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Review Article

Management of ascites in patients with liver cirrhosis: Recent evidence and controversies

Shao-Jung Hsu [a], Hui-Chun Huang [a,b,*]

[a] *Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[b] *Faculty of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC*

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Abstract

Ascites formation in patients with cirrhosis, portal hypertension, or both usually results from hyperdynamic circulatory dysfunction, where the retention of sodium and water is associated with the activation of the sympathetic and renin−angiotensin−aldosterone systems. The presence of ascites indicates the development of liver decompensation. Furthermore, complications seen in conjunction with ascites such as spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatic hydrothorax may result in increased morbidity and mortality. Although non-pharmacological, pharmacological, and surgical approaches have been introduced and clinically practiced, their therapeutic effects are still suboptimal or limited by their potential side effects, such as large-volume paracentesis-induced postparacentesis circulatory dysfunction. Herein, we discuss strategies to prevent and properly manage ascites-related complications, including a review of the literature and controlled studies that assess these strategies.

Keywords: ascites; liver cirrhosis; portal hypertension

1. Introduction

Ascites formation is defined as a condition of abnormal accumulation of fluid in the abdomen. Liver cirrhosis is the most common among the medical and surgical conditions associated with ascites formation, and is responsible for 81% of cases.[1] In fact, ascites is actually the most common complication of liver cirrhosis.[2] Approximately 10% of patients with cirrhosis have ascites, and 50−70% of newly diagnosed patients with cirrhosis develop ascites within 10 years. The presence of ascites is regarded as a turning point in such patients, because it suggests the development of liver decompensation. An elevated risk of mortality has been noted among patients with ascites, with an increasing rate of 15% in the 1st year and 44% in the 5 years[3] after its diagnosis. As cirrhosis progresses, ascites becomes refractory to diuretic control, where the survival rate of the patient 1 year after diagnosis is further reduced to only 50%. Therefore, the presence of refractory ascites is generally considered to be an adverse prognostic indicator.

Because the efficacy of currently available treatments is still unsatisfactory, much effort has been spent searching a better treatment strategy. This review aims to discuss the pathophysiology, pharmacological treatment options, and their impacts on large-volume paracentesis (LVP)-induced post-paracentesis circulatory dysfunction (PCD) in decompensated cirrhotic patients with ascites, partly based on the relevant existing literature.

2. Pathophysiology

The pathophysiology of ascites formation is depicted in Fig. 1. Typically, cirrhosis of the liver increases intrahepatic resistance by the disruption of intrahepatic blood flow through several mechanisms: first, by sinusoidal fibrosis and

* Corresponding author. Dr. Hui-Chun Huang, Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: hchuang2@vghtpe.gov.tw (H.-C. Huang).

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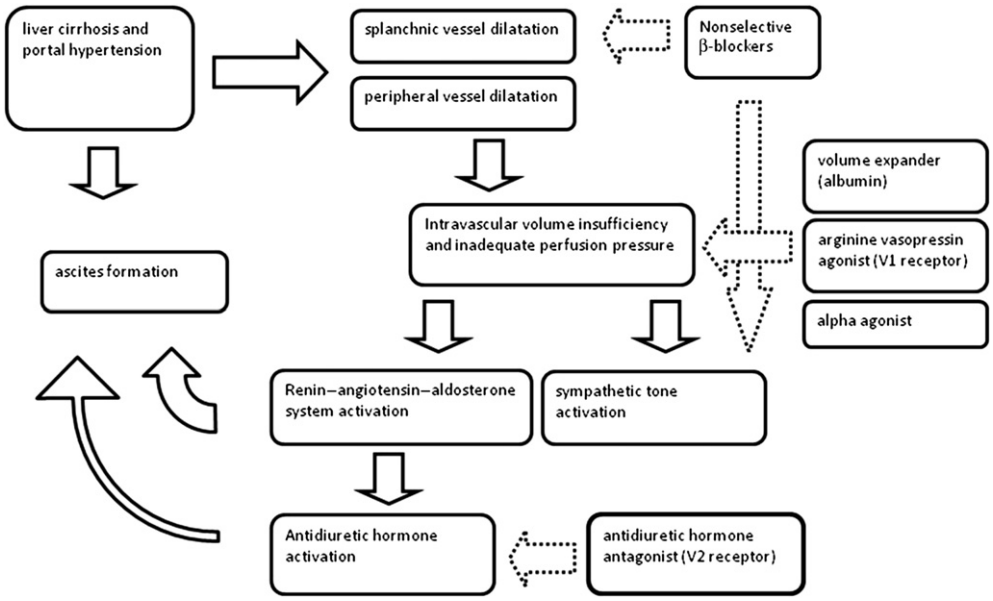

Fig. 1. The pathophysiology of ascites formation in cirrhosis.

regenerative nodules (fixed component), and second, by exaggerated intrahepatic vasoconstriction (functional component). Meanwhile, the enhanced release of splanchnic vasodilatory substances, particularly nitric oxide,[4,5] induces splanchnic hyperemia and increases portal inflow. Taken together, increased hepatic resistance accompanied by hyperdynamic splanchnic circulation results in significantly elevated portal pressure, customarily presenting as portal hypertension.

Hyperdynamic circulation in cirrhosis and/or portal hypertension[6] is characterized by circulatory dysfunction including decreased total peripheral vascular resistance, increased heart rate and cardiac output. The initial event in this process is believed to be peripheral vasodilatation. Consequently, the redistribution of blood flow leads to reduced vital organ perfusion, further causing effective hypovolemia. Along with arterial hypotension, they activate the volume- and baroreceptor-mediated sympathetic system, leading to increased cardiac output and vasoconstriction. Furthermore, the renin–angiotensin–aldosterone (RAA) system is activated to compensate for the effective hypovolemia, with the primary result being retention of renal sodium and water.

Influenced by elevated intrasinusoidal pressure due to liver cirrhosis and increased intravascular volume due to renal hyponatriuresis, hydraulic pressure over the capillary net of portal system gradually increases, which forces the fluid moving across the hepatic capsule into the peritoneum. The process is evidenced by the high serum-ascites albumin gradient in patients with cirrhotic ascites ($\geq$1.1 g/dL), which implies abnormally high intravascular pressure.

3. Management of ascites

The control of ascites should be undertaken whenever it becomes necessary to relieve abdominal discomfort, alleviate shortness of breath, improve appetite, prevent spontaneous bacterial peritonitis (SBP),[7] or reduce the risk of abdominal wall hernia. In brief, the main goal is to improve the quality of life with the prerequisite of maintaining a stable hemodynamic condition.

In the early stage, ascites can be controlled by just restricting dietary salt intake. However, as the disease progresses, the excretion of urinary sodium gradually decreases, and diuretics must be used to promote efficient urinary sodium excretion. Unfortunately, even with diuretic use, the amount of urinary sodium excreted could be $<$10 mmol/day in patients with advanced liver cirrhosis. Eventually, it is customary to find supervening ascites refractory to pharmacological treatment.

4. Control of refractory ascites

4.1. Definition

Refractory ascites are defined by the International Ascites Club as "ascites that cannot be mobilized, or early recurrence of which cannot be satisfactorily prevented by medical therapy."[8] In the largest randomized controlled trial performed in patients with ascites due to liver cirrhosis caused by alcoholism, it was found that more than 90% of ascites could be controlled by a combination of diet modification and treatment with diuretics.[9] This result suggests that approximately 10% of ascites are resistant to treatment with diuretics.

4.2. LVP

It has been observed that LVP removes ascites in a short time and quickly relieves tense ascites. LVP is effective and safe, and thus it has become a routine procedure in clinical practice.[10] However, LVP obviously does not correct the underlying condition of ascites. As a result, LVP is regarded as

an "add-on" therapy to diet and medical control, rather than a definitive treatment choice. It is worth noting that the rapid removal of a large volume of ascites inevitably results in the activation of the RAA system, which will be discussed in the following section.

4.3. Transjugular intrahepatic portosystemic shunt

Transjugular intrahepatic portosystemic shunt (TIPS) is an intrahepatic portosystemic shunt that bypasses the blood flow from the portal venous branch to the hepatic venous branch. It relieves portal hypertension and thus alleviates ascites formation. Results of various studies involving meta-analyses show that TIPS provides better ascites control than serial LVP.[11−13] However, encephalopathy is a concern because the bypassed blood containing neurotoxins, including ammonia, cannot be appropriately processed by the liver. Many studies have been carried out to survey patient selection criteria, trying to improve diagnostic and treatment efficacy and also to reduce the complications of this procedure.

4.4. Pharmacotherapy

Peripheral vasodilatation, activation of the sympathetic system, hyperarousal of the RAA system, and retention of sodium are the main causes of ascites formation. However, the use of novel pharmacologic agents counteracting these effects, including albumin, terlipressin, satavaptan, midodrine, and nonselective β-blocker (NSBB) have been investigated in the past few years (Table 1).

4.5. Albumin

Albumin is a 66-kDa protein that constitutes 50−60% of serum protein. The main physiological function of albumin is to retain ongoing intravascular osmotic pressure and to maintain effective circulating volume. As a colloid volume expander, albumin has been used to "fill" potentially inadequate intravascular volume, especially after LVP.

Removing a large amount of ascites in a short period may induce circulatory dysfunction because of the sudden reduction of effective circulating volume with reactivation of RAA and sympathetic systems, a condition known as PCD (usually defined as an elevation of renin level up to 50% from baseline). Existing evidence indicates that PCD was associated with acute reaccumulation of ascites, hepatorenal syndrome (HRS), and dilutional hyponatremia.[14,15] One study even found that PCD increased the risk of patient mortality.[16]

Until now, the most effective method to prevent LVP-related circulatory dysfunction was the adjuvant administration of albumin.[17] In the European Association for the Study of the Liver (EASL) practice guidelines, it is suggested that cases with LVP greater than 5 L of ascites should involve albumin administration. However, this recommendation is only based on a consensus of expert opinions, notwithstanding the fact that the current available data remain controversial. Furthermore, questions over the effectiveness of any other volume expander, when compared with albumin, exist. A systematic review in 2008 concluded that, regarding morbidity and mortality, there was no evidence that albumin is superior to other volume expanders as an adjunctive therapy to LVP.[18]

In 2011, Bernardi et al reported a meta-analysis comparing the effectiveness of albumin with other volume expanders (dextran, gelatin, hydroxyethyl starch, and hypertonic saline) and vasoconstrictors (terlipressin, epinephrine, and midodrine).[19] They concluded that adjuvant administration of albumin while performing LVP for patients with tense ascites reduces mortality and morbidity rates compared with other agents. However, because the co-administration of albumin and vasoconstrictors had not been introduced until this century, most available data were from pilot studies,[20−24] and therefore, further studies are needed to clarify this issue.

It is worth noting that although EASL guidelines recommended albumin as a plasma expander during LVP, the appropriate dose has not been thoroughly surveyed. The EASL

Table 1
Summary of recent advances in the pharmacological treatment of cirrhotic patients with refractory ascites.

Agent	References	Aim	Note	Level of evidence[a]	Impact on survival
Albumin	Bernardi et al[19]	The role of albumin (6−8 g/L of ascites removal) as adjuvant therapy in LVP	Meta-analysis	A	Possibly positive
Albumin	Alessandria et al[25]	The effect of half-dose (4 g/L of ascites removal) of albumin as adjuvant therapy in LVP	Randomized control pilot study	B	Not applicable
Terlipressin	Fimiani et al[30]	The role of terlipressin in short-term (3 weeks) refractory ascites control	Multicentric, prospective study	B	Not applicable
Satavaptan	Wong et al[35]	The role of satavaptan in long-term (52 weeks) refractory ascites control	Randomized control study	A	Negative
Midodrine	Singh et al[38]	The role of midodrine in long-term (12 months) refractory ascites control	Randomized control pilot study	B	Positive
Propranolol	Sersté et al[43]	The impact of propranolol on cirrhotic patient with refractory ascites	Cross-over study	C	Not applicable

LVP = large-volume paracentesis.
[a] Level A = data derived from randomized clinical trials or meta-analyses; level B = data derived from a randomized pilot study, or nonrandomized studies; level C = only consensus opinion of experts, case studies, or standard of care.

guidelines recommend an infusion of 8 g of albumin for 1 L of ascitic fluid removed, while the American Association for the Study of Liver Diseases guidelines suggest 6–8 g/L of ascites removed. In 2011, Alessandria et al proposed a prospective, randomized unblended pilot study to compare standard versus half doses of albumin.[25] A total of 70 patients treated with LVP were randomized to receive albumin, with one group (35 patients) receiving 4 g of albumin for every liter of ascites removed and another group (35 patients) receiving 8 g of albumin for every liter of ascites removed. The authors found that there was no significant difference in the incidence of PCD, hyponatremia, or renal failure between the two groups. The 6-month survival rates of both groups were also the same.

In conclusion, adjuvant administration of albumin during LVP significantly reduces the incidence of PCD, which is an important risk factor for reaccumulation of ascites and renal failure. Administration of albumin is also beneficial in reducing PCD among colloid agents. Regarding mortality, however, further studies are still required to identify the efficacy of albumin.

4.6. Terlipressin

Terlipressin, an extended-acting vasopressin derivative, elicits splanchnic vasoconstriction by selectively binding vasopressin type 1 receptors located in the smooth muscle cells of the splanchnic vessels. Through redistributing the blood flow of the splanchnic vasculature and the portosystemic collateral vascular bed,[26] terlipressin effectively increases the renal blood flow and is considered to be the standard therapy for HRS.[27]

In recent years, the therapeutic role of terlipressin in cirrhotic patients with refractory ascites has started to draw attention because of its ability to improve renal perfusion. A single dose of terlipressin significantly increases the excretion of sodium and decreases the activity of plasma renin in patients with cirrhosis.[28,29] A randomized control study further demonstrated that terlipressin prevents LVP-induced PCD.[22]

In 2011, a multicenter study aiming to evaluate the effect of terlipressin on refractory ascites was reported.[30] The study included 26 cirrhotic patients with refractory ascites that were controlled by a combination of albumin and diuretics. The result suggested that the combination of terlipressin and albumin controlled ascites better than the combination of diuretics and albumin.

To sum up, terlipressin may have the potential to improve renal sodium excretion by enhancing renal perfusion and thus contributing to improved ascites control. However, further studies are needed to determine the role of terlipressin in adjuvant therapy of LVP.

4.7. Satavaptan

Vaptans selectively antagonize the vasopressin type 2 receptors on principal cells, inhibiting the reabsorption of free water and increasing the concentration of serum sodium. It was first developed for the treatment of syndrome of inappropriate antidiuretic hormone (SIADH) secretion.[31] Currently, vaptans are approved for the management of hyponatremia in patients with cirrhosis and ascites,[32] heart failure, and SIADH. During the treatment of hyponatremia in patients with edema, vaptans were found to diminish the severity of ascites.[33] Short-term phase II studies using satavaptan in cirrhotic patients with ascites also showed a decrease in ascites volume.[34]

In 2012, Wong et al reported the results of three randomized, double-blind studies with a total of 1200 enrolled patients.[35] In cirrhotic patients with ascites, satavaptan could not prevent the deterioration of ascites during 48 weeks of follow-up. Furthermore, in patients who received LVP, satavaptan increased mortality ($p = 0.049$). In conclusion, although satavaptan corrected hyponatremia in patients with cirrhosis, it lacks a therapeutic effect for ascites control. Meanwhile, the long-term safety and efficacy of vaptans in the management of hyponatremia in patients with cirrhosis merits further investigation.

4.8. Midodrine

Midodrine hydrochloride, an oral α1-agonist, has been approved by the US Food and Drug Administration to treat symptomatic orthostatic hypotension. It is a prodrug that is absorbed from the gastrointestinal tract and is metabolized by the liver into an active metabolite, desglymidodrine.[36] It increases effective circulating blood volume and renal perfusion by increasing systemic and splanchnic blood pressure.

Although peripheral vasodilatation has been regarded as the main factor that induces hyperdynamic circulation and sodium retention in patients with cirrhosis, the therapeutic role of arteriole vasoconstrictor remained controversial until the late 1990s. In 1998, Angeli et al reported the acute effect of midodrine on 25 nonazotemic cirrhotic patients with ascites.[37] Midodrine, 6 hours after administration, effectively improved systemic hemodynamics, renal perfusion, and urine sodium excretion. The activity of the RAA system was also suppressed.

In 2012, Singh et al reported a pilot randomized study evaluating the effect of long-term midodrine administration on ascites control.[38] The study included 40 patients with cirrhosis and refractory or recurrent ascites. The result showed that administration of midodrine combined with standard therapy for 3 months significantly controlled ascites when compared with placebo. In addition, significantly decreased cardiac output and plasma renin activity were also observed during the study period. Moreover, the survival rate was significantly improved in the midodrine group ($p < 0.046$).

In conclusion, although the available data are still not sufficiently proven to support the proposition that midodrine can be efficacious in ascites control, the results from pilot studies are encouraging. They highlight an alternative way to ameliorate decompensated liver cirrhosis and ascites by alleviating hyperdynamic circulation, which is different from RAA or sympathetic system control.

4.9. Propranolol

Currently, propranolol, an NSBB, is routinely used to control portal pressure. In 1981, Lebrec et al found that propranolol effectively prevented recurrent esophageal varices bleeding in patients with cirrhosis.[39] Following that encouraging revelation, the roles of NSBBs were extensively evaluated. NSBBs, including propranolol and nadolol, are now considered to be the most effective portal hypotensive agents by inhibiting splanchnic vasodilatation and reducing portal inflow and portal pressure. Patients undergoing NSBBs treatment with a concomitant reduction of hepatic venous pressure gradient (HVPG) >20% of baseline or <12 mmHg have reduced risk of variceal bleeding and had an improved survival rate.[40,41] In addition, NSBBs responders had a lower risk of portal hypertension-related complications, including ascites, SBP, HRS, and hepatic encephalopathy.[42]

In 2010, Lebrec and his colleagues reported that the use of NSBBs may be associated with poor survival rates in cirrhotic patients with refractory ascites.[43] However, the study had some limitations,[44] including the fact that Lebrec's investigation was not a randomized control trial. Nevertheless, the study still raised an important concern about the safety of propranolol use in cirrhotic patients with refractory ascites. Based on these results, in 2011, the same research team conducted a self-controlled cross-over study to evaluate the relationship between β-blockers and PCD.[45] The study included 10 cirrhotic patients with refractory ascites undergoing NSBBs treatment. PCD developed in eight patients during propranolol treatment, even when albumin was administered after LVP. However, once the use of propranolol was discontinued, PCD developed in only one patient after LVP. Although the number of cases analyzed was relatively small, the findings could suggest that NSBBs induced more PCD in patients with cirrhosis and refractory ascites managed by LVP.

Although these two studies provoked a debate on the safety of using NSBB in advanced cirrhotic patients with refractory ascites, in patients with compensated cirrhosis and large varices treated with β-blockers, an HVPG decrease ≥10% significantly reduced the risk of developing ascitic decompensation and other related complications such as refractory ascites or HRS.[46] Therefore, the risk and benefit of NSBBs may vary according to the severity of cirrhosis, and further studies are warranted to identify the impact of NSBBs on patients with refractory ascites.

5. Complications of ascites

5.1. SBP

SBP is diagnosed by a positive ascitic fluid bacterial culture with an absolute ascitic polymorphonuclear neutrophil count >250 cells/mm^3. It develops in 30% of patients with ascites, and even with adequate treatment, the mortality rate is still as high as 20%. As a result, SBP prophylaxis is an important issue in the management of ascites. Because long-term antibiotic prophylaxis inevitably induces resistant bacterial strain, only patients at high risk for SBP are supposed to benefit from prophylaxis.

5.2. Primary prophylaxis of SBP

The strategy of primary prophylaxis is prophylactic application of antibiotics to decrease the incidence of SBP in high-risk patients who never had SBP. Cirrhotic patients with acute gastrointestinal bleeding are at a high risk of developing SBP, and prophylactic antibiotics should routinely be prescribed. In the patients with cirrhosis, oral administration of 400 mg of norfloxacin two times per day for 7 days had been proven to prevent SBP.[47] For those patients with active bleeding that precludes enteral feeding, intravenous administration of 400 mg ofloxacin per day is an alternative.[48] Because of the emergence of quinolone-resistant bacteria, a recent study conducted in Spain showed that intravenous administration of ceftriaxone was superior to oral norfloxacin in patients with acute gastrointestinal bleeding and advanced liver cirrhosis.[49] Therefore, it may be crucial for clinicians to prescribe prophylactic antibiotics according to regional bacterial epidemiology.

Long-term primary prophylaxis is strongly recommended for cirrhotic patients with ascites fluid protein <1.5 g/dL and suffering from either (1) serum creatinine levels greater than 1.2 mg/dL; (2) blood urea nitrogen levels greater than 25 mg/dL; (3) serum sodium levels less than 130 mEq/L; or (4) Child−Pugh class C score with bilirubin levels greater than 3 mg/dL. In these conditions, administration of norfloxacin or trimethoprim/sulfamethoxazole is appropriate. Compared with daily dosing, a single oral weekly dose of ciprofloxacin was also effective in preventing SBP. However, intermittent dosing was later proven to select resistant flora more rapidly.[50]

5.3. Secondary prophylaxis of SBP

In patients who have experienced SBP, the recurrence rate is as high as 70%. However, secondary prophylaxis with norfloxacin dramatically reduced the recurrence rate from 68% to 20%.[51] Other antibiotics such as ciprofloxacin or trimethoprim/sulfamethoxazole are also effective in the prevention of SBP.[52] The secondary prophylaxis should be continued indefinitely until the ascites are resolved or liver transplantation can be performed.

5.4. Treatment of SBP

Once a patient is diagnosed to have SBP, empirical antibiotics should be given as soon as possible. Most pathogens of SBP are Gram-negative bacteria translocating from the gut, such as *Escherichia coli*, *Klebsiella pneumonia*, and *Streptococcus pneumoniae*. Consequently, a third-generation cephalosporin is a reasonable choice. Amoxycillin/clavulanic acid and quinolones are alternative choices. However, using the same category of antibiotics both in acute treatment and in prophylaxis should be avoided because of the rapid selection of resistant strains.[53] In selective patients, antibiotics

treatment for 5 days is enough. Follow-up paracentesis may not be mandatory because most SBP resolved after treatment.[54]

6. HRS

6.1. Prophylaxis of HRS

HRS is a unique form of acute renal failure that only occurs in advanced liver disease, which results from hemodynamic changes and subsequently hypoperfusion of the kidney. Type 1 HRS is characterized by rapidly progressive renal failure, with a doubling of serum creatinine to a level greater than 2.5 mg/dL or a deterioration of creatinine clearance to less than 20 mL/minute over a period of less than 2 weeks. The prognosis of individuals with type 1 HRS is poor, with a mortality rate exceeding 50% after 1 month.[55] In contrast, type 2 HRS is slower in onset and milder in progression.

Until now, only albumin infusion has proven to be effective in the prophylaxis of HRS in patients with SBP.[56] Besides volume expansion, albumin also plays a role in removing cytokines and bacterial products. This is why albumin is superior to other volume expanders in the prevention of HRS.

6.2. Treatment of HRS

The use of vasoconstrictive agents in combination with albumin is currently the most effective pharmaceutical therapy for HRS. However, the use of terlipressin, norepinephrine, or midodrine plus octreotide has been studied as well.[57] Among them, coadministration of terlipressin and albumin significantly improves renal function and should be considered as the first-line therapy.[58] Nevertheless, there is still no definite evidence to support the proposition of an enhanced survival benefit from the regimen. Until now, only liver transplantation improves the survival of patients with HRS.[59]

7. Hepatic hydrothorax

Hepatic hydrothorax indicates a pleural effusion >500 mL in cirrhotic patients without cardiopulmonary disease. It develops in approximately 5% of cirrhotic patients with ascites and is usually right sided, which accounts for 85% of the cases. Hepatic hydrothorax can present without clinically detectable ascites. Nevertheless, compared with those with ascites, those without ascites have larger diaphragmatic defects.[60] The pleural fluid is derived from the pathological transdiaphragmatic migration of ascites, and the defects are usually the ruptured pleuroperitoneal blebs. Because of negative intrathoracic pressure during breathing, there is a unidirectional flow of ascitic fluid to the pleural space. The peritoneal−pleural communication can be revealed by a nuclear medicine scan with radiolabeled albumin or 99mTc-sulfur colloid or thoracoscopy.

7.1. Treatment strategies

The medical treatment modalities include sodium and fluid restriction, diuretics, abdominal paracentesis, intermittent or pig-tail drainage of pleural fluid, chemical pleurodesis with or without continuous positive airway pressure (CPAP), and TIPS. Approximately 10% of those patients not responding to sodium restriction and maximal tolerable doses of diuretics are considered to have refractory hydrothorax, and in such cases alternative treatment options must be considered. It is worth noting that insertion of a chest tube is not recommended, due to severe complications such as massive fluid shifts, protein and electrolyte depletion, and acute renal damage.[61] The effect of chemical pleurodesis, in contrast, is suboptimal as the fluid is formed very rapidly and allows the visceral and parietal pleural surfaces to approximate and adhere. As a result, incomplete adhesions may be formed, which results in loculated pleural effusions. Under such circumstances, CPAP appears to be helpful in decreasing negative pleural pressure and thus preventing the shift of fluid from the peritoneal to the pleural space. In addition, it has been shown that TIPS is another treatment option. In a recent study with 73 enrolled patients, the rates of favorable clinical response within 1 month and at 6 months after TIPS were 79% and 75 %, respectively, and the median survival duration was 517 days. A model for end-stage liver disease score <15 and clinical response were significantly and independently associated with overall survival.[62]

In conclusion, the medical management of ascites by dietary sodium restriction and diuretics therapy has been widely accepted and recommended. However, its therapeutic efficacy is still suboptimal. With accumulating evidence addressing the pathophysiology of ascites formation, several avenues that aim to halt the vicious cycle of refractory ascites are under development (Fig. 1). In the past few years, results from investigations surveying some pharmacological agents have been encouraging. In the meantime, caution should be exercised when interpreting the data. Both the “encouraging signs” and the “warning signs” presented in these investigations may be of some use now, but they continue to highlight the need for further large-scale and randomized studies.

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