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GUIDELINES

Asia–Pacific association for study of liver guidelines on management of ascites in liver disease

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Purpose and scope of these guidelines

The development of ascites is a landmark event in the natural history of cirrhosis. This guidance statement by the Asia–Pacific Association for Study of Liver (APASL) provides an evidence-based approach to managing ascites and its complications in patients with chronic liver disease. These guidelines extensively review the differential diagnosis, diagnostic evaluation, and management of ascites, hyponatremia, hepatic hydrothorax and hepatorenal syndrome (HRS) in patients with cirrhosis and acute-on-chronic liver failure (ACLF). A panel of international experts was invited to formulate the guidelines. The opinions of the experts were collected using two sets of Delphi questionnaires. Then, an online meeting of all the experts was held to discuss the evidence and formulate the final recommendations by consensus. The guidelines were developed using the GRADE system for analysing the level of evidence and strength of recommendation (Table 1). All authors have gone through the guidance document and endorse the same.

In this document, we have also covered the grey areas which have been underexplored in previous guidelines and some of the issues which are relatively peculiar to the Asia–Pacific region. Given the high burden of tuberculosis in some of the countries of the Asia–Pacific region, mixed ascites is not uncommon in these patients with liver disease. We discuss the diagnostic approach to mixed ascites and the role of ascitic fluid adenosine deaminase (ADA) and other tests for tuberculosis. In addition, many countries in the Asia–Pacific region are low-middle-income countries, and financial constraints are an essential barrier to liver transplants and other costly therapies like albumin. Hence, we have discussed the role of low-dose albumin in the prevention of paracentesis-induced circulatory dysfunction (PICD) after large-volume paracentesis (LVP) and the prevention of acute kidney injury (AKI) in patients with spontaneous bacterial peritonitis (SBP). We have also reviewed the current evidence of outpatient albumin in managing patients with ascites and have made practical recommendations. We also highlight the timing of albumin infusion concerning LVP. To decrease adverse events and improve patient compliance with diuretic therapy, the guidelines emphasize initiating low-dose diuretics and gradually increasing the dose to the maximum tolerable dose. Non-alcoholic fatty liver disease (NAFLD), also referred to as Metabolic associated fatty liver disease (MAFLD) by some societies has become a significant cause of chronic liver disease worldwide [1]. Many patients with NAFLD/MAFLD related cirrhosis are on angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) when they present to a hepatologist or gastroenterologist with ascites. For the first time, we provide guidance statements regarding the use of these drugs in patients with cirrhosis and ascites. For refractory ascites, we have now defined renal dysfunction following the International Club of Ascites (ICA) recommendations on AKI. Lastly, we have highlighted the gaps in our knowledge and have provided directions for future research.

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Table 1 GRADE consensus guidelines for analysing the level of evidence and strength of recommendation

	Notes	Symbol
Grading of evidence		
High quality	Future research is very unlikely to change our confidence in the estimate effect	A
Moderate quality	Future research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate effect	B
Low or very low quality	Future research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate effect. Any estimate of effect is uncertain	C
Grading of recommendations		
Strong recommendation	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty; more likely a weak recommendation is warranted. Recommendation is made with less certainty: higher cost or resource consumption	2

Introduction

The burden of ascites due to cirrhosis

The most common decompensation in patients with cirrhosis is ascites, which is seen in more than 50% patients. The rate of development of ascites is 5–10% per year in patients with compensated cirrhosis and once ascites develop, 5-year mortality increases to about 50% [2]. In addition, the development of ascites predisposes patients to bacterial infections and HRS leading to a further increase in mortality.

HRS occurs later in the natural history of decompensated cirrhosis with an incidence of 18% at 1 year and 39% at 5 years [3]. After the development of HRS, the median survival decreases to about 3 months.

Pathogenesis

Patients with cirrhosis develop ascites due to two main pathophysiological events—portal hypertension, and sodium and water retention. Architectural distortion and fibrosis in patients with cirrhosis cause increased resistance to portal venous blood flow. This is manifested as increased sinusoidal pressure, and it has been demonstrated that the formation of ascites does not occur if the portal pressure gradient is below 8 mmHg [4]. Activated hepatic stellate cells also play an important role in ascites pathogenesis by having a contractile function which adds to the intrahepatic vascular resistance. This is further augmented due to the reduced nitric oxide (NO) production in cirrhotic livers. The contribution of vasoconstriction to increased intrahepatic resistance is around 25%. An increase in portal pressure causes the formation of portosystemic collaterals through the effects of vascular endothelial growth factor (VEGF) secreted from the intestinal microvasculature. The rise in portal pressure induces endothelial nitric oxide synthase producing NO and facilitating splanchnic arterial vasodilation. This further leads to increased portal blood flow and a rise in portal pressures. The formation of portosystemic collaterals shunts these vasodilatory molecules like NO to the systemic circulation causing peripheral vasodilation and a state of "effective hypovolemia" and arterial underfilling. Effective arterial hypovolemia leads to reduced renal blood flow causing activation of the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system and vasopressin system. RAAS activation causes renal sodium retention and vasopressin system activation leads to decreased free water clearance. Both these mechanisms ultimately cause fluid accumulation in the form of ascites and pedal edema. Decreased renal perfusion is the predominant mechanism of the development of HRS. Organ dysfunctions in patients with cirrhosis have also been recently linked to systemic inflammation due to increased gut permeability and bacterial translocation secondary to portal hypertension [5]. These pathophysiologic events are summarized in Fig. 1.

Evaluation of a patient with ascites

An essential aspect of managing ascites is identifying the cause of ascites. While the commonest cause is portal hypertension, other causes like tuberculosis, malignancy, renal failure, heart failure and pancreatic diseases need to be ruled out. The initial evaluation should include history to look

for specific pointers for cirrhosis like the presence of high-risk behaviour (alcohol misuse, injection drug abuse, etc.), presence of pre-disposing conditions like hepatitis B and hepatitis C, or the presence of other decompensations like upper gastrointestinal bleed, jaundice and/or hepatic encephalopathy. Clinical examination should focus on stigmata of chronic liver disease and signs of other conditions which can cause ascites (Table 2). Clinically, ascites may be detected by the presence of shifting dullness and/or fluid thrill. However, shifting dullness requires the presence of at least 1.5 L of fluid in the abdomen. Therefore, ultrasonography of the abdomen is considered the gold standard for the detection of ascites. Identification of grade of ascites is important as it has implications for management. Ascites can be classified into grade 1, 2 and 3 with grade 1 or mild ascites being detected only by ultrasound, grade 2 or moderate ascites being identified by the presence of shifting dullness while grade 3 or tense ascites is characterised by the presence of fluid thrill.

Role of diagnostic paracentesis

Laboratory analysis of ascitic fluid is vital in identifying the aetiology in patients with new onset ascites (Fig. 2). Ascitic fluid protein and serum ascites albumin gradient (SAAG) are the investigations of choice to differentiate portal hypertensive ascites from non-portal hypertensive ascites. Classically, patients with cirrhosis have low ascitic fluid protein (< 2.5 g/dL) with elevated serum ascites albumin gradient (SAAG). Initially, ascitic fluid protein < 1.5 g/dL was considered a risk factor for the development of spontaneous bacterial peritonitis (SBP). However, recent reports have not highlighted this increased risk [6]. A value of SAAG ≥ 1.1 g/dL (> 11 g/L) for portal hypertensive ascites has a high diagnostic accuracy of 97% [7]. Patients with heart failure and early Budd-Chiari syndrome also have high SAAG ascites (≥ 1.1 g/dL), but, with a high ascitic fluid protein (> 2.5 g/dL). This occurs because hepatic sinusoids are permeable causing extravasation of protein-rich lymph into the abdomen. Measuring serum brain natriuretic peptide (BNP) has

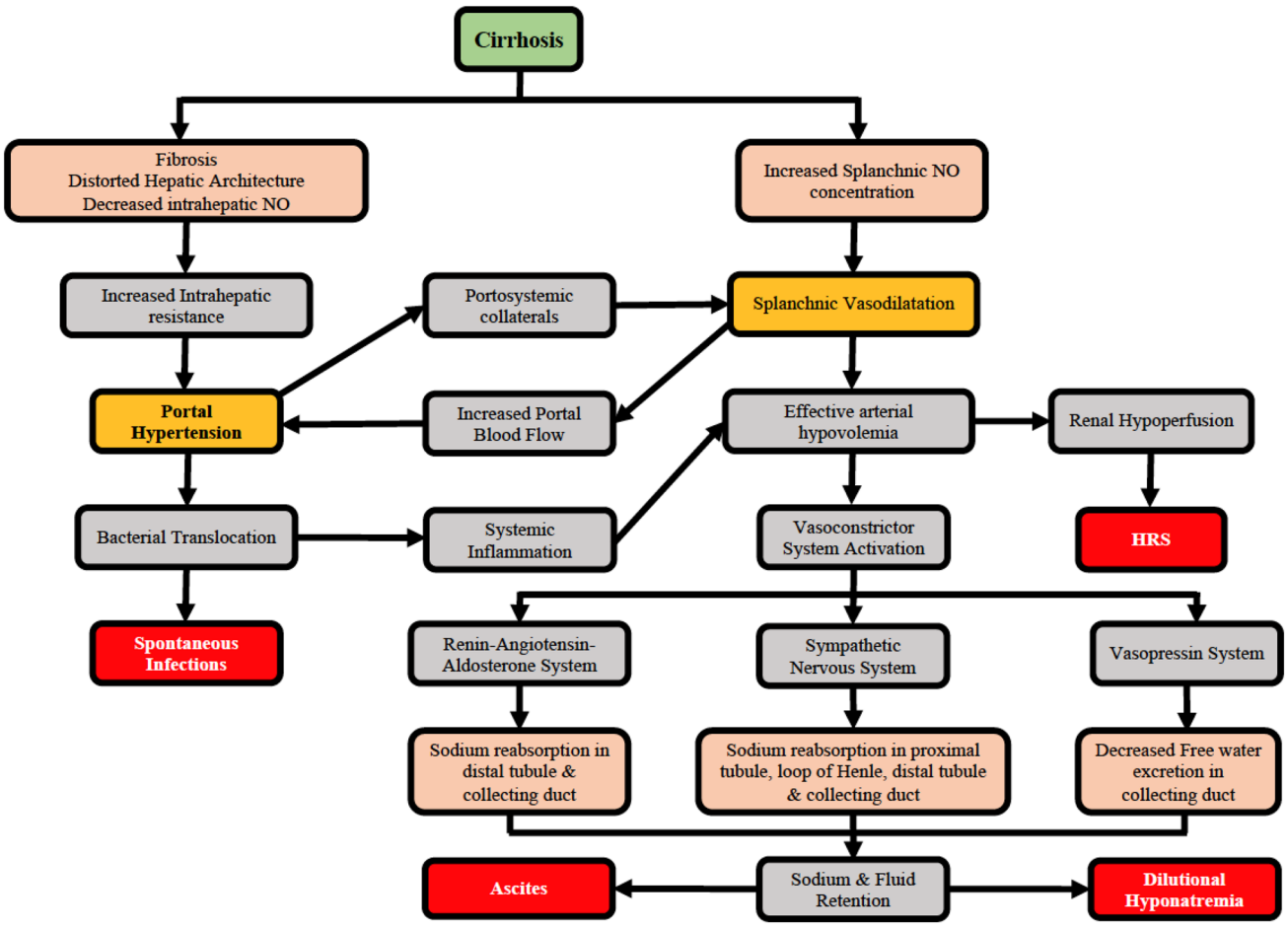

Fig. 1 Pathophysiologic mechanisms leading to the development of ascites and its complications in patients with cirrhosis (*NO* nitric oxide, *HRS* hepatorenal syndrome)

Table 2 Pointers on history and physical examination to identify the cause of ascites

History	Physical examination	
Presence of risk factors for Cirrhosis 1. Injection drug abuse 2. Significant alcohol intake 3. Obesity 4. Diabetes	Shifting dullness or fluid thrill Signs of liver cell failure 1. Icterus 2. Spider Angiomas 3. Paper money skin 4. Gynecomastia 5. Splenomegaly 6. Testicular atrophy	7. Loss of secondary sexual characters 8. Caput medusae 9. Parotid swelling 10. Palmar erythema 11. Purpura 12. Edema 13. Fetor Hepaticus
History of prior decompensations 1. Jaundice 2. Upper gastrointestinal bleed 3. Hepatic Encephalopathy 4. Prior ascites		
Ruling out non-liver causes of ascites 1. Heart Disease—chest pain, orthopnea, syncope, paroxysmal nocturnal dyspnoea 2. Renal Disease—oliguria, frothuria 3. Pancreatic Disease—upper abdominal pain radiating to back	Signs of Heart failure or Constrictive Pericarditis 1. Elevated jugular venous pressure 2. Pulmonary edema 3. Pericardial rub 4. Pedal edema Signs of Pancreatitis 1. Cullen's Sign 2. Grey Turner Sign Signs of Malignancy 1. Lymphadenopathy 2. Abdominal mass Sarcopenia	
History suggestive of malignancy 1. Significant weight loss 2. History of lump		
History suggestive of Tuberculosis 1. Fever 2. Night sweats 3. Weight loss		

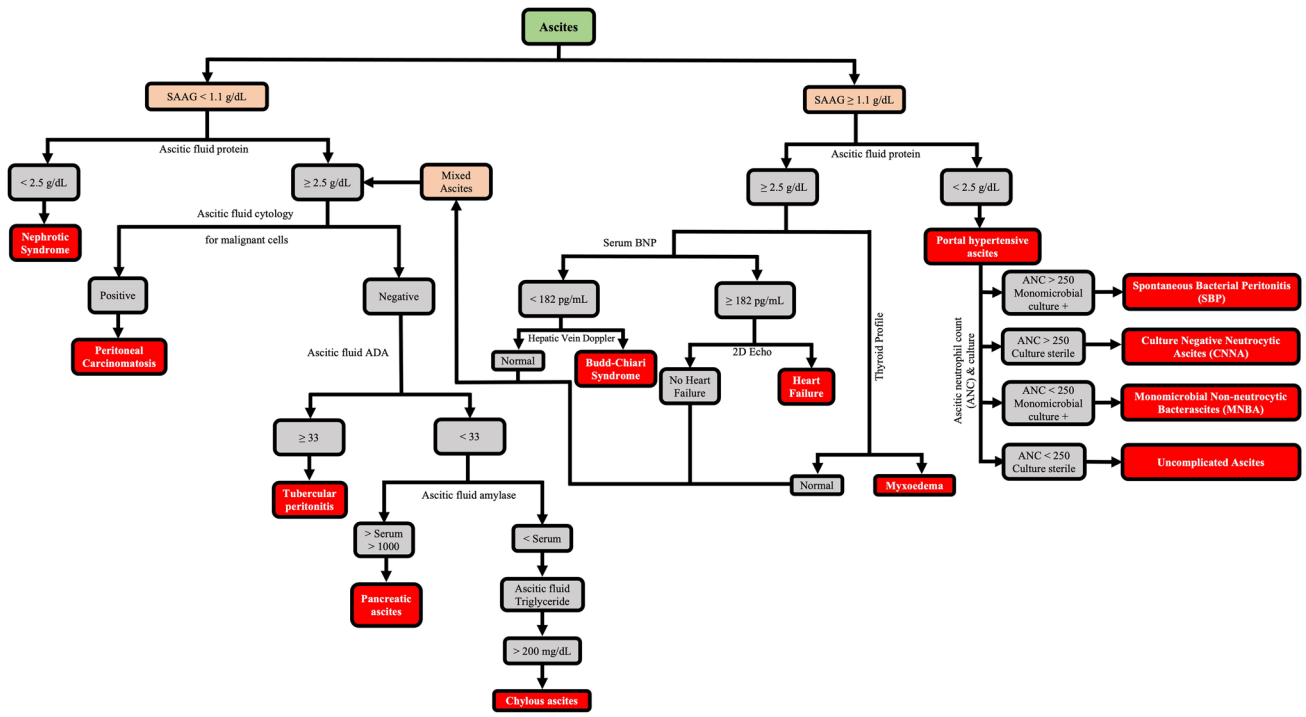

Fig. 2 Diagnostic evaluation and differential diagnosis of ascites in a patient with cirrhosis (SAAG serum ascitic albumin gradient; *BNP* brain natriuretic peptide, *ANC* absolute neutrophil count)

been proposed to identify cardiac failure as a cause of high SAAG and high protein ascites. A serum BNP > 364 pg/mL suggests underlying heart failure, while a BNP value < 182 pg/mL helps rule out underlying heart disease [8]. However, further evidence is required before this can be routinely recommended. Ascitic fluid neutrophil count > 250 cells/cu. mm. signifies the presence of SBP. In patients with suspected SBP, ascitic fluid culture should be sent in a blood culture bottle (~ 10 mL ascitic fluid). Other tests like ascitic fluid pH, amylase, glucose, bilirubin and lactate dehydrogenase are not routinely recommended and should be ordered on a case-to-case basis. Patients who present with grade 3 or tense ascites or respiratory compromise should undergo therapeutic paracentesis to relieve symptoms.

Diagnosis of "mixed ascites" poses a clinical challenge in patients with cirrhosis. Mixed ascites refers to the presence of cirrhosis plus an additional cause of ascites. It is usually associated with peritoneal diseases like peritoneal tuberculosis (TB) or peritoneal carcinomatosis. Approximately 5% of patients with cirrhosis have mixed ascites [7]. Patients suspected to have malignant ascites should undergo ascitic fluid cytology. The yield varies from 0 to 96.7% depending on whether the peritoneum is involved by malignancy or not and can be increased by increasing the volume of ascitic fluid analysed [9], increasing the number of analysis or by combining it with tumor markers in ascitic fluid (carcinoembryonic antigen [CEA], carbohydrate antigen [CA] 15–3 and CA 19–9) [10]. For ascitic fluid cytology, at least 30 mL ascitic fluid should be sent on 3 separate occasions. Diagnosis of peritoneal TB can be made with high specificity by acid-fast bacilli in ascitic fluid or positive *Mycobacterium tuberculosis* culture or polymerase chain reaction (PCR) for TB. However, these have low sensitivity [11]. Also, patients with peritoneal tuberculosis may have a low ascitic fluid glucose. Approximately 30% of patients with peritoneal TB and cirrhosis have low ascitic fluid protein (< 2.5 g/dL) and about 50% of patients will have a low SAAG [11]. Thus, it is crucial to identify other markers for the diagnosis of mixed ascites. Low adenosine deaminase (ADA) in ascitic fluid (< 40 IU/L) was shown to exclude peritoneal TB with an area under the receiver operating characteristic curve (ROC) of 0.98 [12]. A recent study demonstrated that ascitic fluid cholesterol > 45 mg/dL had a higher diagnostic value than SAAG in diagnosing mixed ascites [13]. Also, according to SAAG, 70% patients with peritoneal carcinomatosis and 100% patients with peritoneal TB were misclassified. Therefore, they could be correctly diagnosed using ascitic fluid cholesterol [13]. However, more evidence is needed regarding measuring ascitic fluid cholesterol in patients with mixed ascites. If the diagnosis of ascites is still in doubt, diagnostic laparoscopy may be considered.

Recommendations

- Diagnostic paracentesis is recommended (A1) in all patients with –
  - new onset grade 2–3 ascites,
  - admitted with worsening ascites or any major complication of cirrhosis including acute-on-chronic-liver failure (ACLF),
  - clinical suspicion of SBP,
  - clinical suspicion of a non-portal hypertensive cause of ascites
- Initial laboratory evaluation in patients with first episode of ascites should include ascitic fluid total protein, albumin, SAAG and neutrophil count. In patients with recurrent ascites, neutrophil count should be done routinely with other investigations being restricted to a case-to-case basis (A1).
- At least 10 mL ascitic fluid should be inoculated in a blood culture bottle in patients suspected to have SBP, preferably before the institution of antibiotic therapy (A1).
- Ascitic fluid ADA may be considered an initial investigation in regions with a high prevalence of tuberculosis (C1).

Management of portal hypertensive ascites

General management

Patients with cirrhosis and ascites have effective arterial hypovolemia. Hence, all drugs aggravating this hemodynamic abnormality should not be used in patients with portal hypertensive ascites. The most commonly implicated drugs include nonsteroidal anti-inflammatory drugs (NSAIDs) [14] and ACE inhibitors or ARBs [15]. In addition, nephrotoxic drugs including aminoglycoside antibiotics should be avoided [16]. Alcohol withdrawal along with etiology based treatment (antivirals for hepatitis B and/or C) should be considered an important component of ascites treatment in patients with cirrhosis as it can dramatically improve cirrhotic ascites in certain patients.

The use of ACE inhibitors and ARBs deserves special mention here. As previously mentioned, RAAS activation is a significant factor causing sodium and water retention in patients with cirrhosis. Thus, theoretically, blocking the RAAS through ACE inhibitors or ARBs should have beneficial effects in the form of decreased ascites formation.

The association of ACE inhibitors and ARBs with reduced hepatic fibrosis was shown previously in animal [17] and human studies [18]. Patients with chronic liver disease who received ACE inhibitors or ARBs had less fibrosis than those receiving other agents for hypertension [19]. This could be due to reduced activation of hepatic stellate cells further causing reduced fibrosis progression. Similarly, liver-related events including development of cirrhosis and HCC were lower in patients receiving ACE inhibitors [20]. However, most of these studies were in patients with early liver disease. In patients with cirrhosis and ascites, the activation of the RAAS is crucial in maintaining renal perfusion. Captopril led to a significant decrease in GFR in patients with cirrhosis (with and without ascites) and a substantial reduction in urinary sodium in patients with ascites [21]. A large cohort study from Taiwan demonstrated the 10-year cumulative incidence of end stage renal disease in cirrhotic patients with ascites who received ACE inhibitors/ARBs to be 6.5% [22]. Thus, using ACE inhibitors or ARBs in patients with advanced cirrhosis with ascites may lead to hypotension and renal dysfunction.

Recommendations

- Alcohol abstinence and etiological treatment (like antivirals for chronic viral hepatitis) is strongly advocated for management of ascites in patients with cirrhosis (A1).
- NSAIDs, ACE inhibitors, ARBs and other nephrotoxic agents should be avoided in patients with ascites (B1).
- In patients with arterial hypertension or other cardiovascular indications, ACE inhibitors or ARBs may be cautiously used in those with grade 1–2 ascites (C2).

Dietary salt restriction

Salt restriction is not recommended in patients without ascites, although there is little evidence. Strict sodium restriction (< 10 mmol/day) leads to a greater incidence of hyponatremia and renal dysfunction due to diuretic use [23]. However, a sodium unrestricted diet required a higher dose of diuretics to achieve the same amount of ascites control as patients with strict sodium restriction [23]. Another randomized clinical trial failed to show the benefit of a sodium restricted diet in terms of ascites control, complications of cirrhosis, acceptability of therapy and mortality [24]. Although strict sodium restriction (< 21 mmol/day) led to early ascites control, it did not improve survival [25]. A sodium restricted diet is also associated with poor compliance and leads to a 20% decrease in the daily caloric intake [26]. Because of these reasons, only a moderate sodium restriction of 80–120 mmol/day or 5–6.5 g salt/day is recommended in patients with cirrhosis and ascites. This can be achieved by avoiding pre-cooked meals and following a no-added salt policy. Whenever possible, a formal dietician consult should be taken.

Recommendations

- In patients with cirrhosis and clinical ascites, moderate sodium restriction (80–120 mmol/day, corresponding to 2–3 g of sodium or 5–6.5 g table salt (NaCl) per day is recommended (B1).
- Extreme sodium restriction (< 40 mmol/day) should be avoided and is associated with decreased caloric intake (B1).

Diuretics

Dietary salt restriction alone leads to ascites resolution in only 10% of patients and most require use of diuretics [26]. However, diuretics do not alter the natural history of the disease or lead to a reduction in mortality as it acts downstream in the pathogenesis of ascites. Activation of RAAS has a significant role in ascites formation and thus aldosterone antagonists like spironolactone or potassium Canrenoate are first-line agents for ascites mobilisation. Since, spironolactone acts through a nuclear receptor, it has a slow action, due to which change in doses should not occur before at least three days. Amiloride is an alternative for patients who develop gynaecomastia due to spironolactone, although it has a lower diuretic effect [27].

Another class of diuretics commonly used is loop diuretics which includes furosemide and torsemide. Since spironolactone acts downstream to inhibit sodium reabsorption, it has a more potent effect than furosemide in non-azotemic cirrhotics [28]. However, in patients with long-standing ascites, proximal sodium reabsorption is an important cause of sodium retention, which can be alleviated by loop diuretics. A combination of an aldosterone antagonist and a loop diuretic is preferred in this setting. However, there is conflicting evidence regarding the superiority of sequential or combination therapy. The first study [29] compared sequential treatment, combination therapy and furosemide alone for control of ascites and demonstrated a faster ascites control with combination therapy than sequential therapy. However, the second study [30] did not find any superiority of the combination therapy over sequential therapy in terms of ascites control and adverse events. However, dose reduction was required more frequently in the combination group. The third study [31] demonstrated the superiority of the combination therapy over sequential therapy in the resolution of ascites, lower hyperkalemia and treatment failures.

These conflicting results can be justified by the presence of different inclusion criteria in the three studies. Fogel et al. [29] and Angeli et al. [31] predominantly included patients who had a prior episode of ascites, while Santos et al. [30] included most patients with the first onset of ascites. Thus, spironolactone alone is preferable in patients with a first onset of moderate ascites. However, a combination of spironolactone and furosemide is optimal in patients with persisting ascites or hospitalised patients, where a rapid diuresis is required. Although, it is recommended to start spironolactone at a dose of 100 mg and gradually increased to 400 mg and furosemide at a dose of 40 mg and sequentially increased to 160 mg, it may be reasonable to start these at a lower dose of 50 mg spironolactone and 20 mg furosemide in Asian patients with new onset ascites. Diuretics are usually administered as a single daily dose in the morning to maximize compliance and minimize nocturia. Those with a weak response to furosemide may have better natriuresis with torsemide [32]. There is little evidence about the natural history of grade 1 ascites and whether it is associated with progression to grade 2 or grade 3 ascites or high mortality; thus, treatment for grade 1 ascites cannot be recommended except on a case-to-case basis. A recent retrospective study demonstrated that patients with grade 1 ascites had comparable mortality to patients without ascites and the presence of grade 1 ascites did not predict the development of moderate or severe ascites [33].

Monitoring response to therapy

Monitoring response to diuretic therapy is important to optimise the dose to achieve maximum natriuresis while simultaneously reducing complications. The peritoneum can absorb ascitic fluid at a maximum capacity of 500 mL/day. Hence, the maximum permissible weight loss in patients who do not have pedal edema is 0.5 kg/day, while it is 1 kg/day in patients with pedal edema. If greater weight loss occurs, there is a risk of volume contraction, renal failure and hyponatremia. Patients should be educated about the need for daily weight monitoring and need for frequent biochemical investigations during the initial few weeks of therapy. Measurement of 24-h urinary sodium helps to quantify natriuresis and is a valuable guide to diuretic therapy. The goal should be the excretion of at least 78 mmol/day of sodium in urine (88 mmol dietary intake—10 mmol insensible sodium loss). A lack of response to diuretic therapy is defined as a less than 0.8 kg weight loss over four days with low urinary sodium excretion (less than sodium intake). If 24-h urinary measurements are unavailable, a spot urinary sodium-to-potassium ratio can guide diuretic therapy and dietary compliance [34]. If the 24-h urinary sodium is more than the intake or if the urinary sodium–potassium ratio is > 1, the patient should lose weight. If the patient is not losing weight, dietary non-compliance should be ruled out. If the 24-h urinary sodium is less than sodium intake, or if the spot urinary sodium–potassium ratio is ≤ 1, diuretics may be increased to augment natriuresis. Diuretics should be reduced to the lowest dose as soon as possible after mobilisation of ascites to keep patients ascites free.

Side effects of diuretic therapy (Table 3)

Adverse events due to diuretic therapy can occur in 19–33% of patients [31]. Approximately 50% of patients require dose reduction or discontinuation [29]. Common side effects include hypokalemia, hyperkalemia, hyponatremia, renal dysfunction or hepatic encephalopathy [31]. Spironolactone is frequently associated with gynecomastia, which can be alleviated with amiloride or eplerenone [35]. Muscle cramps are common in advanced cirrhosis, which is often aggravated with diuretics [36]. Recent studies have demonstrated improvement in debilitating muscle cramps through the use of baclofen [37], methocarbamol [38] and taurine [39]. Albumin was also shown to have some benefits in treating muscle cramps [36].

Recommendations

- Patients who present with grade 3 ascites should be treated with a combination of spironolactone (100 mg) and furosemide (40 mg) daily (A1).
- Patients who present with a first episode of moderate ascites may be treated either with daily spironolactone alone or a combination of spironolactone and furosemide (A1). Lower initiating doses of 50 mg of spironolactone with or without 20 mg of furosemide may be used to minimize adverse effects (C2).
- The dose should be gradually increased every 3rd day till control of ascites or maximum tolerated dose (not to exceed 160 mg of furosemide or 400 mg of spironolactone) (A1).
- Patients not responding to spironolactone alone should be treated with a combination of spironolactone and furosemide (C1).
- Patients who develop hyperkalemia to spironolactone alone, should be treated with a combination of spironolactone and furosemide (A1).
- Torsemide (where available) may be used instead of furosemide in patients with grade 3 ascites or those with poor response to furosemide; however, the evidence is limited (C2).
- Once ascites is controlled, diuretics should be tapered to the minimum possible dose (C1).
- Diuretics should be withheld if patients develop complications like (C1)

Table 3 Diagnostic criteria of refractory ascites according to the International Club of Ascites (ICA) consensus statement and diuretic-induced complications

Diagnostic criteria for refractory ascites as per international club of ascites (ICA)	
Diuretic resistant ascites	Ascites that cannot be mobilized or early recurrence which cannot be prevented due to lack of response to a salt-restricted diet and diuretic treatment
Diuretic intractable ascites	Ascites that cannot be mobilized or early recurrence which cannot be prevented due to the development of diuretic-induced complications that prevent the use of maximal diuretic dosage
Treatment duration	Salt-restricted diet (Sodium < 90 mmol/day) and maximal diuretic use (Spironolactone 400 mg + Furosemide 160 mg) for at least 1 week
No response	Weight loss < 0.8 kg over 4 days with net sodium retention (urinary sodium less than dietary sodium intake)
Early ascites recurrence	Recurrence of grade 2 or 3 ascites within 4 weeks of mobilization
Diuretic induced complications	
Hyponatraemia	Decrease in serum sodium by > 10 mmol/L and to < 125 mmol/L
Hyperkalemia	Serum potassium > 6 mmol/L
Hypokalaemia	Serum potassium < 3 mmol/L
Hepatic encephalopathy	Development of encephalopathy in the absence of any other precipitant
Renal dysfunction	Rise in serum creatinine ≥ 0.3 mg/dL (26.5 µmol/L) within 48 h or ≥ 50% from the baseline value (last available outpatient serum creatinine within 3 months) and/or urine output ≤ 0.5 mL/kg body weight for ≥ 6 h
Invalidating muscle cramps	

- acute kidney injury (AKI),
- serum sodium < 125 mmol/L,
- serum potassium < 3 mmol/L or > 6 mmol/L,
- overt hepatic encephalopathy,
- SBP,
- development of incapacitating muscle cramps.

Large volume paracentesis (LVP)

LVP (removal of > 5 L of ascitic fluid) is considered the treatment of choice for patients who present with tense ascites [40]. For patients undergoing LVP, volume replacement with intravenous albumin (6–8 g for each litre of ascitic fluid cleared) should be done to prevent PICD [41]. The rate of albumin infusion (20%) has been proposed to be at 2 mL/min with a 50% dose infused immediately after paracentesis and 50% infused 6 h after paracentesis [42]. However, in the real-world setting it is often infused during paracentesis. Also, regional variations in insurance reimbursement for intravenous albumin often dictate local practices. Although 6–8 g of albumin is infused for each litre of ascitic fluid removed to prevent PICD, one study demonstrated a similar incidence of PICD with albumin infusion of 2 g for each litre of ascitic fluid removed [42]. Once there is a reduction in intra-abdominal pressure by LVP, patients should be started on diuretics, to reduce the need for frequent paracentesis. Patients may require another session of paracentesis due to the mobilisation of fluid from interstitial spaces (as seen in patients with pedal edema) to the abdominal cavity [40].

The left lower quadrant has been suggested as the ideal site for paracentesis, as it is associated with a greater depth of ascites and a lower abdominal wall thickness. Care should be taken to avoid puncturing the inferior epigastric artery and it is proposed to utilise the contralateral McBurney's point (at one-third distance between the left anterior superior iliac spine and umbilicus) as an anatomical landmark for paracentesis. Strict asepsis should be followed during paracentesis.

Paracentesis is usually a safe procedure with minimal adverse events, even in patients with deranged coagulation parameters. A systematic review reported bleeding events after paracentesis in up to 2.7% patients [43]. Risk factors for paracentesis-related hemorrhagic complications include renal failure and severe liver dysfunction, characterized by high MELD and CTP score [44]. Routine prophylactic transfusion of fresh frozen plasma or platelets is not recommended to correct INR or platelet count respectively, before paracentesis. However, paracentesis should not be performed in the presence of disseminated intravascular coagulation (DIC).

Leakage of ascitic fluid after paracentesis can be seen in up to 2.3% of patients [43]. Therefore, paracentesis should be performed by following a Z-track technique to decrease the risk of ascitic fluid leak from the puncture site. Once a leak occurs, patients should be made to lie on the contralateral side for 2 h to keep the puncture site as dry as possible. Leakage of ascitic fluid may also indicate incomplete drainage; if persistent, patients should undergo a repeat LVP. A stoma bag may be applied at the site of leak to prevent soakage of surrounding skin and reducing infection risk. Using ultrasound to guide paracentesis has been shown to be beneficial in reducing the risks of complications and should be used when available [45].

Recommendations

- LVP is the treatment of choice for patients with grade 3 ascites (A1).
- LVP should be done under ultrasound guidance whenever possible to reduce adverse events' risk (C2).
- LVP should be done with volume replacement with intravenous albumin (6–8 g/L of ascitic fluid removed) (A1). Albumin should be infused slowly, preferably over at least 4 h (C2).
- After LVP, diuretics should be continued at the lowest dose possible, to prevent re-accumulation of ascites (A1).

Spontaneous bacterial peritonitis (SBP)

SBP is the most common bacterial infection in a patient with cirrhosis, seen in approximately 35% of patients from Asia [46]. Community-acquired bacterial infections were seen in 56% of patients from Asia, while 24% were healthcare associated (contact with a health-care facility in last 90 days) and 20% were nosocomial [46]. Approximately 10% of hospitalised cirrhotics will have SBP [47]. Out of all patients who have SBP, about 50% will develop the infection in the hospital. The in-hospital mortality seen in patients with SBP was > 90% initially but this has decreased to 20% with appropriate treatment [48]. Long-term survival with SBP is also dismal, with previous studies demonstrating a 6-month survival of 30% [49]. Unfortunately, recurrence of SBP is seen in around 44% [49]. Thus, all patients with a history of SBP should be listed for a liver transplant if there is no contraindication.

Clinical signs and symptoms of SBP

Approximately 3.5% of asymptomatic outpatient people with cirrhosis can have SBP [47]. Commonly seen clinical features of SBP may include (a) features of systemic inflammatory response syndrome (SIRS) like fever or hypothermia, tachycardia, leucocytosis or leukopenia, tachycardia and/or tachypnoea, (b) symptoms and/or signs of peritonitis like abdominal pain, tenderness, vomiting or diarrhoea, and (c) presentation with acute decompensation or ACLF.

Diagnostic evaluation of SBP

Prompt diagnosis of SBP is essential as a delay in doing a diagnostic paracentesis is associated with an approximately 3.3% increase in in-hospital mortality for each hour of delay [50]. Thus, all patients suspected of SBP should undergo a diagnostic paracentesis as soon as possible along with inoculation of 10 mL ascitic fluid in a blood culture bottle at bedside. Traditionally, ascitic fluid neutrophil count > 250 cells/mm^3 along with a positive monomicrobial ascitic fluid culture in the absence of a surgically treatable intra-abdominal source of infection has been used to define SBP (Fig. 2). A few have suggested a cut-off of > 500 neutrophils/ mm^3 to increase specificity [51]. Ascitic fluid neutrophil count > 250 cells/mm^3 in the absence of a positive culture is known as culture negative neutrocytic ascites (CNNA). As clinical course of both SBP and CNNA is similar, for practical purposes, CNNA is also treated as SBP as the yield of ascitic fluid culture is low [52]. In patients with hemorrhagic ascites, defined as an ascitic fluid red blood cell (RBC) count of > 10,000/mm^3, subtraction of 1 neutrophil per every 250 RBC's from the ascitic fluid neutrophil count should be done. Ascitic fluid culture may be negative in up to 60% of patients with SBP. However, it is still crucial in guiding antibiotic therapy, especially in patients with healthcare-associated or nosocomial SBP. Isolated monomicrobial bacterascites without neutrophilia (< 250/mm^3) i.e. monomicrobial non-neutrocytic bacterascites (MNBA) in the ascitic fluid may be seen in patients with an extra-abdominal focus of infection due to secondary localisation, or may be due to spontaneous colonisation of ascitic fluid. If patients are symptomatic or present with organ failures or were on antibiotic therapy before diagnostic paracentesis, they should be managed as SBP.

Recommendations

- SBP is diagnosed when the ascitic fluid neutrophil count is > 250/mm^3 (B1).
- Ascitic fluid cultures are not required to diagnose SBP but are essential in guiding antibiotic therapy. It should be obtained during initial diagnostic paracentesis (B1).
- Blood cultures should also be obtained in patients with suspected SBP before initiating antibiotic therapy (B1).
- Patients with bacterascites and symptoms suggestive of SBP, should receive antibiotic therapy (B1).
- Patients with bacterascites without any symptoms, should have a repeat ascitic fluid work-up at the time of receipt of microbiological culture reports. Patients should receive antibiotic therapy if persistently positive culture or ascitic fluid neutrophil count > 250/mm^3 on repeat work-up (C1).

Spontaneous fungal peritonitis (SFP)

Fungal peritonitis is rare and seen in less than 5% of patients with cirrhosis [46]. Patients with SFP have a higher CTP and MELD score than patients without SFP [53]. The most commonly implicated organisms in decreasing prevalence are *Candida* species (*Candida albicans, Candida krusie, and*

Candida glabrata), *Cryptococcus neoformans* and *Aspergillus* species [54]. SFP is associated with very high short-term mortality, with 1-month mortality reaching up to 73% [54].

Secondary bacterial peritonitis

It is essential to differentiate secondary peritonitis from SBP as patients with secondary peritonitis often require surgery. In addition, approximately 5% of patients with cirrhosis may develop secondary peritonitis [55]. These patients usually present with localised abdominal symptoms or signs such as guarding or rigidity, high neutrophil count, elevated protein (> 1 g/dL) and raised LDH concentration in ascitic fluid (> 225 mU/mL), low ascitic fluid sugars (< 50 mg/dL) and polymicrobial ascitic fluid culture [55].

Recommendations

- Patients should be suspected to have secondary bacterial peritonitis when they have a polymicrobial growth on culture, high ascitic fluid LDH concentration, high ascitic fluid protein concentration, low ascitic fluid sugars or inadequate response to treatment (B1).

Management of SBP

Patients with SBP must be started on empiric antibiotic therapy as early as possible, as a delay in instituting antibiotic treatment correlates with increased mortality [50]. Most commonly isolated organisms include Gram-negative bacteria (*Escherichia coli, Klebsiella pneumonia*) followed by Gram-positive bacteria (*Staphylococcus aureus, Enterococcus faecalis* and *Enterococcus faecium*). Cefotaxime was initially investigated extensively for treating SBP as high ascitic fluid concentrations are achieved and it covers more than 95% of organisms isolated from ascitic fluid [56]. However, antibiotic resistance is increasing with the increased prevalence of multidrug-resistant (MDR) and gram-positive organisms isolated from ascitic fluid [46]. Thus, it is necessary to identify risk factors associated with MDR organisms and to guide antibiotic therapy accordingly.

Risk factors for MDR infection include prior healthcare exposure, antibiotic exposure in the past 3 months and residence in Asia [46]. Interestingly, norfloxacin prophylaxis was not associated with an increased risk of MDR infection [46]. Thus, appropriate empirical antibiotic therapy selection should be guided according to community acquired, healthcare associated or nosocomial SBP and the prevalence of local antibiotic resistance patterns. Third-generation cephalosporins have been shown to be effective in patients with community-acquired infections, with a resolution of more than 80% [57]. However, their efficacy decreases when used in the setting of MDR organisms. The presence of an MDR infection correlates with a lower resolution rate, higher incidence of shock and organ failures and higher mortality [46]. Inappropriate antibiotic use in critically ill patients is associated with an increased risk of death [58]. In this setting, carbapenems have been shown to have a higher resolution of SBP with a lower mortality rate [48]. A randomized controlled trial showed superior efficacy of a combination of meropenem and daptomycin over ceftazidime in the resolution of nosocomial SBP [48].

A repeat diagnostic paracentesis 48 h after antibiotic therapy is recommended in patients with persistent clinical signs or symptoms, persistent organ failures or risk of MDR/nosocomial SBP. This will help assess the response to empiric antibiotics and guide therapy if there is an inadequate response. A decreased ascitic fluid neutrophil count by less than 25% at 48 h indicates an inadequate response. The presence of an inadequate response suggests the presence of MDR organism or secondary bacterial peritonitis. Inadequate response to carbapenems raises the suspicion of extensive drug resistance (XDR) organism or pan-drug resistance (PDR) [59]. XDR is defined as resistance to all but two or fewer antibiotic classes while PDR is defined as resistance to all antimicrobial categories [59]. XDR Enterobacteriaceae can be treated with a combination of tigecycline and a carbapenem. Colistin may need to be added for severe infections. Areas with a high incidence of Gram-positive SBP need to be empirically treated with vancomycin in addition to piperacillin/tazobactam or meropenem. When there is a high prevalence of vancomycin resistance Enterococci (VRE), treatment with daptomycin, tigecycline or linezolid should be considered. However, linezolid use is associated with thrombocytopenia while tigecycline requires dose adjustment in patients with advanced liver disease. Thus, daptomycin is the preferred modality of treatment for VRE. Although teicoplanin is also effective against VRE, it does not achieve therapeutic concentrations in the ascitic fluid. Hence, it is not recommended.

Recommendations

- Empirical antibiotics should be initiated as soon as possible after a diagnosis of SBP (B1).
- Empirical antibiotic therapy should be based on whether the infection is community-acquired, healthcare-associated or nosocomial, and should consider local antibiotic resistance patterns and severity of infection (A1).
- For community-acquired SBP, third-generation cephalosporins are the drug of choice (A1). However, areas

with a high prevalence of MDR may need to be treated with piperacillin/tazobactam or carbapenems (B1).
- For healthcare-associated or nosocomial SBP, piperacillin/tazobactam is preferred in areas with low antibiotic resistance while carbapenems are preferred in regions with high antibiotic resistance (A1).
- In areas with a high prevalence of gram-positive infections, vancomycin should be added if incidence of VRE is low. Daptomycin should be added in areas with an increased risk of VRE (A1).
- Antibiotic therapy should be guided according to the isolate on ascitic fluid culture. Antibiotics should be de-escalated as soon as possible based on the culture report (B1).
- Patients who are not improving clinically, or have risk factors for MDR organism, should undergo a repeat diagnostic paracentesis 48 h after starting empiric antibiotics. In addition, antibiotics should be upgraded in patients with less than a 25% decrease in neutrophil count from baseline (C2).
- The duration of antibiotic therapy for SBP should be at least 5–7 days (C1).

Intravenous albumin in patients with SBP

Approximately 30% of patients with SBP can develop AKI [60]. Patients with SBP who develop AKI have increased mortality [60, 61]. Treatment with intravenous albumin leads to a significantly lower incidence of renal dysfunction and lower mortality than patients who were not treated with albumin [60–62]. Although the dose of albumin used by Sort et al. [60] in their landmark trial was 1.5 g/kg body weight on day 1 and 1 g/kg on day 3, a lower dose of albumin was also found beneficial in preventing AKI in the Asian population [61].

Another question that needs to be answered is which patients with SBP require intravenous albumin. Although all experts in our consensus meeting preferred albumin infusion in all patients with SBP, the evidence is contradictory. A sub-group analysis of the study by Sort et al. [60] showed that patients with serum bilirubin > 4 mg/dL (68.4 µmol/L), blood urea nitrogen > 30 mg/dL or a serum creatinine > 1 mg/dL (88.4 µmol/L) were more likely to develop AKI. Similarly, another randomised controlled clinical trial by Sigal et al. [62] demonstrated that patients who are less likely to develop AKI [stratified by bilirubin < 4 mg/dL (68.4 µmol/L) and/or serum creatinine < 1 mg/dL (88.4 µmol/L)] can be safely managed without intravenous albumin.

Recommendations

- Intravenous albumin is recommended in patients with SBP who are at high risk of AKI [S. Bilirubin > 4 mg/dL (68.4 µmol/L) and/or S. Creatinine > 1 mg/dL (88.4 µmol/L)] (A1); however, it may be considered in all patients with SBP as per expert consensus (C2).
- The dose of albumin should be 1.5 g/kg on day 1 within 6 h of diagnosis and 1 g/kg on day 3 (B1). Lower doses may be used although the evidence is limited (C1).

SBP prophylaxis

Since SBP has a high recurrence rate [49] and mortality [48], patients at risk of SBP must receive antibiotic prophylaxis. The antibiotic used for prevention should be capable of selective gut decontamination while being safe, effective and cheap. Due to the risk of developing antibiotic resistance, prophylaxis is restricted to high-risk groups.

Primary prophylaxis

Primary prophylaxis for SBP is an area open to question. The use of a short course of antibiotics (5–7 days) to prevent SBP in patients presenting with upper gastrointestinal (GI) bleeding is well established. A Cochrane review demonstrated that antibiotic prophylaxis in patients with upper GI bleeding significantly decreased bacterial infection and mortality [63]. The emergence of MDR organisms has shifted the prevention in patients with GI bleeding from oral norfloxacin to intravenous ceftriaxone [64]. Antibiotic prophylaxis in the absence of GI haemorrhage is uncertain. Low ascitic fluid protein is a risk factor for developing SBP. The efficacy of norfloxacin for primary SBP prophylaxis in patients with low ascitic fluid protein was demonstrated by a double-blind randomized controlled trial [65]. In the NORFLOCIR trial, norfloxacin reduced mortality only in patients with low protein in ascitic fluid [66]. A landmark study demonstrated a significant reduction in the first SBP episode due to norfloxacin in patients with low ascitic fluid protein and severe liver disease [CTP ≥ 9 and serum bilirubin ≥ 3 mg/dL (51.3 µmol/L)] or renal dysfunction [serum creatinine ≥ 1.2 mg/dL (106.1 µmol/L), BUN ≥ 25 mg/dL, or serum sodium ≤ 130 mEq/L] [67]. Ciprofloxacin or trimethoprim-sulfamethoxazole can be used in place of norfloxacin for primary SBP prophylaxis [68, 69]. A Cochrane systematic review [70] and a meta-analysis [71] demonstrated reduced mortality with oral antibiotics for primary SBP prophylaxis in patients with ascitic fluid protein less than 1.5 g/dL. However, a recent network meta-analysis [72] demonstrated an uncertain benefit of antibiotic prophylaxis in patients with

SBP, but the evidence was of low quality. Since the evidence for primary prophylaxis is not strong, prophylaxis should be individualised and restricted to high-risk patients.

Secondary prophylaxis

Only one RCT has assessed the role of norfloxacin in secondary prophylaxis of SBP [73]. The use of norfloxacin has decreased SBP recurrence from 68 to 20% [73]. However, this trial was published before the emergence of MDR organisms and it has been proven that fluoroquinolones have lower efficacy in patients colonized with MDR organisms [74]. In a randomized trial of 262 patients, SBP recurrence was only 3.88% with rifaximin, as compared to 14.13% with norfloxacin [75]. Use of Rifaximin was also associated with a lower mortality [75]. Rifaximin has also been shown to be effective in a meta-analysis for primary and secondary prophylaxis [76]. A few clinicians also use sulfamethoxazole/trimethoprim for secondary prophylaxis, although high-quality data is not available [77].

Recommendations

- Patients with cirrhosis presenting with variceal bleeding should receive prophylaxis for SBP (A1). Intravenous ceftriaxone or cefotaxime has been widely used but the antibiotic choice should be guided by local data (C1).
- Patients with cirrhosis and low ascitic fluid protein (<1.5 g/L) are at high risk for SBP (A1). Among this group, patients having a severe liver disease [CTP ≥ 9 and serum bilirubin ≥ 3 mg/dL (51.3 µmol/L)] or renal dysfunction [S. creatinine ≥ 1.2 mg/dL (106.1 µmol/L), BUN ≥ 25 mg/dL, or S. Na ≤ 130 mEq/L] should receive primary antibiotic prophylaxis for SBP (C1).
- Patients who recover from SBP should receive long-term prophylaxis with oral norfloxacin, ciprofloxacin, or co-trimoxazole (C1).
- While evidence for rifaximin use as prophylaxis is promising, more data is needed before it can be recommended as prophylaxis of SBP per se (C2).
- Patients who develop SBP and have recovered should be considered for LT (B1).

Refractory ascites (RA)

Definition

According to the International Club of Ascites, refractory ascites (RA) is defined as "ascites that cannot be mobilised or the early recurrence of which cannot be satisfactorily prevented by medical therapy". It can be further differentiated into diuretic resistant (lack of response to sodium restriction and maximal diuretic therapy) or diuretic intractable (development of diuretic-induced complications that preclude the use of an effective diuretic dose) (Table 3). Development of renal dysfunction in patients with refractory ascites refers to a doubling of serum creatinine to >2 mg/dL. However, the ICA has recently modified the definition of AKI in patients with cirrhosis to include increase in serum creatinine by ≥ 0.3 mg/dL from baseline or 50% increase from baseline and/or decrease in urine output (≤ 0.5 mL/kg/h for ≥ 6 h). This leads to early identification and management of renal dysfunction and should be used preferably. Diuretic induced complications are defined in Table 3. Approximately 5–10% of patients with cirrhosis will develop RA [78]. Development of RA in the natural history of cirrhosis leads to a significant reduction in survival [78], hence, they should be considered for a liver transplant.

Recommendations

- For refractory ascites, AKI should be defined per recent ICA recommendations (C1).

Management (Supplementary Fig. 1)

Sodium restricted diet

Moderate sodium restriction is required for all ascites forms as it prevents rapid re-accumulation of fluid. In patients with rapidly accumulating ascites, it is essential to assess for dietary non-compliance by measuring urinary sodium excretion and body weight (as previously described). There may be substantial improvements in ascitic fluid accumulation once dietary compliance is addressed.

Diuretic use

There is limited evidence on whether diuretics should be continued once RA has developed. Further increments in dose would not cause natriuresis or ascites mobilisation on reaching the maximal dose of diuretics. Hence, diuretics should be discontinued in patients with diuretic-resistant ascites to decrease the risk of complications. Patients with diuretic-intractable ascites may be treated with a lower dose of diuretics than the dose that produced side effects; however, there is no evidence in this regard.

Use of albumin

The use of intravenous albumin at a dose of 40 g every 2 weeks along with midodrine (15–30 mg/day) in patients with advanced cirrhosis awaiting liver transplant did not lead to improved survival or decreased complications of cirrhosis [79]. However, a recent non-randomized study utilising 20 g twice weekly albumin and sodium restriction in patients with refractory ascites undergoing LVP reduced hospitalisation and mortality [80]. Therefore, more evidence is needed before long-term albumin infusion can be recommended for refractory ascites patients.

Large volume paracentesis (LVP)

The first-line therapy for patients with RA is LVP. Repeated LVP is comparable to the use of diuretics in terms of survival but with a favourable safety profile regarding renal impairment, electrolyte imbalance and hemodynamic stability [40].

Albumin infusion is necessary to prevent hemodynamic alterations and PICD when > 5 L of ascitic fluid is removed [41]. PICD is defined as an "increase in plasma renin activity by > 50% of baseline to an absolute value of > 4 ng/mL/h at day 6 after paracentesis" [41]. The pathophysiology of PICD involves effective arterial hypovolemia and decreased systemic vascular resistance [81]. Post-paracentesis, cardiac preload increases, causing an increase in stroke volume. Due to increased cardiac output there is a reflex decrease in systemic vascular resistance. These changes in turn lead to the sympathetic nervous system and RAAS activation. Patients unable to fully compensate the hemodynamic changes associated with paracentesis develop PICD. Patients present with rapid re-accumulation of ascites and its associated symptoms and are at risk of developing renal failure, hyponatremia, hepatic encephalopathy and a reduced survival [41]. Thus prevention of PICD is essential and is done by albumin replacement as previously described. Plasma expanders like Dextran 70, normal saline and polygeline have also been evaluated for the prevention of PICD. When < 5 L of ascitic fluid is removed, all plasma expanders were associated with a similar incidence of PICD [41]. However, albumin fared the best when > 5 L of ascitic fluid was removed [41]. Vasoconstrictors like terlipressin [82, 83], noradrenaline [84] and midodrine [85, 86] have also been used in the prevention of PICD. A meta-analysis demonstrated the superiority of albumin over other plasma expanders and vasoconstrictors [87]. Further studies are required before recommending these vasoconstrictors for routine use. However, in patients with ACLF, even a modest volume of paracentesis (< 5 L) is associated with an increased PICD risk and should be given IV albumin to decrease the risk [88].

Transjugular intrahepatic portosystemic shunt (TIPS)

TIPS creates an artificial connection between the portal and hepatic vein, which leads to decompression of the portal system and reduces portal pressures. Similar to LVP, TIPS will cause increased preload leading to increased cardiac output in the short term [89]. As a result, there is a decrease in effective arterial hypovolemia causing improved renal blood flow and increased urinary sodium excretion [90]. This correlates with decreased plasma renin activity which occurs gradually over 4–6 months. Thus, ascites will resolve slowly over 4–6 months in approximately 80% of patients [91], and a salt-restricted diet should be continued until ascites resolves

The role of TIPS for refractory or recurrent ascites has been analysed by 7 RCTs [92–98]. However, 6 of them used uncovered TIPS stents and had a high incidence of stent stenosis or thrombosis [92–97]. One RCT done in patients with recurrent ascites used polytetrafluoroethylene (PTFE) covered TIPS stent [98]. It was associated with a stent patency rate of 92% at 1-year and 89% at 2-years. TIPS was associated with better ascites control than repeated LVPs [93–98]. The effect of TIPS on improvement in survival is not consistent across different studies. Lebrec et al. [92] reported a poor survival with TIPS while this was not replicated in other studies [93–95]. Three recent studies, including the study utilising PTFE-covered stent [95–98] showed better transplant-free survival with TIPS. A meta-analysis demonstrated survival advantage with uncovered TIPS [99]. However, uncovered TIPS is associated with a high post-TIPS hepatic encephalopathy [92, 95–97] which is mitigated using PTFE-covered TIPS [98].

Patient selection for TIPS is an essential factor in determining transplant-free survival. As PTFE-covered TIPS was shown to be of benefit in improving transplant-free survival [98] and reducing other portal hypertensive complications, patients with recurrent ascites may benefit more by the placement of TIPS. Patients with advanced cirrhosis and severe liver dysfunction were not included in the trials of TIPS [92–98]. In general, MELD > 18 and CTP > 12 are considered contraindications for TIPS and these patients should be evaluated for LT. Presence of recurrent, overt, non-precipitated HE and severe cardiac dysfunction are also a contraindication for TIPS placement. Advanced age, sarcopenia and cardiopulmonary insufficiency correlate with increased post-TIPS HE and other complications. It is proposed that a smaller diameter TIPS stent protects against the development of post-TIPS HE while having a similar efficacy in reducing portal hypertensive complications [100].

Patients with persistent ascites at 12 months, despite a patent TIPS stent should be evaluated for LT. Also, patients with advanced cirrhosis (MELD > 18 or CTP > 12) in which TIPS is contraindicated should be considered for LT.

Automated low-flow ascites pump (Alfapump®)

The Alfapump® is a battery-powered pump implanted subcutaneously in the abdominal wall that aspirates and transports ascitic fluid through a subcutaneous catheter into the urinary bladder. The pump has in-built sensors that monitor peritoneal and bladder pressure to stop pump operation in the event of ascites resolution or a full urinary bladder. Up to 4 L ascitic fluid can be removed by the pump per day. Patient selection is vital for successful Alfapump® function. Patients with loculated ascites, active infection or severe abdominal adhesions from previous surgery are not candidates for Alfapump® placement and due consideration should be given to surgical morbidity and mortality in patients with advanced cirrhosis.

The use of Alfapump® resulted in a significant decrease in the number of LVPs in two multicentre observational studies [101, 102] and RCT [103]. However, there was an increased incidence of pump explant and renal dysfunction [101, 102]. These adverse events were not replicated in the RCT by Bureau et al. [103]. The Alfapump® also led to a significantly improved nutritional status at 3 months [103]. Thus, carefully selected patients may derive clinical benefits in decreasing LVP requirements with the use of Alfapump®.

Role of Vasoconstrictors in RA

Vasoconstrictors have been studied extensively for RA. An RCT comparing terlipressin with placebo in 23 patients with advanced cirrhosis without HRS, 8 having RA, demonstrated increased natriuresis and decreased RAAS activation with terlipressin [104]. The addition of terlipressin to a combination of albumin and diuretics resulted in better ascites control and natriuresis in a multicentric study of 26 patients [105]. Outpatient terlipressin infusion for 28 days decreased the number of therapeutic paracentesis and the volume of fluid removed in each paracentesis in a small report of 5 patients with RA [106]. Midodrine, an alpha-1 adrenergic agonist, has also been shown to suppress RAAS activity and improve natriuresis in patients with ascites [107]. One-month of treatment with midodrine, long-acting octreotide and 50 g albumin thrice weekly resulted in RAAS suppression and a trend towards better ascites control [108]. However, there was a transient worsening in the MELD score in this pilot study [108]. Midodrine along with standard medical therapy led to better ascites control, no further deterioration of MELD score at 3 months and there was improved survival at 1 year in patients with refractory or recurrent ascites [109]. The addition of clonidine to midodrine in such patients did not lead to better ascites control [110]. However, a multicentric study from the USA failed to show the benefits of combination of midodrine and long-acting octreotide for RA when compared with intravenous albumin [111]. Further RCTs are required before routinely adding midodrine for patients with RA.

Vasopressin receptor antagonists for RA

Vaptans are selective V2 receptor antagonists that act on the principal cells in collecting ducts in the nephron and enhance free water excretion. Traditionally used for hyponatremia, vaptans have led to better clinical control of ascites in patients with cirrhosis by increasing free water clearance. A recently conducted multicentre Chinese double-blind randomized controlled clinical trial [112] demonstrated the superior efficacy of tolvaptan for controlling ascites in patients with cirrhosis who have an insufficient response to conventional diuretics. A recent meta-analysis [113] also showed a survival advantage in patients who responded to tolvaptan, with response to tolvaptan being defined as an effective weight loss or effective sodium restoration. Another meta-analysis [114] identified predictors of tolvaptan response—a higher baseline body weight, presence of Hepatitis C, lower blood urea nitrogen, lower serum creatinine, lower C-reactive protein and higher sodium levels. The addition of tolvaptan to furosemide for persistent ascites also led to systematic reduction in the doses of furosemide and improvement in eGFR over a 24-week treatment [115]. A meta-analysis of randomized controlled trials [116] demonstrated that treatment with vaptans did not increase all-cause mortality. Further, it may lead to a lower incidence of hepatic encephalopathy and spontaneous bacterial peritonitis. Most of the studies included in the meta-analysis are from Japan. Indeed, the Japanese guidelines [117] recommend the use of low-dose tolvaptan in patients with portal hypertensive ascites who are resistant to conventional diuretics at a stage when renal dysfunction has not set in. However, further studies are needed before tolvaptan can be recommended routinely. A summary of the studies on use of vaptans in patients with ascites is shown in Supplementary Table S1.

Recommendations

- Dietary salt restriction (5–6.5 g/day) should be continued in patients with RA to decrease the rate of ascitic fluid accumulation (C1).
- Diuretics should be withheld in RA. In patients with diuretic-intractable ascites, diuretics may be initiated in a lower dose after correction of the diuretic-induced complication (C1).
- Repeated LVP is the first line of treatment for RA (A1).
- Albumin should be infused after LVP (> 5 L fluid removed) at the rate of 6–8 g/L for each litre of ascitic fluid removed to prevent PICD (A1)
- Patients with ACLF undergoing modest volume paracentesis should be infused with albumin at the rate of 6–8 g/L for each litre of ascitic fluid removed (B1).
- Long-term albumin infusion may be considered in patients with RA; however, the evidence is limited (C2).
- TIPS may be considered for managing RA as a bridge to liver transplant or in transplant-ineligible patients (A1).
- TIPS stent diameter of < 10 mm is preferred to reduce the incidence of post-TIPS HE (A1).
- Moderate sodium restriction and diuretics should continue after TIPS until ascites resolution (B1).
- Stent thrombosis or stenosis should be suspected if there is recurrence of ascites after TIPS (B1).
- LT should be considered in all patients of RA (A1).
- Midodrine may be used in patients with RA and may be particularly beneficial in patients with low MAP (B1).
- Midodrine should be started at a dose of 5 mg thrice a day and titrated according to the increase in mean arterial pressure (C1).
- Due to the lack of data, use of outpatient terlipressin for ascites control cannot be recommended (C1).
- Low-dose tolvaptan may be used for refractory ascites in a clinical trial setting to improve ascites control and to decrease adverse events to a standard diuretic regimen. (B2)
- Patients with RA who are not candidates for TIPS or LT may benefit from the use of Alfapump®. However, its use is restricted to experienced centres and requires monitoring to prevent adverse events like infection and renal dysfunction (B2).

Hyponatremia

Hyponatremia in patients with cirrhosis was arbitrarily considered as a serum sodium level < 130 mmol/L. However, due to the associated increased morbidity and mortality [118] with hyponatremia including neurological complications and reduced post-LT survival, recent guidelines consider hyponatremia when serum sodium is < 135 mmol/L. Hyponatremia is classified as mild, moderate and severe when serum sodium is 126–135 mmol/L, 120–125 mmol/L and < 120 mmol/L, respectively [119]. The prevalence of mild, moderate and severe hyponatremia is approximately 49%, 22% and 6%, respectively [120]. Clinical symptoms of hyponatremia include nausea, headaches, ataxia, lethargy, muscle cramps, dizziness, confusion and rarely seizures. However, chronic hyponatremia is usually asymptomatic.

Evaluation of a patient with hyponatremia

Assessment of volume status and identifying whether the patient is hypovolemic, euvolemic or hypervolemic is crucial for managing hyponatremia. This differentiation can be done clinically by looking for symptoms/signs of dehydration (history of diarrhoea/vomiting, overzealous diuretic use, dry tongue, parched skin, etc.) or signs of volume overload (ascites or pedal edema). In cirrhosis, hyponatremia is usually hypervolemic (dilutional) due to an increased extracellular fluid volume. However, 10% cases may have hypovolemic hyponatremia. It is important to rule out hypothyroidism and adrenal insufficiency, which can be associated with cirrhosis and present with hyponatremia. An approach to hyponatremia in cirrhosis is provided in Fig. 3. In patients with cirrhosis, management of hyponatremia in the real world is variable, frequently ineffective and associated with relapse after treatment discontinuation [121]. The following section will focus on managing hypervolemic hyponatremia in patients with cirrhosis, including cessation of diuretics and laxatives, fluid restriction, intravenous albumin, vasopressin receptor antagonists (Vaptans) and rarely hypertonic saline.

Recommendations

- Hyponatremia (S. Na < 135 mEq/L) is associated with increased morbidity and mortality in patients with cirrhosis (A1).
- Although most cirrhotics have hypervolemic hyponatremia, evaluation for hypovolemic and euvolemic

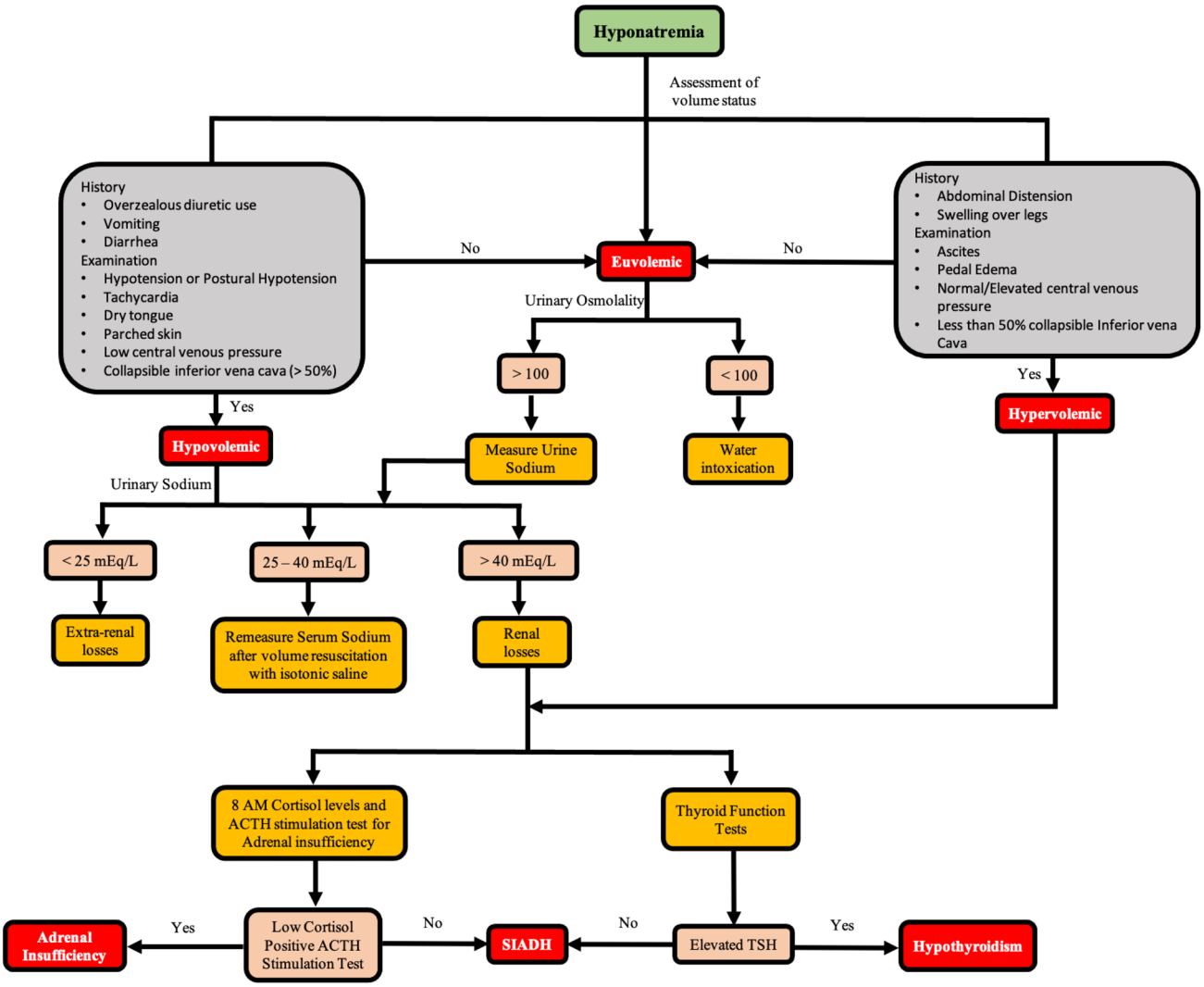

Fig. 3 Algorithm for diagnosis of hyponatremia in patients with cirrhosis (*ACTH* adrenocorticotrophic hormone, *SIADH* syndrome of inappropriate antidiuretic hormone, *TSH* thyroid stimulating hormone)

hyponatremia should also be done including evaluation of thyroid function and adrenal function (B1).

Management of hypervolemic hyponatremia

Fluid restriction

Since hypervolemic hyponatremia occurs due to impaired free water clearance and increased proximal sodium reabsorption by the kidneys, fluid restriction (1–1.5 L/day) is often prescribed in patients with dilutional hyponatremia to maintain a negative water balance. Fluid restriction should be advised to patients with symptomatic or severe hyponatremia only and patients with mild, asymptomatic hyponatremia need not be informed of fluid restriction. Although, free water restriction is the cornerstone of managing dilutional hyponatremia, there is insufficient evidence to support the amount of fluid restriction or the sodium threshold at which fluid restriction should be started. Another problem with fluid restriction is that when used alone, only 55% of patients with a serum sodium level < 125 mEq/L will increase serum sodium by > 5% at day 3 [121]. Also, strict restriction of free water intake (< 1 L/day) is generally not tolerated and may lead to decreased caloric intake. As hyponatremia can also occur due to diuretic use and renal dysfunction, both these factors should be ruled out before starting free water restriction.

Albumin

A preliminary report by McCormick et al. [122] described the use of intravenous albumin to improve serum sodium in 4 cirrhotic patients with hyponatremia. Another recent report of 1126 patients described the better resolution of hyponatremia with albumin infusion [123]. In addition, long-term albumin infusion is associated with a lower hyponatremia incidence [124]. However, the significant cost associated with treatment is an issue.

Vaptans

The initial reports of using vaptans for hyponatremia come from the SALT-1 and SALT-2 trials, which used tolvaptan for 30 days [125]. The authors reported that 15 mg oral tolvaptan improves serum sodium concentration in patients with euvolemic or hypervolemic hyponatremia [125]. A sub-group analysis of the SALT-1 & SALT-2 trial by Cárdenas et al. demonstrated improved serum sodium levels along with patient-reported health status without significant adverse events with use of tolvaptan for up to 30 days [126]. Other vaptans (lixivaptan, satavaptan, etc.) have been studied in cirrhotic patients with hyponatremia and showed similar results of improved serum sodium levels, better weight loss, improved urine output, decreased urine osmolality, better ascites control and decreased paracentesis requirement [127–131]. Most vaptans have been studied for short-term use (up to 30 days) except for satavaptan. Wong et al. [131] showed that satavaptan for 52 weeks in patients with difficulty controlling ascites was associated with increased all-cause mortality. The US-FDA approved an intravenous formulation of a non-selective vasopressin receptor antagonist (conivaptan) for severe hypervolemic hyponatremia [132]. However, the concern of splanchnic vasodilatation and increased risk of variceal bleeding by inhibition of V1A receptors have limited its use. Another concern with using vaptans in patients with cirrhosis is the drug safety communication issued by US-FDA for tolvaptan use for more than 30 days in patients with underlying liver disease. This communication was the result of a study of 1400 patients with autosomal dominant polycystic kidney disease, in which three patients on 120 mg/day tolvaptan developed significantly increased AST/ALT and bilirubin levels [133]. However, lower doses for a short duration (less than 30 days) can be used safely in patients with cirrhosis.

Hypertonic saline

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

Recommendations

- Diuretics should be discontinued in patients developing moderate-severe or symptomatic hyponatremia (C1).
- Free water restriction to < 1L/day is recommended in patients with moderate-severe or symptomatic hyponatremia to prevent further decrease in S. Na levels (C1).
- Intravenous albumin may be used to improve serum sodium level; however good quality evidence supporting its use is lacking (C1).
- The use of vaptans should be restricted to hypervolemic or euvolemic hyponatremia in patients without renal failure (B1).
- Short-term treatment with hypertonic saline may be used in patients with symptomatic or severe hyponatremia or those planned for imminent LT (C2).

Hepatic hydrothorax

Hepatic hydrothorax (HH) is the accumulation of transudative fluid in the pleural cavity in a patient with portal hypertension without any pulmonary, cardiac, or pleural disease. It occurs because of the transmigration of ascitic fluid through small diaphragmatic defects due to negative intrathoracic pressure during inspiration. Approximately 4–12% of patients with cirrhosis have HH, which is mainly seen on the right side [134]. Unilateral left-sided effusion can occur in 17% of patients while bilateral HH is seen in around 10% of patients [134]. A few patients (~9%) can develop HH without clinical ascites [134]. HH can be complicated by the development of infection (spontaneous bacterial empyema; SBE) and respiratory failure or thoracentesis complications including bleeding and pneumothorax [135]. Development of HH in a patient with cirrhosis is associated with a decrease in survival to 8–12 months [135].

Diagnostic evaluation of a patient with hepatic hydrothorax

Diagnostic thoracentesis should be performed in patients with a new onset pleural effusion, unilateral left effusion, without ascites or those hospitalized with acute decompensation (Fig. 4). The work-up includes neutrophil count, pleural fluid protein and serum to pleural albumin gradient (SPAG). Patients with HH have a SPAG > 1.1 g/dL while a pleural effusion secondary to an infection, heart failure,

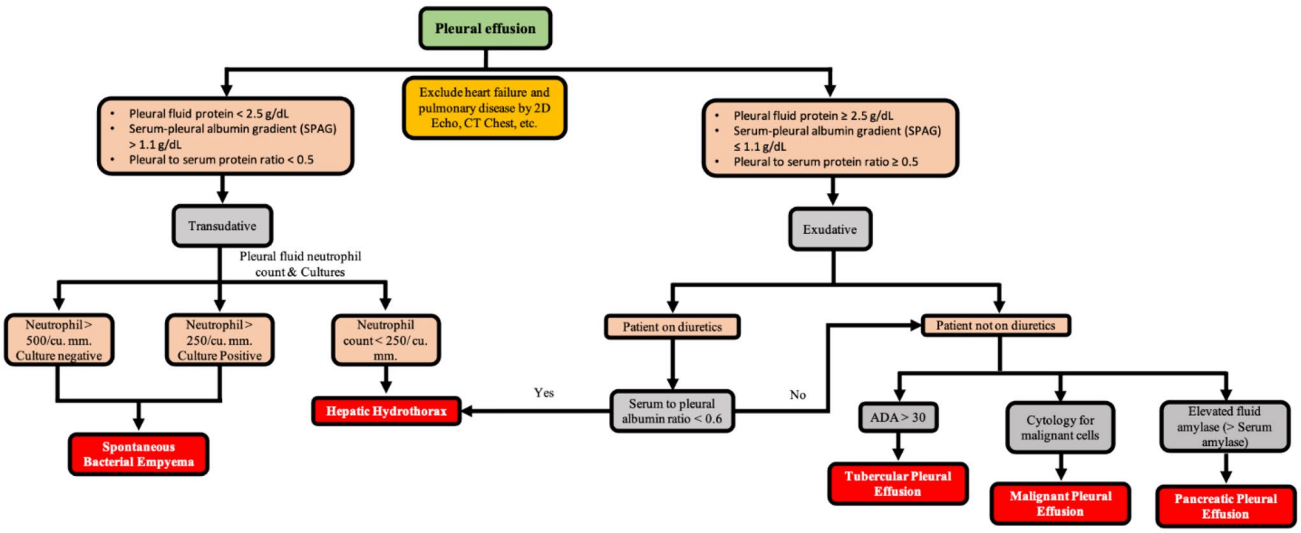

Fig. 4 Algorithm for diagnostic evaluation of pleural effusion in a patient with cirrhosis

malignancy or pancreatitis will have a SPAG ≤ 1.1 g/dL. The diagnosis of SBE is made in the absence of underlying lung consolidation and the presence of more than 250 neutrophils per high power field along with a positive pleural fluid culture or more than 500 neutrophils per high power field in the absence of a positive culture [136]. Diaphragmatic defects can be ascertained using scintigraphy, magnetic resonance imaging or colour Doppler ultrasound.

Management of hepatic hydrothorax

Initial principles for the treatment of HH are similar to those of ascites. The first line of therapy is a salt-restricted diet and diuretics. LVP may be required in cases of grade 3 ascites. However, HH may persist even after control of ascites in around 25% of patients and is known as refractory hydrothorax. Patients presenting with dyspnoea frequently require a therapeutic thoracentesis; however, there is only transient relief, and a repeat thoracentesis is needed. More than 1.5 L removal of pleural fluid is associated with risk of re-expansion pulmonary edema and should be avoided. Risk of complications like bleeding, infection and pneumothorax discourage the use of repeated thoracentesis for HH [136].

Chest tubes have been used previously for the management of HH but are generally avoided as they are associated with multiple complications including protein loss, electrolyte imbalance, pneumothorax, haemothorax, secondary infection and renal dysfunction [137]. Recently, indwelling tunnelled pleural catheters (ITPC) have been used in patients with HH and are associated with a lower complication rate [138]. In addition, a recent multicentre study demonstrated that the rate of spontaneous pleurodesis after ITPC was 28% while the infection rate was 10% [139]. However, the evidence is insufficient for the routine recommendation of ITPC for HH.

TIPS is an effective modality for refractory HH with a recent meta-analysis of 6 studies demonstrating a complete response of 55.8% and partial response of 17.6% [140]. Patients with advanced liver dysfunction (CTP ≥ 10, MELD > 15), elevated creatinine and those with non-response after TIPS have reduced survival and should be offered LT [141].

Various surgical modalities have been utilized to manage HH, including pleurodesis, repair of diaphragmatic defects and pleurovenous shunting. Chemical pleurodesis can be done by a chest tube or video-assisted thoracoscopic surgery (VATS). This is suitable for patients with no clinical ascites as patients with large-volume ascites will have continuous efflux of fluid from the peritoneum to pleural cavity, rendering apposition of visceral and parietal pleura difficult. A meta-analysis of 13 studies including 180 patients demonstrated a complete response to pleurodesis by chest tube of 78% and by VATS of 84% [142]. Although the initial success rate was 72%, symptomatic recurrence was seen in 25% of patients [142]. Surgical repair of diaphragmatic defects can be done by open thoracotomy or VATS. However, they have high morbidity and mortality along with a poor success rate (< 50%) and are usually not preferred in patients with advanced cirrhosis [143]. A pleurovenous or Denver shunt has been described as an alternative therapy for patients with HH [144], however, further evidence is needed to recommend its routine use.

Liver transplantation is the treatment of choice for patients with refractory HH. HH resolves by 3 months after LT and the post-transplant outcomes are similar among patients with and without refractory HH [145, 146].

However, when compared to patients without HH, patients with uncontrolled HH have a higher incidence of post-operative infections and a lower 1-year and 3-year mortality [147].

Recommendations

- First-line management of HH consists of sodium restriction and diuretics (C1).
- Diagnostic thoracentesis should be done in patients with new onset pleural effusion, isolated left-sided pleural effusion, pleural effusion in the absence of ascites or those admitted with acute decompensation or symptoms and signs of infection (C1).
- Therapeutic thoracentesis should be done in patients with respiratory distress (C1).
- Indwelling tunnelled pleural catheters, chemical pleurodesis, VATS or pleurovenous shunt may be offered on a case-to-case basis to patients who are not candidates for TIPS or LT (C2).
- TIPS should be considered in patients without other contraindications (B1).
- Liver transplantation is the modality of choice for patients with refractory HH (A1).

Hepatorenal syndrome (HRS)

Epidemiology

Patients with decompensated cirrhosis and ascites are prone to develop acute kidney injury which is defined by the International Club for Ascites (ICA) and the Kidney Disease: Improving Global Outcomes (KDIGO) as "a rise in serum creatinine by ≥ 0.3 mg/dL (26.53 µmol/L) within 48 h or ≥ 50% increase in serum creatinine from baseline (last available outpatient serum creatinine within 3 months) within the preceding 7 days and/or decrease in urine output to ≤ 0.5 mL/kg/h for ≥ 6 h" [148]. Prevalence of AKI in hospitalised patients ranges from 27 to 53% [149] and development of AKI is associated with a high 30-day mortality which ranges from 29 to 44% [150]. Post-transplant outcomes are also worse in patients with AKI [151].

Definition and diagnosis

Pre-renal AKI and acute tubular necrosis (ATN) are the predominant causes of AKI in patients with cirrhosis, while obstructive uropathy is rare [149]. Pre-renal AKI can be due to hypovolemia or HRS-AKI. ATN can occur due to sepsis, hypovolemic shock or use of nephrotoxic drugs. Other renal causes like glomerulopathies and bile cast nephropathy are rare but should be considered individually. Once a diagnosis of AKI is made, patients should be classified according to severity into stage 1 (rise in serum creatinine ≥ 0.3 mg/dL (26.53 µmol/L) or 1.5–2-fold increase from baseline), stage 2 (increase in serum creatinine 2–3-fold from baseline) or stage 3 (increase in serum creatinine > 3 times from baseline or creatinine > 4 mg/dL (353.6 µmol/L) or the initiation of renal replacement therapy).

ICA defines HRS as per the criteria in Table 4 [148]. Patients with HRS were initially classified into HRS-1 and HRS-2 depending on the rapidity of renal dysfunction. However, recently, it has been proposed to sub-classify HRS (Table 5) into HRS-AKI and HRS-NAKI (non-AKI) [152]. HRS-NAKI is further classified into HRS-acute kidney disease (AKD) if the estimated glomerular filtration rate (eGFR) is < 60 mL/min per 1.73 m^2 for < 3 months and HRS-chronic kidney disease (CKD) if eGFR is < 60 mL/min per 1.73 m^2 for > 3 months (Table 5) [152].

It is crucial to differentiate HRS from ATN due to differences in management and prognosis. Conventionally, the absence of active sediments in urine favour HRS. Various novel urinary and serum biomarkers are under investigation. The most promising urinary biomarkers to differentiate HRS from ATN are neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1) and liver-type fatty acid-binding protein (L-FABP) [153, 154]. These biomarkers are increased in patients with ATN compared to those without ATN. However, they cannot differentiate HRS-AKI from pre-renal AKI. Urinary

Table 4 Diagnostic criteria of Hepatorenal syndrome (HRS)—Acute Kidney Injury (AKI) according to the International Club of Ascites (ICA) consensus statement

Diagnostic Criteria of HRS-AKI
Patient with cirrhosis and ascites who develops a rise in serum creatinine ≥ 0.3 mg/dL (26.5 µmol/L) within 48 h or ≥ 50% from baseline value (last available outpatient serum creatinine within 3 months) and/or urine output ≤ 0.5 mL/kg body weight for ≥ 6 h
No full or partial response after at least 2 days of diuretic withdrawal and volume expansion with albumin given in the dose of 1 g/kg body weight per day to a maximum of 100 g/day
Absence of shock
No current or recent treatment with nephrotoxic drugs
Absence of renal parenchymal disease as indicated by proteinuria > 500 mg/day, microhaematuria (> 50 red blood cells per high power field), urinary injury biomarkers (if available) and/or abnormal renal ultrasonography

Table 5 Classification of Hepatorenal syndrome (HRS)

Classification	Diagnostic criteria	
HRS-AKI	i. Increase in serum creatinine by ≥ 0.3 mg/dL (26.5 µmol/L) within 48 h, and/or ii. Urine output ≤ 0.5 mL/kg body weight for ≥ 6 h, or iii. ≥ 50% increase in serum creatinine from baseline (last available outpatient serum creatinine within 3 months)	
HRS-NAKI	HRS-AKD	i. eGFR < 60 mL/min/1.73 m^2 for < 3 months in the absence of structural causes ii. < 50% increase in serum creatinine from baseline (last available outpatient serum creatinine within 3 months)
	HRS-CKD	eGFR < 60 mL/min/1.73 m^2 for ≥ 3 months in the absence of structural causes

NGAL is the most investigated biomarker and a urinary NGAL > 220 µg/g of creatinine is suggestive of ATN [150]. However, approximately 12% of patients with HRS may have a level > 220, suggesting a continuum from HRS to ATN [150]. In addition, urinary biomarkers are currently unavailable worldwide, hampering their generalisability and applicability.

Recommendations

- The diagnosis of AKI is based on a rise in serum creatinine by ≥ 0.3 mg/dL (26.5 µmol/L) within 48 h or ≥ 50% increase in serum creatinine from baseline (last available outpatient serum creatinine within 3 months) within the preceding 7 days and/or decrease in urine output to ≤ 0.5 mL/kg/h for ≥ 6 h (B1).
- The severity of AKI should be staged in all patients based on the adapted KDIGO criteria (B1).
- Once a diagnosis of AKI is made, its cause should be evaluated, and specific measures should be instituted as soon as possible to prevent the progression of AKI (B1).
- Urinary biomarkers may help in differentiation of HRS from ATN, but currently these tests are limited to investigational centres (B2).
- Diagnosis of HRS should be made based on revised ICA criteria (B1).

Management of HRS

Once AKI develops, diuretics and any nephrotoxic drugs should be stopped and volume expansion with intravenous albumin at 1 g/kg/day to a maximum of 100 g/day should be done (Fig. 5). Simultaneously, measures to treat the precipitating factor need to be instituted soon. In hypotensive patients, non-specific beta blockers (NSBB) should be withheld. Once an HRS diagnosis is made per the ICA criteria, specific treatment needs to be started. The mainstay of therapy for HRS is vasoconstrictor drugs like terlipressin, noradrenaline and midodrine.

Terlipressin is often the first-line drug for patients with HRS. It is a non-selective vasopressin receptor agonist that increases renal perfusion pressure. Terlipressin therapy is associated with a reversal of HRS in 35–80% of patients [155]. The more recent CONFIRM trial [156] demonstrated "verified HRS reversal" in 32% of patients with terlipressin compared to 17% with placebo, however, a recurrence of HRS up to 30 days was seen in 17% of patients treated with terlipressin. When combined with albumin, terlipressin is associated with a greater incidence of respiratory failure [156]. Other terlipressin-related adverse events include abdominal pain, diarrhoea, mesenteric ischemia, cardiac arrhythmias, bradycardia, myocardial ischemia, hyponatremia, cyanosis or skin necrosis [155]. These side effects can be reduced using terlipressin infusion instead of bolus doses of terlipressin while having a similar efficacy [157]. Serum creatinine should be monitored on day 3 and if the decrease is < 25%, the dose of terlipressin should be increased, up to a maximum of 12 mg till day 14 [157].

Noradrenaline has also been used for the treatment of HRS. Few single-centre RCTs had found norepinephrine and albumin combination to have similar efficacy in HRS reversal to a combination of terlipressin and albumin [158]. It is started at a dose of 0.5 mg/hour with a target to increase mean arterial pressure (MAP) by 10 mm Hg or to increase urine output by > 200 mL in 4 h. The dose can be increased in increments of 0.5 mg/hour 4 hourly up to a maximum of 3 mg/hour. Norepinephrine typically requires a central venous catheter and continuous monitoring. Therefore, it is currently recommended for use in ICU only.

Midodrine and octreotide combination along with albumin was also shown to be effective in decreasing serum creatinine levels in patients with HRS, however, the benefit was significantly less than that seen by terlipressin and albumin combination in a single-centre RCT [159]. Treatment with vasopressors should continue till serum creatinine is within 0.3 mg/dL (26.5 µmol/L) of the baseline (complete response). Partial response is when serum creatinine has decreased to a value > 0.3 mg/dL (26.5 µmol/L) from the baseline value.

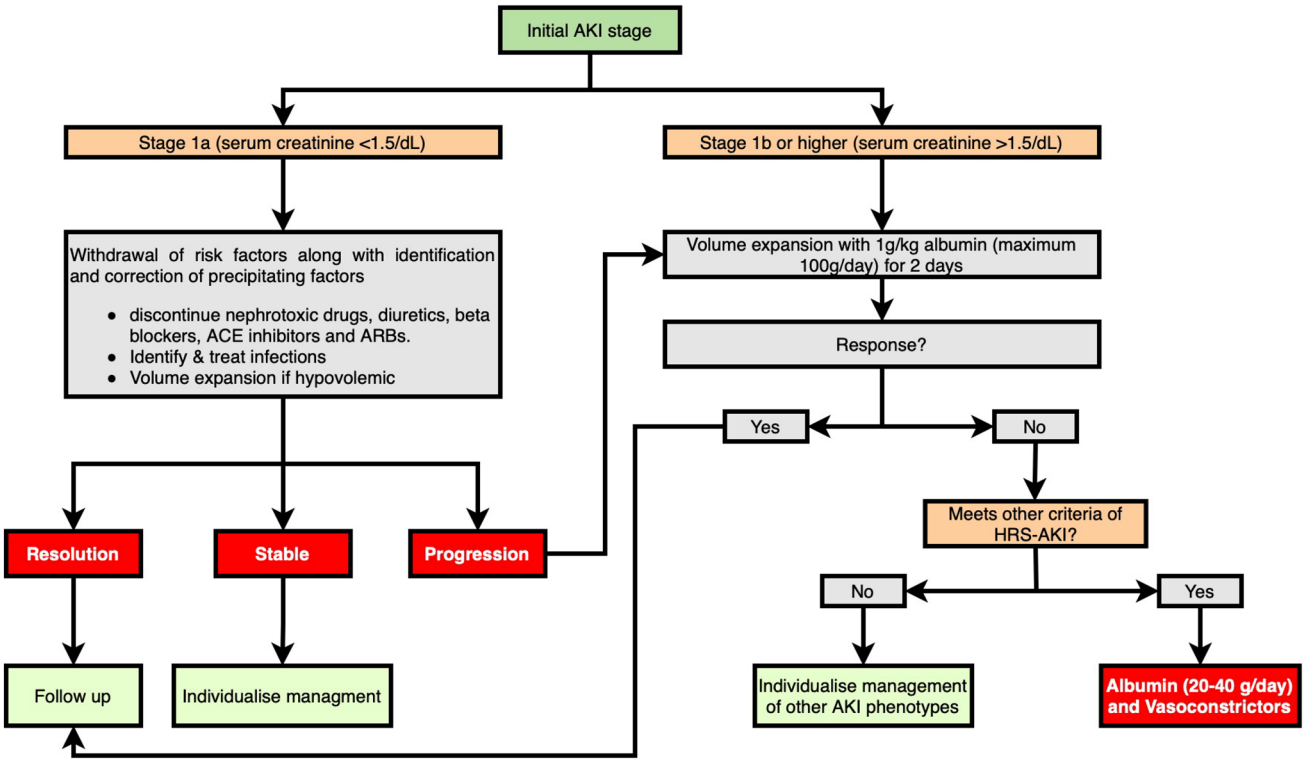

Fig. 5 Approach to management of Acute Kidney Injury (AKI) (*HRS* hepatorenal syndrome, *ACE* angiotensin converting enzyme, *ARB* angiotensin receptor blockers)

TIPS was evaluated for HRS treatment in a study of 14 patients with HRS-1 and 17 patients with HRS-2 [160]. Serum creatinine on follow-up was significantly lower in the TIPS group. Also, patients with HRS-2 who underwent TIPS had better survival than patients with HRS-1 [160]. However, further RCTs are needed to evaluate the role of TIPS in treating HRS. The optimal timing of initiation of renal replacement therapy (RRT) in patients with HRS is not yet known, however, patients who meet standard indications for dialysis (fluid overload, severe acidosis, hyperkalemia, uremia) should be offered RRT. RRT may be considered as a bridge to LT in patients with HRS and patients who are not listed for LT but receive RRT for HRS or ATN have an extremely high mortality rate [161]. LT is the treatment of choice for patients with HRS. However, post-LT, serum creatinine is higher in patients who were transplanted for HRS than those without AKI [162]. Various factors predict renal function recovery after LT including response to vasoconstrictors, pre-existing comorbidities, underlying intrinsic renal disease, intra-operative complications and post-LT immunosuppression [163]. Patients whose renal function is not expected to improve after LT should be considered for a simultaneous liver-kidney transplant (SLKT). The Organ Procurement Transplant Network (OPTN) has recently provided new listing criteria for SLKT [164]. Patients who undergo liver transplantation alone have a "safety net" post-LT where they are prioritized for renal transplant if the renal functions do not improve [165].

Recommendations

- The first steps in managing AKI in patients with cirrhosis are the cessation of nephrotoxic drugs (including diuretics, beta blockers, etc.) and volume replacement (B1).
- Volume replacement with albumin should be done in patients with AKI and serum creatinine > 1.5 mg/dL (132.6 µmol/L) (A1).
- Volume replacement with albumin may be considered in AKI with serum creatinine < 1.5 mg/dL (132.6 µmol/L) on a case-by-case basis (C2).
- All patients with HRS-AKI should be considered for treatment with vasoconstrictors and intravenous albumin (A1).
- The vasopressor of choice is intravenous terlipressin, which should be started as a continuous infusion of 2 mg per day to a maximum dose of 12 mg/day till resolution of AKI (or maximum duration of 14 days). Bolus doses may also be used but are associated with an increased risk of adverse events (A1).

- In patients with ACLF and HRS-AKI, terlipressin is superior to noradrenaline and should be preferred (B1).
- In patients without ACLF, noradrenaline is as effective as terlipressin. However, its use requires central venous access and ICU monitoring (C).
- Noradrenaline may be used in patients who are intolerant to or not candidates for terlipressin therapy (B1).
- The combination of midodrine and octreotide has a lower efficacy than terlipressin and noradrenaline. It should be reserved when other therapies are not available (B1).
- Patients with recurrence of HRS may be retreated with vasoconstrictors (B1).
- There is insufficient evidence to recommend using TIPS for HRS-AKI (C2).
- There is inadequate evidence to suggest early RRT in patients with AKI and a decision to initiate RRT should be made on standard indications (C2).
- LT is the management of choice for patients who develop HRS-AKI (A1).

Use and controversies regarding intravenous human albumin in decompensated cirrhosis

The traditional indications for intravenous human albumin in patients with cirrhosis include SBP, AKI-HRS and for prevention of PICD, as previously described. However, more and more evidence is available regarding the disease-modifying effects of human albumin which has led to it being utilized as a disease-modifying agent in patients with decompensated cirrhosis. A landmark study, the ANSWER trial (Long-term albumin administration in decompensated cirrhosis) carried out by Caraceni et al. [124], demonstrated that weekly albumin for 18 months (40 g twice a week for 2 weeks followed by 40 g weekly) reduced mortality, recurrence of ascites, HE, HRS, infections and admissions when compared to standard medical therapy (SMT). Similar results of mortality benefit (65.5% vs. 41.6%) were demonstrated by Di Pascoli et al. [80] in patients with refractory ascites using 20 g albumin twice weekly. The Pilot-PRECIOSA study showed that long-term high-dose human albumin (1.5 g/kg/week for 12 weeks vs. 1 g/kg every 2 weeks) led to a more significant number of patients achieving normal serum albumin concentration, reduced systemic inflammation and cardiocirculatory dysfunction [166]. However, in the recently conducted ATTIRE (Albumin to prevent infection in chronic liver failure) trial, the benefit of targeted albumin therapy (target serum albumin levels > 3.5 g/dL) by giving human albumin daily for 2 weeks was not seen with respect to reduced 3-month mortality or complications [167]. This is expected as serum albumin undergoes post-translational modifications in patients with cirrhosis, and functional albumin is more important than absolute value of serum albumin. The MACHT (midodrine and albumin to prevent complications in cirrhotic patients awaiting liver transplantation) trial combining 15–30 mg/day midodrine to 40 g albumin every 2 weeks did not lead to a decrease in complications or mortality [79]. However, this group had a sicker cohort of patients with more advanced liver disease when compared to patients recruited in the ANSWER trial. Albumin infusion has also been beneficial in patients with cirrhosis and bacterial infections other than SBP. It leads to a decreased incidence of renal failure, reduced cytokines and improved survival [168, 169]. In critically ill septic patients with cirrhosis, using 5% human albumin was associated with a better reversal of hypotension when compared to 0.9% saline [170]. It also led to improved heart rate, lactate clearance and short-term survival. However, more evidence is needed before recommending 5% albumin for volume resuscitation in this patient population.

Albumin increases the preload and has been shown to improve cardiac output [171]. Because of this it has been proposed to be helpful in patients with cirrhotic cardiomyopathy. However, albumin therapy is known to be associated with fluid overload and pulmonary edema and should be used with caution in patients with decompensated cirrhosis. Patients who are receiving vasoconstrictors like terlipressin are at increased risk of pulmonary edema and should be frequently monitored for the same. Table 6 summarizes the evidence on the use of intravenous albumin in patients with decompensated cirrhosis.

Beta-blockers in patients with ascites

The use of non-selective beta blockers (NSBB's) for long term in patients with cirrhosis has been shown to prevent decompensation by up to half, predominantly by decreasing the formation of ascites [172]. However, once ascites develops, the safety of NSBBs has been questioned. The first study to raise concerns regarding NSBB safety was by Sersté et al. [173]. They showed NSBB use in 151 patients with refractory ascites was associated with reduced survival. This could be due to the presence of more advanced liver disease in the NSBB group in the study by Sersté et al. along with use of higher doses of propranolol (> 160 mg/day). A Danish registry of more than 3500 patients with cirrhosis and ascites demonstrated higher mortality in patients who received > 160 mg/day of propranolol [174]. Similarly, Carvedilol > 25 mg/day is associated with poor outcomes in patients with refractory ascites [175]. Further, patients with refractory ascites and reduced cardiac function (measured by left ventricular stroke volume index < 64.1 gm/m^2) had higher waitlist mortality if treated with NSBB [176]. The mechanism behind the harmful effect of NSBBs in refractory ascites

Table 6 Summary of major studies on the use of intravenous albumin in patients with cirrhosis

Authors	No. of patients	Study design	Inclusion criteria	Exclusion criteria	Study drug and dose	Result	Limitations
Spontaneous bacterial peritonitis (SBP)							
Sort et al. [60]	126	Randomized	Cirrhosis with SBP	Antibiotic treatment within 1 week, GI bleed, structural kidney disease, Serum creatinine ≥ 3 mg/dL, cardiac failure, age > 80 years, septic shock, dehydration	IV Cefotaxime vs. IV Cefotaxime + IV Albumin (1.5 g/kg weight on day 1 followed by 1 g/kg on day 3)	Resolution of SBP similar In-hospital and 3-month mortality lower in combination group	• 3 patients excluded after randomization • Dose of albumin used arbitrary
Xue et al. [61]	112	Randomized	Cirrhosis with SBP	Secondary bacterial peritonitis, other infections, shock, GI bleed, severe encephalopathy, cardiac failure, structural kidney disease, HIV	IV Ceftriaxone (3 g/day) vs. IV Ceftriaxone + IV Albumin (0.5–1 g/kg weight within 6 h followed by same dose every 3 days for 3 weeks)	Renal impairment and in-hospital mortality significantly lower in combination group	• Dose of albumin used arbitrary and for longer duration
Terg et al. [187]	127	Retrospective	Cirrhosis with SBP	Patients who received large plasma volume expansion, HIV, GI bleeding, MAP < 70 mm Hg, heart failure, neoplasia, structural kidney disease	High risk (Bilirubin > 4 mg/dL or creatinine > 1 mg/dL) and low-risk group (Bilirubin < 4 mg/dL or creatinine < 1 mg/dL)	Mortality and renal failure higher among high-risk group	• IV Albumin not given to patients with SBP • Retrospective study
PICD prevention							
Ginès et al. [41]	289	Randomized	Hospitalized patients with cirrhosis and tense ascites	Bilirubin > 10 mg/dL, Prothrombin time < 40%, Platelet count < 40,000/cu.mm., creatinine > 3 mg/dL, GI bleed within 1 month, HCC, respiratory/cardiac/renal disease	Total Paracentesis + either human albumin, Dextran 70 or Polygeline (all 8 g/L of ascitic fluid removed with 50% dose within first 2 h and 50% dose 6–8 h after paracentesis)	PICD occurred more frequently in patients treated with Dextran 70 or polygeline than in those receiving albumin when more than 5L of ascitic fluid removed	• Study not powered to detect differences in complications or survival on follow-up

Table 6 (continued)

Authors	No. of patients	Study design	Inclusion criteria	Exclusion criteria	Study drug and dose	Result	Limitations
Titó et al. [188]	38	Prospective observational	Cirrhosis with tense ascites	Bilirubin > 10 mg/dL, Prothrombin time < 40%, Platelet count < 40,000/cu.mm., creatinine > 3 mg/dL, GI bleed, HCC, infections,	Total paracentesis + 20% human albumin infused at 2 mL/min. 50% dose infused immediately after paracentesis and 50% dose 6 h later	Paracentesis mobilized ascites completely in 37 patients Plasma renin activity, aldosterone and norepinephrine measured at 48 h and 6 days later remained like baseline 13% developed complications 5% died	• Non-randomized study • No control groups
Alsebaey et al. [43]	110	Prospective study	Patients with cirrhosis and tense ascites requiring LVP	Age < 18 or > 70 years, cardiac/renal/respiratory disease, sepsis, HE, SBP, GI bleed within 7 days	Low-dose albumin (2 g/L of fluid removed; $n = 85$) vs. Normal volume albumin (6 g/L of fluid removed; $n = 25$)	Similar incidence of PICD among both groups	• Non-randomized study • Low-dose albumin group had more CTP-B patients and underwent less paracentesis volume
Arora et al. [88]	80	Prospective study	Patients with ACLF undergoing modest volume paracentesis (< 5L)	Age < 18 years, decompensated cirrhosis, DIC, HCC, non-cirrhotic ascites, creatinine > 1.5 mg/dL, sepsis, septic shock, HE grade > 2, CAD, active variceal bleed, CKD, respiratory failure	IV Albumin (8 g/Litre of fluid removed; $n = 40$) vs. no albumin ($n = 40$)	PICD, HE, AKI, Hyponatremia, and in-hospital mortality higher in no-albumin group	• Open label trial
Refractory ascites							
di Pascoli et al. [80]	70	Prospective, non-randomized study	Patients with cirrhosis and refractory ascites	HCC beyond Milan criteria, severe extrahepatic diseases	IV Albumin [20 g twice a week] + SOC ($n = 45$) vs. SOC ($n = 25$)	Cumulative incidence of 24-month mortality lower in albumin group Reduction in incidence of overt HE, ascites, SBP and non-SBP infections	• Single centre, non-randomized study

Table 6 (continued)

Authors	No. of patients	Study design	Inclusion criteria	Exclusion criteria	Study drug and dose	Result	Limitations
Decompensated cirrhosis							
Sola et al. [79]	196	Multicentre, randomized, double-blind trial	Patient with cirrhosis and ascites on LT waitlist	Hypertension (systolic BP ≥ 150 and/or diastolic BP ≥ 90 mm Hg or drug therapy for hypertension), treatment with psychotropic drugs, TIPS, Chronic heart or respiratory failure, HIV, HCV treated with DAA's, previous LT, listed for combined liver-kidney transplant	Midodrine (15–30 mg/day) + IV Albumin (40 g/ 15 days) vs. Placebo for 1 year	No difference in developing complications of cirrhosis or mortality at 1-year Significant decrease in plasma renin activity compared to placebo	• Median duration of treatment was only 80 days • Dose of albumin used was low
Caraceni et al. [124]	440	Multicenter, randomized, open-label trial	Cirrhosis with uncomplicated ascites on diuretic treatment	refractory ascites, recent complications of cirrhosis, TIPS, HCC, LT, ongoing alcohol abuse, extrahepatic organ failures, albumin use for the treatment of ascites in the month preceding enrolment	SMT ($n = 213$) vs. SMT plus Human albumin ($n = 218$; 40 g twice weekly for 2 weeks followed by 40 g weekly) for 18 months	Overall 18-month mortality lower in the SMT + Albumin group	• Open label trial • Patients receiving weekly albumin infusions were more frequently assessed and led to early detection of any complication and management
China et al. [167]	777	Multicenter, randomized, open-label trial	Hospitalized patients with decompensated cirrhosis with serum albumin < 3 g/dL	Advanced HCC with life expectancy < 8 weeks, receiving palliative care, pregnant, severe cardiac dysfunction	Targeted 20% albumin infusion for 14 days or discharge (whichever earlier) vs. SMT	• No difference in new onset infection, kidney dysfunction or death between day 3 and day 15 after treatment initiation • More serious adverse events in albumin group	• Open label trial • Amount of albumin infused in SMT group was lower than anticipated • Rate of albumin infusion very fast (100 mL/h)

Table 6 (continued)

Authors	No. of patients	Study design	Inclusion criteria	Exclusion criteria	Study drug and dose	Result	Limitations
Bacterial infections							
Fernández et al. [166]	118	Randomized, open-label, multicentre trial	Cirrhosis with bacterial infection	More than 72 h after infection diagnosis, septic shock, infective endocarditis, fungal infection, ALF, Grade 3 ACLF, severe extrahepatic chronic disease, HIV, SBP	Antibiotics + Albumin (1.5 g/kg on Day 1 and 1 g/kg on day 3) vs. Antibiotics alone for 1 week	• Patients given albumin had significant reduction in the plasma levels of cytokines • No difference in in-hospital mortality • Higher ACLF resolution and lower nosocomial infections in albumin group on follow-up	• Open label trial • Patients receiving albumin were sicker at admission
Guevara et al. [169]	110	Randomized trial	Hospitalized patients with cirrhosis for infections unrelated to SBP	GI bleed, current/recent antibiotic use, HCC, HIV, septic shock, SBP	Antibiotics + Albumin ($n=56$; 1.5 g/kg on day 1 and 1 g/kg on day 3) vs. antibiotics alone ($n=54$)	• Albumin group had improvement in renal and circulatory function • Similar 3-month survival	• 3-month mortality in control group was lower than that used for sample size calculation
Thévenot et al. [168]	193	Multi-centre, randomized trial	Cirrhosis with CTP score > 8 and sepsis unrelated to SBP	Creatinine > 160 µmol/L, SBP, septic shock and use of antibiotics within last 1 week	Antibiotics + Albumin ($n=96$; 1.5 g/kg on day 1 and 1 g/kg on day 3) vs. antibiotics alone ($n=97$)	• Albumin infusion delayed the onset of renal failure, but 3-month renal failure rate was similar • 3-month survival similar	• Diagnosis of AKI was based on old criteria • Albumin given out of protocol in 17 patients • Trial under-powered to detect differences in renal failure
Hyponatremia							
Bajaj et al. [123]	1126	Retrospective analysis of a prospectively collected database	Hospitalized cirrhotic patients in NACSELD cohort with hyponatremia (Sodium ≤ 130 mEq/L)	HIV, prior LT, unclear aetiology of cirrhosis, patients admitted electively	777 patients received IV Albumin (Mean cumulative dose—225 gm)	Albumin led to significantly higher rate of hyponatremia resolution	• Albumin infusion not specifically used for hyponatremia • Daily diuretics/lactulose dose not measured • Reasons for not giving albumin in remaining patients not controlled for

ACLF acute-on-chronic liver failure, *AKI* acute kidney injury, *ALF* acute liver failure, *CAD* coronary artery disease, *CKD* chronic kidney disease, *CTP* Child Turcotte Pugh, *DAAs* direct acting antivirals, *DIC* disseminated intravascular coagulation, *GI* gastrointestinal, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *HE* hepatic encephalopathy, *HIV* human immunodeficiency virus; HRS Hepatorenal syndrome; INR International normalized ratio, *IV* intravenous, *LT* liver transplant, *LVP* large-volume paracentesis, *MAP* mean arterial pressure, *NACSELD* North American consortium for end stage liver disease, *PICD* paracentesis induced circulatory dysfunction, *SBP* spontaneous bacterial peritonitis, *SMT* standard medical therapy, *TIPS* transjugular intrahepatic portosystemic shunt

was tried to be answered by Téllez et al. [177] in their study of 40 patients (20 with RA and 20 with diuretic-responsive ascites). They demonstrated that the use of NSBB in patients with RA is associated with reduced renal perfusion pressure and reduced LV systolic function. However, the sample size was small, and the duration of beta-blocker use was brief to draw definite conclusions. Patients with SBP receiving NSBB had more evidence of hypotension, AKI, HRS and lower transplant-free survival in a retrospective study of 607 patients with cirrhosis [178]. However, like the study by Sersté et al. [173], patients in this study [178] who received NSBB had more advanced liver disease which could have contributed to increased adverse outcomes. A recent randomized controlled trial of 160 patients comparing the efficacy of propranolol with endoscopic variceal ligation (EVL) for primary prophylaxis of variceal bleeding in patients with moderate to severe ascites showed that the use of propranolol was associated with a greater incidence of AKI, poor ascites control and lower 12-month transplant-free survival as compared to patients who underwent EVL while having similar efficacy in preventing first episode of variceal hemorrhage [179].

Subsequently, many studies have demonstrated the beneficial effects of beta blockers in patients with cirrhosis and ascites. In a post hoc analysis of 1198 patients with ascites, including 588 patients with RA, beta blockers were not shown to increase mortality [180]. Similarly, Bhutta et al. in their study of 707 patients with cirrhosis and ascites, including 51% of patients with RA failed to show increase in mortality with NSBB use [175]. Beta-blockers also improve transplant-free survival in patients with cirrhosis and ascites [181]. Daily propranolol doses < 160 mg significantly improved survival in patients with cirrhosis and ascites [174]. The concern with the safety of carvedilol was assessed by Sinha et al. in their study of 264 patients [182]. Patients with mild ascites had significantly improved survival compared to those who did not receive carvedilol. Patients with grade 3 ascites receiving carvedilol did not lead to increased mortality. Regarding use of NSBB in patients with SBP, Bang et al. showed improved survival with the use of NSBB in patients with SBP [174]. Tergast et al., in their study of 257 patients demonstrated that only patients with SBP and a mean arterial pressure < 65 mm Hg had renal impairment with NSBBs [183]. A summary of the studies on NSBB use in patients with cirrhosis and ascites is given in Supplementary Table S2.

As beta blockers reduce the risk of developing first episode of ascites [172] and SBP [184], their use should not be limited in patients who develop ascites. However, if patients develop hypotension or AKI, it is wise to discontinue beta blockers temporarily.

Recommendations

- Refractory ascites, SBP or ACLF are not contraindications for NSBBs. However, high doses of NSBBs (> 160 mg/day of propranolol or > 80 mg/day of nadolol) should be avoided (B1).
- NSBBs should be withheld in patients with severe circulatory dysfunction as evidenced by systolic BP < 90 mm Hg, serum Na < 130 mEq/L or AKI (B1).

Future research prospects

With the rising incidence of MAFLD related cirrhosis, it is pertinent that aspects of the metabolic syndrome are adequately addressed in these patients. A common dilemma is the use of ACE inhibitors and ARBs for management of hypertension in patients with ascites. While these drugs may reduce GFR [21], they also improve fibrosis [18]. Therefore, studies are urgently needed to identify in granular detail the specific subpopulations that may potentially benefit from these therapies.

Another area of limited evidence is the optimal dose of diuretics and albumin in the Asian population. Traditionally, all the major guidelines recommend starting diuretics with 100 mg spironolactone and 40 mg furosemide [119, 185]. However, in clinical practice, gastroenterologists and hepatologists often begin with a lower dose and gradually titrate it to reach the maximum tolerable dose. Similarly, IV albumin is recommended in patients with SBP at a dose of 1.5 g/kg on day 1 and 1 g/kg on day 3 with a maximum of 100 g in a day. But the evidence for this is based on a single study [60], and the use of low-dose albumin needs further research because of the high cost and potential adverse effects of albumin. We need good quality trials in the Asian population to find the optimal/minimum dose, frequency, and duration of albumin therapy for standard indications like prevention of PICD after LVP, SBP and HRS as well as to identify its role in patients with sepsis, refractory ascites, hepatic hydrothorax, CKD, cirrhotic cardiomyopathy and ACLF. Because of the high cost of albumin treatment, low-cost, synthetic recombinant albumin is the need of the hour. Public insurance companies in certain regions approve albumin infusions only for patients with serum albumin levels < 2.5 g/dL due to which a large majority of patients with cirrhosis might have to incur out-of-pocket expenditure for albumin infusion. There is no strong evidence to follow this policy and data on cost-effectiveness apart from hard clinical outcomes is the need of the hour to better inform policy decisions. Albumin is quantitatively low and qualitatively dysfunctional in patients with cirrhosis. Many of the putative

benefits of albumin are attributable to its non-oncotic properties. While the administration of exogenous albumin can increase serum albumin levels quantitatively, the effect on the quality and biological properties needs further research.

The indications for primary prophylaxis of SBP need to be re-visited in the current age from a holistic point of the "gut-liver axis" rather than liver-specific parameters alone. With the rise in MDR bugs, the use of norfloxacin viz a viz other antibiotics for primary and secondary prevention of SBP needs to be further examined. The risks and benefits of prolonged prophylaxis also need investigation.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors—which are generally used for treating hyperglycemia in patients with type 2 diabetes mellitus—hold theoretical promise as a treatment of ascites. These drugs act synergistically with loop diuretics by inhibiting the reabsorption of sodium and glucose in the proximal convoluted tubule. Notably, treatment with SGLT2 inhibitors of patients with cirrhosis and comorbid diabetes has resulted in improvement of ascites and lower extremity edema, without significant adverse events in few case reports [186]. Since these drugs are being used in patients with advanced heart failure regardless of glycemia, they should undergo further clinical testing in patients with cirrhotic ascites independent of the presence or absence of comorbid diabetes.

There is no evidence on the role of albumin and vasoconstrictors in patients with stage 1a HRS-AKI. It should be noted that renal dysfunction in the definition of refractory ascites in prevailing guidelines continues to be a doubling in serum creatinine to > 2 mg/dL (176.8 µmol/L), which contradicts the recent ICA definition of AKI. The impact of our suggestion to modify renal dysfunction for defining refractory ascites following ICA definitions needs to be assessed in a real-world setting. The role of TIPS for HRS-AKI and hepatic hydrothorax needs to be evaluated further.

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Declarations

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