sarcopenic obesity and is observed in a significant number of patients with MASH related cirrhosis. [40]

4.3.5 Mechanism of Sarcopenia in Cirrhosis of Liver

Skeletal muscle mass is the largest protein store in the body. A balance between skeletal muscle protein synthesis and break down is responsible for protein homeostasis (or proteostasis) that maintains skeletal muscle mass. [41-43]

Hepatocellular dysfunction and portosystemic shunting also result in biochemical and hormonal perturbations in cirrhosis that contribute to sarcopenia. Increased skeletal muscle ammonia, reduction in testosterone and growth hormone, endotoxemia, as well as decreased dietary nutrient intake contribute to sarcopenia. In addition, altered protein metabolism, particularly of branched-chain amino acids (BCAAs) that are essential for supporting glutamine synthesis and extrahepatic ammonia detoxification, results in reduced levels of circulating BCAAs, which leads to accelerated muscle breakdown. [40]

4.3.6 Assessment of Malnutrition and Sarcopenia in Cirrhosis of Liver

The components of a detailed nutritional assessment include evaluation of muscle mass, global assessment tools, and a detailed dietary intake assessment. Body mass assessment can be performed by simple bedside anthropometric methods including mid-arm muscle

circumference (MAMC), mid-arm muscular area, and Triceps skin fold (TSF), which are simple to perform, rapid, low cost, and not affected by the presence of fluid retention. [44,45]

Direct quantification of skeletal muscle mass requires cross-sectional imaging. Computed tomographic (CT) image analysis at the L3 vertebra is almost universally recognized as a specific method to quantify muscle loss. Sarcopenia can be assessed by skeletal muscle index based on a bioelectrical impedance analyzer (BIA) Measurement of grip strength is used to assess muscle strength. [40]

In a case of fluid retention, body weight should be corrected by evaluating the patient's dry weight by post-paracentesis body weight or weight recorded before fluid retention if available, or by subtracting a percentage of weight based upon the severity of ascites (mild, 5%; moderate, 10%; severe, 15%), with an additional 5% subtracted if bilateral pedal edema is present. [46,47]

4.3.7 Management

In general, oral nutritional supplements are recommended. If patients are not able to maintain adequate oral intake, tube feeding is recommended (even when esophageal varices are present). Parenteral nutrition is safe and improves the mental state in patients with cirrhosis and severe HE.

A decreased serum ratio of BCAA to aromatic amino acids has been associated with a poor prognosis. BCAA supplements, in daily divided doses, may facilitate the provision of an adequate nitrogen intake in patients who are intolerant to meat protein. [48-50] Oral Branched Chain Amino Acids are recommended for cirrhotic patients because it relieve hypoalbuminemia, and hepatic encephalopathy, improve quality of life, and increase muscle mass.

Perioperative supplementation with BCAA-enriched nutrient mixture reduces the morbidity associated with postoperative complications, preserves albumin levels, and shortens the duration of hospitalization of patients undergoing liver resection for HCC. It is also associated with reduced incidence of HCC in patients with CTP A cirrhosis and in patients with a BMI of 25 kg/m^2 or higher. [54]

Timing of nutritional intake is essential to manage nutritional status in patients with cirrhosis. Prolonged periods of fasting should be avoided in cirrhosis, with evidence supporting the benefits in muscle mass of early morning breakfast, late evening snack, and intake of small,

frequent meals and snacks every 3-4 hours while awake.[51,52,53] In a study randomizing 103 patients to daytime or nighttime supplemental nutrition of 710 kcal/day who otherwise had isocaloric, isonitrogenous diets, significant improvement in total body protein and fat-free mass was demonstrated in patients receiving nocturnal supplementation across all Child-Turcotte-Pugh classes. [51]

Calorie needs should be personalized to the patient. Weight-based equations (using ideal body weight). For nonobese patients, the target of at least 35 kcal/kg body weight/day should be used. For obese patients (non-hospitalized, clinically stable), use of caloric targets stratified by BMI: 25-35 kcal/kg/day for individuals with BMI 30-40 kg/m2 and 20-25 kcal/kg/day for individuals with BMI ≥ 40 kg/m^2. [39]

Recommended protein intake for adults with cirrhosis is 1.2-1.5 g/kg ideal body weight per day. For adults with cirrhosis who are critically ill, a target of 1.2-2.0 g/kg ideal body weight per day is recommended. [39]

4.3.7.1 Dietary Tips

For a 60 kg man, daily protein intake should be 72 g to 90 g per day. One serving of meat (around the size of a palm) contains 20g of protein. One large egg contains 6g protein. One cup of milk contains 9 g of protein. One bottle of meal supplement drinks contains 12-15g of protein.

The patients should eat a variety of protein-rich foods at every meal and snack. Eating multiple sources of protein-rich foods will reduce the chance of repetition and food boredom.

The patient should eat 4-6 meals per day, for example, one cup of meal supplement or milk and bread or Myanmar breakfast in the morning (20g), rice and 2 tsp of meat and one egg (around 20g), one meal supplement drink in the afternoon (10g), rice or soup with 2 tsp of meat (13g), late evening snack (10g) will give around 80g of protein per day.

4.3.7.2 Low salt diet

One teaspoon (6 g) of salt (table salt, sea salt, iodized salt) contains 2,300 mg of sodium. Patients with advanced liver disease should consume less than 2,000 mg of sodium per day. In addition to not adding salt to food, it is important to cook and eat foods with low sodium content.

Recommendation (Nutrition Therapy in Cirrhosis of Liver)

49. Recommends 1-1.5 g of protein per kg body weight. [e.g. 70 kg man requires 105 g or 6 ticals (kyat –thar) of protein daily] [1 tical (kyat-thar) = 16 g)].
50. High protein diets are well-tolerated and are associated with sustained improvement in mental status.
51. A diverse range of protein sources, including vegetable and dairy products, should be encouraged.
52. High-calorie intake is recommended for cirrhotic patients except patients with DM and patients with high BMI.
53. Fasting time should be minimized, with a maximum interval of 3-4 hours between nutritional intake while awake.
54. Early breakfast or late evening snack of 200 kcal such as a rice bowl or liquid nutrient is recommended
    - to improve nocturnal fasting
    - to improve nutritional status by increasing body protein content and
    - to diminish fat and protein oxidation
55. Avoid protein restriction in patients with HE.
56. Branched-chain amino acids (leucine, isoleucine, valine) supplementation should be considered to improve neuropsychiatric performance and to reach the recommended nitrogen intake in patients with HE.
57. BCAA supplements and leucine-enriched amino acid supplements should be considered in decompensated cirrhotic patients when adequate nitrogen intake is not achieved by oral diet.
58. Patients with cirrhosis, whenever possible, can be encouraged to avoid hypomobility and to progressively increase physical activity to prevent and/or ameliorate sarcopenia.
59. In cirrhotic patients, administer micronutrients and vitamins to treat confirmed or clinically suspected deficiency.
60. Supplement vitamin D orally in cirrhotic patients with vitamin D levels less than 30 ng/ml.
61. In cirrhotic patients with ascites under sodium restriction, care should be taken to improve diet palatability as a low salt diet may cause a reduction in caloric intake.
62. Diet with high sodium content (Mohin-gar, Salted fish, Food with preservatives, cheese, MSG) should be avoided.

5. Management of Complications

5.1 Management of Decompensation

The management of patients with decompensated cirrhosis should ideally focus on preventing the progression of cirrhosis (i.e., further decompensation) rather than just treating complications as they arise. Currently, no treatment is available that can effectively target the pathological changes in the liver and restore the integrity of liver architecture by reducing inflammation, regressing fibrosis, regulating the portal and arterial circulation, and normalizing cell number and function. [55]

Meanwhile, the overall management of decompensated cirrhosis involves two strategies: (1) removal of the etiological causes that have suppressed liver inflammation and cirrhosis and (2) targeting key factors in the progression of cirrhosis decompensation. [55]

Removal of the etiological factor(s) causing liver injury, such as alcohol consumption[2] and hepatitis B[56] or C infection [57,58], is an important cornerstone in the management of cirrhosis. This approach is associated with beneficial effects on liver function and portal hypertension and is likely to improve outcomes.

Several strategies have been evaluated to prevent disease progression in patients with decompensated cirrhosis, including (1) targeting microbiome abnormalities and bacterial translocation to improve the gut-liver axis, (2) improving the disturbed circulatory function, (3) treating the inflammatory state, and (4) targeting portal hypertension. [55]

Strategies based on targeting abnormalities in the gut-liver axis by antibiotic administration (e.g., rifaximin), improving disturbed systemic circulatory function (e.g., long-term albumin administration), decreasing the inflammatory state (e.g., statins), and reducing portal hypertension (e.g., beta-blockers) have shown potential benefit in decreasing cirrhosis progression in patients with decompensated cirrhosis. However, further clinical research is needed with these strategies to confirm their safety and potential benefits as therapeutic approaches with the aim of preventing cirrhosis progression in decompensated patients. [55]

Recommendation (Management of Decompensation)

63. People diagnosed with cirrhosis should be followed up by a specialist with expertise in managing liver diseases.
64. In patients with decompensated cirrhosis, it's crucial to address the underlying causes, especially by discontinuing alcohol consumption and treating hepatitis B or C infection. This approach has been linked to a reduced risk of decompensation and improved survival rates.
65. The management of specific complications of decompensated cirrhosis, including ascites, hyponatremia, gastrointestinal bleeding, infection, spontaneous bacterial peritonitis (SBP), renal impairment, acute-on-chronic liver failure, relative adrenal insufficiency, cardiopulmonary syndrome, and hepatopulmonary syndrome, will be directed to the relevant sections.

5.2 Management of Acute Liver Failure

5.2.1 Definitions of Acute Liver Failure

Acute liver failure (ALF) is a life-threatening condition that occurs in patients with no preexisting liver disease and is characterized by liver injury (abnormal liver tests), coagulopathy (international normalized ratio [INR] > 1.5), and hepatic encephalopathy (HE).[60] The presentation of ALF has been further differentiated (O'Grady classification) based on the rapidity of onset of time elapsed from jaundice to HE. [61,62] (Table 4).

Table 4. Acute Liver Failure (ALF) presentation

Type of ALF	Time frame	Examples	Risk of cerebral edema	Risk of death
Hyperacute	< 7 days	Acetaminophen Hepatitis A & E Ischemic injury	High	Low
Acute	1 – 4 weeks	Hepatitis B	Intermediate	Intermediate
Subacute	4 – 12 weeks	Non acetaminophen DILI	Low	High

ALF - acute liver failure; DILI - drug-induced liver injury

5.2.2 Causes of Acute Liver Failure

The causes of ALF vary according to the geography. Common causes of ALF in adults (Table 5) include drug toxicity, hepatotropic and non-hepatotropic viruses, herbal and dietary supplements, antituberculosis drugs, and autoimmune hepatitis. [53] It is crucial to determine the cause of liver failure in order to manage it effectively and predict the prognosis, and therefore, a thorough investigation of the cause is strongly recommended (Table 6). Sepsis with multiorgan failure and cerebral edema are the leading causes of death in patients with ALF.

It is important for clinicians to identify ALF early in presentation and initiate appropriate management that can significantly impact the outcome and could be lifesaving. Liver transplantation is the best current therapy, although the role of artificial liver support systems, particularly therapeutic plasma exchange, can be helpful in patients with ALF, especially in non-transplant centers. ALF carries high morbidity and mortality without liver transplantation. [63-65] It remains imperative to identify the disease so that the patient is referred to a liver transplant center in a timely fashion.

Table 5. Cause of Acute Liver Failure

Viral cause	
Hepatotropic viruses	• Hepatitis A virus • Hepatitis E virus • Hepatitis B virus with or without hepatitis D virus • Hepatitis D virus
Non-hepatotropic viruses	• Herpes simplex virus (HSV) • Varicella zoster virus (VZV) • Epstein-Barr virus (EPV) • Dengue virus • Adenovirus • COVID-19 virus • Cytomegalovirus (CMV)
Drugs and toxins	
	• Paracetamol • Amanita phalloides • Anti-tuberculous drugs (especially isoniazid) • Alternative medicines including herbal-induced liver injury • Nitrofurantoin • Phenytoin • Propylthiouracil • Immune checkpoint inhibitors
Metabolic causes	
	• Wilson's disease
Other causes	
	• Autoimmune hepatitis • Acute fatty liver of pregnancy • Hemolysis elevation in liver enzymes and low platelet syndrome (HELLP) • Ischemic hepatitis • Tumor infiltrates in the liver • Hepatic venous outflow tract obstruction • Hemophagocytic lymphohistiocytosis • Budd–Chiari syndrome

Table 6. Cause and Diagnosis of Acute Liver Failure

Causes	Diagnosis in ALF	Comments
Hepatitis A	Anti-HAV IgM	Possible ↑ rate of ALF in concomitant viral hepatitis B or C infection
Hepatitis B	Anti-HBcore IgM (HBsAg may be -ve in ALF)	ALF in 1% of acute infection, especially if coinfection with HDV
Hepatitis C	HCV RNA (Ab often – ve)	Rarely causes ALF
Hepatitis E	Anti-HEV IgM and viral load	ALF in 20% of females infected during pregnancy
Other infections (e.g. EBV, HSV, Leptospirosis)	PCR for HSV and EBV; ELISA and PCR for leptospirosis, with organism found in urine after 7-10 d	
Paracetamol overdose	Blood level	
Drug reaction: e.g. NSAIDs, isoniazid, herbal remedies	Drug history, eosinophilia	
Toxins (Amanita phalloides mushrooms)	History of ingestion	
Acute fatty liver of pregnancy	History, bloods, US	Mainly clinical diagnosis, especially 3rd trimester
HELLP syndrome	History, bloods	Mainly clinical diagnosis, occurs in 2nd and 3rd trimester
Wilson's disease	Urinary copper, ceruloplasmin	Usually present with ALF < 20 years of age
Hepatic ischemia	↑ ALT/AST (>1,000 U/L), CT, ECG for arrhythmia	Especially following an episode of hypotension
Budd-Chiari Syndrome	US, history of risk factors	May present with ascites
Autoimmune hepatitis	Auto Abs (ANA, SMA), Igs	
Malignant infiltration	Imagining, histology	
Seronegative hepatitis	All above excluded	15% of cases

5.2.3 Complications of Acute Liver Failure

5.2.3.1 Encephalopathy

Encephalopathy is the defining feature of ALF and may progress rapidly with a significantly lower survival rate of 33%. Unlike hepatic encephalopathy from chronic liver disease, hepatic encephalopathy associated with ALF is associated with cerebral edema and

intracranial hypertension. Intracranial hypertension compromises cerebral perfusion pressure (CPP) and can lead to ischemic brain damage or brainstem herniation, which accounts for up to half of ALF mortality.

Factors contributing to cerebral edema in ALF include hypoxia, systemic hypotension, decreased cerebral perfusion pressure (CPP), and swelling of astrocytes as a result of elevated blood ammonia levels and increased glutamine production within the brain. Elevated arterial ammonia levels over 200 ug/dL have been strongly correlated with cerebral herniation and death.

5.2.3.2 Coagulopathy

Multiple factors contribute to the coagulopathy associated with ALF, including decreased hepatic synthesis of both procoagulant and anticoagulant factors and low-grade disseminated intravascular coagulation. Coagulopathy, as measured by the prothrombin time/INR, develops following decreased hepatic synthesis of factors 2,5,7 and 10. The prothrombin time/INR is one of the most sensitive liver function tests available in the setting of ALF and monitors the prognosis and course of the disease. Despite an elevated INR, most patients with ALF maintain normal hemostasis as measured by thromboelastography and a rate of spontaneous bleeding is less than 10%.

There are also both quantitative and qualitative platelet dysfunction in patients with ALF. A dramatic decline in platelet count can be seen in patients with SIRS and is associated with a greater likelihood of death or liver transplantation. The decrease in platelets during days 1-7 after admission is proportional to the grade of hepatic encephalopathy and the requirement for vasopressor and renal replacement therapy.

5.2.3.3 Infection

Patients with ALF are highly susceptible to infection due to multiple immunological deficits. Incidence rates as high as 90% are reported but the rate of culture-positive infection is 35%. Gram-positive organisms accounted for 35% of bloodstream infections, Gram-negative organisms 17%, and 9% of fungemia.

Pulmonary and bloodstream infections are most frequently seen, followed by urinary tract. Fungal infections, especially Candida, are seen in about 20% occur later in the course of illness, particularly after the use of antibiotics or in the setting of renal dysfunction. Surveillance culture of blood, sputum, and urine should be obtained in patients with ALF.

5.2.3.4 Acute kidney injury

AKI develops in up to 70% of patients with ALF and renal replacement therapy (RRT) is required in 30%. Patients with ALF with higher INR, higher coma grade, hypotension requiring vasopressor support, and paracetamol toxicity as the underlying cause are significantly more likely to develop AKI and require RRT.

5.2.3.5 Metabolic disorders

Electrolytes and metabolic derangement contribute to progressive hepatic encephalopathy and an increased risk of cerebral edema; therefore, they must be corrected promptly.

- **Hypoglycemia** may result from decreased hepatic glycogen production and impaired gluconeogenesis. Blood glucose levels must be measured at frequent intervals.
- **Hypophosphatemia** may be seen in ALF as a result of ATP consumption in the setting of rapid hepatocyte regeneration, which has been reported to be associated with a more favorable prognosis. Life-threatening hypophosphatemia can occur, and phosphorous levels should be monitored frequently and repleted promptly.
- **Acidosis** is one of the most important predictors of mortality; metabolic acidosis with a pH < 7.3 may be associated with a mortality rate of up to 95% in patients with acetaminophen toxicity in the absence of liver transplantation.
- **Alkalosis** may be present in ALF; hyperventilation is common.
- **Hypoxemia** may result from acute respiratory distress syndrome (ARDS), aspiration, or pulmonary hemorrhage, patients with grade 3 to 4 hepatic encephalopathy should undergo endotracheal intubation.

5.2.4 Prognosis Model for of Acute Liver Failure

Patients with ALF have the potential for spontaneous liver regeneration due to the absence of background liver disease. Identifying patients with a low chance of spontaneous recovery is of utmost importance. Several prognostic criteria have been proposed to assess the likelihood of spontaneous recovery versus progressive hepatic dysfunction with a high mortality risk. The most widely studies criteria for ALF in both APAP-induced ALF and non-APAP-induced ALF is the King's College criteria (KCC) (Table 7); these criteria are characterized by a high specificity for mortality; however, failure to fulfill the criteria does not ensure survival.

The Model for End-stage Liver Disease (MELD) score carries a specificity and sensitivity of <75% in predicting outcomes in both APAP-induced ALF and non-APAP-induced ALF. A meta-analysis comparing KCC and MELD scores suggested that KCC more accurately predicts mortality in APAP-induced ALF whereas MELD scores are superior in predicting mortality in non-APAP-induced ALF.

Table 7. King's College Criteria

King's College Criteria	
APAP-induced ALF	Arterial pH <7.3 (following adequate volume resuscitation) independent of the grade of encephalopathy **OR** • Grade 3 or 4 encephalopathy • INR > 6.5 (PT > 100 s) • Serum Creatinine > 3.4 mg/dL (301 mol/L)
Non-APAP-induced ALF	INR > 6.5 (PT > 100 s) **OR** **Any 3 of the following**, irrespective of coma grade • Age < 10 years or > 40 years • Drug toxicity, indeterminate cause of ALF • Jaundice to coma interval > 7 days • INR > 3.5 (PT > 50 s) • Serum bilirubin > 17.5 mg/dL (> 300 umol/L)

5.2.5 Management of Acute Liver Failure

Early recognition of ALF, establishment of time course and exposure risk, implementation of specific therapies with indicated, and aggressive intensive care monitoring are critical to effective management; liver transplantation should be considered in all patients.

Recommendation (Management of Acute Liver Failure)

66. Acute liver failure (ALF) is a life-threatening disorder characterized by rapid deterioration of liver function, coagulopathy, and hepatic encephalopathy in the absence of pre-existing liver disease.
67. The cause of ALF varies across the world. Common causes of ALF in adults include drug toxicity, hepatotropic and non-hepatotropic viruses, herbal and dietary supplements, antituberculosis drugs, and autoimmune hepatitis.
68. The cause of liver failure affects the management and prognosis, and therefore extensive investigation for cause is strongly suggested.
69. Sepsis with multiorgan failure and cerebral edema remain the leading causes of death in patients with ALF and early identification and appropriate management can alter the course of ALF.
70. Liver transplantation is the best current therapy, although the role of artificial liver support systems, particularly therapeutic plasma exchange, can be useful for patients with ALF, especially in non-transplant centers.

5.3 Management of Acute-on-Chronic Liver Failure

In patients with chronic liver disease, acute-on-chronic liver failure (ACLF), a relatively recently described entity, is diagnosed with a combination of hepatic and extrahepatic organ failures. The current definitions of ACLF vary worldwide, but despite these differences, patients with ACLF have a uniformly poor prognosis. The role of ACLF prediction, precipitating factors, individual organ failures, management strategies, and impact on liver transplantation or end-of-life care is evolving.

5.3.1 Definition of Acute-on-Chronic Liver Failure

There are 3 major definitions of ACLF depending on the part of the world.

5.3.1.1 The Asian Pacific Association for the Study of the Liver (APASL) defines ACLF as "an acute hepatic insult manifesting as jaundice (serum bilirubin ≥ 5 mg/dL [85 mmol/L]) and coagulopathy (international normalized ratio [INR] ≥ 1.5 or prothrombin activity, 40%) complicated within 4 weeks by clinical ascites and/or hepatic encephalopathy (HE) in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis and is associated with a high 28-day mortality." Extrahepatic organ failure is not required to make the diagnosis.

5.3.1.2 European Association for the Study of the Liver - Chronic Liver Failure (EASL-CLIF) consortium defines ACLF as a specific syndrome in patients with cirrhosis that is characterized by acute decompensation (AD), organ failure, and high short-term mortality. The development of ascites, HE, gastrointestinal hemorrhage, and/or bacterial infections defines AD; however, patients may develop ACLF without a history of AD. Organ failures include liver, kidney, brain, respiratory system, circulation, and coagulation, and they are assessed and graded by the CLIF-Consortium Organ Failures (CLIF-C-OF) score. (https://www.efclif.com/scientific-activity/score-calculators/clif-c-aclf)

- **Grade 1 ACLF:** Single kidney failure (serum creatinine ≥ 2.0 mg/dL or RRT) **or** another organ failure with kidney dysfunction (serum creatinine ≥ 1.5 – 2 mg/dL) and/or hepatic encephalopathy grade I or II, **or** singe cerebral failure with kidney dysfunction (serum creatinine ≥ 1.5 – 2 mg/dL).
- **Grade 2 ACLF:** 2 organ failure.
- **Grade 3 ACLF:** ≥3 organ failure.

5.3.1.2 North American Consortium for the Study of End-Stage Liver Disease (NACSELD) defines ACLF by the presence of at least 2 severe extrahepatic organ failures including shock, grade III/IV HE, renal replacement therapy (RRT), or mechanical ventilation (www.nacseld.org)

The lack of a universal definition of ACLF hinders epidemiological studies to assess the prevalence, natural history, and mortality of ACLF. Regardless of how ACLF is defined, the number of hospitalizations and readmissions within 90 days for patients with cirrhosis who have or develop ACLF is growing.

Table 8. Outlines of the 3 major ACLF definitions

Organ	APASL ACLF Research Consortium	EASL CLIF-C ACLF	NACSELD
Liver	Total Bilirubin PT/INR	Total Bilirubin PT/INR	---
Kidney	Creatinine	Creatinine/Dialysis	Dialysis
Brain	HE grade	HE grade	HE grade III/IV
Circulatory	Lactate	MAP, vasopressors	MAP, vasopressors
Respiratory	---	PaO_2 or SpO_2/FiO_2	Mechanical ventilation
Major Organ Failure Category	Predominantly Hepatic failure variable	Combination of hepatic and extrahepatic organ failure variable	Predominantly extrahepatic failure variable

Table 9. Variability in the definition of organ failure

Type of organ failure	APASL organ failure definitions	EASL-CLIF organ failure definitions	NACSELD organ failure definition
Liver	Total bilirubin ≥ 5 mg/dL and INR ≥ 1.5	Bilirubin ≥ 12 mg/dL	_
Kidney	AKI Network criteria	Creatinine level of ≥ 2.0 mg/dL or RRT	Need for dialysis or other form of RRT
Brian	West-Heaven HE grade 3-4	West-Heaven HE grade 3-4	West-Heaven HE grade 3-4
Coagulation	INR ≥ 1.5	INR ≥ 1.5	_
Circulation	_	Use of vasopressor (terlipressin and/or catecholamines)	Presence of shock defined by mean arterial pressure (MAP) <60 mmHg or reduction of 40 mmHg in SBP from baseline, despite adequate fluid resuscitation and cardiac output
Respiration	_	PaO_2/FiO_2 of ≤ 200 or SpO_2/FiO_2 of ≤ 214 or need for mechanical ventilation	Need for mechanical ventilation

5.3.2 Precipitating Factors for Acute-on-Chronic Liver Failure

Precipitating factors for ACLF are only identified in 50% of cases and often do not predict prognosis even when recognized. Infections are frequent precipitant of hospital admission and readmissions. There can be an exaggerated immunologic response to infection, which can lead to organ failure. After the successful resolution of infection, the compensatory anti-inflammatory response syndrome (CARS) can create immune paralysis. This immune dysregulation leaves patients vulnerable to subsequent infections. Risk factors for recurrent infections include older age, proton-pump inhibitor (PPI) use, development of the first infection while on spontaneous bacterial peritonitis (SBP) prophylaxis, and a higher MELD score at admission.

Other precipitating factors for the development of ACLF include acute exacerbation of hepatitis B, active alcoholism or alcoholic binge, drug-induced liver injury (DILI) such as various herbs, health supplements, anti-tuberculous, acute GI bleeding, major surgery in patients with advanced cirrhosis, ablative therapies such as radiofrequency ablation or transarterial chemoembolization in patients with HCC.

5.3.3 Pathophysiology of Acute-on-Chronic Liver Failure

Cirrhosis is known to be associated with the development of systemic inflammation, as indicated by increased white cell count, C-reactive protein, the presence of various inflammatory cytokines, and oxidative stress. The extent of inflammation seems to parallel the degree of liver dysfunction and the severity of decompensation.

5.3.4 Management of Acute-on-Chronic Liver Failure

There are significant challenges in appropriately identifying and managing patients with ACLF. The goals of the management of ACLF include identifying the predisposing factors and taking control of the precipitating event(s), managing the inflammatory response, and providing specific treatment for organ failures. The ICU is the most appropriate place for the management of these patients once ACLF has developed. Urgent evaluation for liver transplantation in the appropriate patient can be lifesaving.

As the outcome can be poor, preventive strategies in patients with cirrhosis are crucial and include:

- Early identification of infection

- Discontinuation of PPI therapy when clear ongoing need is found and removal of indwelling catheters unless strongly indicated
- Use of IV albumin for volume expansion per guidelines
- Early diagnosis and treatment of AKI
- NSBB use for primary prophylaxis of variceal hemorrhage whenever possible

Recommendation (Management of Acute-on-Chronic Liver Failure)

71. Acute-on-chronic liver failure (ACLF) is a potentially reversible condition in patients with chronic liver disease with or without cirrhosis that is associated with the potential for multiple organ failure and mortality within 3 months in the absence of treatment of the underlying liver disease, liver support or liver transplantation.
72. Patients with ACLF are best managed in the ICU and some may benefit from early liver transplantation.
73. Prevention of major precipitating factors such as infection and alcohol is critical in improving the prognosis of individual organ failure (brain, circulatory, renal, respiratory, and coagulation), and judicious use of antibiotic and antifungal medication is required.

5.4 Management of Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a common neuropsychiatric complication of both acute and chronic liver diseases . [64,65] and characterized by the presence of hepatocellular failure, portosystemic shunting (PSS), or both. [66] Patients with HE usually experience a wide spectrum of cognitive impairments that range in severity from alterations of psychomotor speed and working memory to more progressive psychiatric manifestations, such as gross disorientation and coma. [67,68]

5.4.1 Definition of Hepatic Encephalopathy

In 2014, The American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) joint practice guideline defined HE as “A brain dysfunction caused by liver insufficiency and/or PSS; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma”. [66]

In 2017, the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) endorsed the HE definition introduced by the AASLD/EASL practice guideline, and no further changes were proposed. [69]

5.4.2 Nomenclature of Hepatic Encephalopathy

The currently adopted approach to classifying HE is multiaxial to reflect on the complex nature of the disease. [69,70] This multiparametric method was first put forward by the working party of the 11th World Congress of Gastroenterology in their 1998 final report. [69,71] In 2011, the ISHEN implemented minor changes to the classification scheme introduced in 1998. [69] The updated scheme was then officially introduced in the joint AASLD/EASL practice guideline, and it is the currently followed method for HE classification.

According to the AASLD/EASL guidelines, HE should be classified using **4 main factors or axes**. [66]

(1) the underlying cause
(2) the severity of the disease manifestation
(3) the time course of the disease
(4) the existence of precipitating factors

Axis 1

Based on etiology, hepatic encephalopathy is either type A, type B, or type C (Table)

- **Type A** – associated with (**A**)cute liver failure
- **Type B** – associated with (**B**)ypasses or portosystemic shunts with no intrinsic liver disease
- **Type C** – associated with (**C**)hronic liver disease or (**C**)irrhosis

Axis 2

Based on severity, HE is classified into covert HE (**CHE**) and overt HE (**OHE**). The severity of OHE is classified based on the modified West Haven Criteria (**WHC**).

Table 10. Hepatic Encephalopathy Classification based on severity

ISHEN Classification	WHC grade	Description
CHE	Minimal	Normal mentation clinically Abnormal psychometric and neurophysiological tests.
	Grade 1	Trivial lack of awareness, Euphoria or anxiety, Shortened attention span, Impairment of basic addition or subtraction, Altered sleep rhythm
OHE	Grade 2	Lethargy or apathy, Disorientation for time, Obvious personality change, Inappropriate behaviors, Dyspraxia and asterixis
	Grade 3	Somnolence to semi-stuporous, Responsive to stimuli, Confused, Gross disorientation, Bizarre behavior.
	Grade 4	Coma

Axis 3

Based on the time course, OHE has been classified into three categories:

(1) **Episodic HE** happens infrequently not more frequently than every 6 months and each episode varies in severity and duration.

(2) **Recurrent HE** is defined as HE that occurs at least twice or more in 1 year.

(3) **Persistent HE** is a progression and is the presence of cognitive deficits that last more than 2 months. Each episode is essentially a new baseline and typically is due to no clear precipitating factor.

Axis 4

Each episode of OHE can be ***precipitated by any of the known factors*** **and etiologies** for HE they can be classified into those that trigger episodic OHE or recurrent OHE. OHE can also be ***spontaneous (i.e., without a clear precipitating factor)***, which is commonly associated with persistent OHE.

Table 11. Precipitating factors for episodic and recurrent overt HE (OHE) by decreasing frequency

Episodic OHE	Recurrent OHE
(1) Bacterial infection	(1) Electrolyte imbalance
(2) Gastrointestinal bleeding	(2) Bacterial infection
(3) Diuretic overdose	(3) Unidentified factors
(4) Electrolyte imbalance	(4) Constipation
(5) Constipation	(5) Diuretic overdose
(6) Unidentified factors	(6) Gastrointestinal bleeding

Table 12. Classification of HE

Based on etiology	Based on severity of WHC scale	Based on ISHEN scale	Based on time course	Based on precipitating factors
Type A	MHE	CHE	Episodic	Precipitated
	Grade 1			
Type B	Grade 2	OHE	Recurrent	
	Grade 3			Nonprecipitated
Type C	Grade 4		Persistent	

5.4.3 Natural History and Epidemiology of Hepatic Encephalopathy

Among patients with cirrhosis, the prevalence of subclinical HE (i.e., MHE or covert HE) ranges between 20% and 80%. [72-74] At the time of first cirrhosis diagnosis, the prevalence of overt HE is between 10% and 20%. [75]. In decompensated cirrhosis, the prevalence of overt HE ranges between 16% and 21%. [66] An estimated 30% to 40% of cirrhotic patients will experience overt HE during the clinical course of their illnesses . [66,76] The development of HE is associated with poor survival in cirrhotic patients. [77,78] Such low survival is not only limited to the occurrence of overt HE, but patients with covert HE also experienced higher risks of mortality. [79,80]

5.4.4 Pathogenesis of Hepatic Encephalopathy

In acute liver failure (ALF), abrupt loss of hepatocyte function is associated with significant ammonia accumulations. Such accumulations result in hyperammonemia once past the blood-brain barriers, and ammonia combines with glutamate to form glutamine (via

glutamine synthase). Increased glutamine causes astrocyte swelling which in turn can cause neuronal dysfunction, intracranial hypertension, cerebral edema, and HE. [65,81] The mechanisms underlining the onset of HE in cirrhosis are multifactorial. Primarily, the development of HE among cirrhotic patients was understood to be the direct effect of elevated levels of ammonia, which are shunted into the systemic circulation because of impaired liver function and hepatic decompensation. However, ammonia is currently identified as a risk factor for HE that is not sufficient for its diagnosis in cirrhosis.[70] Recent studies have identified other factors, such as inflammatory cytokines, manganese, benzodiazepine-like compounds, mercaptans, aromatic amino acids, and microbiota to be involved in the pathophysiology of HE. [65,82]

5.4.5 Precipitating factors of Hepatic Encephalopathy

Identifying and correcting the precipitating factor is the cornerstone of the clinical management of HE and could aid in recurrence prevention for both episodic and recurrent HE (Table 13). [66] The most common precipitants of HE include infections, gastrointestinal bleeding, intravascular hypovolemia often secondary to diuretic overdosing, and constipation.[66] There are a variety of HE precipitants that act through one or more of the 3 major pathways related to ammonia metabolism and toxicity: (1) increased production, (2) impaired excretion, and (3) increased neurotoxicity.

Table 13. Pathophysiology of clinical precipitants of HE

Pathophysiologic pathway	Precipitants
Increased Ammonia Production	Gastrointestinal bleed Intravascular hypovolemia, over diuresis Hypokalemia Acidosis Diabetes mellitus
Impaired Ammonia Excretion	Constipation Renal dysfunction Hypovolemia, over diuresis Sarcopenia Portosystemic shunting Zinc deficiency Branched-chain amino acid deficiency
Increased Neurotoxicity	Infection Medications/substance abuse Hyponatremia Hyperglycemia

5.4.6 Diagnosis of Hepatic Encephalopathy

5.4.6.1 Clinical manifestation of Hepatic Encephalopathy

The clinical presentation of HE includes a wide range of symptoms with different levels of severity. These symptoms mainly affect the neurologic, psychiatric, and musculoskeletal systems. Symptoms may be as subtle as disturbances in the sleep-wake cycle or may be as severe as a coma. Because of the various presentations, classification schemes are used to better categorize patients with HE. Regarding severity, patients can be graded by using the West Haven Criteria (WHC), which ranges from minimal to grade IV. For patients with advanced coma (grade 3 or 4), the Glasgow Coma Scale (GCS) allows a more accurate assessment of progression. [83]

Many patients with only minimal or early-stage encephalopathy simply report disturbances in their sleep-wake cycles. [84] As the symptoms of HE progress, patients commonly show personality changes, such as apathy, disinhibition, and irritability. In many cases, the patients do not report these symptoms themselves, but family members or close friends may bring up their concerns. Ultimately, if not treated, these psychological symptoms turn into cognitive impairments, disorientation, memory impairment, slurred speech, confusion, and shortened attention span. [85]

The hallmark of the early to middle stages of HE is asterixis. Grade II is signified by asterixis. Notably, the signs of asterixis weaken in grade III and disappear in grade IV. [86] Asterixis is described as a flapping tremor; however, this is not a true tremor but a negative myoclonus that results in loss of postural tone. It is caused by abnormal function of the diencephalic motor centers that regulate the tone of paired agonist/antagonist muscles. [87] It is most commonly elicited when patients hyperextend their wrists, but it can be observed in the patient's feet, legs, arms, tongue, and eyelids. [66] Although it is the physical examination finding most attributed to HE, it is not pathognomonic, because it can be seen in other clinical entities, such as uremic encephalopathy, encephalopathy from cardiac failure, respiratory failure, and severe hypokalemia.

In its most severe form, HE-induced musculoskeletal changes can lead to hyperreflexia, clonus, and rigidity. [66] In cases of persistent HE, cirrhosis-related parkinsonism symptoms may occur, resulting in extrapyramidal symptoms, including masked facies, rigidity, bradykinesia, slowed speech, and parkinsonian tremors. [88,89]

5.4.6.2 Laboratory testing for Hepatic Encephalopathy

HE is a clinical diagnosis that is obtained through the history and physical examination. Currently, no gold-standard diagnostic laboratory tests exist for HE. Ammonia is commonly used, but not specific to HE and does not correlate with severity, and is easily influenced by testing methods. Other causes of altered mentation in patients with cirrhosis must be excluded. (Table 14). Cross-sectional imaging (CT or MRI) of the head is useful for identifying alternative diagnoses, and imaging of the portosystemic circulation may identify large portosystemic shunts.

Specialized neuropsychometric testing is necessary to diagnose minimal HE, which is particularly important for patients at risk of accidents and may be useful to monitor and uncover subtle mental status changes. [90] These tests include psychometric testing of attention, working memory, psychomotor speed, and visuospatial ability. More specifically, this includes a myriad of neuropsychological or neuropsychometric tests that use either paper-and-pencil or computerized tests. Psychometric Hepatic Encephalopathy Score, The Repeatable Battery for the Assessment of Neuropsychological Status, Inhibitory Control Test, Cognitive Drug Research, Scan Test, and the Stroop App Test. Although these tests are promising given their high sensitivity and low cost, they are limited by time, the necessity of trained test administrators, and results that are affected by the patient's age and baseline education. [91] Alternatives that need to be looked for in patients with cirrhosis with altered mentation. [66]

Table 14. Causes of altered mentation in patients with Cirrhosis of Liver

Causes of altered mentation in patients with cirrhosis of liver
• Alcohol intoxication, alcohol withdrawal, Wernicke encephalopathy • Electrolyte imbalance – hyponatremia, hypercalcemia, hypomagnesemia • Drug – neuroleptics, benzodiazepine, anesthetic agents, opioids • Diabetes mellitus-related ketoacidosis, hyperosmolar state, hypoglycemia • Neurological disorder – infection, (meningitis, encephalitis), space-occupying lesions, intracranial bleeds, cerebrovascular accidents, nonconvulsive epilepsy • Psychiatric disorder • Organ failure, acute kidney injury, uremic encephalopathy • Sepsis

5.4.7 Management of Hepatic Encephalopathy

When treating a patient with cirrhosis and altered mental status one must adopt a four-pronged approach as recommended by the current hepatic encephalopathy guidelines:

(1) Initiation of care for the patients with altered consciousness
(2) Evaluation for alternate possibilities for altered mentation and treatment of them
(3) Identification of precipitating factors and correcting them
(4) Initiation of empiric hepatic encephalopathy treatment

Initiation of care for patients with altered consciousness

- This involves basic supportive measures such as starting IV fluid for dehydration/AKI and correcting electrolytes.
- Grade 4 OHE may need ICU care for airway management and administration of lactulose via a nasogastric tube.
- GI bleeding may require intensive care as well as prophylactic antibiotics.
- Sepsis management should be started according to guidelines.

Evaluation for alternate possibilities for altered mentation and treatment of them

- This involves looking at all other similar conditions (Table) and managing them appropriately.

Identification of precipitating factors and correcting them

- In the early stages, many patients with HE can be reversed by control of the (Table 11) precipitating etiology (up to 80 – 90%).
- Sepsis/bacterial infection is a leading etiology.
- When there is no obvious etiology for the HE, sepsis becomes the default etiology.
- Treat and prophylaxis should be initiated in SBP-related HE.
- Hyponatremia can aggravate or precipitate sepsis.
- Hyponatremia aggravates cerebral edema and the correction of hyponatremia results in correction of cerebral edema while improving cognition and quality of life.

Initiation of empiric hepatic encephalopathy treatment

- This can be broadly divided into four types of therapies based on mechanism of action:
    i. Reducing intestinal nitrogen load
    ii. Nitrogen excretion from the body
    iii. Intracerebral neurotransmitter corrections
    iv. Miscellaneous therapies

5.4.7.1 Reducing Intestinal Nitrogen Load

Drugs that work to reduce nitrogenous products in the intestine are still the mainstay of therapy.

(a) Lactulose

Lactulose is the mainstay of therapy for most patients for treatment of an acute episode and it has been shown to reduce the recurrence of HE. Lactulose (β-glactosidofructose) is a nonabsorbable synthetic disaccharide. Treatment of lactulose is based on the absence of a specific disaccharidase on the microvillus membrane of enterocytes in the human small bowel, thereby permitting entry of the disaccharides into the colon. Bacteria in the colon catabolize lactulose to short-chain fatty acids (e.g., lactic acid and acetic acid), lowering the colonic pH to approximately 5. The reduction in pH favors the formation of the nonabsorbable ammonium from ammonia, trapping ammonium in the colon and thus decreasing plasma ammonia concentrations.

Additionally, it increases the incorporation of ammonia by bacteria for the synthesis of nitrogenous compounds, modifies the colonic flora, and displaces urease-producing bacteria with non–non-urease-producing Lactobacillus. [92] The cathartic effects of a hyperosmolar load in the colon improve gastrointestinal transit, allowing less time for ammonia absorption [93]. Finally, the decreased formation of potentially toxic short-chain fatty acids (e.g., propionate, butyrate, valerate) is theorized to aid in encephalopathy symptoms. [94]

Lactulose dosage

- Acute HE grade 2/3: 30 – 45 mL orally every 2 – 3 hours with a goal of a minimum of 2 – 3 bowel movements a day till improves clinically
- Acute HE grade 3/4: 300 ml every 2 – 3 hours per rectally till clinically improved.
- Prophylaxis/outpatients: 15 – 45 ml orally two or three times daily for 2 – 3 bowel movements a day.

Lactulose has also been shown to be a precipitating factor or OHE due to overuse, resulting in diarrhea and volume loss-related dehydration and AKI. [95]

(b) Polyethylene glycol (PEG)

Polyethylene glycol (PEG) solution is a cathartic that may help to treat hepatic encephalopathy by increasing the excretion of ammonia in the stool. In a small RCT, PEG was reported to be superior to lactulose for the management of acute OHE episodes. [96]

(c) Antibiotics

Antibiotics such as neomycin, vancomycin, and metronidazole have historically been used for the treatment of hepatic encephalopathy. However, rifaximin has become the most widely used antibiotic for this indication owing to its safety, efficacy, and tolerability. [97] Although neomycin decreases the intestinal production of ammonia from glutamine, its clinical use is limited by its tendency to cause ototoxicity and nephrotoxicity. [98] Similarly, the use of vancomycin is limited by nephrotoxicity and risk of bacterial resistance, and long-term use of metronidazole is associated with nephrotoxicity and neurotoxicity. [98,99]

(d) Rifaxamin

Rifaxamin (550 mg two times daily) remains the most widely used antibiotic in the management of HE. Rifaxamin is a broad-spectrum gut-specific antibiotic that belongs to the rifamycin class of antibiotics that block RNA synthesis in bacteria. It is nonabsorbable and achieves a great concentration in the intestinal lumen and despite its broad nature, preserves the gut flora. [100] Furthermore, studies of the safety and tolerability of rifaximin have shown no increase in adverse events, infection with Clostridium difficile, or bacterial antibiotic resistance. [101]

Current guidelines recommend lactulose as the initial first-line treatment for hepatic encephalopathy; however, there is evidence that monotherapy with rifaximin can be effective, and rifaximin has been demonstrated to be non-inferior to lactulose alone. [66,102] For patients with severe hepatic encephalopathy or recurrent hepatic encephalopathy on lactulose, combination therapy with lactulose and rifaximin should be considered. [98,103] The combination of lactulose and rifaximin seems to be more effective than those treated with lactulose alone. And had decreased mortality and hospital length of stay when compared with those on monotherapy. [104] Another recent literature review found that the addition of rifaximin to lactulose therapy decreases the risk of recurrence of overt hepatic encephalopathy and encephalopathy-related hospitalizations, and this combination is well-tolerated. [105]

5.4.7.2 Nitrogen excretion from body

Although the mainstay of therapy is the reduction of intestinal nitrogenous products, the removal of excess nitrogen from the body by either manipulating the existent ammonia or by enhancing the liver's capacity to synthesize urea and glutamine has been evaluated.

(a) L-Ornithine L-Aspartate (LOLA)

L-Ornithine L-aspartate (LOLA) is the stable salt of amino acids ornithine and aspartate and has been found to be effective in hepatic encephalopathy. It works via a substrate

mechanism on the liver and skeletal muscle. Carbamoyl phosphate synthetase and glutamine synthetase are both key enzymes for urea and glutamine synthesis, respectively.

In a cirrhosis state, these enzymes are impaired, resulting in hyperammonemia. Ornithine activates carbamoyl phosphate synthetase in the liver, and both ornithine and aspartate act peripherally by stimulating glutamine synthesis via glutamine synthetase. [106,107] A 2018 Cochrane meta-analysis of 29 trials involving 1,891 participants examined LOLA compared with placebo and other anti–hepatic encephalopathy treatments. It was found that LOLA demonstrated improvement in mortality, hepatic encephalopathy, and prevention of serious adverse effects when compared with placebo or no treatment. [108]

A 2017 randomized, controlled trial found intravenous LOLA to be effective in reverting overt hepatic encephalopathy at day 5 of treatment when compared with placebo, as well as decreasing the duration of hospitalization and length of treatment. [109]

The dose and duration are varied across studies and routes of administration. Oral dosages have ranged between 9 and 18 g/d in previous trials, and intravenous dosages between 20 and 30 g/d for 3 to 8 days. Overall, the quality of evidence was low, and additional data and further investigation are needed. [108]

5.4.7.3 Correction of intracerebral neurotransmitters

(a) Branched Chaing Amino Acid (BCAA)

The BCAAs (isoleucine, leucine, and valine) have attracted particular attention for their therapeutic efficacy in hepatic encephalopathy. The pathophysiology had been suggested that decreased BCAAs resulted in an increased ratio of aromatic amino acids (AAA) to BCAA. This led to an increased number of aromatic amino acids (AAA) crossing the blood-brain barrier, leading to inefficient dopaminergic neurotransmission. [110] BCAAs also aid in the detoxification of ammonia by its effects on skeletal muscle. Skeletal muscle detoxifies ammonia via conversion to glutamine. In cirrhosis, hyperammonemia impairs skeletal muscle protein synthesis via alteration of mTOR signaling; BCAAs have been shown to counteract this pathway. [111]

A 2016 Cochrane review examined the effects of BCAAs on hepatic encephalopathy. Sixteen randomized, controlled trials including 827 participants classified as having overt hepatic encephalopathy (12 trials) or minimal hepatic encephalopathy (4 trials). Eight trials assessed BCAA supplements and 7 trials assessed intravenous BCAA. It found that BCAAs had a beneficial effect on manifestations of hepatic encephalopathy. No significant effect was found on mortality, quality of life, or nutritional measures. [112]

5.4.7.4 Miscellaneous agents

(a) Probiotics

The gut microbiome plays an important role in hepatic encephalopathy because gut bacteria are involved in the production of ammonia. Thus, it has been theorized that the use of probiotics to alter gut flora may be beneficial in the management of hepatic encephalopathy.

A systematic review of 9 randomized, controlled trials also showed that probiotics were associated with the improvement of minimal hepatic encephalopathy, prevention of overt hepatic encephalopathy, and was also associated with a reduction in severe adverse events. [113] However, most data available are of low quality and there has been no evidence of any improvement in mortality. [114]

(b) Acarbose

Acarbose is a competitive inhibitor of the alpha-amylase (pancreatic enzyme) and alpha-glucoside (intestinal enzyme). A significant limiting factor in the usage of acarbose is a rare side-effect of fulminant hepatitis, as well as elevated transaminases and bilirubin, as reported by multiple investigators. [115]

(c) Albumin

Albumin has many benefits for numerous complications of cirrhosis but has not shown any statistically significant changes for HE management along with rifaxamin. [116]

5.4.7.5 Dietary Management

Evidence shows that malnutrition correlates with HE in a relationship that seems to be linked with ammonia metabolism in the muscles. Although historically protein restriction was hypothesized to reduce plasma ammonia levels [117], studies have consistently shown no beneficial effect of dietary protein restriction and even observed this practice to contribute to detrimental muscle wasting, also known as sarcopenia. [118] Current EASL and AASLD guidelines recommend that caloric intake should be 35 to 40 kcal/kg of ideal body weight with 1.2 to 1.5 g/kg protein per day [12]. In patients with HE, demonstrated or suspected vitamin or micronutrient deficiencies should be treated, as they can compound HE. [119]

5.4.7.6 Liver Transplantation

Patients with end-stage liver disease and recurrent or persistent HE not responding to other treatments should be assessed for liver transplantation. This requires careful work-up and

the patient, family, and other health professionals should be aware that the manifestations of HE are not always resolved as quickly as expected after liver transplantation. [120,121]

Recommendation (Management of Hepatic Encephalopathy)

74. HE should be classified using 4 main factors or axes: (1)the underlying cause, (2) the severity of the disease manifestation, (3) the time course of the disease, (4) the existence of precipitating factors.
75. HE should be graded by using the West Haven Criteria (WHC) which range from minimal to grade IV as a severity assessment.
76. For patients with advanced coma (grade 3 or 4), the Glasgow Coma Scale (GCS) allow more accurate assessment of progression.
77. In patients with HE, precipitating factors should be sought and managed.
78. Patients with overt HE grade 3 and 4 are at risk of aspiration and should be treated in the ICU.
79. Patients with recurrent or persistent HE should be considered for liver transplantation and a first episode of overt HE should prompt referral to a transplant centre for evaluation.
80. Lactulose combination with rifaxamin is recommended as a mainstay of treatment in overt HE.
81. Rifaximin as an adjunct to lactulose is recommended as secondary prophylaxis.
82. In patients with HE, demonstrated or suspected vitamin/ micronutrient deficiencies should be treated.
83. Dietary protein restriction is not recommended in management of HE.
84. BCAAs (Branched-Chain Amino Acids) supplementation is recommended for long-term use to improve manifestations of hepatic encephalopathy (HE), reduce the recurrence of HE episodes, and aid in the treatment and prevention of sarcopenia.

6. Diagnosis and Risk Stratification of Portal Hypertension and Varices in Cirrhosis

6.1 Introduction

Portal hypertension (PH) is a clinical syndrome in which portal venous blood flow obstruction or abnormal increase in blood flow of different etiologies leads to a continuous increase in portal venous system pressure and formation of extensive collateral circulation. The most common cause is liver cirrhosis. The main clinical manifestation of PH is bleeding from gastroesophageal varices (GOV) and portal hypertensive gastropathy. [131]

6.2 Diagnosis of portal hypertension

Gastroesophageal varices are commonly seen in patients with cirrhosis or other diseases causing PH. Patients may be asymptomatic or present with signs of upper gastrointestinal bleeding (hematemesis, melena), or signs of advanced chronic liver disease (ACLD) (ascites, jaundice). The physical examination can also detect signs of PH such as caput medusa, splenomegaly, and enlarged hemorrhoids. [128] These clinical features are helpful in predicting the presence of PH. Although direct portal pressure measurements can be performed by means of endoscopic ultrasound or percutaneous access, it can be influenced by changes in intra-abdominal pressure. Hepatic Venous Pressure Gradient (HVPG) measurement is the gold-standard method to assess portal pressure indirectly in patients with cirrhosis. To measure HVPG, transjugular catheter is placed into a hepatic vein and the balloon occlusion method is used to get wedge pressure. The difference between wedge hepatic vein pressure and unwedged (free hepatic vein pressure) is HVPG. PH is defined as HVPG >5 mmHg while clinically significant portal hypertension (CSPH) is defined as HVPG >10 mmHg. [125] Measurement of HVPG is moderately invasive and carries small risks of injury related to access to the jugular vein, induction of arrhythmias, and radiation exposure. Interpretation of HVPG also requires specific expertise. These limitations restrict its routine use to specialized centers and as such have stimulated efforts to validate noninvasive surrogates usable in regular clinical practice.

Conventional cross-sectional imaging such as ultrasound, CT, and MRI have a limited but defined role in identifying specific imaging surrogate markers of CSPH such as visualization of collaterals (peri-esophageal varices, recanalization of the umbilical vein, presence of splenorenal shunt) and presence of ascites. Likewise, Doppler ultrasound can show collateral circulation or portal flow reversal. Currently, the best validated noninvasive staging system for estimation of CSPH is provided by the combination of liver stiffness measurement (LSM) by Transient Elastography (TE) and platelet count. CSPH can be presumed in the

presence of (1) LSM >25 kPa, (2) LSM between 20 and 25 kPa and platelets < 150 K/mm^3, or (3) LSM between 15 and 20 kPa and a platelet count < 110 K/mm3. LSM can also be determined by non-TE elastography methods, such as magnetic resonance elastography (MRE), point shear wave elastography (pSWE), and two-dimensional shear wave elastography. However, these methods are less well-validated to define CSPH and may be subject to cross-manufacturer variability. [125]

Despite the presence of invasive and non-invasive assessment of PH, the gold standard for the diagnosis of GOV is esophagogastroduodenoscopy (EGD). [128] EGD has the stage-specific role of identifying varices needing treatment (VNT), serial monitoring, and alternative approaches. EGD should be used to identify GOV at the first diagnosis of cirrhosis. For patients with decompensated advanced chronic liver disease (ACLD), endoscopic surveillance should be encouraged when LSM ≥ 20 kPa or platelet count ≤ 150 × 10^9/L. [125] For patients with compensated ACLD who are not candidates for non-selective beta-blockers (NSBBs) (e.g., contraindication/intolerance), variceal surveillance should be done when LSM ≥ 20 kPa or spleen stiffness measurement (SSM) ≥ 40 kPa or a platelet count ≤ 150 × 10^9/L. Patients who are not candidates for screening endoscopy can be monitored with yearly TE and platelet counts. Patients with compensated ACLD without varices who develop decompensation should have a repeat endoscopy when this occurs. [122] To identify the development and progression of GOV, endoscopic surveillance should be performed at 2–3-year intervals in patients with compensated ACLD and at 1–2-year intervals in those with decompensated ACLD. The frequency of endoscopic surveillance could be modified according to the severity and ongoing activity of underlying liver disease. [126]

6.3 Risk Stratification

Patients with ACLD presenting with suspected acute variceal bleeding should be risk stratified according to the Child-Pugh score and MELD score, and by documentation of active/inactive bleeding at the time of EGD. Patients with Child-Pugh A or Child-Pugh B without active bleeding at endoscopy or MELD score < 11 points are at low risk of poor outcome. Patients with Child-Pugh B with active bleeding at endoscopy despite vasoactive agents or patients with Child-Pugh C are at high risk of poor outcomes. Patients with MELD score ≥ 19 are also at high risk of poor outcomes. [123]

6.4 Esophageal Varices

The primary goal of EGD is the diagnosis and risk stratification of gastric varices (EV) and gastric varices (GV) by determining the size and high-risk stigmata. [128] EVs are classified by size: small (minimally elevated veins above the esophageal mucosal surface), medium (tortuous veins occupying less than one-third of the esophageal lumen), and large (occupying more than one-third of the esophageal lumen). [127] The risk of bleeding from esophageal varices mainly depends on the size of the varices, the level of HVPG, the severity of ACLD, and high-risk stigmata on endoscopy (red wale sign, cherry red spot, hematocystic spot, and white nipple sign). [130]

Table 15. Classification of Esophageal Varices [122,125,127]

<table>
<tr><th colspan="2">Size</th><th colspan="2">Description</th></tr>
<tr><td>Small</td><td>Small</td><td>Minimally elevated veins above the esophageal mucosal surface</td><td><5 mm in diameter</td></tr>
<tr><td rowspan="2">Large</td><td>Medium</td><td>Tortuous veins occupying less than one-third of the esophageal lumen</td><td rowspan="2">>5 mm in diameter</td></tr>
<tr><td>Large</td><td>Occupying more than one-third of the esophageal lumen</td></tr>
<tr><td>High risk</td><td colspan="3">Medium/large varices or any size varices with red wale marks or in a patient with CTP class C</td></tr>
</table>

6.5 Gastric Varices

Gastric varices (GV) are commonly classified according to the Sarin classification. This classification divides GV among those that are a continuation of EV along the lesser curvature (GOV1) or greater curvature (GOV2) and isolated GV, which can be found in the fundus (IGV1) or in other areas of the stomach (IGV2). [129] Varices along the lesser curvature (GOV1) share a natural history and can be treated comparably with EV. Varices along the greater curvature (GOV2) and in the fundus (IGV1) are referred to as cardiofundal varices. They have a different natural history than EVs and are associated with higher rates of treatment failure, rebleeding, and mortality. Predictors of bleeding among patients with GV appear similar to those of EV: size (>10 mm for cardio fundal varices), presence of red marks, discoloration or platelet plugs, and liver disease severity. The vascular anatomy of GV can be highly variable,

unlike EV. The presence of portosystemic shunts, splanchnic vein thromboses, or other portal hypertensive complications should inform treatment options. Therefore, cross-sectional imaging with either CT or MRI using the portal venous phase of contrast is necessary for planning definitive therapy for GV. [124]

Table 16. Classification of Gastric Varices [125,129]

Type	Description
GOV 1	Gastric varices along the lesser curvature as a continuation of esophageal varices
GOV 2	Gastric varices along the greater curvature as a continuation of esophageal varices
IGV1	Isolated gastric varices in fundus
IGV2	Isolated gastric varices in other areas of the stomach
High risk	Cardiofundal (GOV2 or IGV1) varices (≥ 10 mm, red wale signs, CTP class B/C)

6.6 Portal hypertensive gastropathy

Portal hypertensive gastropathy (PHG) is a common endoscopic observation in patients with ACLD. The condition results from increased portal pressure and submucosal vascular hyperemia resulting in associated mucosal venous and capillary ectasia. Endoscopic classification of PHG severity is clinically important because severity is correlated with bleeding risk. [125] PHG can be simply categorized as mild (mild mucosa reddening or congestion), moderate (severe redness and a fine reticular pattern separating areas of raised edematous mucosa -mosaic pattern), and severe (with added point bleeding). [132]

Table 17. Classification of Portal Hypertensive Gastropathy [122,125,127]

Feature		Score
Mucosal mosaic pattern	Mild	1
	Severe	2
Red markings	Isolated	1
	Confluent	2
Gastric antral vascular ectasia (GAVE)	Absent	1
	Present	2
Mild PHG ≤ 3, Severe PHG ≥ 4		

Recommendation
(Diagnosis and Risk Stratification of Portal Hypertension and Varices)

85. CSPH can be diagnosed at the time of clinical decompensation, gastroesophageal varices on endoscopy, or portosystemic collaterals on imaging.

86. CSPH can be noninvasively identified by LSM by vibration-controlled TE and platelet count. CSPH is diagnosed at LSM ≥ 25 kPa irrespective of platelet count, LSM 20–24.9 kPa with platelet count < 150 K/mm^3, or LSM 15–19.9 kPa with platelet count <110 K/mm^3.

87. Endoscopic variceal surveillance should be performed at the first diagnosis of cirrhosis or cirrhosis with LSM ≥ 20 kPa or SSM ≥ 40 kPa or platelet count ≤ 150 K/mm^3.

88. To identify the development and progression of GOV, endoscopic surveillance should be performed at 2–3-year intervals in patients with compensated liver cirrhosis and at 1–2-year intervals in those with decompensated liver cirrhosis. The frequency of endoscopic surveillance could be modified according to the severity and ongoing activity of underlying liver disease.

89. Patients with cACLD without varices on screening endoscopy should have endoscopy repeated every 2 years (with ongoing liver injury or associated conditions, such as obesity and alcohol use) or every 3 years (if liver injury is quiescent, e.g., after viral elimination, alcohol abstinence). Patients with cACLD without varices who develop decompensation should have a repeat endoscopy when this occurs.

90. Esophageal varices are classified by small, medium, and large size. The risk of bleeding from esophageal varices mainly depends on the size of varices, level of HVPG, severity of ACLD, and high-risk stigmata on endoscopy (Medium/large varices or any size varices with red wale marks or in a patient with CTP class C).

91. Gastric varices are classified according to the Sarin classification and predictors of bleeding include size of GV, presence of red marks, discoloration or platelet plugs and liver disease severity. High risk features are cardiofundal (GOV2 or IGV1) varices (≥ 10 mm, red wale signs, CTP class B/C).

92. PHG can be simply categorized as mild and severe according to the Baveno classification and the severity of PHG is correlated with risk of bleeding.

7. Management of Portal Hypertensive Bleeding

7.1 Pharmacological Management in Compensated Cirrhosis

Nonselective β-blockers (eg, carvedilol or propranolol) reduce portal pressure by reducing splanchnic blood flow and are standard of care for people with large varices or prior bleeding. Because of its α-blocking effects, reduction in intrahepatic resistance and greater portal pressure lowering effect, carvedilol (optimally dosed at 12.5 mg daily) is preferred to other β-blockers when large varices are encountered on endoscopy. [136,137]

Recommendation (Pharmacological Management in Compensated Cirrhosis)
88. NSBB is not recommended in patients with cirrhosis without CSPH for prevention of decompensation. Life style modification and treat underlying cause.
89. NSBB (carvedilol 12.5 mg/day) should be considered in patients with compensated ACLD with CSPH if there is no contraindication such as asthma, advanced heart block, and bradyarrhythmias.

7.2 Variceal Surveillance

7.2.1 Indication for Endoscopy

Compensated cirrhosis portends a better prognosis than decompensated cirrhosis. To assess the severity of cirrhosis, there are less costly and less invasive interventions with substantial benefits, ranging from simple blood tests to transient elastography. [133] Regarding noninvasive tests, Baveno VI criteria suggested that patients with a liver stiffness measurement (LSM) of <20 kPa and platelet count (PLT) > 150 × 109/L could safely avoid an OGD for variceal surveillance as the risk of developing HRVs is considered acceptably low (risk < 5%).[134] The most recent real-world cohort of cACLD patients in Australia supported that B6C in the right clinical context enables the omission of OGD screening for 33.8% of cACLD patients with a high sensitivity of 96.2% and negative predictive value of 98.6% for ruling out HRVs. Therefore, the use of the B6C in regular clinical practice is safe and dependable in cACLD patients. [135]

Recommendation (Variceal Surveillance)

90. In patients with compensated ACLD and liver stiffness measurement < 20 kPa and platelet count ≥150×109/L, screening upper GI endoscopy can be avoided since these patients have a low probability of having high-risk varices.
91. In patients with compensated ACLD, but with liver stiffness measurement ≥ 20 kPa or platelet count ≤150×109/L who are not receiving NSBB therapy, should be screened by upper GI endoscopy to identify high-risk esophagogastric varices (esophageal varices that are medium or large; or small-sized esophageal varices with red wale markings).
92. In patients with decompensated ACLD (liver stiffness measurement by transient elastography ≥ 20 kPa or platelet count ≤150×109/L) should be screened by upper GI endoscopy to identify high-risk esophagogastric varices.
93. Patients with cACLD without varices of screening endoscopy should have endoscopy repeated every 2 years (with ongoing liver injury or associated condition, such as obesity and alcohol use) or every 3 years (if liver injury is quiescent, e.g. after viral elimination, alcohol abstinence).

7.3 Primary Prophylaxis of Variceal Bleeding

7.3.1 Primary Prophylaxis of Variceal Bleeding in Compensated COL

Primary prophylaxis is universally recommended for patients with ACLD and high-risk varices. Both NSBB therapy and endoscopic band ligation are accepted primary prophylaxis options for esophageal varices, as they have significantly reduced the risk of a first episode of esophageal variceal hemorrhage. A meta-analysis (including 32 RCTs comparing NSBBs, isosorbide mononitrate, carvedilol, and EVL, alone or in combination with each other or placebo; 3362 adults who had cirrhosis with large esophageal varices and no prior history of bleeding) showed that both NSBB therapy and EVL have similar efficacy in reducing the risk of a first variceal bleed. [138]

If endoscopic variceal ligation (EVL) is selected for primary prophylaxis of high-risk varices, EVL should be repeated until all varices are eradicated. Intervals between endoscopies evaluated in clinical trials for primary and secondary prophylaxis have ranged from 1 to 8 weeks. After eradication, periodic endoscopy should be repeated every 6–12 months.

ESGE suggests in those patients unable to receive NSBB therapy with a screening upper GI endoscopy which demonstrates gastric varices (Sarin GOV-2 or IGV-1; cardiofundal varices), no treatment, cyanoacrylate injection alone, or endoscopic ultrasound-guided coil plus cyanoacrylate injection can be considered. EUS-guided injection therapy should be decided on a case-by-case basis and limited to centers with expertise in this endoscopic technique. [147]

Recommendation (Primary Prophylaxis of Variceal Bleeding in Compensated COL)
94. Presence of varices of any size should prompt the initiation of NSBB.
95. Primary prophylaxis with EVL should be performed in patients with cACLD and CSPH and high-risk varices that cannot receive NSBB.
96. Band ligation should be repeated every 2-4 weeks until obliteration and then endoscopy repeated at 6 months and then every 12 months to assess reappearance of varices.

7.3.2 Primary Prophylaxis of Variceal Bleeding in Decompensated COL

Patients with decompensated cirrhosis not taking NSBB who had never bleed from varices should undergo annual endoscopic screening.

If high-risk varices are detected, NSBBs or endoscopic band ligation are recommended. If the high-risk varices are small, the only method is the administration of NSBB. If the high-risk varices are large, both NSBB as well as EVL are possible approaches. A recent systematic review with network meta-analysis showed that EVL is associated with a higher risk of complications and higher mortality than NSBB. [140,141]

The preferred NSBB for primary prophylaxis is carvedilol based on its greater portal pressure-lowering effect compared with propranolol or nadolol, and the improvement in the outcome of nonresponders to propranolol. [136]

Recommendation (Primary Prophylaxis of Variceal Bleeding in Decompensated COL)
97. Patients with decompensated cirrhosis not taking NSBBs who have never bled from varices should undergo annual endoscopic screening.
98. If high-risk varices are detected, NSBBs or endoscopic band ligation are recommended; preference is given to NSBBs (including carvedilol) because of benefits beyond the prevention of variceal hemorrhage.

7.4 Management of Acute Variceal Hemorrhage

AVH remains an emergent complication of cirrhosis and requires timely and effective management to prevent short-term mortality.

Urgent assessment of the hemodynamic status in patients presenting with suspected acute variceal hemorrhage is recommended. Prompt, careful, intravascular volume replacement, initially using crystalloid fluids, is important if hemodynamic instability exists in order to restore tissue perfusion while avoiding intravascular volume overexpansion. On presentation of gastrointestinal hemorrhage, those with a known or suspected history of advanced liver disease should be managed as having a portal hypertensive-related source until endoscopic confirmation. [141]

7.4.1 Blood Transfusion

Packed red blood cell transfusions should target a hemoglobin ~7 g/dL unless higher targets are required related to comorbid conditions.

Fresh frozen plasma and platelet transfusions should not be given based on international normalized ratio or platelet count targets, because there is no evidence of benefit of such transfusions in AVH, and in the case of fresh frozen plasma, there is evidence of potential harm.

In the AVB episode, transfusion of fresh frozen plasma is not recommended as it will not correct coagulopathy and may lead to volume overload and worsening of portal hypertension. (Baveno VII – Renewing consensus in portal hypertension). [137]

Recommendation (Initial Management of Acute Variceal Haemorrhage)
99. Patients with ACLD presenting with suspected acute variceal bleeding, be risk stratified according to Child-Pugh score and MELD score. 100. Vasoactive agents terlipressin, octreotide should be initiated at the time of presentation and be continued for a duration up to 5 days. 101. Recommended dose of terlipressin is 2 mg IV every 4 h then 1 mg IV every 4-6 hrly or octride is given a 50 mcg bolus followed by infusion of 25-50 mcg/h. 102. In case of successful endoscopic hemostasis, vasoactive agents may be stopped 24-48 hrs later in selected patients. 103. Antibiotic prophylaxis using ceftriaxone 1g/day or CS1 1 G 12 hourly should be given for up to 7 days or in accordance with local antibiotic resistance and patient allergies

7.4.2 Endoscopic Management

Endoscopic evaluation should take place within 12 - 24 hours from the time of patient presentation provided the patient has been hemodynamically resuscitated. If varices are visualized, the endoscopist can determine the location of varices, if actively bleeding, and the presence of varix characteristics (large column size, red wale signs). EVL and repeated after discharge every 2–4 weeks until variceal obliteration, should be the standard endoscopy approach for esophageal varices.

Initial management of acute gastric or ectopic variceal bleeding should follow the guidance for acute esophageal variceal bleeding. If local expertise in the management of bleeding GV is not available, the patient should be referred to a tertiary care center.

In patients presenting with AVB, rapid removal of blood from the gastrointestinal tract (lactulose oral or enemas) should be used to prevent hepatic encephalopathy.

Recommendation (Endoscopic Management of Acute Variceal Haemorrhage)
104. EVL is recommended for the treatment of acute EVH.
105. In refractory variceal bleeding, self-expandable metal stents (SEMS) or balloon tamponade might be used as a bridge therapy to a more definite treatment such as PTFE-covered TIPS.
106. Recombinant factor VIIa and tranexamic acid are not recommended in AVB.
107. Endoscopic cyanoacrylate injection is recommended for acute gastric (cardiofundal) variceal (GOV2, IGV1) hemorrhage.
108. Antibiotic prophylaxis using ceftriaxone 1g/day or CS1 1g 12 hourly should be given for up to 7 days or in accordance with local antibiotic resistance and patient allergies.
109. Endoscopic cyanoacrylate injection or EVL in patients with GOV1-specific bleeding.

7.5 Secondary Prophylaxis of Variceal Bleeding

Recommendation (Secondary Prophylaxis of Variceal Bleeding)
110. Patients who have undergone EVL for acute EVH should be scheduled for follow-up EVLs at 1- to 4-week intervals to eradicate esophageal varices.
111. Use of NSBBs (propranolol or carvedilol) in combination with endoscopic therapy for secondary prophylaxis.

7.6 Use of Proton Pump Inhibitor Therapy in Variceal Bleeding

Recommendation (Use of Proton Pump Inhibitor Therapy in Variceal Bleeding)
112. Routine use of proton pump inhibitors (PPI) in the post-endoscopic management of acute variceal bleeding is not recommended and if initiated before endoscopy, it should be discontinued.

8. Management of Ascites

Ascites is the most common cause of decompensation in cirrhosis, as 5% to 10% of patients with compensated cirrhosis per year develop this complication. [143] The mainstay of ascites formation is renal sodium retention due to the activation of sodium-retaining systems, such as the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. Fig 1 illustrates pathophysiologic mechanisms leading to the development of ascites and its complications in patients with cirrhosis.

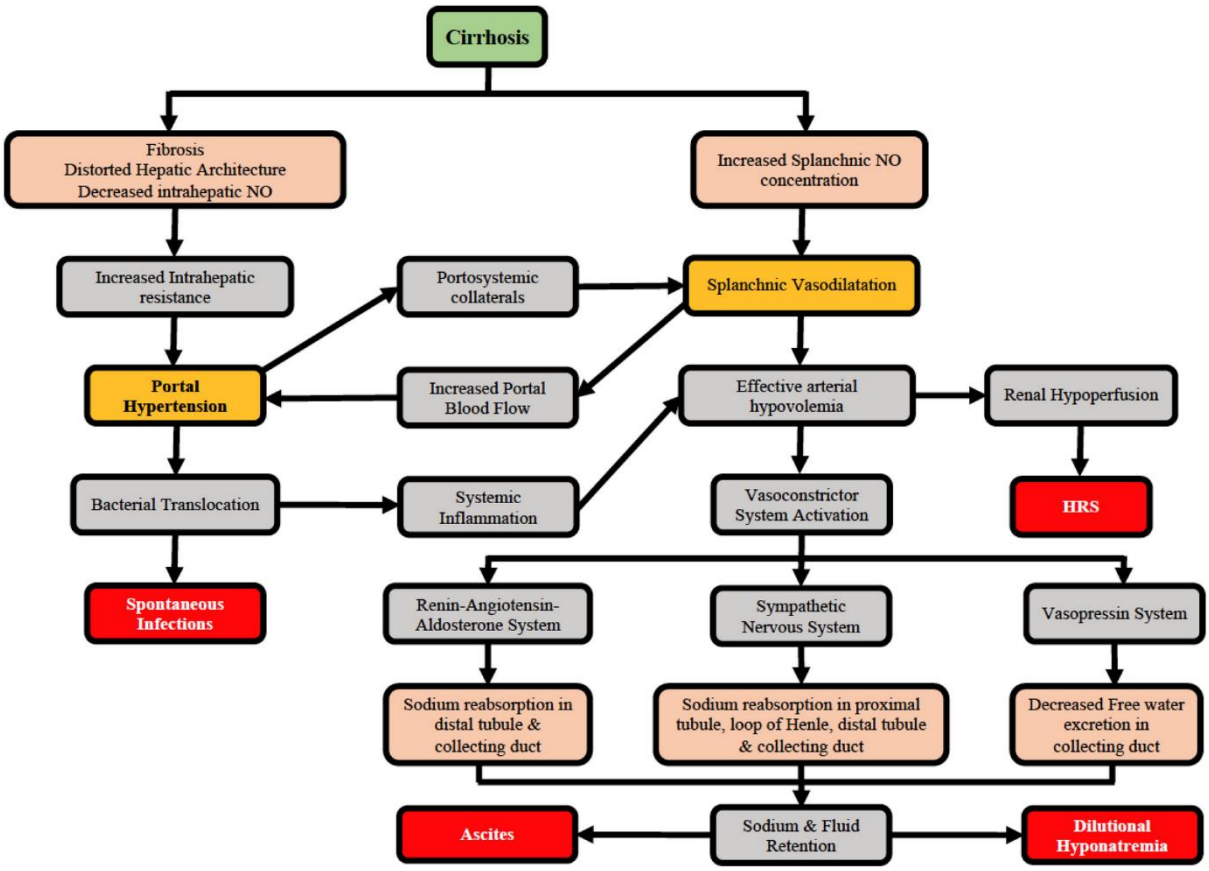

Figure 1. Pathophysiologic mechanisms leading to the development of ascites and its complications in patients with cirrhosis (NO nitric oxide, HRS hepatorenal syndrome

8.1 Diagnosis of ascites

Clinically, ascites may be detected by the presence of shifting dullness and/or fluid thrill. However, shifting dullness requires the presence of at least 1.5 L of fluid in the abdomen. Therefore, ultrasonography of the abdomen is considered the gold standard for the detection of ascites. Ascites can be graded from 1 to 3 according to the amount of fluid in the abdominal cavity. [144]

Table 18. Grading of ascites

Grade 1	Mild ascites	Only detectable by ultrasound examination
Grade 2	Moderate ascites	Moderate symmetrical distension of abdomen
Grade 3	Large or gross ascites	Marked abdominal distension

8.1.1 Evaluation of a patient with ascites

An essential aspect of managing ascites is identifying the cause of ascites. Initial patient evaluation should include history, physical examination, abdominal ultrasound, and laboratory assessment of liver and renal functions, serum and urine electrolytes, as well as an analysis of the ascitic fluid. While the commonest cause is portal hypertension, other causes like tuberculosis, malignancy, renal failure, heart failure, and pancreatic diseases need to be ruled out.

8.1.2 Diagnostic paracentesis

Ascitic fluid protein and serum ascites albumin gradient (SAAG) are the investigations of choice to differentiate portal hypertensive ascites from non-portal hypertensive ascites. Classically, patients with cirrhosis have low ascitic fluid protein (< 2.5 g/dL) with elevated serum ascites albumin gradient (SAAG). A value of SAAG ≥ 1.1 g/dL (> 11 g/L) for portal hypertensive ascites has a high diagnostic accuracy of 97%. [145] Fig.2 illustrates Diagnostic evaluation and differential diagnosis of ascites in a patient with cirrhosis. Other tests, such as amylase, cytology, or culture for mycobacteria should be guided by clinical presentation.

Table 19. Contraindications to paracentesis.

Uncooperative patient
Abdominal skin infection at the proposed puncture sites
Pregnancy
Severe coagulopathy (accelerated fibrinolysis or disseminated intravascular coagulation)
Severe bowel distension

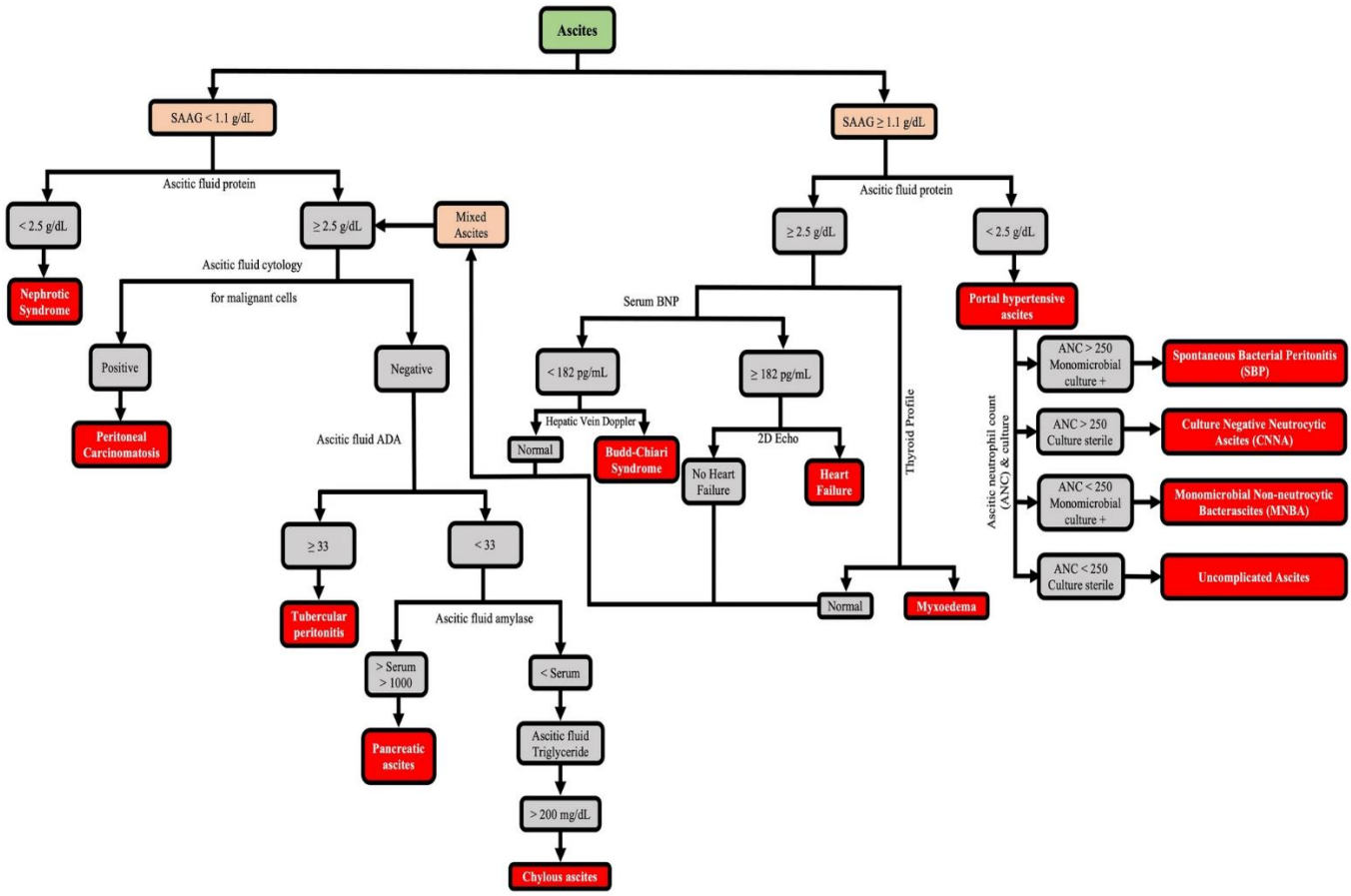

Fig 2: Diagnostic evaluation and differential diagnosis of ascites in a patient with cirrhosis (SAAG serum ascitic albumin gradient; *BNP* brain natriuretic peptide, *ANC* absolute neutrophil count)

Diagnosis of "mixed ascites" poses a clinical challenge in patients with cirrhosis. Mixed ascites refers to the presence of cirrhosis plus an additional cause of ascites. It is usually associated with peritoneal diseases like peritoneal tuberculosis (TB) or peritoneal carcinomatosis. Approximately 5% of patients with cirrhosis have mixed ascites. [145]

Recommendation (Diagnosis of ascites)

113. A diagnostic paracentesis is recommended in all patients with new onset grade 2 or 3 ascites, or in those hospitalized for worsening of ascites or any complication of cirrhosis.

114. Initial laboratory evaluation in patients with the first episode of ascites should include ascitic fluid total protein, albumin, SAAG, and neutrophil count.

115. Neutrophil count and culture of ascitic fluid (bedside inoculation blood culture bottles with 10 ml fluid each) should be performed to exclude bacterial peritonitis. A neutrophil count above 250 cells/µl is required to diagnose SBP.

116. Cytology should be performed to differentiate malignancy-related from non-malignant ascites. At least 30 mL of ascitic fluid should be sent.

8.2 Management of ascites

8.2.1 General Management of ascites

Patients with cirrhosis and ascites have effective arterial hypovolemia. The drugs aggravating this hemodynamic abnormality such as nonsteroidal anti-inflammatory drugs (NSAIDs) [147] and ACE inhibitors or ARBs [148] should not be used. Nephrotoxic drugs including aminoglycoside antibiotics should be avoided. [149]

Dietary salt restriction is not recommended in patients without ascites. Strict sodium restriction (< 10 mmol/day) leads to a greater incidence of hyponatremia and renal dysfunction due to diuretic use. [149] A sodium-restricted diet is also associated with poor compliance and leads to a 20% decrease in the daily caloric intake. [150] Therefore, only a moderate sodium restriction of 80–120 mmol/day or 5–6.5 g salt/day (one teaspoon) is recommended in patients with cirrhosis and ascites. That means no added salt diet with avoidance of precooked meals, and processed foods (dried fish, salted fish in dry and wet forms, and pickles). Patients with cirrhosis and ascites should receive nutritional counseling on the sodium content in the diet.

Recommendation (General Management of ascites)
117. Alcohol abstinence and etiological treatment (like antivirals for chronic viral hepatitis) is strongly advocated for the management of ascites in patients with cirrhosis.
118. NSAIDs, ACE inhibitors, ARBs, and other nephrotoxic agents should be avoided in patients with ascites.
119. Neutrophil count and culture of ascitic fluid (bedside inoculation blood culture bottles with 10 ml fluid each) should be performed to exclude bacterial peritonitis. A neutrophil count above 250 cells/µl is required to diagnose SBP.
120. In patients with cirrhosis and clinical ascites, moderate sodium restriction (80–120 mmol/day, corresponding to 2–3 g of sodium or 5–6.5 g table salt (NaCl) per day is recommended (no added salt diet with avoidance of pre-cooked meals and processed foods). Extreme sodium restriction (< 40 mmol/day) should be avoided and is associated with decreased caloric intake.

8.2.2 Diuretics therapy for ascites

Activation of RAAS has a significant role in ascites formation and aldosterone antagonists like spironolactone are the first-line agents for ascites mobilization. Another class of diuretics commonly used is loop diuretics which includes furosemide and torsemide. Since spironolactone acts downstream to inhibit sodium reabsorption, it has a more potent effect than furosemide in non-azotemic cirrhosis. [151]

However, in patients with long-standing ascites, proximal sodium reabsorption is an important cause of sodium retention, which can be alleviated by loop diuretics. A combination of an aldosterone antagonist and a loop diuretic is preferred in this setting. Spironolactone alone is preferable in patients with a first onset of moderate ascites whereas a combination of spironolactone and furosemide is optimal in patients with persisting ascites or hospitalized patients, where a rapid diuresis is required. It is recommended to start spironolactone at a dose of 100 mg and gradually increased to 400 mg and furosemide at a dose of 40 mg and sequentially increased to 160 mg, it may be reasonable to start these at a lower dose of 50 mg of spironolactone and 20 mg furosemide in Asian patients with new onset ascites. Diuretics are usually administered as a single daily dose in the morning to maximize compliance and minimize nocturia. [152]

8.2.2.1 Monitoring response to therapy

Monitoring response to diuretic therapy is important to optimize the dose to achieve maximum natriuresis while simultaneously reducing complications. The maximum permissible weight loss in patients who do not have pedal edema is 0.5 kg/day, while it is 1 kg/ day in patients with pedal edema. Measurement of 24-hour urinary sodium helps to quantify natriuresis and is a valuable guide to diuretic therapy. The goal should be the excretion of at least 78 mmol/day of sodium in urine (88 mmol dietary intake—10 mmol insensible sodium loss).

A lack of response to diuretic therapy is defined as a less than 0.8 kg weight loss over four days with low urinary sodium excretion (less than sodium intake). Diuretics should be reduced to the lowest dose as soon as possible after mobilization of ascites to keep the patients' ascites free.

8.2.2.2 Side effects of diuretic therapy

Common side effects include hypokalemia, hyperkalemia, hyponatremia, renal dysfunction, or hepatic encephalopathy. [153] Spironolactone is frequently associated with gynecomastia, which can be alleviated with amiloride or eplerenone. [154] Muscle cramps are common in advanced cirrhosis, which is often aggravated with diuretics. [155] Recent studies have demonstrated improvement in debilitating muscle cramps through the use of baclofen [156] , methocarbamol [157], and taurine. [158] Albumin was also shown to have some benefits in treating muscle cramps. [155] Although Quinidine 400 mg/day for four weeks in patients with cirrhosis is effective for painful muscles, it was associated with diarrhea in about one-third of cases requiring treatment withdrawal. [159]

Recommendation (Diuretics therapy for ascites)

121. Patients who present with grade 3 ascites should be treated with a combination of spironolactone (100 mg) and furosemide (40 mg) daily.
122. Patients who present with a first episode of moderate ascites may be treated either with daily spironolactone alone or a combination of spironolactone and furosemide.
123. The dose should be gradually increased every 3rd day till control of ascites or maximum tolerated dose (not to exceed 160 mg of furosemide or 400 mg of spironolactone). Urinary Na level should be monitored, and diuretics dose can be adjusted according to it.
124. As the maximum doses of diuretics are influenced by the patients' profiles and conditions such as race, statures, age, and dietary habits, Myanmar cirrhotic patients can't tolerate high doses of diuretics.
125. Patients who develop hyperkalemia to spironolactone alone should be treated with a combination of spironolactone and furosemide.
126. Once ascites is controlled, diuretics should be tapered to the minimum possible dose.
127. Diuretics should be withheld if patients develop complications like acute kidney injury (AKI), serum sodium < 125 mmol/L, serum potassium < 3 mmol/L or > 6 mmol/L, overt hepatic encephalopathy, SBP, development of incapacitating muscle cramps.

8.2.3 Large volume paracentesis (LVP) for ascites

LVP (removal of > 5 L of ascitic fluid) is considered the treatment of choice for patients who present with tense ascites. [160] For patients undergoing LVP, volume replacement with intravenous albumin (6–8 g for each liter of ascitic fluid cleared) should be done to prevent paracentesis-induced circulatory dysfunction (PICD). [161] Once there is a reduction in intra-abdominal pressure by LVP, patients should be started on diuretics, to reduce the need for frequent paracentesis. The left lower quadrant has been suggested as the ideal site for paracentesis, as it is associated with a greater depth of ascites and a lower abdominal wall thickness.

Routine prophylactic transfusion of fresh frozen plasma or platelets is not recommended to correct INR or platelet count respectively, before paracentesis. However, paracentesis should not be performed in the presence of disseminated intravascular coagulation (DIC). Using ultrasound to guide paracentesis has been shown to be beneficial in reducing the risks of complications and should be used when available. [162]

Recommendation (Large volume paracentesis for ascites)

128. LVP is the treatment of choice for patients with grade 3 ascites.
129. LVP should be done with volume replacement with intravenous albumin (6–8 g/L of ascitic fluid removed).
130. Because of the risk of PICD after LVP, paracentesis is routinely done to get symptomatic relief.
131. LVP is rather hazardous and should be carried out with care. In Myanmar, this is not recommended because albumin is prohibitively expensive and impractical to use.
132. After LVP, diuretics should be continued at the lowest dose possible, to prevent re-accumulation of ascites.

8.3 Refractory Ascites (RA)

According to the International Club of Ascites, refractory ascites (RA) is defined as "ascites that cannot be mobilized or the early recurrence of which cannot be satisfactorily prevented by medical therapy". It can be further differentiated into diuretic resistance (lack of response to sodium restriction and maximal diuretic therapy) or diuretic intractable (development of diuretic-induced complications that preclude the use of an effective diuretic dose). Approximately 5–10% of patients with cirrhosis will develop RA that leads to a significant reduction in survival [163] hence, they should be considered for a liver transplant.

8.3.1 Sodium-restricted Diet and Diuretic Use

Moderate sodium restriction is required for all ascites forms as it prevents rapid reaccumulation of fluid. Diuretics should be discontinued in patients with diuretic-resistant ascites to decrease the risk of complications. Patients with diuretic-intractable ascites may be treated with a lower dose of diuretics.

8.3.2 Use of albumin

The use of intravenous albumin at a dose of 40 g every 2 weeks along with midodrine (15–30 mg/day) in patients with advanced cirrhosis awaiting liver transplant did not lead to improved survival or decreased complications of cirrhosis. [164] However, a recent non-randomized study utilizing 20 g twice weekly albumin and sodium restriction in patients with refractory ascites undergoing LVP reduced hospitalization and mortality. [165] Therefore, more evidence is needed before long-term albumin infusion can be recommended for patients with refractory ascites.

8.3.3 Large Volume Paracentesis (LVP)

The first-line therapy for patients with RA is LVP. Repeated LVP is comparable to the use of diuretics in terms of survival but with a favorable safety profile regarding renal impairment, electrolyte imbalance, and hemodynamic stability. [166] Albumin infusion is necessary to prevent hemodynamic alterations and PICD when > 5 L of ascitic fluid is removed.[167]

8.3.4 Transjugular intrahepatic portosystemic shunt (TIPS)

TIPS creates an artificial connection between the portal and hepatic vein, which leads to decompression of the portal system and reduces portal pressures. MELD > 18 and CTP > 12 are considered contraindications for TIPS and these patients should be evaluated for LT. The presence of recurrent, overt, non-precipitated HE and severe cardiac dysfunction is also a contraindication for TIPS placement. Advanced age, sarcopenia, and cardiopulmonary insufficiency correlate with increased post-TIPS HE and other complications. It is proposed that a smaller diameter TIPS stent protects against the development of post-TIPS HE while having a similar efficacy in reducing portal hypertensive complications. [168] Patients with persistent ascites at 12 months, despite a patent TIPS stent, should be evaluated for LT. Also, patients with advanced cirrhosis (MELD > 18 or CTP > 12) in which TIPS is contraindicated should be considered for LT.

8.3.5 Medical treatment

Midodrine may be used in patients with RA and may be particularly beneficial in patients with low MAP. [169] Midodrine should be started at a dose of 5 mg thrice a day and titrated according to the increase in mean arterial pressure. Low-dose tolvaptan may be used for refractory ascites in a clinical trial setting to improve ascites control and to decrease adverse events to a standard diuretic regimen. [170]

Recommendation (Management of Refractory ascites)

133. Dietary salt restriction (5–6.5 g/day) should be continued in patients with RA to decrease the rate of ascitic fluid accumulation.
134. Diuretics should be withheld in refractory ascites. In patients with diuretic-intractable ascites, diuretics may be initiated at a lower dose after correction of the diuretic-induced complication.
135. Repeated LVP is the first line of treatment for RA.
136. Albumin should be infused after LVP (> 5 L fluid removed) at the rate of 6–8 g/L for each liter of ascitic fluid removed to prevent PICD.
137. Although the procedure is not available in Myanmar, TIPS may be considered for managing RA as a bridge to liver transplants or in transplant-ineligible patients.
138. Liver Transplantation should be considered in all patients with RA.

8.4 Prognosis of Patients with Ascites

The development of ascites in patients with cirrhosis is associated with a poor prognosis, as their one and two-year mortality is about 40 and 50%, respectively. [171] Thus, patients with ascites should generally be considered for referral for LT. Hyponatremia, low arterial pressure, glomerular filtration rate (GFR), and low renal sodium excretion are independent predictors of mortality in cirrhosis with ascites. [172]

9. Spontaneous Bacterial Peritonitis (SBP)

9.1 Diagnosis

SBP is the most common bacterial infection in a patient with cirrhosis, seen in approximately 35% of patients from Asia. Community-acquired bacterial infections were seen in 56% of patients from Asia, while 24% were healthcare-associated (contact with a health-care facility in the last 90 days) and 20% were nosocomial. [173]

Commonly seen clinical features of SBP may include features of systemic inflammatory response syndrome (SIRS) like fever or hypothermia, leukocytosis or leukopenia, tachycardia and/or tachypnoea, symptoms and/or signs of peritonitis like abdominal pain, tenderness, vomiting or diarrhea, and presentation with acute decompensation or ACLF.

All patients suspected of SBP should undergo a diagnostic paracentesis as soon as possible along with inoculation of 10 mL ascitic fluid in a blood culture bottle at the bedside. Traditionally, ascitic fluid neutrophil count > 250 cells/mm^3 along with a positive monomicrobial ascitic fluid culture in the absence of a surgically treatable intra-abdominal source of infection has been used to define SBP. Ascitic fluid neutrophil count > 250 cells/mm3 in the absence of a positive culture is known as culture-negative neutrocytic ascites (CNNA). As the clinical course of both SBP and CNNA is similar, for practical purposes, CNNA is also treated as SBP as the yield of ascitic fluid culture is low. [174]

Recommendation (Diagnosis of Spontaneous Bacterial Peritonitis)
139. SBP is diagnosed when the ascitic fluid neutrophil count is > 250/mm3.
140. Ascitic fluid cultures should be obtained during initial diagnostic paracentesis. It is not required to diagnose SBP but is essential in guiding antibiotic therapy.
141. Blood cultures should also be obtained in patients with suspected SBP before initiating antibiotic therapy.
142. Patients with bacterascites and symptoms suggestive of SBP should receive antibiotic therapy.
143. Patients with bacterascites without any symptoms should have a repeat ascitic fluid work-up at the time of receipt of microbiological culture reports.
144. Patients should receive antibiotic therapy if persistently positive culture or ascitic fluid neutrophil count > 250/mm3 on repeat work-up.

9.2 Management of Spontaneous Bacterial Peritonitis

Patients with SBP must be started on empiric antibiotic therapy as early as possible, as a delay in instituting antibiotic treatment correlates with increased mortality. [175] Most commonly isolated organisms include Gram-negative bacteria (Escherichia coli, Klebsiella pneumonia) followed by Gram-positive bacteria (Staphylococcus aureus, Enterococcus faecalis, and Enterococcus faecium).

Empirical antibiotic therapy must be initiated immediately after the diagnosis of SBP.[176] Cefotaxime, a third-generation cephalosporin was initially investigated extensively for treating SBP as high ascitic fluid concentrations are achieved and it covers more than 95% of organisms isolated from ascitic fluid. [177] However, antibiotic resistance is increasing with the increased prevalence of multidrug-resistant (MDR) and gram-positive organisms isolated from ascitic fluid. [173] Thus, it is necessary to identify risk factors associated with MDR organisms and to guide antibiotic therapy accordingly. Appropriate empirical antibiotic therapy selection should be guided according to community-acquired, healthcare-associated, or nosocomial SBP and the prevalence of local antibiotic resistance patterns. Treatment with intravenous albumin leads to a significantly lower incidence of renal dysfunction and lower mortality than patients who were not treated with albumin. [178-180] Although the dose of albumin used by Sort et al. [178] in their landmark trial was 1.5 g/kg body weight on day 1 and

1 g/kg on day 3, a lower dose of albumin was also found beneficial in preventing AKI in the Asian population. [179]

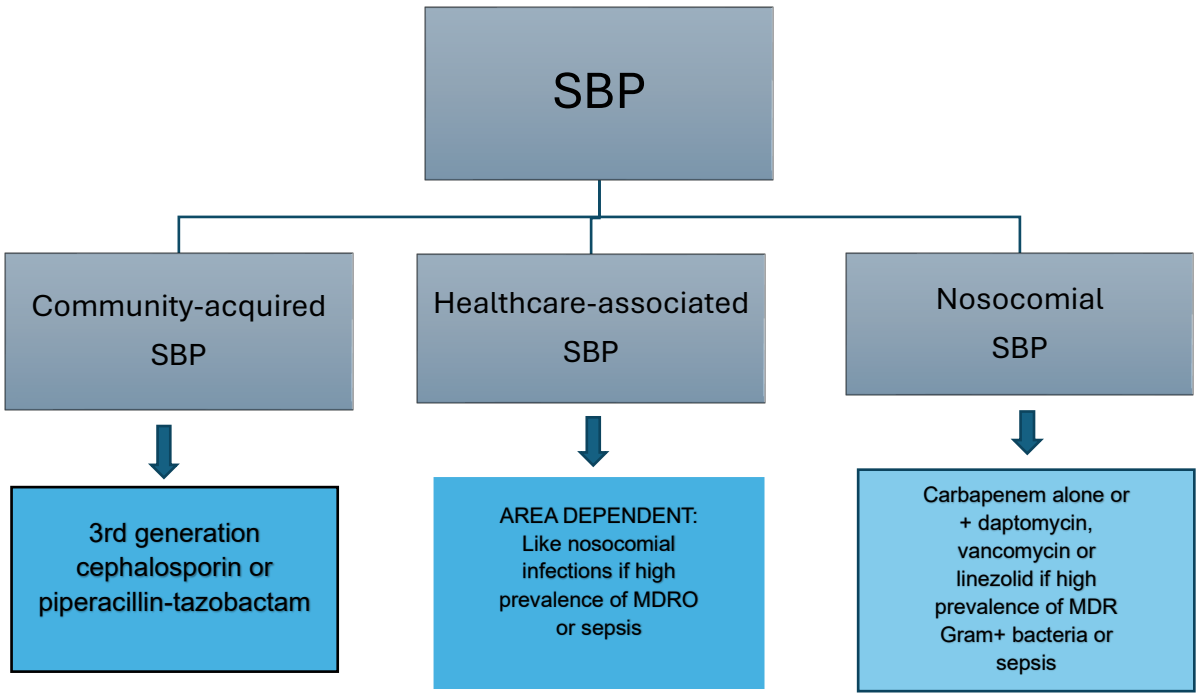

Fig. 3. Recommended empirical antibiotic treatment of SBP or SBE (adapted from Ref. 6). SBE, spontaneous bacterial empyema; SBP, spontaneous bacterial peritonitis; MDRO, multidrug-resistant organism

Recommendation (Management of Spontaneous Bacterial Peritonitis)

145. Empirical antibiotics should be initiated as soon as possible after a diagnosis of SBP.
146. For community-acquired SBP, third-generation cephalosporins are the drug of choice. However, areas with a high prevalence of MDR may need to be treated with piperacillin/tazobactam or carbapenems.
147. For healthcare-associated or nosocomial SBP, piperacillin/tazobactam is preferred in areas with low antibiotic resistance while carbapenems are preferred in regions with high antibiotic resistance.
148. In areas with a high prevalence of gram-positive infections, vancomycin should be added if the incidence of VRE is low. Daptomycin should be added in areas with an increased risk of VRE.
149. Antibiotic therapy should be guided according to the isolate on ascitic fluid culture. Antibiotics should be de-escalated as soon as possible based on the culture report.
150. Patients who are not improving clinically, or have risk factors for MDR organism, should undergo a repeat diagnostic paracentesis 48 hours after starting empiric antibiotics. In addition, antibiotics should be upgraded in patients with less than a 25% decrease in neutrophil count from baseline.
151. The duration of antibiotic therapy for SBP should be at least 5–7 days.
152. Intravenous albumin is recommended in patients with SBP who are at high risk of AKI [S. Bilirubin > 4 mg/ dL (68.4 µmol/L) and/or S. Creatinine > 1 mg/dL (88.4 µmol/L). The dose of albumin should be 1.5 g/kg on day 1 within 6 hours of diagnosis and 1 g/kg on day 3.

9.3 Prophylaxis for Spontaneous Bacterial Peritonitis

9.3.1 Primary Prophylaxis for Spontaneous Bacterial Peritonitis

The use of a short course of antibiotics (5–7 days) to prevent SBP in patients presenting with upper gastrointestinal (GI) bleeding is well established. Low ascitic fluid protein is a risk factor for developing SBP. A landmark study demonstrated a significant reduction in the first SBP episode due to norfloxacin in patients with low ascitic fluid protein and severe liver disease [CTP ≥ 9 and serum bilirubin ≥ 3 mg/dL (51.3 µmol/L)] or renal dysfunction [serum creatinine

≥ 1.2 mg/dL (106.1 µmol/L), BUN ≥ 25 mg/dL, or serum sodium ≤ 130 mEq/L].[39]Ciprofloxacin or trimethoprim-sulfamethoxazole can be used in place of norfloxacin for primary SBP prophylaxis. [182,183]

9.3.2 Secondary Prophylaxis for Spontaneous Bacterial Peritonitis

The use of norfloxacin has decreased SBP recurrence from 68 to 20%. [184] The use of Rifaximin was also associated with lower mortality. [185] Rifaximin has also been shown to be effective in a meta-analysis for primary and secondary prophylaxis. [186]

As norfloxacin is used widely for the secondary prophylaxis of SBP, there is an increased incidence of quinolone-resistant and Gram-positive SBP. Rifaximin is a nonabsorbable broad-spectrum, gut-selective, low microbe-resistant antibiotic, has been proposed as an oral alternative antibiotic to norfloxacin to prevent SBP. [185,187]

Recommendation (Prophylaxis for Spontaneous Bacterial Peritonitis)

153. Patients with cirrhosis presenting with variceal bleeding should receive prophylaxis for SBP. Intravenous ceftriaxone or cefotaxime has been widely used.

154. Patients with cirrhosis and low ascitic fluid protein (< 1.5 g/L) are at high risk for SBP. Among this group, patients having severe liver disease [CTP ≥ 9 and serum bilirubin ≥ 3 mg/dL (51.3 µmol/L)] or renal dysfunction [S. creatinine ≥ 1.2 mg/dL (106.1 µmol/L), BUN ≥ 25 mg/dL, or S. Na ≤ 130 mEq/L] should receive primary antibiotic prophylaxis for SBP.

155. Patients who recover from SBP should receive long-term prophylaxis with oral norfloxacin, ciprofloxacin, or cotrimoxazole.

156. While evidence for rifaximin use as prophylaxis is promising, more data is needed before it can be recommended as prophylaxis of SBP per se.

157. Patients who develop SBP and have recovered should be considered for Liver Transplantation.

10. Hyponatremia

Hyponatremia is common in patients with advanced cirrhosis and has been arbitrarily defined as serum sodium concentration lower than 130 mmol/L. [188] Patients with hyponatremia have a poor prognosis, as it is associated with increased mortality [189,190] and morbidity, particularly neurological complications. [191,192]

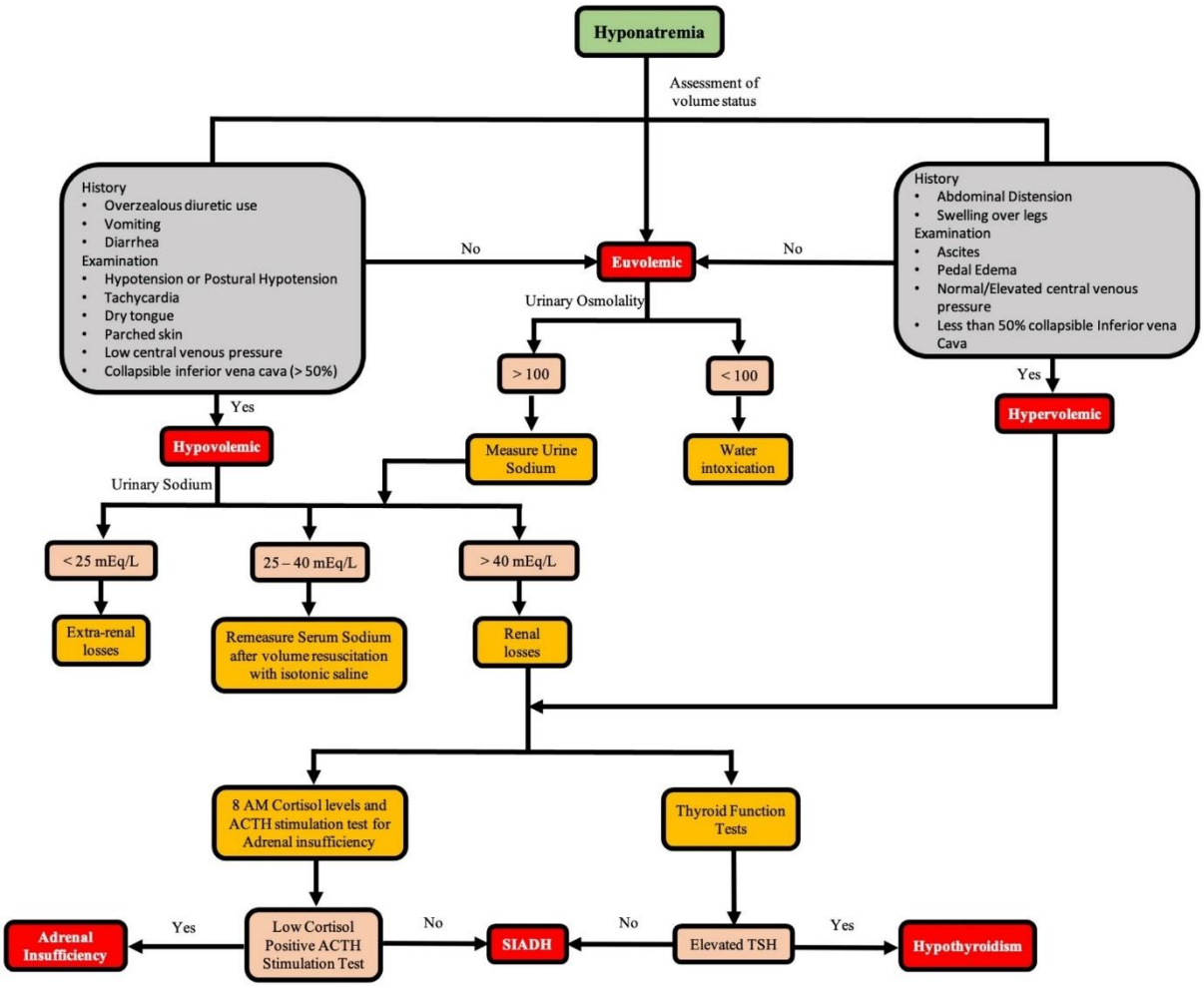

Fig 4 Algorithm for diagnosis of hyponatremia in patients with cirrhosis

10.1 Management of Hypervolemic Hyponatremia

10.1.1 Fluid Restriction

Fluid restriction (1–1.5 L/day) is often prescribed in patients with dilutional hyponatremia to maintain a negative water balance. Fluid restriction should be advised for patients with symptomatic or severe hyponatremia. Although free water restriction is the cornerstone of managing dilutional hyponatremia, there is insufficient evidence to support the amount of fluid restriction or the sodium threshold at which fluid restriction should be started.

Another problem with fluid restriction is that when used alone, only 55% of patients with a serum sodium level < 125 mEq/L will increase serum sodium by > 5% at day 3. [193]

10.1.2 Hypertonic Saline

Hypertonic saline is associated with volume overload and worsening of ascites and pedal edema and hence its use should be restricted to patients with severe symptomatic hyponatremia, i.e., associated with seizures, coma, or cardio-respiratory distress or those expecting a liver transplant within a few days. However, caution should be exerted regarding rapid sodium correction as it predisposes to central pontine myelinolysis, and a target sodium increase of less than 8 mEq/L per day should be kept. [194]

10.1.3 Albumin

Albumin infusion appears to improve serum sodium concentration, but more information is needed. [195] Hospitalized patients with cirrhosis and hyponatremia who received intravenous albumin had a higher rate of hyponatremia resolution independent of renal function and baseline sodium levels, which was in turn associated with a better 30-day survival. [196] In addition, long-term albumin infusion is associated with a lower hyponatremia incidence. [197] However, the significant cost associated with treatment is an issue.

10.1.4 Vaptans

Vaptans are selective V2 receptor antagonists that act on the principal cells in collecting ducts in the nephron and enhance free water excretion. oral tolvaptan 15 mg for 30 days improves serum sodium concentration in patients with euvolemic or hypervolemic hyponatremia in the SALT-1 and SALT-2 trials. [198]

Recommendation (Management of Hyponatremia)
158. Diuretics should be discontinued in patients developing moderate-severe or symptomatic hyponatremia.
159. Free water restriction to < 1L/day is recommended in patients with moderate-severe or symptomatic hyponatremia to prevent further decrease in serum Na levels.
160. Short-term treatment with hypertonic saline may be used in patients with symptomatic or severe hyponatremia or those planned for imminent Liver Transplantation.

11. Hepatic Hydrothorax

Hepatic hydrothorax (HH) is the accumulation of transudative fluid in the pleural cavity in a patient with portal hypertension without any pulmonary, cardiac, or pleural disease. It occurs because of the transmigration of ascitic fluid through small diaphragmatic defects due to negative intrathoracic pressure during inspiration. Approximately 4–12% of patients with cirrhosis have HH, which is mainly seen on the right side. [199] Unilateral left-sided effusion can occur in 17% of patients while bilateral HH is seen in around 10% of patients. [199] Initial management is similar to that of ascites, with sodium restriction and diuretics. If ascites is present, LVP with IV albumin may improve ventilatory function. Therapeutic thoracentesis is required to provide symptomatic relief from dyspnoea but the effect is transient. Repeated procedures increase the risks of complications, including pneumothorax, bleeding, and pleural infection. [200] Refractory or recurrent HH is best treated with TIPS or LT. Indwelling tunneled pleural catheters, chemical pleurodesis, video-assisted thoracoscopic surgery (VATS) or pleurovenous shunt may be offered on a case-to-case basis to patients who are not candidates for TIPS or LT. [201-203]

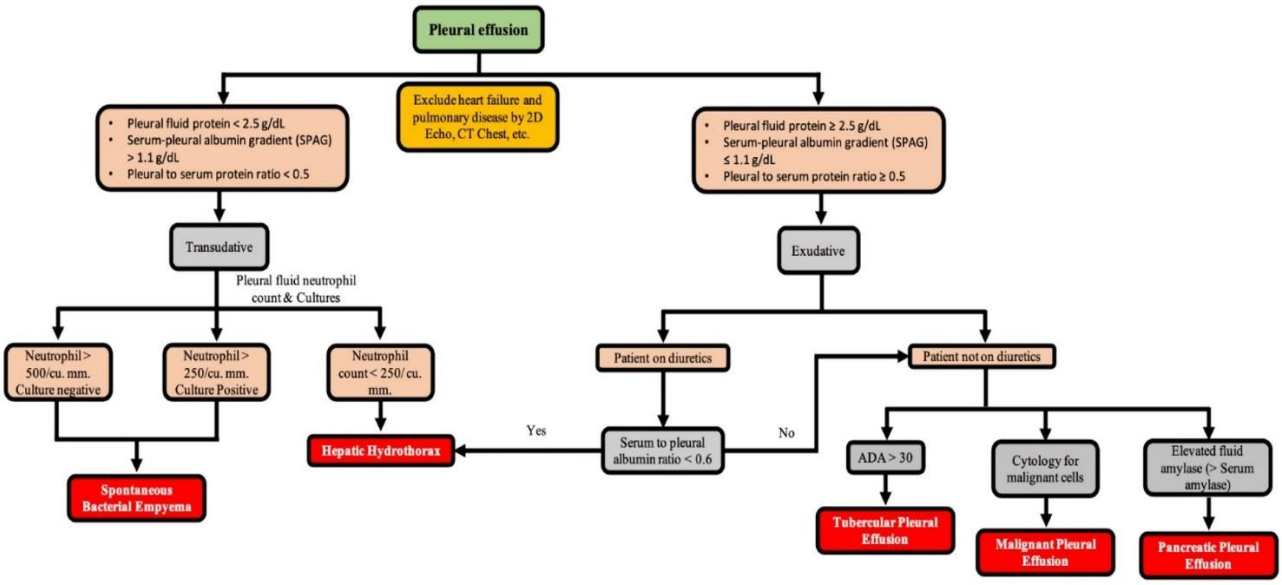

Fig. 5 Algorithm for diagnostic evaluation of pleural effusion in a patient with cirrhosis

Recommendation (Management of Hepatic Hydrothorax)

161. First-line management of Hepatic Hydrothorax consists of sodium restriction and diuretics.

162. Diagnostic thoracentesis should be done in patients with new onset pleural effusion, isolated left-sided pleural effusion, and pleural effusion in the absence of ascites.

163. Therapeutic thoracentesis is indicated in patients with dyspnea. Chronic pleural drainage should not be performed because of the frequent occurrence of complications.

164. TIPS should be considered in patients without other contraindications.

165. Liver transplantation is the modality of choice for patients with refractory Hepatic Hydrothorax.

166. Chemical Pleurodesis can be suggested to patients with refractory hepatic hydrothorax not amenable to LT or TIPS insertion.

12. Cardiopulmonary Complications: Cirrhotic Cardiomyopathy

12.1 Definition of Cirrhotic Cardiomyopathy

Cirrhotic cardiomyopathy (CCM) is defined as cardiac dysfunction in patients with cirrhosis in the absence of prior heart disease. [204,205] CCM refers to chronic cardiac dysfunction in a patient with established cirrhosis, characterized by a blunted contractile response to stress (pharmacological /surgical or inflammatory). There is an altered diastolic relaxation, often associated with electrophysiological abnormalities such as prolongation of the QTc interval.[206] Systemic inflammation is thought to be key in inducing myocardial dysfunction associated with impaired diastolic relaxation and decreased left ventricular ejection fraction. Shear stress generated by portal hypertension exhibiting mechanical forces on myocardial fibers may also play a part. [207]

12.2 Diagnosis of Cirrhotic Cardiomyopathy

Cirrhotic cardiomyopathy is clinically asymptomatic in most patients due to peripheral vasodilation, which reduces afterload and compensates for abnormal cardiac function. However, during periods of stress, rapid hemodynamic changes and impaired cardiac response can lead to acute heart failure symptoms. CCM should be suspected in patients with moderate-to-advanced cirrhosis (Child-Pugh Class B or C) who present with exercise intolerance, worsening fatigue, and peripheral edema, especially in the absence of known cardiac disease. These nonspecific symptoms often overlap with those of advancing cirrhosis, contributing to frequent under-recognition and misdiagnosis of CCM. [208]

12.2.1 Systolic Dysfunction in Cirrhotic Cardiomyopathy

Systolic dysfunction refers to impaired left ventricle contractile responses to stress on echo, translating to a resting left ventricular ejection fraction (LVEF) <55%. For most patients with cirrhosis, the resting systolic function is normal or even increased, due to the hyperdynamic circulation and reduced afterload to maintain cardiac output. To investigate systolic dysfunction in cirrhosis, it is necessary to induce circulatory stress either pharmacologically or through exercise. Systolic dysfunction then manifests as a lack of an appropriate left ventricular contractile response to the applied stress. As the disease advances, the progressive reduction in peripheral vascular resistance unmasks systolic dysfunction. [209]

12.2.2 Diastolic Dysfunction in Cirrhotic Cardiomyopathy

Four echocardiographic parameters are required for diastolic dysfunction (DD) assessment: septal and lateral mitral annular peak early diastolic velocity (e'), the ratio of the peak velocity of mitral inflow during early diastole (E) to the average of septal and lateral e' (E/e'), left atrial volume indexed to body surface area, and tricuspid regurgitation (TR) velocity.[209]

The initial diagnostic criteria for CCM resulted from a consensus conference at the 2005 World Congress of Gastroenterology,[210] and are called the WCG criteria. In 2019, a group of multidisciplinary experts in the field (the Cirrhotic Cardiomyopathy Consortium, CCC), generated a new set of diagnostic criteria based on updated echocardiographic imaging parameters, called the CCC criteria.1 The comparisons are shown in Table 20. [204]

Table 20. Diagnostic criteria system for cirrhotic cardiomyopathy

Criteria	Systolic Dysfunction	Diastolic Dysfunction
WCG criteria (2005)	LVEF <55% (or) Blunted increase in contractility on stress testing	E/A ratio <1.0 (or) DT >200 ms (or) IVRT >80 ms
CCC criteria (2019)	LVEF ≤50% (or) GLS <18	**≥3 of the following** - E/e' ratio ≥15 - e' septal<7 cm/s - TR velocity >2.8 m/s - LAVI >34 ml/m2

CCC, Cirrhotic Cardiomyopathy Consortium; DT, mitral deceleration time; E/A, E-wave to A-wave ratio; GLS, global longitudinal strain (absolute value); IVRT, isovolumetric relaxation time; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation; WCG, World Congress of Gastroenterology

12.3 Clinical Relevance of Cirrhotic Cardiomyopathy Consortium (CCM)

CCM, although subclinical in resting status, is significant because when the cardiovascular system is challenged, such as by liver transplantation, trans jugular intrahepatic portosystemic shunt (TIPS), drugs, and exercise [211], cardiac dysfunction can become overt. Liver transplantation challenges the cardiovascular system. Intravenous fluids augment

preload, an increased systemic vascular resistance elevates afterload, and therefore, liver transplantation significantly increases the cardiac workload which aggravates the preexisting CCM. It was demonstrated that cardiovascular complications are the third-leading cause of death in patients after liver transplantation, accounting for 7–21% of deaths. [212] Cardiac events such as arrhythmias, angina, and heart failure decrease the rates of patient and graft survival.[213]

The study by Ruiz-del-Arbol et al. demonstrated that in patients with resolving spontaneous bacterial peritonitis, lower cardiac output is significantly correlated with the development of hepatorenal syndrome (HRS). [214] It also showed that the number of patients who developed HRS type 1 within 3 months was higher in patients with low cardiac index than in those with high cardiac index. [215] These studies suggest that inadequate systolic contractile response to a significant cardiovascular challenge posed by infection or the peripheral vasodilatation of end-stage cirrhosis, with reduced renal perfusion, contributes to the pathogenesis of acute kidney injury and hepatorenal syndrome.

12.4. Management of Cirrhotic Cardiomyopathy

There are currently no guidelines on the treatment of cirrhotic cardiomyopathy. The general management of overt non-cirrhotic heart failure usually requires oxygen and afterload and preload reduction. [74] Preload reduction includes water and sodium restriction and diuretics. Unfortunately, long-term diuretic application may cause electrolyte imbalances and renal injury. [217] Afterload reduction mainly consists of vasodilation. However, vasodilators are usually not suitable for treating heart dysfunction in cirrhosis because these patients often have significant vasodilatation and hypotension. Thus, there is a real risk that vasodilators may worsen a cirrhotic patient's clinical condition. [218] Therefore, ACE inhibitors or angiotensin receptor blockers are not feasible in patients with advanced cirrhosis. The potential therapies for CCM may include nonselective beta-blockers (NSBBs), antioxidants, and anti-apoptotic and anti-inflammatory agents.

Beta-blockers alleviate systemic inflammation by reducing portal pressure, mesenteric venous congestion, and intestinal permeability, thereby reducing the entry of inflammatory cytokines into the circulation. The alleviation of systemic inflammation may benefit the heart.[211] Moreover, b-blockers shorten the QTc interval in cirrhosis. [219] and thus decrease the risk of ventricular arrhythmias. There is a "window theory" on the use of NSBBs in patients with cirrhosis. Sympathetic nervous system activity is near normal in early-stage cirrhosis, thus

NSBBs may not be effective; in advanced stages of cirrhosis, NSBBs may not be appropriate because they reduce cardiac contractility and arterial pressure. The window phase is thus between “too early and too late”. However, the time points at which the window “opens and closes” remain unclear. [220]

Liver transplantation remains the definitive ‘cure’ for cardiovascular anomalies of cirrhosis. A recent study showed that within one year after liver transplantation, 34% of CCM patients recovered according to the 2005 Montreal criteria and 57% according to the 2019 CCC criteria. [221] However, the recovery process is challenging, and the overall cardiovascular system experiences both risks and benefits. After liver transplantation, the peripheral vascular resistance immediately increases, as does the blood pressure, which raises both cardiac preload and afterload. These challenges may result in overt cardiac failure in patients with CCM. [222]

Currently, a standardized protocol or specific medications are unavailable for the treatment of CCM. Patients should receive standard medical therapy for the management of heart failure and undergo evaluation for liver transplantation.

Recommendation (Management of Cirrhotic Cardiomyopathy)

167. Evaluation of cirrhosis patients with echocardiography should be performed with dynamic stress testing either pharmacologically, or through exercise, because systolic dysfunction may be masked by the hyperdynamic circulation and reduced afterload. Failure to increment cardiac output after physiological/pharmacological stress (and in the absence of influence of beta-blockade) indicates systolic dysfunction.

168. Diastolic dysfunction may occur as an early sign of cardiomyopathy in the setting of normal systolic function, and should be diagnosed using the recent CCC criteria.

169. In patients with advanced cirrhosis, reduced cardiac output (as a manifestation of CCM) is of prognostic significance as it is associated with the development of AKI (specifically hepatorenal dysfunction) after infections such as SBP.

170. Prolongation of the QTc interval is common in cirrhosis and can be evaluated since it may indicate a poor outcome. Agents that can prolong the QT interval should be used cautiously.

171. Detailed functional cardiac characterization should be part of the assessment for TIPS insertion or LT.

172. Treatment of CCM according to the usual Heart failure treatment guideline. Although there are some treatment options beneficial in CCM, the only therapeutic agent is NSBB.

13. Hepatorenal syndrome (HRS)

13.1. Epidemiology of Hepatorenal syndrome

Patients with decompensated cirrhosis and ascites are prone to develop acute kidney injury. Prevalence of AKI in hospitalized patients ranges from 27 to 53% [223] and development of AKI is associated with a high 30-day mortality which ranges from 29 to 44%. [224] post-transplant outcomes are also worse in patients with AKI. [225] Moreover, AKI is an independent negative predictor of transplant-free survival and post-LT outcomes. HRS is a type of AKI, known as HRS-AKI under the current terminology, unique to patients with cirrhosis that occurs in the absence of hypovolemia or significant abnormalities in kidney histology.

13.2 Etiological factors of Hepatorenal Syndrome

Main etiologies for AKI in cirrhosis are prerenal AKI and acute tubular necrosis (ATN).[225] The two main causes of prerenal AKI are hypovolemia and HRS-AKI. ATN is usually due to septic or hypovolemic shock and, less commonly, nephrotoxic drugs/agents. Bile cast nephropathy in patients with hyperbilirubinemia, glomerulonephritis (e.g., immunoglobulin A in alcohol-associated cirrhosis, membranous or membranoproliferative glomerulonephritis in hepatitis B virus/hepatitis C virus cirrhosis), or postrenal obstruction are less common causes of AKI, which should be considered as part of the differential diagnosis.

Once a diagnosis of AKI is made, patients should be classified according to severity into stage 1 (rise in serum creatinine ≥ 0.3 mg/dL (26.53 μmol/L) or 1.5–2-fold increase from baseline), stage 2 (increase in serum creatinine 2–3-fold from baseline) or stage 3 (increase in serum creatinine > 3 times from baseline or creatinine > 4 mg/dL (353.6 μmol/L) or the initiation of renal replacement therapy). [226]

Table 21. Stages of AKI

Stage 1	Increase of creatinine ≥0.3 mg/dL up to 2-fold of baseline
Stage 2	Increase in creatinine between 2-fold and 3-fold of baseline
Stage 3	Increase in creatinine >3-fold of baseline or creatinine >4 mg/dL (353.6 μmol/L) with an acute increase ≥0.3 mg/dL (26.5 μmol/L) or initiation of RRT

13.3 Diagnosis of Hepatorenal Syndrome

Diagnosis of HRS-AKI is made using the consensus criteria after excluding hypovolemia, shock, nephrotoxic agents, and structural kidney damage (Table 22). [227]

Table 22. Diagnosis of HRS-AKI [227]

Diagnosis of HRS-AKI
• Cirrhosis with ascites • Diagnosis of AKI according to International Club of Ascites-Acute Kidney Injury† criteria • No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin infusion (1 g/kg body weight per day) • Absence of shock • No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, or iodinated contrast media) • No signs of structural kidney injury, as indicated by proteinuria (>500 mg per day), microhematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasonography

13.4 Classification of Hepatorenal Syndrome

Patients with HRS were initially classified into HRS-1 and HRS-2 depending on the rapidity of renal dysfunction. However, recently, it has been proposed to sub-classify HRS into HRS-AKI and HRS-NAKI (non-AKI). HRS-NAKI is further classified into HRS-acute kidney disease (AKD) if the estimated glomerular filtration rate (eGFR) is < 60 mL/min per 1.73 m2 for < 3 months and HRS-chronic kidney disease (CKD) if eGFR is < 60 mL/min per 1.73 m2 for > 3 months (Table 23). [228]

Table 23. Classification of Hepatorenal Syndrome (HRS)

Classification	Diagnostic criteria
HRS-AKI	i. Increase in serum creatinine by ≥ 0.3 mg/dL (26.5 μmol/L) within 48 h, and/or ii. Urine output ≤ 0.5 mL/kg body weight for ≥ 6 h, or iii. ≥ 50% increase in serum creatinine from baseline (last available outpatient serum creatinine within 3 months)
HRS-NAKI	**HRS-AKD** i. eGFR < 60 mL/min/1.73 m2 for < 3 months in the absence of structural causes ii. < 50% increase in serum creatinine from baseline (last available outpatient serum creatinine within 3 months) **HRS-CKD** - eGFR < 60 mL/min/1.73 m2 for ≥ 3 months in the absence of structural causes

Determining the cause of AKI in cirrhosis may be difficult, and the differential diagnosis depends on a combination of data from history, physical examination, and urine findings, including urine sediment, fractional excretion of sodium or urea, and urine sodium concentration in patients receiving diuretics.

Differentiating ATN from the severe form of HRS-AKI is particularly challenging because of the lack of clear diagnostic indicators. In recent years, several urine biomarkers of tubular damage have been shown to be potentially useful for differential diagnosis of AKI in cirrhosis, including neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18, liver fatty-acid binding protein, and albumin.[229] Among those, urine NGAL is the most promising biomarker. [230,231]

Recommendation (Diagnosis of Hepatorenal Syndrome)

173. The diagnosis of AKI is based on a rise in serum creatinine by ≥ 0.3 mg/dL (26.5 μmol/L) within 48 h or ≥ 50% increase in serum creatinine from baseline (last available outpatient serum creatinine within 3 months) within the preceding 7 days and/or decrease in urine output to ≤ 0.5 mL/kg/h for ≥ 6 h.
174. Diagnosis of HRS should be made based on revised ICA criteria.
175. The severity of AKI should be staged in all patients based on the adapted KDIGO criteria.
176. Once a diagnosis of AKI is made, its cause should be evaluated, and specific measures should be instituted as soon as possible to prevent the progression of AKI.

13.5 Management of Hepatorenal Syndrome

A diligent search must be conducted for treatable causes such as hypovolemia, drug-induced nephrotoxicity, or urinary tract obstruction. Indwelling bladder catheterization should be avoided. Measurement of urine volume, a component in the diagnosis of AKI, is important because oliguria is associated with poor prognosis. [232] Diuretics should be stopped after the diagnosis of AKI. Withholding NSBBs should be considered, particularly in patients who are hypotensive. [233] The efficacy of prophylactic antibiotics in patients with AKI has not been assessed.

13.5.1 Vasoconstrictors Plus Albumin

Vasoconstrictor drugs are maintained until creatinine returns to baseline values up to 14 days, although in a few cases with very high pretreatment creatinine value, treatment needs to be longer than 14 days to reach the baseline value. Other patients may need prolonged infusions to prevent early recurrence of AKI-HRS after treatment discontinuation. In patients whose creatinine remains at or above the pretreatment level over 4 days with the maximum tolerated doses of the vasoconstrictor, therapy may be discontinued.

Terlipressin, in combination with albumin, is associated with higher likelihood of reversal of HRS and 10-day survival without RRT compared with placebo. Terlipressin is often the first-line drug for patients with HRS. It is a non-selective vasopressin receptor agonist that increases renal perfusion pressure. Terlipressin therapy is associated with a reversal of HRS in 35–80% of patients. [234] Terlipressin-related adverse events include abdominal pain, diarrhoea,

mesenteric ischemia, cardiac arrhythmias, bradycardia, myocardial ischemia, hyponatremia, cyanosis or skin necrosis. [234] The risk of ischemic side effects related to terlipressin may be reduced by administration of the drug in a continuous IV infusion (start dose 2 mg/day, increased every 24-48 hours up to 12 mg/day until creatinine decreases). [235]

Serum creatinine should be monitored on day 3 and if the decrease is < 25%, the dose of terlipressin should be increased, up to a maximum of 12 mg till day. [236] In conjunction with terlipressin, albumin is infused at a dose of 1 g/kg on day 1 of therapy followed by 40-50 g/day, continued for the duration of therapy

Norepinephrine appears to be equally effective to terlipressin, although there are fewer data. [237] Norepinephrine is given as continuous IV infusion, typically in an intensive care unit setting, starting at 0.5 mg/hour to achieve an increase in mean arterial pressure of at least 10 mm Hg or an increase in urine output of >200 mL/4 hours. The dose of norepinephrine is increased every 4 hours in increments of 0.5 mg/hour up to a maximum of 3 mg/hour. [238] Albumin is also given to maintain a central venous pressure between 4 and 10 mmHg.

Oral midodrine (5 to 15 mg per os every 8 hours) in combination with octreotide (100 to 200 µg every 8 hours or 50 µg/hour IV) is of much lower efficacy than terlipressin. [239]

13.5.2 Transjugular Intrahepatic Portosystemic (TIPS)

TIPS is not recommended in patients with AKI-HRS because of insufficient information. [240,241]

13.5.3 Renal Replacement Therapy

Initiation of RRT should be made on clinical grounds, including worsening kidney function, electrolyte disturbances such as severe acidosis, hyponatremia or hyperkalemia not improving with medical management, diuretic intolerance, or increasing volume overload. Continuous RRT is the modality preferred to intermittent dialysis in patients who are hemodynamically unstable.

The initiation of RRT in patients with HRS remains controversial and has typically been reserved for patients considering transplant candidates as a bridge to LT. RRT may be considered in selected patients who are not transplant candidates, depending on the reversibility of other organ failures. [242]

13.5.4 Liver transplant

Restoring liver function by LT is the ultimate therapy for HRS-AKI. However, recovery of kidney function after LT is not always predictable for a number of factors, such as preexisting comorbidities (e.g., CKD or diabetes), unrecognized intrinsic renal disease, unexpected intraoperative events, and posttransplant immunosuppression. [242] In patients unlikely to recover kidney function, simultaneous liver and kidney transplantation may improve posttransplant outcomes. However, because of the shortage of donated kidneys, the optimal use of simultaneous liver and kidney transplantation has been debated.

Recommendation (Management of Hepatorenal Syndrome)

177. HRS management should include by multidisciplinary teams including specialists in hepatology, nephrology, critical care, and transplant surgery.
178. The treatment of choice for HRS-AKI is vasoconstrictor drugs in combination with albumin. The preferred drug is terlipressin, administered either as IV bolus or continuous IV infusion.
179. In settings where terlipressin is not available, nor- epinephrine should be given.
180. Patients should be closely monitored for the possible development of side effects of vasoconstrictors and albumin, including ischemic complications and pulmonary edema.
181. Response to terlipressin or norepinephrine is defined by creatinine decreases to <1.5 mg/dL or return to within 0.3 mg/dL of baseline over a maximum of 14 days. Patients not respond to terlipressin therapy by day 4 with the maximum tolerated doses of the vasoconstrictor, therapy may be discontinued.
182. Recurrence may occur after treatment discontinuation and should be retreated.
183. All patients with cirrhosis and AKI should be considered for urgent LT evaluation given the high short-term mortality even in responders to vasoconstrictors.
184. RRT should be used in candidates for LT with worsening renal function, electrolyte disturbances, or increasing volume overload unresponsive to vasoconstrictor therapy.
185. Given the complexity of patients with suspected HRS-AKI, decisions about management including initiation of vasoconstrictor therapy and RRT should be made, if possible, by multidisciplinary teams including specialists in hepatology, nephrology, critical care, and transplant surgery.

14. Hepato-Pulmonary Syndrome (HPS)

14.1 Definition of Hepato-Pulmonary Syndrome

HPS is defined as a disorder in pulmonary oxygenation, caused by intrapulmonary vasodilatation and, less commonly, by pleural and pulmonary arteriovenous communications occurring in the clinical setting of portal hypertension.

14.2 Clinical manifestations of Hepato-Pulmonary Syndrome

Clinical manifestations of HPS in patients with chronic liver disease primarily involve dyspnoea and platypnoea. Dyspnoea is the most common respiratory complaint in patients with HPS, but it is non-specific. Its onset is insidious, usually occurring on exertion. Platypnoea, which is a shortness of breath exacerbated by sitting up and improved by lying supine, is a less sensitive but a more specific finding in these patients. Hypoxemia with exertion or at rest is common and it is exacerbated in the upright position (orthodeoxia). There are no signs or hallmarks of HPS on physical examination. However, tachypnoea and polypnoea, digital clubbing and/or cyanosis in patients with the hall mark of chronic liver disease suggest the presence of HPS.

14.3 Diagnosis of Hepato-Pulmonary Syndrome

In patients with portal hypertension and the clinical suspicion of HPS partial pressure of oxygen (PaO2) in arterial blood gas (ABG) should be assessed. A PaO2 lower than 80 mmHg and or an alveolar-arterial oxygen gradient (P[A-a] O2) ≥15 mmHg while breathing ambient air at sea level should lead to further investigations. HPS can be categorized as mild (PaO2 ≥80 mmHg), moderate (PaO2 60–79 mmHg), severe (PaO2 50–59 mmHg), and very severe (PaO2 <50 mmHg). [243]

Table 24. Diagnostic Criteria of Hepato-Pulmonary Syndrome

Diagnostic Criteria of Hepato-Pulmonary Syndrome
• Hypoxia with partial pressure of oxygen <80 mmHg or alveolar–arterial oxygen gradient ≥15 mmHg in ambient air (≥20 mmHg in patients older than 65 years). • Pulmonary vascular defect with positive findings on contrast-enhanced echocardiography or abnormal uptake in the brain (>6%) with radioactive lung-perfusion scanning • Commonly in presence of portal hypertension, and in particular: - hepatic portal hypertension with underlying cirrhosis - pre-hepatic or hepatic portal hypertension in patients without underlying cirrhosis • Less commonly in presence of: - acute liver failure, chronic hepatitis

All criteria were determined by means of positive contrast-enhanced echocardiography (i.e., microbubble opacification of the left heart chambers three to six cycles after right atrial passage). The abbreviated formula for the alveolar-arterial gradient is as follows: PaO2. PaO2 = (FIO2 [Patm–PH2O] [PaCO2/0.8]), where PaO2 denotes partial pressure of alveolar oxygen, PaO2 partial pressure of arterial oxygen, FIO2 fraction of inspired oxygen, Patm atmospheric pressure, PH2O partial pressure of water vapor at body temperature, and PaCO2 partial pressure of arterial carbon dioxide (0.8 corresponds to the standard gas-exchange respiratory ratio at rest); the normal range is 4 to 8 mmHg.

Contrast-enhanced transthoracic echocardiography with saline (shaken to produce microbubbles >10 lm in diameter) is the most useful method to detect pulmonary vascular dilatation. Quantitative imaging of the MAA scan in the brain and lung enables the calculation of the degree of shunting. [244] The measurement of shunting with MAA scans may be useful as a complementary diagnostic tool in patients with HPS in two clinical situations. Firstly, in patients with severe hypoxaemia and a coexistent HPS and intrinsic lung disease since a shunting >6% at MAA scan proves the major contribution of HPS to hypoxaemia. Secondly, in patients with HPS and very severe hypoxaemia (PaO2 <50 mmHg), since the presence of shunting >20% is associated with a poor outcome after LT.

Pulmonary angiography should not be performed in all patients with suspected HPS, but only in: a) patients with the severe hypoxaemia (PaO2 <60 mmHg) poorly responsive to administration of 100% oxygen, and b) patients strongly suspected (by means of a CT chest scan) of having arteriovenous communications that would be amenable to embolization.

Recommendation (Diagnosis of Hepato-Pulmonary Syndrome)

186. In presence of tachypnoea platypnoea and orthodeoxia, digital clubbing and/or cyanosis in a patient with the hallmarks of chronic liver disease, HPS should be suspected and investigated.

187. Pulse oximetry is the screening tool for HPS in adult patients, but not in paediatric patients. For patients with SpO2 <96%, ABG analysis should be performed. A PaO2 lower than 80 mmHg and or an alveolar-arterial oxygen gradient (P[A-a] O2) ≥15 mmHg while breathing ambient air, should lead to further investigations. For adults ≥65 years a P[A-a] O2 ≥20 mmHg cut-off should be used.

188. Pulmonary angiography should be performed only in patients with the severe hypoxaemia poorly responsive to administration of 100% oxygen, and in whom there is a strong suspicion of arteriovenous communications that are amenable to embolization.

14.4 Management of Hepato-Pulmonary Syndrome

14.4.1 Medical treatment of Hepato-Pulmonary Syndrome

There is no established medical therapy currently available for HPS Data from several uncontrolled clinical studies and anecdotal evidence indicate that treatment with beta-blockers, cyclooxygenase inhibitors, systemic glucocorticoids and cyclophosphamide, almitrine bismesylate, inhaled nitric oxide, nitric oxide inhibitors, and antimicrobial agents has been uniformly unsuccessful.

TIPS has been proposed to reduce portal pressure in patients with HPS. However, data are insufficient even when a systemic analysis review is considered. [245] long-term oxygen therapy remains the most frequently recommended therapy for symptoms in patients with severe hypoxaemia.

Recommendation (Medical Management of Hepato-Pulmonary Syndrome)
189. Long-term oxygen therapy is recommended in patients with HPS and severe hypoxaemia.
190. No recommendation can be proposed regarding the use of drugs or the placement of TIPS for the treatment of HPS.

14.4.2 Liver transplantation for Hepato-Pulmonary Syndrome

The most common and the only successful treatment for HPS is LT. LT results in a complete reversal or a significant improvement of HPS in more than 85% of patients with severe hypoxaemia. [246]

Recommendation (Liver transplantation for Hepato-Pulmonary Syndrome)
191. Patients with HPS and PaO2 <60 mmHg should be evaluated for LT since it is the only treatment for HPS that has been proven to be effective to date.
192. Since a severe hypoxaemia (PaO2 <45–50 mmHg) is associated with increased post-LT mortality, an ABG analysis should be carried out every six months in order to facilitate prioritisation to LT).

15 Porto-pulmonary Hypertension (PPH)

15.1 Definition and diagnosis of Porto-pulmonary Hypertension

A diagnosis of PPHT should be considered in a patient with established portal hypertension in the absence of other causes of pulmonary artery or venous hypertension. namely: chronic thromboembolism, chronic lung disease/hypoxia; chronic left heart disease. Patients may be asymptomatic but often present with exertional dyspnoea and they may have clinical signs of right heart failure when moderate to severe disease develops. [247] PPHT is graded as mild (mPAP ≥25 and <35 mmHg); moderate (mPAP ≥35 and <45 mmHg), and severe (mPAP ≥45 mmHg). [248] Transthoracic Doppler Echocardiography (TDE) is the main screening tool for evaluating the presence of PPHT when screening high-risk patients, such as those being considered for TIPS or LT. [249]

15.2 Medical treatment of Porto-pulmonary Hypertension

15.2.1 Endothelin receptor antagonists

Bosentan has been shown to improve pulmonary artery hemodynamics and exercise tolerance in patients with PPHT, independently of liver disease severity .[250]

15.2.2 Phosphodiesterase subtype-5 inhibitors.

Blockade of phosphodiesterase-5 inhibitors facilitate the vasodilatory effects of nitric oxide, through reduced metabolism of cGMP.

15.2.3 Prostacyclin analogs

Prostacyclin analogs have many potential benefits including vasodilatory, reduced vascular smooth muscle proliferation, and anti-thrombotic.

15.2.4 Liver transplantation

Historically, severe PPHT has been a relative contraindication for LT because of very poor outcomes. However, with the advent of improved hemodynamic control with agents such as i.v. prostacyclin, there are case series showing normal pulmonary hemodynamics almost two years post-LT. [251]

15.2.4.1 Stratifying risk for Liver transplantation

In patients with an mPAP ≥45–50 mmHg, most centers would deem this an absolute contraindication to transplantation irrespective of the therapy applied.[252] Patients with an mPAP >35 have increased risk post-LT, associated with increased hospital stay and longer

ventilator requirements. [252] If LT is considered in such patients, it is suggested that their PPHT is treated aggressively to lower mPAP and improve right ventricular function. [253] Patients are considered surgical candidates if, after targeted therapy to lower PAP, they have improved mPAP (<35 mmHg) and PVR (<400 dyne/s per cm 5) and/or normalize their PVR. Applying this exception has been noted to reduce waitlist mortality. [254]

Recommendation (Management of Porto-pulmonary Hypertension)

193. Screening for PPHT should be via TDE in patients.
194. In patients with PPHT who are listed for transplantation, echocardiography should be repeated on the waitlist, albeit, the specific interval is unclear.
195. Beta-blockers should be stopped and varices managed by endoscopic therapy in cases of proven PPHT.
196. Therapies that have been approved for primary pulmonary arterial hypertension may have benefits in PPHT to improve exercise tolerance and hemodynamics. However, endothelin antagonists should be used with caution because of concerns over hepatic impairment (II-2;1).
197. TIPS should not be used in patients with PPHT.
198. If mPAP <35 mmHg and right ventricular function is preserved, LT should be considered. A mPAP of ≥45 mmHg should be considered an absolute contraindication to LT irrespective of the therapy applied.
199. Therapy to lower mPAP and improve right ventricular function should be commenced in patients with mPAP ≥35 mmHg. Right ventricular function should be periodically evaluated.

16. Surveillance for HCC

HCC is a highly fatal tumor, with most cases detected at late stages and an incidence-to-mortality ratio that approaches. [256] HCC surveillance should be performed in at-risk individuals, including those with cirrhosis. HCC surveillance is a secondary prevention strategy associated with improved overall survival through the detection of HCC at a very early or early stage. Patients detected at an early stage are eligible to receive potentially curative treatment and can achieve 5-year survival exceeding 70%. [257] Table (25) shows the population at risk for HCC that should undergo surveillance. [255]

16.1 Surveillance tests

HCC surveillance should be performed using ultrasound (USG) and alpha-fetoprotein (AFP). A meta-analysis of available data showed the sensitivity and specificity of ultrasound alone for early-stage HCC detection is only 53% (95% CI, 35%–70%) and 91% (95%CI, 86%–94%), respectively, whereas ultrasound plus AFP achieves a sensitivity of 63% for early-stage HCC (95% CI, 48%–75%). [255] Although contrast-enhanced computed tomography (CECT) and Magnetic resonance imaging (MRI) have superior sensitivity for early-stage HCC detection compared with USG-based surveillance, their uses are limited by concerns about cost-effectiveness, potential harm associated with radiation exposure, and contrast-related injuries. [258] In very obese cases with clinically suspicious HCC (increased AFP) with difficult to examine for detection of HCC, CECT or MRI might be necessary to confirm the diagnosis of HCC.

Although several biomarkers and biomarker panels (for example, GALAD score, [gender, age, Lens culinaris-agglutinin-reactive fraction of AFP (AFP-L3%), AFP, des-gamma-carboxy prothrombin (DCP)]) have shown promising results in early phases of evaluation, most still require validation in large Phase III and Phase IV biomarker cohort studies. [255] Two well-studied biomarkers include AFP-L3%, which measures a subfraction of AFP, and des gamma-carboxy prothrombin (DCP), also called protein induced by vitamin K absence/antagonist-II (PIVKA-II), a variant of prothrombin that is also specifically produced at high levels by a proportion of HCCs. DCP has insufficient sensitivity to detect early-stage HCC when used alone; however, this biomarker may be complementary to AFP. [255]

16.2 Surveillance interval

Semiannual surveillance (approximately every 6 months) is associated with earlier tumor stages and improved survival compared with annual surveillance. This recommendation

is based on HCC tumor doubling time. A subsequent multicenter RCT demonstrated quarterly surveillance did not improve early HCC detection or survival compared with semiannual surveillance. [254] If there are features of cirrhosis of the liver as manifested by clinically or Fibroscan ≥14 kPa, the follow-up should be done 4 monthly. However, the surveillance interval can be tailored to the individualized patients with low risk for HCC such as those young age, advanced fibrosis but without cirrhotic in patients with post-SVR for HCV infection, MASH, alcoholic liver diseases, and family history of HCC present but no history of chronic viral infection.

Table 25. At-risk population for surveillance

Population at high risk
Patients with cirrhosis of liver regardless of any etiology (1) All chronic HBsAg carrier (2) HCV infection including treatment naïve and treated with or without SVR achieved (3) Chronic alcoholic (4) MASLD/MASH

Recommendation (Surveillance for HCC)
200. HCC surveillance should be performed in populations at high risk by using ultrasound and AFP at semiannual (approximately every 6 months) intervals or as required.

17. Liver Transplantation

17.1 Indications for Liver Transplantation

Liver transplantation (LT) is indicated for severe acute or advanced chronic liver disease when the limits of medical therapy have been reached (Table 26). Patients with cirrhosis have diminished survival compared to the population as a whole, however, recognition of cirrhosis per se does not imply a need for LT. In patients with decompensated or advanced cirrhosis, the patient's prognosis deteriorates rapidly, as additional complications including Hepatorenal Syndrome Type 1 or sepsis supervene and the 1-year survival rate drops below 50%. [259] Furthermore, decompensation reduces the median survival from > 12 years to approximately 2 years [260,261]; moreover, the accumulation of multiple decompensations further decreases survival. In these patients, the indication for LT should be assessed independently of the etiology. If a determination has been made that LT is indicated, evaluation should be prompt, as most potential recipients face at least several months on the waiting list before receiving a donor organ.

Generally, patients with MELD scores < 15 are not qualified for LT, as the operative risk exceeds their predicted mortality on the waiting list. However, several studies have shown that the stages of liver cirrhosis, which depend on variceal bleeding and ascites, are significant predictors in cirrhotic patients, particularly those with a MELD score of < 15. [262,263] Therefore, irrespective of the MELD score, once complications of cirrhosis develop, the indication for LT should be made, and the patient should be evaluated for LT. It is generally accepted that LT is indicated in patients with (1) a complication of decompensated cirrhosis, such as ascites, variceal hemorrhage, HE, and jaundice, or (2) a MELD score of ≥ 15. [264,265]

It also should be noted that, for some patients, recovery from decompensation may be potentially reversible. Stable recompensation has been reported after effective antiviral treatment in patients with hepatitis B virus (HBV) [266] or hepatitis C virus (HCV) [267] -related decompensated cirrhosis, and with abstinence in patients with alcohol-related cirrhosis. [268] In these limited circumstances, decompensation may be reversed with appropriate therapies, and the indication for LT may need to be reevaluated. [261,264,269]

Table 26. Indications for liver transplantation in patients with cirrhosis

I. Acute Decompensation in Cirrhosis of Liver (2 or 3 organ failure) • Total Bilirubin > 12 mg/dl • INR > 2.5 • Hepatic Encephalopathy Grade 3 or 4 • Creatinine > 2 mg/dl • Use of vasopressors PaO2/FiO2 ≤ 200 or SpO2/FiO2 < 214 or Need for mechanical ventilation
II. Decompensated Cirrhosis of Liver • Recurrent Hepatic Encephalopathy • Recurrent Variceal Hemorrhage • Chronic gastrointestinal blood loss due to severe portal hypertensive gastropathy • Persistent Jaundice • Hepato-Renal Syndrome • Refractory Ascites • Spontaneous Bacterial Peritonitis • Synthetic dysfunction (MELD Score >15)
III. Systemic complications of chronic liver disease: • Hepatopulmonary syndrome • Portopulmonary hypertension
IV. Very early and early stage Hepatocellular Carcinoma (HCC)

16.2 Contraindications for Liver Transplant

Table 27. Contraindications to liver transplant in patients with cirrhosis

- MELD Score<15
- Severe cardiac or pulmonary disease
- AIDS
- Ongoing alcohol or illicit substance abuse
- Hepatocellular carcinoma with metastatic spread
- Uncontrolled sepsis
- Anatomic abnormality that precludes liver transplantation
- Intrahepatic Cholangiocarcinoma
- Extrahepatic malignancy
- Fulminant hepatic failure with sustained ICP >50 mm Hg or CPP <40 mm Hg
- Hemangiosarcoma
- Persistent noncompliance
- Lack of adequate social support system

Recommendation (Liver Transplantation)

201. Evaluation for liver transplant should be considered once a patient with cirrhosis has experienced an index complication such as ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepato-renal syndrome, variceal hemorrhage, persistent jaundice or hepatocellular dysfunction results in a MELD Score >15.

202. Potential liver transplant candidates with worsening renal dysfunction or other evidence of rapid hepatic decompensation should have a prompt evaluation for the liver transplant.

203. The indication for liver transplant may be reevaluated in patients who have recovered from decompensation with successful treatment of the underlying etiology.

References

1. Adams P, Alexander G, Bansal MB et al, Sherlock's Diseases of the Liver and Biliary System: Thirteenth Edition, Sheila Sherlock Liver Centre, Royal Free London NHS Foundation Trust, London, UK
2. Friedman SL. Hepatic fibrosis. Schiff's Diseases of the Liver. 2017 Oct 25:269-89.
3. Sepanlou SG, Safiri S, Bisignano C, Ikuta KS, Merat S, Saberifiroozi M, Poustchi H, Tsoi D, Colombara DV, Abdoli A, Adedoyin RA. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet gastroenterology & hepatology. 2020 Mar 1;5(3):245-66.
4. The Global Health Observatory. Global health estimates: Leading causes of death. WHO https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ ghe-leading-causes-of-death. (2023).
5. Moon AM, Singal AG, Tapper EB. Contemporary epidemiology of chronic liver disease and cirrhosis. Clinical Gastroenterology and Hepatology. 2020 Nov 1;18(12):2650-66.
6. Alberts CJ, Clifford GM, Georges D, Negro F, Lesi OA, Hutin YJ, de Martel C. Worldwide prevalence of hepatitis B virus and hepatitis C virus among patients with cirrhosis at country, region, and global levels: a systematic review. The Lancet Gastroenterology & Hepatology. 2022 Aug 1;7(8):724-35.
7. Orman ES, Roberts A, Ghabril M, Nephew L, Desai AP, Patidar K, Chalasani N. Trends in characteristics, mortality, and other outcomes of patients with newly diagnosed cirrhosis. JAMA network open. 2019 Jun 5;2(6):e196412-.
8. Díaz LA, Ayares G, Arnold J, Idalsoaga F, Corsi O, Arrese M, Arab JP. Liver diseases in Latin America: current status, unmet needs, and opportunities for improvement. Current Treatment Options in Gastroenterology. 2022 Sep;20(3):261-78.
9. World Health Organization. Global status report on alcohol and health 2018. World Health Organization; 2018.
10. Mukherjee PS, Vishnubhatla S, Amarapurkar DN, Das K, Sood A, Chawla YK, Eapen CE, Boddu P, Thomas V, Varshney S, Hidangmayum DS. Etiology and mode of presentation of chronic liver diseases in India: A multi centric study. PloS one. 2017 Oct 26;12(10):e0187033.
11. Alvi H, Zuberi BF, Rasheed T, Ibrahim MA. Evaluation of endoscopic variceal band ligation sessions in obliteration of esophageal varices. Pakistan Journal of Medical Sciences. 2020 Jan;36(2):37.
12. Alberts CJ, Clifford GM, Georges D, Negro F, Lesi OA, Hutin YJ, de Martel C. Worldwide prevalence of hepatitis B virus and hepatitis C virus among patients with cirrhosis at country, region, and global levels: a systematic review. The Lancet Gastroenterology & Hepatology. 2022 Aug 1;7(8):724-35.

13. Blach S, Terrault NA, Tacke F, Gamkrelidze I, Craxi A, Tanaka J, Waked I, Dore GJ, Abbas Z, Abdallah AR, Abdulla M. Global change in hepatitis C virus prevalence and cascade of care between 2015 and 2020: a modelling study. The Lancet Gastroenterology & Hepatology. 2022 May 1;7(5):396-415.
14. Razavi-Shearer D, Blach S, Gamkrelidze I, Estes C, Mooneyhan E, Razavi-Shearer K, Razavi H. The disease burden of hepatitis B and hepatitis C from 2015 to 2030: the long and winding road. Journal of Hepatology. 2022;77:S43.
15. Kondili LA, Buti M, Riveiro-Barciela M, Maticic M, Negro F, Berg T, Craxì A. Impact of the COVID-19 pandemic on hepatitis B and C elimination: an EASL survey. JHEP Reports. 2022 Sep 1;4(9):100531.
16. Julien J, Ayer T, Bethea ED, Tapper EB, Chhatwal J. Projected prevalence and mortality associated with alcohol-related liver disease in the USA, 2019–40: a modelling study. The Lancet Public Health. 2020 Jun 1;5(6):e316-23.
17. Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, Colombo M, Craxi A, Crespo J, Day CP, Eguchi Y. Modeling nafld disease burden in china, france, germany, italy, japan, spain, united kingdom, and united states for the period 2016–2030. Journal of hepatology. 2018 Oct 1;69(4):896-904.
18. Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, Krag A, Laleman W, Gines P. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. Journal of hepatology. 2018 Aug 1;69(2):406-60.
19. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, S. Sulkowski M, Torriani FJ, Dieterich DT, Thomas DL, Messinger D. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006 Jun;43(6):1317-25.
20. Zhong LK, Zhang G, Luo SY, Yin W, Song HY. The value of platelet count in evaluating the degree of liver fibrosis in patients with chronic hepatitis B. Journal of Clinical Laboratory Analysis. 2020 Jul;34(7):e23270.
21. Gotlieb N, Schwartz N, Zelber-Sagi S, Chodick G, Shalev V, Shibolet O. Longitudinal decrease in platelet counts as a surrogate marker of liver fibrosis. World Journal of Gastroenterology. 2020 Oct 10;26(38):5849.
22. Li S, Sun X, Chen M, Ying Z, Wan Y, Pi L, Ren B, Cao Q. Liver fibrosis conventional and molecular imaging diagnosis update. Journal of liver. 2019;8(1).
23. European Association for the Study of the Liver. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. Journal of hepatology. 2015 Jul 1;63(1):237-64.
24. Panel CP, Berzigotti A, Tsochatzis E, Boursier J, Castera L, Cazzagon N, Friedrich-Rust M, Petta S, Thiele M, European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis–2021 update. Journal of hepatology. 2021 Sep 1;75(3):659-89.
25. World Health Organization. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. World Health Organization; 2024 Mar 28.

26. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology. 2009 Mar;49(3):1017-44.
27. UpToDate 2024
28. Wolf DC. Cirrhosis: Practice Essentials, Overview, Etiology. eMedicine [Internet]. 2021 Jul 22. Available from: https://emedicine.medscape.com/article/185856-overview#a10.
29. Dooley JS, Lok AS, Garcia-Tsao G, Pinzani M, editors. Sherlock's diseases of the liver and biliary system. John Wiley & Sons; 2018 Aug 6.
30. Kaplan DE, Ripoll C, Thiele M, Fortune BE, Simonetto DA, Garcia-Tsao G, Bosch J. AASLD practice guidance on risk stratification and management of portal hypertension and varices in cirrhosis. Hepatology. 2024 May 1;79(5):1180-211.
31. Sohrabpour AA, Mohamadnejad M, Malekzadeh R. the reversibility of cirrhosis. Alimentary pharmacology & therapeutics. 2012 Nov;36(9):824-32.
32. Rogal SS, Hansen L, Patel A, Ufere NN, Verma M, Woodrell CD, Kanwal F. AASLD Practice Guidance: palliative care and symptom-based management in decompensated cirrhosis. Hepatology. 2022 Sep;76(3):819-53.
33. Pawlotsky JM, Negro F, Aghemo A, Berenguer M, Dalgard O, Dusheiko G, Marra F, Puoti M, Wedemeyer H, European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: final update of the series☆. Journal of hepatology. 2020 Nov 1;73(5):1170-218.
34. American Association for the Study of Liver Diseases. Recommendations for testing, managing, and treating hepatitis C. Arlington: AASLD-IDSA. 2014 Mar.
35. Thursz M, Gual A, Lackner C, Mathurin P, Moreno C, Spahr L, Sterneck M, Cortez-Pinto H. EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. Journal of hepatology. 2018 Jul 1;69(1):154-81.
36. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, Kleiner DE, Loomba R. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023 May 1;77(5):1797-835.
37. Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, Vierling JM, Alsawas M, Murad MH, Czaja AJ. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the Study of Liver Diseases. Hepatology. 2020 Aug;72(2):671-722.
38. Kumar R, Kumar S, Prakash SS. Compensated liver cirrhosis: natural course and disease-modifying strategies. World Journal of Methodology. 2023 Sep 9;13(4):179.
39. Lai JC, Tandon P, Bernal W, Tapper EB, Ekong U, Dasarathy S, Carey EJ. Malnutrition, frailty, and sarcopenia in patients with cirrhosis: 2021 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021 Sep;74(3):1611-44.

40. Merli M, Berzigotti A, Zelber-Sagi S, Dasarathy S, Montagnese S, Genton L, Plauth M, Parés A. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. Journal of hepatology. 2019 Jan 1;70(1):172-93.
41. Dasarathy J, McCullough AJ, Dasarathy S. Sarcopenia in alcoholic liver disease: clinical and molecular advances. Alcoholism: Clinical and Experimental Research. 2017 Aug;41(8):1419-31.
42. Rennie MJ, Tipton KD. Protein and amino acid metabolism during and after exercise and the effects of nutrition. Annual review of nutrition. 2000 Jul;20(1):457-83.
43. Periyalwar P, Dasarathy S. Malnutrition in cirrhosis: contribution and consequences of sarcopenia on metabolic and clinical responses. Clinics in liver disease. 2012 Feb 1;16(1):95-131.
44. Plauth M, Cabre E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, Ferenci P, Holm E, Vom Dahl S, Müller MJ, Nolte W. ESPEN guidelines on enteral nutrition: liver disease. Clinical nutrition. 2006 Apr 1;25(2):285-94.
45. Tandon P, Low G, Mourtzakis M, Zenith L, Myers RP, Abraldes JG, Shaheen AA, Qamar H, Mansoor N, Carbonneau M, Ismond K. A model to identify sarcopenia in patients with cirrhosis. Clinical Gastroenterology and Hepatology. 2016 Oct 1;14(10):1473-80.
46. Tandon P, Ney M, Irwin I, Ma MM, Gramlich L, Bain VG, Esfandiari N, Baracos V, Montano-Loza AJ, Myers RP. Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. Liver Transplantation. 2012 Oct;18(10):1209-16.
47. Tandon P, Low G, Mourtzakis M, Zenith L, Myers RP, Abraldes JG, Shaheen AA, Qamar H, Mansoor N, Carbonneau M, Ismond K. A model to identify sarcopenia in patients with cirrhosis. Clinical Gastroenterology and Hepatology. 2016 Oct 1;14(10):1473-80.
48. Kawaguchi T, Izumi N, Charlton MR, Sata M. Branched-chain amino acids as pharmacological nutrients in chronic liver disease. Hepatology. 2011 Sep 2;54(3):1063-70.
49. Holecek M. Three targets of branched-chain amino acid supplementation in the treatment of liver disease. Nutrition. 2010 May 1;26(5):482-90.
50. Dam G, Ott P, Aagaard NK, Vilstrup H. Branched-chain amino acids and muscle ammonia detoxification in cirrhosis. Metabolic brain disease. 2013 Jun;28:217-20.
51. Plank LD, Gane EJ, Peng S, Muthu C, Mathur S, Gillanders L, McIlroy K, Donaghy AJ, McCall JL. Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: a randomized 12-month trial. Hepatology. 2008 Aug 1;48(2):557-66.
52. Tsien CD, McCullough AJ, Dasarathy S. Late evening snack: exploiting a period of anabolic opportunity in cirrhosis. Journal of gastroenterology and hepatology. 2012 Mar;27(3):430-41.
53. Vaisman N, Katzman H, Carmiel-Haggai M, Lusthaus M, Niv E. Breakfast improves cognitive function in cirrhotic patients with cognitive impairment. The American journal of clinical nutrition. 2010 Jul 1;92(1):137-40.
54. Fukui H, Saito H, Ueno Y, Uto H, Obara K, Sakaida I, Shibuya A, Seike M, Nagoshi S, Segawa M, Tsubouchi H. Evidence-based clinical practice guidelines for liver cirrhosis 2015. Journal of gastroenterology. 2016 Jul;51:629-50.

55. Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, Krag A, Laleman W, Gines P. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. Journal of hepatology. 2018 Aug 1;69(2):406-60.

56. Alvarez MA, Cirera I, Solà R, Bargalló A, Morillas RM, Planas R. Long-term clinical course of decompensated alcoholic cirrhosis: a prospective study of 165 patients. Journal of clinical gastroenterology. 2011 Nov 1;45(10):906-11.

57. Shim JH, Lee HC, Kim KM, Lim YS, Chung YH, Lee YS, Suh DJ. Efficacy of entecavir in treatment-naive patients with hepatitis B virus-related decompensated cirrhosis. Journal of hepatology. 2010 Feb 1;52(2):176-82.

58. Cheung MC, Walker AJ, Hudson BE, Verma S, McLauchlan J, Mutimer DJ, Brown A, Gelson WT, MacDonald DC, Agarwal K, Foster GR. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. Journal of hepatology. 2016 Oct 1;65(4):741-7.

59. Lens S, Alvarado-Tapias E, Mariño Z, Londoño MC, LLop E, Martinez J, Fortea JI, Ibañez L, Ariza X, Baiges A, Gallego A. Effects of all-oral anti-viral therapy on HVPG and systemic hemodynamics in patients with hepatitis C virus-associated cirrhosis. Gastroenterology. 2017 Nov 1;153(5):1273-83..

60. Shingina A, Mukhtar N, Wakim-Fleming J, Alqahtani S, Wong RJ, Limketkai BN, Larson AM, Grant L. Acute liver failure guidelines. Official journal of the American College of Gastroenterology| ACG. 2023 Jul 1;118(7):1128-53.

61. Williams R, Schalm SW, O'Grady JG. Acute liver failure: redefining the syndromes. The Lancet. 1993 Jul 31;342(8866):273-5.

62. Bernuau J, Benhamou JP. Classifying acute liver failure. The Lancet. 1993;342(8866):252-3.

63. Maiwall R, Kulkarni AV, Arab JP, Piano S. Acute liver failure. The Lancet. 2024 Aug 24;404(10454):789-802.

64. Prakash R, Mullen KD. Mechanisms, diagnosis and management of hepatic encephalopathy. Nature reviews Gastroenterology & hepatology. 2010 Sep;7(9):515-25.

65. Wijdicks EF. Hepatic encephalopathy. New England Journal of Medicine. 2016 Oct 27;375(17):1660-70.

66. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, Weissenborn K, 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 Aug;60(2):715-35.

67. Bajaj JS, Schubert CM, Heuman DM, Wade JB, Gibson DP, Topaz A, Saeian K, Hafeezullah M, Bell DE, Sterling RK, Stravitz RT. Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. Gastroenterology. 2010 Jun 1;138(7):2332-40.

68. Campagna F, Montagnese S, Schiff S, Biancardi A, Mapelli D, Angeli P, Poci C, Cillo U, Merkel C, Gatta A, Amodio P. Cognitive impairment and electroencephalographic alterations before and after liver transplantation: what is reversible?. Liver Transplantation. 2014 Aug;20(8):977-86.

69. Dharel N, Bajaj JS. Definition and nomenclature of hepatic encephalopathy. Journal of Clinical and Experimental Hepatology. 2015 Mar 1;5:S37-41.

70. Amodio P. Current diagnosis and classification of hepatic encephalopathy. Journal of clinical and experimental hepatology. 2018 Dec 1;8(4):432-7.

71. 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 Mar 1;35(3):716-21.

72. Goyal O, Sidhu S, Kishore H. Incidence, prevalence and natural history of minimal hepatic encephalopathy in cirrhosis. Journal of Hepatology. 2016;2(64):S279.

73. Hartmann IJ, Groeneweg M, Quero JC, Beijeman SJ, De Man RA, Hop WC, Schalm SW. The prognostic significance of subclinical hepatic encephalopathy. Official journal of the American College of Gastroenterology| ACG. 2000 Aug 1;95(8):2029-34.

74. Das A, Dhiman RK, Saraswat VA, Verma M, Naik SR. Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis. Journal of gastroenterology and hepatology. 2001 May;16(5):531-5.

75. D'amico G, Morabito A, Pagliaro L, Marubini E, Liver Study Group of "V. Cervello" Hospital. Survival and prognostic indicators in compensated and decompensated cirrhosis. Digestive diseases and sciences. 1986 May;31:468-75.

76. Amodio P, Del Piccolo F, Pettenò E, Mapelli D, Angeli P, Iemmolo R, Muraca M, Musto C, Gerunda G, Rizzo C, Merkel C. Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients. Journal of hepatology. 2001 Jul 1;35(1):37-45.

77. Bustamante J, Rimola A, Ventura PJ, Navasa M, Cirera I, Reggiardo V, Rodés J. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. Journal of hepatology. 1999 May 1;30(5):890-5.

78. Stewart CA, Malinchoc M, Kim WR, Kamath PS. Hepatic encephalopathy as a predictor of survival in patients with end-stage liver disease. Liver transplantation. 2007 Oct;13(10):1366-71.

79. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. Journal of hepatology. 2006 Jan 1;44(1):217-31.

80. Wong RJ, Gish RG, Ahmed A. Hepatic encephalopathy is associated with significantly increased mortality among patients awaiting liver transplantation. Liver Transplantation. 2014 Dec;20(12):1454-61.

81. Butterworth RF. Pathogenesis of hepatic encephalopathy and brain edema in acute liver failure. Journal of clinical and experimental hepatology. 2015 Mar 1;5:S96-103..

82. Elwir S, Rahimi RS. Hepatic encephalopathy: an update on the pathophysiology and therapeutic options. Journal of clinical and translational hepatology. 2017 Jun 6;5(2):142.

83. Sakamoto M, Perry W, Hilsabeck RC, Barakat F, Hassanein T. Assessment and usefulness of clinical scales for semiquantification of overt hepatic encephalopathy. Clinics in Liver Disease. 2012 Feb 1;16(1):27-42.

84. Córdoba J, Cabrera J, Lataif L, Penev P, Zee P, Blei AT. High prevalence of sleep disturbance in cirrhosis. Hepatology. 1998 Feb 1;27(2):339-45.

85. Weissenborn K. Diagnosis of encephalopathy. Digestion. 1998;59(Suppl. 2):22-4.

86. Basu PP, Shah NJ. Clinical and neurologic manifestation of minimal hepatic encephalopathy and overt hepatic encephalopathy. Clinics in Liver Disease. 2015 Aug 1;19(3):461-72.

87. Timmermann L, Gross J, Butz M, Kircheis G, Haussinger D, Schnitzler A. Mini-asterixis in hepatic encephalopathy induced by pathologic thalamo-motor-cortical coupling. Neurology. 2003 Sep 9;61(5):689-92.

88. Tryc AB, Goldbecker A, Berding G, Rümke S, Afshar K, Shahrezaei GH, Pflugrad H, Barg-Hock H, Strassburg CP, Hecker H, Weissenborn K. Cirrhosis-related Parkinsonism: prevalence, mechanisms and response to treatments. Journal of Hepatology. 2013 Apr 1;58(4):698-705.

89. Weissenborn K, Bokemeyer M, Krause J, Ennen J, Ahl B. Neurological and neuropsychiatric syndromes associated with liver disease. Aids. 2005 Oct 1;19:S93-8.

90. Khungar V, Poordad F. Hepatic encephalopathy. Clinics in Liver Disease. 2012 May 1;16(2):301-20.

91. Nabi E, Bajaj JS. Useful tests for hepatic encephalopathy in clinical practice. Current gastroenterology reports. 2014 Jan;16:1-8.

92. Riggio O, Varriale M, Testore GP, Di Rosa R, Di Rosa E, Merli M, Romiti A, Candiani C, Capocaccia L. Effect of lactitol and lactulose administration on the fecal flora in cirrhotic patients. Journal of clinical gastroenterology. 1990 Aug 1;12(4):433-6.

93. Mortensen PB. The Effect of Oral–Administered Lactulose on Colonic Nitrogen Metabolism and Excretion. Hepatology. 1992 Dec 1;16(6):1350-6.

94. Mortensen PB, Holtug K, Bonnén H, Clausen MR. The degradation of amino acids, proteins, and blood to short-chain fatty acids in colon is prevented by lactulose. Gastroenterology. 1990 Feb 1;98(2):353-60.

95. Bajaj JS, Sanyal AJ, Bell D, Gilles H, Heuman DM. Predictors of the recurrence of hepatic encephalopathy in lactulose-treated patients. Alimentary pharmacology & therapeutics. 2010 May;31(9):1012-7.

96. Rahimi RS, Singal AG, Cuthbert JA, Rockey DC. Lactulose vs polyethylene glycol 3350-electrolyte solution for treatment of overt hepatic encephalopathy: the HELP randomized clinical trial. JAMA internal medicine. 2014 Nov 1;174(11):1727-33.

97. Suraweera D, Sundaram V, Saab S. Evaluation and management of hepatic encephalopathy: current status and future directions. Gut and liver. 2016 Jul;10(4):509.

98. Leise MD, Poterucha JJ, Kamath PS, Kim WR. Management of hepatic encephalopathy in the hospital. InMayo Clinic Proceedings 2014 Feb 1 (Vol. 89, No. 2, pp. 241-253). Elsevier.

99. Morgan MH, Read AE, Speller DC. Treatment of hepatic encephalopathy with metronidazole. Gut. 1982 Jan 1;23(1):1-7.

100. Brigidi P, Swennen E, Rizzello F, Bozzolasco M, Matteuzzi D. Effects of rifaximin administration on the intestinal microbiota in patients with ulcerative colitis. Journal of chemotherapy. 2002 Jan 1;14(3):290-5.

101. Mullen KD, Sanyal AJ, Bass NM, Poordad FF, Sheikh MY, Frederick RT, Bortey E, Forbes WP. Rifaximin is safe and well tolerated for long-term maintenance of remission from overt hepatic encephalopathy. Clinical Gastroenterology and Hepatology. 2014 Aug 1;12(8):1390-7.

102. Jiang Q, Jiang XH, Zheng MH, Jiang LM, Chen YP, Wang L. Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy: a meta-analysis. European journal of gastroenterology & hepatology. 2008 Nov 1;20(11):1064-70.

103. Mohammad RA, Regal RE, Alaniz C. Combination therapy for the treatment and prevention of hepatic encephalopathy. Annals of Pharmacotherapy. 2012 Nov;46(11):1559-63.

104. Sharma BC, Sharma P, Lunia MK, Srivastava S, Goyal R, Sarin SK. A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. Official journal of the American College of Gastroenterology| ACG. 2013 Sep 1;108(9):1458-63.

105. Hudson M, Schuchmann M. Long-term management of hepatic encephalopathy with lactulose and/or rifaximin: a review of the evidence. European journal of gastroenterology & hepatology. 2019 Apr 1;31(4):434-50.

106. Acharya C, Bajaj JS. Current management of hepatic encephalopathy. Official journal of the American College of Gastroenterology| ACG. 2018 Nov 1;113(11):1600-12.

107. Kircheis G, Nilius R, Held C, Berndt H, Buchner M, Gortelmeyer R, Hendricks R, Kruger B, Kuklinski B, Meister H, Otto H. Therapeutic efficacy of L-ornithine-L-aspartate infusions in patients with cirrhosis and hepatic encephalopathy: results of a placebo-controlled, double-blind study. Hepatology. 1997 Jun;25(6):1351-60.

108. Goh ET, Stokes CS, Sidhu SS, Vilstrup H, Gluud LL, Morgan MY. L-ornithine L-aspartate for prevention and treatment of hepatic encephalopathy in people with cirrhosis. Cochrane Database of Systematic Reviews. 2018(5).

109. Sidhu SS, Sharma BC, Goyal O, Kishore H, Kaur N. L-ornithine L-aspartate in bouts of overt hepatic encephalopathy. Hepatology. 2018 Feb;67(2):700-10.

110. Dam G, Aamann L, Vistrup H, Gluud LL. The role of Branched Chain Amino Acids in the treatment of hepatic Encephalopathy. Journal of clinical and experimental hepatology. 2018 Dec 1;8(4):448-51.

111. Tsien C, Davuluri G, Singh D, Allawy A, Ten Have GA, Thapaliya S, Schulze JM, Barnes D, McCullough AJ, Engelen MP, Deutz NE. Metabolic and molecular responses to leucine-enriched branched chain amino acid supplementation in the skeletal muscle of alcoholic cirrhosis. Hepatology. 2015 Jun;61(6):2018-29.

112. Gluud LL, Dam G, Les I, Marchesini G, Borre M, Aagaard NK, Vilstrup H. Branched-chain amino acids for people with hepatic encephalopathy. Cochrane Database of Systematic Reviews. 2015(9).

113. Zhao LN, Yu T, Lan SY, Hou JT, Zhang ZZ, Wang SS, Liu FB. Probiotics can improve the clinical outcomes of hepatic encephalopathy: an update meta-analysis. Clinics and Research in Hepatology and Gastroenterology. 2015 Dec 1;39(6):674-82.

114. McGee RG, Bakens A, Wiley K, Riordan SM, Webster AC. Probiotics for patients with hepatic encephalopathy. Cochrane Database of Systematic Reviews. 2011(11).

115. Hsiao SH, Liao LH, Cheng PN, Wu TJ. Hepatotoxicity associated with acarbose therapy. Annals of Pharmacotherapy. 2006 Jan;40(1):151-4.

116. Sharma BC, Singh J, Srivastava S, Sangam A, Mantri AK, Trehanpati N, Sarin SK. Randomized controlled trial comparing lactulose plus albumin versus lactulose alone for treatment of hepatic encephalopathy. Journal of Gastroenterology and Hepatology. 2017 Jun;32(6):1234-9.

117. Riordan SM, Williams R. Treatment of hepatic encephalopathy. New England Journal of Medicine. 1997 Aug 14;337(7):473-9.

118. Yao CK, Fung J, Chu NH, Tan VP. Dietary interventions in liver cirrhosis. Journal of clinical gastroenterology. 2018 Sep 1;52(8):663-73..

119. Montagnese S, Rautou PE, Romero-Gómez M, Larsen FS, Shawcross DL, Thabut D, Vilstrup H, Weissenborn K. EASL Clinical Practice Guidelines on the management of hepatic encephalopathy. Journal of hepatology. 2022 Sep 1;77(3):807-24.

120. Hopp AE, Dirks M, Petrusch C, Goldbecker A, Tryc AB, Barg-Hock H, Strassburg C, Klempnauer J, Weissenborn K, Pflugrad H. P: 10 Hepatic Encephalopathy Is Reversible in the Long-term after Liver Transplantation. Official journal of the American College of Gastroenterology| ACG. 2019 Sep 1;114:S4.

121. Albhaisi SA, Bajaj JS. Cognitive function in liver transplantation. Current transplantation reports. 2020 Jun;7:31-7.

122. De Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Abraldes JG, Albillos A, Baiges A, Bajaj J, Bañares R, Barrufet M. Baveno VII–renewing consensus in portal hypertension. Journal of hepatology. 2022 Apr 1;76(4):959-74.
123. Gralnek IM, Duboc MC, Garcia-Pagan JC, Fuccio L, Karstensen JG, Hucl T, Jovanovic I, Awadie H, Hernandez-Gea V, Tantau M, Ebigbo A. Endoscopic diagnosis and management of esophagogastric variceal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2022 Nov;54(11):1094-120.
124. Henry Z, Patel K, Patton H, Saad W. AGA clinical practice update on management of bleeding gastric varices: expert review. Clinical Gastroenterology and Hepatology. 2021 Jun 1;19(6):1098-107.
125. Kaplan DE, Ripoll C, Thiele M, Fortune BE, Simonetto DA, Garcia-Tsao G, Bosch J. AASLD practice guidance on risk stratification and management of portal hypertension and varices in cirrhosis. Hepatology. 2024 May 1;79(5):1180-211.
126. Korean Association for the Study of the Liver (KASL. KASL clinical practice guidelines for liver cirrhosis: varices, hepatic encephalopathy, and related complications. Clinical and molecular hepatology. 2020 Apr;26(2):83.
127. LaBrecque D, Khan AG, Sarin SK, Le Mair AW. Esophageal varices. World Gastroenterol Organ Glob Guidel. 2014 Jan;2014:1-4.
128. Pallio S, Melita G, Shahini E, Vitello A, Sinagra E, Lattanzi B, Facciorusso A, Ramai D, Maida M. Diagnosis and management of esophagogastric varices. Diagnostics. 2023 Mar 8;13(6):1031.
129. Sarin SK, Kumar A. Gastric varices: profile, classification, and management. American Journal of Gastroenterology (Springer Nature). 1989 Oct 1;84(10).
130. Sarin SK, Kumar A, Angus PW, Baijal SS, Chawla YK, Dhiman RK, Janaka de Silva H, Hamid S, Hirota S, Hou MC, Jafri W. Primary prophylaxis of gastroesophageal variceal bleeding: consensus recommendations of the Asian Pacific Association for the Study of the Liver. Hepatology international. 2008 Dec;2:429-39.
131. Sun L, Long L, Wang Q, Xiang H, Huangxing C, Yanfang C, Feng C, Wei C, Jianguo C, Aijun S, Ying D. Expert consensus on emergency procedures for portal hypertension bleeding (2022). Journal of Interventional Medicine. 2023 Feb 1;6(1):1-9.
132. Tanoue K, Hashizume M, Wada H, Ohta M, Kitano S, Sugimachi K. Effects of endoscopic injection sclerotherapy on portal hypertensive gastropathy: a prospective study. Gastrointestinal endoscopy. 1992 Sep 1;38(5):582-5.

133. Sonderup MW, Kamath PS, Awuku YA, Desalegn H, Gogela N, Katsidzira L, Tzeuton C, Bobat B, Kassianides C, Spearman CW. Managing cirrhosis with limited resources: perspectives from sub-Saharan Africa. The Lancet Gastroenterology & Hepatology. 2024 Feb 1;9(2):170-84.
134. De Franchis R. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. Journal of hepatology. 2015 Sep 1;63(3):743-52.
135. Kurup R, Kalo E, Read S, Ma WS, George J, Ahlenstiel G. Validation and Comparison of Non-Invasive Tests for the Exclusion of High-Risk Varices in Compensated Advanced Chronic Liver Disease. Livers. 2024 Apr 12;4(2):182-92.
136. Reiberger T, Ulbrich G, Ferlitsch A, Payer BA, Schwabl P, Pinter M, Heinisch BB, Trauner M, Kramer L, Peck-Radosavljevic M. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. Gut. 2013 Nov 1;62(11):1634-41.
137. De Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Abraldes JG, Albillos A, Baiges A, Bajaj J, Bañares R, Barrufet M. Baveno VII–renewing consensus in portal hypertension. Journal of hepatology. 2022 Apr 1;76(4):959-74.
138. Northup PG, Garcia-Pagan JC, Garcia-Tsao G, Intagliata NM, Superina RA, Roberts LN, Lisman T, Valla DC. Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021 Jan;73(1):366-413.
139. Sharma M, Singh S, Desai V, Shah VH, Kamath PS, Murad MH, Simonetto DA. Comparison of therapies for primary prevention of esophageal variceal bleeding: a systematic review and network meta-analysis. Hepatology. 2019 Apr;69(4):1657-75.
140. LAY CS, TSAI YT, LEE FY, LAI YL, YU CJ, CHEN CB, PENG CY. Endoscopic variceal ligation versus propranolol in prophylaxis of first variceal bleeding in patients with cirrhosis. Journal of gastroenterology and hepatology. 2006 Feb;21(2):413-9.
141. Sheibani S, Khemichian S, Kim JJ, Hou L, Yan AW, Buxbaum J, Dara L, Laine L. Randomized trial of 1-week versus 2-week intervals for endoscopic ligation in the treatment of patients with esophageal variceal bleeding. Hepatology. 2016 Aug;64(2):549-55.
142. Sharma M, Singh S, Desai V, Shah VH, Kamath PS, Murad MH, Simonetto DA. Comparison of therapies for primary prevention of esophageal variceal bleeding: a systematic review and network meta-analysis. Hepatology. 2019 Apr;69(4):1657-75.

143. Fogel MR, Sawhney VK, Neal EA, Miller RG, Knauer CM, Gregory PB. Diuresis in the ascitic patient: a randomized controlled trial of three regimens. Journal of Clinical Gastroenterology. 1981 Jan 1;3:73-80.

144. Moore KP, Wong F, Gines P, Bernardi M, Ochs A, Salerno F, Angeli P, Porayko M, Moreau R, Garcia-Tsao G, Jimenez W. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology. 2003 Jul 1;38(1):258-66.

145. Runyon BA, Montano AA, Akriviadis EA, Antillon MR, Irving MA, McHutchison JG. The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. Annals of internal medicine. 1992 Aug 1;117(3):215-20.

146. Arroyo V, Ginés P, Rimola A, Gaya J. Renal function abnormalities, prostaglandins, and effects of nonsteroidal anti-inflammatory drugs in cirrhosis with ascites: an overview with emphasis on pathogenesis. The American journal of medicine. 1986 Aug 25;81(2):104-22.

147. Pariente EA, Bataille C, Bercoff E, Lebrec D. Acute effects of captopril on systemic and renal hemodynamics and on renal function in cirrhotic patients with ascites. Gastroenterology. 1985 May 1;88(5):1255-9.

148. Cabrera J, Arroyo V, Ballesta AM, Rimola A, Gual J, Elena M, Rodes J. Aminoglycoside nephrotoxicity in cirrhosis: value of urinary β2-microglobulin to discriminate functional renal failure from acute tubular damage. Gastroenterology. 1982 Jan 1;82(1):97-105.

149. Reynolds TB, Lieberman FL, Goodman AR. Advantages of treatment of ascites without sodium restriction and without complete removal of excess fluid. Gut. 1978 Jun 1;19(6):549-53.

150. Morando F, Rosi S, Gola E, Nardi M, Piano S, Fasolato S, Stanco M, Cavallin M, Romano A, Sticca A, Caregaro L. Adherence to a moderate sodium restriction diet in outpatients with cirrhosis and ascites: a real-life cross-sectional study. Liver International. 2015 May;35(5):1508-15.

151. Angeli P, Dalla Pria M, de Bei E, Albino G, Caregaro L, Merkel C, Ceolotto G, Gatta A. Randomized clinical study of the efficacy of amiloride and potassium canrenoate in nonazotemic cirrhotic patients with ascites. Hepatology. 1994 Jan 1;19(1):72-9.

152. Gerbes AL, Bertheau-Reitha U, Falkner C, Jüngst D, Paumgartner G. Advantages of the new loop diuretic torasemide over furosemide in patients with cirrhosis and ascites: A randomized, double blind cross-over trial. Journal of hepatology. 1993 Jan 1;17(3):353-8.

153. Angeli P, Fasolato S, Mazza E, Okolicsanyi L, Maresio G, Velo E, Galioto A, Salinas F, D'Aquino M, Sticca A, Gatta A. Combined versus sequential diuretic treatment of ascites in non-azotaemic patients with cirrhosis: results of an open randomised clinical trial. Gut. 2010 Jan 1;59(01):98-104.

154. Dimitriadis G, Papadopoulos V, Mimidis K. Eplerenone reverses spironolactone-induced painful gynaecomastia in cirrhotics. Hepatology International. 2011 Jun;5:738-9.

155. Angeli P, Albino G, Carraro P, Pria MD, Merkel C, Caregaro L, De Bei ER, Bortoluzzi A, Plebani M, Gatta A. Cirrhosis and muscle cramps: evidence of a causal relationship. Hepatology. 1996 Feb;23(2):264-73.

156. Elfert AA, Ali LA, Soliman S, Zakaria S, El-Din IS, Elkhalawany W, Abd-Elsalam S. Randomized placebo-controlled study of baclofen in the treatment of muscle cramps in patients with liver cirrhosis. European Journal of Gastroenterology & Hepatology. 2016 Nov 1;28(11):1280-4.

157. Abd-Elsalam S, Arafa M, Elkadeem M, Elfert A, Soliman S, Elkhalawany W, Badawi R. Randomized-controlled trial of methocarbamol as a novel treatment for muscle cramps in cirrhotic patients. European journal of gastroenterology & hepatology. 2019 Apr 1;31(4):499-502.

158. Vidot H, Cvejic E, Carey S, Strasser SI, McCaughan GW, Allman-Farinelli M, Shackel NA. Randomised clinical trial: oral taurine supplementation versus placebo reduces muscle cramps in patients with chronic liver disease. Alimentary pharmacology & therapeutics. 2018 Oct;48(7):704-12.

159. Corbani A, Manousou P, Calvaruso V, Xirouchakis I, Burroughs AK. Muscle cramps in cirrhosis: the therapeutic value of quinine. Is it underused?. Digestive and Liver Disease. 2008 Sep 1;40(9):794-9.

160. Ginés P, Arroyo V, Quintero E, Planas R, Bory F, Cabrera J, Rimola A, Viver J, Camps J, Jiménez W, Mastai R. Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites: results of a randomized study. Gastroenterology. 1987 Aug 1;93(2):234-41.

161. Ginés A, Fernandez-Esparrach G, Monescillo A, Vila C, Domenech E, Abecasis R, Angeli P, Ruiz-del-Arbol L, Planas R, Sola R, Ginès P. Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. Gastroenterology. 1996 Oct 1;111(4):1002-10.

162. Cho J, Jensen TP, Reierson K, Mathews BK, Bhagra A, Franco-Sadud R, Grikis L, Mader M, Dancel R, Lucas BP, Soni NJ. Recommendations on the use of ultrasound guidance for adult abdominal paracentesis: a position statement of the Society of Hospital Medicine. Journal of hospital medicine. 2019;14:E7.

163. Salerno F, Borroni G, Moser P, Badalamenti S, Cassarà L, Maggi A, Fusini M, Cesana B. Survival and prognostic factors of cirrhotic patients with ascites: a study of 134 outpatients. American Journal of Gastroenterology (Springer Nature). 1993 Apr 1;88(4).

164. Solà E, Solé C, Simón-Talero M, Martín-Llahí M, Castellote J, Garcia-Martínez R, Moreira R, Torrens M, Márquez F, Fabrellas N, de Prada G. Midodrine and albumin for prevention of complications in patients with cirrhosis awaiting liver transplantation. A randomized placebo-controlled trial. Journal of hepatology. 2018 Dec 1;69(6):1250-9.

165. Di Pascoli M, Fasolato S, Piano S, Bolognesi M, Angeli P. Long-term administration of human albumin improves survival in patients with cirrhosis and refractory ascites. Liver International. 2019 Jan;39(1):98-105.

166. Ginés P, Arroyo V, Quintero E, Planas R, Bory F, Cabrera J, Rimola A, Viver J, Camps J, Jiménez W, Mastai R. Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites: results of a randomized study. Gastroenterology. 1987 Aug 1;93(2):234-41.

167. Ginés A, Fernandez-Esparrach G, Monescillo A, Vila C, Domenech E, Abecasis R, Angeli P, Ruiz-del-Arbol L, Planas R, Sola R, Ginès P. Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. Gastroenterology. 1996 Oct 1;111(4):1002-10.

168. Wang Q, Lv Y, Bai M, Wang Z, Liu H, He C, Niu J, Guo W, Luo B, Yin Z, Bai W. Eight millimetre covered TIPS does not compromise shunt function but reduces hepatic encephalopathy in preventing variceal rebleeding. Journal of hepatology. 2017 Sep 1;67(3):508-16.

168. Singh V, Dhungana SP, Singh B, Vijayverghia R, Nain CK, Sharma N, Bhalla A, Gupta PK. Midodrine in patients with cirrhosis and refractory or recurrent ascites: a randomized pilot study. Journal of Hepatology. 2012 Feb 1;56(2):348-54.

170. Yoshiji H, Nagoshi S, Akahane T, Asaoka Y, Ueno Y, Ogawa K, Kawaguchi T, Kurosaki M, Sakaida I, Shimizu M, Taniai M. Evidence-based clinical practice guidelines for Liver Cirrhosis 2020. Journal of gastroenterology. 2021 Jul;56(7):593-619.

171. European Association For The Study Of The Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. Journal of hepatology. 2010 Sep 1;53(3):397-417.

172. Llach J, Ginès P, Arroyo V, Rimola A, Titó L, Badalamenti S, Jiménez W, Gaya J, Rivera F, Rodés J. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. Gastroenterology. 1988 Feb 1;94(2):482-7.

173. Piano S, Singh V, Caraceni P, Maiwall R, Alessandria C, Fernandez J, Soares EC, Kim DJ, Kim SE, Marino M, Vorobioff J. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. Gastroenterology. 2019 Apr 1;156(5):1368-80.

174. Kim SU, Kim DY, Lee CK, Park JY, Kim SH, Kim HM, Choi EH, Kim S, Han KH, Chon CY, Ahn SH. Ascitic fluid infection in patients with hepatitis B virus-related liver cirrhosis: culture-negative neutrocytic ascites versus spontaneous bacterial peritonitis. Journal of gastroenterology and hepatology. 2010 Jan;25(1):122-8.

175. Kim JJ, Tsukamoto MM, Mathur AK, Ghomri YM, Hou LA, Sheibani S, Runyon BA. Delayed paracentesis is associated with increased in-hospital mortality in patients with spontaneous bacterial peritonitis. Official journal of the American College of Gastroenterology| ACG. 2014 Sep 1;109(9):1436-42.

176. Rimola A, García-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B, Inadomi JM. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. Journal of hepatology. 2000 Jan 1;32(1):142-53.

177. Runyon BA, Akriviadis EA, Sattler FR, Cohen J. Ascitic fluid and serum cefotaxime and desacetyl cefotaxime levels in patients treated for bacterial peritonitis. Digestive diseases and sciences. 1991 Dec;36:1782-6.

178. Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, Castells L, Vargas V, Soriano G, Guevara M, Ginès P. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. New England Journal of Medicine. 1999 Aug 5;341(6):403-9.

179. Xue HP, LIN B, MO JZ, LI JQ. Effect of albumin infusion on preventing the deterioration of renal function in patients with spontaneous bacterial peritonitis. Chinese Journal of Digestive Diseases. 2002 Feb;3(1):32-4.

180. Sigal SH, Stanca CM, Fernandez J, Arroyo V, Navasa M. Restricted use of albumin for spontaneous bacterial peritonitis. Gut. 2007 Apr 1;56(4):597-9.

181. Fernández J, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G, Vila C, Pardo A, Quintero E, Vargas V, Such J. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology. 2007 Sep 1;133(3):818-24.

182. Terg R, Fassio E, Guevara M, Cartier M, Longo C, Lucero R, Landeira C, Romero G, Dominguez N, Muñoz A, Levi D. Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis: a randomized, placebo-controlled study. Journal of hepatology. 2008 May 1;48(5):774-9.

183. Lontos S, Shelton E, Angus PW, Vaughan R, Roberts SK, Gordon A, Gow PJ. A randomized controlled study of trimethoprim-sulfamethoxazole versus norfloxacin for the prevention of infection in cirrhotic patients. Journal of Digestive Diseases. 2014 May;15(5):260-7.

184. Ginés P, Rimola A, Planas R, Vargas V, Marco F, Almela M, Forne M, Miranda ML, Llach J, Salmerón JM, Esteve M. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. Hepatology. 1990 Oct;12(4):716-24.

185. Elfert A, Ali LA, Soliman S, Ibrahim S, Abd-Elsalam S. Randomized-controlled trial of rifaximin versus norfloxacin for secondary prophylaxis of spontaneous bacterial peritonitis. European journal of gastroenterology & hepatology. 2016 Dec 1;28(12):1450-4.

186. Goel A, Rahim U, Nguyen LH, Stave C, Nguyen MH. Systematic review with meta-analysis: rifaximin for the prophylaxis of spontaneous bacterial peritonitis. Alimentary Pharmacology & Therapeutics. 2017 Dec;46(11-12):1029-36.

187.Praharaj DL, Premkumar M, Roy A, Verma N, Taneja S, Duseja A, Dhiman RK. Rifaximin vs. norfloxacin for spontaneous bacterial peritonitis prophylaxis: a randomized controlled trial. Journal of Clinical and Experimental Hepatology. 2022 Mar 1;12(2):336-42.

188. Angeli P, Wong F, Watson H, Ginès P, Capps Investigators. Hyponatremia in cirrhosis: results of a patient population survey. Hepatology. 2006 Dec;44(6):1535-42.

189.Biggins SW, Rodriguez HJ, Bacchetti P, Bass NM, Roberts JP, Terrault NA. Serum sodium predicts mortality in patients listed for liver transplantation. Hepatology. 2005 Jan;41(1):32-9.

190. Porcel A, Díaz F, Rendón P, Macías M, Martín-Herrera L, Girón-González JA. Dilutional hyponatremia in patients with cirrhosis and ascites. Archives of internal medicine. 2002 Feb 11;162(3):323-8.

191. Córdoba J, García-Martinez R, Simón-Talero M. Hyponatremic and hepatic encephalopathies: similarities, differences and coexistence. Metabolic brain disease. 2010 Mar;25:73-80.

192. Amodio P, Del Piccolo F, Pettenò E, Mapelli D, Angeli P, Iemmolo R, Muraca M, Musto C, Gerunda G, Rizzo C, Merkel C. Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients. Journal of hepatology. 2001 Jul 1;35(1):37-45.

193.Sigal SH, Amin A, Chiodo III JA, Sanyal A. Management strategies and outcomes for hyponatremia in cirrhosis in the hyponatremia registry. Canadian Journal of Gastroenterology and Hepatology. 2018;2018(1):1579508.

194. Singh V, De A, Mehtani R, Angeli P, Maiwall R, Satapathy S, Singal AK, Saraya A, Sharma BC, Eapen CE, Rao PN. Asia–Pacific association for study of liver guidelines on management of ascites in liver disease. Hepatology International. 2023 Aug;17(4):792-826.

195. McCormick PA, Mistry P, Kaye G, Burroughs AK, McIntyre N. Intravenous albumin infusion is an effective therapy for hyponatraemia in cirrhotic patients with ascites. Gut. 1990 Feb 1;31(2):204-7.

196. Bajaj JS, Tandon P, O'Leary JG, Biggins SW, Wong F, Kamath PS, Garcia-Tsao G, Maliakkal B, Lai JC, Fallon M, Thuluvath P. The impact of albumin use on resolution of hyponatremia in hospitalized patients with cirrhosis. Official journal of the American College of Gastroenterology| ACG. 2018 Sep 1;113(9):1339.

197. Caraceni P, Riggio O, Angeli P, Alessandria C, Neri S, Foschi FG, Levantesi F, Airoldi A, Boccia S, Svegliati-Baroni G, Fagiuoli S. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. The Lancet. 2018 Jun 16;391(10138):2417-29.

198. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, Orlandi C. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. New England Journal of Medicine. 2006 Nov 16;355(20):2099-112.

199. Badillo R, Rockey DC. Hepatic hydrothorax: clinical features, management, and outcomes in 77 patients and review of the literature. Medicine. 2014 May 1;93(3):135-42.

200. Orman ES, Lok AS. Outcomes of patients with chest tube insertion for hepatic hydrothorax. Hepatology international. 2009 Dec;3:582-6.

201. Hou F, Qi X, Guo X. Effectiveness and safety of pleurodesis for hepatic hydrothorax: a systematic review and meta-analysis. Digestive diseases and sciences. 2016 Nov;61:3321-34.

202. De Campos JR, Andrade Filho LO, de Campos Werebe E, Sette Jr H, Fernandez A, Filomeno LT, Jatene FB. Thoracoscopy and talc poudrage in the management of hepatic hydrothorax. Chest. 2000 Jul 1;118(1):13-7.

203. Artemiou O, Marta GM, Klepetko W, Wolner E, Müller MR. Pleurovenous shunting in the treatment of nonmalignant pleural effusion. The Annals of thoracic surgery. 2003 Jul 1;76(1):231-3.

204. Izzy M, VanWagner LB, Lin G, Altieri M, Findlay JY, Oh JK, Watt KD, Lee SS, Cirrhotic Cardiomyopathy Consortium. Redefining cirrhotic cardiomyopathy for the modern era. Hepatology. 2020 Jan;71(1):334-45.

205. Yoon KT, Liu H, Lee SS. Cirrhotic cardiomyopathy. Current gastroenterology reports. 2020 Sep;22:1-9.

206. Mehta G, Gustot T, Mookerjee RP, Garcia-Pagan JC, Fallon MB, Shah VH, Moreau R, Jalan R. Inflammation and portal hypertension–the undiscovered country. Journal of hepatology. 2014 Jul 1;61(1):155-63.

207. De Binay K, Majumdar D, Das D, Biswas PK, Mandal SK, Ray S, Bandopadhyay K, Das TK, Dasgupta S, Guru S. Cardiac dysfunction in portal hypertension among patients with cirrhosis and non-cirrhotic portal fibrosis. Journal of hepatology. 2003 Sep 1;39(3):315-9.

208. Lyssy LA, Soos MP. Cirrhotic Cardiomyopathy. [Updated 2024 Jul 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556089/

209. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European Journal of Echocardiography. 2016 Jul 15;17(12):1321-60.

210. Liu H, Jayakumar S, Traboulsi M, Lee SS. Cirrhotic cardiomyopathy: Implications for liver transplantation. Liver Transplantation. 2017 Jun;23(6):826-35.

211. Yoon KT, Liu H, Lee SS. β-blockers in advanced cirrhosis: More friend than enemy. Clinical and molecular hepatology. 2020 Dec 3;27(3):425.

212. Liu H, Jayakumar S, Traboulsi M, Lee SS. Cirrhotic cardiomyopathy: Implications for liver transplantation. Liver Transplantation. 2017 Jun;23(6):826-35.

213. Liu H, Yoon KT, Zhang J, Lee SS. Advances in cirrhotic cardiomyopathy. Current Opinion in Gastroenterology. 2021 May 1;37(3):187-93.

214. Ruíz-del-Árbol L, Achécar L, Serradilla R, Rodríguez-Gandía MÁ, Rivero M, Garrido E, Natcher JJ. Diastolic dysfunction is a predictor of poor outcomes in patients with cirrhosis, portal hypertension, and a normal creatinine. Hepatology. 2013 Nov;58(5):1732-41.

215. Krag A, Bendtsen F, Henriksen JH, Møller S. Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. Gut. 2010 Jan 1;59(01):105-10.

216. Chayanupatkul M, Liangpunsakul S. Cirrhotic cardiomyopathy: review of pathophysiology and treatment. Hepatology international. 2014 Jul;8:308-15.

217. Nobbe AM, McCurdy HM. Management of the Adult Patient with Cirrhosis Complicated by Ascites. Critical Care Nursing Clinics. 2022 Sep 1;34(3):311-20.

218. Yoon KT, Liu H, Lee SS. Cirrhotic cardiomyopathy. Current gastroenterology reports. 2020 Sep;22:1-9.

219. Bodys-Pełka A, Kusztal M, Raszeja-Wyszomirska J, Główczyńska R, Grabowski M. What's New in Cirrhotic Cardiomyopathy?. Journal of Personalized Medicine. 2021 Dec 3;11(12):1285.

220. Krag A, Wiest R, Albillos A, Gluud LL. The window hypothesis: haemodynamic and non-haemodynamic effects of β-blockers improve survival of patients with cirrhosis during a window in the disease. Gut. 2012 Jul 1;61(7):967-9.

221. Ali SA, Arman HE, Shamseddeen H, Elsner N, Elsemesmani H, Johnson S, Zenisek J, Khemka A, Jarori U, Patidar KR, Orman E. Cirrhotic cardiomyopathy: Predictors of major adverse cardiac events and assessment of reversibility after liver transplant. Journal of Cardiology. 2023 Aug 1;82(2):113-21.

222. Rahman S, Mallett SV. Cirrhotic cardiomyopathy: Implications for the perioperative management of liver transplant patients. World Journal of Hepatology. 2015 Mar 3;7(3):507.

223. `Ginès P, Solà E, Angeli P, Wong F, Nadim MK, Kamath PS. Hepatorenal syndrome. Nature Reviews Disease Primers. 2018 Sep 13;4(1):23.

224. Huelin P, Solà E, Elia C, Solé C, Risso A, Moreira R, Carol M, Fabrellas N, Bassegoda O, Juanola A, de Prada G. Neutrophil gelatinase-associated lipocalin for assessment of acute kidney injury in cirrhosis: a prospective study. Hepatology. 2019 Jul;70(1):319-33.

225. MacDonald AJ, Nadim MK, Durand F, Karvellas CJ. Acute kidney injury in cirrhosis: implications for liver transplantation. Current opinion in critical care. 2019 Apr 1;25(2):171-8.

226. Angeli P, Ginès P, Wong F, Bernardi M, Boyer TD, Gerbes A, Moreau R, Jalan R, Sarin SK, Piano S, Moore K. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut. 2015 Apr 1;64(4):531-7.

227. Huelin P, Piano S, Solà E, Stanco M, Solé C, Moreira R, Pose E, Fasolato S, Fabrellas N, de Prada G, Pilutti C. Validation of a staging system for acute kidney injury in patients with cirrhosis and association with acute-on-chronic liver failure. Clinical Gastroenterology and Hepatology. 2017 Mar 1;15(3):438-45.

228. Angeli P, Ginès P, Wong F, Bernardi M, Boyer TD, Gerbes A, Moreau R, Jalan R, Sarin SK, Piano S, Moore K. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut. 2015 Apr 1;64(4):531-7.

229. Allegretti AS, Solà E, Ginès P. Clinical application of kidney biomarkers in cirrhosis. American Journal of Kidney Diseases. 2020 Nov 1;76(5):710-9.

230. Huelin P, Solà E, Elia C, Solé C, Risso A, Moreira R, Carol M, Fabrellas N, Bassegoda O, Juanola A, de Prada G. Neutrophil gelatinase-associated lipocalin for assessment of acute kidney injury in cirrhosis: a prospective study. Hepatology. 2019 Jul;70(1):319-33.

231. Francoz C, Nadim MK, Durand F. Kidney biomarkers in cirrhosis. Journal of hepatology. 2016 Oct 1;65(4):809-24.

232. Amathieu R, Al-Khafaji A, Sileanu FE, Foldes E, DeSensi R, Hilmi I, Kellum JA. Significance of oliguria in critically ill patients with chronic liver disease. Hepatology. 2017 Nov 1;66(5):1592-600.

233. Moctezuma-Velazquez C, Kalainy S, Abraldes JG. Beta-blockers in patients with advanced liver disease: Has the dust settled?. Liver Transplantation. 2017 Aug;23(8):1058-69.

234. Kulkarni AV, Arab JP, Premkumar M, Benítez C, Tirumalige Ravikumar S, Kumar P, Sharma M, Reddy DN, Simonetto DA, Rao PN. Terlipressin has stood the test of time: Clinical overview in 2020 and future perspectives. Liver International. 2020 Dec;40(12):2888-905.

235. Cavallin M, Piano S, Romano A, Fasolato S, Frigo AC, Benetti G, Gola E, Morando F, Stanco M, Rosi S, Sticca A. Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: a randomized controlled study. Hepatology. 2016 Mar;63(3):983-92.

236. Ginès P, Solà E, Angeli P, Wong F, Nadim MK, Kamath PS. Hepatorenal syndrome. Nature Reviews Disease Primers. 2018 Sep 13;4(1):23.

237. Duvoux C, Zanditenas D, Hézode C, Chauvat A, Monin JL, Roudot-Thoraval F, Mallat A, Dhumeaux D. Effects of noradrenalin and albumin in patients with type I hepatorenal syndrome: a pilot study. Hepatology. 2002 Aug 1;36(2):374-80.

238. Cavallin M, Kamath PS, Merli M, Fasolato S, Toniutto P, Salerno F, Bernardi M, Romanelli RG, Colletta C, Salinas F, Di Giacomo A. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: a randomized trial. Hepatology. 2015 Aug;62(2):567-74.

239. Belcher JM, Garcia-Tsao G, Sanyal AJ, Bhogal H, Lim JK, Ansari N, Coca SG, Parikh CR, TRIBE-AKI Consortium. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. Hepatology. 2013 Feb;57(2):753-62.

240. Boyer TD. American Association for the Study of Liver Diseases. The role of transjugular intrahepatic portosystemic shunt in the management of portal hypertension. Hepatology. 2005;41:386-400.

241. Angeli P, Rodríguez E, Piano S, Ariza X, Morando F, Solà E, Romano A, García E, Pavesi M, Risso A, Gerbes A. Acute kidney injury and acute-on-chronic liver failure classifications in prognosis assessment of patients with acute decompensation of cirrhosis. Gut. 2015 Oct 1;64(10):1616-22.

242. Durand F, Francoz C, Asrani SK, Khemichian S, Pham TA, Sung RS, Genyk YS, Nadim MK. Acute kidney injury after liver transplantation. Transplantation. 2018 Oct 1;102(10):1636-49.

243. Kaymakoglu S, Kahraman T, Kudat H, Demir K, Cakaloglu Y, Adalet I, Dincer D, Besisik F, Boztas G, Sözen AB, Mungan Z. Hepatopulmonary syndrome in noncirrhotic portal hypertensive patients. Digestive diseases and sciences. 2003 Mar;48:556-60.

244. Wolfe JD, Tashkin DP, Holly FE, Brachman MB, Genovesi MG. Hypoxemia of cirrhosis: detection of abnormal small pulmonary vascular channels by a quantitative radionuclide method. The American Journal of Medicine. 1977 Nov 1;63(5):746-54.

245. Tsauo J, Weng N, Ma H, Jiang M, Zhao H, Li X. Role of transjugular intrahepatic portosystemic shunts in the management of hepatopulmonary syndrome: a systemic literature review. Journal of Vascular and Interventional Radiology. 2015 Sep 1;26(9):1266-71.

246. Krowka MJ, Mandell MS, Ramsay MA, Kawut SM, Fallon MB, Manzarbeitia C, Pardo Jr M, Marotta P, Uemoto S, Stoffel MP, Benson JT. Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. Liver Transplantation. 2004 Feb;10(2):174-82.

247. Writing Committee Members, McLaughlin, V.V., Archer, S.L., Badesch, D.B., Barst, R.J., Farber, H.W., Lindner, J.R., Mathier, M.A., McGoon, M.D., Park, M.H. and Rosenson, R.S., 2009. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation task force on expert consensus documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation*, *119*(16), pp.2250-2294.

248. Rodriguez-Roisin R, Krowka MJ, Herve PH, Fallon MB. Pulmonary–hepatic vascular disorders (PHD). European Respiratory Journal. 2004 Nov 1;24(5):861-80.

249. Cotton CL, Gandhi S, Vaitkus PT, Massad MG, Benedetti E, Mrtek RG, Wiley TE. Role of echocardiography in detecting portopulmonary hypertension in liver transplant candidates. Liver Transplantation. 2002 Nov;8(11):1051-4.

250. Halank M, Miehlke S, Hoeffken G, Schmeisser A, Schulze M, Strasser RH. Use of oral endothelin-receptor antagonist bosentan in the treatment of portopulmonary hypertension. Transplantation. 2004 Jun 15;77(11):1775-6.

251. Yoshida EM, Erb SR, Pflugfelder PW, Ostrow DN, Ricci DR, Ghent CN, Wall WJ, Grant D, Scudamore CH, Shackleton CB. Single-lung versus liver transplantation for the treatment of portopulmonary hypertension--a comparison of two patients. Transplantation. 1993 Mar 1;55(3):688-90.

252. Cartin-Ceba R, Krowka MJ. Portopulmonary hypertension. Cirrhosis: A practical guide to management. 2015 Mar 13:212-24.

253. Raevens S, De Pauw M, Reyntjens K, Geerts A, Verhelst X, Berrevoet F, Rogiers X, Troisi RI, Van Vlierberghe H, Colle I. Oral vasodilator therapy in patients with moderate to severe portopulmonary hypertension as a bridge to liver transplantation. European journal of gastroenterology & hepatology. 2013 Apr 1;25(4):495-502.

254. DuBrock HM, Goldberg DS, Sussman NL, Bartolome SD, Kadry Z, Salgia RJ, Mulligan DC, Kremers WK, Kawut SM, Krowka MJ, Channick RN. Predictors of waitlist mortality in portopulmonary hypertension. Transplantation. 2017 Jul 1;101(7):1609-15.

255. Singal AG, Llovet JM, Yarchoan M, Mehta N, Heimbach JK, Dawson LA, Jou JH, Kulik LM, Agopian VG, Marrero JA, Mendiratta-Lala M. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. 2023 Dec 1;78(6):1922-65.

256. Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: New trends. Journal of hepatology. 2020 Feb 1;72(2):250-61.

257. Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. PLoS medicine. 2014 Apr 1;11(4):e1001624.

258. Kobayashi K, Sugimoto T, Makino H, Kumagai M, Unoura M, Tanaka N, Kato Y, Hattori N. Screening methods for early detection of hepatocellular carcinoma. Hepatology. 1985 Nov 1;5(6):1100-5.

259. Gustot T, Stadlbauer V, Laleman W, Alessandria C, Thursz M. Transition to decompensation and acute-on-chronic liver failure: Role of predisposing factors and precipitating events. Journal of hepatology. 2021 Jul 1;75:S36-48.

260. D'Amico G, Morabito A, D'Amico M, Pasta L, Malizia G, Rebora P, Valsecchi MG. Clinical states of cirrhosis and competing risks. Journal of hepatology. 2018 Mar 1;68(3):563-76.

261. Jalan R, D'Amico G, Trebicka J, Moreau R, Angeli P, Arroyo V. New clinical and pathophysiological perspectives defining the trajectory of cirrhosis. Journal of hepatology. 2021 Jul 1;75:S14-26.

262. Somsouk M, Kornfield R, Vittinghoff E, Inadomi JM, Biggins SW. Moderate ascites identifies patients with low model for end-stage liver disease scores awaiting liver transplantation who have a high mortality risk. Liver Transplantation. 2011 Feb;17(2):129-36.

263. Wedd J, Bambha KM, Stotts M, Laskey H, Colmenero J, Gralla J, Biggins SW. Stage of cirrhosis predicts the risk of liver-related death in patients with low Model for End-Stage Liver Disease scores and cirrhosis awaiting liver transplantation. Liver Transplantation. 2014 Oct;20(10):1193-201.

264. Mahmud N. Selection for liver transplantation: indications and evaluation. Current hepatology reports. 2020 Sep;19(3):203-12.

265. Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, Krag A, Laleman W, Gines P. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. Journal of hepatology. 2018 Aug 1;69(2):406-60.

266. Shiffman ML. Approach to the patient with chronic hepatitis B and decompensated cirrhosis. Liver International. 2020 Feb;40:22-6.

267. An J, Park DA, Ko MJ, Ahn SB, Yoo JJ, Jun DW, Yim SY. Direct-acting antivirals for HCV treatment in decompensated liver cirrhosis patients: a systematic review and meta-analysis. Journal of Personalized Medicine. 2022 Sep 15;12(9):1517.

268. Thomes PG, Rasineni K, Saraswathi V, Kharbanda KK, Clemens DL, Sweeney SA, Kubik JL, Donohue Jr TM, Casey CA. Natural recovery by the liver and other organs after chronic alcohol use. Alcohol research: current reviews. 2021;41(1).

269. Artru F, Samuel D. Approaches for patients with very high MELD scores. JHEP Reports. 2019 May 1;1(1):53-65.

LIVACT® Granules

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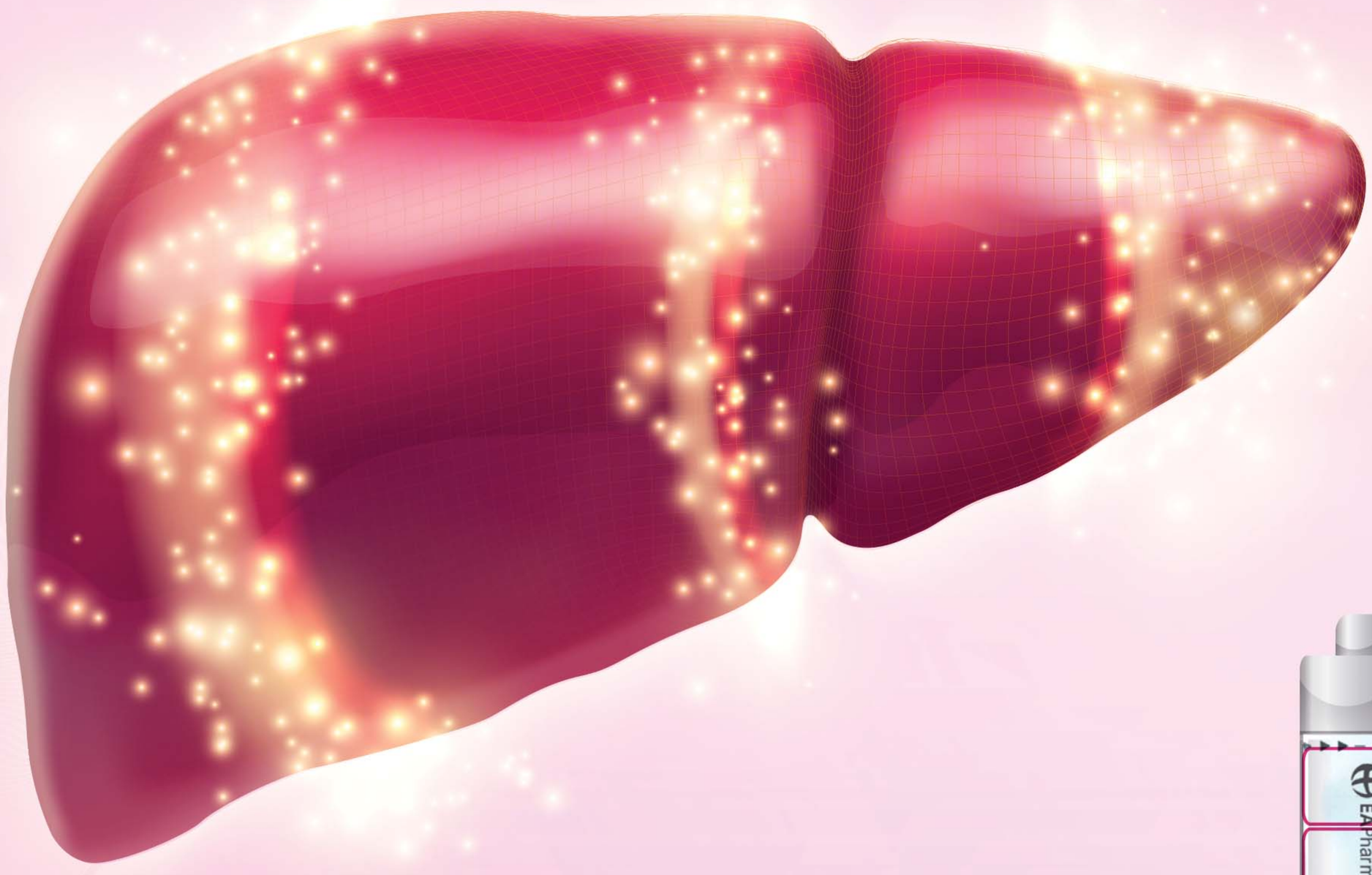
Unfit liver? Energize daily with LIVACT.

Recommended by ESPEN practical guideline:
Clinical nutrition in liver disease[4]



Composition[1]
L-Isoleucine - 952 mg
L-Leucine - 1,904 mg
L-Valine - 1,144 mg

Branched Chain Amino Acid Formula indicated for Improvement of Hypoalbuminemia in Patients with Decompensated Hepatic Cirrhosis[1]

3 times daily after meal[1]

LIVACT® Granules

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Better Event Free Survival Rate in Patients Taking BCAA group[3]

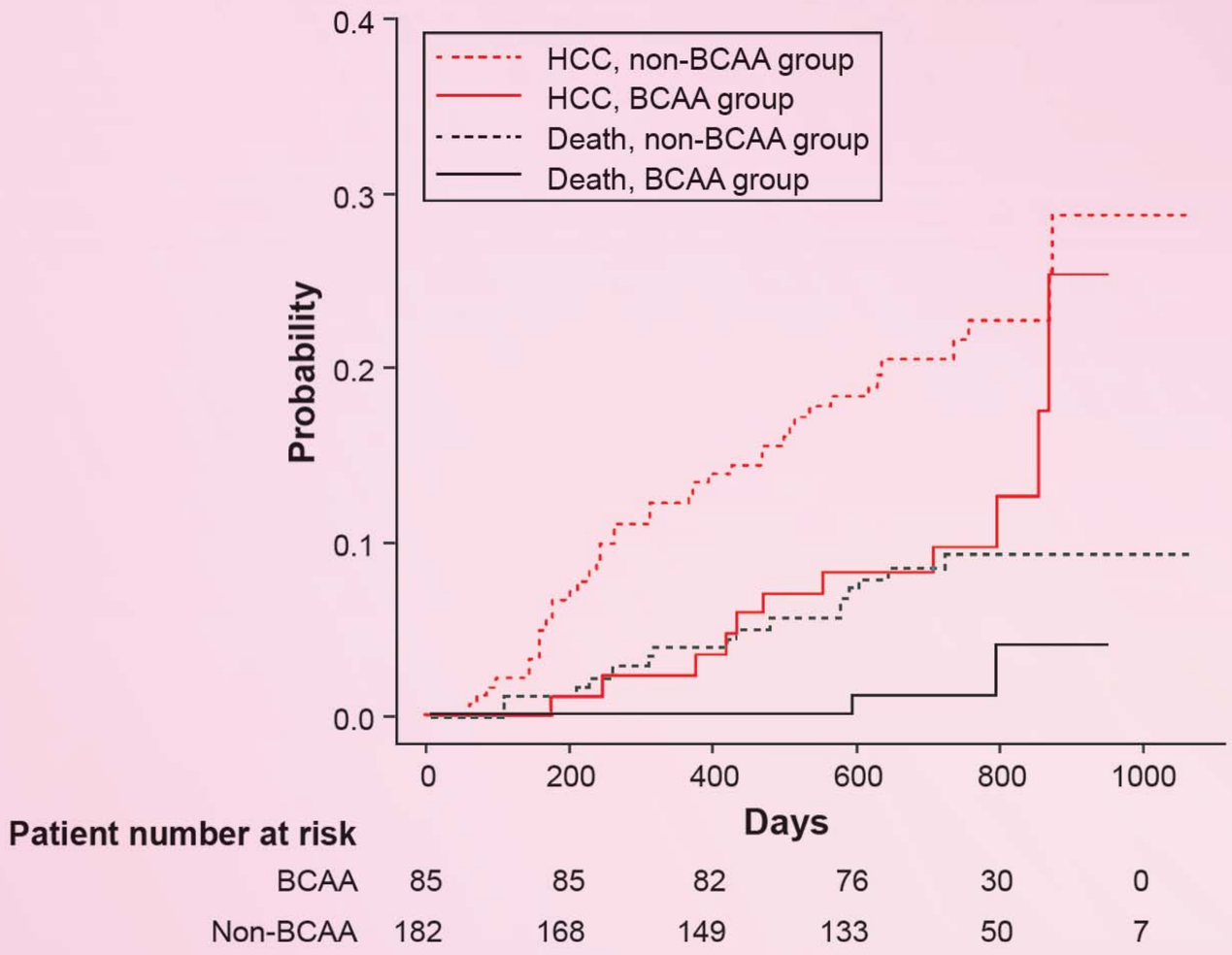
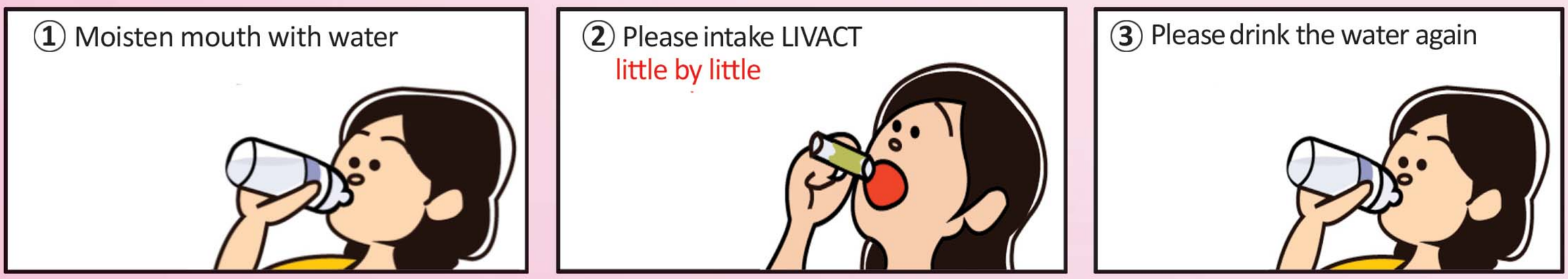


Figure 1. Cumulative incidences of HCC (red lines) and death (black lines) between BCAA and non-BCAA groups. Solid lines indicate the BCAA group, and dashed lines indicate the non-BCAA group.

For Healthcare Professionals ONLY - Issue Date: 09/2024

How To Take LIVACT?[2]



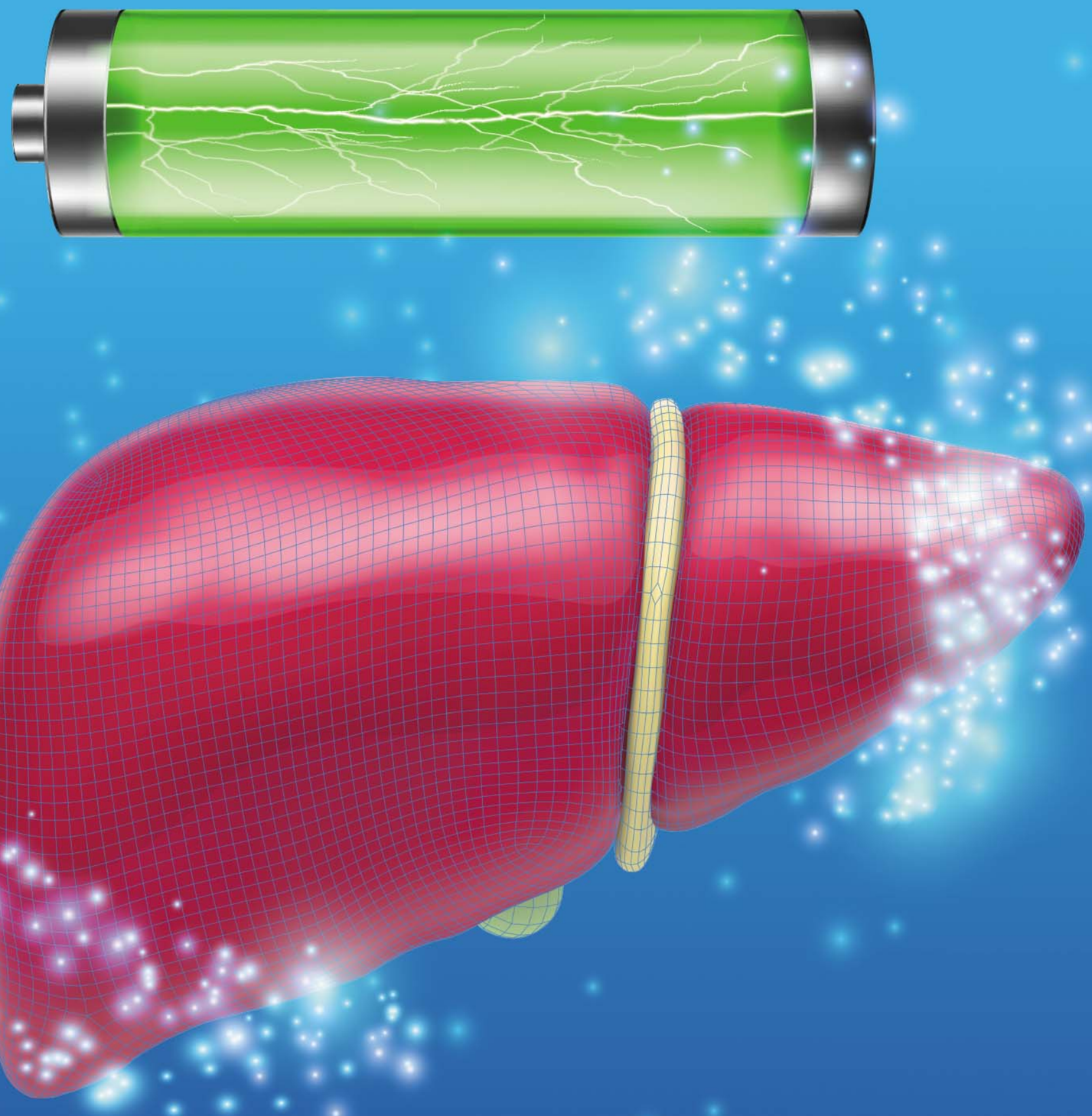
- **By dividing the large amount of granules into two or three, wrap each portion with an oblate membrane, and take each, while avoiding spreading the product in the oral cavity;**
- **By taking this product using an oral jelly.**

1. LIVACT Package Insert
2. https://www.eapharma.co.jp/en/products/livact/useful/qa.html
3. Kawaguchi YT et al. Clinical Gastroenterology and Hepatology 2014; 12:1012-1018
4. S.C. Bischoff, W. Bernal, S. Dasarathy et al. Clinical Nutrition 39 (2020) 3533-3562

MORIHEPAMIN®

EAPharma

A Better Option: MORIHEPAMIN



Indication

For supportive treatment of hepatic encephalopathy syndrome in patients with chronic liver disorder.

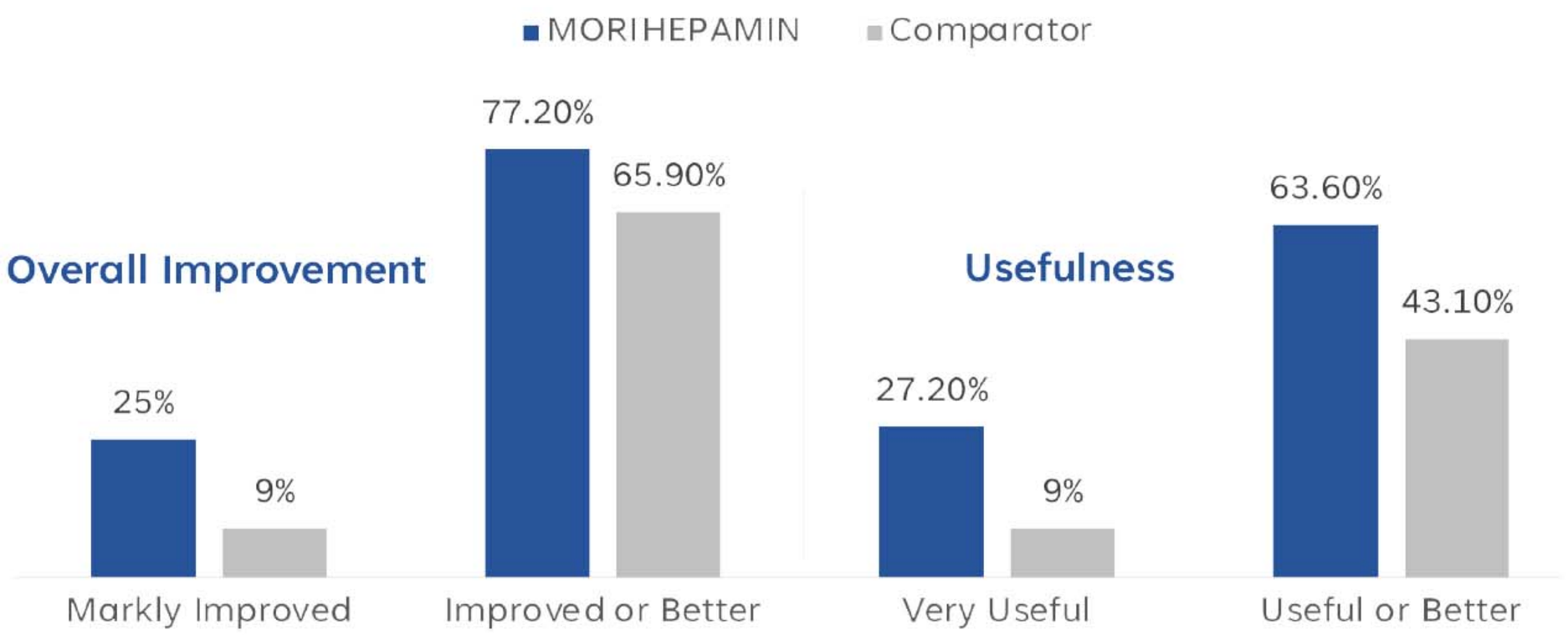
Dosage

Usually intravenously drip-infused at a single dose of 500 ml in adult patients. The standard infusion rate in adults is 180 minutes or longer per 500 ml.

Why MORIHEPAMIN is a better option...

	MORIHEPAMIN	Comparator
A Better Fischer Ratio	54.13	37.05
High Content of Arginine	7.685 g/500 ml	3 g/500 ml
Lesser Content of Ammonia-Producing Amino Acid (per 500ml)		
L-Methionine	0.22 g	0.50 g
L-Phenylalanine	0.15 g	0.50 g
L-Serine	1.30 g	2.50 g
L-Threonine	1.070 g	2.25 g
L-Lysine	1.975 g	3.05 g

Clinical Evaluation of MORIHEPAMIN on Hepatic Encephalopathy : Phase III Study in Comparison with Comparator...



- Superior to Comparator in overall improvement
- Significantly superior to Comparator in terms of utility ($p<0.05$)

95 patients enrolled in the study. Either MORIHEPAMIN or Comparator was administered intravenously to patients by drip infusion at the dose of 500ml once daily for 3 days.

1. MORIHEPAMIN Package Insert
2. Japanese Pharmacology & Therapeutics (Jpn Pharmacal Ther) Vol. 19, No.1 p269, Jan. 1991

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Clinical Practice Guidance for Cirrhosis of Liver

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