LIVER CIRRHOSIS

CHI Formulary Development Project

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Related Documents

Related SOPs

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Abbreviations

ACLF	Acute-on-Chronic Liver Failure
AKI	Acute Kidney Injury
AVB	Acute Variceal Bleeding
BASL	British Association for the Study of the Liver
BCAA	Branched-Chain Amino Acid
BL	Band Ligation
BMD	Bone Mineral Density
BRTO	Balloon-Occluded Retrograde Transvenous Obliteration
BSG	British Society of Gastroenterology
CADTH	Canadian Agency for Drugs and Technologies in Health
CART	Cell-free and Concentrated Ascites Reinfusion Therapy
CHI	Council of Health Insurance
DC	Decompensated Cirrhosis
EASL	European Association for the Study of the Liver
EBL	Endoscopic Band Ligation
EMA	European Medicines Agency
EV	Esophageal Varices
EVL	Endoscopic Variceal Ligation
EVO	Endoscopic Variceal Obturation
FDA	Food and Drug Administration
FIB-4	Fibrosis-4 Index
GOV	Gastroesophageal Varices
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HAS	Haute Autorité de Santé
HCC	Hepatocellular Carcinoma
HE	Hepatic Encephalopathy
HRS	Hepatorenal Syndrome
HSA	Human Serum Albumin
HTA	Health Technology Assessment

IAD	Indwelling Abdominal Drains
IDF	Insurance Drug Formulary
IGV	Isolated Gastric Varices
IQWIG	Institute for Quality and Efficiency in Health Care
kPa	Kilopascals
LOLA	Intravenous L-ornithine-L-aspartate
LSM	Liver Stiffness Measurement
LT	Liver Transplantation
LVP	Large-Volume Paracentesis
MARS	Molecular Adsorbent Recirculating System
MELD	Model for End-Stage Liver Disease
MMF	Mycophenolate Mofetil
NASH	Nonalcoholic Fatty Liver Disease
NICE	National Institute for Health and Care Excellence
NSBB	Non-Selective Beta-Blocker
OGD	Oesophagogastroduodenoscopy
PARTO	Partial Splenic Embolization
PBAC	Pharmaceutical Benefits Advisory Committee
PICD	Paracentesis-Induced Circulatory Dysfunction
PICO	Population, Intervention, Control, and Outcomes
PVS	Peritoneovenous Shunt
QoE	Quality of Evidence
RRT	Renal Replacement Therapy
RTO	Retrograde Transvenous Obliteration
SBP	Spontaneous Bacterial Peritonitis
SFDA	Saudi Food and Drug Authority
SoR	Strength of Recommendation
TIPS	Trans-jugular Intrahepatic Portosystemic Shunting
UGI	Upper Gastrointestinal
VBL	Variceal Band Ligation
VH	Variceal Hemorrhage

Executive Summary

Liver cirrhosis is a chronic, progressive liver disease characterized by the replacement of normal liver tissue with fibrous scar tissue. This scarring disrupts the liver's structure and function, impairing its ability to perform essential tasks, such as detoxification, nutrient processing, and the production of proteins. Cirrhosis often develops because of long-term liver damage and inflammation caused by conditions such as chronic alcoholism, viral hepatitis, nonalcoholic fatty liver disease (NASH), or other liver disorders[1].

Diagnosing liver cirrhosis typically involves a combination of medical history assessment, physical examination, and various diagnostic tests. Assessment for risk factors and signs of cirrhosis should be the first step such as hepatitis B & C, alcohol use disorder, jaundice, palmar erythema, decreased body hair, etc. The conduction of liver function tests (LFTs) and the assessment of liver synthetic function are also deemed appropriate. The second step is to use the noninvasive laboratory measurements Fibrosis-4 Index (FIB-4) score and the liver stiffness measurement (LSM)[2]. If these tools aren't sufficient to confirm the diagnosis of liver cirrhosis, the final and definitive step would be to conduct a liver biopsy. The Metavir Score is the tool used to evaluate the severity of fibrosis on a liver biopsy sample. It is staged from F0 to F4 starting with no/minimal fibrosis to cirrhosis at stage F4. Treatment is usually considered for F2 or greater when fibrosis is at a moderate intensity[1].

The global prevalence of cirrhosis, as indicated by autopsy studies, varies between 4.5% and 9.5% among the general population. Hence, it is estimated that over fifty million individuals worldwide, considering the adult population, would be affected with chronic liver disease. Prevalence of cirrhosis is likely to be underestimated as almost a third of the patients remain asymptomatic[3]. Among NASH cases in Saudi Arabia, 185,500 were estimated to have F3/F4 fibrosis or advanced liver disease (decompensated cirrhosis or HCC), encompassing approximately 13.5% of all NASH cases and 0.56% of the total population (all ages). By 2030, this number was expected to increase 216% to 586,000 cases, and account for 21.8% of all NASH cases[4].In the initial stages, clinical manifestations of liver cirrhosis may exhibit subtle signs that could be compensated. Common symptoms during this early phase include fatigue. However, as the condition progresses, it may transition to decompensated liver cirrhosis, marked by various complications. Decompensated liver cirrhosis can be associated with synthetic dysfunction, leading to issues such as compromised blood clotting, evident through easy bruising and an increased risk of bleeding. Additionally, individuals may experience jaundice due to impaired bilirubin processing and hypoalbuminemia. Furthermore, cirrhosis can result in portal hypertension, giving rise to complications such as ascites, esophageal varices, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome. Another potential complication is hepatoma, a serious consequence of

cirrhosis, whether in a compensated or decompensated state. Therefore, early detection and management are crucial in addressing these complications and improving the overall quality of life for individuals with liver cirrhosis [1].

This report compiles all clinical and economic evidence related to liver cirrhosis according to the relevant sources. The ultimate objective of issuing liver cirrhosis guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to liver cirrhosis patients in Saudi Arabia**.

The main focus of the review was on North American, European, and other international guidelines issued within the last five years. To clarify, North American guidelines delivered an overview of the diagnosis, causes, complications, and management of liver cirrhosis while also tackling palliative care. The European guidelines provided guidance for the outpatient management of compensated and decompensated cirrhosis in addition to special circumstances such as pregnancy and portal vein thrombosis. The international guidelines heavily focused on the management of the complications of liver cirrhosis by providing lengthy and thorough recommendations while finalizing the topic with a consensus of pediatric cirrhosis.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in liver cirrhosis were reviewed and summarized under each drug therapy table in Section 2.0. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

The treatment of liver cirrhosis focuses on managing its underlying cause, alleviating symptoms, and preventing complications as early intervention is the key to improving prognosis. Lifestyle modifications, such as abstaining from alcohol and maintaining a healthy diet, are essential. Medications may be prescribed to address specific symptoms or to target the underlying condition causing cirrhosis. For instance, in cases of portal hypertension, medications such as non-selective beta blockers (carvedilol, propranolol, and nadolol) can help reduce pressure in the portal vein which prevents the rupture of esophageal varices. Complications such as ascites require sodium restriction and diuretics such spironolactone and furosemide with the possible addition of vasopressin antagonist tolvaptan[5] and vasopressin analogue terlipressin[6] (also first line for hepatorenal syndrome) in refractory ascites. Hepatic encephalopathy will require lactulose or rifaximin for the prevention or treatment. Albumin is also an important drug since hypoalbuminemia is a common manifestation of liver cirrhosis. Liver transplantation is considered for advanced

cirrhosis when other treatments are no longer effective. Regular medical monitoring, including imaging studies and blood tests, is crucial to detect and manage complications promptly. Routine monitoring of cirrhotic patients for the development of hepatocellular carcinoma (HCC) is recommended, with at least screenings every 6 months using abdominal ultrasonography[7]. Multidisciplinary care involving hepatologists, liver transplant surgeons, nutritionists, and other specialists such as oncologists and interventional radiologists, is often necessary to provide comprehensive management for individuals with liver cirrhosis.

Liver cirrhosis may lead to a variety of complications. This report discusses in detail a few of them, including ascites, hepatorenal syndrome, variceal bleeding, hepatic encephalopathy, and thrombocytopenia. Other manifestations include venous thromboembolism, spontaneous bacterial peritonitis, coagulopathies (including venous thromboembolism and pulmonary embolism), and hepatocellular carcinoma. These are discussed in detail in separate indication reports.

Section 2.0 provides a full description of each pharmacological agent with final statements on the placement of therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of liver cirrhosis.

Finally, the report concludes with the addition of a key recommendation synthesis section, which emphasizes the utilization of each drug class for specific patient groups.

Major recommendations for suggested drug therapies are summarized in the tables below:

Table 1. SFDA-Registered Drugs for the Management of Liver Cirrhosis

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation	HTA Recommendations
Lactulose	Prevention and treatment of **hepatic encephalopathy** in liver cirrhosis	**1st Line**	A1	Not available
Rifaximin	Prevention and treatment of **hepatic encephalopathy** in liver cirrhosis	**2nd Line**	A1	**NICE**[8] **- Conditional Positive Recommendation – March 2015** Although the most plausible incremental cost-effectiveness ratio (ICER) was subject to several uncertainties, the Committee was aware of the important unmet medical need in this population and the innovative aspects of this treatment The Committee concluded that rifaximin could be considered a cost-effective use of NHS resources for preventing episodes of overt hepatic encephalopathy. **CADTH**[9] **- Conditional Positive Recommendation April 2015** One double-blind, phase 3, randomized controlled trial (RCT) (study 3001; N = 299), in which 91% of

				participants were using concomitant lactulose therapy, demonstrated that treatment with rifaximin significantly reduced the risk of breakthrough overt HE (hazard ratio [HR] 0.421; 95% confidence interval [CI], 0.276 to 0.641]) and HE-related hospitalization (HR 0.500; 95% CI, 0.287 to 0.873) compared with placebo. **HAS[10] - Conditional Positive Recommendation August 2021** Favorable opinion for reimbursement only in the prevention of recurrence of episodes of breakthrough overt hepatic encephalopathy (with at least two previous episodes of hepatic encephalopathy) and following elimination of triggering factors. Unfavorable opinion for reimbursement in other situations.
Spironolactone	Treatment of **ascites** in liver cirrhosis	**1st Line**	B1	Not available
Furosemide	Treatment of **ascites** in liver cirrhosis	**2nd Line**	B1	Not available

Albumin	Treatment of **ascites**, **hepatorenal syndrome, and hypoalbuminemia** in liver cirrhosis	**4th Line (Ascites)** **1st Line (Hepatorenal Syndrome)**	A1 A1	Not available
Tolvaptan	Treatment of **ascites** and **hyponatremia** in liver cirrhosis	**3rd Line**	A1	Not available
Terlipressin	Treatment of **hepatorenal syndrome** (combined with albumin) and **management of variceal bleeding**	**1st Line in both**	A1 A1	**NICE**[11] **- Conditional Positive Recommendation June 2012** Offer terlipressin to patients with suspected variceal bleeding at presentation. Stop treatment after definitive haemostasias has been achieved, or after 5 days, unless there is another indication for its use.
Octreotide	Management of **Variceal Bleeding and Hepatorenal Syndrome**	**1st Line for Variceal Bleeding and Alternative for Hepatorenal Syndrome**	B	**HAS**[12] **- Positive Recommendation - August 2016** Octreotide is important in emergency treatment, and prevention of recurrence of hemorrhage from gastroesophageal varices in cirrhotic patients. Sandostatin should be used in combination with

				specific therapy such as endoscopic sclerotherapy.
Norepinephrine	Treatment of **hepatorenal syndrome** (combined with albumin)	**2nd Line**	No level of evidence	Not available

Table 2. Non-SFDA-Registered Drugs for the Management of Liver Cirrhosis

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation
Cholestyramine	**Cholestatic Pruritis**	1st line	American Association for the Study of Liver Diseases (AASLD) Practice Guidance[13]
Naltrexone	**Cholestatic Pruritis**	Alternative Agent	American Association for the Study of Liver Diseases (AASLD) Practice Guidance[13]

The report concludes with the addition of a key recommendation synthesis section, which emphasizes the utilization of each drug class for specific patient groups.

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

1.1 KSA Guidelines

To date, no clinical practice guidelines have been issued by Saudi societies for the management of liver cirrhosis.

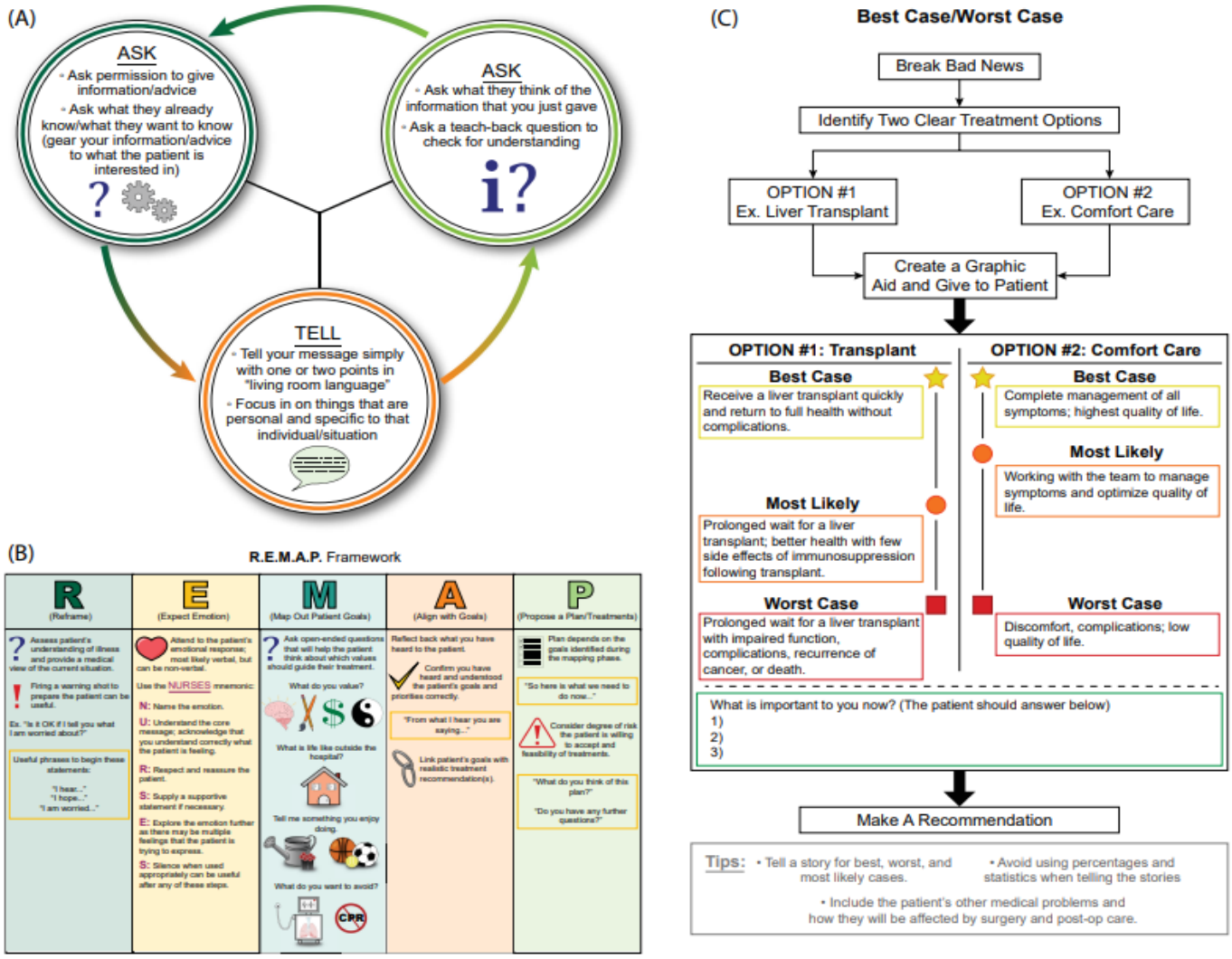
1.2 North American Guidelines

1.2.1 American Association for the Study of Liver Diseases (AASLD) Practice Guidance: Palliative Care and Symptom-Based Management in Decompensated Cirrhosis [2022]

The following guidelines do not provide a specified grade of evidence or level of recommendation.

Palliative care is defined as multidisciplinary, specialized medical care that addresses the physical, spiritual, and psychosocial needs of patients with serious illness and their caregivers. The benefits of palliative care are increasingly recognized across disease states and for patients with decompensated cirrhosis (DC)[13].

The AASLD guidelines adapted structured communication frameworks to support complex conversations regarding prognosis and goals of care as shown in figure 1:



(A) Ask-Tell-Ask is a simple approach that can be used to deliver bad news. (B) The R.E.M.A.P. Framework is a stepwise approach to engaging patients in more-complex decision making. (C) Best-case worst-case provides a way to frame difficult choices, such as the choice to pursue a transplant.

Figure 1. *Structured frameworks for goals-of-care conversations*

Overview of the approach to symptom assessment, triage, and management in patients with decompensated cirrhosis (DC)

- Effectively managing symptoms is a fundamental element of providing high-quality care for individuals with DC, who experience a range of symptoms that are frequently interconnected.
- In the case of individuals with DC, following general principles of palliative care, a systematic assessment of a broad spectrum of symptoms is suggested,

prioritizing the management of those deemed most significant to the patients.

- Assessment and handling of symptoms should involve interdisciplinary collaboration, whenever feasible, incorporating the expertise of nursing, social work, and chaplaincy.

The following table represents a summary of pharmacotherapies and side effects of the symptomatic treatment for patients with decompensated cirrhosis:

Table 3. Summary of Pharmacotherapies for Symptomatic Treatment and their Respective Side Effects for Patients with Decompensated Cirrhosis

Symptom & Medication	Side effects & Cautions
Nociceptive Pain	
Acetaminophen	Generally safe at low dose (2-gram daily maximum), can cause hepatic failure at high dose
Topical non-steroidal anti-inflammatory drugs (NSAIDs)	Not tested in patients with cirrhosis (note that systemic NSAIDs are generally avoided in patients with cirrhosis).
Lidocaine patch	Site reactions (erythema), petechia, edema, pruritus, nausea, vomiting.
Capsaicin cream	Site reactions (burning, pain, erythema), limb pain, hypertension.
Opioids	Hepatic encephalopathy (HE), habit forming, respiratory depression, constipation/obstipation, overdose; preferred are oxycodone and hydromorphone.
Neuropathic Pain	
Gabapentin & Pregabalin	Ataxia, sedation, myoclonus/asterixis, dose adjust in renal impairment, withdrawal syndrome, possible increased viral infections.
Serotonin–norepinephrine reuptake inhibitors (SNRIs)	Discontinuation syndrome, nausea, vomiting, sexual dysfunction.
Tricyclic antidepressants (TCAs)	Anticholinergic, orthostasis, drowsiness, weight gain, sexual dysfunction.
Muscle Cramps	

Baclofen	Hepatic Encephalopathy (HE), confusion, dizziness, sedation, nausea, vomiting, rare neurotoxicity in patients with renal failure, discontinuation syndrome.
Zinc	Gastric irritation, rare neurological side effects.
Methocarbamol	Hypotension, bradycardia, dyspepsia, pruritis, confusion, ataxia, HE, headache, sedation, changes in taste, seizure, vertigo, leukopenia, jaundice, changes in vision (dose reduced in cirrhosis).
Orphenadrine	Palpitations, tachycardia, confusion, sedation, pruritis, constipation, nausea, vomiting, tremor, urinary retention, blurred vision, central nervous system depression.
L-Carnitine	Side effects common with intravenous formulation; oral formulation generally tolerated well at normal doses.
Vitamin E	Nausea, diarrhea.
Taurine	Nausea, dizziness, headache.
Branched-chain amino acid (BCAAs)	Possible nausea.
Depression/Anxiety	
SNRIs	Discontinuation syndrome, nausea, vomiting, sexual dysfunction, rare hepatitis
Selective serotonin reuptake inhibitors (SSRIs)	QTc prolongation and seizure risk with citalopram, sedation with mirtazapine, nausea, vomiting, weight gain, sexual dysfunction, insomnia, bleeding risk.
Benzodiazepines	Physical dependence, sedation, HE, only for short-term use at the end of life in cirrhosis.
Dyspnea	
Opioids	HE, habit forming, respiratory depression, constipation/obstipation.
Benzodiazepines	Physical dependence, sedation, HE, only for short-term use at the end of life in cirrhosis
Hepatic Encephalopathy	
Zinc	Gastric irritation, rare neurological side effects.
L-Carnitine	Side effects common with intravenous formulation; oral generally tolerated well at normal doses.
Insomnia	

Melatonin	Headache, fragmented sleep, confusion.
Zolpidem	Headache, drowsiness, dizziness, palpitations, anxiety, disorientation, hallucination, use with caution and only in low doses for short time periods in patients with cirrhosis, particularly in the presence of HE.
Fatigue	
Modafinil	Headache, abdominal pain, decreased appetite, chest pain, tachycardia, anxiety, insomnia, confusion, diarrhea, exacerbation of psychiatric symptoms, dose reduction is generally recommended; evidence is poor.
Methylphenidate	Not studied in cirrhosis, insomnia, headache, irritability, weight loss, anorexia, xerostomia, nausea, tachycardia, hypertension, emotional lability, dizziness, depression, anxiety, nausea, vomiting, diarrhea, abdominal pain, possible increased infection risk; evidence is poor.
Pruritis	
Cholestyramine	Edema, syncope, abdominal pain, anorexia, arthralgia, headache (caution in renal impairment).
Antihistamines	Sedation, dizziness, HE, rare QT prolongation, hallucination, headache.
Nausea, Vomiting, & Dyspepsia	
Ondansetron	QTc prolongation, headache, constipation.
Metoclopramide	QTc prolongation, drowsiness, fatigue, restlessness, dystonic reaction (age related, but can be severe), arrhythmia, hypotension, caution in renal impairment.
Haloperidol	Increased risk of death in older adults with dementia, extrapyramidal symptoms (e.g., dystonia, akathisia, and tardive dyskinesia), aspiration risk, cytopenia, hyperprolactinemia, neuroleptic malignant syndrome, metabolic derangements, QTc prolongation, seizures, sexual dysfunction.
Medical Cannabinoids	Psychosis, encephalopathy, ascites, hyperemesis.
Antihistamines	Sedation, dizziness, HE, rare QT prolongation, hallucination, headache.
Proton Pump Inhibitors	Increased infection risk in cirrhosis, abdominal pain, diarrhea, nausea, dizziness, headache, rash.
Erectile Dysfunction	

Tadalafil	Dyspepsia, headache, caution if encephalopathy or low blood pressure.

The AASLD Guidelines (2022) provides guidance statements to summarize the recommendations for the non-pharmacological and pharmacological management of decompensated cirrhosis symptoms & complications:

Muscle cramps

- Examining the levels of electrolytes in the serum and replenishing potassium, magnesium, and zinc constitute an initial measure in addressing muscle cramps among patients with decompensated cirrhosis.
- Taurine at a daily dosage of 2–3 grams, vitamin E at 200 milligrams three times a day, and baclofen at 5–10 milligrams three times a day possess preliminary supporting evidence and may be considered for individuals with cirrhosis experiencing substantial muscle cramps.

Sleep disturbances

- Short-term use of melatonin 3 mg or hydroxyzine 25 mg nightly can improve sleep quality in patients with Child-Pugh A and B cirrhosis, but data on long-term use of these medications are limited.
- While it is generally advisable to refrain from prolonged use of benzodiazepines in patients with DC, certain clinical situations may justify their administration, particularly in cases of end-of-life anxiety where prioritizing comfort is the primary goal.

Fatigue

- There is insufficient data to support the use of stimulants to treat fatigue in patients with cirrhosis.

Pruritis

- The suggested approach to pruritus in patients with DC includes starting with nonpharmacological options, including using moisturizing creams, avoiding hot baths and harsh soaps, and using loose-fitting clothes and cool humidified air.
- The initial recommended treatment for pruritus is cholestyramine at a daily dose of 4 grams, with an option for titration up to 16 grams per day.
- Other options include low-dose naltrexone, rifaximin-α (in patients without jaundice), and sertraline. However, cautious titration is necessary when using these agents in the context of DC.

Sexual dysfunction

- Limited information is available regarding the treatment of erectile dysfunction in this demographic. However, tadalafil might be a secure temporary choice for specific patients and is currently subject to additional assessment.

Nausea and vomiting

- First-line pharmacotherapy for addressing nausea and vomiting is ondansetron, with a maximum daily dosage of 8 mg. Caution is advised due to its constipating effects. It's important to note that many antiemetic medications necessitate monitoring for potential QTc prolongation.
- Utilizing medical marijuana is not the initial choice for managing any symptom in patients with DC. Nevertheless, healthcare providers should be capable of participating in an informed discussion regarding the potential advantages and disadvantages of its use.

1.2.2 American Academy of Family Physicians (AAFP) Guideline of the Diagnosis and Management of Cirrhosis [2019]

The American Academy of Family Physicians (AAFP) developed recommendations that are based on the SORT Evidence Rating System[1,14]:

Table 4. SORT Evidence Rating System Adapted by the AAFP

Grade	Interpretation
Grade A	Consistent, good-quality patient-oriented evidence.
Grade B	Inconsistent or limited-quality patient-oriented evidence.
Grace C	Consensus, disease-oriented evidence, usual practice, expert opinion, or case series.

A summary of the recommendations issued by the AAFP can be found in table 5:

Table 5. Key Recommendations for Practice (AAFP 2019 Guidelines)

Clinical Recommendation	Evidence Rating & Comments
Further evaluation of individuals exhibiting clinical signs or symptoms of liver disease or abnormal liver function tests is recommended. This evaluation should be undertaken to identify the potential etiology, irrespective of the duration of the observed abnormalities.	**Grade C** Expert opinion and consensus guidelines in the absence of clinical trials.
All patients with liver cirrhosis should be evaluated for hepatocellular carcinoma with ultrasonography every six months.	**Grade C** Expert opinion and consensus guidelines with low-quality trials.
Patients diagnosed with cirrhosis, who present with a Model for End-Stage Liver Disease (MELD) score of 15 or higher, or experiencing complications such as ascites, hepatic encephalopathy, or variceal hemorrhage, should be directed to a transplant center for further evaluation and management.	**Grade B** Randomized controlled trials demonstrate acceptable survival benefits based on clinical criteria and Model for End-Stage Liver Disease results with some variability.
Patients exhibiting clinically evident (moderate to severe) ascites should undergo management involving restricted salt intake and the administration of spironolactone, either alone or in combination with loop diuretics.	**Grade B** Data from multiple randomized controlled trials demonstrate more benefit than harm regarding patient comfort and reduced hospitalization times.
Patients diagnosed with cirrhosis who possess medium, large, or high-risk varices (characterized by red wale markings) should undergo treatment involving nonselective beta blockers and/or endoscopic band ligation as a primary preventive measure against variceal bleeding.	**Grade B** Randomized controlled trials and meta-analyses comparing nonselective beta blockers, endoscopic band ligation, and placebo or no therapy, which generally show a reduction in variceal hemorrhage.
Hepatic encephalopathy that remains unresponsive to conservative approaches should be treated with lactulose and/or rifaximin.	**Grade B** Low-quality randomized controlled trials that demonstrate less recurrence of

	hepatic encephalopathy using lactulose and/or rifaximin.
Patients with a previous occurrence of spontaneous bacterial peritonitis or ascitic fluid protein levels below 1.5 g per dL (15 g per L), coupled with advanced liver disease (Child-Pugh score of 9 or higher, or bilirubin levels of 3 mg per dL), or kidney disease (serum creatinine levels of 1.2 mg per dL or higher, and serum sodium levels of 130 mmol per L or lower) should initiate oral antibiotic prophylaxis against spontaneous bacterial peritonitis.	**Grade A** Multiple randomized controlled trials demonstrate a reduction in bacterial infections as well as mortality.
Patients with decompensated cirrhosis or compensated cirrhosis, coupled with liver stiffness > 20 kilopascals (assessed through transient elastography) or a platelet count < 150,000 per mm3, should undergo screening for gastroesophageal varices using endoscopy. Subsequent endoscopy should be conducted every one to two years if small varices are identified and every two to three years in the absence of varices.	**Grade C** Expert opinion, consensus guidelines, and unpublished studies in progress.

1.2.3 Review Article: Diagnosis and Management of Cirrhosis and Its Complications [*JAMA*, 2023]

This review article was published by Tapper and Parikh in May 2023 in the Journal of the American Medical Association (JAMA). 115 articles were included, consisting of 9 practice guidelines, 3 consensus statements, 25 RCTs, 17 meta-analyses, 7 systematic reviews (without meta-analysis), and 54 observational cohort studies. The main findings are summarized below[2].

Diagnosis

Figure 2 summarizes risk stratification and diagnosis for patients at risk for cirrhosis:

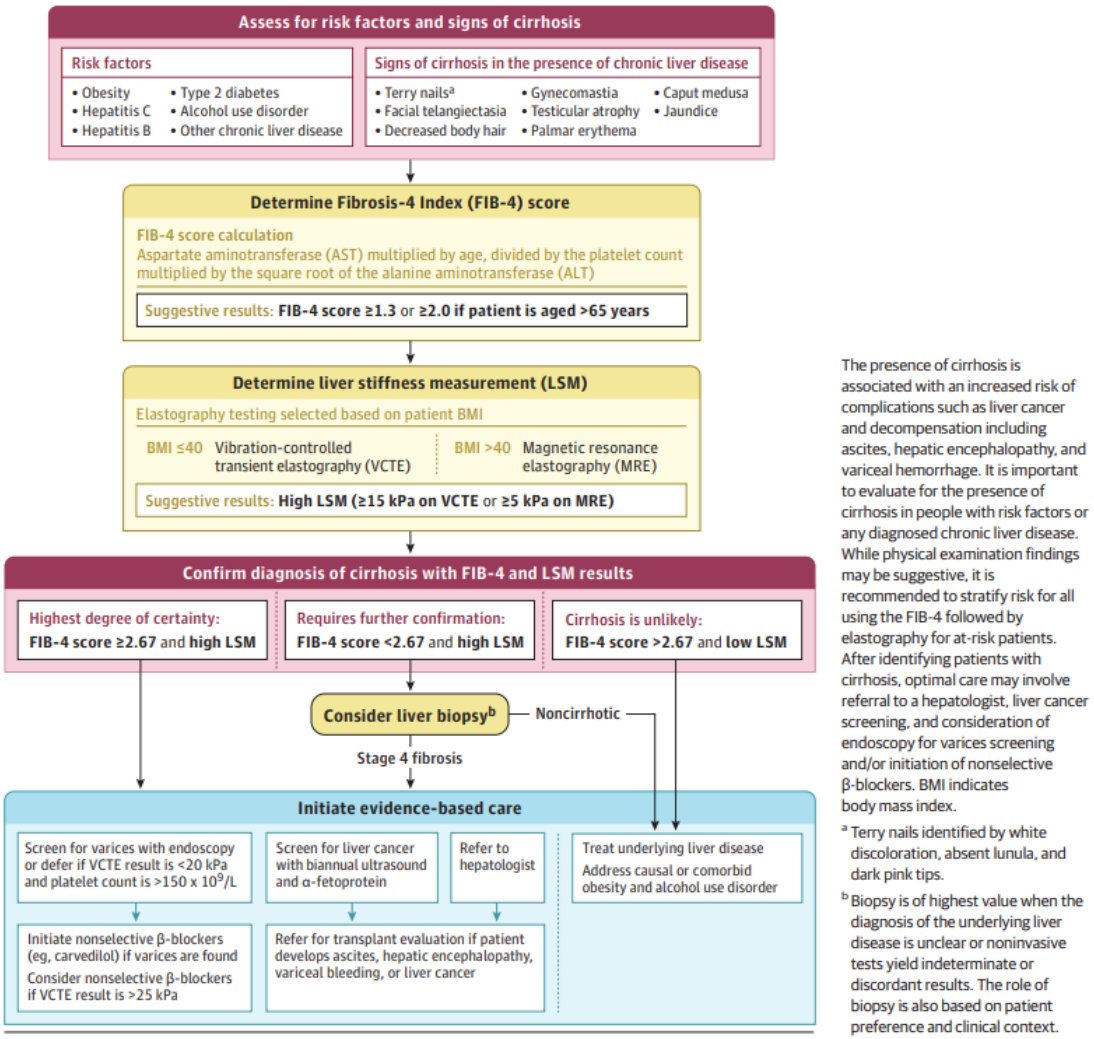


Figure 2. *Diagnosis and risk stratification of patients at risk for cirrhosis. Retrieved from Tapper & Parrikh, 2023.*

Management

The management of liver cirrhosis is based on:

- Addressing and treating the underlying cause.
- Symptomatic treatment and complication management.
- Complication monitoring and intervention.
- Liver transplantation in advanced/end stage cirrhosis.

The goal is to treat patient symptoms, prevent complications and further decompensation to the liver.

Table 6 details the therapies for liver cirrhosis based on symptoms followed by complications:

Table 6. Treatment of Cirrhosis. Adapted from Tapper & Parrikh, 2023.

Symptoms and diagnosis		First-line therapies	Effectiveness	Adverse effects
Symptoms of cirrhosis				
Muscle cramps	Patient reported	Acute therapy: sips of pickle juice at cramp onset. Preventive therapy: taurine, 500-1000 mg twice daily.	Pickle juice: reduction of 2.3 points on VAS for cramp severity compared with 0.4 for a tap-water control among 80 patients in a randomized trial. Taurine: 7 fewer cramps compared with placebo over 2 weeks in a randomized, double-blind crossover trial of 30 patients.	Pickle juice: none observed in trial. Taurine: non observed in trial.
Pruritis		Moisturizers Cholestyramine 4-16 g daily Naltrexone 50 mg daily	Cholestyramine: efficacy data from trials enrolling people with cirrhosis are lacking but considered first-line therapy given safety. Naltrexone: placebo-controlled RCT of 16 patients followed up for 4 weeks; naltrexone significantly improved pruritis as measured by a 100-mm VAS of pruritis severity with a mean (SD)	Cholestyramine: none observed in trials. Naltrexone: 50% experienced 3 days of malaise with nausea (vs 0% with placebo); 62.5% experienced mild abdominal cramps (vs 12.5% with placebo).

			54% (10%) reduction from baseline compared with an 8% (10%) with placebo.	
Sleep disorder		Sleep hygiene (improving environment, relaxation, limiting caffeine) Hydroxyzine 25 mg nightly	Hydroxyzine: in a 10-day randomized, double-blind, placebo-controlled trial of 35 patients with covert HE, 40% with improved self-reported sleep and 70% with improved sleep efficiency by actigraphy compared with 0% and 16% worsening among those receiving placebo, respectively.	Hydroxyzine: risk of increased confusion after 10 days (6% vs 0% with placebo).
Sexual dysfunction		Cessation of smoking and alcohol use, counseling, PDE-5i (tadalafil 10 mg)	Cessation of alcohol use associated with 25% rate of achieving self-reported normal sexual function among 60 men abstinent form alcohol for > 6 months. Tadalafil: in a 12-week, randomized, placebo-controlled trial of 140 men, 63% had improved erectile function compared with 30% receiving placebo.	None observed in trial.
Complication of cirrhosis				

Hepatic encephalopathy (HE)	Covert HE: deficits in executive function, sleep disorder, vegetative behavior, and gait disturbance. Overt HE: asterixis, disorientation, lethargy, and coma.	Lactulose 10-20 grams 2-3 times daily with goal of 2-3 soft bowel movements. Rifaximin 550 mg twice daily. Nutrition 1.25 g of protein/kilogram of actual body weight/d and nighttime snack (> 250 kcal).	In meta-analyses of randomized trials, lactulose was associated with reduced mortality relative to placebo (8.5% vs 14%) in randomized trials involving 705 patients and reduced risk of recurrent overt HE (25.5% vs 46.8%) in randomized trials involving 1415 patients. In a 6-month placebo-controlled double-blind RCT, rifaximin reduced hospitalization for HE to 13.6% vs 22.6% with placebo among 299 patients with prior HE with lactulose. In a 6-month RCT of 120 patients with covert HE, the 60 patients receiving protein supplements to achieve 1-1.5 g/kg daily protein intake had lower rates of overt HE relative to placebo (10% vs 21.7%).	Lactulose: relative to placebo, bloating (46% vs 15%), diarrhea (29% vs 37% but higher if excess intake), nausea (15% vs 2%). Rifaximin: high cost, no other adverse events seen in trial. High-protein diet: none.
Ascites	Physical examination (distended	Aldosterone antagonists	Combined aldosterone antagonists and loop diuretics resolved ascites in	Combination aldosterone antagonists and loop

	abdomen, shifting dullness) and free fluid on abdominal imaging.	(spironolactone 50-400 mg) Loop diuretics (furosemide 40-160 mg)	76% of patients compared with 56% who received aldosterone antagonists alone in a randomized trial of 100 patients. Paracentesis relieves abdominal symptoms, but ascites recurs.	diuretics: hyperkalemia (4%), kidney injury 12%). Aldosterone antagonists alone: hyperkalemia (18%), kidney injury (16%). Not reported in trials of patients with ascites but observed in other trials of spironolactone: gynecomastia (rate unknown).
Varices and variceal bleeding	Endoscopic evaluation	Prevention of bleeding: carvedilol 12.5 mg daily (can be used for primary or secondary prophylaxis); propranolol 40 mg twice a day increased up to 160 mg twice a day with goal heart rate of 55 beats/min. Active bleeding: intravenous octreotide/terlipressin ceftriaxone (1 g/day	Primary prophylaxis with carvedilol or propranolol in a double-blind, placebo-controlled trial of 201 patients with CSPH, carvedilol or propranolol reduced risk of decompensation or death (16% vs 27%) by 3 years. Treatment of hemorrhage: vasoactive medications (in addition to endoscopic therapy). Octreotide: associated with hemostasis at 5 days in 77%	Carvedilol or propranolol: weakness (23% vs 27%). Octreotide: hyperglycemia (23% vs 13% with placebo). Terlipressin: no difference compared with placebo in meta-analysis of trials, can be associated with digital ischemia and

		for 5 days); band ligation or sclerotherapy of varices.	compared with 58% with placebo in a meta-analysis of randomized trials. Terlipressin: associated with hemostasis at 5 days in 65% compared with 46% with placebo in a meta-analysis of randomized trials. Prophylactic antibiotics (in addition to endoscopic therapy): associated with reduced mortality to 18.5% vs 22.2% with placebo in a meta-analysis of randomized trials. Secondary prophylaxis with preemptive TIPS: in a randomized trial of 63 patients with acute variceal bleeding, preemptive TIPS within 72 hours improved 1-year survival to 86% vs 61% for the control group.	abdominal cramping. TIPS: none observed in trial.
Spontaneous bacterial peritonitis (SBP)	Ascites concentrations of neutrophils > 250/μL can present without fever or pain in up	Third-generation cephalosporin for 5 days. Albumin 1.5 g/kg on day 1 and 1 g/kg on day 2.	Albumin: compared with antibiotics alone, reduces 3-month mortality in RCT of 126 patients from 41% to 22%; kidney injury occurred in 33% vs 6%.	Not reported in trial. However, albumin infusions can increase risk of pulmonary edema (4% vs 1% from

	to one-third of cases.	Meropenem and daptomycin for nosocomial SBP.	If nosocomial SBP: in a randomized trial of 32 patients, compared with ceftazidime, meropenem and daptomycin increased SBP resolution (87% vs 25%) but not 90-day survival.	placebo in a trial of albumin for hospitalized patients with cirrhosis).
Hepatorenal syndrome (HRS)	50% or ≥ 0.3 mg/dL increase in serum creatinine within 7 days from the last measure and does not respond to 2 days of volume expansion.	Terlipressin 0.85 mg IV every 6 hours. Norepinephrine 0.5-3 mg/h IV.	In placebo-controlled (1:2 ratio), randomized trial, terlipressin improved kidney recovery (39% vs 18%) in 300 patients with HRS. In a randomized trial of 46 patients comparing terlipressin vs norepinephrine, the rate of achieving creatinine < 1.5 mg/dL was 39.1% vs 43.4%.	Terlipressin: death due to respiratory failure (11% vs 2% from placebo). Norepinephrine: none reported in trial; however, 25% experienced tachyarrhythmia in a cohort study, 10% requiring treatment discontinuation.

Abbreviations: CSPH, clinically significant portal hypertension; IV, intravenous; PDE-5i, phosphodiesterase-5 inhibitor; RCT, randomized clinical trial; TIPS, transjugular intrahepatic portosystemic shunt; VAS, visual analog scale.

Table 7 details etiologies of liver cirrhosis and their respective risk factors and therapies:

Table 7. Treatment of Cirrhosis According to Etiology. Retrieved from Tapper & Parrikh, 2023.

	Risk factors	First-line therapies	Effectiveness	Adverse effects
Alcohol-related liver disease	Alcohol use disorder, obesity	Abstinence from alcohol. Counseling and medications such as naltrexone	In a meta-analysis of observational studies, abstinence was associated with reduced risk of mortality after 1.5 y (HR, 0.51 [95% CI, 0.33-0.81])[12]	NA
Nonalcoholic fatty liver disease (NAFLD)	Insulin resistance, obesity, metabolic syndrome	Weight loss. Nutritionist referral, medical weight loss therapies, and bariatric surgery in highly selected patients (ie, without portal hypertension)	No randomized trials in patients with cirrhosis Among 1158 patients with NAFLD and fibrosis, bariatric surgery was associated with 2.3% 10-y risk of cirrhosis or decompensation compared with 9.6% for 508 matched patients who did not undergo surgery[6]	Rates of adverse events are unknown. Inadvertent protein restriction while dieting could worsen sarcopenia and increase the risk of hepatic encephalopathy. Bariatric surgery is associated with a 4.7% risk of decompensation in patients with compensated cirrhosis[99]
Hepatitis C	Blood transfusions prior to 1990, shared needles or drug implements, rarely sexual transmission	Direct-acting antivirals (eg, sofosbuvir/velpatisvir or glecaprevir/pibrentasvir)	Observational data sources: SVR, compared with not achieving SVR, is associated with lower 10-y all-cause mortality (8.9% vs 26.0%)[7] SVR, compared with not achieving SVR, is associated with a lower risk of HCC (3.3 vs 13.2/1000 person-years)[100]	Headache: 25%
Hepatitis B	Vertical transmission, sexual transmission, shared needles, or drug implements	Virological control with antiviral therapy (eg, tenofovir alafenamide, tenofovir disoproxil fumarate, entecavir)	Randomized (2:1), placebo-controlled trial of lamivudine in 651 patients with advanced fibrosis or cirrhosis: compared with placebo, treatment lowered risk of HCC (3.9% vs 7.4%)[8] Observational study of tenofovir disoproxil fumarate: compared with no treatment (291 patients), antiviral therapy (797 patients) was associated with a lower risk of HCC (9.8% vs 14.9%), decompensation (1.1% vs 13.1%), and death (1.1% and 13.1%) in people with cirrhosis from Hong Kong, South Korea, and California[101]	Lamivudine associated with cough relative to placebo (14% vs 7%)[8] Tenofovir disoproxil fumarate was associated with decreased bone density (1.72% in hip, 2.29% in spine) after 48 wk of therapy[102] Among patients with hepatitis B and HIV coinfection, 0% receiving tenofovir alafenamide discontinued therapy for kidney complications within 144 wk compared with 3.6% receiving tenofovir disoproxil fumarate[103]
Hemochromatosis	Autosomal recessive inheritance; 2 copies of the C282Y variant of the *HFE* gene	Iron depletion (phlebotomy) with a goal of 50-100 µg/L of ferritin	In a nationwide, observational study of Danish patients, 10-y overall survival was 70% among 66 patients receiving phlebotomy and 20% of 62 untreated patients[9]	Venipuncture site bleeding and infection, anemia, and syncope (rates unknown)
Primary biliary cholangitis (PBC)	More common among women and first-degree relatives of patients with PBC	Ursodeoxycholic acid (UDCA) at 13-15 mg/kg/d	In a pooled analysis of 548 patients in 3 randomized trials, UDCA improved transplant-free 4-y survival compared with placebo (17% vs 24%)[10]	Not observed in trials[10] Rare adverse events may include weight gain (<5 lbs),[104] loose stool, and hair thinning
Primary sclerosing cholangitis (PSC)	Ulcerative colitis	No proven therapy	NA	NA
Autoimmune hepatitis	Unknown	Combination prednisone (20-40 mg/d) and azathioprine (50-150 mg/d)	In a meta-analysis of randomized trials of 3-4 y duration, the rates of remission and overall mortality associated with combination therapy (received by 44 patients) was 43% and 0% while placebo (received by 33 patients) was associated with 39% mortality and 0% remission[11]	Not reported in meta-analysis Prednisone is associated with adverse effects such as weight gain, rash, cataracts, infection risk, and osteoporosis Azathioprine is associated with leukopenia, pancreatitis, nonmelanoma skin cancer, lymphoma, and increased infection risk

Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; NA, not applicable; SVR, sustained virologic response (cure of hepatitis C).

[a] Liver transplant is the definitive therapy for decompensated cirrhosis of any cause; the underlying chronic liver disease may recur and require treatment.

1.3 European Guidelines

1.3.1 British Society of Gastroenterology (BSG) Best Practice Guidance: Outpatient Management of Cirrhosis [2023]

The BSG guidance is written in three parts, to cover the outpatient management of compensated cirrhosis (part 1)[15], decompensated cirrhosis (part 2)[16], and special circumstances, including surgery, pregnancy, and travel in patients with cirrhosis (part 3)[17]. The aim of these documents is to provide a practical guide and service framework, including cirrhosis care bundles, for clinicians caring for patients with cirrhosis in secondary care, and to promote best practice and multidisciplinary teamwork.

1.3.1.1 Part 1: Compensated Cirrhosis

Screening and surveillance of varices

- Endoscopic screening is recommended in all patients with cirrhosis.
- Patients who avoid endoscopic screening are recommended for the assessment of cirrhosis using the Baveno VI criteria.
    - Liver Stiffness Measurement (LSM) < 20kPa on transient elastography → Low risk
    - Platelet Count > 150x 10^9/L → Low risk
- Patients with LSM > 20kPa & Platelet Count < 150x 10^9/L are at a high risk for cirrhosis and are recommended for endoscopy.

Primary prevention of variceal bleeding

- Primary prevention of variceal bleeding includes 2 options: non-selective beta blockers (NSBBs) & variceal band ligation (VBL) which are used in medium to large varices (> 5mm in diameter).
- The choice of NSBBs versus VBL depends on patient comorbidities, tolerances, and patient choice.
    - Individuals who undergo variceal band ligation (VBL) should undergo banding sessions at intervals of around four weeks until the varices are eliminated.
- **A recent meta-analysis, incorporating findings from the PREDESCI trial, indicates that non-selective beta-blockers (NSBB) like carvedilol might decrease decompensation and mortality rates in individuals with compensated cirrhosis, especially when varices are present. Therefore,**

based on this evidence, carvedilol may be favored over VBL (variceal band ligation) in patients with compensated cirrhosis and medium to large varices, if tolerated. Moreover, carvedilol could be an option for patients with small varices and compensated cirrhosis in the presence of active liver disease. However, poor tolerance could make VBL a preferable option in some patients such as those with ARLD (Alcohol-Related Liver Disease).

Figure 3 summarizes the screening, surveillance, and primary prophylaxis in patients with compensated cirrhosis:

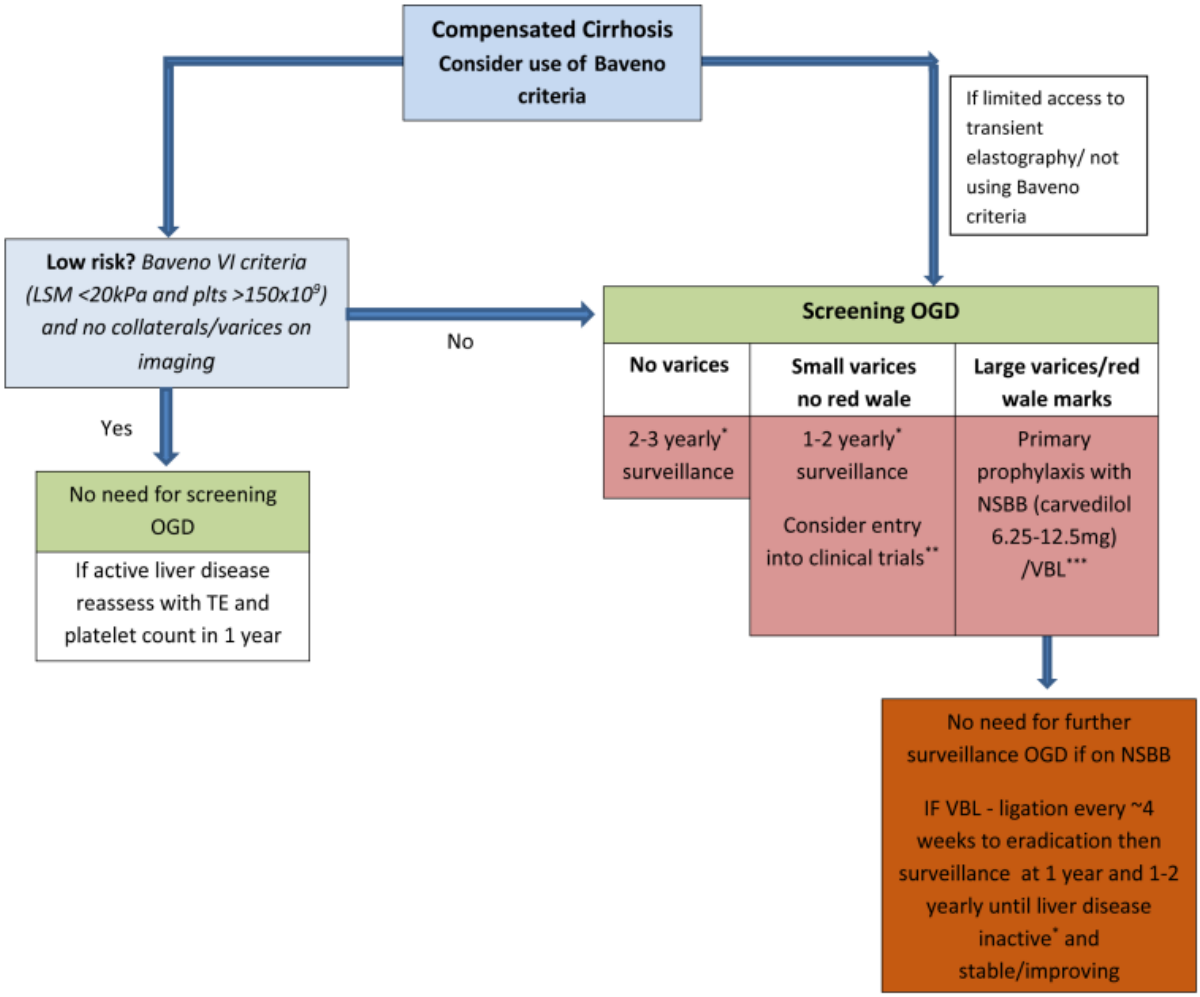


Figure 3. *Screening, surveillance, and primary prophylaxis in patients with compensated cirrhosis. Retrieved from the BSG 2023 guidelines.*

Osteoporosis screening

Figure 4 summarizes the screening for osteoporosis in patients with cirrhosis:

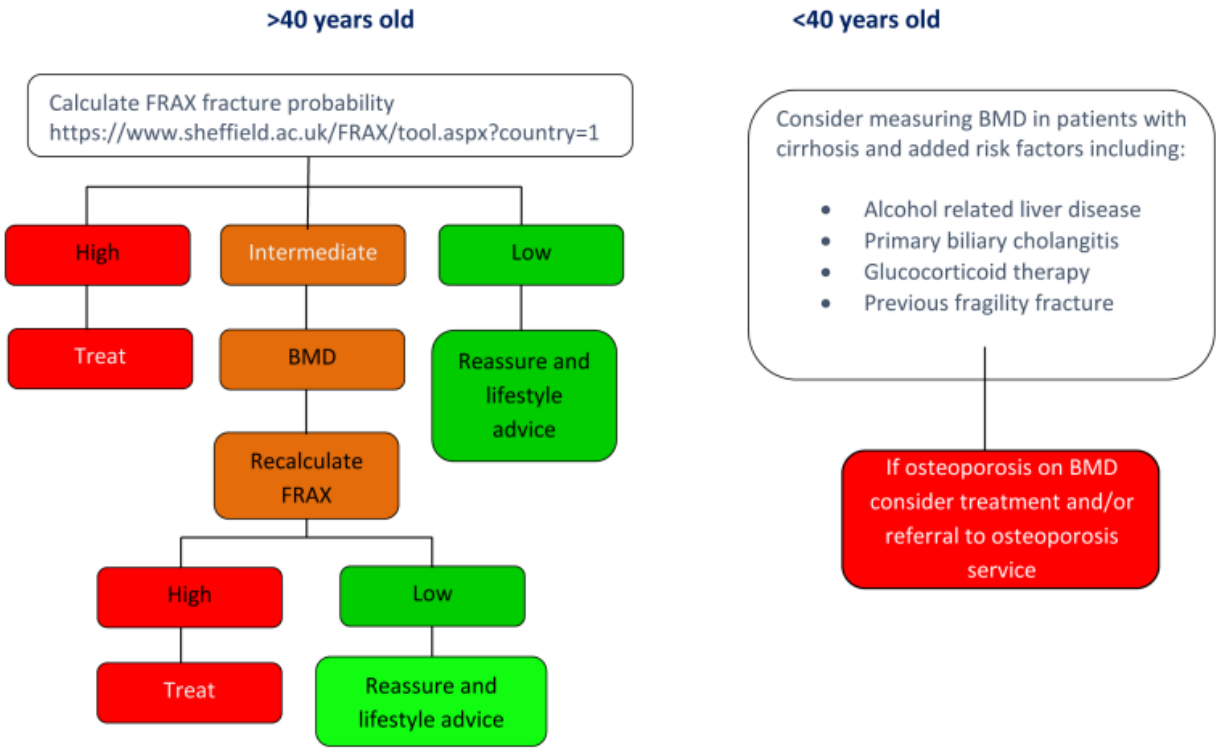


Figure 4. *Screening for osteoporosis in patients with cirrhosis. Retrieved from the BSG 2023 guidelines.*

Routine vaccinations

- Individuals with cirrhosis have a weakened immune system, increasing their susceptibility to complications, as well as a higher risk of serious morbidity and mortality from infectious diseases.
- The UK Health Security Agency recommends all individuals with chronic liver disease should receive the annual influenza vaccine, pneumococcal, hepatitis A and B vaccination, and SARS-CoV-2 vaccination in line with government guidelines for people at higher risk of COVID-19, in addition to all routine vaccinations.

Nutrition

- It is recommended that patients follow a diverse diet consisting of three meals daily, and they should be motivated to incorporate protein into each meal, aiming for a daily intake of 1.2–1.5 grams per kilogram of body weight.
- Having a meal or snack in the evening that includes both protein and carbohydrates helps minimize the duration of the overnight fast, thereby reducing the breakdown of proteins and muscle catabolism.

A summary of the recommendations in this BSG 2023 Part 1 Guideline are combined into a care bundle to be used in outpatient clinics as shown in the figure below:

Patient details

Cirrhosis (compensated) Outpatient Clinic Care Bundle

1. Diagnosis				
Aetiology of liver disease				
Modality of diagnosis of cirrhosis	Biopsy	LSM	Imaging	Clinical
Liver stiffness measurement	kPa	IQR/Med ratio		
2. Observations				
Weight (kg)	Height (m)	BMI	BP (mmHg)	Pulse
3. Alcohol				
Record recent daily alcohol intake	..... Units			
Thiamine 100mg BD (if potentially harmful alcohol consumption; >50u/week male or >35 U/week female)	Y N N/A			
Advise controlled reduction in alcohol consumption to abstinence	Y N N/A			
Refer to the alcohol team if not already under review	Y N N/A Decline			
4. HCC surveillance				
Under active HCC surveillance	Y N Decline			
Date of last imaging				
Result:				
AFP:				
Arrange follow up imaging (6 monthly ultrasound first line; those with significant comorbidities or poor performance status should be counselled against active monitoring)	Y Stop Decline			
5. Portal Hypertension (see over)				
Varices Y N	Data of last assessment	OGD LSM/pl no-assess		
Size of oesophageal varices	Small (grade 1)	Medium (grade 2)	Large (grade 3)	
Gastric varices	Y N			
Previous variceal bleed	Y N			
Treatment	Beta-blocker	Banding	N/A	
Beta-blocker dose optimised (aim HR 60/min with SBP >100 mmHg)	Y N N/A			
Variceal assessment requested	Y N N/A decline			
6. Fracture risk (see over)				
FRAX (+/-BMD)	Date	Low intermediate high N/A		
Treat if high FRAX or osteoporosis	Bisphosphonate denosumab decline			
7. Any features of hepatic decompensation				
Ascites	**HE**	**Jaundice**	**UKELD**	
If any features of decompensation and/or UKELD >49 then consider whether Liver transplantation may be indicated. Complete the decompensated cirrhosis outpatient bundle				
8. Vaccinations				
Advise patients to have relevant vaccinations (Influenza, COVID, Pneumococcal, Hep A & B) Y N Decline				
9. Provide information				
Patient relevant given written information about their liver disease Y N previously				

Figure 5. *British Society of Gastroenterology/British Association for the Study of the Liver compensated cirrhosis outpatient care bundle. Retrieved from the BSG 2023 guidelines.*

BD, two times per day; BMI, body mass index; BP, blood pressure; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HR, heart rate; kPa, kilopascals; LSM, liver stiffness measurement; N, no; N/A, not applicable; OGD, esophagogastroduodenoscopy; SBP, systolic BP; UKELD, UK Model for End Stage Liver Disease; Y, yes

1.3.1.2 Part 2: Decompensated Cirrhosis

Secondary prevention of variceal bleeding

- A combination of a Non-Selective Beta Blocker (NSBB) and Variceal Band Ligation (VBL) is recommended.
- Trans-jugular intrahepatic portosystemic shunting (TIPSS) plays a role in secondary prevention in high-risk scenarios, such as cases where patients experience rebleeding despite non-selective beta-blockers (NSBB) and variceal band ligation (VBL), or when there are additional indications like refractory or recurrent ascites.

Figure 6 summarizes the surveillance and treatment of non-bleeding gastroesophageal varices in DC:

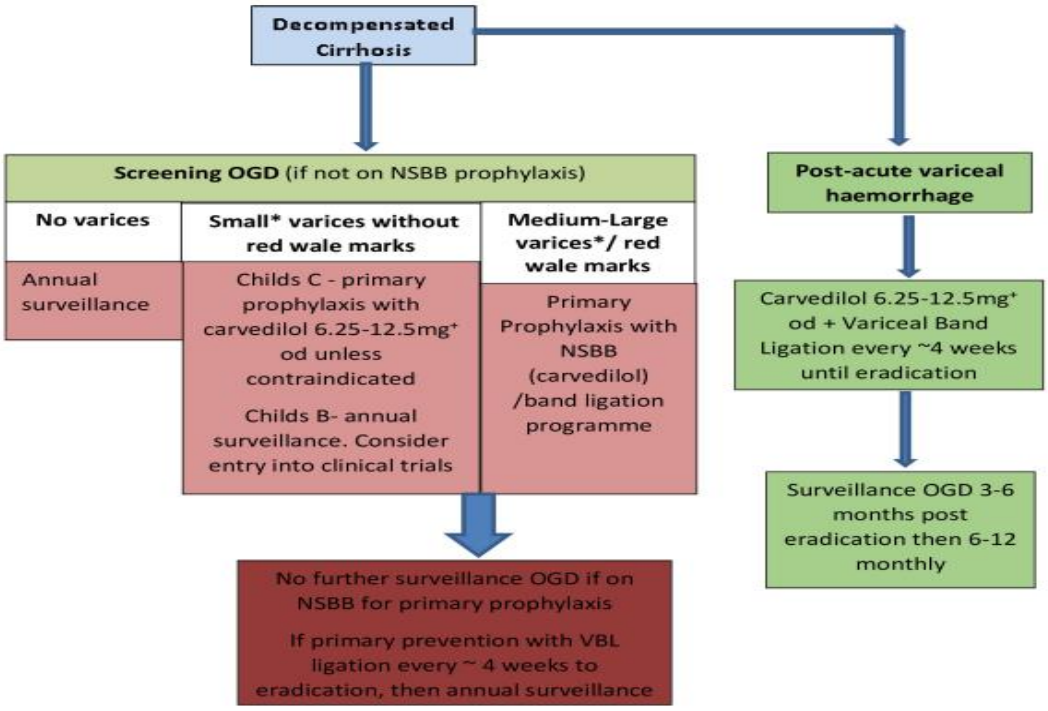


Figure 6. *Surveillance and treatment of non-bleeding gastroesophageal varices in decompensated cirrhosis. Retrieved from the BSG 2023 guidelines.*

+Titrate from 6.25 mg daily to target 12.5 mg daily in single or divided doses if tolerated (maintain HR, 50–60, systolic blood pressure >90 mm Hg). *Small varices defined as 5 mm diameter.

Assessment and management of chronic hepatic encephalopathy

- Hepatic encephalopathy (HE) in cirrhosis results in a spectrum of neuropsychiatric disturbances, ranging from stupor and coma to subtle irregularities in higher executive function.

- Assessment and investigation in suspected HE is summarized in table 8:

Table 8. Summary of Investigation and Assessment of Suspected Hepatic Encephalopathy. Adapted from the BSG 2023 Guidelines.

Investigation/clinical assessment		
West-Haven criteria		
Covert encephalopathy		
Grade 0 (minimal HE)	Animal naming test	Examples of psychometric/neurophysiological tests
	Critical flicker frequency	
	Stroop test	
	Psychometric Hepatic Encephalopathy Score	
	EEG	Poor sensitivity and specificity in minimal HE
Grade 1	Trivial lack of awareness, impaired attention span, altered sleep, euphoria, or depression	
Overt encephalopathy		
Grade 2	Asterixis, minimal disorientation to time/place, behavior/ personality change, lethargy, ataxia/slurred speech	
Grade 3	Marked confusion/stupor, gross disorientation, somnolence but responsive to verbal stimuli	Should be used in conjunction with the Glasgow Coma Scale
Grade 4	Coma	
Exclusion of differentials (if alternative diagnosis suspected)/precipitating factors		
Brain MRI	Hippocampal atrophy suggests Alzheimer's disease. Small vessel changes suggest vascular dementia	
Ammonia	Not required routinely. A normal value brings HE diagnosis into question and other potential causes of confusion	
Electrolytes	Hypokalemia common HE precipitant—aim potassium > 4	

Confusion/infection screen (including CT head)	Useful in possible delirium or acute intracranial event suspected
Vascular-phase abdominal CT	Exclude large spontaneous portosystemic shunts (can be drivers of HE in otherwise well-compensated patients)

EEG, electroencephalogram; HE, hepatic encephalopathy.

- Most HE treatments are directed towards the gut and so lactulose is recommended as the first line therapy.
- Rifaximin 550mg twice daily is recommended as second line to reduce recurrent episodes of overt HE.
- The deterioration of hepatic encephalopathy (HE) can be exacerbated by weight loss and sarcopenia. Hence, it is advisable to steer clear of low-protein diets and ensure a sufficient intake of both protein and energy.

Outpatient management of ascites

The mainstay treatment of ascites in the outpatient setting is diuretic therapy. The stepwise approach is shown in figure 7 in addition to the following recommendations:

- Patients who have experienced a previous episode of spontaneous bacterial peritonitis (SBP) are for the consideration for the use of secondary antibiotic prophylaxis. Suitable antibiotic options include norfloxacin at 400mg, ciprofloxacin at 500mg, or co-trimoxazole at 960mg, administered once daily.
- Non-selective beta-blockers (NSBB), when deemed necessary, are not prohibited in cases of refractory ascites. However, close monitoring is essential, and in individuals experiencing hypotension or acute/progressive renal dysfunction, dose reduction or discontinuation may be considered.
- Long-term outpatient albumin administration to patients with cirrhosis and ascites is not currently recommended.
- Patients experiencing refractory ascites and requiring frequent large-volume paracentesis should undergo these procedures as scheduled day-case interventions. This approach helps cut costs and enhances patient outcomes, especially in the last year of life.
- Abdominal drains that are permanently placed are still in the experimental stage but may be contemplated in palliative patients with advanced disease. This could serve as an alternative to repeated large-volume paracentesis, with

careful deliberation involving the patient regarding the balance of risks and benefits, particularly the potential risk of infection.

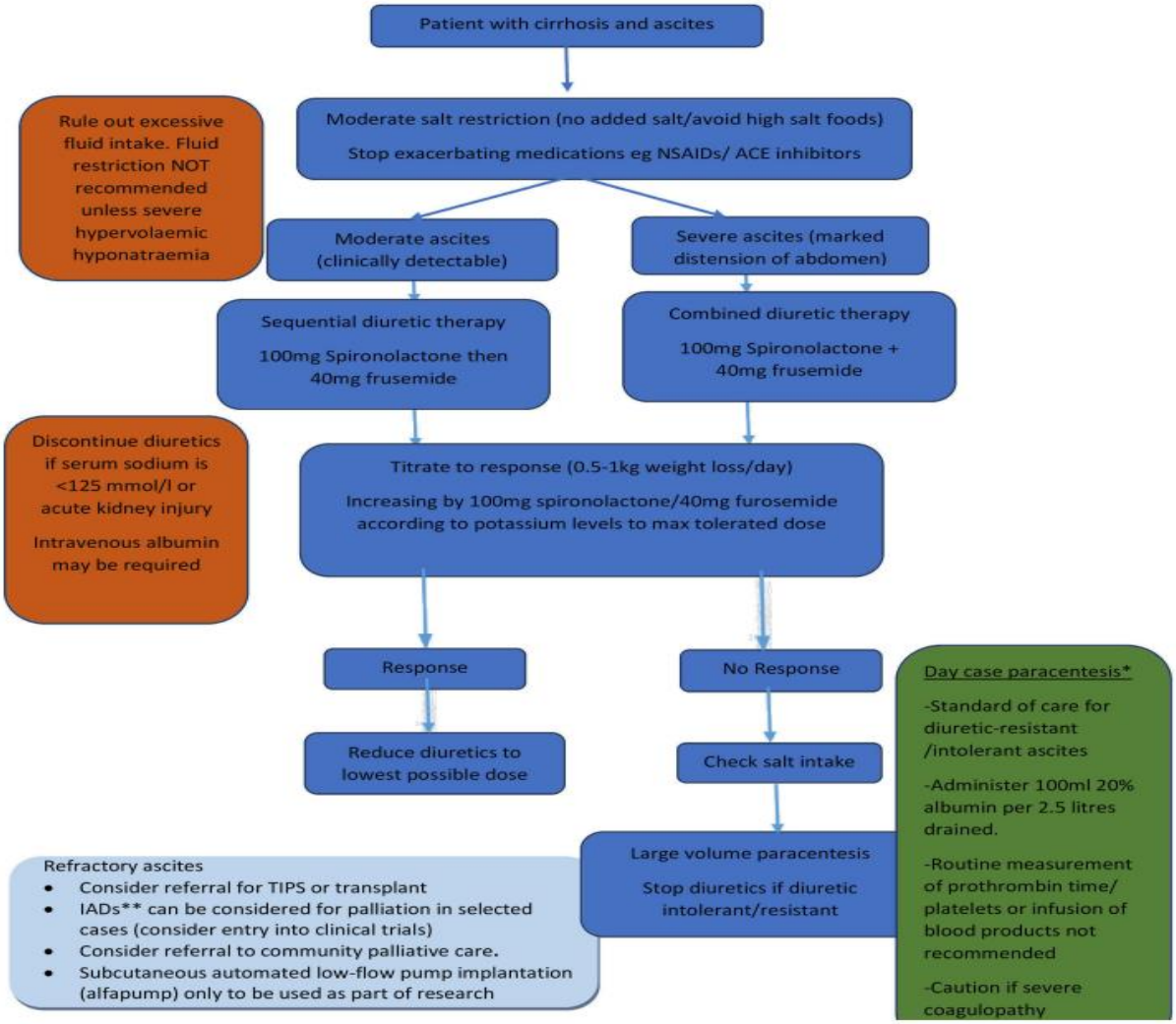


Figure 7. *Management approach to the patient with cirrhosis and ascites. Retrieved from the BSG 2023 guidelines.*

IADs Indwelling abdominal drains. NSAID, nonsteroidal anti-inflammatory drug; TIPSS, trans jugular intrahepatic portosystemic shunting.

Special considerations for prescribing in decompensated cirrhosis

The alterations in the pathophysiology of decompensated liver disease can markedly impact the pharmacokinetic and pharmacodynamic characteristics of numerous drugs, leading to changes in pharmacological and toxicological responses. Furthermore, several medications have the potential to worsen fluid overload and/or hepatic encephalopathy in patients with DC.

Table 9 provides a summary for prescribing adjustments to consider in commonly used medications:

Table 9. Summary of Prescribing Commonly Used Medicines in Patients with Decompensated Cirrhosis. Adapted from the BSG 2023 Guidelines.

Therapeutic category	Considered safe with monitoring	Avoid	Caution/modify dose	Notes
Gastric acid suppression	Simple antacids, for example, calcium carbonate		Proton pump inhibitors H2 antagonists	Altered gut microbiome may increase risk of infection and disease progression
Analgesics		NSAIDs, COX-2 inhibitors	Paracetamol Opiates	
Antimicrobials	Most antibiotics	Azithromycin Erythromycin Rifampicin Isoniazid	Aminoglycosides antifungals	Monitor renal and liver function
Antidiabetic drugs	Insulin GLP-1 agonists SGLT-2 inhibitors	Pioglitazone (in patients with fluid overload)	Metformin Sulphonylureas	Risk of lactic acidosis (metformin) Fluid accumulation
Drugs used in cardiovascular disease	Calcium antagonists	ACE-inhibitors ARBs Amiodarone	Beta blockers	Risk of acute kidney injury
Lipid lowering agents	Cholestyramine		Statins	Risk of accumulation/DILI
Anticonvulsants	Levetiracetam	Sodium valproate Phenobarbitone	Phenytoin Carbamazepine Lamotrigine	Risk of accumulation and increased toxicity

Antidepressants/ sedatives		Duloxetine	SSRI Venlafaxine Mirtazapine Benzodiazepines	Limited data in severe disease
DMARDs	TNF inhibitors	Methotrexate Leflunomide Budesonide	Prednisolone	Pre-screen for HBV
Drugs affecting clotting	LMWH	DOAC (Child Pugh C)	Warfarin Thrombopoietin Receptor Agonists	Lack of evidence in use of DOACs in DC

ARB, angiotensin receptor blocker; DC, decompensated cirrhosis; DILI, drug induced liver injury; DOAC, direct oral anticoagulant; HBV, hepatitis B virus; LMWH, low molecular weight heparin; NSAIDs, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitor.

Liver Transplant

- Liver transplantation (LT) stands as the ultimate and decisive treatment for specific individuals with decompensated cirrhosis (DC). It should be contemplated in situations where the severity of liver disease poses a risk of diminished survival or compromised quality of life.
- A UK Model for End-stage Liver Disease (UKELD) score of 49 represents the point of balance at which the anticipated one-year mortality without liver transplantation (LT) aligns with that after LT. Consequently, this score serves as the existing minimum listing threshold for elective LT in individuals experiencing irreversible decompensation.
- **Liver Transplant is recommended when the decompensation is irreversible and the patient does not have contraindications to LT, contraindications include:**
    - Coexisting significant extrahepatic comorbidity (with predicted mortality of >50% at 5 years).
    - Presence of extrahepatic sepsis
    - Active malignancy

A summary of the recommendations in this BSG 2023 Part 2 Guideline are combined into a care bundle to be used in outpatient clinics as shown in the figure below:

Patient details

Decompensated Cirrhosis Outpatient Bundle

Varices (see over for management)		
Varices present?	**Y**	**N**
Size of varices? Small (grade 1) Medium (grade 2) Large (grade 3)		
Previous variceal bleed?	**Y**	**N**
Prophylaxis:		
Is patient on a B Blocker? (carvedilol preferred)	**Y**	**N**
If not, why not? _____		
Has dosage been optimised? (aim HR 60/min and SBP >100)	**Y**	**N**
Variceal band ligation?	**Y**	**N**
Is a repeat OGD required? If so, date booked for_____	**Y**	**N**
Hepatic encephalopathy		
Encephalopathy present:	**Y**	**N**
Lactulose	**Y**	**N**
Rifaximin	**Y**	**N**
Lactulose+/- rifaximin advised for patients with persistent or previous un-provoked HE, unless contraindicated		
Ascites		
Ascites present?	**Y**	**N**
Previous SBP?	**Y**	**N**
If yes: Date: Organism (if known)		
Prophylactic antibiotics	**Y**	**N**
If yes: name _____		
If no: reason why_____		
Patients with ascites and an episode of SBP should be considered for antibiotics (secondary prophylaxis) as per local protocol		
Current management of ascites		
Diuretics	**Y**	**N**
Paracentesis	**Y**	**N**
Weight	_____	**Kg**
If ascites controlled consider reducing diuretics	Y	**N/A**
If requiring paracentesis:		
Predicted interval _____weeks		
Day case paracentesis booked for _____		
Or Information given to patient to contact		
Monitoring Renal function and electrolytes		
Recommended frequency of U&Es monitoring in the community:		
Nutrition		
Dietician review?	Y	N
Supplements required?	Y	N
Substance / alcohol misuse		
Alcohol misuse	**Y**	**N**
Input from alcohol care team/ Community follow up plans	**Y**	**N**
Advice on controlled reduction to abstinence	**Y**	**N**
Thiamine prescribed	**Y**	**N**

Treatment plan			
Has liver transplantation been considered?	**Y**	**N**	
Has prognosis been discussed?	**Y**	**N**	
Has information been given about complications of cirrhosis	**Y**	**N**	
Has a treatment escalation plan been documented	**Y**	**N**	
Has palliative care referral been considered	**Y**	**N**	

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Figure 8. *Decompensated Cirrhosis Outpatient Bundle. Retrieved from the BSG 2023 guidelines.*

HR, heart rate; OGD, Oesophagogastroduodenoscopy; SBP, spontaneous bacterial peritonitis.

1.3.1.3 Part 3: Special Circumstances

Pregnancy in compensated cirrhosis

- Pre-pregnancy counseling (PPC) is recommended for all women in their childbearing years who have cirrhosis.
- Those at risk of pre-eclampsia should be considered prophylactic use of aspirin, folic acid, and vitamin D.
- Commencing aspirin prophylaxis before the full formation of the placenta (≤16 weeks gestation) is recommended. There is debate surrounding whether to initiate low-dose (75mg) or high-dose (150mg) aspirin.
- It is recommended to maintain most immunosuppressant and antiviral treatments throughout pregnancy. However, exceptions include mycophenolate mofetil (MMF) due to its teratogenicity and risk of spontaneous abortion, ribavirin due to its teratogenic effects, and sirolimus because of the absence of safety data.
- Before conception, a wash-out period of 6 weeks is recommended for mycophenolate mofetil (MMF) and 6 months for ribavirin. Individuals taking entecavir should switch to tenofovir prior to pregnancy. Copper chelators should undergo a dosage reduction during pregnancy to mitigate their teratogenic impact.
- Variceal screening is recommended during second trimester in women with suspected significant portal hypertension.
- Patients with grade 1 esophageal varices (OV) can initiate or continue non-selective β-blockers.

Pregnancy in decompensated cirrhosis

- During pregnancy, the use of β-blockers and lactulose can be maintained.
- Diuretics, rifaximin, and most preventive antibiotics should be stopped during pregnancy because of potential risks to the fetus and insufficient human safety data.
- Paracentesis should also be avoided where possible.
- The use of terlipressin is not recommended due to the risks of utero-placental ischemia.
- In cases of acute variceal hemorrhage that does not respond to endoscopic therapy, the consideration of TIPSS insertion is appropriate.

- In cases of liver failure, transplantation can be carried out successfully in pregnant women.

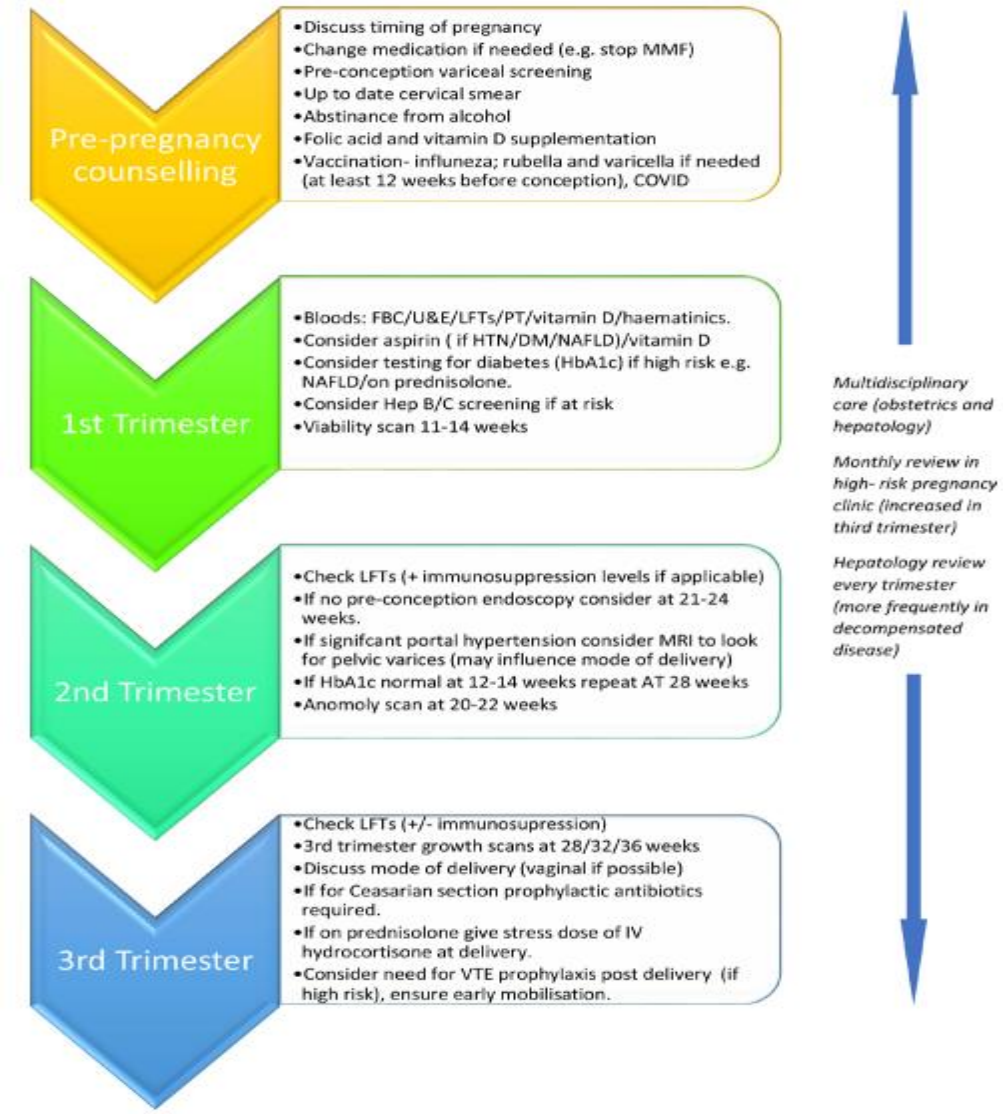


Figure 9. *Pregnancy care in cirrhosis. Retrieved from the BSG 2023 guidelines.*

DM, diabetes mellitus; FBC, full bloods count; HbA1c, glycated hemoglobin; HTN, hypertension; IV, intravenous; LFTs, liver function tests; MMF, mycophenolate mofetil; NAFLD, non-alcoholic fatty liver disease/ metabolic dysfunction associated steatotic liver disease (MASLD); PT, prothrombin time, U&E, urea and electrolytes; VTE, venous thromboembolism.

Management of portal vein thrombosis

The BSG 2023 guidelines summarize the management of portal vein thrombosis in patients with cirrhosis in the following figure:

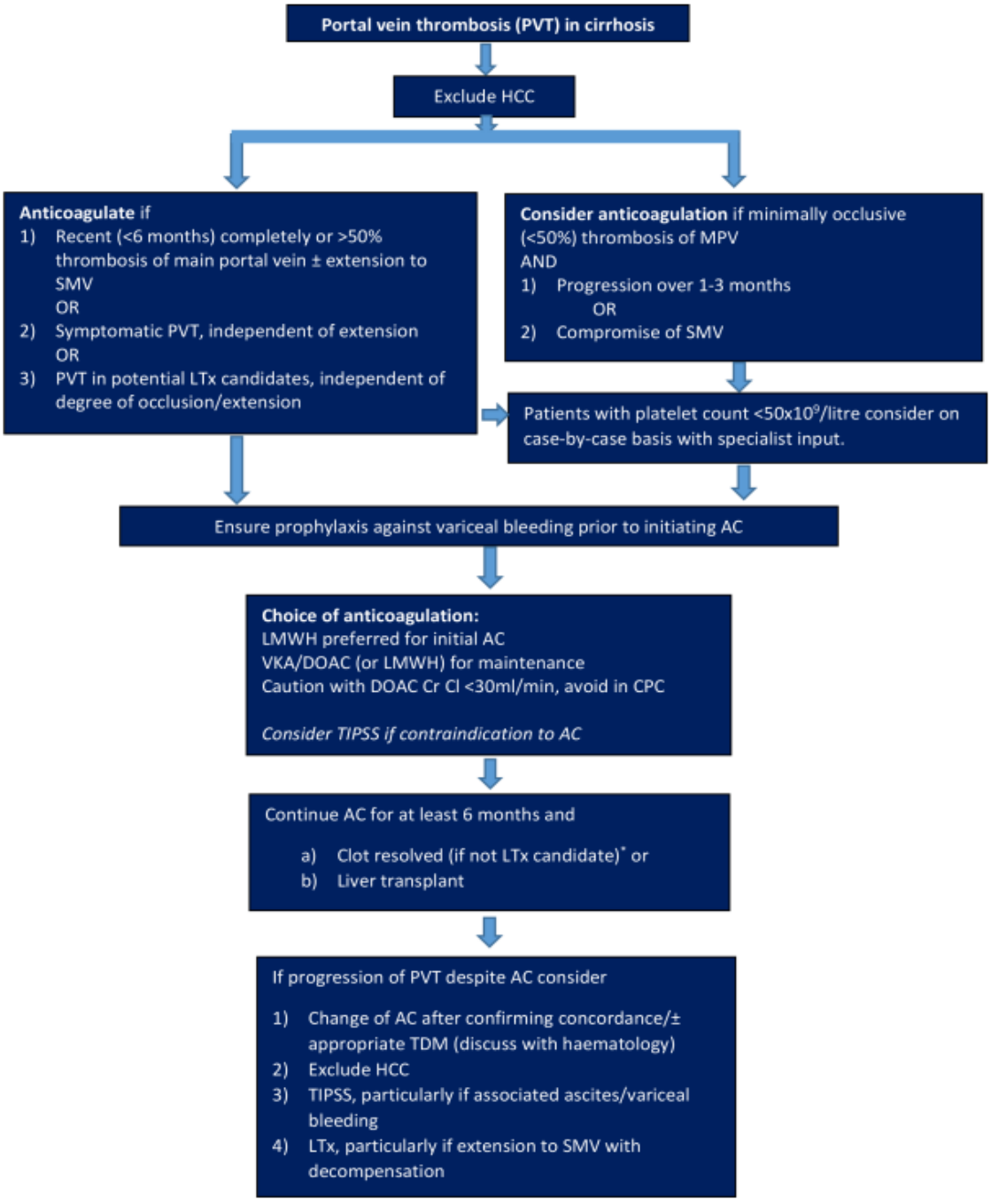


Figure 10. *Management of portal vein thrombosis in cirrhosis. Retrieved from the BSG 2023 guidelines.*

*Consider long-term anticoagulation if the risk of recurrence outweighs bleeding risk. AC, anticoagulation; CPC, Child-Pugh C; DOAC, direct-acting oral anticoagulants; HCC, hepatocellular carcinoma; LMWH, low-molecular weight heparin; LTx, liver transplant; MPV, main portal vein; SMV, superior mesenteric vein; TDM, therapeutic drug monitoring; TIPSS, trans jugular intrahepatic porto-systemic shunt; VKA, vitamin K antagonist (i.e., warfarin).

1.3.2 British Society of Gastroenterology (BSG)/British Association for the Study of the Liver (BASL) Guidelines on the Management of Ascites in Cirrhosis [2021]

The aim of this guideline is to review and summarize the evidence that guides clinical diagnosis and management of ascites in patients with cirrhosis, since substantial advances have been made in this area since the publication of the last guideline in 2007. The specific recommendations have been made according to the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE)' system[18].

Table 10. GRADE - Quality of Evidence & Strength of Recommendation

Quality of Evidence	
High	Further research cannot change the reliability of the therapeutic efficacy evaluation results.
Moderate	Further research might change the reliability of the therapeutic efficacy evaluation results and might also change the evaluation results themselves.
Low	Further research will likely change the reliability of the therapeutic efficacy evaluation results and will likely also change the evaluation results themselves.
Grading of Recommendation	
Strong	Clearly indicates that the advantages of the intervention measures are greater than the disadvantages, or that the disadvantages are greater than the advantages.
Weak	The advantages and disadvantages are indeterminate or the evidence, whether its quality is high or low, which indicates that the advantages and disadvantages are equivalent.

An executive summary of recommendations is listed below:

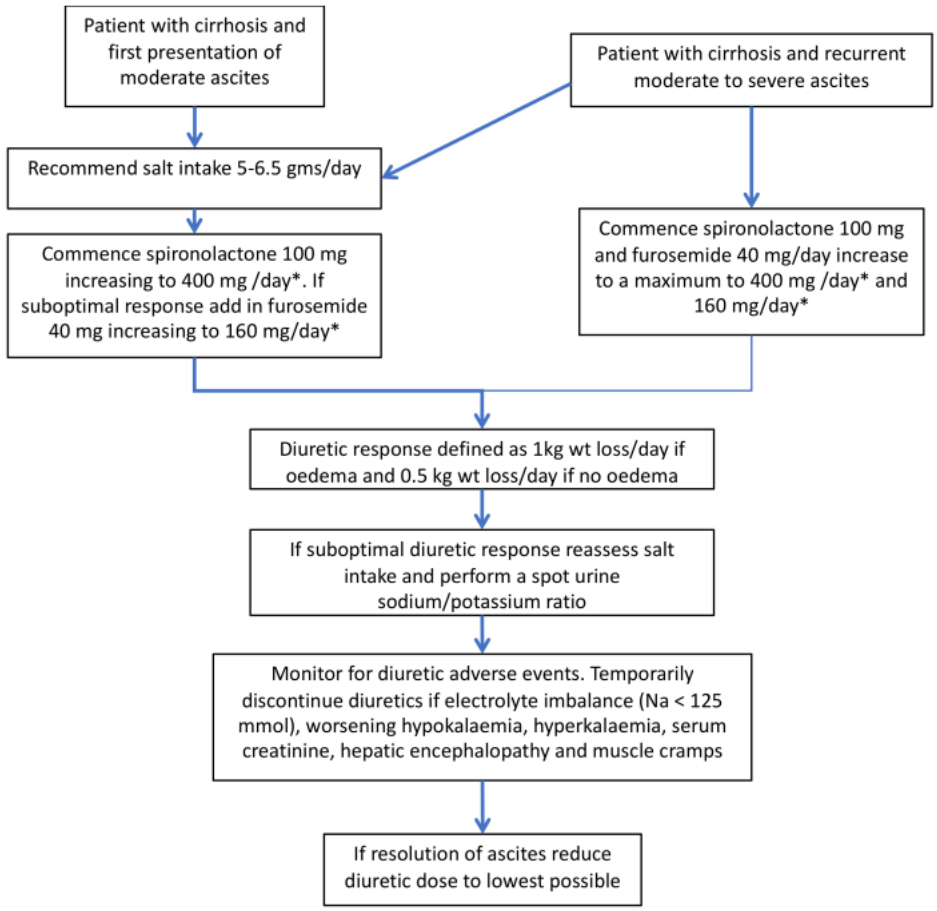
Dietary salt restriction

- Patients diagnosed with cirrhosis and ascites should adhere to a moderately salt-restricted diet, ensuring a daily salt intake not exceeding 5–6.5 g (87–113 mmol sodium). This equates to a diet with no added salt, and avoidance of pre-cooked meals should be practiced. (Quality of evidence: moderate; Recommendation: strong).

- Patients with cirrhosis and ascites should receive nutritional counselling on the sodium content in the diet. (Quality of evidence: weak; Recommendation: strong)

Diuretics

- For patients experiencing their initial occurrence of moderate ascites, it is reasonable to consider spironolactone monotherapy, with an initial dose of 100 mg that can be increased to 400 mg. In cases of recurrent severe ascites or when a more rapid diuretic response is necessary, especially during hospitalization, a recommended approach involves a combination therapy of spironolactone (initial dose 100 mg, increased to 400 mg) and furosemide (initial dose 40 mg, increased to 160 mg) (Quality of evidence: moderate; Recommendation: strong).
- Continuous monitoring for adverse events is essential for all patients starting diuretics. Nearly half of those who experience adverse events necessitate either discontinuation of diuretics or a reduction in dosage (Quality of evidence: low; Recommendation: weak).
- To address hypovolemic hyponatremia arising from diuretic therapy, the recommended approach involves halting diuretics and increasing plasma volume through the administration of normal saline (Quality of evidence: low; Recommendation: weak).
- Hypertonic sodium chloride (3%) administration should be reserved for those who are severely symptomatic with acute hyponatremia. Serum sodium should be slowly corrected. (Quality of evidence: low; Recommendation: weak)
- It might be suitable to contemplate the use of midodrine in cases of refractory ascites, with decisions made on an individual basis (Quality of evidence: low; Recommendation: weak).



*These maximal diuretic doses are often not achieved in clinical practice.

Figure 11. *Approach to the use of diuretics in the management of ascites in patients with cirrhosis. Retrieved from the BSG/BASL 2021 guidelines.*

Human albumin solution

- Following the completion of paracentesis involving the removal of more than 5 L, it is strongly recommended to infuse albumin (either as a 20% or 25% solution) at a dosage of 8 g of albumin per liter of ascites removed (Quality of evidence: high; Recommendation: strong).
- In individuals with ACLF (Acute-on-Chronic Liver Failure) or a high risk of post-paracentesis acute kidney injury, it is possible to contemplate the use of albumin (in the form of a 20% or 25% solution) after paracentesis involving less than 5 L, at a dosage of 8 g of albumin per liter of ascites removed (Quality of evidence: low; Recommendation: weak).

Non-selective beta-blockers (NSBB) & ascites

- Refractory ascites should not be viewed as a contraindication to NSBB. (Quality of evidence: moderate; Recommendation: strong).

- Patients with refractory ascites who are prescribed NSBB should undergo close monitoring. In cases where individuals experience hypotension or acute/progressive renal dysfunction, it is strongly recommended to consider dose reduction or discontinuation of NSBB (Quality of evidence: moderate; Recommendation: strong).

Palliative care

- Individuals with refractory ascites who are not being assessed for a liver transplant should be presented with the option of a referral to palliative care. In addition to repeated Large Volume Paracentesis (LVP), it is advisable to contemplate alternative palliative interventions for refractory ascites (Quality of evidence: weak; Recommendation: strong).

1.3.3 National Institute for Health and Care Excellence (NICE) Guideline of the Assessment and Management of Cirrhosis in Over 16s (Published 2016, Updated 2023)

The following guidelines do not provide a specified grade of evidence or level of recommendation.

The NICE recommendations that are summarized below entail the management of complications in liver cirrhosis[19]:

Safe prescribing and use of carvedilol and propranolol in people with cirrhosis

- Carvedilol and propranolol should be approached carefully in individuals with cirrhosis, as these medications may exert a more pronounced impact on their heart rate and blood pressure.
- People with severe hepatic impairment, such as those with extensive or resistant ascites, should refrain from using carvedilol. **[2023]**

When initiating therapy with either carvedilol or propranolol in individuals with cirrhosis to prevent decompensation or bleeding from medium or large varices:

- Administer a minimal dose (such as 6.25 mg daily for carvedilol or 40 mg twice daily for propranolol) **and**
- Increase or decrease the dose depending on the results of blood pressure and heart monitoring. **[2023]**

In September 2023, the utilization of the following was off label:

- Carvedilol and propranolol for the primary prevention of decompensation.
- Carvedilol for preventing variceal bleeding.

Primary prevention of decompensation

For individuals diagnosed with cirrhosis and established or suspected clinically significant portal hypertension (such as indicated by a hepatic venous pressure gradient exceeding 10 mmHg or the existence of esophageal varices), consider the following choices for the primary prevention of decompensation:

- Carvedilol is recommended as the preferred first-line treatment due to its lower incidence of side effects and a more substantial impact on portal vein pressure **or**
- Propranolol as second-line treatment if carvedilol is contraindicated.

Preventing bleeding from medium or large esophageal varices

If the individual with cirrhosis presents with medium or large esophageal varices:

- The benefits and harms of all treatment options should be discussed in line with NICE's guidelines on shared decision making and patient experience in adult NHS services.
- Clarify the components of the treatment and inquire about any possible obstacles that might hinder their access to it. For instance, explore whether they face challenges in adhering to a regular tablet regimen due to alcohol dependence or homelessness. **[2023]**

For those with medium or large esophageal varices, recommend:

- Carvedilol or propranolol **or**
- Endoscopic variceal band ligation if either carvedilol or propranolol is not well-tolerated or contraindicated, or if the individual faces difficulties in regularly taking tablets due to their circumstances.

Preventing spontaneous bacterial peritonitis

- Avoid the routine administration of antibiotics for the prevention of spontaneous bacterial peritonitis (SBP) in individuals with cirrhosis and ascites. **[2023]**

Antibiotics should be considered in SBP only if:

- The individual is at a heightened risk of developing spontaneous bacterial peritonitis (SBP) due to severe liver disease, indicated by factors such as ascitic protein of ≤ 15g/L, a Child–Pugh score >9, or a Model for End-Stage Liver Disease (MELD) score > 16 **or**

- The repercussions of an infection could significantly impact the individual's care, particularly if it could influence their waiting time for a transplant or a trans jugular intrahepatic portosystemic stent insertion (TIPS). **[2023]**

When providing antibiotics for the prevention of SBP:

- Local microbiological advice should be followed. (NICE's guideline on antimicrobial stewardship)
- Treatment should be continued until the ascites are resolved. **[2023]**

Treatment for upper gastrointestinal bleeding

- Administer prophylactic intravenous antibiotics to individuals with cirrhosis experiencing upper gastrointestinal bleeding. **[2016]**
- Evaluate the utilization of intravenous antibiotics prescribed for upper gastrointestinal bleeding in accordance with the guidance provided in the section on prescribing intravenous antimicrobials in the NICE guideline on antimicrobial stewardship[20].

Treatment for refractory ascites

- Consider a TIPS procedure in those with cirrhosis who have refractory ascites. **[2016]**

1.3.4 Portal Hypertension and Ascites: Patient-and Population-Centered Clinical Practice Guidelines by the Italian Association for the Study of the Liver (AISF) [2021]

This guideline is summarized in the form of population, intervention, control, and outcomes (PICO) followed by recommendations for portal hypertension and ascites using the GRADE (table 9 above) & ADOpT (table 11) approaches[21,22]:

Table 11. ADOpT Recommendations

Recommendation Label	Interpretation
Adopted	The original European Association for the Study of the Liver (EASL) recommendation was maintained.
New	If the recommendation was not present in the original EASL Guideline
Adapted	The text was modified from the original version to adapt the recommendations to the Italian context

Management of cirrhotic patients with portal hypertension without clinical complications

The most effective therapy for the risk reduction of a first decompensation of cirrhosis (e.g., bleeding, ascites)

- NSBB (Non-Selective Beta-Blockers) or Carvedilol are the suggested therapeutic options for averting variceal hemorrhage in individuals with small varices at high risk. Additionally, they might be advantageous for those with small varices not classified as high risk in preventing decompensation. (Quality of Evidence: Moderate; Strength of Recommendation: Conditional (Adapted)).
- NSBBs, Carvedilol, or Band Ligation (BL) are recommended for the prevention of VH in patients with medium-large sized varices. (QoE: High; SoR: Strong (Adopted)
- The combination therapy with NSBBs & BL is not recommended for primary prophylaxis of VH. (QoE: High; SoR: Strong (Adapted)
- TIPS is not recommended for the primary prophylaxis of VH (QoE: Moderate; SoR: Strong (Adapted)

Management of cirrhotic patients with portal hypertension-related complications

Timing and best strategies for secondary prophylaxis of variceal bleeding (re-bleeding)

- Endoscopic band ligation (EBL) combined with an NSBB stands as the preferred treatment in the secondary prevention following acute variceal bleeding (AVB) and has the potential to enhance survival. (QoE: High; SoR: Strong (Adopted))
- Caution is advised when administering Non-Selective Beta-Blockers (NSBB) to patients experiencing severe circulatory dysfunction. (QoE: Low; SoR: Moderate (Adopted))
- Trans-jugular Intrahepatic Portosystemic Shunting (TIPS) is indicated in the case of first re-bleeding while on adequate secondary prophylaxis (QoE: High; SoR: Strong (Adopted))

Diuretic use in patients with cirrhosis & ascites

- It is safe and advisable for patients without peripheral edema to experience a weight loss of up to 0.5 kg/day and for those with edema on diuretic therapy to have a weight loss of up to 1 kg/day. (QoE: Moderate; Strong (Adopted))

- Individuals experiencing their initial onset of at least moderate ascites are recommended to be treated with an anti-mineralocorticoid drug (such as spironolactone, canrenone, or K-canrenoate) as the sole treatment. The dosage should be gradually increased, starting at 100 mg every 72 hours, up to a maximum of 400 mg per day. If there is no response, a loop diuretic (either furosemide or torsemide) should be added, with the dosage increasing in a stepwise manner. For furosemide, this typically involves increments of 25–50 mg at each step, reaching a maximum of 150–200 mg per day. (QoE: High; SoR: Strong (Adapted))
- For individuals with moderate to large ascites, it is advisable to combine low doses of loop diuretics (25–50 mg of furosemide per day or 10–20 mg of torsemide per day) with an anti-mineralocorticoid drug. This combination helps expedite the mobilization of ascites while minimizing the risk of hyperkalemia. (QoE: High; SoR: Strong (Adapted))
- For individuals with cardiovascular co-morbidities and/or diabetes accompanied by even subtle intrinsic nephropathy, adjustments in the type and dosage of diuretics can be made to achieve a higher ratio between loop diuretics and anti-mineralocorticoids. (QoE: Low; SoR: Strong (New Recommendation))

Prevention and management of adverse effects of diuretic treatment

- For individuals with cardiovascular co-morbidities and/or diabetes accompanied by even subtle intrinsic nephropathy, adjustments in the type and dosage of diuretics can be made to achieve a higher ratio between loop diuretics and anti-mineralocorticoids. (QoE: Low; SoR: Strong (Adapted))
- Following the commencement of diuretics or a substantial alteration in their dosage, it is advisable to conduct a serum creatinine, sodium, and potassium assessment within 7–14 days. This is essential for promptly identifying renal impairment and electrolyte imbalances. Subsequently, routine measurements are recommended, with a more frequent schedule for patients experiencing compromised renal perfusion. (QoE: Low; SoR: Strong (Adapted))
- After the successful reduction of ascites, the dosage of diuretics should be gradually reduced to the lowest effective levels necessary to sustain minimal or no ascites. This is done with the goal of preventing or minimizing adverse effects. (QoE: Low; SoR: Strong (Adopted))
- For patients experiencing gastrointestinal bleeding, acute kidney injury (AKI), electrolyte imbalances, hepatic encephalopathy, and bacterial infections, the use of diuretic therapy should be temporarily halted or approached with significant caution. Regular clinical and/or biochemical evaluations are advised in such cases. (QoE: Low; SoR: Strong (Adapted))

- Furosemide administration should be stopped in the presence of severe hyponatremia (<125 mmol/L) or severe hypokalemia (<3 mmol/L). Discontinue anti-mineralocorticoids if severe hyperkalemia (>6 mmol/L) arises. (QoE: Low; SoR: Strong (Adopted))
- Fluid restriction up to 1000 ml/day is recommended in the management of hypervolemic hyponatremia since it may prevent a further reduction in serum sodium levels. (QoE: Low; SoR: Strong (Adopted))
- Avoid the use of potential nephrotoxic medications, such as non-steroidal anti-inflammatory drugs and aminoglycosides, in individuals with ascites. (QoE: Moderate; SoR: Strong (Adapted))
- In individuals with ascites, it is generally advisable to avoid the use of angiotensin-converting-enzyme inhibitors, angiotensin II antagonists, or alpha-1-adrenergic receptor blockers due to the heightened risk of renal impairment. (QoE: Moderate; SoR: Strong (Adopted))

Effectiveness of long-term administration of human albumin in the treatment of ascites in association with diuretics

- Long-term albumin treatment should be included among the treatment options of patients with ascites. (QoE: High; SoR: Strong (New Recommendation))
- Individuals with non-complicated ascites of at least grade 2 that does not respond to moderate diuretic doses (at least 200 mg/day of an anti-mineralocorticoid drug and 25 mg/day of furosemide) may be considered for long-term albumin administration. The current recommendation is a dosage of 40 g twice a week for the initial 2 weeks, followed by once a week thereafter. (QoE: High; SoR: Strong (New Recommendation))
- Individuals with refractory ascites can also benefit from long-term albumin administration. (QoE: Moderate; SoR: Strong (New Recommendation))
- The decision regarding the duration of extended albumin treatment should be made based on the specific needs and characteristics of each patient. (QoE: Moderate; SoR: Conditional (New Recommendation)

1.4 International Guidelines

1.4.1 JSGE & JSH Joint Guideline: Evidence-Based Clinical Practice Guidelines for Liver Cirrhosis [2020]

The first edition of the clinical practice guidelines for liver cirrhosis was published in 2010, and the second edition was published in 2015 by the Japanese Society of

Gastroenterology (JSGE). The revised third edition was recently published in 2020. This version has become a joint guideline by the JSGE and the Japan Society of Hepatology (JSH), and summarizes the recommendations for best clinical practices for liver cirrhosis using the GRADE system which is shown in the below tables[5]:

Table 12. Grade of Evidence System Adapted by the JSGE & JSH Guideline

Grade of Evidence	Evidence
Grade A	High-quality
Grade B	Medium-quality
Grade C	Low-quality
Grade D	Very low-quality

Table 13. Strength of Recommendation System Adapted by the JSGE & JSH Guideline

Strengths of Recommendation	Comments
Strong	The outcome of the vote is denoted as the consensus rate. Following the formation of the preparation committee, each Clinical Question (CQ) underwent a voting process by all members to determine the recommendation grade (3–12). Consensus was previously established as having 70% or more votes in agreement. Subsequently, the preparation committee iteratively revised the proposals, and the final recommendation was subjected to consultation with the evaluation committee.
Weak	

Nutritional therapy

- Necessary steps, including nutritional intervention, are essential as the prognosis of patients with cirrhosis is influenced by both under-nutrition and obesity.
- A late evening snack enhances the pathological condition of individuals with liver cirrhosis.
- Administering branched-chain amino acids (BCAAs) is recommended when patients with cirrhosis exhibit protein-energy malnutrition.
- Caloric intake should range from 25 to 35 kcal/kg (standard body weight) per day in the absence of glucose intolerance. Protein needs should be met with

1.0–1.5 g/kg/day, including BCAA preparations, in the absence of protein intolerance.

Figure 12 shows the algorithm for nutritional therapy in patients with cirrhosis:

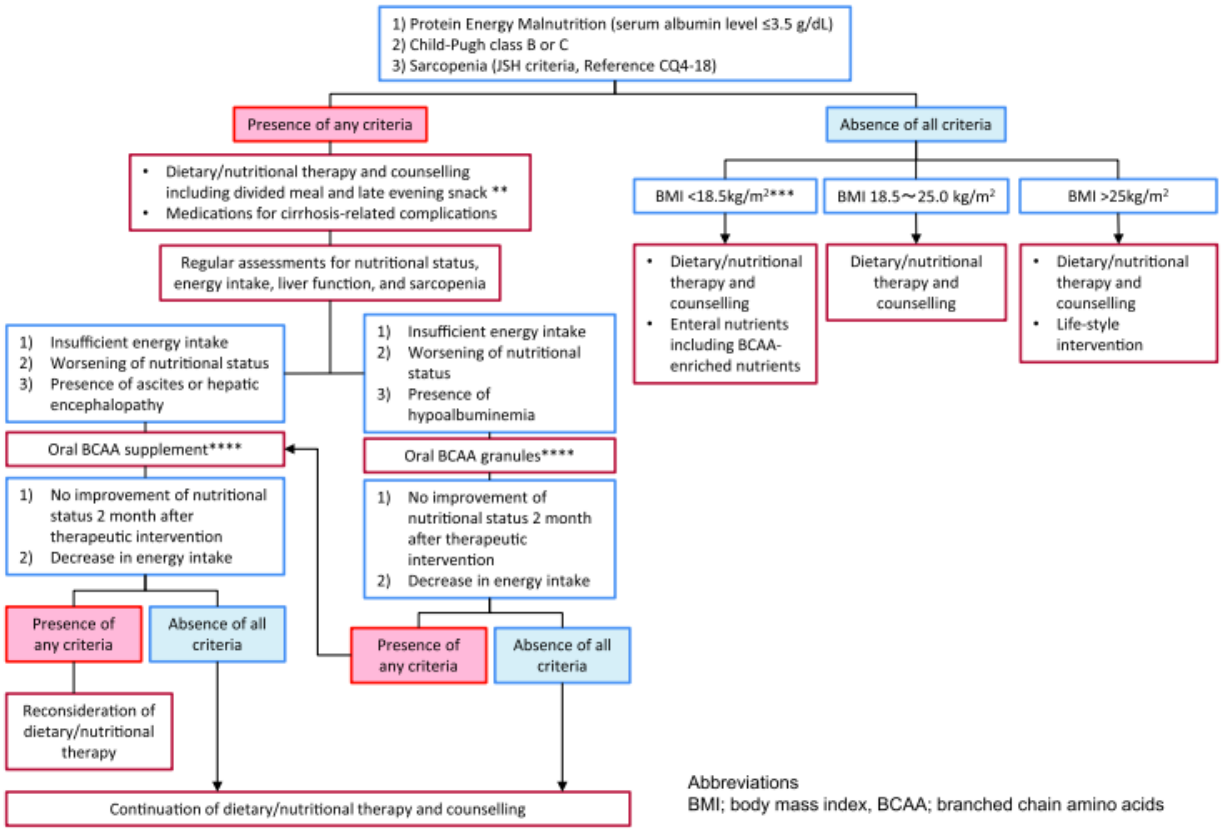


Figure 12. *Nutritional therapy for patients with cirrhosis. Retrieved from the JSGE/JSH 2020 guideline.*

Esophagogastric bleeding and portal hypertension

Useful drugs in the bleeding prevention from esophagogastric varices

- To prevent esophagogastric variceal bleeding, the recommendation includes the use of nonselective beta-blockers, isosorbide mononitrate, or a combination of both drugs. (Recommendation: weak, 100% agreed, evidence level B)

Effectiveness of vasoactive agents for the management of esophagogastric variceal bleeding

- Vasoactive agents, including terlipressin and octreotide, are suggested for controlling esophageal variceal bleeding. (Recommendation: weak, 100% agreed, evidence level B)

Useful drugs in the management of portal hypertensive gastropathy

- The utilization of nonselective beta-blockers (NSBBs) is recommended for the management of portal hypertensive gastropathy (PHG). (Recommendation: weak, 100% agreed, evidence level B)

Effectiveness of acid suppressing drugs in preventing gastrointestinal bleeding in patients with cirrhosis

- A brief course of acid suppression therapy is suggested for preventing the recurrence of esophagogastric varices (EV). (Recommendation: weak, 100% agreed, evidence level B)

Ascites

Effectiveness of albumin infusion for treatment of cirrhosis with ascites

- For individuals with low levels of albumin, the co-administration of albumin along with diuretics facilitates the resolution of ascites, diminishes the likelihood of ascites recurrence, lowers the occurrence of complications, and enhances overall prognosis.
    - The use of albumin during large-volume paracentesis (LVP) averts circulatory dysfunction and enhances prognosis.
    - The use of albumin in patients with spontaneous bacterial peritonitis (SBP) or type 1 hepatorenal syndrome (HRS-AKI) is efficacious in improving prognosis.

The effective method of spironolactone and loop diuretic administration for ascites in cirrhosis

- When initiating monotherapy for ascites in cirrhosis, spironolactone is recommended as the first-line treatment. If the therapeutic response to spironolactone alone is insufficient, combining spironolactone with a loop diuretic is advised to mitigate the adverse effects linked to higher spironolactone doses. The superiority between sequentially adding a loop diuretic after initial spironolactone monotherapy and initiating a combination of spironolactone and a loop diuretic as the initial treatment has not been definitively established.

The use of vasopressin V_2 receptor antagonists in the management of cirrhotic ascites

- Combining a vasopressin V2 receptor antagonist with conventional diuretics (such as spironolactone with or without furosemide) is effective in managing cirrhotic ascites.

Large-volume paracentesis (LVP) for patients with refractory ascites

- Large-volume paracentesis (LVP) is effective in managing ascites. Paracentesis is advised as the primary therapy for individuals with diuretic-resistant ascites. In patients undergoing paracentesis, paracentesis-induced circulatory dysfunction (PICD) may occur. Hence, it is recommended to administer albumin infusion in combination to prevent PICD.

Peritoneovenous shunt (PVS) therapy for patients with refractory ascites

- For patients experiencing refractory ascites with no viable therapeutic alternatives, portosystemic venous shunting (PVS) should be considered after thorough assessments and obtaining informed consent.

Prophylactic antibiotics for patients with severe cirrhosis with ascites

- Prophylactic antibiotics are recommended based on the risk of infection. (Recommendation: weak, 73% agreed, evidence level B)

Cell-free and concentrated ascites reinfusion therapy (CART) in the use of refractory ascites in cirrhotic patients

- It is suggested for the management of patients that it could be as effective as large-volume paracentesis (LVP) with albumin infusion. (Recommendation: weak, 100% agreed, evidence level B)

Appropriate time for vasopressin V_2 receptor antagonist administration for cirrhotic ascites

- In cirrhotic ascites patients resistant to conventional diuretics, it is advisable to initiate tolvaptan early on when renal function is preserved, without escalating the dose of spironolactone (25–50 mg/day) with or without loop diuretics like furosemide (20–40 mg/day). (Recommendation: strong, 100% agreed, evidence level B)

A complete therapeutic algorithm for cirrhotic ascites is shown in figure 13:

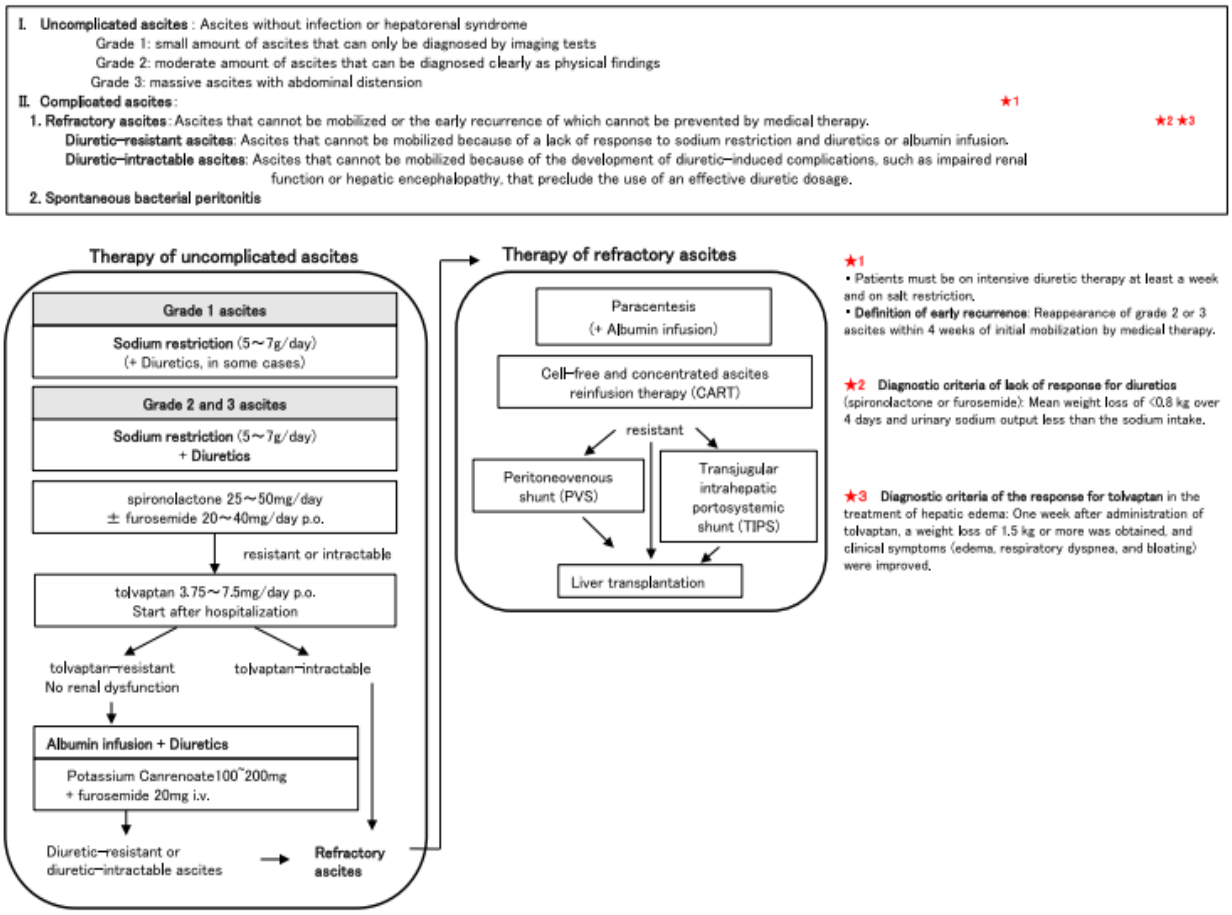


Figure 13. *Therapeutic algorithm for cirrhotic ascites. Retrieved from the JSGE/JSH 2020 guideline.*

Hepatorenal syndrome

Effective drugs for hepatorenal syndrome (HRS)

- Currently, the suggested approach involves the combined administration of noradrenaline and albumin. (Recommendation: weak, 73% agreed, evidence level B)

Hepatic encephalopathy (HE)

Non-absorbable synthetic disaccharide effectiveness for hepatic encephalopathy

- Nonabsorbable synthetic disaccharides are effective and constitute essential treatment for hepatic encephalopathy, recommended for administration.

BCAA-related medication effectiveness for the management of HE

- BCAA-related drugs are effective for the management of HE.

Treatment versus no treatment for covert HE

- It is suggested to treat patients with covert hepatic encephalopathy who are at a high risk of developing overt hepatic encephalopathy, particularly those with deteriorating background liver conditions or the manifestation of symptoms related to decompensated cirrhosis other than hepatic encephalopathy. (Recommendation: weak, 100% agreed, evidence level B)

Non-absorbable antimicrobials effectiveness for HE

- Given the effectiveness of non-absorbable antimicrobial agents for hepatic encephalopathy in both initial and recurrent episodes, their administration serves as fundamental treatment for this condition. (Recommendation: strong, 100% agreed, evidence level A)

Zinc preparation effectiveness for HE

- As zinc deficiency is frequently observed in individuals with cirrhosis, we recommend administering zinc supplements to patients with hepatic encephalopathy who may be experiencing a deficiency in zinc. (Recommendation: weak, 77% agreed, evidence level B)

Carnitine supplementation effectiveness for HE

- As carnitine deficiency is commonly found in individuals with cirrhosis, we recommend supplementing with carnitine for patients with hepatic encephalopathy who may have a deficiency in carnitine. (Recommendation: weak, 92% agreed, evidence level B).

Probiotics effectiveness for HE

- Probiotics have been shown to enhance hepatic encephalopathy parameters in individuals with mild hepatic encephalopathy. (Evidence level C)

<u>Portal vein thrombosis (PVT)</u>

Effective treatment for cirrhosis associated with PVT.

- The suggestion is to administer anticoagulants, considering the prognostic impact of portal vein thrombosis (PVT). (Recommendation: weak, 100% agreed, evidence level B)

Sarcopenia

Effective treatment for cirrhosis associated with sarcopenia.

- Proposal of exercise and nutritional therapies (Recommendation: weak, 92% agreed, evidence level C)

Others

Thrombopoietin receptor agonist effectiveness for thrombocytopenia in liver cirrhotic patients

- Thrombopoietin receptor agonist (Lusutrombopag) treatment is advised for managing thrombocytopenia in patients with liver cirrhosis before elective invasive procedures. (Recommendation: strong, 100% agreed, evidence level B).

1.4.2 Chinese Society of Hepatology (CSH) Guidelines on the Management of Ascites and its Related Complications in Cirrhosis [2019]

The Chinese Society of Hepatology (CSH) developed the current guidelines for the management of ascites and its related complications in cirrhosis based on the published evidence and the panelists' consensus. The guidelines provided recommendations for the diagnosis and management of cirrhotic ascites emphasizing a stepwise approach with the first-, second-, and third-line therapy. In these guidelines, the evidence and recommendations are graded according to the GRADE system (table 14)[6]:

Table 14. Grading Evidence and Recommendations

Grading of Evidence	
High (A)	Further research cannot change the reliability of the therapeutic efficacy evaluation results.
Medium (B)	Further research might change the reliability of the therapeutic efficacy evaluation results and might also change the evaluation results themselves.
Low or extremely low (C)	Further research will likely change the reliability of the therapeutic efficacy evaluation results and will likely also change the evaluation results themselves.
Grading of Recommendation	
Strong (1)	Clearly indicates that the advantages of the intervention measures are greater than the disadvantages, or that the disadvantages are greater than the advantages.

Weak (2)	The advantages and disadvantages are indeterminate or the evidence, whether its quality is high or low, which indicates that the advantages and disadvantages are equivalent.

Ascites

Generally, the decision to admit a patient to the hospital for treatment is typically determined by considering the volume of ascites present and the concurrent medical conditions.

The following table shows the grades of ascites which affects the treatment approach:

Table 15. Grade of Ascites with Respective Intervention

Ascites Grade	Interpretation & Intervention
Grade 1	Most patients show no symptoms, and only a small number of those patients experience additional complications related to cirrhosis. They respond well to diuretic treatment, allowing for outpatient care. Encouraging regular follow-up appointments is advisable.
Grade 2	Most patients exhibit symptoms, along with additional complications of cirrhosis, necessitating hospitalization.
Grade 3	Patients must be hospitalized for treatment.

Treatment objective is to eliminate or control ascites, improve clinical symptoms and quality of life, as well as prolonging survival time. The following sequential treatment approaches below should be adopted:

Table 16. Treatment Approach for Ascites in Liver Cirrhosis

Line of Therapy	Approach
1st Line Therapy	1. Etiological Treatment 2. Sodium restriction (4-6g/day) & diuretic therapy (spironolactone and/or furosemide) 3. Avoidance of nephrotoxic drugs
2nd Line Therapy	1. The use of vasoconstrictor medications and other diuretic/aquaretic drugs, including terlipressin, midodrine hydrochloride, and tolvaptan. 2. Performing a substantial-volume paracentesis with the addition of human serum albumin (HSA).

	3. Trans jugular intra-hepatic portosystemic shunt (TIPS) 4. Discontinuation of NSAIDs and vasodilators, such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB).
3rd Line Therapy	1. Liver Transplantation 2. The concentration and reintroduction of ascitic fluid into the peritoneal cavity or the utilization of renal replacement therapy (RRT). 3. The use of an α-drainage pump in the abdominal cavity or a Denver shunt for Peritoneovenous drainage.

The CSH guidelines for the management of ascites and its related complications 2019 are summarized in the form of key recommendations:

- Patients who have recently developed ascites and those with ascites graded 2, 3, or higher should undergo paracentesis and a standard ascites examination. This examination should include an ascites differential cell count, total protein assessment, and albumin level analysis. The calculation of the Serum-Ascites Albumin Gradient (SAAG) should be performed on the same day as the paracentesis. A SAAG value equal to or greater than 11 g/L is categorized as portal hypertension ascites **(B, 1)**.
- If there is a suspicion of an abdominal cavity infection, blood culture bottles can be employed to culture ascites and anaerobic bacteria directly at the bedside. Samples must be collected using sterile techniques before initiating antibiotic treatment. About 10–20 mL of ascites should be carefully transferred into the blood culture bottle at the bedside and promptly dispatched for testing **(A, 1)**.
- The diagnosis of refractory ascites should be established based on the following criteria: (1) lack of response following at least 1 week of diuretic treatment (spironolactone 160 mg/day, furosemide 80 mg/day) OR paracentesis (4000–5000 mL per procedure) in conjunction with human serum albumin (HSA) (20–40 g/time/day) treatment for 2 weeks; (2) occurrence of uncontrollable complications or adverse reactions associated with diuretic drugs. It is important to note that malignant ascites and ascites caused by presinusoidal portal hypertension are excluded **(B, 1)**.
- The initial spironolactone (aldosterone antagonist) dosage should range from 40 to 80 mg per day, with an incremental increase of 40 mg per day over 3–5 days. The standard dosage upper limit is 100 mg/day, and the maximum daily dose is 400 mg. For furosemide, the starting dosage is 20–40 mg/day, and the

dosage should be raised by 40 mg/day for 3–5 days. The routine dosage upper limit for furosemide is 80 mg/day, with a maximum daily dose of 160 mg **(B, 1)**.

- Tolvaptan, a V2 receptor antagonist, is a successful medication for managing cirrhotic ascites, especially when hyponatremia is present. The initial dose should be 15 mg/day, and adjustments should be made according to the blood sodium level to prevent excessively rapid increases. The minimum dosage is 3.75 mg/day, and the maximum dosage is 60 mg/day **(A, 1)**.
- Terlipressin, a vasoconstrictor, is a suitable option for treating refractory cirrhotic ascites. The recommended dosage is 1–2 mg administered once every 12 hours, either through a slow intravenous (IV) injection lasting at least 15 minutes or a continuous IV drip. If a positive treatment response is observed, administration should be maintained for 5–7 days. In cases where there is no response, the treatment should be adjusted to 1–2 mg once every 6 hours, either through a slow IV injection or continuous IV drip. If the condition recurs after discontinuation of the drug, the same dose can be repeated **(B, 1)**.
- Patients with cirrhotic ascites should refrain from the use of NSAIDs and aminoglycoside antibiotics **(C, 1)**.
- Patients experiencing refractory ascites should receive guidance on limiting their sodium intake to 4–6 g/day **(B, 1)**. If the blood sodium level is below 125 mmol/L, patients should restrict their fluid intake. However, this restriction is not required if the blood sodium level is equal to or greater than 125 mmol/L **(C, 2)**.
- Infusions of human serum albumin (HSA) at a dosage of 20–40 g/day may enhance the prognosis of individuals with cirrhotic ascites, particularly those with refractory ascites and spontaneous bacterial peritonitis (SBP) **(A, 1)**.
- Performing large-volume paracentesis, extracting 4000–5000 mL per procedure, along with administering human serum albumin (HSA) at a rate of 4 g for every 1000 mL removed, is an effective approach for managing refractory ascites **(B, 1)**.
- TIPS therapy is a viable option for treating early-stage refractory cirrhotic ascites that shows limited responsiveness to diuretics, provided there are no contraindications in the patient **(B, 1)**.
- In general, the placement of a peritoneal drainage tube for ascites paracentesis is not recommended **(B, 1)**. Patients experiencing refractory cirrhotic ascites should be given priority for liver transplantation **(B, 2).**
- Whenever feasible, eligible individuals should receive proactive etiological treatment to stabilize the patient's condition, revert decompensated cirrhosis,

attain compensated cirrhosis, or reach a state without cirrhosis (e.g., through liver transplantation) **(A, 1).**

Spontaneous bacterial peritonitis (SBP)

The early diagnosis and initiation of empirical anti-infective empirical anti-infective treatment for spontaneous bacterial peritonitis (SBP) remain significant clinical hurdles. The differentiation between community-acquired and hospital-acquired SBP infections is crucial for the empirical choice of antibiotics. Patients are categorized as having hospital acquired SBP if they manifest cirrhotic ascites, display signs and symptoms of SBP, or meet the criteria for a laboratory diagnosis of SBP within 48 hours after admission.

Recommendations are the following:

- In patients with cirrhosis, the presence of abdominal signs and symptoms (like fever, abdominal pain, or tenderness) or abnormal infection-related laboratory test results can act as indicators for the initiation of early empirical anti-infective treatment **(B, 1)**.
- For patients with mild-to-moderate community-acquired SBP who have recently been treated with a β-lactam, the preferred initial treatment option should be a third-generation cephalosporin (A, 1). Alternatively, fluoroquinolone can be used as a standalone treatment if it has not been administered to the patients previously **(B, 2).**
- In the case of patients with SBP who are either in a hospital setting or have recently been treated with a β-lactam, empirical anti-infective therapy should be guided by antibiotic sensitivity testing or incorporate the use of carbapenem **(A, 1)**.
- Patients should undergo empirical anti-infective treatment if the polymorphonuclear leukocyte (PMN) count in ascites is less than 250/mm3 and they are displaying infection symptoms such as abdominal pain or tenderness **(B, 1)**.
- It is important to closely monitor adverse reactions in patients with cirrhotic ascites who are undergoing treatment with anti-infective drugs **(C, 1)**. Rifaximin can be beneficial in preventing the recurrence of SBP **(B, 2)**.

Hepatorenal syndrome (HRS)

The prognosis for hepatorenal syndrome (HRS) is unfavorable; therefore, it is crucial to commence treatment promptly upon confirming the diagnosis to prevent additional deterioration of kidney function.

Recommendations are the following:

- HRS should be taken into consideration when a patient with cirrhotic ascites exhibits signs such as upper gastrointestinal bleeding, electrolyte imbalances, ascitic infections, undergoing large-volume paracentesis, experiencing excessive urination, severe vomiting and diarrhea, or a sudden decline in kidney function **(C, 2)**.
- Diagnosis of HRS involves the following criteria: (1) presence of cirrhosis with ascites; (2) absence of shock; (3) an increase in serum creatinine (SCr) exceeding 50% of the baseline level or reaching more than 1.5 mg/dL (133 μmol/L); (4) lack of improvement in renal function following volume expansion and discontinuation of diuretics (SCr < 133 μmol/L); (5) no recent history of nephrotoxic drug use; and (6) absence of renal parenchymal disease **(A, 1)**.
- Type 1 HRS is defined by swift and advancing renal damage, marked by a twofold increase in the initial SCr or exceeding 226 μmol/L (2.5 mg/dL) within a span of 2 weeks. Additionally, it involves a decline in estimated glomerular filtration rate (eGFR) by more than 50%, reaching less than 20 mL/min.

  On the other hand, Type 2 HRS exhibits characteristics such as gradual and progressive renal injury, SCr levels ranging from 133 to 226 μmol/L (1.5–2.5 mg/dL), often accompanied by refractory ascites **(A, 1)**.
- Terlipressin, administered at a dose of 1 mg every 4–6 hours along with human serum albumin (HSA) at a dosage of 20–40 g per day, can be employed to address both type 1 and type 2 HRS. If, after 3 days of treatment, there is no reduction in SCr of at least 25%, the terlipressin dose can be gradually increased, reaching a maximum of 2 mg every 4–6 hours. If the treatment proves effective, the course typically spans 7–14 days; termination of terlipressin is recommended if the treatment proves ineffective within this period. In instances where the treatment is effective, but the condition recurs, reinitiating terlipressin treatment is an option **(A, 1)**.
- Individuals with HRS, refractory cirrhotic ascites, and hyponatremia may be prescribed tolvaptan. The temporary discontinuation of non-selective β-blockers is advisable, while the utilization of vasodilators is not recommended for HRS **(C, 2)**.
- If individuals with type 1 HRS do not show a positive response to vasoconstrictor therapy, renal replacement therapy (RRT) or an artificial liver support system can be considered (provided the patients meet the criteria). Conversely, patients with type 2 HRS should not undergo RRT **(B, 1)**.
- Individuals with type 2 HRS and a significant amount of ascites, who do not exhibit a positive response to vasoconstrictor therapy, may undergo TIPS therapy. TIPS therapy is not recommended for type 1 HRS. Patients with either type 1 or type 2 HRS should be given priority for liver transplantation **(B, 1)**.

1.4.3 Korean Association for the Study of the Liver (KASL) Clinical Practice Guidelines for Liver Cirrhosis: Varices, Hepatic Encephalopathy, and Related Complications [2020]

The key recommendations from the KASL 2020 guideline for the management of liver cirrhosis and its complications using the GRADE approach (table 13 above) are listed below[23]:

VARICES

Preventing the formation and progression of esophageal varices (EV)

- It is advisable to pursue suitable treatment for the underlying liver disease to prevent the development of esophageal varices (EVs) **(A1)**.
- Non-selective beta-blockers (NSBBs) such as propranolol and nadolol are not advised for preventing the formation of esophageal varices in cirrhotic patients who do not have existing varices **(A1)**.
- For individuals with small non-bleeding esophageal varices, the use of non-selective beta-blockers (NSBBs) such as propranolol and nadolol, or carvedilol, may be considered to impede the advancement of varices **(B2)**.

Preventing the first variceal bleeding in patients with EVs

- For cirrhotic individuals with small esophageal varices at a heightened risk of bleeding (such as those with decompensated cirrhosis or red color signs on endoscopy), the consideration of non-selective beta-blockers (NSBBs) like propranolol or nadolol is recommended to prevent the initial occurrence of variceal bleeding **(B1)**. The adjustment of NSBBs should occur every 2–3 days until the resting heart rate reaches 55–60 beats per minute.
- For individuals with cirrhosis and large esophageal varices, the recommendation is to use non-selective beta-blockers (NSBBs) such as propranolol or nadolol, carvedilol, or endoscopic variceal ligation (EVL) to prevent the initial occurrence of variceal bleeding **(A1)**. Additionally, the option of considering a combination of NSBBs and EVL is also suggested **(B2)**.

Diagnosis and management of acute esophageal variceal bleeding

- Endoscopy should be performed in patients with suspected esophageal variceal bleeding **(A1)**.
- Patients experiencing acute esophageal variceal bleeding should undergo endoscopic treatment **(A1)**.
- Antibiotic prophylaxis for a brief duration should be initiated in individuals experiencing acute esophageal variceal bleeding **(A1)**.

- If there is suspicion of esophageal variceal bleeding, vasoactive agents should be promptly initiated upon admission **(A1)**.
- Early consideration for the placement of trans jugular intrahepatic portosystemic shunt (TIPS) can be given to patients at a high risk of rebleeding **(B2)**.
- Transjugular intrahepatic portosystemic shunt (TIPS) is a potential intervention for patients in whom bleeding control proves ineffective despite the combination of pharmacological and endoscopic therapy **(A2)**.
- Balloon tamponade may be contemplated as an interim intervention for patients who do not attain hemostasis following endoscopic treatment **(B2)**.

Secondary prevention of EV

- For patients experiencing acute esophageal variceal bleeding, it is advisable to pursue treatment to prevent the recurrence of variceal bleeding **(A1)**.
- The preferred approach for treating esophageal variceal bleeding is the combination of endoscopic variceal ligation (EVL) with non-selective beta-blockers (NSBBs) as the primary treatment **(A1)**. If implementing the combination treatment is challenging, the use of NSBBs or EVL alone is recommended **(A1)**.
- If the initial treatment for esophageal variceal rebleeding proves ineffective, the consideration of transjugular intrahepatic portosystemic shunt (TIPS) placement is recommended as a rescue therapy **(B1)**.
- Liver transplantation may be contemplated for patients experiencing recurrent variceal rebleeding **(B1)**.

Prevention of gastric varices bleeding

- The initial preventive measures against bleeding in patients with gastroesophageal varices type 1 (GOV1s) align with the guidelines for esophageal varices (EVs) **(B1)**.
- Individuals at a heightened risk of bleeding, particularly those with redness or severe liver dysfunction associated with gastroesophageal varices type 2 (GOV2s) or isolated gastric varices type 1 (IGV1s), may undergo treatment with balloon-occluded retrograde transvenous obliteration (BRTO), partial splenic embolization (PARTO), or endoscopic variceal obturation (EVO) **(B2)**.

  The following figure represents a summary of the prevention of primary variceal bleeding:

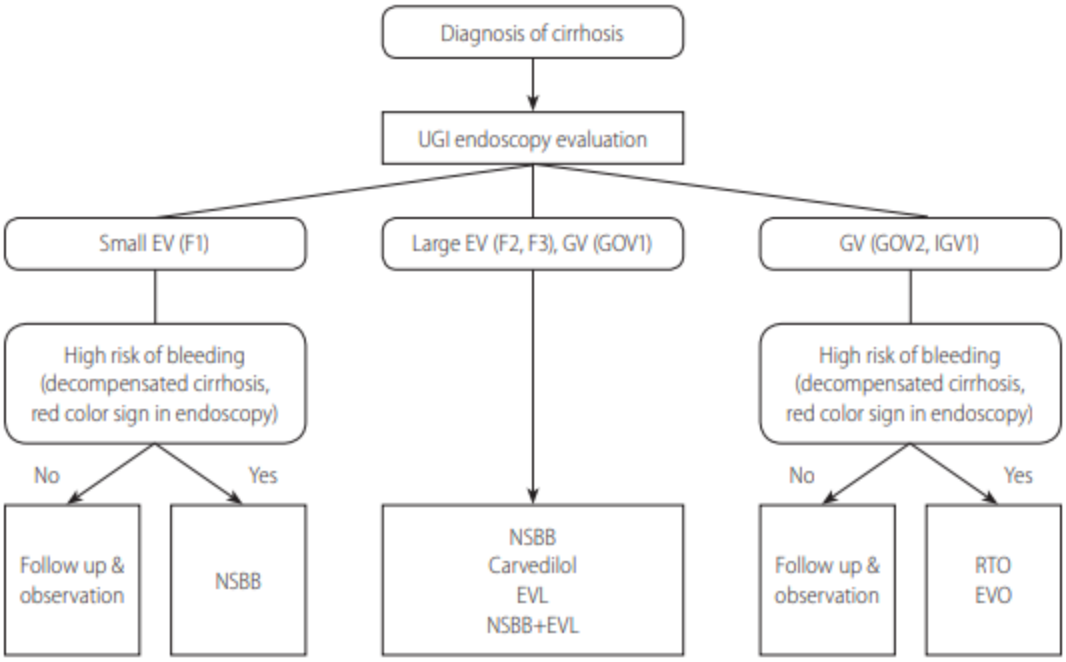


Figure 14. *The prevention of initial variceal bleeding. Retrieved from the KASL 2020 guideline.*

UGI, upper gastrointestinal; EV, esophageal varix; GV, gastric varix; GOV, gastroesophageal varix; IGV, isolated gastric varix; NSBB, non-selective beta blocker; EVL, endoscopic variceal ligation; RTO, retrograde transvenous obliteration; EVO, endoscopic variceal obturation.

Management of gastric varices bleeding

- For individuals experiencing gastric variceal bleeding, standard management practices such as prophylactic antibiotics, conservative transfusion approaches, and the use of vasoactive agents can be administered, mirroring the protocols for esophageal variceal bleeding **(B1)**.
- Gastric varices extending from esophageal varices along the lesser curvature (GOV1s) can be addressed through either endoscopic variceal obturation (EVO) or endoscopic variceal ligation (EVL), with the choice dependent on the size and location of the bleeding varix **(B1)**.
- In cases of bleeding from fundic varices (GOV2s, IGV1s), priority should be given to EVO **(A1)**. Retrograde transvenous obliteration (balloon-occluded retrograde transvenous obliteration - BRTO or partial splenic embolization - PARTO) or trans jugular intrahepatic portosystemic shunt (TIPS) may be considered based on the bleeding status (active or stabilized) and the presence of an accessible shunt **(B1)**.
- Proton pump inhibitors (PPIs) can be utilized in post-endoscopic treatments to prevent post-procedure ulcer bleeding **(B2)**.

- When endoscopic treatments prove ineffective, the consideration of retrograde transvenous obliteration (BRTO or PARTO) or TIPS is recommended as a rescue therapy **(B1)**.
- As bridging therapy until a rescue treatment is available, balloon tamponade can be applied **(B2)**.

Table 17 lists vasoactive agents that can be used in the management of acute variceal bleeding:

Table 17. Vasoactive Agents Used in the Management of Acute Variceal Bleeding. Adapted from the KASL 2020 Guideline.

Type	Initial dose	Maintenance dose	Side effects
Terlipressin	2 mg intravenously	1–2 mg intravenously every 4–6 hours	Hyponatremia, myocardial ischemia, abdominal pain, diarrhea
Somatostatin	250 μg intravenously	250 μg/hr intravenously	Nausea/vomiting, abdominal pain, headache, hyperglycemia
Octreotide	50 μg intravenously	50 μg/hr intravenously	Nausea/vomiting, abdominal pain, headache, hyperglycemia

Secondary prevention of GOV

- For individuals with persisting or recurring GOV1s after initial treatments, repeated endoscopic variceal obturation (EVO) or endoscopic variceal ligation (EVL) can be undertaken to prevent rebleeding **(B2)**.
- Individuals with remaining or recurring fundic varices (GOV2s, IGV1s) may undergo either EVO or retrograde transvenous obliteration (RTO, involving BRTO or partial splenic embolization - PARTO) **(B2)**. In cases where there is no accessible shunt or complications related to severe portal hypertension (such as recurrent bleeding from esophageal varices, refractory ascites, or hydrothorax) are not controlled, the placement of a trans jugular intrahepatic portosystemic shunt (TIPS) is an option **(B2)**.

Portal hypertensive gastropathy

- For chronic bleeding attributed to portal hypertensive gastropathy, the administration of nonselective beta-blockers is a suitable option **(B1)**.

The following figure represents a summary of the management and secondary prevention of acute variceal bleeding:

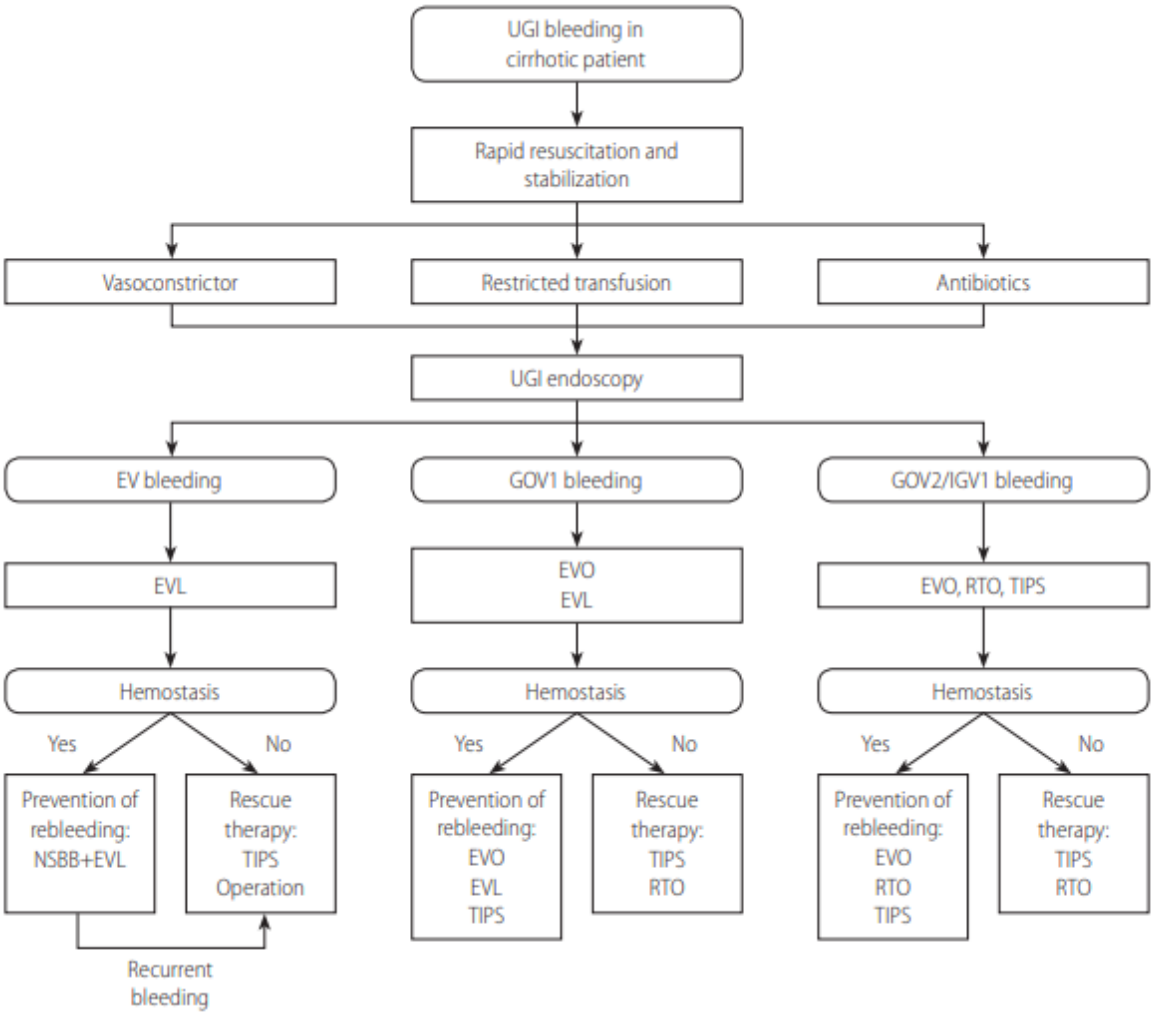


Figure 15. *The treatment of acute variceal bleeding and prevention of variceal rebleeding. Retrieved from the KASL 2020 guideline.*

UGI, upper gastrointestinal; EV, esophageal varix; GOV, gastroesophageal varix; IGV, isolated gastric varix; EVL, endoscopic variceal ligation; EVO, endoscopic variceal obturation; RTO, retrograde transvenous obliteration; TIPS, trans jugular intrahepatic portosystemic shunt; NSBB, non-selective beta blocker.

HEPATIC ENCEPHALOPATHY

Management of overt HE

- Factors that can precipitate hepatic encephalopathy (HE) include gastrointestinal bleeding, infection, constipation, excessive protein intake, dehydration, renal function disorder, electrolyte imbalance, psychoactive medication, and acute hepatic injury. Therefore, the initial approach involves recognizing and managing these factors **(A1)**.

- For the management of acute episodic overt HE, non-absorbable disaccharides such as lactulose or lactitol are recommended. Enema is advised in cases of severe HE (West Haven criteria grade ≥3) or situations where oral intake is inappropriate **(A1)**.
- Rifaximin may be combined with non-absorbable disaccharides in the treatment of patients with HE **(B1)**.
- Additionally, oral branched-chain amino acids (BCAA) and intravenous L-ornithine L-aspartate (LOLA) or albumin can be used **(B2)**.
- Oral neomycin (1 to 4 g daily in divided doses) has been shown to have some efficacy for the treatment of hepatic encephalopathy; however, this agent is not routinely used due to major potential adverse effects, including ototoxicity and nephrotoxicity. Neomycin should be considered only as an alternative agent for treating overt hepatic encephalopathy[24].
- Treatment of overt hepatic encephalopathy with metronidazole targets the treatment of gram-negative anaerobic gut bacteria. These anaerobic bacteria produce urease that hydrolyzes urea to ammonia; decreasing the quantity of anaerobic organisms is postulated to result in decreased ammonia production in the gut. In one study, oral metronidazole 200 mg 4 times daily had similar efficacy as neomycin. Long-term use of metronidazole is associated with potential neurotoxicity. Metronidazole should be considered only as an alternative agent for short-term treatment of overt hepatic encephalopathy[24].
- Liver transplantation is considered appropriate for patients with severe HE who do not respond to medical treatments **(A1)**.

Table 18 lists the pharmacological options used for managing overt encephalopathy:

Table 18. Pharmacological Options for Managing Overt Hepatic Encephalopathy. Adapted from the KASL 2020 Guideline.

Non-absorbable disaccharides	Lactulose (20–30 g) should be administered orally 3–4 times per day (an equivalent daily dose of lactitol is 67–100 g). Goals: it should be administered orally until the patient is having at least 2 bowel movements a day. Thereafter, the dose should be titrated to achieve two to three soft stools per day. If patients cannot take medications orally, administration via nasogastric tube might be tried. Enema with

	lactulose 200 g and 700 mL water might be performed 3–4 times per day in severe cases.
Rifaximin	400 mg three times/day or 550 mg twice/day
Oral BCAA	0.25 g/kg/day
Intravenous LOLA	30 g/day
Albumin	1.5 g/kg/day until clinical improvement or for 10 days, maximum
Polyethylene glycol	A substitute for non-absorbable disaccharides 4 liters orally

BCAA, branched-chain amino acid; LOLA, L-ornithine-L-aspartate.

Prevention of overt HE

- To prevent the recurrence of overt hepatic encephalopathy (HE), the recommendation is the use of a nonabsorbable disaccharide (such as lactulose or lactitol) or rifaximin, either as single therapy or in combination **(A1)**.
- The recurrence of overt HE can be prevented through the supplementation of oral branched-chain amino acids or oral L-ornithine L-aspartate (LOLA) **(B1)**.
- Ensuring adequate education for both patients and caregivers upon discharge is essential to reduce the likelihood of overt HE recurrence **(B1)**.
- Patients with decompensated liver cirrhosis who have experienced overt HE requires nutritional assessment and management. Long-term protein restriction should be avoided, and it is crucial to maintain sufficient energy and protein intakes **(B1)**.

Covert HE

- Administration of lactulose **(B1)** or rifaximin **(B2)** is a viable approach for enhancing cognitive function and quality of life in individuals with covert hepatic encephalopathy (CHE).

Figure 16 the treatment and prevention plan for patients with hepatic encephalopathy:

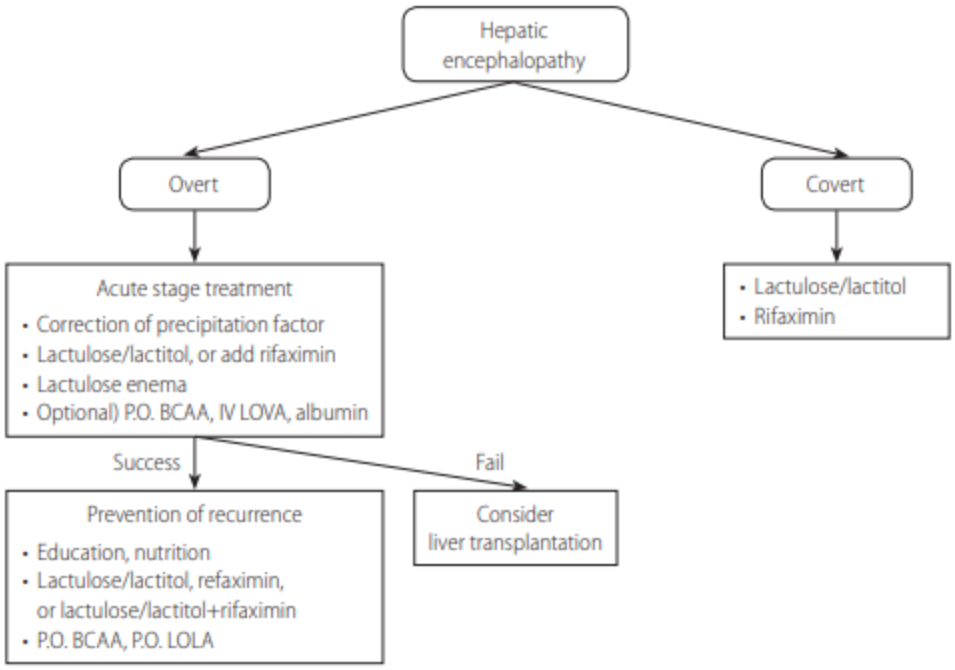


Figure 16. *The treatment and prevention of recurrence of hepatic encephalopathy. Retrieved from the KASL 2020 guideline.*

P.O., per oral; BCAA, branched-chain amino acid; IV LOLA, intravenous L-ornithine-L-aspartate.

1.4.4 Mexican Association of Gastroenterology Consensus on the Management of Complications of Cirrhosis of the Liver in Pediatrics [2022]

The statements that reached a consensus (agreement > 75%) were accepted and those that did not reach a consensus (agreement < 75%) were re-evaluated, to be either eliminated or reformulated by the members. These statements are presented as the following[25]:

- Cirrhosis in children can remain unnoticed until signs and symptoms related to complications emerge, as there is no specific biomarker for diagnosis. Level of agreement: in complete agreement 95.45%.
- The Pediatric End-Stage Liver Disease (PELD) score, designed for children aged 12 years, stands as the most widely used marker for assessing liver disease severity, prognosis, and prioritizing liver transplantation (LT). Level of agreement: in complete agreement 95.45%.
- While the Child-Pugh scale and CLIF-SOFA score are employed in adults to predict prognosis and the need for liver transplantation, their application in children lacks sufficient evidence. Level of agreement: in complete agreement 83.33%.

- Liver biopsy, an invasive procedure, delivers a definitive cirrhosis diagnosis, evaluates disease severity and prognosis, and monitors treatment response, emphasizing the need for individualization. Level of agreement: in complete agreement 91.67%.
- Careful consideration of weight is essential in cirrhotic pediatric patients, influenced by ascites and visceromegaly. Level of agreement: in complete agreement 100%.
- A recommended dietary energy supply from carbohydrates is 50-65%, preferably from complex carbohydrates for glucose control in hypoglycemic or insulin-resistant patients. Level of agreement: in complete agreement 100%.
- Protein restriction is not advised in pediatric cirrhosis patients. Level of agreement: in complete agreement 90.91%.
- Cirrhotic patients with cholestasis benefit from vitamin and medium-chain triglyceride supplementation, up to 80% of total dietary fat, to prevent essential fatty acid deficiency. Level of agreement: in complete agreement 90.91%.
- Consideration of feeding tube use, preferably nasogastric or transpyloric, is suggested for high-energy-dense enteral nutrition in patients failing to meet calorie intake goals. Level of agreement: in complete agreement 79.17%.
- Parenteral nutrition is recommended when oral or enteral routes are inaccessible for over 72 hours or as a caloric complement if adequate growth is not achieved despite full enteral support. Level of agreement: in complete agreement 81.82%.
- Sodium restriction is advised only in cases of decompensated ascites. Level of agreement: in complete agreement 91.67%.

Hepatic encephalopathy

- A normal ammonia level does not rule out the presence of HE. Level of agreement: in complete agreement 100%.
- HE prevention aims at optimizing nutritional status, identifying precipitating factors, and establishing pharmacologic prophylaxis when necessary. Level of agreement: in complete agreement 86.96%.
- First-line pharmacologic treatment for HE involves lactulose administration (by enema or oral route) and intraluminal antibiotics in both children and adults. Level of agreement: in complete agreement 100%.

- After a recurrent HE episode, secondary prophylaxis recommends lactulose and/or intraluminal antibiotics (rifaximin) use. Level of agreement: in complete agreement 81.82%.
- The combination of l-carnitine and zinc has demonstrated improvement in HE grades. Level of agreement: in complete agreement 80.95%.

Portal hypertension and coagulopathy

- Nonselective beta-blockers for variceal bleeding prevention in adults lack pediatric clinical trial evidence, necessitating careful risk-benefit consideration. Level of agreement: in complete agreement 100%.
- Variceal ligation may be considered for preventing first bleeding episodes in high-risk cases, such as multiple grade 2 or 3 esophageal varices with cherry-red spots. Level of agreement: in complete agreement 95.65%.
- Acute bleeding episode management involves resuscitation, blood volume restoration, vasoactive therapy (octreotide), and endoscopic therapy in stable patients. Level of agreement: in complete agreement 91.3%.
- Antimicrobial prophylaxis within the first 48 hours post-admission can positively impact reducing bacteremia and the 30-day readmission rate. Level of agreement: in complete agreement 78.26%.
- Secondary prophylaxis for variceal bleeding includes sclerotherapy and/or esophageal variceal ligation. Level of agreement: in complete agreement 95.65%.
- In cases of severe rebleeding after endoscopic treatment, Hemospray® application serves as a useful rescue procedure for EVs, GVs, or portal hypertensive gastropathy. Level of agreement: in complete agreement 78.26%.
- Portal hypertensive gastropathy bleeding treatment includes argon or laser coagulation, significantly reducing transfusion need in localized involvement and showing a lower response in diffuse disease. Level of agreement: in complete agreement 86.36%.
- Bleeding due to coagulopathy management involves FFP administration, vitamin K for prolonged prothrombin time correction, cryoprecipitates for hypofibrinogenemia, and platelet concentrates if platelet count is <50,000 for invasive procedures. Level of agreement: in complete agreement 90.91%.
- If FFP fails to correct prothrombin time, prothrombin complex concentrate is recommended as an alternative, especially in cases of circulatory overload risk. Level of agreement: in complete agreement 90.91%.

- Surgical portosystemic shunting and liver transplantation are considered if variceal bleeding persists despite pharmacologic and endoscopic therapy. Palliative transjugular intrahepatic portosystemic shunt is indicated if those interventions are not feasible. Level of agreement: in complete agreement 86.96%.

Acute kidney injury and hepatorenal syndrome

- Acute kidney injury (AKI) management involves diuretic and nephrotoxic medication suspension, infectious process treatment, and maintenance of adequate intravascular volume. Level of agreement: in complete agreement 90.91%.
- In cirrhotic patients with AKI unresponsive to initial treatment, evaluation for HRS-AKI criteria is necessary, and treatment initiation with vasoconstrictors like terlipressin or norepinephrine plus albumin is recommended. Level of agreement: in complete agreement 90.91%.
- Renal replacement therapy (RRT) is indicated for HRS-AKI patients unresponsive to pharmacologic treatment with volume overload or uremia, reserved as bridging therapy to liver transplantation. Level of agreement: in complete agreement 86.36%.
- Liver/kidney transplantation should be considered in patients with significant chronic kidney disease (HRS-CKD) or acute persistent disease, including sepsis-associated AKI unresponsive to pharmacologic treatment. Level of agreement: in complete agreement 95.45%.

Hepatopulmonary syndrome

- There is no effective medical therapy for hepatopulmonary syndrome reversal; liver transplantation remains the only therapy. Level of agreement: in complete agreement 100%.

Portopulmonary hypertension

- Medical treatment for portopulmonary hypertension relies on pulmonary vasodilators, aiming for a mean pulmonary artery pressure (mPAP) under 35 mmHg. Level of agreement: in complete agreement 100%.
- Liver transplantation can resolve portopulmonary hypertension, but severe forms with mPAP >45 mmHg have high perioperative mortality and contraindicate liver transplant. Level of agreement: in complete agreement 100%.

Cholangitis and other infections

- Cholangitis is primarily attributed to Gram-negative bacteria and, to a lesser extent, Gram-positive bacteria. Empirical treatment with piperacillin/tazobactam, ceftriaxone combined with metronidazole, and third generation cephalosporins has demonstrated positive outcomes. Level of agreement: In complete agreement 95%.
- Hospitalization should be contemplated when there is suspicion of an infectious process in patients with cirrhosis. Level of agreement: In complete agreement 86.36%.
- Approximately 30% of patients with infection and liver cirrhosis may not exhibit fever and abnormal leukocyte values. In such instances, reliable markers such as procalcitonin and C-reactive protein should be assessed. Level of agreement: In complete agreement 81.82%.
- There is insufficient evidence supporting the initiation of antimicrobial prophylaxis for cholangitis in patients with biliary atresia after the Kasai procedure. Although there is limited evidence, secondary oral prophylaxis does decrease the recurrence of cholangitis. Level of agreement: In complete agreement 80%.

Ascites and peritonitis

- An adequate response to the treatment of ascites involves reduced weight due to ascitic fluid loss, resolved edema, reduced abdominal circumference, and increased diuresis. Level of agreement: in complete agreement 77.27%.
- The recommended management for grade 1, or mild, ascites is a low-sodium diet (1-2 mEq/kg/day). Level of agreement: in complete agreement 76.19%.
- The management of grade 2, or moderate, ascites includes dietary sodium restriction and diuretics. Level of agreement: in complete agreement 81.82%.
- The primary approach for managing grade 3 ascites, or tense ascites, in adults involves paracentesis as the first-line treatment, despite controversy surrounding its use in the pediatric population. Some centers employ this procedure, but its recommendation lacks solid scientific evidence. Level of agreement: In complete agreement 94.1%.
- Albumin infusion, along with diuretic administration, is recommended for treating ascites in cases with hypoalbuminemia <2.5g/dL. Level of agreement: In complete agreement 90%.
- For cases of initial ascitic fluid infection, community-acquired infection, and no antimicrobial use in the past 4 weeks, empirical treatment with third

generation cephalosporins is indicated. Level of agreement: In complete agreement 86.36%.

- Children suspected of having spontaneous bacterial peritonitis (SBP) should undergo diagnostic paracentesis for cytochemical study, aerobic and anaerobic bacterial cultures, hemoculture, and urine culture. Level of agreement: In complete agreement 90.91%.
- Antimicrobial treatment should be initiated empirically before suspecting infection (SBP) in cases of recurrence, in-hospital acquisition, and antibiotic use in the past month. Level of agreement: In complete agreement 86.36%.
- There is no evidence supporting antimicrobial prophylaxis for SBP in children. In adults, the administration of trimethoprim-sulfamethoxazole or rifaximin has been associated with a reported decrease in infection events. Level of agreement: In complete agreement 86.36%.

1.5 Systematic Reviews & Meta Analyses

Table 19 tackles a systematic review and meta-analysis issued in 2023 for decompensated liver cirrhosis.

Table 19. Systematic Review and Meta Analysis for Liver Cirrhosis

Author (year)	Study Title	Primary Objective	Outcomes	Results
Dimachkie et al. (2023)[26]	***"Granulocyte-colony stimulating factor in decompensated liver cirrhosis: a meta-analysis of four randomized controlled trials"***	Granulocyte-colony stimulating factor (GCSF) shows potential for liver disease treatment with its regenerative and immunomodulatory properties. To assess the controversial use of GCSF in DC, a meta-analysis of randomized controlled trials (RCTs) compared survival benefits in patients receiving GCSF plus standard medical therapy (SMT) versus SMT alone.	The primary outcome was survival time. The authors also considered the overall survival results. The secondary outcomes were model of end-stage liver disease (MELD) score, CPT score, and CD34 levels.	The results indicated that GCSF + SMT led to higher odds of survival compared to SMT alone [risk ratio 1.28, 95% CI (1.08–1.5)]. Heterogeneity existed among the studies, but overall, GCSF showed potential in improving survival. The intervention group exhibited improved Child-Pugh-Turcotte scores [−2.51, CI (−4.33 to −0.70)], and increased CD34 levels, but no significant improvement in MELD scores. These findings suggest GCSF may benefit patients with decompensated cirrhosis in terms of survival and liver function. The results suggest that the combination of GCSF and SMT may have a positive impact on the survival rate and improvement in CPT score in patients with DC. Further RCTs are needed to shed more light on this promising modality in end-stage liver disease.

Section 2.0 Drug Therapy

2.1 Nonabsorbable Disaccharides

2.1.1 Lactulose

Information on Lactulose is detailed in the table below[27,28]:

Table 20. Drug Therapy with Lactulose

SCIENTIFIC NAME Lactulose	
SFDA Classification	OTC
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	K74
Drug Class	Nonabsorbable disaccharide
Drug Sub-class	Osmotic Laxative, ammonium detoxicant
ATC Code	A06AD11
Pharmacological Class (ASHP)	Osmotically acting laxative
DRUG INFORMATION	
Dosage Form	Syrup
Route of Administration	Oral
Dose (Adult) [DDD]*	**Prevention:** 20 to 30 g (30 to 45 mL) 2 to 4 times daily; may adjust dose every 1 to 2 days to achieve 2 to 3 soft stools/day **Treatment:** Initial: 20 to 30 g (30 to 45 mL) every 1 to 2 hours to induce ~2 soft stools/day, then reduce to 20 to 30 g (30 to 45 mL) 2 to 4 times daily; may adjust dose every 1 to 2 days to achieve 2 to 3 soft stools/day
Maximum Daily Dose Adults*	30 g, 4 times daily
Dose (pediatrics)	**Portal systemic encephalopathy, prevention (PSE):**

	Infants: 1.7 to 6.7 g/day (2.5 to 10 mL/day) in divided doses; adjust dosage to produce 2 to 3 stools/day. Children and adolescents: 26.7 to 60 g/day (40 to 90 mL/day) in divided doses; adjust dosage to produce 2 to 3 stools/day.
Maximum Daily Dose Pediatrics*	Infants: 6.7g/day Children & Adolescents: 60g/day
Adjustment	None
Prescribing edits*	N/A
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** abdominal cramps, bloating, diarrhea **Most serious:** anorexia
Drug Interactions*	**Category X:** • Acenocoumarol • Dichlorphenamide • Glutamine • Phenindione • Phenprocoumon [INT] • Warfarin
Special Population	Elderly individuals are prone to exhibiting signs of central nervous system (CNS) dehydration and electrolyte depletion at a higher rate than their younger counterparts. Consequently, it is advisable to closely observe for fluid and electrolyte loss,

	particularly sodium, during prolonged usage. Periodic monitoring of serum electrolyte levels, including potassium, chloride, carbon dioxide, and sodium, is recommended.
Pregnancy	Lactulose is safe in pregnancy
Lactation	It is not known if lactulose is present in breast milk; however, lactulose is poorly absorbed following oral administration. The manufacturer recommends that caution be exercised when administering lactulose to nursing women.
Contraindications	Patients requiring a low galactose diet
Monitoring Requirements	BP, standing/supine; serum electrolytes; bowel movement frequency; fluid status; serum ammonia.
Precautions	***Concerns related to adverse effects:*** Electrolyte imbalance: Monitor periodically for electrolyte imbalance when lactulose is used >6 months or in patients predisposed to electrolyte abnormalities (eg, elderly, debilitated patients). Hepatic disease may predispose patients to electrolyte imbalance. Infants receiving lactulose may develop hyponatremia and dehydration. ***Disease-related concerns:*** Diabetes: Use with caution in patients with diabetes mellitus; solution contains galactose and lactose.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of liver cirrhosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency

in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for lactulose.**

Table 21. Lactulose HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Lactulose	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Lactulose

The use of the nonabsorbable disaccharide lactulose is most recommended as a first line therapeutic agent for the treatment and prevention of recurrence of hepatic encephalopathy in patients with liver cirrhosis. Dosing will be adjusted to achieve at least 2-3 stools/day. Duration may continue indefinitely for patients with recurrent hepatic encephalopathy.

2.2 Rifamycin Analogue

2.2.1 Rifaximin

Information on Rifaximin is detailed in the table below[27,28]:

Table 22. Drug Therapy with Rifaximin

SCIENTIFIC NAME Rifaximin	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	K74
Drug Class	Non-absorbable antibiotic
Drug Sub-class	Rifamycin analogue
ATC Code	L01BA01

Pharmacological Class (ASHP)	Rifamycin analogue
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	550 mg twice daily **or** 400 mg 3 times daily. When used for treatment of an acute episode, continue therapy for at least 3 months.
Maximum Daily Dose Adults*	550 mg twice daily **or** 400 mg 3 times daily
Dose (pediatrics)	Use and dose must be determined by doctor
Maximum Daily Dose Pediatrics*	Use and dose must be determined by doctor
Adjustment	None
Prescribing edits*	CU, ST
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): May be combined with lactulose for hepatic encephalopathy	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Is used as an alternative for patients who cannot tolerate or failed on lactulose	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Nausea, ascites, dizziness, fatigue **Most severe:** hypersensitivity reactions, Clostridium difficile infection, severe abdominal pain
Drug Interactions*	**Category X**: • Cholera Vaccine • Fecal Microbiota (Live) (Oral) • Fecal Microbiota (Live) (Rectal)

Special Population	N/A
Pregnancy	Adverse events have been observed in some animal reproduction studies. Due to the limited oral absorption of rifaximin in patients with normal hepatic function, **exposure to the fetus is expected to be low.**
Lactation	Because of the limited oral absorption of rifaximin in patients with normal hepatic function, **exposure to the nursing infant is expected to be low.**
Contraindications	Hypersensitivity to rifaximin, other rifamycin antibiotics, or any component of the formulation
Monitoring Requirements	Hypersensitivity reactions, temperature, blood in stool, change in symptoms; serum ammonia
Precautions	***Disease-related concerns:*** Hepatic impairment: Efficacy for prevention of encephalopathy has not been established in patients with a Model for End-Stage Liver Disease (MELD) score >25; use caution in patients with severe hepatic impairment (Child-Pugh class C). ***Dosage-form specific issues:*** Propylene glycol: Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated hyperosmolality, lactic acidosis, seizures, and respiratory depression; use caution. ***Other warnings/precautions:*** Appropriate use: Not for treatment of systemic infections; <1% is absorbed orally.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of liver cirrhosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for rifaximin.**

Table 23. Rifaximin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Rifaximin	NICE[8]	**Conditional Positive Recommendation March 2015** The Committee concluded that rifaximin was effective in preventing episodes of overt hepatic encephalopathy in the trial population, although the long-term benefits associated with rifaximin were uncertain, and that the current evidence indicates that rifaximin has an acceptable adverse event profile. The Committee concluded that, on balance, the most plausible incremental cost-effectiveness ratio (ICER) was likely to be close to the top end of the range normally considered cost effective. Although the most plausible ICER was subject to several uncertainties, the Committee was aware of the important unmet medical need in this population and the innovative aspects of this treatment. **The Committee concluded that rifaximin could be considered a cost-effective use of NHS resources.**
	CADTH[9]	**Conditional Positive Recommendation April 2015** One double-blind, phase 3, randomized controlled trial (RCT) (study 3001; N = 299), in which 91% of participants were using concomitant lactulose therapy, demonstrated that treatment with rifaximin significantly reduced the risk of breakthrough overt HE (hazard ratio [HR] 0.421; 95% confidence interval [CI], 0.276 to 0.641]) and HE-related hospitalization (HR 0.500; 95% CI, 0.287 to 0.873) compared with placebo. At the submitted price ($15.36 per day), the CADTH Common Drug Review (CDR) estimated that the incremental cost-utility ratio (ICUR) for rifaximin plus lactulose versus lactulose alone ranges from being

		dominant to $22,571 per quality adjusted life-year (QALY).
	HAS[10]	**Conditional Positive Recommendation August 2021** Data from the pivotal studies already evaluated (RFHE3001 double-blind study and RFHE3002 open-label study) having demonstrated the efficacy of rifaximin 550 mg versus placebo in terms of the risk of occurrence of a breakthrough overt HE episode, in combination with lactulose, at 6 months, with maintenance of efficacy after 2 years. Favorable opinion for reimbursement only in the prevention of recurrence of episodes of breakthrough overt hepatic encephalopathy (with at least two previous episodes of hepatic encephalopathy) and following elimination of triggering factors. Unfavorable opinion for reimbursement in other situations.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Rifaximin

The use of the non-absorbable antibiotic rifaximin is most recommended as a second line therapeutic agent with or without lactulose for the treatment and prevention of recurrence of hepatic encephalopathy in patients with liver cirrhosis. Dosing can be 550mg twice daily or 400mg three times day, and it should be continued for at least 3 months. Several HTA bodies such as NICE, CADTH, and HAS show a positive recommendation in the use of rifaximin for the treatment of liver cirrhosis, however the recommendation is only in the case of prevention of the recurrence of overt hepatic encephalopathy.

2.3 Diuretics

2.3.1 Spironolactone

Information on Spironolactone is detailed in the table below[27,28]:

Table 24. Drug Therapy with Spironolactone

SCIENTIFIC NAME Spironolactone	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	K74
Drug Class	Anti-hypertensive, potassium sparing diuretic
Drug Sub-class	Aldosterone receptor antagonist
ATC Code	C03DA01
Pharmacological Class (ASHP)	Aldosterone receptor antagonist
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	**Initial:** 100 mg once daily; titrate every 3 to 5 days based on response and tolerability For small-volume ascites in patients who weigh ≤50 kg, some experts recommend a starting dose of 50 mg once daily.
Maximum Daily Dose Adults*	400mg once daily
Dose (pediatrics)	2-4 mg/kg/day, increasing up to 6 mg/kg/day every 3-5 days, according to response.
Maximum Daily Dose Pediatrics*	6mg/kg/day
Adjustment	**Renal**:

	There are no specific dosage adjustments provided in the manufacturer's labeling (has not been studied); use with caution. **Hepatic:** initiate with low dose and titrate slowly (cirrhosis). Use with caution; minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Prescribing edits*	CU
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Generally used in combination with furosemide but may be used as monotherapy for patients with hypokalemia. **For combination therapy, a dosing ratio of spironolactone 100 mg to furosemide 40 mg should generally be maintained, but can be adjusted for electrolyte abnormalities**	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Gynecomastia, nausea, dizziness, abdominal upset **Most severe:** hyperkalemia
Drug Interactions*	**Category X**: • AMILoride • Bromperidol • CycloSPORINE (Systemic) • Eplerenone • Potassium Acetate • Potassium Chloride • Potassium Citrate • Potassium Gluconate • Potassium Iodate • Potassium Iodide • Potassium Phosphate • Triamterene

Special Population	**Older adults:** When used in combination with ACE inhibitors or ARBs, monitor patient for increased risk of hyperkalemia.
Pregnancy	Pregnancy category C, spironolactone crosses the placenta. Agents other than spironolactone are preferred.
Lactation	Spironolactone is considered compatible with breastfeeding. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	• Hyperkalemia. • Addison disease • Concomitant use with eplerenone • Concomitant use with heparin or low molecular weight heparin • Acute kidney insufficiency
Monitoring Requirements	BP, serum electrolytes (potassium [within 1 week of initiation or dose titration, again 2 to 4 weeks later, and regularly thereafter, especially in patients taking other medications that can cause hyperkalemia], sodium), uric acid, glucose, kidney function, volume status.
Precautions	***Concerns related to adverse effects:*** Fluid/electrolyte imbalance: Fluid and electrolyte imbalance (e.g., hypomagnesemia, hyponatremia, hypocalcemia, hyperglycemia, hyperkalemia) may occur. Patients with heart failure, kidney disease, or cirrhosis may be particularly susceptible. Monitor and correct electrolyte disturbances; adjust dose to avoid dehydration.

	Tumorigenic: Shown to be a tumorigen in chronic toxicity animal studies. Recent retrospective and observational studies do not suggest an increased risk of prostate or breast cancer. ***Disease-related concerns:*** Adrenal vein catheterization: Discontinue use prior to adrenal vein catheterization. Heart failure: When evaluating a heart failure patient for spironolactone treatment, eGFR should be >30 mL/minute/1.73 m^2 or creatinine should be ≤2.5 mg/dL (men) or ≤2 mg/dL (women) with no recent worsening and potassium <5 mEq/L with no history of severe hyperkalemia. Discontinue therapy if serum potassium cannot be maintained <5.5 mEq/L or if kidney function worsens. Consider the entire medical regimen and other potential causes of hyperkalemia.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of liver cirrhosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for spironolactone.**

Table 25. Spironolactone HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Spironolactone	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A

	PBAC	N/A

CONCLUSION STATEMENT- Spironolactone

The use of spironolactone is recommended as a first line agent for the treatment of ascites in patients with liver cirrhosis. It is either used as a monotherapy or in combination with furosemide as first line treatment. Initial dosing should be 100mg once daily, and then titrated every 3-5 days (based on response and tolerability) to a maximum dose of 400mg. Most notable side effects include hyperkalemia and gynecomastia.

2.3.2 Furosemide

Information on Furosemide is detailed in the table below[27,28]:

Table 26. Drug Therapy with Furosemide

SCIENTIFIC NAME Furosemide	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	K74
Drug Class	Antihypertensive, diuretic
Drug Sub-class	Loop diuretic
ATC Code	CO3CA01
Pharmacological Class (ASHP)	Loop diuretic
DRUG INFORMATION	
Dosage Form	Tablet, solution for injection
Route of Administration	Oral, IV
Dose (Adult) [DDD]*	**Oral:** Initial: 40 mg once daily; titrate every 3 to 5 days based on response and tolerability, once-daily dosing is preferred For small-volume ascites in patients who weigh <50 kg, some experts

	recommend a starting dose of 20 mg once daily
Maximum Daily Dose Adults*	160mg once daily
Dose (pediatrics)	No specific dose for cirrhosis ascites
Maximum Daily Dose Pediatrics*	No specific dose for cirrhosis ascites
Adjustment	**Older Adult:** Initial: 20 mg/day; increase slowly to desired response. **Renal:** eGFR <30 mL/minute/1.73 m^2: ***Continuous infusion:*** **IV:** Initial: 20 mg/hour; if diuretic response is not adequate, repeat IV bolus dose and increase continuous infusion to 40 mg/hour.
Prescribing edits*	ST
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): May be 2nd line after or combined with spironolactone	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** polyuria, headache, diarrhea **Most severe:** Acute kidney injury, ototoxicity, hypersensitivity (immediate and delayed)
Drug Interactions*	**Category X**: • Aminolevulinic Acid (Systemic) • Bromperidol • Cefaloridine [Cephaloridine] • Chloral Hydrate • Desmopressin • Ethacrynic Acid • Levosulpiride

	• Mecamylamine • Netilmicin (Ophthalmic) • Promazine • Taurursodiol
Special Population	**Pediatrics:** May lead to nephrocalcinosis or nephrolithiasis in premature infants and in infants and children <4 years of age with chronic use. May prevent closure of patent ductus arteriosus in premature infants. **Surgical patients:** If given the morning of surgery, furosemide may render the patient's volume depleted and blood pressure may be labile during general anesthesia.
Pregnancy	Human data suggests low risk. Administration of furosemide during pregnancy does not significantly alter amniotic fluid volume
Lactation	Furosemide is excreted into breast milk. No reports of adverse effects in nursing infants have been found
Contraindications	• Hypersensitivity to furosemide or any component of the formulation • Anuria • Ascites or hepatic cirrhosis
Monitoring Requirements	BP; serum electrolytes; kidney function; fluid intake and output.
Precautions	***Concerns related to adverse effects:*** Hyperuricemia: Asymptomatic hyperuricemia has been reported with use; rarely, may precipitate gout. Sulfonamide ("sulfa") allergy: The approved product labeling for many medications containing a sulfonamide chemical group includes a broad contraindication in patients with a prior allergic reaction to sulfonamides. There is a potential for cross-reactivity

	between members of a specific class (eg, two antibiotic sulfonamides). However, concerns for cross-reactivity have previously extended to all compounds containing the sulfonamide structure (SO_2NH_2). An expanded understanding of allergic mechanisms indicates cross-reactivity between antibiotic sulfonamides and nonantibiotic sulfonamides may not occur or at the very least this potential is extremely low. Mechanisms of cross-reaction due to antibody production (anaphylaxis) are unlikely to occur with nonantibiotic sulfonamides. T-cell-mediated (type IV) reactions (eg, maculopapular rash) are not well understood, and it is not possible to completely exclude this potential based on current insights. In cases where prior reactions were severe (Stevens-Johnson syndrome/toxic epidermal necrolysis), some clinicians choose to avoid exposure to these classes. Thyroid effects: Doses >80 mg may result in transient increase in free thyroid hormones, followed by an overall decrease in total thyroid hormone levels. ***Disease-related concerns:*** Cirrhosis: In cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy; correct electrolyte and acid/base imbalances prior to initiation when hepatic coma is present. Supplemental potassium or an aldosterone antagonist, when appropriate, may reduce risk of hypokalemia and metabolic alkalosis. Close monitoring warranted, especially with initiation of therapy.

	Other warnings and precautions: Diuretic resistance: For some patients, despite high doses of loop diuretic, an adequate diuretic response cannot be attained. Diuretic resistance may be overcome by IV rather than oral administration or the use of two diuretics together (eg, a loop diuretic in combination with a thiazide diuretic). When multiple diuretics are used, serum electrolytes need to be monitored even more closely
Black Box Warning	Fluid/electrolyte loss
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of liver cirrhosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Furosemide.**

Table 27. Furosemide HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Furosemide	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Furosemide

The use of furosemide is recommended as a second line agent in combination to spironolactone for the treatment of ascites in liver cirrhosis. Initial dosing should be 40mg/day and titrated every 3-5 days up to a maximum dose of 160mg (Based on response and tolerability). Most common side effects include electrolyte imbalances, orthostatic hypotension, and dehydration.

2.4 Colloids

2.4.1 Albumin

Information on Albumin is detailed in the table below[27,28]:

Table 28. Drug Therapy with Albumin

SCIENTIFIC NAME Albumin	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	K74
Drug Class	Blood product derivative, plasma volume expander
Drug Sub-class	Colloid
ATC Code	B05AA01
Pharmacological Class (ASHP)	Colloid
DRUG INFORMATION	
Dosage Form	Solution for infusion
Route of Administration	Intravenous Infusion
Dose (Adult) [DDD]*	***High concentration 20 to 25% albumin is used.*** **Cirrhotic Ascites: therapeutic large volume paracentesis (adjunctive agent):** IV: 6 to 8 g for every liter removed or 50 g total for paracentesis >5 L. Note: Administer at the time of or soon after the procedure to avoid post paracentesis complications (eg, hypovolemia, hyponatremia, kidney impairment). **Hepatorenal syndrome type 1 or acute kidney injury in cirrhosis, treatment (adjunctive agent) (off-label use):** **IV:** Initial: 1 g/kg daily for 2 days

	(maximum: 100 g/day), followed by 20 to 50 g daily until clinical outcome is achieved. (Used before or in combination with norepinephrine, terlipressin, or midodrine plus octreotide). **Spontaneous bacterial peritonitis, treatment (off-label use):** IV: Initial: 1.5 g/kg within 6 hours of diagnosis in combination with appropriate antimicrobial therapy, followed by 1 g/kg on day 3; a possible alternative dose is 1 g/kg once daily for 2 days, but it is not well studied. While the maximum albumin dose varies in clinical practice, some suggest not exceeding 100 g per dose.
Maximum Daily Dose Adults*	100 g/day
Dose (pediatrics)	**Ascites with hypoalbuminemia:** Infants, Children, and Adolescents: 25% albumin: IV: 0.5 to 1 g/kg/dose over 2 to 3 hours; may repeat up to 3 times per day until albumin is >2.5 g/dL
Maximum Daily Dose Pediatrics*	25g/dose
Adjustment	None
Prescribing edits*	CU, ST, QL
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): **Uncomplicated Ascites**: Can be combined with diuretics (spironolactone/furosemide) **Refractory Ascites:** Can be combined with large volume paracentesis to avoid paracentesis-induced circulatory dysfunction. **Hepatorenal syndrome:** Used before or in combination with norepinephrine, terlipressin, or midodrine plus octreotide**.** **Spontaneous bacterial peritonitis:** Can be combined with third generation cephalosporins or other antibiotics.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	

QL (Quantity Limit): 25 g/dose for pediatric patients.	
ST (Step Therapy): Used in refractory ascites after failure of conventional diuretics.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** nausea & vomiting, fever **Most severe:** Anaphylaxis, fluid overload, risk clotting disorders
Drug Interactions*	No severe reactions
Special Population	Sodium restricted patients: Use with caution in those patients for whom sodium restriction is necessary. Albumin 5% and 25% solutions contain 130 to 160 mEq/L sodium and are considered isotonic with plasma.
Pregnancy	Safe in pregnancy, albumin is an endogenous substance
Lactation	Safe in lactation, albumin is an endogenous substance
Contraindications	• Hypersensitivity to albumin or any component of the formulation • Severe anemia • Heart failure • Patients at risk of volume overload (e.g., patients with kidney insufficiency, severe anemia, stabilized chronic anemia, or heart failure) • Dilution with sterile water for injection (may cause hemolysis or acute kidney failure).
Monitoring Requirements	Monitor electrolytes, hemoglobin/hematocrit, and urine output regularly; monitor hemodynamic parameters, BP, heart rate, volume status, and signs and symptoms of pulmonary edema, central

	venous pressure, pulmonary artery occlusion pressure.
Precautions	***Concerns related to adverse effects:*** • Hypersensitivity: Severe allergic or anaphylactic reaction may occur. Discontinue immediately and manage appropriately if allergic or anaphylactic reactions are suspected. • Coagulation abnormality: Large replacement volumes may result in coagulation abnormality. Monitor and replete with blood constituents if indicated. • Electrolyte imbalance: Large replacement volumes may result in electrolyte imbalance. Monitor electrolytes and replace or maintain as indicated. • Hemodynamic effects: Cardiac or respiratory failure, kidney failure, or increasing intracranial pressure can occur; closely monitor hemodynamic parameters in all patients. • Hypervolemia/hemodilution: Use with caution in conditions where hypervolemia and its consequences or hemodilution may increase the risk of adverse effects (eg, heart failure, pulmonary edema, hypertension, hemorrhagic diathesis, cirrhosis, esophageal varices). Adjust rate of administration per hemodynamic status and solution concentration; monitor closely with rapid infusions. Avoid rapid infusions in patients with a history of cardiovascular disease (may cause volume overload and pulmonary edema). Discontinue at the first signs of cardiovascular overload (eg, headache, dyspnea, jugular venous distention, rales, abnormal elevations in systemic or

	central venous BP). All patients should be observed for signs of hypervolemia, such as pulmonary edema. Monitor BP. ***Disease-related concerns:*** • Critical illness: Avoid use for resuscitation in patients with traumatic brain injury due to increased mortality when used in this population. • Hepatic impairment: Use with caution in patients with hepatic impairment; protein load may exacerbate or precipitate encephalopathy. • Kidney impairment: Use with caution in patients with kidney impairment; protein load may precipitate azotemia. Patients with chronic kidney insufficiency receiving albumin solution may be at risk for accumulation of aluminum and potential toxicities (eg, hypercalcemia, vitamin D refractory osteodystrophy, anemia, severe progressive encephalopathy).
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of liver cirrhosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Albumin.**

Table 29. Albumin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Albumin	NICE	Not available
	CADTH	Not available
	HAS	Not available
	IQWIG	Not available

	PBAC	Not available

CONCLUSION STATEMENT- Albumin

Albumin, or human serum albumin, is one of the most important medications in liver cirrhosis as it's used in all the different complications such as ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatorenal syndrome. The dose and infusion rate depends on the type of complication. It is mostly used at a high concentration of 20-25%.

2.5 Vasopressin Antagonist

2.5.1 Tolvaptan

Information on Tolvaptan is detailed in the table below[27,28]:

Table 30. Drug Therapy with Tolvaptan

SCIENTIFIC NAME Tolvaptan	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	K74
Drug Class	Vasopressin antagonist
Drug Sub-class	Vasopressin V2 receptor antagonist
ATC Code	C03XA01
Pharmacological Class (ASHP)	Vasopressin V2 receptor antagonist
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	**Grade 2/3 Ascites accompanied by hyponatremia:** Initial: 15 mg once daily while the patient is still hospitalized; titrate as needed after initial 24 hours to 30 mg once daily, then after subsequent 24 hours may titrate as needed to a

	maximum of 60 mg once daily. Do not use for more than 30 days due to the risk of hepatotoxicity.
Maximum Daily Dose Adults*	60mg once daily
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal**: CrCl <10 mL/minute: Use not recommended **Hepatic:** Use is contraindicated in patients with significant hepatic impairment or disease (or a history of). Monitor closely for hepatoxicity developing during use. **Hypervolemic or euvolemic hyponatremia:** Avoid use in patients with underlying liver disease, including cirrhosis; monitor closely for hepatotoxicity developing during use; discontinue use if signs/symptoms of hepatotoxicity develop (do not use for more than 30 days due to this potential risk).
Prescribing edits*	MD, PA, ST
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): This medication is to be prescribed by nephrologists, urologists, or cardiologists.	
PA (Prior Authorization): Tolvaptan was approved in March 2014 by the PMDA in Japan for the treatment of ascites in patients with hepatic cirrhosis who have not been adequately responsive to diuretics such as spironolactone and furosemide. In cases of diuretic resistant ascites, tolvaptan (3.75–7.5 mg/day) is additionally administered after hospitalization. It should not be used for more than 30 days.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Second line after failure of spironolactone & furosemide therapy for grade 2/3 ascites.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	

Main Adverse Drug Reactions (most common and most serious)	**Most common:** Polydipsia, diarrhea, polyuria. **Most severe:** dehydration, liver injury, hypernatremia.
Drug Interactions*	**Category X**: • Adagrasib • Apalutamide • Atazanavir • CarBAMazepine • Ceritinib • Clarithromycin • Cobicistat • Darunavir • Desmopressin • Encorafenib • Enzalutamide • Fexinidazole • Fosphenytoin • Fusidic Acid (Systemic) • Grapefruit Juice • Idelalisib • Indinavir • Itraconazole • Ketoconazole (Systemic) • Levoketoconazole • Lonafarnib • Lopinavir • Lumacaftor and Ivacaftor • MiFEPRIStone • Mitotane • Nefazodone • Nelfinavir • Nirmatrelvir and Ritonavir • Ombitasvir, Paritaprevir, and Ritonavir • Ombitasvir, Paritaprevir, Ritonavir, and Dasabuvir • PAZOPanib

	• PHENobarbital • Phenytoin • Posaconazole • Primidone • RifAMPin • Ritonavir • Saquinavir • Sodium Chloride (Depends on Dose) • Topotecan (Depends on Route) • Tucatinib • Voriconazole
Special Population	N/A
Pregnancy	No reports describing the use of tolvaptan in human pregnancy have been located. The animal reproduction data suggests low risk because all of the toxic effects occurred in the presence of maternal toxicity and at doses that were >10 times the human dose. Although human pregnancy experience is needed for a better risk assessment, there does not appear to be a reason to withhold the drug in pregnancy if indicated.
Lactation	It is not known if tolvaptan is present in breast milk. Due to the potential for adverse events in a breastfed infant, breastfeeding is not recommended by the manufacturer.
Contraindications	• Hypersensitivity (e.g., anaphylactic shock, generalized rash) to tolvaptan or any component of the formulation • Concurrent use with strong CYP3A inhibitors (e.g., clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin)

	• Use in patients unable to sense or respond to thirst. • Anuria Additional contraindications may be present in brand specific drug.
Monitoring Requirements	Serum sodium concentration, rate of serum sodium increase, serum potassium concentration (if >5 mEq/L prior to administration or receiving medications known to elevate serum potassium); volume status; and/or signs of drug-induced hepatotoxicity (eg, anorexia, fatigue, right upper abdominal discomfort, jaundice, dark urine, itching); neurologic status (at initiation and after titration).
Precautions	***Concerns related to adverse effects:*** CNS effects: Dizziness, asthenia, and/or syncope have been reported when used for autosomal dominant polycystic kidney disease (ADPKD); advise patients to use caution when performing dangerous tasks (eg, driving, operating machinery). Hepatotoxicity: Tolvaptan may increase the risk of serious hepatotoxicity, including fatal hepatotoxicity. ***Disease-related concerns:*** Hyperkalemia: Reductions in extracellular fluid volumes may cause hyperkalemia. Patients using concomitant medications that may increase potassium levels or with a pretreatment serum potassium >5 mEq/L should be monitored after initiation of therapy. Urinary obstruction: Avoid use in patients with uncorrected urinary outflow obstruction (eg, partial obstruction including patients with prostatic hypertrophy or impairment of

	micturition); may have increased risk for developing acute retention.
Black Box Warning	• Treatment initation and monitoring (Samsca®): Used only in hospital setting where serum sodium can be closely monitored.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of liver cirrhosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Tolvaptan.**

Table 31. Tolvaptan HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Tolvaptan	NICE	Not available
	CADTH	Not available
	HAS	Not available
	IQWIG	Not available
	PBAC	Not available

CONCLUSION STATEMENT- Tolvaptan

Tolvaptan is a Vasopressin V2 receptor antagonist that can be used as a second line therapy to treat grade 2/3 ascites accompanied by hyponatremia refractory to diuretic treatment. It is initiated at a dose of 7.5-15 mg once daily in hospitalized patients due to the need for monitoring of serum sodium. Warning and precautions of this drug are dependent on the brand formulation.

2.6 Vasopressin Agonist

2.6.1 Terlipressin

Information on Terlipressin is detailed in the table below[27,28]:

Table 32. Drug Therapy with Terlipressin

SCIENTIFIC NAME Terlipressin	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	K74
Drug Class	Vasopressin
Drug Sub-class	Antidiuretic hormone, posterior pituitary hormone
ATC Code	H01BA04
Pharmacological Class (ASHP)	V1 receptor agonist
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	**Note: Dosages expressed as terlipressin diacetate. Terlipressin diacetate 1 mg is equivalent to terlipressin (free base) 0.85 mg.** **Esophageal varices bleeding:** *Initial*: IV: 2 mg every 4 hours until bleeding has been controlled for at least 24 hours or up to 48 hours. Frequency can be reduced to 6 hours to alleviate pain due to peripheral vasoconstriction. *Maintenance*: **IV:** 1 mg every 4 to 6 hours for a total treatment duration of 2 to 5 days **Hepatorenal Syndrome – Type 1 or acute kidney injury**:

	Used in combination with albumin. *Initial (days 1 and 2)*: **IV:** 1 mg every 4 to 6 hours (bolus dosing) **or** 2 mg/**24 hours** as a continuous infusion *Duration of therapy:* Continue treatment until complete response (serum creatinine <1.5 mg/dL [133 micromole/L] based on traditional criteria, **or** serum creatinine within 0.3 mg/dL [26.5 micromole/L] of baseline value based on revised/dynamic criteria) **or** for a maximum of 14 days. Discontinue therapy if no reduction in serum creatinine which prompted initiation of therapy after 14 days, **or** if patient undergoes dialysis or liver transplant
Maximum Daily Dose Adults*	**Esophageal varices bleeding:** Day 1: 2mg every 4 hours Day 2-5: 1mg every 4 hours **Hepatorenal Syndrome – Type 1 or acute kidney injury**: 2mg every 4 hours (bolus dosing), or 12mg/24hours as continuous infusion
Dose (pediatrics)	15-20mcg/kg every 4 hours
Maximum Daily Dose Pediatrics*	20mcg/kg every 4 hours
Adjustment	**Hepatorenal Syndrome:** Dosage adjustment: If a reduction in baseline serum creatinine of at least 25% is not achieved after at least 2 days, may gradually increase to a maximum dose of 2 mg every 4 to 6 hours (bolus dosing) **or** 12 mg/**24 hours** as a continuous infusion. **Fluid Overload:** In conjunction with reducing or discontinuing the administration of albumin and/or other fluids and judicious use of diuretics, temporarily interrupt, reduce, or

	discontinue terlipressin until patient volume status improves. **Ischemic signs or symptoms:** Discontinue terlipressin in patients with signs of ischemia (e.g., angina, ECG changes, abdominal pain, peripheral cyanosis, or extremity pain). **Respiratory effects:** Discontinue terlipressin in patients who develop hypoxia or increase in respiratory symptoms.
Prescribing edits*	CU, MD, PA, ST, PE
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Terlipressin is usually combined with albumin for the management of hepatorenal syndrome type 1.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): This medication is to be prescribed by hepatologists, gastroenterologists, nephrologists, and critical care specialists.	
PA (Prior Authorization): Terlipressin in combination with albumin is the first line treatment for hepatorenal syndrome. It was approved by the FDA recently on September 14, 2022, for the treatment of adults hospitalized with hepatorenal syndrome with rapid reduction in kidney function (HRS-1). The initial dose is 1mg IV every 4 -6 hours (bolus) or 2mg/24hours as continuous IV infusion. Duration may continue until complete response (serum creatinine <1.5mg/dL) or for a maximum of 14 days.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Can be a step therapy in treating grades 2/3 ascites that have failed prior conventional diuretic therapy.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): **Esophageal Varices Bleeding:** Day 1: 2mg IV every 4 hours until bleeding has been controlled for at least 24hours or up to 48 hours. Day 2-5: 1mg IV every 4-6 hours.	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Vomiting, abdominal pain, diarrhea

	Most severe: Hyponatremia, ischemic events (acute MI, peripheral ischemia, mesenteric ischemia), respiratory failure
Drug Interactions*	**Category X**: • Fexinidazole **Category D:** • Ceritinib • Fingolimod • Ponesimod • Siponimod
Special Population	Older adult: Use caution in elderly patients (limited data).
Pregnancy	Terlipressin may cause uterine contractions and increased intrauterine pressure in early pregnancy and may decrease uterine blood flow. If treatment for esophageal varices is required during pregnancy, initial treatment with other therapies is preferred. **Use during pregnancy is specifically contraindicated in some product labeling.**
Lactation	It is not known if terlipressin is present in breast milk. Breastfeeding is not recommended by the manufacturer.
Contraindications	• Hypersensitivity to terlipressin or any component of the formulation • Additional contraindications (may vary per region; consult product labeling): Pregnancy; septic shock with low cardiac output
Monitoring Requirements	Blood pressure, heart rate, ECG (in select patients); fluid balance; electrolytes, serum creatinine.
Precautions	***Concerns related to adverse effects:***

	• Bradycardia: Due to the increase in systemic vascular resistance after administration, a reflexive reduction in heart rate may occur. Monitor heart rate after administration. • Cardiac arrhythmias: QT prolongation and ventricular arrhythmias (including torsade de pointes) have been reported (rarely) with terlipressin. Use caution in patients with cardiac arrhythmias, prolonged QT interval, uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, or concurrent use of medications that can prolong the QT interval. • Hemodynamic effects: Due to the increase in systemic vascular resistance after administration, a reduction in cardiac output may occur. Use it with extreme caution in patients with heart failure. • Ischemic events: Ischemic events, including cardiac, gastrointestinal, and skin (unrelated to injection site) have been reported (rarely). Signs of ischemia (angina, ECG changes, abdominal pain, peripheral cyanosis, or extremity pain) may require temporary interruption, dosage reduction, or discontinuation of therapy. Cutaneous ischemia and necrosis may be more common in patients with peripheral venous hypertension or morbid obesity. Injections must only be given intravenously to avoid localized skin necrosis. ***Disease-related concerns:*** • Cardiovascular disease: Use with caution in patients with cerebral or peripheral vascular disease, coronary

	artery disease, previous myocardial infarction, or unstable angina. • Hypertension: Use with caution in patients with uncontrolled hypertension. • Hypovolemia: Use with caution in hypovolemic patients; may react with increased vasoconstriction or atypical cardiac reactions. • Renal impairment: Use with caution in patients with chronic renal impairment. • Respiratory disorders: Bronchospasm has been rarely reported. Use caution in patients with asthma and COPD. • Septic shock: Currently, the use of terlipressin is not recommended for use in patients with septic shock. If used as vasopressor monotherapy in septic shock, terlipressin may significantly reduce cardiac index and heart rate. Avoid use in septic shock patients with low cardiac index. Some manufacturers contraindicate use with septic shock and a low cardiac output.
Black Box Warning	**Serious or fatal respiratory failure:** Do not initiate terlipressin in patients experiencing hypoxia (eg, SpO2 <90%) until oxygenation levels improve.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of liver cirrhosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Terlipressin.**

Table 33. Terlipressin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Terlipressin	NICE[11]	**Conditional Positive Recommendation June 2012** Offer terlipressin to patients with suspected variceal bleeding at presentation. Stop treatment after definitive haemostasias has been achieved, or after 5 days, unless there is another indication for its use. At the time of publication (June 2012), terlipressin was indicated for the treatment of bleeding from esophageal varices, with a maximum duration of treatment of 72 hours (3 days). Prescribers should consult the relevant summary of product characteristics. Informed consent for off-label use of terlipressin should be obtained and documented.
	CADTH	Not available
	HAS	Not available
	IQWIG	Not available
	PBAC	Not available

CONCLUSION STATEMENT- Terlipressin

Terlipressin is a vasopressin V1 receptor agonist that can be used for multiple complications of liver cirrhosis such as the management of esophageal varices bleeding and hepatorenal syndrome type 1. Its use in EV bleeding should be for a total duration of 5 days and is combined with non-pharmacological management such as endoscopic treatment. It has also been recently approved by the FDA in September 2022 as the first line agent combined with albumin for the management of hepatorenal syndrome type 1. Terlipressin is also recommended by the HTA body NICE in the treatment of esophageal varices bleeding. Its use is limited by side effects such as hyponatremia, ischemic events, and respiratory failure.

2.7 Sympathomimetic Agent

2.7.1 Norepinephrine

Information on Norepinephrine is detailed in the table below[27,28]:

Table 34. Drug Therapy with Norepinephrine

SCIENTIFIC NAME Norepinephrine	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	K74
Drug Class	Sympathomimetic agent
Drug Sub-class	Non-selective Alpha/beta-1 agonist
ATC Code	C01CA03
Pharmacological Class (ASHP)	Non-selective Alpha/beta-1 agonist
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous infusion
Dose (Adult) [DDD]*	**Hepatorenal syndrome type 1 or AKI treatment:** **Non–weight-based dosing: IV:** Initial: 5 to 8 mcg/minute; dose may be increased every 4 hours based on clinical end points (e.g., increase mean arterial pressure of ~10 mm Hg from baseline, improved urine output); maximum dose: 10 mcg/minute non-ICU; 50 mcg/minute in ICU
Maximum Daily Dose Adults*	10mcg/minute non-ICU 50mcg/minute in ICU
Dose (pediatrics)	0.5-1mcg/kg/min
Maximum Daily Dose Pediatrics*	1mcg/kg/min
Adjustment	**Obesity (Adults) (BMI ≥30kg/m^2):** Use ideal body weight for dosing if institution uses weight-based dosing.
Prescribing edits*	CU, MD, QL
AGE (Age Edit): N/A	

CU (Concurrent Use Edit): Should be combined with albumin for the treatment of HRS-1.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): This medication is to be prescribed by intensive care specialists, anesthesiologists, emergency medicine physicians.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): For adults: 10mcg/minute non-ICU and 50mcg/minute in ICU; For pediatrics: 1mcg/kg/min	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** headache, nausea/vomiting **Most severe:** Cardiac arrhythmia, dyspnea, bradycardia
Drug Interactions*	**Category X**: • Dihydroergotamine • Ergonovine • Ergotamine • Kratom • Lisuride • Methylergonovine • Methysergide
Special Population	N/A
Pregnancy	Norepinephrine is an endogenous catecholamine and crosses the placenta. No identification of an increased risk of miscarriage or adverse maternal or fetal outcomes.
Lactation	It is not known if norepinephrine is present in breast milk. The manufacturer recommends that caution be exercised when administering norepinephrine to breastfeeding women.
Contraindications	• Hypotension from hypovolemia except as an emergency measure to maintain coronary and

	cerebral perfusion until volume could be replaced. • Mesenteric or peripheral vascular thrombosis unless it is a lifesaving procedure; during anesthesia with cyclopropane or halothane anesthesia.
Monitoring Requirements	Blood pressure (or mean arterial pressure), heart rate; cardiac output (as appropriate), intravascular volume status, pulmonary capillary wedge pressure (as appropriate); urine output, peripheral perfusion; monitor infusion site closely. Consult individual institutional policies and procedures.
Precautions	***Concerns related to adverse effects:*** Extravasation: Vesicant; ensure proper needle or catheter placement prior to and during infusion. Avoid extravasation; infuse into a large vein if possible. Avoid infusion into leg veins. Monitor IV site closely. If extravasation occurs, infiltrate the area with diluted phentolamine (5 to 10 mg in 10 mL saline in adult patients) with a fine hypodermic needle. Phentolamine should be administered as soon as possible after extravasation is noted to prevent sloughing/necrosis. ***Disease-related concerns:*** **Hypovolemia:** Address hypovolemia before initiating therapy; patients who are hypotensive from hypovolemia may experience severe peripheral and visceral vasoconstriction, decreased renal perfusion and reduced urine output, tissue hypoxia, lactic acidosis, and reduced systemic blood flow despite normal BP.

	Hypoxia/hypercarbia: Use in patients with profound hypoxia or hypercarbia may produce ventricular tachycardia or fibrillation; use with extreme caution. ***Other warnings/precautions:*** Abrupt discontinuation: Gradually reduce infusion rate while expanding blood volume with IV fluids during discontinuation of therapy; severe hypotension may occur with abrupt discontinuation. Appropriate use: Assure adequate circulatory volume to minimize need for vasoconstrictors. Avoid hypertension; monitor BP closely and adjust infusion rate. Avoid in patients with mesenteric or peripheral vascular thrombosis; use may increase ischemia and extend the area of infarction.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of liver cirrhosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Norepinephrine.**

Table 35. Norepinephrine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Norepinephrine	NICE	Not available
	CADTH	Not available
	HAS	Not available
	IQWIG	Not available
	PBAC	Not available

CONCLUSION STATEMENT- Norepinephrine

Norepinephrine has a specific use in liver cirrhosis. It is an alternative agent to terlipressin + albumin in the treatment of hepatorenal syndrome type 1 induced by liver cirrhosis. Dosing should be non-weight-based and as continuous infusion of 5 to 8mcg/minute and increase every 4 hours based on clinical end points. Max dose is 10mcg/minute and 50mcg/minute for Non-ICU and ICU respectively.

2.8 Octapeptides

2.8.1 Octreotide

The following table describes the characteristics of Octreotide[29,30]:

Table 36. Drug Therapy with Octreotide

SCIENTIFIC NAME Octreotide	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	K74
Drug Class	Somatostatin Analogue
Drug Sub-class	Octapeptide
ATC Code	H01CB02
Pharmacological Class (ASHP)	Synthetic Somatostatin Analogue
DRUG INFORMATION	
Dosage Form	Solution/Suspension for Injection, Powder, and Solvent for Prolonged-Release Suspension for Injection
Route of Administration	Intramuscular Use, Subcutaneous Use, and Intravenous Use
Dose (Adult) [DDD]*	**Gastroesophageal Variceal Hemorrhage, Acute:** IV: Initial: 50 mcg bolus, followed by continuous infusion of 50 mcg/hour for

	2 to 5 days; may repeat bolus in first hour if hemorrhage is not controlled. **For Hepatorenal Syndrome Type 1:** Used in combination with midodrine and albumin in patients who cannot receive norepinephrine or terlipressin. SUBQ: Initial: 100 mcg 3 times daily; may increase to 200 mcg 3 times daily until midodrine is discontinued (goal to increase mean arterial pressure by ~10 to 15 mm Hg from baseline). IV: 50 mcg/hour as a continuous infusion until midodrine is discontinued. Note: Some experts prefer continuous infusion over SUBQ injection.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Esophageal varices; gastrointestinal bleed: Limited data available: Infants, Children, and Adolescents: IV: Initial: 1 to 2 mcg/kg bolus followed by 1 to 2 mcg/kg/hour continuous IV infusion; titrate infusion rate to response; taper dose by 50% every 12 hours when no active bleeding occurs for 24 hours; may discontinue when dose is 25% of initial dose.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered kidney function:** Hemodialysis, intermittent (thrice weekly): SUBQ, IV: There are no specific dosage adjustments recommended by the manufacturer; however, clearance is reduced by ~50%. Consider initiation at the low end of the normal range; titrate based on tolerability and response. IM (depot): Initial: 10 mg intragluteally every 4 weeks; may titrate based on tolerability and response. Peritoneal dialysis:

	SUBQ, IV: No dosage adjustment provided by manufacturer; clearance is reduced by ~50%. Consider initiation at the low end of the normal range and titrate based on efficacy and tolerability. IM (depot): Initial: 10 mg intragluteally every 4 weeks; titrate based on tolerability and response. Prolonged intermittent renal replacement therapy (PIRRT) (eg, sustained, low-efficiency diafiltration): IV, SUBQ: There are no data available on removal by PIRRT (has not been studied); however, some removal is expected based on physicochemical characteristics. Consider initiation at the low end of the normal range; titrate based on tolerability and response. IM: There are no data available on removal by PIRRT (has not been studied); consider reducing initial dose to 10 mg every 4 weeks; titrate based on tolerability and response. **Dosing: Hepatic Impairment: Adult** Injection solution: There are no dosage adjustments provided in the manufacturer's labeling. Long-Acting Release (LAR) depot suspension: Patients with established cirrhosis of the liver: IM: Initial: 10 mg IM every 4 weeks; titrate based upon response.
Prescribing edits*	MD, PE
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	This medication is to be prescribed by a physician who has experience in the management of Variceal Bleeding.
PA (Prior Authorization)	N/A

QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	In patients with cirrhosis and active variceal bleeding, administer prophylactic antibiotics for up to 7 days.
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Sinus bradycardia, hypertension, diaphoresis, abdominal distress/pain and pain at the injection site. **Most serious**: Cholelithiasis, glucose dysregulation and necrotizing enterocolitis.
Drug Interactions*	**Category X:** Fexinidazole Macimorelin
Special Population	Older adults: Dosage adjustment may be necessary; significant increases in elimination half-life have been observed in older adults. Pediatrics: Postmarketing cases of serious and fatal events, including hypoxia and necrotizing enterocolitis, have been reported with octreotide use in children (usually with serious underlying conditions), particularly in children <2 years of age. In studies with octreotide LAR depot suspension, the incidence of cholelithiasis in children is higher than the reported incidences for adults and efficacy was not demonstrated.
Pregnancy	Octreotide crosses the placenta and can be detected in the newborn at delivery.
Lactation	Octreotide is present in breast milk. Information related to octreotide use in breastfeeding women is limited. According to the manufacturer, the decision to breastfeed during therapy

	should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Hypersensitivity to octreotide or any component of the formulation.
Monitoring Requirements	Thyroid function (baseline and periodic); vitamin B12 level; blood glucose, glycemic control, and antidiabetic regimen (patients with diabetes mellitus) should be assessed following initiation, then periodically or following dosage adjustments; cardiac function (heart rate, ECG); zinc level (patients with excessive GI fluid loss maintained on TPN); biliary tract abnormality monitoring if clinically indicated; routine gallbladder ultrasound is not considered necessary.
Precautions	Abnormal Schillings test: Chronic treatment has been associated with abnormal Schillings test; monitor vitamin B12 levels. Cardiovascular events: Complete atrioventricular block has been reported in patients receiving IV therapy during surgical procedures; most causes occurred with continuous IV infusion at higher than recommended doses. Safety of continuous IV infusion has not been established in patients receiving octreotide for approved indications. Hypothyroidism: Suppresses secretion of TSH; monitor for hypothyroidism. Cardiovascular disease: Use with caution in patients with heart failure or concomitant medications that alter heart rate or rhythm; bradycardia, conduction abnormalities, and arrhythmia have been observed in acromegalic and carcinoid syndrome

	patients. Cardiovascular medication requirements may change. Excessive GI fluid loss: In patients with conditions associated with excessive GI fluid loss receiving TPN, concomitant use of octreotide may reverse fluid losses and cause increases in serum zinc; monitor zinc levels. Hepatic impairment: Use caution in patients with hepatic impairment; dosage adjustment may be required in patients with established cirrhosis. Renal impairment: Use with caution in patients with renal impairment; dosage adjustment may be required in patients receiving dialysis. QTc-prolonging agents: Octreotide may enhance the adverse/toxic effects of other QTc-prolonging agents. LAR depot suspension: Mild to moderate injection-site pain (usually lasting 1 hour) may occur with the LAR depot suspension. Do not use LAR depot suspension formulation for the treatment of sulfonylurea-induced hypoglycemia. Vehicle used in LAR depot suspension (polylactide-co-glycolide microspheres): Has rarely been associated with retinal artery occlusion in patients with abnormal arteriovenous anastomosis (eg, patent foramen ovale).
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Liver Cirrhosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency

in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Octreotide.**

Table 37. Octreotide HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Octreotide	NICE	Not available
	CADTH	Not applicable
	HAS[12]	Positive Recommendation - 23 August 2016 Octreotide is important in emergency treatment, and prevention of recurrence of hemorrhage from gastroesophageal varices in cirrhotic patients. Sandostatin should be used in combination with specific therapy such as endoscopic sclerotherapy.
	IQWIG	Not available
	PBAC	Not applicable

CONCLUSION STATEMENT- Octreotide

Acute bleeding episode management involves resuscitation, blood volume restoration, vasoactive therapy as octreotide, and endoscopic therapy in stable patients. Octreotide may also be considered as an alternative in the management of Hepatorenal Syndrome Type 1. For Variceal Bleeding, it is given as 50 mcg bolus, followed by continuous infusion of 50 mcg/hour for 2 to 5 days. As for Hepatorenal Syndrome, it is given either intravenously as 50 mcg/hour as a continuous infusion until midodrine is discontinued or subcutaneously as 100 mcg 3 times daily; may increase to 200 mcg 3 times daily until midodrine is discontinued. Its use is backed by HTA bodies as HAS. Its use is limited by the heightened risk of developing cholelithiasis, glucose dysregulation and necrotizing enterocolitis.

2.9 Other Drugs

This section includes drugs that are FDA and/or EMA approved for the management of liver cirrhosis and its complications but are not registered by the SFDA.

2.9.1 Cholestyramine

The initial recommended treatment for pruritus is cholestyramine at a daily dose of 4 grams, with an option for titration up to 16 grams per day. Adverse effects include edema, syncope, abdominal pain, anorexia, arthralgia, and headache. Caution is recommended in patients with renal impairment[13]. As per Hegade et al, four

controlled trials and a meta-analysis have confirmed that cholestyramine significantly improves cholestatic pruritus[31].

2.9.2 Naltrexone

Naltrexone is an alternative agent used in the management of cholestatic pruritis, given as 50 mg daily[13]. Adverse effects of Naltrexone include nausea, asthenia, hepatotoxicity, and injection site reactions[29].

Section 3.0 Key Recommendations Synthesis

Diagnosis

- Liver biopsy remains the reference standard for assessing liver fibrosis; however, use of noninvasive methods has become increasingly common in clinical practice. (No grade)

Management

Ascites

- Patients experiencing clinically evident (moderate to severe) ascites should undergo treatment involving restricted salt intake and the administration of spironolactone, with or without the combination of loop diuretics. (Evidence Rating B)
- For combination therapy, a dosing ratio of spironolactone 100 mg to furosemide 40 mg should generally be maintained but can be adjusted for electrolyte abnormalities. (No grade)
- Tolvaptan, a V2 receptor antagonist, effectively manages cirrhotic ascites, particularly in the presence of hyponatremia. Initiate at 15 mg/day, adjusting based on sodium levels to prevent rapid increases, with a minimum of 3.75 mg/day and a maximum of 60 mg/day (A, 1).
- For cirrhotic ascites patients who show resistance to standard diuretics, it is recommended to commence tolvaptan early, while preserving renal function, instead of increasing the dose of spironolactone with or without loop diuretics like furosemide. (Strong, 100% agreed, evidence level B)
- Terlipressin, a vasoconstrictor, is a suitable option for treating refractory cirrhotic ascites. (B,1)
- Administering human serum albumin (HSA) infusions at a dose of 20–40 g/day may improve the prognosis for individuals with cirrhotic ascites, especially those dealing with refractory ascites and spontaneous bacterial peritonitis (SBP) (A, 1).
- Performing large-volume paracentesis along with administering human serum albumin is an effective approach for managing refractory ascites (B, 1).

Varices

- Patients with cirrhosis displaying medium, large, or high-risk varices (distinguished by red wale markings) should undergo treatment with nonselective beta blockers and/or endoscopic band ligation to **prevent** the **primary occurrence** of variceal bleeds. (Evidence Rating B)

- For people who have cirrhosis and confirmed, or suspected, clinically significant portal hypertension, carvedilol is used at the first-choice agent for the primary prevention of decompensation, followed by propranolol (if carvedilol is contraindicated) (No grade).
- Patients experiencing acute esophageal variceal bleeding should undergo endoscopic treatment (A1).
- If there is suspicion of esophageal variceal bleeding, vasoactive agents (terlipressin) should be promptly initiated upon admission (A1).
- In cases of gastric variceal bleeding, standard management includes applying prophylactic antibiotics, employing conservative transfusion strategies, and using vasoactive agents (terlipressin). **These procedures align with protocols for managing esophageal variceal bleeding** (B1).
- The recommended approach for preventing esophageal variceal **rebleeding** involves the combined application of endoscopic variceal ligation (EVL) and non-selective beta-blockers (NSBBs) as the primary intervention (A1). If the implementation of this combined treatment proves difficult, it is advised to opt for either NSBBs or EVL alone (A1).

Hepatic Encephalopathy

- For the management of acute episodic overt HE, it is recommended to use non-absorbable disaccharides like lactulose or lactitol. In instances of severe HE (West Haven criteria grade ≥3) or when oral intake is impractical, enema administration is advised (A1).
- Rifaximin may be combined with non-absorbable disaccharides in the treatment of patients with HE (B1).
- To prevent the recurrence of overt hepatic encephalopathy (HE), it is recommended to use a nonabsorbable disaccharide (like lactulose or lactitol) or rifaximin, either as a single treatment or in combination (A1).
- Giving lactulose (B1) or rifaximin (B2) is a valid strategy for improving cognitive function and quality of life in individuals with **covert** hepatic encephalopathy (CHE).

Hepatorenal Syndrome

- The prognosis for hepatorenal syndrome (HRS) is unfavorable; therefore, it is crucial to commence treatment promptly upon confirming the diagnosis to prevent additional deterioration of kidney function (No grade).
- Terlipressin, in combination with human serum albumin (HSA), can be used to treat both type 1 and type 2 hepatorenal syndrome (HRS) (A, 1).

Palliative Care

- For individuals with Decompensated Cirrhosis (DC), adhering to the fundamental principles of palliative care involves systematically evaluating a wide range of symptoms. The focus should be on addressing and managing those symptoms that are considered most significant to the patients.

Liver Transplant

- Individuals with cirrhosis having a Model for End-Stage Liver Disease (MELD) score of 15 or higher, or experiencing complications like ascites, hepatic encephalopathy, or variceal hemorrhage, should be directed to a transplant center. (No grade)
- Liver transplantation (LT) is considered the definitive and crucial treatment for individuals with decompensated cirrhosis (DC). It should be considered when the severity of liver disease threatens reduced survival or compromised quality of life. (No grade)

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of Liver Cirrhosis.

These recommendations should be used to support and not supplant decisions in individual patient management.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

II. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose. If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

III. What information is available in the notes?

“Notes” section provides details of the prescribing edits, extra important drug information and special warning and precautions.

IV. Drug interactions

- A: No known interaction
- B: No action needed
- C: Monitor therapy
- D: Consider therapy modification
- X: Avoid combination

V. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

VI. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B. MeSH Terms PubMed

The following is the result of the PubMed search conducted for guideline search:

Query	Filters	Search Details	Results
(((((Liver Cirrhosis[MeSH Terms]) OR (Hepatic Cirrhosis[Title/Abstract])) OR (Cirrhosis, Hepatic[Title/Abstract])) OR (Cirrhosis, Liver[Title/Abstract])) OR (Fibrosis, Liver[Title/Abstract])) OR (Liver Fibrosis[Title/Abstract])	Guideline, in the last 5 years	("liver cirrhosis"[MeSH Terms] OR "hepatic cirrhosis"[Title/Abstract] OR "cirrhosis hepatic"[Title/Abstract] OR "cirrhosis liver"[Title/Abstract] OR "fibrosis liver"[Title/Abstract] OR "liver fibrosis"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	60

Appendix C. Treatment Algorithms

The following algorithm for the management of hepatic encephalopathy is adapted from the Chinese Guidelines on the Management of Ascites and its Related Complications in Cirrhosis [2019][6]:

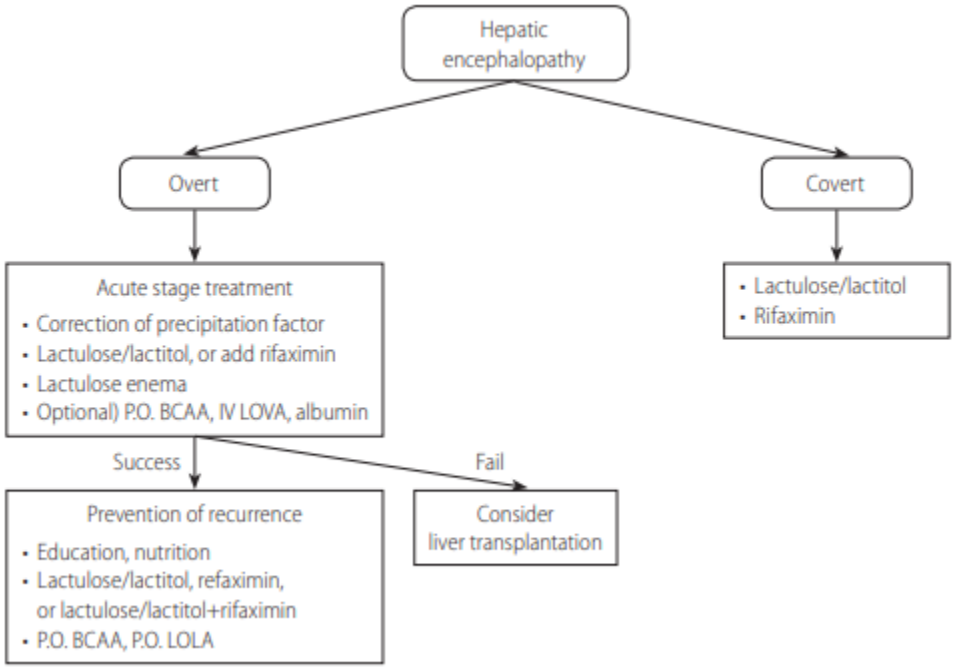

Figure 17. *The treatment and prevention of hepatic encephalopathy. P.O., per oral; BCAA, branched-chain amino acid; IV LOLA, intravenous L-ornithine-L-aspartate.*

The following algorithm for the management of ascites is adapted from Evidence-Based Clinical Practice Guidelines for Liver Cirrhosis [2020][5]:

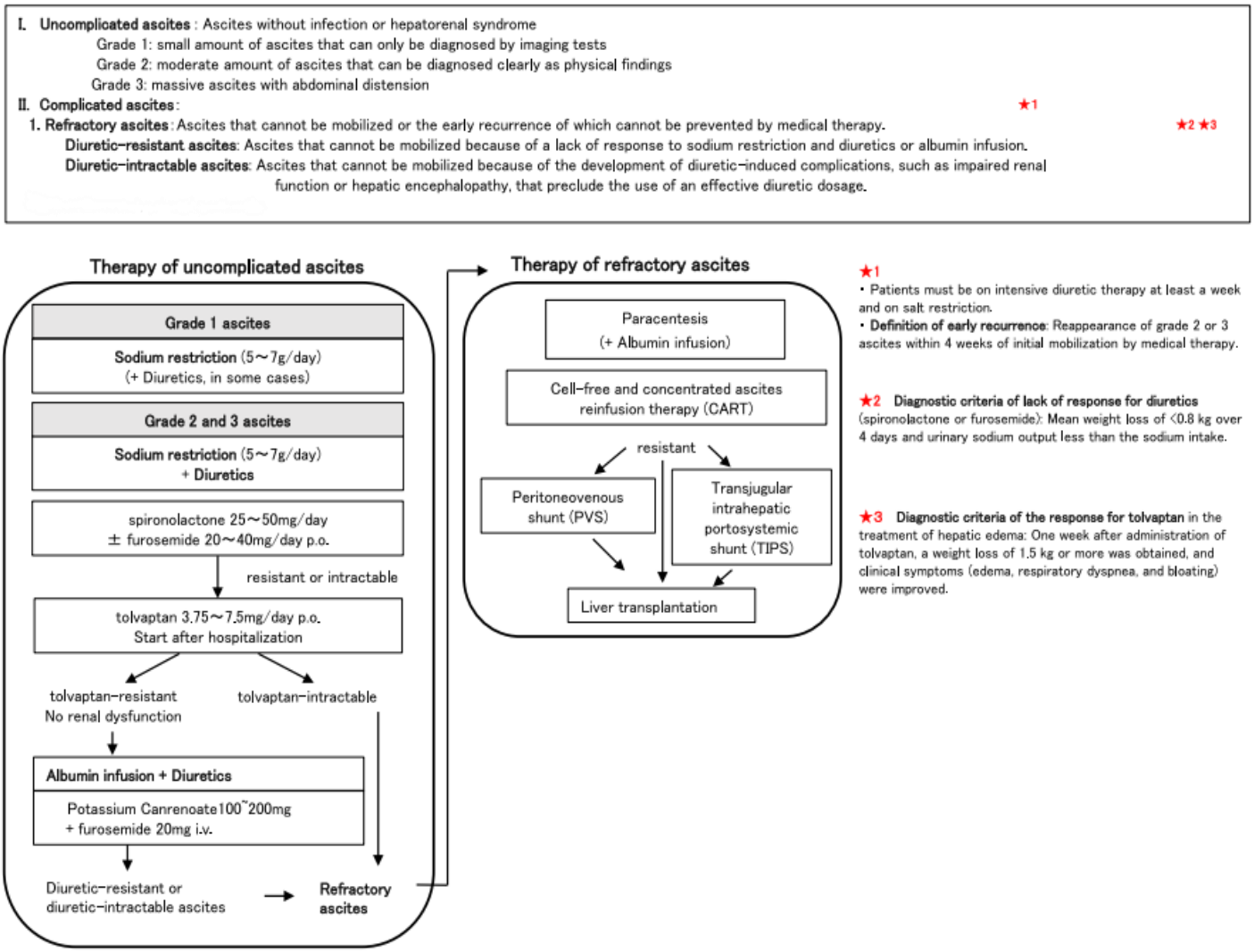

Figure 18. *Therapeutic algorithm for cirrhotic ascites.*

Grade 1 ascites is treated with sodium restriction (5–7 g/day) and, in some cases, diuretics. For grade 2 and 3 ascites, spironolactone (25–50 mg/day) is administered as a first-line drug with sodium restriction. When the effect is insufficient, furosemide (20–40 mg/day) is used in combi- nation. In cases of resistant or intractable tolvaptan (3.75–7.5 mg/day) is additionally administered after hospitalization. For tolvaptan-resistant patients without renal dysfunction, intravenous injection of potassium canrenoate (100–200 mg) and furosemide (20 mg) is started. For severe hypoalbuminemia (<2.5g/dL), albumin infusion is considered. For refractory ascites, paracentesis or cell-free and concentrated ascites reinfusion therapy (CART) is recommended. Albumin infusion in large- volume paracentesis is effective in preventing paracentesis-induced circulatory dysfunction (PICD). Peritoneovenous shunts or transjugular intrahepatic portosystemic shunt (TIPS) are recommended for resistant cases. If these treatments are ineffective, liver transplantation should be considered.

The following algorithms for the primary prevention, treatment, and secondary prevention of variceal bleeding is adapted from (KASL) Clinical Practice Guidelines for Liver Cirrhosis: Varices, Hepatic Encephalopathy, and Related Complications [2020][23]:

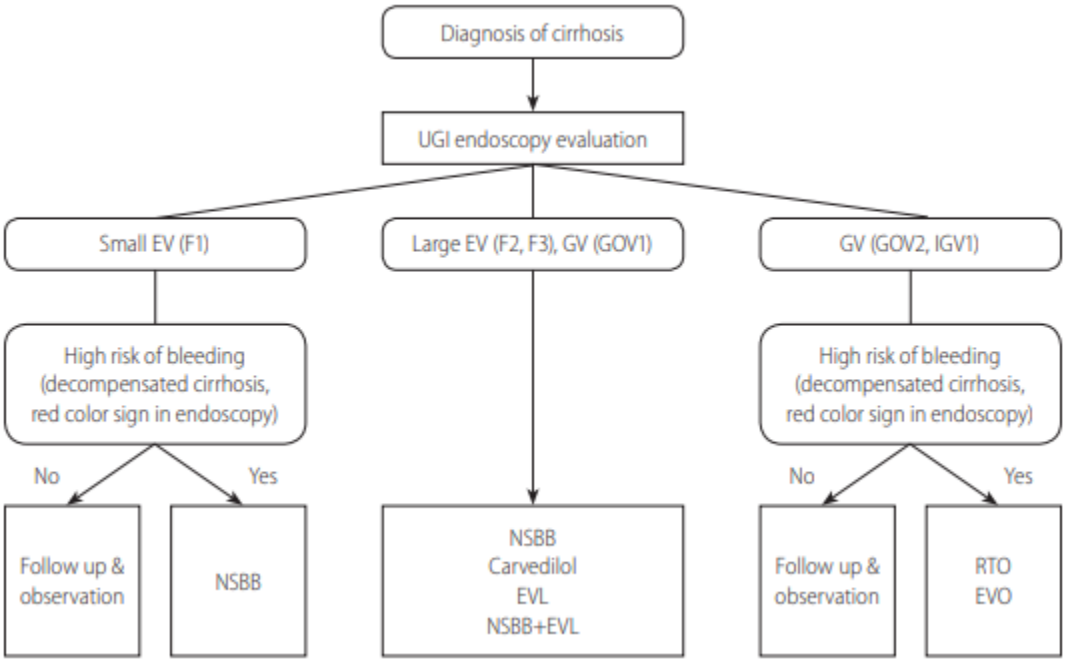

Figure 19. *Primary prevention of variceal bleeding.*

UGI, upper gastrointestinal; EV, esophageal varices; GV, gastric varix; GOV, gastroesophageal varix; IGV, isolated gastric varix; NSBB, non-selective beta blocker; EVL, endoscopic variceal ligation; RTO, retrograde transvenous obliteration; EVO, endoscopic variceal obturation.

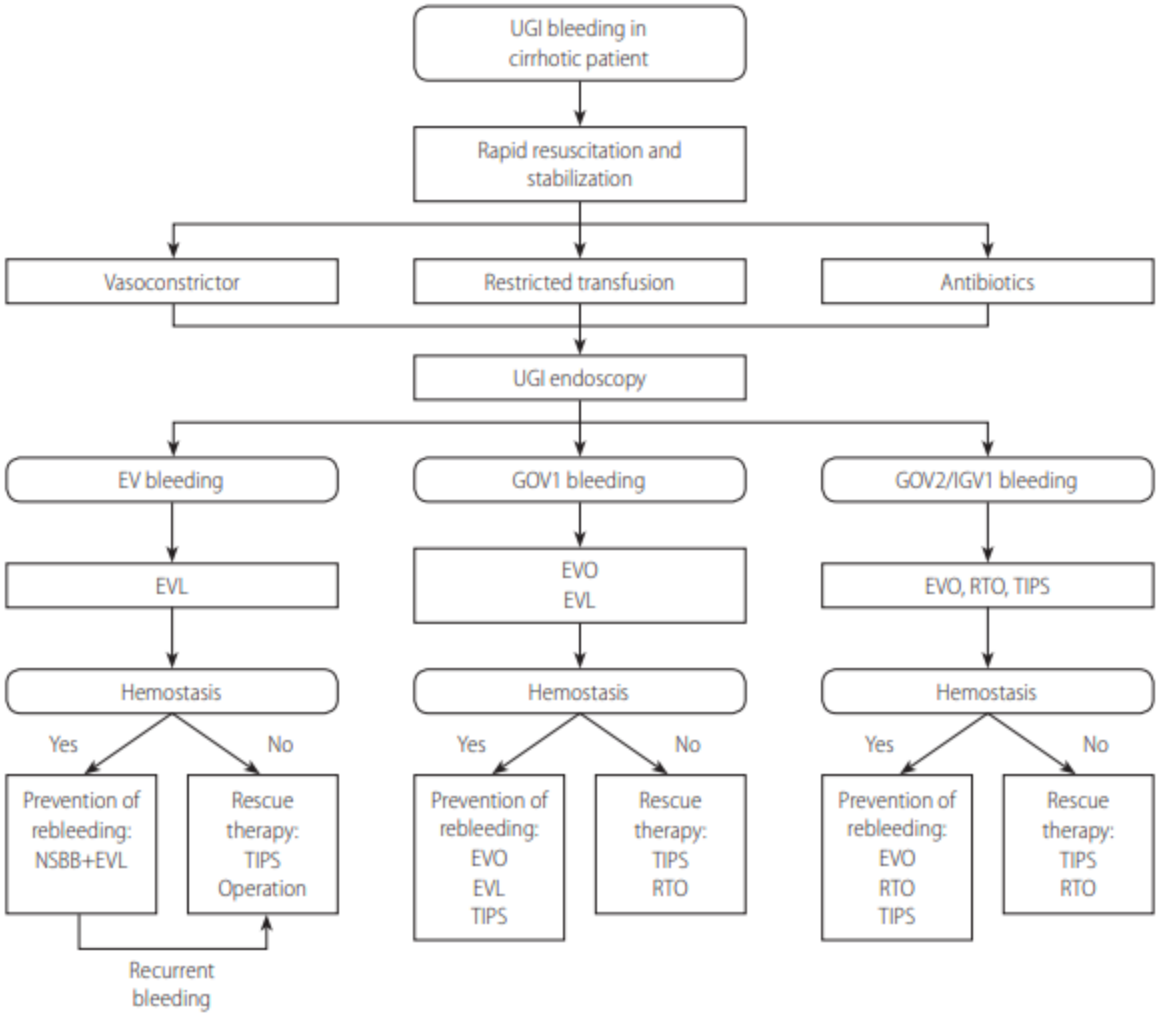

Figure 20. *Treatment and secondary prevention of variceal bleeding.*

UGI, upper gastrointestinal; EV, esophageal varices; GOV, gastroesophageal varix; IGV, isolated gastric varix; EVL, endoscopic variceal ligation; EVO, endoscopic variceal obturation; RTO, retrograde transvenous obliteration; TIPS, trans jugular intrahepatic portosystemic shunt; NSBB, non-selective beta blocker.

The following algorithm is adapted from Hepatorenal Syndrome: Pathophysiology and evidence-based management update [2021][32]:

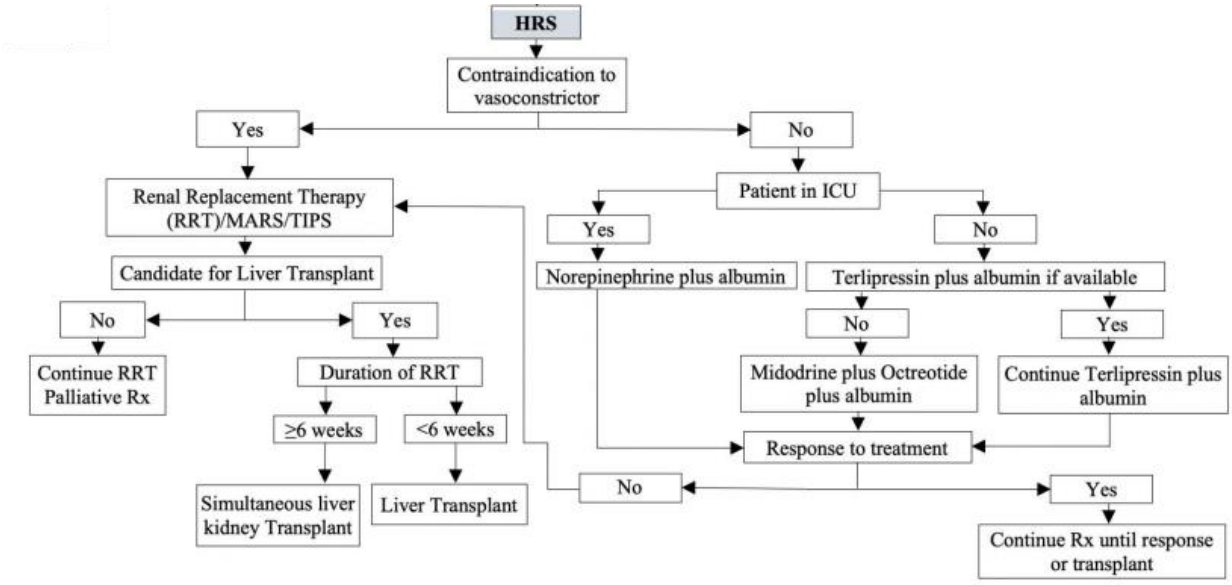

Figure 21. *Treatment algorithm for hepatorenal syndrome.*

HRS, hepatorenal syndrome; RRT, renal replacement therapy; MARS, molecular adsorbent recirculating system; TIPS, trans jugular intrahepatic portosystemic shunt.