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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

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Purpose and Scope of the Guidance

This is a comprehensive guidance on the diagnosis, evaluation, and management of ascites and hepatorenal syndrome (HRS) in patients with chronic liver disease from the American Association for the Study of Liver Diseases (AASLD). It replaces the prior AASLD guideline on the same topic published in 2012 (Table 1).[(1)]

This AASLD *Guidance* provides a data-supported approach to the management of ascites and HRS. It differs from the AASLD *Guidelines*, which are supported by systematic reviews of the literature, formal rating of the quality of the evidence, and strength of the recommendations. In contrast, this Guidance was developed by consensus of an expert panel and provides guidance statements based on comprehensive review and analysis of the literature on the topics, with oversight provided by the AASLD Practice Guidelines Committee. The AASLD Practice Guidelines Committee chose to perform a Guidance on this topic because a sufficient number of randomized controlled trials were not available to support meaningful systematic reviews and meta-analyses.

Introduction

BURDEN OF CIRRHOTIC ASCITES AND HRS

Hepatic decompensation, defined by ascites, hepatic encephalopathy, and portal hypertensive gastrointestinal bleeding, is an important landmark in the natural history of cirrhosis.[(2)] Ascites is commonly the first decompensation-defining event, with 5%-10% of

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AKI, acute kidney injury; ATN, acute tubular necrosis; CKD, chronic kidney disease; HH, hepatic hydrothorax; HRS, hepatorenal syndrome; K, potassium; LT, liver transplantation; LVP, large-volume paracentesis; MDRO, multidrug-resistant organisms; MELD, Model for End-Stage Liver Disease; Na, sodium; NGAL, neutrophil gelatinase-associated lipocalin; NSBB, nonselective beta-blocker; ODS, osmotic demyelination syndrome; PMN, polymorphonuclear; PPCD, postparacentesis circulatory dysfunction; RA, refractory ascites; RRT, renal replacement therapy; SBE, spontaneous bacterial empyema; SBP, spontaneous bacterial peritonitis.

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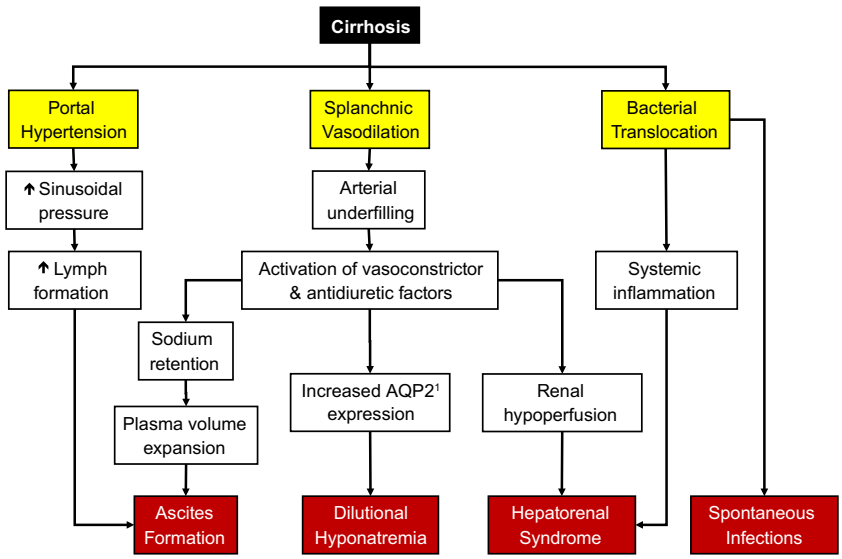

FIG. 1. Pathogenesis of ascites and related complications of cirrhosis. The central event consists of effective arterial underfilling as a result of splanchnic vasodilation leading to activation of vasoconstrictor (e.g., renin-angiotensin) and antidiuretic (e.g., arginine vasopressin) factors. Portal hypertension leading to increased sinusoidal hydrostatic pressure and increased gut permeability allowing bacterial translocation, contributing further to the pathogenesis of complications associated with ascites, including hyponatremia, AKI, HRS, and spontaneous bacterial infections. Abbreviation: AQP2[1], Aquaporin-2.

patients with compensated cirrhosis developing ascites per year.[3] The development of ascites is associated with a reduction in 5-year survival from 80% to 30%,[4] which is due in part to patients with ascites being prone to additional complications, such as bacterial infections, electrolyte abnormalities, HRS, and nutritional imbalances, and, consequently, further clinical decline.[5] Patients with cirrhosis who develop clinically significant ascites and related complications should be considered for referral for liver transplantation (LT) evaluation and, when appropriate, palliative care.[6]

HRS is a late complication of cirrhosis that accounted for 3.2% of all hospital discharges related to cirrhosis according to a 2012 study based on a large inpatient health care database of patients representative of community hospitals in the United States.[4] Moreover, the number of HRS discharges in the United States has increased significantly in the past 2

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decades.[7] HRS was also associated with high inpatient mortality (~46%) as well as longer lengths of stay and higher costs of hospitalizations compared with cirrhosis discharges without HRS.

PATHOGENESIS

Figure 1 summarizes the key steps in the pathogenesis of ascites and related complications discussed in this document. From the perspective of the management of ascites, pathogenetic events of importance are renal sodium retention, arterial underfilling, and portal hypertension, which may be mitigated by diuretics, albumin infusion, and portal decompressive procedures, respectively.[8,9] More recently, the advent of vasopressin receptor antagonists provided further insights on the contribution of water retention in the pathogenesis of ascites.[10] Recent reviews provide more detailed discussion of the pathogenesis of ascites.[11-13]

HRS is a functional renal failure resulting from hemodynamic changes occurring in patients with ascites and portal hypertension.[14] The primary pathophysiologic mechanism of HRS is reduced renal perfusion secondary to renal vasoconstriction mediated by increased activities of the sympathetic, renin-angiotensin-aldosterone, and vasopressin systems,[5] which may be further aggravated by decreased cardiac output in patients with cirrhosis-associated cardiomyopathy. In addition, systemic inflammation that is common among patients with decompensated cirrhosis may trigger immune-mediated renal injury.[15] Finally, emerging evidence suggests that renal autoregulation, a natural defense mechanism to maintain renal blood flow, is impaired in patients with cirrhosis, predisposing them to additional direct hemodynamic renal injury.[16] Together, structural kidney damage can follow severe and/or repeated episodes of such renal events.[17,18]

Initial Diagnosis and Management of Ascites

DIAGNOSTIC EVALUATION OF A PATIENT WITH ASCITES

Although cirrhosis is the most common cause of ascites in the Western world, other potential causes should be considered, including malignancy, heart failure, tuberculosis, and pancreatic disease. The initial evaluation of ascites should include history, physical examination, abdominal doppler ultrasound, laboratory assessment of liver and renal function, serum and urine electrolytes, and a diagnostic paracentesis for analysis of the ascitic fluid (Fig. 2; Tables 2-4).[19,20] In evaluating the etiology of ascites, the serum albumin ascites gradient is calculated by subtracting the ascitic fluid albumin from the serum albumin in simultaneously obtained samples.[21] A serum albumin ascites gradient ≥1.1 g/

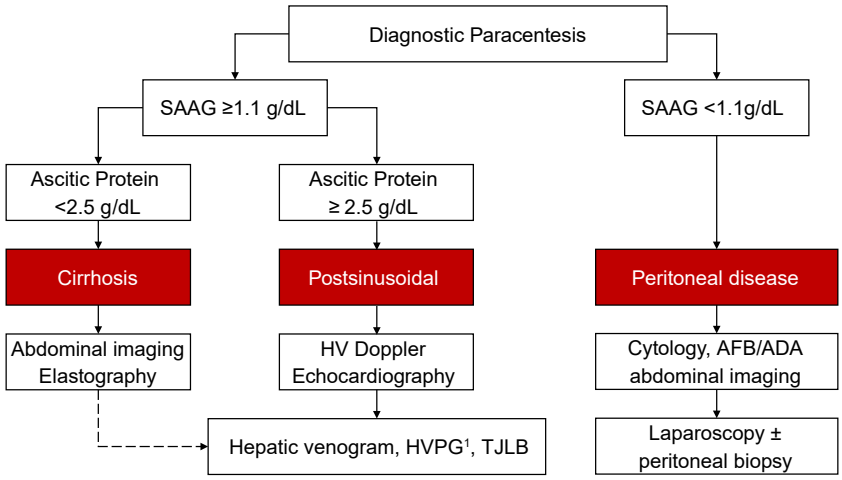

FIG. 2. Diagnostic approach to new-onset ascites. [1]May include right heart catheterization. Abbreviations: Abd, abdominal; ADA, adenosine deaminase; AFB, acid fast bacterium; HV, hepatic venous; SAAG, serum-ascites albumin gradient; TJLB, transjugular liver biopsy.

TABLE 1. What's New in This Guidance

Because this guidance represents an update covering nearly a decade, numerous changes are made. Instead of enumerating the individual changes, the following list represents noticeable revisions:

- Table 3 includes specific directions on the diagnostic evaluation of ascites by clinical setting and clinical course.
- Tables 5 and 7 highlight specific definitions and characteristic of ascites.
- Figure 3 provides updated information on management of ascites, including the use of albumin in ascites.
- More specific definitions of hyponatremia and management are included.
- Updated guidance on LT for patients with HH (Table 8) and for potential candidates of simultaneous liver-kidney transplantation
- Table 9 has expanded and updated description of antibiotics for infections in patients with cirrhosis.
- The AKI section is substantially expanded and updated (Fig. 4; Tables 10-12).
- The pediatric section is new.

TABLE 2. Initial Evaluation of Patients With Ascites

Medical history: Risk factors for chronic liver disease (alcohol, metabolic, viral hepatitis, family history of liver disease), heart disease, hematologic disorder (thrombosis, excessive bleeding), thyroid disease, autoimmune disorder, malignancy, pancreatitis, travel history, and risk factors for tuberculous
Physical examination: Shifting abdominal dullness, abdominal masses or tenderness or guarding, umbilical/inguinal hernias, evidence of HH (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, pericardial rub), signs of malignancy or infection (lymphadenopathy), signs of malnutrition (sarcopenia), signs of thyroid disease
Abdominal ultrasonography with Doppler
Complete blood count
Liver function tests (INR, serum total bilirubin, serum albumin)
Renal function tests (serum creatinine, BUN)
Serum and urine electrolytes (Na, K) and urine analysis with spot urine protein
Ascitic fluid analysis (see Table 3 and Fig. 2): SAAG, total protein concentration, polymorphonuclear leukocyte count, and culture

Abbreviations: BUN, blood urea nitrogen; INR, international normalized ratio; SAAG, serum albumin ascites gradient.

dL is highly suggestive of portal hypertension, usually caused by liver disease with an accuracy of approximately 97%, whereas a serum albumin ascites gradient <1.1 g/dL suggests other causes of ascites (Table 4). In contrast, a high ascitic fluid protein (>2.5 g/dL) supports a cardiac source for ascites.[22] Other tests of the ascitic fluid, such as amylase, cytology, or culture for mycobacteria, are not routinely indicated but should be guided by the patient's clinical context.

TABLE 3. Guidance to Diagnostic Paracentesis in Patients With Cirrhosis

What to Test	First Episode of Ascites			Recurrent Ascites		
	Inpatients	Outpatients		Inpatients	Outpatients*	
SAAG	Yes	Yes		No	No	
PMN count	Yes	Yes		Yes	Yes	
Culture	Yes	No		Yes	No	
Protein concentration	Yes	Yes		Only when a primary prophylaxis of SBP is clinically indicated or a secondary bacterial peritonitis is suspected	Only when a primary prophylaxis of SBP is clinically indicated	
Glucose concentration	Only when a secondary bacterial peritonitis is suspected	No		Only when a secondary bacterial peritonitis is suspected	No	
Lactate dehydrogenase	Only when a secondary bacterial peritonitis is suspected	No		Only when a secondary bacterial peritonitis is suspected	No	
Cytology	Only when causes of ascites other than cirrhosis are suspected	Only when causes of ascites other than cirrhosis are suspected		No	No	
Amylase concentration	Only when a pancreatic origin of ascites is suspected	Only when a pancreatic origin of ascites is suspected		No	No	

*Including those admitted to one day hospital for LVP.
Abbreviation: SAAG, serum albumin ascites gradient.

TABLE 4. Interpretation of SAAG in Discriminating the Cause of Ascites

SAAG ≥ 1.1 g/dL Reflects Portal Hypertension	SAAG < 1.1 g/dL Excludes Portal Hypertension
Potential cause of ascites	Potential cause of ascites
Ascites in cirrhosis	Peritoneal carcinomatosis
Ascites related to massive liver metastasis	Tuberculosis peritonitis
Ascites related to liver involvement in right heart failure	Other clinical conditions

Abbreviation: SAAG, serum albumin ascites gradient.

In patients with cirrhosis, ascites can be graded according to the amount of fluid accumulated in the abdominal cavity and classified according to response to treatment (Table 5).[19] No treatment is recommended for grade 1 ascites, as there is no evidence that it improves patient outcomes. Response to therapy and subsequent outcome in patients with grade 2 or 3 ascites depends on several factors such as the underlying cause of cirrhosis; feasibility and effectiveness of therapy to alter the natural course of cirrhosis; presence of superimposed complications such as renal failure, hyponatremia, and spontaneous bacterial peritonitis (SBP); and adherence of the patient to dietary sodium restriction and diuretics.

Guidance Statements

- A diagnostic paracentesis should be performed in all patients with new-onset ascites that is accessible for sampling.
- The initial laboratory investigation of ascitic fluid should include ascitic fluid neutrophil count, ascitic fluid total protein, ascitic fluid albumin, and serum albumin to calculate the serum-ascites albumin gradient.

DIETARY SODIUM RESTRICTION AND DIURETIC THERAPY

Moderate dietary sodium restriction (2 g or 90 mmol/day) should be prescribed to achieve a negative sodium balance and net fluid loss. Fluid restriction is not indicated unless hyponatremia is present. Patient education for sodium restriction is essential to maximize adherence while avoiding malnutrition and sarcopenia.[23-25] Instructions about a sodium-restricted diet should include advice on sodium contents of preprepared meals, avoiding adding salt to cooked meals, and guarding against nutritional deficiency.[23] A formal consultation with a dietician should be considered.

In most patients with cirrhosis presenting with ascites, dietary sodium restriction alone is insufficient and diuretic therapy is necessary. The patient should be made aware that daily monitoring of body weight, preferably at the same time of the day, is essential in assessing the efficacy of diuretics and preventing their adverse effects. The peritoneal membrane's ability to reabsorb ascites from the abdominal cavity is limited to approximately 500 mL per day. Thus, in a patient without peripheral edema, weight loss exceeding 0.5 kg per day may result in plasma volume contraction, predisposing the patient to renal failure and hyponatremia. In those with edema, weight loss up to 1 kg/day may be tolerated.[19,26] In addition, patients should understand the need for laboratory monitoring (e.g., serum electrolyte concentrations), particularly during the first weeks of treatment.

Assessment of 24-hour urinary sodium excretion may be useful to guide therapy; 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. When a 24-hour urine collection is not feasible, a random "spot" urine sodium concentration that is greater than the potassium (K) concentration correlates well with 24-hour urine sodium excretion.[27,28] When the spot urine sodium (Na)/K ratio is >1, the patient should be losing fluid weight,[28] and, if not, dietary noncompliance should be suspected. If the spot urine Na/K ratio is ≤1, there is insufficient natriuresis, and an increase in diuretics should be considered.

Aldosterone antagonists (e.g., spironolactone) and loop diuretics (e.g., furosemide, torsemide, bumetanide) are the mainstay of diuretic treatment of cirrhotic ascites.[29,30] Two studies addressing the best way to use these diuretics showed that for the first episode of ascites, treatment with aldosterone antagonists alone generated an adequate response with few side effects,[29,30] whereas those with long-standing ascites responded better to a combined diuretic treatment.[31] The recommended initial dose of spironolactone is 100 mg/day, which can be progressively

TABLE 5. Classification of Ascites

According to Amount of Fluid Accumulation		According to the Response to Treatment	
Grade 1. Mild ascites	Only detected by ultrasound	Responsive ascites	Ascites that can be fully mobilized or limited to grade 1 with diuretic therapy associated or not to moderate dietary sodium restriction
Grade 2. Moderate ascites	Moderate symmetric distension of abdomen	Recurrent ascites	Ascites that recurs on at least 3 occasions within a 12-month period despite dietary sodium restriction and adequate diuretic dosage
Grade 3. Large or gross ascites	Marked distension of the abdomen	Refractory Ascites	Ascites that cannot be mobilized or the early recurrence of which (i.e., after LVP) cannot be satisfactorily prevented by medical therapy

increased up to 400 mg/day. Spironolactone and its active metabolites have a long half-life; the full effect of a dose change may not be seen for up to 3 days. When the dose is increased, it should be done cautiously and in a stepwise fashion, with an interval of at least 72 hours.

The dose of furosemide (initially 40 mg/day) may be progressively increased, according to the response and tolerability toward 160 mg/day, which is the generally accepted threshold to determine medical treatment refractoriness.[19,26] Torsemide or bumetanide may improve natriuresis in patients with a suboptimal response to furosemide.[32] Patients with chronic kidney disease (CKD) in general are treated with higher doses of loop diuretics and lower doses of aldosterone antagonists.

When ascites is adequately mobilized, attempts should be made to taper the diuretics to the lowest dosages to maintain minimal or no ascites. Adverse effects of diuretic therapy may occur in 20% and 40% of patients with cirrhosis and ascites (Table 6).[23] Painful gynecomastia can be caused or exacerbated by spironolactone, which may respond to switching to amiloride or eplerenone[33,34]; see Table 6 for conversion doses. Muscle cramps are common in patients with liver disease, particularly in patients on diuretic treatment for ascites, and adversely influence the quality of life.[35] The exact mechanisms by which they occur remain unclear; however, besides the correction of electrolyte alterations (e.g., hypokalemia and hypomagnesemia), muscle cramps may respond to medications, such as baclofen (10 mg/day, with a weekly increase of 10 mg/day up to 30 mg/day)[36] and albumin (20-40 g/week).[35] Other drugs such as orphenadrine[37] and methocarbamol[38] have been proposed for muscle cramps in patients with cirrhosis. Finally, quinidine at a dose of 400 mg/day for 4 weeks in patients with cirrhosis was more effective than placebo against painful muscle cramps; however, toxicities such as diarrhea in about one-third of cases requiring treatment withdrawal may limit its use.[39]

TREATMENT OF GRADE 3 ASCITES

For patients presenting with tense ascites, large-volume paracentesis (LVP) combined with hyperoncotic human albumin is the initial treatment of choice, even in the presence of hyponatremia.[40,41] Patients with massive peripheral edema may require a second paracentesis shortly after the first because a rapid shift of fluid may occur from interstitial tissue to the abdominal cavity.[19,26,40,42] After LVP and a significant reduction in the intra-abdominal pressure, diuretics can be instituted, which may eliminate or reduce the frequency of paracentesis.[43] More detailed discussion about LVP is found in the section on refractory ascites (RA).

Guidance Statements

- Moderate sodium restriction (2 g or 90 mmol/day) and diuretics (spironolactone with or without furosemide) are the first-line treatment in patients with cirrhosis and grade 2 ascites.
- After ascites is adequately mobilized, attempts should be made to taper the diuretics to the lowest dose necessary to maintain minimal or no ascites to prevent the development of adverse effects.
- Fluid restriction is not necessary for ascites management unless there is concomitant moderate or severe hyponatremia (serum sodium ≤ 125 mmol/L).
- In patients receiving diuretics, body weight and serum creatinine and sodium should be regularly monitored to assess response and to detect the development of adverse effects.
- Human albumin solution (20-40 g/week) or baclofen administration (10 mg/day, with a weekly

increase of 10 mg/day, up to 30 mg/day) can be considered in cases of severe muscle cramps.
- LVP is the first-line treatment of grade 3 ascites. After paracentesis, sodium restriction and diuretics should be started.
- Referral for LT evaluation should be considered in patients with grade 2 or 3 ascites.

GENERAL MEDICAL MANAGEMENT OF PATIENTS WITH CIRRHOSIS AND ASCITES

Given the hemodynamic abnormalities in patients with cirrhosis and ascites, medications that may further reduce effective arterial volume and renal perfusion should be avoided. The most commonly encountered example is nonsteroidal anti-inflammatory drugs, which may precipitate hyponatremia, diuretic refractoriness, and acute kidney injury (AKI).[44] The angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists, α1-adrenergic blockers, and dipyridamole should also be avoided.[45-48]

Similarly, all potential nephrotoxins should be avoided in patients with cirrhosis and ascites. Aminoglycoside antibiotics should be avoided whenever possible in the treatment of bacterial infections.[49] Finally, in patients with cirrhosis and ascites, the use of IV contrast media is not contraindicated[50]; however, caution needs to be exercised in patients with impaired renal function.

Albumin, the most abundant serum protein, is the main component that generates the oncotic pressure. In addition, albumin has a multitude of other functions, including ligand binding, anti-inflammatory, antioxidant, and endothelial stabilizing effects.[51-53] Recently, long-term albumin administration to patients with decompensated cirrhosis has been studied.[54,55] In the ANSWER study, 431 patients with diuretic-responsive ascites were randomized to either standard medical treatment or standard medical treatment plus 40 g of albumin twice a week for the initial 2 weeks and then 40 g once a week for 18 months. A significantly better overall survival was seen in patients receiving albumin, with a 38% reduction in mortality.[54] In the MACTH study, 173 patients with ascites listed for LT were randomized to receive standard medical treatment plus 40 g of albumin every 15 days and an α1-receptor agonist, midodrine (15-30 mg/day depending on the response), or standard medical treatment plus placebo. Despite some improvement in parameters reflecting improved effective plasma volume, no difference was observed in the complication rates or death during 12 months of follow-up.[55] Thus, the discrepant results between the two trials point to the need for further studies to address the role of albumin as well as cost-effectiveness[56] in the management of ascites.

Given the complexity of medical care of patients with cirrhosis and ascites, the use of a multidisciplinary team is likely beneficial but has not been studied extensively. A model of specialized care has been proposed: an integrated team including hepatologists, dedicated nurses, physicians in training, and diagnostic facilities improved 12-month survival and reduced the rate of hospitalization for liver-related complications in outpatients with cirrhosis and ascites compared with standard practice.[57]

Guidance Statements

- Nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers should be avoided in patients with cirrhosis and ascites.
- Aminoglycosides should be avoided whenever possible in the treatment of bacterial infections.
- For patients with cirrhosis and diuretic-responsive ascites, controversial data suggest potential benefits of long-term infusion of human albumin solution. At present, no recommendation can be made for its use in routine clinical practice.

Management of Refractory Ascites

RA occurs in approximately 5%-10% of all patients with cirrhosis and ascites and is associated with poor survival of 50% at 6 months.[58] RA is defined as ascites that cannot be mobilized or recurs after LVP despite dietary sodium restriction and diuretic therapy.[19] Thus, 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 (Table 7).[59] Recurrent ascites,

TABLE 6. Adverse Effects of Diuretic Agents

AKI (rise of at least 0.3 mg/dL in 48 hours): mostly related to loop diuretics, as these patients are highly vulnerable to rapid reduction of extracellular fluid volume due to their hemodynamic status
Hyponatremia (<135 mmol/min): more common with loop diuretics, as they inhibit Na-K-Cl transporter and, therefore, solute-free water generation
Hypokalemia (serum potassium <3.5 mmol/L): more common with loop diuretics
Hyperkalemia (serum potassium >5.5 mmol/L): more common with aldosterone antagonists, especially if concomitant impaired renal perfusion; also with use of angiotensin-converting enzyme inhibitors
Hepatic encephalopathy: more common with other diuretic-induced side effects (i.e., hyponatremia, reduction of extracellular volume)
Gynecomastia: often painful, more common with aldosterone antagonist; more common with spironolactone than with eplerenone or amiloride*
Muscle cramps: can lead to impairment of quality of life and mobility

*Suggested conversion of spironolactone of 100 mg, ~50 mg of eplerenone, ~10 mg of amiloride.
Abbreviations: Cl, chlorine; Na-K-Cl, sodium-potassium-chloride.

which is defined as ascites that recurs at least three times within 1 year despite dietary sodium restriction and diuretic therapy, may be a forerunner of RA.[59] Figure 3 outlines the suggested treatment algorithm for RA management.

MEDICAL TREATMENT OPTIONS FOR RA

Dietary Sodium and Fluid Restriction

Dietary sodium restriction is important in the management of patients at all stages of ascites, including those with recurrent or refractory ascites, as it lowers the rate of ascites accumulation. Frequent review of a food diary can help identify high-sodium food items if the patient is reaccumulating ascites rapidly. Some patients who have been labeled as having RA may reduce their ascites once they adhere to a low-sodium diet. This is especially true in patients who excrete approximately 80 mmol of sodium in their urine per day.[28]

Fluid restriction in a patient with cirrhosis and RA is difficult to enforce and is often impractical. These patients' daily urine output is usually less than 1 L, making it virtually impossible to achieve a negative fluid balance by restricting fluid intake to less than the urine output. The serum sodium concentration at which fluid restriction should be instituted has not been well defined[60] but is recommended when serum sodium is ≤125 mmol/L or its onset is rapid (see the section on hyponatremia).

Continued Diuretic Use

In patients who have diuretic-resistant ascites, the continued use of diuretics is ineffective while predisposing patients to complications, especially renal impairment. Furthermore, loop diuretics have a sigmoidal dose-response curve, which means that once the ceiling dose is reached, further increase in doses will not increase renal sodium excretion. For patients with liver cirrhosis, this ceiling dose is reduced compared with healthy controls.[61] In patients with diuretic intractable ascites, there are no data as to whether diuretic doses lower than those that have produced side effects should be used once the side effects have abated.

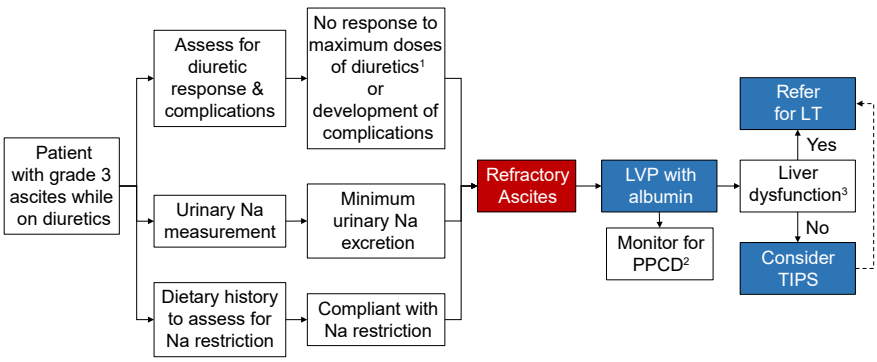

FIG. 3. Treatment algorithm for management of RA. All three criteria should be met for diagnosis of RA. [1]Typically 160 mg furosemide and 400 mg spironolactone. [2]PPCD. [3]For example, MELD >18. Abbreviation: LT, liver transplant.

Albumin Infusions

Chronic albumin infusion in patients with cirrhosis and RA was evaluated in a cohort of 70 participants, 45 of whom received 20 g of albumin twice weekly.[62] There was a significant reduction in the 24-month hospital admissions for complications of cirrhosis and mortality.[62] These results suggest that the use of albumin is generally safe and may be beneficial in patients with RA, but randomized controlled trials are needed to support these findings. The dose of albumin used may be critical in achieving positive results.[63]

Guidance Statements

- Continued dietary sodium restriction (<2 g/day) is required in patients with RA to reduce the rate of ascites accumulation.
- Fluid restriction is ineffective for the management of RA, but restricting fluid intake to less than 1,000 mL/day is recommended for treatment of hyponatremia (e.g., <125 mEq/L).
- In the management of RA, there are insufficient data to recommend the long-term use of albumin infusions outside the setting of large-volume paracenteses.

LVP

LVP, arbitrarily defined as a paracentesis of >5 L, has been shown to be safe and effective in the management of RA. When done repeatedly, LVP has a lower incidence of electrolyte abnormalities, renal dysfunction, and hemodynamic disturbance with similar survival compared with continued diuretic use.[40]

In patients undergoing LVP, the use of albumin is crucial to prevent a further reduction of effective arterial blood volume, which may precipitate postparacentesis circulatory dysfunction (PPCD). The clinical manifestations of PPCD include renal impairment, including HRS, dilutional hyponatremia, hepatic encephalopathy, and death.[64,65] Albumin infusion is particularly important if more than 5 L of ascites are removed to prevent the development of PPCD.[28,66] Paracenteses of a smaller volume are not associated with significant hemodynamic changes,[67] and albumin infusion may not be required. Although there has not been a dose-response study on albumin use with LVP, the administration of 6-8 g of albumin per liter of ascites removed has been recommended.[19] For example, after the fifth liter, approximately 40 g of albumin should be infused, and after 8 L removal, the amount of albumin given should be approximately 64 g.

It has been held that there is no limit for the amount of ascites that can be removed in a single session, provided an appropriate amount of albumin is administered. However, the risk of PPCD increases with >8 L of fluid evacuated in one single session. A recent study showed that by limiting the LVP volume to <8 L per session and providing a higher than recommended dose of albumin (9.0 ± 2.5 g per liter of ascites removed), renal function and survival may be better preserved over a mean period of 2 years despite the development of PPCD in 40% of patients.[68] In patients with hemodynamic instability (systolic blood pressure <90 mm Hg), hyponatremia (serum sodium <130 mmol/L), and/or the presence of AKI, albumin infusion should be strongly considered for paracentesis of a smaller volume.[69]

LVP is a safe procedure even in the presence of coagulopathy. In a study that included patients with an international normalized ratio of >1.5 and a platelet count of $<50 \times 10^9$/L, only 1% of patients experienced minimal cutaneous bleeding after LVP.[70] Therefore, elevated prothrombin time or thrombocytopenia is not a contraindication for paracentesis, nor is transfusion of clotting factors or platelets recommended. Possible exceptions may include patients with disseminated intravascular coagulation or uremia and thrombocytopenia. In the latter patients, desmopressin may be considered, particularly if there is history of prior bleeding.[71]

Guidance Statements

- LVP is the first-line treatment for RA.
- 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.
- The recommended dose of albumin replacement, based on expert opinion, is 6-8 g for every liter of ascites removed.

TIPS AND LT

Given its ability to reduce the portal pressure effectively, TIPS in well-selected patients with RA has been shown to be better than repeated LVP in the

control of ascites.[72,73] Survival advantage with TIPS insertion in patients with RA is reported in recent studies, including a meta-analysis.[74-76] This may be especially true for younger patients with low Model for End-Stage Liver Disease (MELD) scores, those who received a smaller diameter covered stent, and those who had a complete response to TIPS with total elimination of ascites.[77-80]

Physiologically, reduction of portal pressure with TIPS insertion allows gradual return of the splanchnic volume to the systemic circulation through the TIPS, thereby improving the effective blood volume. In turn, there is gradual suppression of the activated neurohormonal vasoconstrictor systems over 4-6 months, at which time, a significant diuresis occurs with elimination of ascites.[81] Therefore, it is important to manage patients' expectations that the clearance of ascites is not immediate post-TIPS, and patients should be maintained on a sodium-restricted diet until ascites is adequately controlled. Caution is recommended about the use of diuretics post-TIPS, as diuretics reduce the intravascular volume, which may slow the refilling of the effective arterial blood volume and counteract the volume refilling effects of TIPS insertion, potentially delaying ascites clearance. Eventually, approximately 80% of patients will clear their ascites with TIPS.[77] Patients who fail to do so despite a widely patent TIPS at 12 months should be referred for LT evaluation.

Complications of TIPS may be related to the insertion procedure, the TIPS prosthesis, or the presence of a shunt, which are discussed in detail in the AASLD guidance on the topic.[82] In patients with RA undergoing TIPS, TIPS prostheses covered with polytetrafluoroethylene have lessened the incidence of TIPS dysfunction significantly.[83] The utility of Doppler ultrasound in the management of TIPS depends on the setting.[84] Confirmation of the function soon after the stent placement is helpful. Follow-up interrogation of the stent in asymptomatic patients with a covered stent probably has little therapeutic impact; however, long-term surveillance has been suggested in patients who received revisions for TIPS dysfunction and in patients with a prothrombotic state.[85] Conversely, as Doppler studies may miss TIPS stenosis, venography should be considered in patients with persistent or recurrent ascites even if the Doppler is reportedly unremarkable.

Patient selection and timing for TIPS is of critical importance for a successful outcome. In general, patients with high MELD scores of ≥18 are poor candidates to receive a TIPS.[79] Certain risk factors (e.g., advanced age, cardiopulmonary insufficiency, and sarcopenia) predispose patients to more complications post-TIPS and hepatic encephalopathy,[86-88] although sarcopenia *per se* may not affect survival after TIPS insertion for RA.[89] TIPS stents with a smaller (8-10 mm) diameter than conventional ones have been associated with lower incidence of post-TIPS hepatic encephalopathy without compromising the efficacy on ascites control.[90-92] A recent study suggests that TIPS inserted at an earlier stage of ascites' natural history (such as those with recurrent ascites) could result in fewer side effects and improved survival when compared with LVP.[93] The 1-year transplant-free survival of 93% was significantly better than 53% in patients who received repeat LVP, albumin, and diuretics. There was also no difference in the incidence of hepatic encephalopathy during follow-up. However, this concept of early TIPS insertion will need to be replicated in a randomized controlled trial before it can be recommended.

For patients who are not TIPS candidates, the safety and efficacy of permanent indwelling peritoneal catheters remain to be established.[94] The studies published so far are of low quality, in which the average bacterial infection rate was 13%.[81] The risk and benefit ratios are even less certain for Child C patients, for whom repeat LVP remains a treatment option. The automatic low flow ascites pump (alfapump; Sequana Medical NV; Ghent, Belgium) is an implantable battery-powered pump that transports ascites from the peritoneal cavity into the bladder, allowing the elimination of ascites by urination. Insertion of an alfapump was reported to reduce paracentesis requirement, together with improvement in quality of life and nutritional status.[95] Currently, the alfapump is not available in North America.

Patients who have RA and concomitant significant liver dysfunction that precludes TIPS placement should be considered for LT. Patients who have RA but preserved liver function may be disadvantaged under the current MELD-based organ allocation system, as patients with ascites may bear an additional mortality risk equivalent to 4.5 MELD

points,[96] especially in patients whose MELD score is <21.[97] Many patients with RA also have hyponatremia, which is addressed by the MELD-sodium score.[98-101] Following LT, the hemodynamic abnormalities of decompensated cirrhosis will take weeks to months to correct. Patients may continue to have ascites for some time in the posttransplant period and will need to stay on a sodium-restricted diet until clearance of ascites.

Guidance Statements

- Careful patient selection is the key to the success of TIPS in the management of RA.
- A small-diameter coated stent of less than 10 mm is preferred to reduce the likelihood of post-TIPS complications, including hepatic encephalopathy.
- If ascites recurs after initial clearance, a TIPS venogram should be considered, and TIPS revision should be performed if stenosis is identified. In those patients, periodic Doppler ultrasound surveillance should be considered.
- LT should be considered in patients with RA.

CONTROVERSY ABOUT NONSELECTIVE BETA-BLOCKERS IN PATIENTS WITH RA

Nonselective beta-blockers (NSBBs) are the standard of care for the prevention of variceal bleeding in patients with cirrhosis and portal hypertension. More recently, the use of NSBB was found to be associated with a higher likelihood of PPCD[102] and shorter survival in decompensated cirrhosis, including patients with RA[103,104] and SBP.[105] Other publications soon followed that showed no impact of NSBB use on AKI development[106] or on mortality,[107,108] even in patients with severe liver dysfunction and those with acute-on-chronic liver failure.[109] These seemingly contradictory results led to the proposal of the "window period" hypothesis, suggesting that NSBBs were only useful during a certain window of period in the natural history of cirrhosis.[110] Beyond that time, NSBB use could be detrimental.

It is important to note that none of the studies quoted so far are randomized controlled trials. In the only randomized controlled trial conducted in patients with compensated cirrhosis, the use of NSBB was associated with a reduced incidence of ascites, suggesting that the use of NSBB in the early stage of cirrhosis is beneficial.[111] To resolve the controversy, adequately powered, randomized controlled studies using hard end points such as survival are needed in patients with decompensated cirrhosis. For now, we can only caution the use of NSBB in patients with RA, especially in those with hemodynamic abnormalities as indicated by low systolic blood pressure <90 mm Hg, hyponatremia with serum sodium <130 mmol/L, or serum creatinine of >1.5 mg/dL.[112] NSBBs might be reintroduced if circulatory dysfunction improves with improvement of these parameters.

Guidance Statements

- Based on currently available data, NSBBs are not necessarily contraindicated in patients with RA. However, caution is recommended in patients with hypotension, hyponatremia, or AKI.

Hyponatremia and Other Complications of Ascites

EVALUATION OF HYPONATREMIA IN PATIENTS WITH CIRRHOSIS AND ASCITES

Hyponatremia, defined as a serum Na concentration ≤135 mEq/L, is present in nearly half (49%) of patients with cirrhosis and ascites, with over a fifth (22%) having serum Na levels ≤130 mEq/L.[113] Most patients with cirrhosis, ascites, and hyponatremia have hypervolemic hyponatremia; however, hypovolemic and euvolemic hyponatremia should be considered. Hypovolemic hyponatremia can occur because of poor oral intake or from urinary or gastrointestinal losses related to an excess of diuretic or laxative treatments, respectively. Euvolemic hyponatremia is uncommon among patients with cirrhosis unless there is a specific cause, such as syndrome of inappropriate antidiuretic hormone secretion, medications (e.g., sertraline, carbamazepine), and severe hypothyroidism or adrenal insufficiency.

Symptoms of hyponatremia, although infrequent in patients with cirrhosis, range from nausea, muscle cramps, gait instability, lethargy, headache, and dizziness to confusion and seizure. Improvement in hyponatremia is associated with reduced brain edema and

improved cognition, quality of life,[114] and complex information processing.[115]

The severity of hyponatremia with cirrhosis is graded as mild (126-135 mEq/L), moderate (120-125 mEq/L), and severe (<120 mEq/L). Mild hyponatremia often does not require specific management apart from monitoring and water restriction; however, patients with symptomatic hyponatremia, moderate or severe hyponatremia, and imminent LT may require specific management.

Hyponatremia reflects worsening of hemodynamic status as cirrhosis advances (Fig. 1). Patients with cirrhosis and serum Na ≤130 mEq/L are at increased risk for developing hepatic encephalopathy (odds ratio, 3.4), HRS (odds ratio, 3.5), and SBP (odds ratio, 2.4),[113] and they have a higher in-hospital[86] and waitlist mortality.[98,100,101] Even patients with modest hyponatremia (serum Na 131-135 mEq/L) may be at increased risk of these serious complications.[113] This finding prompted the inclusion of serum Na into the liver allocation system in the United States in 2016, giving access to LT for patients with hyponatremia.[99]

MANAGEMENT OF HYPONATREMIA IN PATIENTS WITH CIRRHOSIS AND ASCITES

Treatment of hyponatremia in cirrhotic ascites depends on etiology, chronicity, severity, and urgency. Acute hyponatremia (onset within 48 hours) is much less common than chronic hyponatremia in cirrhosis. Patients with acute hyponatremia can, and typically should, have hyponatremia corrected rapidly to prevent cerebral edema without a concern for osmotic demyelination syndrome (ODS). Patients with chronic hyponatremia require more gradual and measured correction to avoid overcorrection and mitigate the risk of ODS. For hypovolemic hyponatremia, treatment is the discontinuation of diuretics and/or laxatives and providing fluid resuscitation, typically with 5% IV albumin or crystalloid (preferentially lactated Ringer's) solution. Euvolemic hyponatremia should be managed based on the specific underlying cause.

Treatment of hypervolemic hyponatremia includes fluid restriction, reduction or discontinuation of diuretics and laxatives, administration of hyperoncotic albumin, and/or vasopressin receptor antagonists ("vaptans").[116-122] An observational study of 595 patients with hyponatremia and cirrhosis demonstrated highly variable and frequently ineffective treatment of hyponatremia with relapse occurring in 55% after correction.[116] Only 36% of patients with moderate and severe hyponatremia had serum Na increase by ≥5 mEq/L with fluid restriction by day 3, whereas 71% of patients who were treated with tolvaptan and 78% of patients who were treated with hypertonic saline met this endpoint.[116]

Although fluid restriction can increase or limit the further decline in serum sodium levels, patient tolerance and compliance are significant barriers. Raising serum sodium by fluid restriction alone necessitates a decrease in intake below urine output plus insensible losses, which, in a patient with cirrhosis, generally means fluid intake <750 mL/day.[118] Prolonged fluid restrictions to this level are very poorly tolerated and may contribute to reduced overall nutritional intake. Fluid restriction to 1,500 mL/day[123] and 1,000 mL/day[124] in the control arm of vaptan trials in cirrhosis showed stabilization of hyponatremia, particularly in patients who had been on diuretics.[124] Albumin infusion was associated with improvement in hyponatremia in a large observational cohort of patients with cirrhosis who were hospitalized.[117] Thus, a trial of fluid restriction to 1,000 mL/day is recommended in the management of moderate hyponatremia (120-125 mEq/L), and more severe fluid restriction together with albumin infusion is recommended for severe hyponatremia (<120 mEq/L). Correction of hypokalemia aids in the correction of hyponatremia through improved cellular Na-K exchange.

Vaptans are effective in raising serum sodium, although their effect is transient. In one study, only a minority (22%) of patients achieved an increase in serum sodium >130 mEq/L that persisted throughout treatment,[121] whereas in another study, hyponatremia relapsed by 7 days after discontinuation of tolvaptan.[122] Importantly, the US Food and Drug Administration limits treatment duration for tolvaptan to 30 days, with a "black box" warning related to the risk of serious hepatocellular liver injury. This was, in part, driven by data in patients with polycystic kidney disease,[125] whereas hepatotoxicity was not noted in patients with cirrhosis.[119] Therefore, cautious use of vaptans in cirrhosis is reasonable after considering risks and benefits.

Hypertonic saline can correct serum sodium but often results in worsening hypervolemia and ascites. It is reserved for short-term treatment of patients with symptomatic or severe hyponatremia or those with imminent LT. When hypertonic saline is used preceding LT, perioperative or intraoperative renal replacement

therapy (RRT) may be needed to manage hypervolemia.[126] The decision to proceed with LT must be individualized based on urgency for transplant, severity of hyponatremia, and local expertise. Patients with hyponatremia who undergo LT are at an increased risk for postoperative complications, including infections, renal failure, and ODS.[126-130] ODS is rare in LT, occurring in an estimated 0.5%-1.5% of recipients.[131-135] Intraoperative administration of large amounts of products containing sodium, such as packed red blood cells and fresh frozen plasma as well as saline solutions, may raise serum sodium too rapidly. The prototypical course of ODS has an onset 2 to 7 days after rapid serum Na correction. Patients present with seizure or encephalopathy followed by short-term improvement, and subsequently, clinical deterioration with dysarthria, dysphagia, oculomotor dysfunction, and quadriparesis.[136] ODS can be diagnosed by physical examination and with brain magnetic resonance imaging.[127,137]

ODS may be more common in advanced liver disease, alcoholism, more severe cases of hyponatremia, malnutrition, severe metabolic derangements (hypophosphatemia, hypokalemia, or hypoglycemia), low cholesterol, and prior encephalopathy.[133-135] The risk of ODS may be mitigated with multidisciplinary, coordinated care, and LT need not be prohibited by hyponatremia alone.[126,127] A US expert panel recommends the goal rate of change of serum sodium of 4-8 mEq/L per day, not to exceed 10-12 mEq in a 24-hour period, with average ODS risk and a lower goal of 4-6 mEq/L per day, not to exceed 8 mEq per 24-hour period in patients at high risk of ODS—which included patients with advanced liver disease.[118] If overcorrection occurs, relowering with electrolyte-free water or desmopressin may be considered.[118] The use of tromethamine (also called tris[hydroxymethyl]aminomethane) may reduce the risk of ODS.[126,138]

Guidance Statements

- Mild hyponatremia (Na 126-135 mEq/L) in cirrhosis without symptoms does not require specific management apart from monitoring and water restriction.
- Water restriction to 1,000 mL/day and cessation of diuretics is recommended in the management of moderate hyponatremia (120-125 mEq/L), and a more severe restriction of water intake with albumin infusion is recommended for severe hyponatremia (<120 mEq/L).
- The use of vasopressin receptor antagonists in cirrhosis can raise serum sodium during treatment. However, they should be used with caution only for a short term (≤30 days).
- The use of hypertonic saline is reserved for short-term treatment of patients with symptomatic or severe hyponatremia or those with imminent LT.
- When correction of chronic hyponatremia is indicated in patients with cirrhosis, the goal rate of increase of serum (Na) is 4-6 mEq/L per 24-hour period, not to exceed 8 mEq/L per 24-hour period to ameliorate the risk of ODS.
- Severe hyponatremia (<120 mEq/L) at time of LT increases the risk of ODS with LT. Multidisciplinary coordinated care may mitigate the risk of ODS.

HEPATIC HYDROTHORAX

Hepatic hydrothorax (HH) is a transudative pleural effusion that occurs in portal hypertension. The prevalence of HH in cirrhosis is 4%-12%[139-142] and is typically unilateral. In a study of 77 patients with HH, 73% had HH on the right side, 17% had HH on the left side, and 10% had HH bilaterally; 9% did not have clinical ascites.[143] In HH, the pleural fluid originates in the peritoneal cavity and is drawn through defects in the diaphragm by the negative intrathoracic pressure at inspiration.[141] A serum to pleural fluid albumin gradient of >1.1 g/dL is suggestive of HH.[143] A pleural effusion caused by infection, pancreatitis, malignancy, or cardiopulmonary causes should be considered, particularly if serum to pleural fluid albumin gradient is ≤1.1 g/dL, if the effusion is left-sided, or in the absence of ascites. Pleural fluid in HH may have higher protein content than concurrent ascites, a finding attributed to the hydrostatic pressure gradient.

Patients with HH have a poor prognosis with a mortality risk that exceeds that predicted by the MELD score and should be considered for LT.[143,144] Mortality at 90 days after hospitalization with HH was 74% despite a mean MELD of 14 that would otherwise predict a 90-day mortality of 6%-8%.[143] Complications of HH include spontaneous bacterial empyema (SBE), progressive respiratory failure, trapped lung, and complications of thoracentesis such as pneumothorax and bleeding.[144]

Initial management is similar to that of ascites, with sodium restriction and diuretics. If ascites is present, LVP with IV albumin may improve ventilatory

function, but thoracentesis is generally also required. Thoracentesis can be performed without transfusion of platelets or plasma.[145] There are no data to guide the upper limit of pleural fluid volume for removal. Fluid can reaccumulate rapidly after thoracentesis, and thus, repeated thoracenteses are commonly required.[146]

Refractory or recurrent HH is best treated with TIPS or LT.[147-150] Based on the increased mortality, additional priority for LT is granted for patients with HH meeting defined criteria[151] (Table 8). There are no data about the potential use of intermittent albumin infusions in these patients; however, if ascites control can be improved with albumin infusions, it is plausible there may also be a benefit in HH. Chest tubes in HH are associated with high morbidity, clinical deterioration resulting in death or necessitating urgent TIPS or LT,[152-154] and development of a fistula and should be avoided. More recently, lower rates of complications are reported for indwelling tunneled pleural catheters (infections, 4.5%; fluid reaccumulation, 20%; spontaneous pleurodesis, 31%), which may be considered with caution as an alternative to repeated thoracentesis.[155] Patients in whom pleural fluid is frequently removed through an indwelling pleural catheter are at risk to develop protein depletion and malnutrition. Chemical pleurodesis often leads to loculated collections and is not recommend. Video-assisted thoracoscopic surgery repair of diaphragmatic defects has been reported.[156] Management of SBE is addressed in the SBP section.[157]

TABLE 7. Characteristics of RA

Diuretic-resistant ascites
- Ascites that cannot be mobilized
- Early recurrence of which cannot be prevented

Because of the lack of response to dietary sodium restriction and maximal doses of diuretics

Diuretic-intractable ascites
- Ascites that cannot be mobilized
- Early recurrence that cannot be prevented

Because of the development of diuretic-induced complications* that precludes the use of effective doses of diuretics

Fails sodium restriction
- 88 mmol or 2,000 mg/day

Fails maximum doses of diuretics
- Spironolactone 400 mg/day or amiloride 30 mg/day
- Furosemide 160 mg/day

Both for at least 1 week

Lack of treatment response
- Mean weight loss of <0.8 Kg over 4 days
- Urinary sodium less than sodium intake

Early recurrence of ascites
- Reappearance of grade 2 or grade 3 ascites within 4 weeks of initial mobilization

*Diuretic-induced complications
- Renal impairment: increase in serum creatinine by >100% to a value >2.0 mg/dL
- Hyponatremia with a decrease of >10 mmol/L or an absolute value of <125 mmol/L
- Hypo- or hyperkalemia of <3 mmol/L or >6 mmol/L
- Hepatic encephalopathy

Note: Adapted from Salerno et al.[59]

Guidance Statements

- First-line therapy of HH consists of dietary sodium restriction and diuretics plus thoracentesis as required.
- TIPS can be considered in selected patients as a second-line treatment for refractory HH.
- Chest tube insertion for HH should be avoided, but indwelling tunneled catheters may be considered in carefully selected patients who do not respond to medical therapy and are not candidates for TIPS.
- Patients with HH should be considered for LT.

ABDOMINAL HERNIAS

Abdominal wall and inguinal hernias are common in patients with cirrhosis and ascites. Umbilical hernias develop in approximately 20% of patients with cirrhosis.[158] Increased abdominal pressure from ascites, weakened abdominal muscles, and poor nutrition can lead to rapidly enlarging hernias. Conversely, optimal fluid control, appropriate nutrition, and conservative management with binders may minimize or prevent hernia development and progression. Hernias may present with incarceration, pressure necrosis, rupture, evisceration, and peritonitis. A rapid decline in the ascitic fluid volume (e.g., LVP) can paradoxically cause incarceration.[159-161]

Patients who are candidates for LT in the near future should defer hernia repair until during or after transplantation.[162] For patients in whom transplantation is not imminent (i.e., low MELD), elective herniorrhaphy may be offered in select patients after careful consideration of its risks and benefits in comparison with nonoperative management, with a possible need for an emergent operation.[163-166] Clinically apparent ascites should be controlled before elective herniorrhaphy, for which laparoscopic approaches are preferred.[167] The use of prosthetic mesh may reduce the recurrence rate but may increase the risk of infections and other complications.[167] Postoperatively, control of ascites and optimization of nutrition are the key determinants of successful outcome. Postoperative sodium intake

should be restricted to 2 g/day (90 mmol/day), whereas IV maintenance fluids are eliminated or minimized. In patients with RA who are considered to be at high risk of developing complications related to a hernia, elective preoperative TIPS can be considered before surgery.[168] A multidisciplinary approach, including consideration of TIPS placement, has yielded operative mortality rates as low as 5% for incarcerated or spontaneously ruptured hernias.[168]

Emergent surgery for a strangulated or ruptured umbilical hernia in a patient with cirrhosis and RA is best performed by a surgeon who is experienced in the care of patients with cirrhosis in consultation with a hepatologist for postoperative control of ascites, which is necessary for wound healing and prevention of secondary bacterial peritonitis. In such cases, TIPS placement may be considered in the postoperative period if ascites cannot be controlled medically.

Guidance Statements

- Elective hernia repair in cirrhosis is best performed through a multidisciplinary approach after ascites has been controlled and the patient's overall condition, including nutritional status, has been optimized.
- TIPS insertion should be considered before elective hernia repair or after an emergent operation in patients with cirrhosis and uncontrolled ascites.

SBP

BACTERIAL INFECTIONS IN CIRRHOSIS

Bacterial infections are present in approximately one-third of patients with cirrhosis who are hospitalized, a much higher prevalence than in those without cirrhosis.[169] A common yet unique type of infection in this setting is "spontaneous" infections that occur in the absence of an obvious source of infection. These include SBP, spontaneous bacteremia, and SBE (infection of the HH). Bacterial translocation, the passage of bacteria from the gut to the bloodstream and other extraintestinal sites, together with decreased host defenses have been implicated in the pathogenesis of these spontaneous infections.[157,170]

Other common infections in cirrhosis are urinary tract infection, pneumonia, and soft tissue infection.[171-173] In a recent prospective worldwide study that included more than 1,300 patients with cirrhosis, spontaneous infections accounted for 36% of infections, followed by urinary tract infection (22%), pneumonia (19%), and skin/soft tissue infections (8%).[171,173] Approximately half of the infections were community acquired and present at or within the first 48 hours of admission, with no prior contact with a health care facility for >90 days. A quarter was health care associated (diagnosed within 48 hours of admission in patients with contact with a health care facility <90 days), and the remaining 25% were nosocomial, defined as acquisition of the infection >48 hours after admission.[171,172]

The presence of fever or hypothermia, chills, and localizing symptoms should raise suspicion for a bacterial infection. However, typical symptoms may be absent in patients with cirrhosis. Bacterial infection should be suspected when a patient with cirrhosis deteriorates, particularly with encephalopathy, AKI, and/or jaundice. Workup should be initiated promptly, including skin examination, leukocyte count with differential, diagnostic paracentesis, blood cultures, urine culture, and chest x-ray. If suspicion for infection is strong (e.g., association with systemic inflammatory response), empirical antibiotic therapy should be initiated as soon as samples for cultures have been collected, particularly in the presence of hemodynamic instability. In patients with cirrhosis, in septic shock, mortality increases by 10% for every hour's delay in initiating antibiotics.[171,174,175]

SBP AND OTHER SPONTANEOUS INFECTIONS UNIQUE TO CIRRHOSIS

Symptoms/signs specific to SBP are abdominal pain, tenderness on palpation (with or without rebound tenderness), and ileus. However, up to one-third of the patients with spontaneous infections may be entirely asymptomatic or present with only encephalopathy and/or AKI. The diagnosis of SBP or SBE is established with a fluid (ascites or pleural, respectively) absolute neutrophil count greater than 250/mm^3, a cutoff with the highest sensitivity chosen to avoid SBP being untreated.[176] Spontaneous bacteremia is established with positive blood cultures.

Because the presentation of SBP is variable and a delay in instituting therapy can lead to increased

mortality,[177] a diagnostic paracentesis should be performed as soon as a patient with cirrhosis and ascites is hospitalized emergently for any reason, even in the absence of symptoms suggestive of infection[28,178] or whenever a patient (hospitalized or not) develops signs suggestive of infection.[19,20] In patients with tense ascites and AKI, a diagnostic paracentesis is recommended to exclude SBP as a cause of the AKI. If pleural effusion is present, a diagnostic thoracentesis should be performed when there is no ascites or when diagnostic paracentesis has ruled out SBP while bacterial infection is suspected.

Although the diagnosis is established by ascites cell count, it is very important to isolate a microorganism either from ascites or from blood so that antibiotic susceptibility results may guide antibiotic therapy.[179] Thus, ascitic fluid culture is essential in the evaluation of SBP and should be performed before the administration of the first dose 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% in the diagnosis of SBP.[180] Obtaining simultaneous blood samples for culture increases the possibility of isolating a causative organism.[179]

Spontaneous infections are typically monobacterial, with the most common (~60%) being gram-negative bacteria and with fungi representing less than 5% of infections. Specific microorganisms are mostly enteric (with the most common being *Escherichia coli*, followed by *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecalis*, and *Enterococcus faecium*).[171] More recently, there has been a shift toward gram-positive and multidrug-resistant organisms (MDRO), particularly in nosocomial and health care–associated SBP.[172,181,182] Infections by MDRO represent 35% of overall infections in patients with cirrhosis,[171,172] which has led to a decreased response to the recommended initial empirical antibiotic.[172]

Guidance Statements

- Patients with ascites due to cirrhosis emergently admitted to the hospital should undergo a diagnostic abdominal paracentesis to rule out SBP even in the absence of symptoms/signs of infection.
- Patients with ascites who develop signs, symptoms, or laboratory abnormalities suggestive of infection should undergo workup for infection plus a diagnostic abdominal paracentesis (for cell count and bacteriological culture). If the workup is negative and the patient has a pleural effusion, the patient should undergo a diagnostic thoracentesis.
- The ascitic fluid should be cultured at the bedside in aerobic and anaerobic blood culture bottles before initiation of antibiotics.
- The diagnosis of SBP/SBE is established with a fluid polymorphonuclear (PMN) leukocyte count >250/mm^3.

MANAGEMENT OF SBP

Antibiotics

IV antibiotics should be started empirically (before obtaining culture results) in all patients with an ascites PMN count >250/mm^3. Patients with a focal intra-abdominal inflammatory entity (e.g., diverticulitis, cholecystitis) may have an ascites PMN count >250/mm^3 and should be treated not for SBP but for the specific condition per standard of care, including a surgical consult. Empirical antibiotics should also be started in patients with SBE (pleural fluid PMN count >250/mm^3). Although the term "empyema" carries the implicit need for drainage, a chest tube should not be placed in patients with SBE.

Traditionally, third-generation cephalosporins (ceftriaxone, cefotaxime) were recommended in all patients with SBP, with resolution rates of approximately 90%. Currently, they are recommended as the first-line antibiotics (e.g., IV cefotaxime 2 g every 12 hours) in settings where MDROs are not prevalent (Table 9). With a growing number of infections by MDROs,[172,183] cephalosporins have become less effective, and initial antibiotic therapy should be broader in those with a high likelihood of harboring MDRO infections, specifically those with nosocomial infection or recent hospitalization and critically ill patients admitted in the intensive care unit.[183,184] Inappropriate initial antimicrobial therapy in patients admitted with septic shock increases the risk of death by 10 times.[175] Initial use of carbapenems may lead to higher resolution of SBP and lower mortality in patients with nosocomial[185] or critically ill patients.[184]

The emerging threat of MDROs highlights the importance of antibiotic stewardship—antibiotic coverage should be narrowed as soon as culture results are available and given for as short a time as possible. Additionally, the type of broad-spectrum

TABLE 8. Transplant Criteria for HH

Adult candidates for LT with chronic, recurrent, confirmed HH could be considered on an individual basis for a MELD exception provided that infectious and malignant causes have been ruled out. Documentation submitted for case review should include the following:

- At least 1 thoracentesis >1 L weekly in last 4 weeks; report date and volume of each thoracentesis
- Pleural fluid is transudative by pleural albumin-serum albumin gradient of at least 1.1 and by cell count.
- No evidence of heart failure; provide objective evidence excluding heart failure
- Pleural fluid culture negative on 2 separate occasions
- Pleural fluid cytology is benign on 2 separate occasions
- There is contraindication to TIPS; specify specific contraindication
- Diuretic refractory

antibiotics should be tailored to local prevalence and type of MDRO. In general, patients with risk factors for MDRO should receive piperacillin/tazobactam with vancomycin added in patients with prior infection or a positive surveillance swab for methicillin-resistant *S. aureus*. Daptomycin should be added in patients with prior infection or positive surveillance swab for vancomycin-resistant enterococcus. Patients with current or recent exposure to piperacillin/tazobactam should receive meropenem with or without a glycopeptide (vancomycin or teicoplanin).

Given increasing recent failure rates of initial antibiotic therapy, which may lead to increased mortality,[186,187] it is recommended that a diagnostic paracentesis (or thoracentesis for SBE) be performed 48 hours after initiating antibiotic therapy to assess response. A negative response is defined by a decrease in PMN count <25% from baseline and should lead to broadening the antibiotic spectrum and investigating secondary peritonitis (abdominal imaging studies). Repeat paracentesis/thoracentesis may be unnecessary if an organism is isolated, it is susceptible to the antibiotic used, and the patient is improving clinically. The recommended duration of antibiotic therapy is 5-7 days.[187] A small study showed that length of antibiotic therapy was significantly shorter in those in whom antibiotics were discontinued once PMN count decreased to <250/mm^3 (mean, 4.8 days) compared with duration determined empirically (mean, 9.6 days).[188]

Patients with ascites PMN <250/mm^3 and a positive bacteriological culture (bacterascites) in the absence of any signs of infection should not receive antibiotics, as in most cases it self-resolves or is a contaminant.[189] A repeat diagnostic paracentesis should be performed to investigate progression to SBP.

Albumin

Bacterial infections in patients with cirrhosis are a common precipitant of acute deterioration leading to worsening hepatic decompensation and multiorgan failure, with the kidney being the most commonly affected organ.[190] Conversely, the development of AKI is the main predictor of in-hospital mortality in patients with SBP.[191-193] It is essential to pay close attention to renal function in patients with cirrhosis and an infection, as progressive AKI in this setting portends the poorest prognosis.[194]

In patients with cirrhosis and an infection, albumin plays a much more important role than as a simple expander of the intravascular volume.[195,196] IV albumin improves survival in patients with cirrhosis and SBP.[192] Importantly, patients who most benefited from albumin were those who already had evidence of renal dysfunction (blood urea nitrogen >30 mg/dL or creatinine >1.0 mg/dL) or severe hepatic decompensation (bilirubin >5 mg/dL). The use of albumin plays an important role in preventing the progression of AKI. Although the dose of albumin used in the randomized controlled trial was arbitrarily determined (1.5 g/kg at day 1 and 1 g/kg at day 3), it has remained the standard recommendation. Alternatively, following the recommendations for the use of albumin in patients with AKI would also be appropriate (Fig. 4).[15]

NSBBs

Although a study had suggested an association between NSBB use and higher mortality in patients with SBP,[105] more recent evidence correlates a deleterious or beneficial effect of NSBB in these patients related to mean arterial pressure.[197,198] Therefore, NSBBs do not need to be discontinued in patients with SBP unless hypotensive (e.g., mean arterial pressure <65 mm Hg). If stopped, restarting NSBB may be considered depending on recovery of the systemic arterial blood pressure.[199]

Guidance Statements

- IV antibiotics should be started empirically in all patients with an ascites/pleural fluid PMN count >250/mm^3.

- First-line empirical antibiotic therapy for community-acquired SBP/SBE is IV third-generation cephalosporin.
- In patients with a health care–associated or nosocomial infection or recent exposure to broad-spectrum antibiotics or who are admitted with sepsis or septic shock, empirical therapy with broad-spectrum antibiotics should be initiated as the first line.
- Response to empirical antibiotic therapy may be assessed by repeating diagnostic paracentesis/thoracentesis 2 days after initiation. A decrease in fluid PMN <25% from baseline indicates lack of response and should lead to broadening of antibiotic coverage and further evaluation to rule out secondary bacterial peritonitis.
- Patients with SBP should be treated with IV albumin in addition to antibiotics (1.5 g/kg at day 1 and 1 g/kg at day 3). Patients with AKI and/or jaundice at time of diagnosis of SBP are more likely to benefit from albumin.
- NSBBs should be temporarily held in patients with SBP who develop hypotension (mean arterial pressure <65 mm Hg) or AKI.

SBP PROPHYLAXIS

Prevention of Recurrence (Secondary Prophylaxis)

Patients with a prior episode of SBP are at a very high risk of SBP recurrence. In a landmark multicenter randomized controlled trial, the 1-year probability of developing recurrent SBP was significantly lower with norfloxacin (20%) compared with placebo (68%).[200] Although the trial preceded the emergence of gram-positive or MDRO infections, norfloxacin was considered the antibiotic of choice until it was withdrawn from the US market in 2014.

A reasonable alternative to norfloxacin is oral ciprofloxacin (500 mg/day), although direct evidence in support for this regimen is lacking. Moreover, the effectiveness of quinolones in patients with MDRO or organisms other than gram-negatives is uncertain—it has been shown that quinolone prophylaxis in patients colonized with MDRO is less effective.[201] More recently, limited data have been reported comparing norfloxacin with other antibiotics. For example, a single-center open-label randomized trial showed rifaximin had a lower 6-month incidence of recurrent SBP compared with norfloxacin (4% vs. 14%, respectively).[202] Similarly, high-quality data in support of sulfamethoxazole/trimethoprim for secondary prophylaxis are lacking, although some experts have advocated its use. To date, prevention of spontaneous bacteremia or SBE has not been studied.

Prevention of First Episode of SBP (Primary Prophylaxis)

In principle, antibiotics should be used judiciously and sparingly in patients without a prior history of SBP and reserved only for those at the highest risk of infection.[182] The risk of SBP and other bacterial infections is high in patients with cirrhosis and acute upper gastrointestinal hemorrhage. In a meta-analysis of five studies, short-term (5-7 days) selective intestinal decontamination (mostly oral norfloxacin) reduced the rate of infections, including SBP, and improved survival.[203] Because the emergence of quinolone-resistant organisms has decreased the prophylactic efficacy of norfloxacin,[204] IV ceftriaxone is currently the recommended antibiotic in patients with hemorrhage,[205] administered until hemorrhage has resolved and vasoactive drugs are discontinued. SBP and other infections should be ruled out before starting the antibiotic.

In patients without gastrointestinal hemorrhage and without a prior episode of SBP, antibiotic prophylaxis may be considered in selected patients at a high risk of SBP. For example, low (<1.5 g/dL) ascitic fluid protein concentration predisposes to the development of SBP, presumably from decreased ascitic complement levels and opsonic activities.[206] Additional risk factors affect the incidence of SBP, even in patients with low ascites protein—the 1-year probability of SBP may vary between 20% and 60%, depending on the severity of liver and/or kidney dysfunction.[207]

Helpful insights may be gleaned from a landmark trial, in which norfloxacin was associated with a significantly reduced 1-year probability of first SBP compared with placebo (60% vs. 7%) in patients with low protein ascites and advanced liver failure (Child-Turcotte-Pugh score >9 points with serum bilirubin level >3 mg/dL) or impaired renal function (serum creatinine level >1.2 mg/dL, blood urea nitrogen level >25 mg/dL, or serum sodium level <130 mEq/L).[207,208] Importantly, the incidence of HRS was also lower in patients randomized to

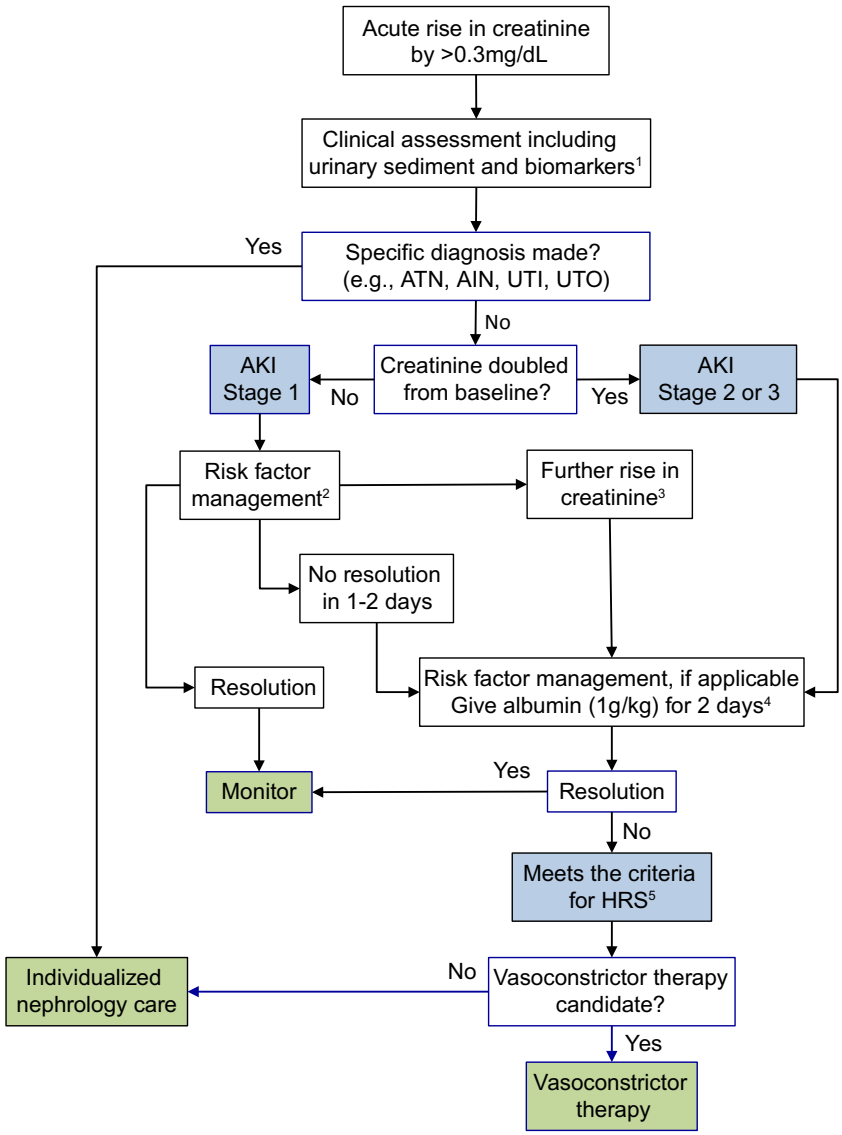

FIG. 4. Proposed algorithm for the diagnosis and management of AKI in cirrhosis. The key diagnostic steps include (1) clinical assessment and examination of urinary sediments and biomarkers, (2) response to risk factor management, and (3) response to albumin infusion. [1]Clinical assessment includes evaluation for prerenal (e.g., overdiuresis, dehydration) or structural (e.g., shock, nephrotoxins, obstructive uropathy) etiologies. Urinary sediments and biomarkers (particularly NGAL [see Table 12]) may indicate ATN, whereas fractional excretion of sodium <1% may suggest HRS. [2]Risk factor management includes the withdrawal of nephrotoxic drugs, reduction or withdrawal of diuretics, detection, and treatment of infections, if present, and volume replacement (if severely volume-depleted) using 5% albumin or crystalloids, preferentially balanced, initially. [3]Patients experiencing a further rise in serum creatinine despite risk factor management may immediately proceed to the next step, namely albumin challenge. Some members of the writing group advocate taking into account the absolute creatinine value in addition to the change in creatinine to expedite this step to allow earlier institution of vasoconstrictors in patients with a high (e.g., >1.5 mg/dL) creatinine. [4]These patients are expected to have ascites, commonly refractory, and almost always hyponatremia. [5]HRS defined as described in Table 11. AIN, acute interstitial nephritis; UTI, urinary tract infection; UTO, urinary tract obstruction.

norfloxacin. However, mortality past 3 months was not improved on norfloxacin. A recent large randomized controlled trial of norfloxacin versus placebo in Child C patients failed to achieve its primary endpoint of improved survival, although norfloxacin prevented SBP.[208] More recently, the efficacy of norfloxacin is shown to have decreased over time,[209] particularly in patients colonized with MDRO.[201]

Similar to secondary prophylaxis, antibiotic alternatives to norfloxacin, such as ciprofloxacin, rifaximin, and sulfamethoxazole/trimethoprim, have been studied, including a number of meta-analyses.[210-212] Altogether, the studies are of variable quality and considered insufficient to support a consensus guidance recommendation. Thus, evidence for primary prophylaxis with antibiotics is not strong and is restricted to patients with very advanced cirrhosis. SBP prophylaxis should be individualized based on estimated risks and benefits with the patient characteristics and the limited data on various antibiotics taken into account. For example, a hospitalized patient in whom LT is imminent would be a good candidate for prophylaxis, and ciprofloxacin would be a reasonable choice. However, the growing concerns regarding the safety profile of fluoroquinolones that have led to restrictions/warnings by both the US Food and Drug Administration and European Medicines Agency[213] must be kept in mind.

Guidance Statement

- Patients who have recovered from an episode of SBP should receive long-term prophylaxis with daily norfloxacin. In settings in which norfloxacin is unavailable, oral ciprofloxacin is acceptable.
- Antibiotic prophylaxis for SBP should be instituted in patients with cirrhosis and upper gastrointestinal hemorrhage. IV ceftriaxone 1 g/24 hours is the antibiotic of choice and should be used for a maximum of 7 days.
- In patients with cirrhosis and low protein (<1.5 g/L) ascites, primary SBP prophylaxis can be considered in selected patients with renal dysfunction (serum creatinine level >1.2 mg/dL, blood urea nitrogen level >25 mg/dL, or serum sodium level <130 mEq/L) or liver failure (Child-Turcotte-Pugh score >9 and bilirubin >3 mg/dL).

INFECTIONS NOT UNIQUE TO CIRRHOSIS

Diagnostic criteria for non-SBP infections (e.g., pneumonia, cellulitis) should, in general, follow the guidelines for the general population, stratified by the risk of having an infection due to a MDRO. In a randomized trial of patients with advanced cirrhosis and non-SBP infections, albumin infusion did not improve in-hospital mortality.[214] In patients with non-SBP infections, AKI may develop, which should be managed accordingly.

AKI and HRS

DEFINITION AND EPIDEMIOLOGY

AKI is common in patients with decompensated cirrhosis and ascites, with a prevalence in hospitalized patients that ranges between 27% and 53%.[215] The development of AKI entails a poor prognosis in patients with cirrhosis, with 30-day mortality ranging from 29% to 44%.[216,217] Moreover, AKI is an independent negative predictor of transplant-free survival and post-LT outcomes.[15,215,218-220] HRS is a type of AKI, known as HRS-AKI under the current terminology, unique to patients with cirrhosis that occurs in the absence of hypovolemia or significant abnormalities in kidney histology.[215,218,219] In contrast to AKI, the chronic impairment in kidney function, known as CKD, is defined as a reduction in estimated glomerular filtration rate <60 mL/1.73 m^2 per minute for at least 3 months.[15,221]

DIAGNOSIS, CLASSIFICATION, AND ETIOLOGICAL FACTORS

AKI is diagnosed by an increase in serum creatinine ≥0.3 mg/dL within 48 hours or ≥50% increase in serum creatinine that is known or presumed to have occurred within the preceding 7 days.[15] By convention, stable creatinine values within the previous 3 months before hospitalization can be used as the baseline in the diagnosis of AKI.[15,66] If a previous creatinine before admission is not available, a formal diagnosis of AKI can only be made if creatinine continues to rise during hospitalization. AKI can be staged according to the criteria listed in Table 10.[66,222]

Main etiologies for AKI in cirrhosis are prerenal AKI and acute tubular necrosis (ATN).[15,215,218-220,222] The two main causes of prerenal AKI are hypovolemia and HRS-AKI. ATN is usually due to septic or hypovolemic shock and, less commonly, nephrotoxic drugs/agents. Bile cast nephropathy in patients with hyperbilirubinemia, glomerulonephritis (e.g., immunoglobulin A in alcohol-associated cirrhosis, membranous or membranoproliferative glomerulonephritis

TABLE 9. Antibiotics for Infections in Cirrhosis

Recommended antibiotics in hospitalized patients with cirrhosis and infection	
(1) Spontaneous infections (peritonitis, bacteremia, empyema)	
Community acquired	Nosocomial
• Third-generation cephalosporin	• Piperacillin/tazobactam AND • Daptomycin (if known VRE in past or evidence of GI colonization) OR • Meropenem if known to harbor MDR gram-negative organisms
(2) Pyelonephritis[273]	
Uncomplicated pyelonephritis	Severe pyelonephritis
• Fluoroquinolone (ciprofloxacin or levofloxacin)	• Third-generation cephalosporin complications (e.g., ceftriaxone) If recent with recent antibiotic exposure: • Piperacillin/tazobactam OR • Carbapenem
(3) Pneumonia[274,275]	
Community acquired	Hospital acquired (not ventilator associated)
(1) Nonsevere • β-lactam + macrolide OR respiratory fluoroquinolone (2) Severe • β-lactam + macrolide or β-lactam + fluroquinolone Vancomycin can be added if patient has prior respiratory isolation of MRSA	(1) Nonsevere (not septic, not intubated): • One of the following: • Piperacillin/tazobactam or • Cefepime or • Levofloxacin Vancomycin can be added if MRSA culture or screening or prior antibiotics in last 90 days (2) Severe (presence of sepsis or requiring intubation): • One of the following: • Piperacillin/tazobactam or • Cefepime or • Meropenem and levofloxacin Vancomycin can be added if MRSA culture or screening or prior antibiotics in last 90 days *Pseudomonas* coverage: if there is prior respiratory isolation of *Pseudomonas* or recent use of parenteral antibiotics or hospitalization
(4) Cellulitis[276]	
Moderate (with systemic signs of infection)	Severe (failed antibiotics, presence of sepsis)
• Penicillin or ceftriaxone or cefazolin or clindamycin	• Vancomycin plus piperacillin/tazobactam

Note: We acknowledge the assistance of Dr. Maricar Malinis (Section of Infectious Diseases and Transplant Surgery, Yale University School of Medicine) in the development of this table.
Abbreviations: GI, gastrointestinal; MDR, multidrug resistant; MRSA, methicillin-resistant *S. aureus*; VRE, vancomycin-resistant *enterococcus*.

TABLE 10. Stages of AKI

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

*Within stage 1, the absolute level of serum creatinine has clinical significance. For example, patients with AKI stage 1 with serum creatinine ≥1.5 mg at diagnosis fared significantly worse than those with lower serum creatinine. Some members of the writing group favored adopting literature proposing stage 1A (creatinine <1.5 mg/dL) and stage 1B (creatinine ≥1.5 mg/dL).[222] The rest of the group felt the effect of creatinine on the patient outcome is continuous.

in hepatitis B virus/hepatitis C virus cirrhosis), or postrenal obstruction are less common causes of AKI, which should be considered as part of the differential diagnosis. In large studies, AKI is attributed to hypovolemia (27%-50% of all cases), HRS-AKI (15%-43%), and ATN (14%-35%).[215]

TABLE 11. Diagnosis of HRS-AKI

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

*The old terminology, type-1 HRS, has been replaced by HRS-AKI. For reference, therapeutic studies to date have used the historical definition: sudden impairment of kidney function, namely a 100% increase in serum creatinine to a value >2.5 mg/dL (221 μmol/L) within <2 weeks.
†Increase in serum creatinine ≥0.3 mg/dL from baseline within 48 hours or a percent increase in serum creatinine of ≥50% which is known or presumed to have occurred within the preceding 7 days.[15]
Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

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 into the current criteria of AKI (100% increase in creatinine to a value greater than 2.5 mg/dL), and a second pattern, known as type-2 HRS, falls into the current definition of CKD.[26]

Determining the cause of AKI in cirrhosis may be difficult, and the differential diagnosis depends on a combination of data from history, physical examination, and urine findings, including urine sediment, fractional excretion of sodium or urea, and urine sodium concentration in patients receiving diuretics. Differentiating ATN from the severe form of HRS-AKI is particularly challenging because of the lack of clear diagnostic indicators.[15,215,218-220,223,224] Currently, the diagnosis of HRS-AKI is made using the consensus criteria after excluding hypovolemia, shock, nephrotoxic agents, and structural kidney damage (Fig. 4; Table 11).[15,26,215] In recent years, several urine biomarkers of tubular damage have been shown to be potentially useful for differential diagnosis of AKI in cirrhosis, including neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18, liver fatty-acid binding protein, and albumin.[225,226] Among those, urine NGAL is the most promising biomarker, with area under the receiver operating characteristic curve ≥0.80 for ATN diagnosis (Table 12), but is not widely available in many parts of the world.[17,18,216,225,227-230] The best time to measure NGAL seems to be day 3 of diagnosis.[216]

Guidance Statement

- Once AKI is diagnosed, an investigation to uncover and treat precipitating factors must be conducted swiftly. Relevant risk factors include fluid losses, bacterial infections, hemodynamic instability, and potentially nephrotoxic agents (e.g., particularly nonsteroidal anti-inflammatory drugs).
- Hypovolemia-induced AKI should be managed with fluid replacement therapy, correction of the cause that led to volume depletion, and diuretic withdrawal.
- Differential diagnosis of AKI, HRS, and ATN is challenging and should follow the consensus criteria presented in the algorithm in Fig. 4.

PREVENTION OF AKI

The first principle in the prevention of AKI is the treatment or prevention of possible precipitating factors, particularly gastrointestinal bleeding and bacterial infections, and avoiding LVP without albumin administration. In addition, there are specific circumstances for which management recommendations may be made to prevent AKI. For example, IV albumin, together with antibiotics, reduces the incidence of HRS-AKI and improves survival in patients with SBP.[192] By contrast, albumin in patients with cirrhosis and bacterial infections other than SBP neither prevents HRS-AKI nor improves survival.[231,232]

MANAGEMENT OF AKI

Once AKI is diagnosed, it should be treated as soon as possible, and if the patient has concomitant complications such as severe hepatic encephalopathy or multiorgan failure or requires RRT, management in an intensive or intermediate care unit should be considered. Patients should be monitored closely for worsening of kidney function and emergence of further complications, particularly bacterial infections.[233,234] Although there is no specific therapy to reverse AKI,

a diligent search must be conducted for treatable causes such as hypovolemia, drug-induced nephrotoxicity, or urinary tract obstruction. Indwelling bladder catheterization should be avoided. Measurement of urine volume, a component in the diagnosis of AKI, is important because oliguria is associated with poor prognosis.[235] Diuretics should be stopped after the diagnosis of AKI. As discussed above, withholding NSBBs should be considered, particularly in patients who are hypotensive.[236] The efficacy of prophylactic antibiotics in patients with AKI has not been assessed.

TREATMENT OF HRS-AKI

Because HRS-AKI is a relatively new term, published therapeutic trials employ the old terminology, namely type-1 HRS (Table 11).[26] It is not certain whether the results of those studies apply to patients with less severe forms of HRS-AKI who fall outside the diagnostic criteria of type-1 HRS.[66] Several randomized controlled trials and meta-analyses have shown that vasoconstrictors, either terlipressin or norepinephrine, in combination with albumin are effective in improving kidney function in patients with HRS-AKI, with the response rate of 20%-80% (average ~50%).[215]

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

Terlipressin is available in many countries but not in United States and Canada. Recently, a large randomized, placebo-controlled trial comparing terlipressin versus placebo (CONFIRM trial) in patients with HRS-AKI performed in North America has been reported in an abstract form. The results of this study confirm findings that terlipressin, in combination with albumin, is associated with higher likelihood of reversal of HRS and 10-day survival without RRT compared with placebo (29.1% vs. 15.8%, $P = 0.012$).[237] As of the time of writing, however, terlipressin is not yet approved in United States for the management of type-1 HRS.

In conjunction with terlipressin, albumin is infused at a dose of 1 g/kg on day 1 of therapy followed by 40-50 g/day, continued for the duration of therapy. Side effects are mainly related to vasoconstrictive effects of the drugs (abdominal pain or ischemia of fingers, skin, intestines, heart, and so on) or development of pulmonary edema from albumin infusion. These side effects occur not infrequently and should be actively looked for, as they are usually not severe and improve after dose reduction or discontinuation of therapy. The risk of ischemic side effects related to terlipressin may be reduced by administration of the drug in a continuous IV infusion (start dose 2 mg/day, increased every 24-48 hours up to 12 mg/day until creatinine decreases).[238]

Norepinephrine appears to be equally effective to terlipressin, although there are fewer data.[215] Norepinephrine is given as continuous IV infusion, typically in an intensive care unit setting, starting at 0.5 mg/hour to achieve an increase in mean arterial pressure of at least 10 mm Hg or an increase in urine output of >200 mL/4 hours. If at least one of these goals is not achieved, the dose of norepinephrine is increased every 4 hours in increments of 0.5 mg/hour up to a maximum of 3 mg/hour.[239] Albumin is also given to maintain a central venous pressure between 4 and 10 mm Hg.

The orally active vasoconstrictor midodrine in combination with octreotide (subcutaneous or IV) is of much lower efficacy than terlipressin.[240] TIPS is not recommended in patients with AKI-HRS because of insufficient information.[194,241]

RENAL REPLACEMENT THERAPY

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

The initiation of RRT in patients with HRS remains controversial and has typically been reserved for patients considered transplant candidates as a bridge to LT. Mortality rates are extremely high in

TABLE 12. NGAL as a Urinary Biomarker for AKI

Author, Year	Patients Included			Day of Urine Collection	AUROC ATN vs. Other	Cutoff Value	Sn/Sp (%)
	AKI, n	HRS, n	ATN, n				
Fagundes et al., 2012[18]	84	33	11	AKI diagnosis	NA	194 μg/g	91/82
Verna et al., 2012[227]	52	20	15	AKI diagnosis	0.86	110 ng/mL	88/85
Belcher et al., 2014[17]	76	16	39	Median 2 days after AKI diagnosis	0.78	365 ng/mL	NA
Ariza et al., 2015[228]	39	12	15	AKI diagnosis ±1 day	0.95	294 μg/g	92/89
Huelin et al., 2019[216]	320	93	39	AKI diagnosis and day 3*	0.87	220 μg/g	88/85

*Urine was collected at diagnosis of AKI and at day 3. Values shown in the table are those from day 3. The best cutoff values of NGAL for differentiating between ATN and other types of AKI, including HRS-AKI, are 365 ng/mL and 220 μg/g creatinine for ELISA and particle-enhance turbidimetry techniques, respectively, according to Belcher et al.[17] and Huelin et al.[216]
Abbreviations: AUROC, area under receiver operating curve; NA, not applicable; sn, sensitivity; sp, specificity.

patients not listed for LT who receive RRT whether the AKI was due to HRS or ATN.[242] A limited trial of RRT may be considered in selected patients who are not transplant candidates, depending on reversibility of other organ failures.[243,244]

LT AND SIMULTANEOUS LIVER-KIDNEY TRANSPLANTATION

Restoring liver function by LT is the ultimate therapy for HRS-AKI. However, recovery of kidney function after LT is not always predictable for a number of factors, such as preexisting comorbidities (e.g., CKD or diabetes), unrecognized intrinsic renal disease, unexpected intraoperative events, and posttransplant immunosuppression.[245] In patients unlikely to recover kidney function, simultaneous liver and kidney transplantation may improve the posttransplant outcomes. However, because of the shortage of donated kidneys, the optimal use of simultaneous liver and kidney transplantation has been debated.

In 2017, the Organ Procurement Transplant Network[244,246-248] introduced new listing criteria for simultaneous liver and kidney transplantation, which include the duration of AKI, need for dialysis, and evidence of CKD.[247,249,250] In addition, the safety net approach was introduced to provide a period after LT to allow for renal recovery and, at the same time, guarantee prioritization of kidney transplantation in patients who have persistent or develop kidney dysfunction (Table 13). However, factors that may impact kidney recovery such as age, comorbidities, or etiology of AKI[251-253] are currently not included in the criteria.

Most patients with AKI-HRS, particularly those meeting the old type-1 HRS criteria, have very high MELD scores. Successful treatment of their AKI leads to a reduction in MELD score because of improvement in creatinine values, which disadvantages the patient, whereas the decrease in MELD may not translate to a meaningful gain in survival.[215] To overcome this problem, some countries have implemented policies such as maintaining the pretreatment MELD score or assigning extra points for patients treated for HRS regardless of treatment response.[254] In the absence of such considerations, risks and benefits of vasoconstrictor therapy must be weighed, including the need for RRT in the perioperative period, need for simultaneous liver and kidney transplantation, and short and longer posttransplantation course.

Guidance Statement

- The treatment of choice for HRS-AKI is vasoconstrictor drugs in combination with albumin. The preferred drug is terlipressin, administered either as IV bolus or continuous IV infusion.
- In settings where terlipressin is not available, norepinephrine should be given. If neither can be administered, a trial of oral midodrine (5 to 15 mg per os every 8 hours) in combination with octreotide (100 to 200 μg every 8 hours or 50 μg/hour IV) may be considered, yet the efficacy is low.

- Patients should be closely monitored for the possible development of side effects of vasoconstrictors and albumin, including ischemic complications and pulmonary edema.
- Response to terlipressin or norepinephrine is defined by creatinine decreases to <1.5 mg/dL or return to within 0.3 mg/dL of baseline over a maximum of 14 days. 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 treatment discontinuation and should be retreated.
- All patients with cirrhosis and AKI should be considered for urgent LT evaluation given the high short-term mortality even in responders to vasoconstrictors.
- RRT should be used in candidates for LT with worsening renal function or electrolyte disturbances or increasing volume overload unresponsive to vasoconstrictor therapy. Initiation of RRT in patients who are not candidates for LT must be made with a clear endpoint in mind.
- Given the complexity of patients with suspected HRS-AKI, decisions about management including initiation of vasoconstrictor therapy and RRT should be made, if possible, by multidisciplinary teams including specialists in hepatology, nephrology, critical care, and transplant surgery.
- Simultaneous liver-kidney transplantation may be necessary for patients who are not expected to recover kidney function posttransplantation.

Management of Ascites in Cirrhosis in Children

EPIDEMIOLOGY

Among children with ascites due to cirrhosis, the underlying causes of cirrhosis include biliary atresia, primary sclerosing cholangitis, autoimmune hepatitis, cholestatic genetic disorders, Wilson disease, alpha-1 antitrypsin deficiency, and many other genetic metabolic disorders. Ascites in newborns and infants can be secondary to cirrhosis caused by congenital infections, mitochondrial disorders, tyrosinemia, and biliary atresia, among other diagnoses. The incidence of cirrhotic ascites overall in children has been poorly quantified, although in biliary atresia, approximately 13% will develop ascites within 90 days of their Kasai procedure and 38% will develop it by 2 years of age.[255,256] Chronic viral hepatitis and nonalcoholic fatty liver disease very rarely cause ascites in children. As in adults, the development of ascites in a child with cirrhosis typically signifies decompensation, a worsening prognosis, and the need to evaluate for LT.[257]

DIAGNOSIS AND MANAGEMENT OF ASCITES IN CHILDREN

The diagnosis of ascites, its underlying cause, and the presence of complications require a comprehensive evaluation of the child (Table 2). Ultrasonography is used to confirm the presence of ascites, differentiate abdominal distension due to fluid accumulation from that due to organomegaly, and identify important associated abnormalities (e.g., venous thromboses, kidney abnormalities). Although the indications for diagnostic paracentesis in children have been poorly defined, it has generally been recommended when the cause of ascites is unclear or when SBP is suspected (Table 3).[258]

Salt restriction remains a key component in the management of ascites in children. A sodium intake of less than 2 mmol/kg per day is recommended for children with cirrhotic ascites. Infants fed only with breast milk or infant formula feeds receive about 1 mmol/kg per day, and those taking weaning foods with no added salt will also fall within the 2 mmol/kg per day limit. Based on expert opinion and adult recommendations, water restriction is generally recommended when serum sodium is reduced ≤125 mEq/L.[259]

Diuretic therapy for pediatric ascites is commenced with spironolactone or spironolactone and furosemide in combination. Although the pharmacokinetics of spironolactone have not been studied in children, a dose range of 1-4 mg/kg per day is commonly used, typically starting with 1-2 mg/kg per day and escalating to higher dose as needed. Dose changes should occur at 3 to 5-day intervals because the clinical response is slow to appear. Furosemide treatment is added either from the outset or when dose increases in spironolactone are required and/or if hyperkalemia occurs. Furosemide is started at 0.5 mg/kg per dose twice daily and increased as needed. The adequacy of diuretic therapy can be monitored as in adults by weight loss and by urine sodium estimation.

TABLE 13. Eligibility Criteria for simultaneous Liver-Kidney Transplantation

Eligibility Criteria for SLK
1. AKI ≥6 consecutive weeks with one or a combination of both (weekly documentation) • Dialysis • eGFR/CrCl ≤25 mL/min
2. CKD with GFR ≤60 mL/min for >90 days with one of the following: • End-stage renal disease • eGFR/CrCl ≤30 mL/min at the time or after registration on kidney waiting list
3. Metabolic diseases
4. Safety net: • Any patient who is registered on the kidney waitlist between 60 and 365 days after LT and is either on chronic hemodialysis or has an eGFR <20 mL/min will qualify for increased priority

Abbreviations: CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; SLK, simultaneous liver-kidney transplantation.

TABLE 14. Challenges and Future Direction in Ascites and HRS

Key Areas of Uncertainty and for Future Research
Multidisciplinary care for patients with cirrhosis and ascites: As ascites is the most common decompensation-defining complication, patients with hepatic decompensation may be best served by a team of health care providers consisting of physicians, advanced practitioners, nurses, medical assistants, dieticians, social workers, and psychologists. The best practice for a multidisciplinary program needs to be defined.
Optimal use of albumin: It was pointed out that albumin is more than a protein that generates the oncotic pressure. It is used for diverse indications in patients with cirrhotic ascites. There are many issues to be defined with high-quality studies, including the benefits of long-term infusion in patients with ascites, including RA, optimal dosing in various settings such as LVP, SBP, and so on.
Selection of candidates and timing for TIPS in patients with RA: The MELD score was developed initially to define patients who are too ill to receive TIPS. The other end of the spectrum is not well defined, namely whether the early deployment of TIPS may improve outcomes in patients with RA
Role of vaptans in patients with cirrhosis: Although the arginine vasopressin antagonists are approved for hyponatremia, their aquaretic property may be useful in patients with ascites, including grade 3 and RA.
Window for NSBBs: Beta-blockers are firmly established as a standard of care for patients with portal hypertension. Whether and when NSBBs may become harmful in patients with ascites and related complications needs to be clearly defined.
Spontaneous infection by MDROs: Spontaneous infections in patients with cirrhosis are increasingly caused by MDROs. Early, accurate microbial diagnosis, perhaps using molecular diagnostic tools, guiding antimicrobial therapy may help antibiotic stewardship.
Biomarkers for renal injury and recovery: In patients with HRS and AKI, predictive biomarkers to guide vasopressor therapy may streamline management. For patients undergoing LT, biomarkers to predict renal recovery will help select candidates for simultaneous liver-kidney transplantation and inform postoperative management.
Liver allocation after vasoconstrictor therapy: Anticipating more widespread use of vasoconstrictor therapy in the United States in the near future, mortality risk in patients who recover their renal function from HRS-AKI needs to be accurately captured by the organ allocation system.
Pediatric patients with ascites: Given the low prevalence of cirrhosis and ascites in children, it is inevitable that large-scale high-quality data are difficult to generate. Nonetheless, we advocate for more support for research in children with cirrhosis and ascites.

In children with grade 3 and RA, IV infusion of 25% albumin combined with 0.5-1.0 mg/kg furosemide has been used to improve the mobilization of ascites when serum albumin is low (e.g., <2.5 g/dL), although pediatric-specific data are not available.[260]

There are few data on the indications, safety, and efficacy of LVP in children, although it is used for the treatment of large-volume, tense ascites in children.[261,262] Albumin infusion appears to reduce the risk of PPCD in children, which is highest when a high volume of ascites is removed and if the flow rate is fast, based on results of a single pediatric study.[262] In this small observational study of 32 children, for children not receiving albumin infusion (n = 15), the mean flow rate differed between those developing PPCD (n = 10, 1,224 ± 476 mL/hour) compared with those who did not (n = 5, 678 ± 214 mL/hour).[262] However, the area under the receiver operating characteristic curve for the flow rate to predict PPCD was only 0.6, which precludes a strong recommendation based on the data. Many children will require general anesthesia or deep sedation for paracentesis, and repeated paracentesis may therefore become challenging.[261] Children undergoing LVP are generally given 25% albumin infusion of 0.5-1.0 g/kg, or 6-8 g per liter of ascites removed.[262,263]

Case series have reported the feasibility of inserting TIPS in children, primarily for the treatment or prevention of variceal bleeding.[263-266] In small numbers of children with RA, TIPS has been shown to be a highly effective treatment approach for ascites.[263,264] Reported rates of hepatic encephalopathy after TIPS in children vary between 0% and 48%.

COMPLICATIONS OF ASCITES IN CHILDREN

SBP in children may present with symptoms and signs, such as abdominal pain, fever, worsening ascites, and/or with worsening liver biochemistry (elevated aminotransferases, elevated bilirubin). The diagnosis of SBP is established with an ascites PMN count of >250/mm^3. SBP was identified in 19% of children

admitted to hospital with ascites and fever or clinical deterioration in a small report from Brazil and in 28% of children in a case series from India.[267,268] Following their initial admission with SBP, children had a higher risk of death or LT than those without SBP.[269] If bacteria grew when the ascites fluid samples from these children were cultured, the majority were gram-negative organisms. Broad-spectrum antibiotic coverage against both gram-positive and negative organisms should be commenced in children with ascites PMN count >250/mm^3, or children with suspected SBP in whom diagnostic paracentesis cannot be achieved. The role of prophylactic antibiotics to prevent SBP in children has not been studied.

The prevalence of AKI in children with cirrhosis is not known, and there is no agreed-on definition of AKI in this population. There are very few reports of pediatric HRS in the literature, and this condition is not commonly encountered in children.[270,271] HRS was identified in 6% of children waiting for LT in one center.[270] Data on pharmacologic therapy with vasoconstrictors such as terlipressin are emerging but still very limited in pediatric population.[270,272]

Guidance Statements

- Diagnosis of ascites and its cause in children requires a comprehensive evaluation of clinical history, examination, and diagnostic testing, including abdominal ultrasound.
- Children with cirrhosis and ascites should be referred for evaluation for LT.
- Ascites in children is initially managed with restricted sodium intake to below 2 mmol/kg per day and administration of spironolactone (1-4 mg/kg per day) and furosemide (1-3 mg/kg per day in divided doses).
- Symptomatic children with grade 3 and treatment RA should usually undergo therapeutic paracentesis, although the indications, risks, and benefits of this procedure in children have not been fully defined.
- Children undergoing LVP should receive 25% albumin infusion of 0.5-1.0 g/kg, or 6-8 g per liter of ascites removed.
- Diagnostic paracentesis should be performed in children with ascites and fever, abdominal pain, or clinical deterioration. The risks and benefits of this procedure for use in all children with new ascites but without these symptoms have not been defined.
- Children with proven or suspected SBP should be treated with broad-spectrum antibiotic cover against both gram-positive and gram-negative organisms.
- No recommendation can be given for the management of AKI and HRS in children with cirrhosis because of the absence of relevant definitions and lack of data on treatment and outcomes.

FUTURE DIRECTIONS

Key areas of uncertainly and for future direction are included in Table 14.

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