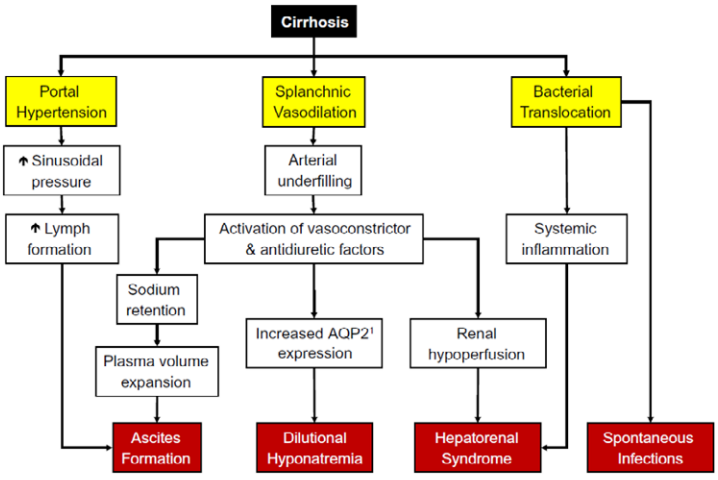
Expert Perspectives from the Chronic Liver Disease Foundation (CLDF) on the 2021 AASLD Cirrhosis Guidance

Hepatorenal Syndrome, Ascites, and Spontaneous Bacterial Peritonitis

Introduction

The "Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases" is a comprehensive guidance on the diagnosis, evaluation, and management of the aforementioned complications of cirrhosis. It serves to replace the prior AASLD guideline on the same topics published in 2012. The Chronic Liver Disease Foundation (CLDF) is a nonprofit 501(c)(3) educational organization dedicated to raising awareness of liver disease. Members of the CLDF cirrhosis committee, actively involved in the management and treatment of patients with advanced liver disease, cirrhosis, and its complications, have provided their expert perspectives on this updated guidance. The result is this summary, which provides a streamlined version of the practical recommendations set forth in the guidance to facilitate their use in clinical practice.

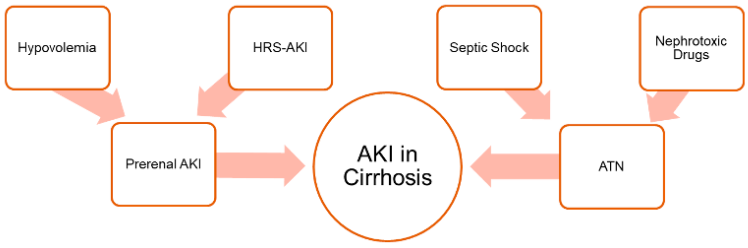
Cirrhosis directly results in the development of splanchnic vasodilation, portal hypertension, and bacterial translocation. Specifically, splanchnic vasodilation leads to effective arterial underfilling associated with the activation of vasoconstrictor (e.g., renin-angiotensin) and antidiuretic (e.g., arginine vasopressin) factors. Both portal hypertension (increases sinusoidal hydrostatic pressure) and bacterial translocation (because of gut permeability) contribute to the pathogenesis of **complications associated with ascites, including hyponatremia, acute kidney injury, hepatorenal syndrome, and spontaneous bacterial infections.**



Hepatorenal Syndrome

Defining HRS-AKI

Acute kidney injury (AKI) is diagnosed by an increase in serum creatinine (SCr) ≥ 0.3 mg/dL within 48 hours or a ≥ 50% increase in SCr that is known or presumed to have occurred within the preceding 7 days. AKI in cirrhosis is mainly caused by prerenal AKI or acute tubular necrosis (ATN). The two main causes of prerenal AKI are hypovolemia and **hepatorenal syndrome (HRS).**



AKI, acute kidney injury; ATN, acute tubular necrosis; HRS, hepatorenal syndrome

AKI commonly occurs in cirrhosis, and its causes must be evaluated before HRS is diagnosed. AKI must be differentiated from HRS. HRS, a type of AKI known as **HRS-AKI** under the current terminology, is unique to patients with cirrhosis and occurs in the absence of hypovolemia or significant abnormalities in kidney histology. HRS almost always occurs in patients with cirrhosis who also have ascites and hyponatremia, not compensated disease. Before the development of the new AKI criteria, patients with HRS were classified according to two clinical patterns. The first pattern, known as type-1 HRS, defined by an abrupt decline in kidney function, falls under the current criteria of AKI (100% increase in creatinine to a value greater than 2.5 mg/dL). The second pattern, previously known as type-2 HRS, falls into the current definition of chronic kidney disease.

Old classification	New classification		Criteria
HRS-1*	HRS-AKI		a) Absolute increase in sCr ≥ 0.3 mg/dL within 48 h AND/OR b) Urinary output ≤ 0.5 mL/kg body weight ≥ 6 h* OR c) Percent increase in sCr ≥ 50% using the last available value of outpatient sCr within 3 months as the baseline value
HRS-2*	HRS-NAKI	HRS-AKD	a) eGFR <60 ml/min per 1.73 m² for < 3 months in the absence of other (structural) causes OR b) Percent increase in sCr < 50% using the last available value of outpatient sCr within 3 months as the baseline value
		HRS-CKD	a) eGFR < 60 mL/min per 1.73 m² for ≥ 3 months in the absence of other (structural) causes

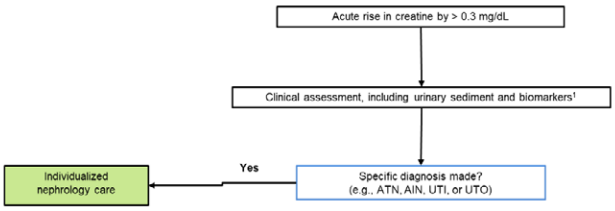
HRS, hepatorenal syndrome; HRS-AKI, acute kidney injury type of HRS; HRS-NAKI, non-acute kidney injury type of HRS; HRS-AKD, HRS acute kidney disease; HRS-CKD, HRS chronic kidney disease

Supported by Mallinckrodt Pharmaceuticals.

CLDF Chronic Liver Disease Foundation

Streamlining the Diagnostic Algorithm

- **Acute rise in SCr is detected:** Per the definition of AKI, an increase in serum creatinine ≥ 0.3 mg/dL within 48 hours or a ≥ 50% increase in SCr that is known or presumed to have occurred within the preceding 7 days should lead to suspicion of AKI.



AIN, acute interstitial nephritis; ATN, acute tubular necrosis; UTI, urinary tract infection; UTO, urinary tract obstruction

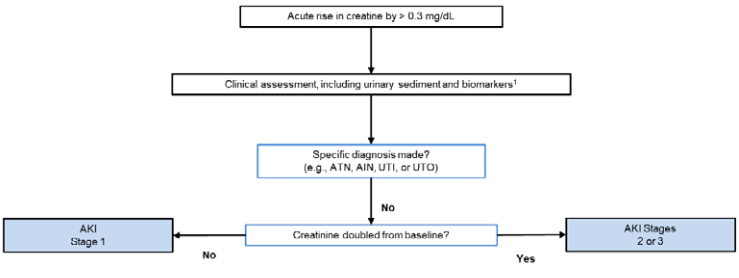
- **Clinical assessment and serum and urine tests:** Assess for the following:

Serum tests	**Elevations seen in hemoglobin/hematocrit, total protein/albumin, calcium bicarbonate, or uric acid**
Urine tests	**Decreased urine volume (< 500 mL/day), urine specific gravity > 1.105, urine sodium < 20 mEq/L, fractional excretion of Na < 1%, fractional excretion of urea < 35%*, or fractional excretion of uric acid < 10%***

*Not affected by diuretic use
Na, sodium

- **If, a specific diagnosis is made, other than AKI:** (e.g., ATN, acute interstitial nephritis (AIN), urinary tract infection (UTI), urinary tract obstruction (UTO)), individualized nephrology care is recommended.

If Other Diagnoses Are Ruled Out and AKI Is Confirmed, Assess for Doubling of SCr:



AKI, acute kidney injury; AIN, acute interstitial nephritis; ATN, acute tubular necrosis; UTI, urinary tract infection; UTO, urinary tract obstruction

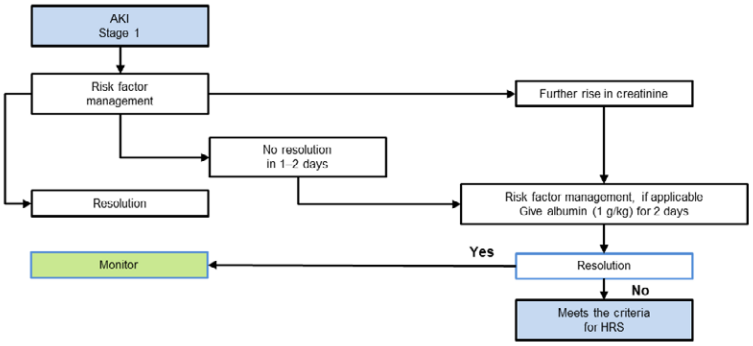
- If the SCr has not doubled, manage as **AKI Stage 1.**
- If the SCr has doubled, manage as **AKI Stages 2 or 3.**

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

RRT, renal replacement therapy

Managing AKI Stage 1

Although there is no specific therapy to reverse AKI, a diligent search must be conducted for treatable causes.



AKI, acute kidney injury; HRS, hepatorenal syndrome

- If **AKI stage 1 is diagnosed, implement risk factor management,** which includes the following:

AKI Risk Factor Management
Withdrawal of nephrotoxic drugs
Reduction or withdrawal of diuretics
Detection and treatment of infections
Volume replacement (if severely volume depleted) initially using 25% salt-poor albumin or crystalloids, preferentially balanced

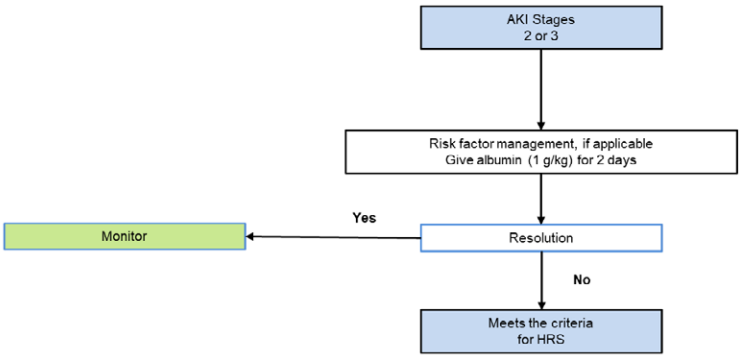
- **Assess for one of the following scenarios:**
  1. **SCr normalizes with risk factor management:** Continue to monitor.
  2. **SCr does not normalize within 1 to 2 days, despite risk factor management:** Implement the albumin challenge (albumin 1g/kg for 2 days).
  3. Absolute SCr > 1.5 mg/dL should expedite the use of vasoconstrictors.

- **If there is no resolution following the albumin challenge,** refer to the HRS-AKI criteria below to diagnose HRS-AKI:

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

AKI, acute kidney injury; NSAIDs, nonsteroid anti-inflammatory drugs

Managing AKI Stages 2 or 3



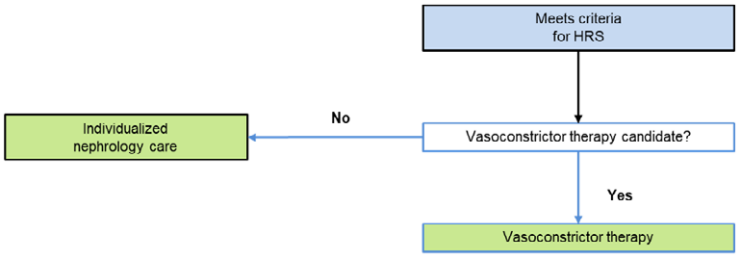
AKI, acute kidney injury; HRS, hepatorenal syndrome

- **If AKI Stage 2 or 3 is diagnosed:**
  Implement risk factor management, if applicable
  AND
  implement the albumin challenge (albumin 1g/kg for 2 days).
- **Assess for one of the following scenarios:**
  - **SCr normalizes:** Continue to monitor.
  - **There is no resolution following the albumin challenge:** Refer to the below HRS criteria to diagnose HRS.

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

AKI, acute kidney injury; NSAIDs, nonsteroid anti-inflammatory drugs

Treating HRS-AKI



HRS, hepatorenal syndrome

Vasoconstrictors, in combination with **albumin**, are effective in improving kidney function in patients with HRS-AKI. The vasoconstrictor of choice for HRS-AKI is terlipressin. In settings where terlipressin is not available, norepinephrine should be considered, typically in an intensive care setting. If neither can be administered, a trial of oral midodrine in combination with octreotide may be considered, but its efficacy is low. All vasoconstrictors should be dosed according to the table; albumin 25% should be administered in combination with each vasoconstrictor and dosed according to clinical parameters. Response to vasoconstrictor therapy is defined by SCr decreasing to < 1.5 mg/dL or returning to within 0.3 mg/dL of baseline over a maximum of 14 days. In patients whose creatinine remains at or above the pretreatment level over 4 days with the maximum tolerated doses of the vasoconstrictor, therapy may be discontinued. Recurrence may occur after discontinuation of treatment, so close follow-up is warranted. If there is recurrence, patients should be retreated.

Patients with HRS-AKI have a better response to therapy if therapy is started earlier rather than later. Terlipressin, when available, should be considered the treatment of choice, as response rates are better than the poor response rates of midodrine, octreotide, and albumin.

Drug	Dosing and Administration
Terlipressin	Vasoconstrictor of choice for treating HRS-AKI*
Norepinephrine	Continuous IV infusion starting at 0.5 mg/h to achieve an increase in mean arterial pressure of at least 10 mmHg or an increase in urine output of > 200 mL/4 h If at least one of these goals is not achieved, increase every 4 h in increments of 0.5 mg/h up to a maximum of 3 mg/h
Oral midodrine in combination with octreotide	Midodrine 5–15 mg po every 8 h Octreotide 100–200 µg every 8 h or 50 µg/h via IV

*Terlipressin is currently an investigational agent being evaluated for the treatment of HRS in the U.S., and its safety and effectiveness have not yet been established by the FDA.

AKI, acute kidney injury; HRS, hepatorenal syndrome

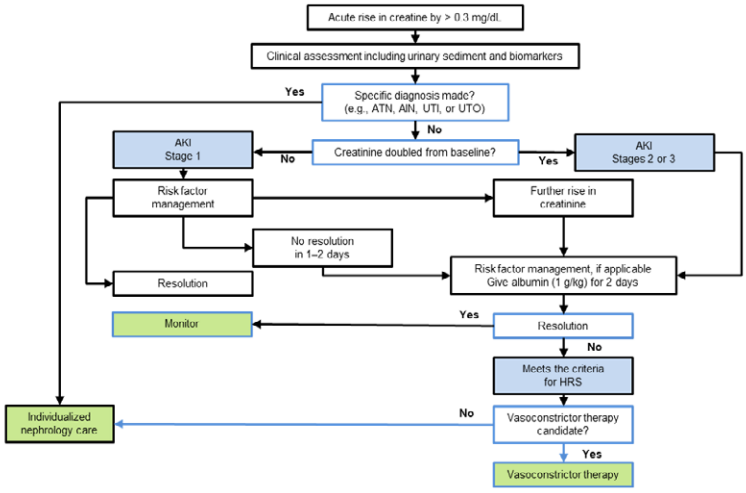
Patients on vasoconstrictors and albumin should be closely monitored for the possible development of adverse effects. Adverse effects are infrequent, are mainly related to vasoconstrictors, and include hypertension, peripheral ischemia, abdominal pain, nausea, diarrhea, headache, intestinal ischemia, and cardiac ischemia. Pulmonary edema may develop from fluid overload related to albumin infusion. Early intervention may prevent more serious consequences, and most resolve after dose reduction or discontinuation of therapy.

Additional Special Considerations in HRS Management

Transplantation	**All patients with cirrhosis and AKI should be considered for urgent liver transplant (LT) evaluation given the high short-term mortality even in responders to vasoconstrictors.** **Simultaneous liver–kidney transplantation may be necessary for patients who are not expected to recover kidney function following transplantation.**
Renal Replacement Therapy (RRT)	**Use RRT in candidates for LT with worsening renal function, electrolyte disturbances, or increasing volume overload unresponsive to vasoconstrictor therapy.** **Initiation of RRT in patients who are not candidates for LT must be made after defining goals of care with the patient and their families.**
Multidisciplinary Teams	**Given the complexity of cases of patients with suspected HRS-AKI, decisions about management should be made by multidisciplinary teams.** **Team should include specialists in hepatology, nephrology, critical care, and transplant surgery.**

AKI, acute kidney injury; HRS, hepatorenal syndrome

The full HRS diagnostic algorithm is shown here:



Ascites

Defining Ascites

Ascites, the pathologic accumulation of free fluid within the peritoneal cavity, is frequently the first decompensation-defining event in patients with cirrhosis. From an ascites-management perspective, the pathogenic events of importance include renal sodium retention, arterial underfilling, and portal hypertension.

Streamlining the Diagnostic Algorithm

The **initial evaluation** of ascites should include the following:

Medical history	• Risk factors for chronic liver disease (e.g., alcoholism, metabolic issues, viral hepatitis, or family history of liver disease) • Heart disease • Hematologic disorder (thrombosis or excessive bleeding)	• Thyroid disease • Autoimmune disorder • Malignancy • Pancreatitis • Travel history • Risk factors for tuberculous
Physical examination	• Shifting abdominal dullness; abdominal masses, tenderness, or guarding; umbilical/inguinal hernias; evidence of hiatal hernia (decreased breath sounds or thoracic dullness to percussion) • Stigmata of chronic liver disease (splenomegaly, spider angioma, palmar erythema, or abdominal wall collaterals)	• Signs of heart failure or constrictive pericarditis (jugular venous distension, pulmonary congestion, or pericardial rub) • Signs of malignancy or infection (lymphadenopathy) • Signs of malnutrition (sarcopenia) • Signs of thyroid disease
Abdominal ultrasonography	Doppler	
Liver function tests	INR, serum total bilirubin, and serum albumin	
Renal function tests	Serum creatinine and BUN	
Serum electrolytes	Na and K	
Urine electrolytes	Urine analysis with spot urine protein	
Complete blood count		
Paracentesis for analysis of the ascitic fluid		

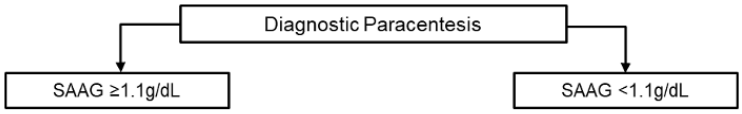
BUN, blood urea nitrogen; INR, international normalized ratio; Na, sodium; K, potassium

Diagnostic Paracentesis

A diagnostic paracentesis should be performed in all patients with new-onset ascites that is accessible for sampling. A **paracentesis** is a procedure performed to obtain a sample of ascitic fluid for diagnostic purposes or a large volume for therapeutic purposes. The initial laboratory investigation of ascitic fluid should include ascitic fluid cell count as well as neutrophil count, culture, ascitic fluid total protein, and ascitic fluid albumin. A concomitant serum albumin should also be measured to calculate the serum-ascites albumin gradient (SAAG). To evaluate whether ascites is portal hypertensive in origin, the **SAAG** is calculated by subtracting the ascitic fluid albumin from the serum albumin in simultaneously obtained samples.

For example, if the measured ascites albumin in a patient was 1.2 g/dL while the serum albumin taken on the same day was 3.1 g/dL, the calculated SAAG in this patient would be 3.1 – 1.2, or 1.9. This SAAG of 1.9 is consistent with portal hypertensive ascites.

Following paracentesis, assess the SAAG:



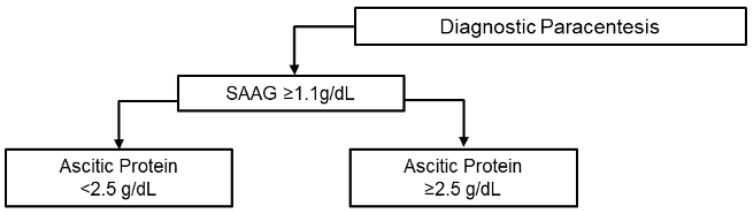
SAAG, serum-albumin ascites gradient

- **SAAG ≥ 1.1 g/dL** is highly suggestive of portal hypertension, usually caused by advanced liver disease.
- **SAAG < 1.1 g/dL** suggests causes of non-portal hypertensive ascites.
- **Cell count, total protein, and ascites fluid culture should be performed on all samplings of ascites fluid.**
- **Other tests of the ascitic fluid,** such as cytology, tuberculosis smear and culture, lactate dehydrogenase, triglycerides, amylase, and adenosine deaminase level, should be guided by the practitioner's clinical suspicions. Measuring serum pro-brain natriuretic peptide may also be helpful.

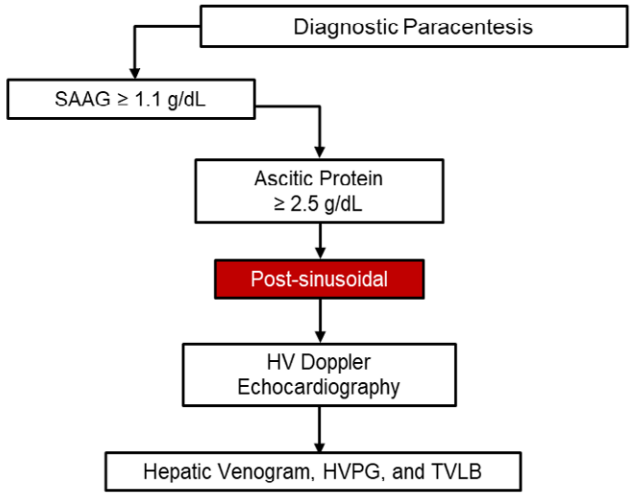
If the SAAG is < 1.1 g/dL, potential causes of ascites include the following:

- Peritoneal carcinomatosis
- Tuberculosis peritonitis
- Nephrotic syndrome
- Pancreatitis

If the SAAG is ≥ 1.1 g/dL, evaluate the ascitic protein content:



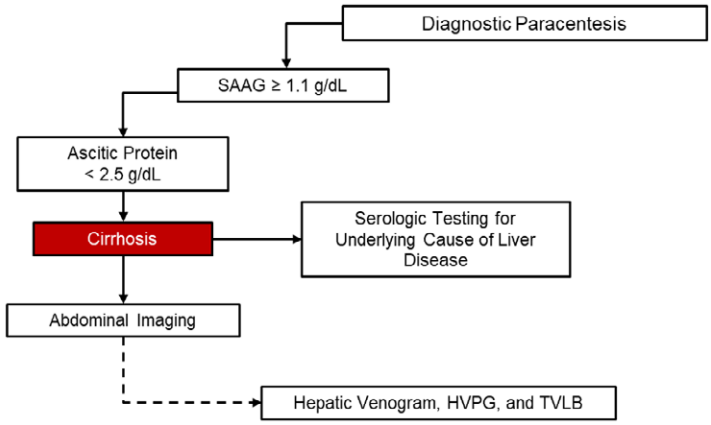
- **A high ascitic fluid protein (> 2.5 g/dL)** suggests a cardiac source for ascites, although this finding can be seen in patients with cirrhosis.



SAAG, serum-albumin ascites gradient; HVPG, hepatic venous pressure gradient; TVLB, transvenous liver biopsy

- **o** An echocardiogram is recommended to evaluate for congestive heart failure and the presence of pericardial effusion or pericardial wall thickening.
- **o** If the echocardiogram and/or HV Doppler are non-diagnostic, then one can consider performing a hepatic venogram, hepatic venous pressure gradient (HVPG), and/or transvenous liver biopsy (TVLB).

- **Low ascitic fluid protein (< 2.5 g/dL)** supports ascites secondary to cirrhosis.



SAAG, serum-albumin ascites gradient; HVPG, hepatic venous pressure gradient; TVLB, transvenous liver biopsy

- **o** Abdominal imaging is needed to assess the amount of ascites and to evaluate for space-occupying lesions, such as hepatocellular carcinoma.
- **o** A Doppler ultrasound of the hepatic vein and portal vessels should be performed to assess vessel patency.

- Hepatic venogram, HVPG, and TVLB are performed if the evaluation listed above is non-diagnostic.gradient (HVPG), and/or transvenous liver biopsy (TVLB).

Grading Cirrhosis According to Fluid Accumulation
Once cirrhosis is determined, ascites should be graded according to the amount of fluid present in the abdominal cavity.

Grade 1	Mild ascites	Only detected by ultrasound
Grade 2	Moderate ascites	Moderate symmetric distension of the abdomen
Grade 3	Large or gross ascites	Marked distension of the abdomen

Treatment of Grade 1 Ascites
Moderate dietary sodium restriction of less than 2 g/day should be prescribed, and the patient should be referred to a dietician, if available. No pharmaceutical treatment is recommended for grade 1 ascites, as there is no evidence that it improves patient outcomes, and patients are generally asymptomatic.

Treatment of Grade 2 Ascites
In most patients with cirrhosis presenting with ascites, dietary sodium restriction alone is insufficient, and diuretic therapy is necessary. Dietary sodium indiscretion, perhaps inadvertent, should always be suspected with worsening ascites despite medical therapy, and nutrition services referral should be strongly considered, if possible. In the first episode of mild ascites, treatment with aldosterone antagonists alone may generate an adequate response with few side effects. Moderate to severe ascites and long-standing ascites are best treated with combination diuretic therapy. Generally, the usual diuretic regimen consists of oral spironolactone (100 mg) and furosemide (40 mg) taken in the morning. Additional treatment considerations are described in the table below. Consider referring the patient to a dietician and for liver transplant evaluation in appropriate candidates.

First-line treatment	Moderate Na restriction	• 2 g or 90 mmol/day
	Diuretics	• Spironolactone 100 mg/day, with dose increases cautiously and in a stepwise fashion, at an interval of at least 72 h • Furosemide may be added; start at 40 mg/day and progressively increase in dosage according to the response and tolerability toward 160 mg/day. • Torsemide or bumetanide may improve natriuresis in patients with a suboptimal response to furosemide.
Fluid restriction		Not necessary for ascites management unless there is concomitant moderate or severe hyponatremia (serum Na ≤ 125 mmol/L).

Na, sodium

Assessment of 24-hour urinary sodium excretion may be useful to guide therapy. When a 24-hour urine collection is not feasible, a random “spot” urine sodium concentration greater than the potassium (K) concentration correlates well with 24-hour urine sodium excretion.

24 h urinary sodium excretion	• In the absence of renal dysfunction, sodium excretion lower than the intake (e.g., 80 mmol/day) indicates an insufficient diuretic dose. • Persistent ascites, despite adequate urinary sodium excretion, indicates dietary indiscretion.
Random “spot” urine Na and K concentration	• Correlates well with 24 h urinary sodium excretion when that test is not feasible • If the Na/K ratio is > 1, the patient should be losing fluid weight; if not, dietary noncompliance should be suspected. • If the Na/K ratio is ≤ 1, there is insufficient natriuresis, and an increase in diuretics should be considered.

Na, sodium; K, potassium

After ascites is adequately mobilized, attempts should be made to taper the diuretics to the lowest dose necessary to maintain minimal or no ascites while preventing the development of adverse effects. Adverse effects of diuretic therapy may occur in 20% to 40% of patients with cirrhosis and ascites. Additional details on these adverse effects are given in the table below.

AKI	• Rise of sCr of at least 0.3 mg/dL in 48 h • Mostly related to loop diuretics, as these patients are highly vulnerable to the rapid reduction of extracellular fluid volume due to their hemodynamic status
Hyponatremia	• Na < 135 mEq/L • More common with loop diuretics, as they inhibit the Na-K- Cl transporter and therefore solute-free water generation
Hypokalemia	• Serum K < 3.5 mmol/l. • More common with loop diuretics
Hyperkalemia	• Serum K > 5.5 mmol/L • More common with aldosterone antagonists, especially if there is concomitant impaired renal perfusion • Also observed with the use of angiotensin-converting enzyme inhibitors
Hepatic encephalopathy	• More common with other diuretic-induced side effects (e.g., hyponatremia or reduction of extracellular volume)
Gynecomastia	• Often painful • More common with aldosterone antagonists • More common with spironolactone than with epierenone or amiloride*
Muscle cramps	• Can lead to impairment of quality of life and mobility • Consider albumin (20–40 g/week) or baclofen (10 mg/day with a weekly increase of 10 mg/day up to 30 mg/day) in cases of severe muscle cramps

*Suggested conversion of spironolactone of 100 mg, ~50 mg of eplerenone, ~10 mg of amiloride

SCr, serum creatinine; Na, sodium; K, potassium; Cl, chlorine; Na-K-Cl, sodium-potassium-chloride

Treatment of Grade 3 Ascites
For patients presenting with tense ascites, large-volume paracentesis (LVP) combined with 25% human albumin is the initial treatment of choice, even in the presence of hyponatremia. In patients undergoing LVP, the use of albumin is crucial to prevent a further reduction of effective arterial blood volume, which may precipitate **post-paracentesis circulatory dysfunction (PPCD)**. The clinical manifestations of PPCD include renal impairment as well as HRS, dilutional hyponatremia, hepatic encephalopathy, and death. After paracentesis, sodium restriction and diuretics should be started, and treatment should follow the grade 2 recommendations.

First-line treatment	LVP	• There is no limit for ascites that can be removed in a single session. • However, the use of albumin is particularly important if more than 5 L of ascites are removed to prevent the development of PPCD.
	Albumin	• Albumin infusion at the time of LVP of >5 L is recommended to mitigate the risk of PPCD; the risk of PPCD may increase with >8 L of fluid evacuated in one single session. • Give 1 unit of 25% salt-poor albumin for each liter of ascites removed.

LVP, large-volume paracentesis;
PPCD, post-paracentesis circulatory dysfunction

Patient Counseling Points for Grades 2 and 3 Ascites

- Avoid preprepared meals, as they contain a high sodium content.
- Avoid adding salt to cooked meals.
- Encourage a consultation with a dietician.
- Advise the patient to weigh themselves daily and at the same time to assess the efficacy of the medication and prevent adverse effects.
- Advise the client to report weight loss exceeding 1 lb per day.
- Explain the need for laboratory monitoring, particularly in the first few weeks of treatment.

Refractory Ascites

Refractory ascites (RA) is ascites that cannot be mobilized or recurs after LVP despite dietary sodium restriction and diuretic therapy. RA is further divided into (1) diuretic resistant (persistent ascites despite maximal doses of diuretics) and (2) diuretic intractable, in which the side effects of diuretics preclude the use of maximum doses. Refractory ascites should be treated with albumin infusions and LVP as needed clinically. Select patients may benefit from TIPS placement to control their ascites. Continued diuretic use is not recommended, as it has been shown to be ineffective and may predispose the patient to complications, such as worsening renal impairment. Liver transplantation should be considered in patients with RA who are otherwise appropriate candidates.

A summary of the key terms that apply to ascites is given below.

Ascites	The pathologic accumulation of fluid within the peritoneal cavity is typically the first decompensation-defining event of cirrhosis	
	Grade 1:	Mild ascites only detected by ultrasound; no treatment indicated
	Grade 2:	Moderate ascites detected by moderate abdominal distention; treated with sodium restriction and diuretics
	Grade 3:	Large or gross ascites marked by distention of the abdomen; treated with LVP and albumin, followed by sodium restriction and diuretics
Paracentesis	A procedure performed to obtain a small sample of or drain ascitic fluid for both diagnostic or therapeutic purposes	
Serum albumin ascites gradient (SAAG)	Used to evaluate the etiology of ascites, the SAAG is calculated by subtracting the ascitic fluid albumin from the serum albumin in simultaneously obtained samples.	
Postparacentesis circulatory dysfunction (PPCD)	May be precipitated in patients undergoing LVP but can be prevented with albumin administration. The clinical manifestations of PPCD include renal impairment, including HRS, dilutional hyponatremia, hepatic encephalopathy, and death.	
Refractory ascites (RA)	Ascites that cannot be mobilized or recur after LVP despite dietary sodium restriction and diuretic therapy RA is further divided into (1) diuretic resistant (i.e., persistent ascites despite maximal doses of diuretics) and (2) diuretic intractable, in which side effects of diuretics preclude the use of maximum doses.	

HRS, hepatorenal syndrome; LVP, large-volume paracentesis; PPCD, post-paracentesis circulatory dysfunction; RA, refractory ascites; SAAG, serum-albumin ascites gradient

Spontaneous Bacterial Peritonitis

Spontaneous infections (bacteremia) in patients with cirrhosis are common and occur in the absence of an obvious source of infection. **Spontaneous bacterial peritonitis (SBP)** is specifically an infection of the abdominal fluid that can present as abdominal pain, tenderness on palpation (with or without rebound), and ileus, with an overall mortality rate of 35%. Hepatic encephalopathy is frequently the only presenting symptom of SBP. However, patients with SBP are frequently asymptomatic.

In patients with cirrhosis, the presence of fever or hypothermia, chills, and localizing symptoms should raise suspicions of a bacterial infection, but these signs may not always occur. Bacterial infection should be suspected when a patient with cirrhosis deteriorates, particularly with encephalopathy, AKI, and/or jaundice. Patients with ascites who develop signs, symptoms, or laboratory abnormalities suggestive of infection should undergo a prompt general workup for infection prior to initiation of antibiotics, including complete physical examination (including evaluation of the skin for cellulitis), assessment of total white blood cell count and differential, chest radiograph, urine analysis and culture, and blood cultures, plus a diagnostic abdominal paracentesis (for cell count and culture).

Diagnostic Paracentesis

Recommendations for diagnostic paracentesis are summarized here.

When to perform	• As soon as a patient with cirrhosis and ascites is hospitalized emergently for any reason, even in the absence of symptoms suggestive of infection • Whenever a patient (hospitalized or not) develops signs suggestive of infection • In patients with tense ascites and AKI to exclude SBP as a cause of the AKI
Where to perform	• The ascitic fluid should be cultured at the bedside in aerobic and anaerobic blood culture bottles before the initiation of antibiotics. • Bedside inoculation of at least 10 mL of the ascitic sample into blood culture bottles increases the sensitivity of the culture to >90% for the diagnosis of SBP.
What to look for	• The diagnosis of SBP is established with a fluid PMN leukocyte count ≥ 250/mm3.
Obtaining simultaneous blood samples	• Culturing blood samples simultaneously increases the possibility of isolating a causative organism.

AKI, acute kidney injury; PMN, polymorphonuclear leukocyte count; SBP, spontaneous bacterial peritonitis

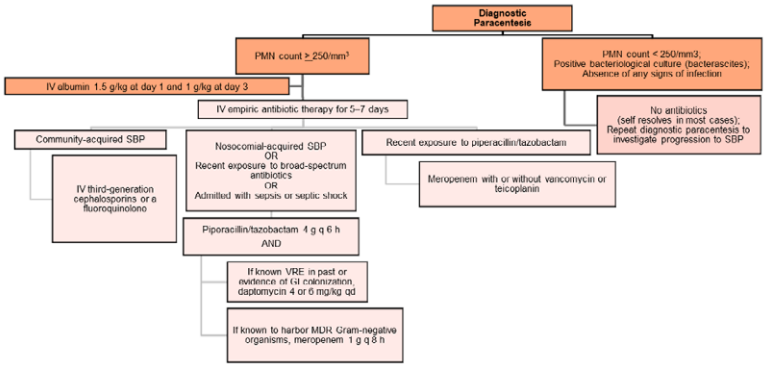
Five variants of ascitic fluid infection are possible, based on the fluid polymorphonuclear leukocyte (PMN) count, culture results, and method of entry of the organism into the fluid. SBP is the prototype and is the most common.

It is very important to isolate a microorganism either from ascites or from blood so that antibiotic susceptibility results may guide antibiotic therapy. Refer to the section that follows for treatment recommendations based on PMN and culture findings.

	PMN count (cells/mm³)	Organism detected in culture
Spontaneous bacterial peritonitis	≥ 250	Single
Secondary bacterial peritonitis	≥ 250	Usually polymicrobial
Culture-negative neutrocytic ascites	≥ 250	Absent (obtained prior to the administration of antibiotics)
Monomicrobial non-neutrocytic bacterascites	< 250	Single
Polymicrobial bacterascites	< 250	Polymicrobial

Management of SBP

Patients with presumed SBP should be started on empiric broad-spectrum antibiotics following diagnostic paracentesis, and antibiotic therapy can be narrowed based upon the identification of the organism and its specific antibiotic sensitivities. A thorough history of antibiotic allergy should be obtained prior to treatment initiation. Response to empiric antibiotic therapy may be assessed by repeating diagnostic paracentesis/thoracentesis 2 days after initiation if no clinical improvement is noted. A decrease in fluid PMN < 25% from baseline indicates a lack of response and should lead to broadening of antibiotic coverage based upon the antibiotic sensitivity panel. Non-specific beta blockers should be temporarily held in patients with SBP who develop hypotension (mean arterial pressure < 65 mm Hg) or AKI.



PMN, polymorphonuclear leukocytes; VRE, vancomycin-resistant enterococcus; MDR, multi-drug resistance

Treatment Choices for SBP

	First choice	Secondary	Treatment duration
Third-generation cephalosporin	Cefotaxime 2 g IV q 8 h	Ceftriaxone 2 g/day	5 days
Fluoroquinolone	Ciprofloxacin 400 mg IV BID		5 days

SBP Prophylaxis

Patients at a high risk of SBP, including patients with a prior history of SBP, require prophylaxis. Recommendations for SBP prophylaxis are provided in the table. Antibiotic prophylaxis is given in patients with:

- One or more episodes of SBP and low-protein ascites (ascitic fluid is < 1.5 g/d)
- Cirrhosis and a history of gastrointestinal bleeding
- Cirrhosis, low-protein ascites (ascitic fluid is < 1.5 g/d), *AND*
  - Liver failure (serum bilirubin > 3 mg/dL and Child-Turcotte-Pugh score > 9)

    OR
  - Renal dysfunction (serum creatinine level > 1.2 mg/dL, blood urea nitrogen level > 25 mg/dL, or serum sodium level < 130 mEq/L)

Treatment choices for SBP prophylaxis:

	First choice	Secondary
History of SBP and low-protein ascites	Trimethoprim-sulfamethoxazole 1 double strength daily	Ciprofloxacin 500 mg daily
Advanced cirrhosis and gastrointestinal bleeding	Ceftriaxone IV 1 g/d then switch to oral trimethoprim–sulfamethoxazole for 7 days	Ciprofloxacin 500 mg BID can be used as an alternate to trimethoprim-sulfamethoxazole

A summary of the key terms that apply to SBP is given below.

Spontaneous infections	Common in cirrhosis and occur in the absence of an obvious source of infection
Spontaneous bacterial peritonitis	An infection of the abdominal fluid that may present as abdominal pain, tenderness on palpation (with or without rebound tenderness), and ileus, but can also be asymptomatic
Diagnostic paracentesis	Important in determining the PMN and isolating the microorganism from ascites; antibiotic susceptibility results can then guide antibiotic therapy The diagnosis of SBP is established with a PMN > 250/mm³.
SBP management	All patients with a PMN count of ≥ 250/mm³ require IV albumin in combination with IV antibiotic therapy.
SBP prophylaxis	Patients at a high risk of SBP, including patients with a prior history of SBP, require long-term antibiotic prophylaxis.

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