Section A-Research paper

Recent Lines of Management of Refractory Ascites

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Abstract

Background: About 10% of patients with decompensated cirrhosis will develop refractory ascites, which indicates that their cirrhosis is progressing to a more severe stage. Significant hemodynamic alterations, starting with portal hypertension and progressing to renal hypoperfusion and excessive salt retention, are associated with its pathophysiology. Portal microthrombi, which inflammation can cause, keep the portal hypertension going and contribute to the pathophysiology of refractory ascites. Refractory ascites can lead to a number of problems, the most prevalent of which is renal failure. Preventing paracentesis-induced circulatory dysfunction begins with maintaining sodium restriction, which requires regular reviews to ensure adherence. Another component of management includes performing large-volume paracentesis (5 L or more) with albumin infusions on a regular basis. The therapy of these patients may use albumin infusions that are not dependent on paracentesis. If a patient is eligible and has a fair amount of liver reserve, a covered, smaller-diameter transjugular intrahepatic porto-systemic stent shunt (TIPS) can be inserted to improve quality of life and survival after ascites clearance. One potential future tool for treating ascites is an automated low-flow pump. Referral for liver transplant should be considered for patients with refractory ascites due to their poor prognosis. It is important to incorporate palliative care into the treatment plans of patients with advanced cirrhosis who are not candidates for definitive ascites control treatments in order to enhance their quality of life. Midodrine along with octreotide and albumin, has been shown to better control of ascites in a short-term pilot study in patients with refractory ascites.

Keywords: Refractory Ascites

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Introduction

In the natural course of cirrhosis, the development of ascites signals the beginning of decompensation. Newer UK statistics show that decompensation happens at a rate of 31% in the first year following cirrhosis diagnosis, and at a rate of 5-7 percent annually thereafter, with ascites being the most prevalent form of decompensation [1]. In the early stages of ascites, diuretic treatment is typically effective. Renal sodium retention becomes more ardent as the cirrhotic process progresses, necessitating increased diuretic dosages to control ascites. At some point, the patient either has diuretic-related side effects or the ascites stops responding to the medication. Refractory ascites (RA) is the medical diagnosis, and the patient will require second-line treatment. On any one day, RA affects around 10% of cirrhosis and ascites patients. A continual sensation of fullness, diminished appetite, the development of different hernias, nutritional deficiencies, and sarcopenia are some of the specific symptoms that can occur when RA is present alongside the more common complications of ascites, such as the risk of spontaneous bacterial peritonitis, electrolyte abnormalities, and renal dysfunction. As a result, RA patients' quality of life is extremely low [2]. There is a 50% 1-year mortality rate for RA patients according to older research [3], a slightly improved prognosis according to more recent data [4], but the mortality rate is still around 20%.

Tense ascites can be recurrent or refractory. Recurrent ascites is ascites that recurs at least three times a year despite dietary sodium restriction and diuretic therapy. It may be a forerunner of RA [5]. RA is defined as ascites that cannot be mobilized or the early recurrence of which (after a large volume paracentesis [LVP]) cannot be prevented by medical therapy [5]. RA can be divided into two subtypes: diuretic resistant or diuretic intolerant.

PATHOPHYSIOLOGY OF RA

Significant hemodynamic abnormalities are observed in patients with decompensated cirrhosis, which begin with architectural deformation of the liver caused by cirrhosis. The fixed component of portal flow blockage is the creation of nodules and fibrous scar tissues within the liver, whereas the dynamic component is increased resistance to portal flow due to stellate cell activation. Stellate cells contribute to the steady rise in intrahepatic resistance due to their production of extracellular matrix and collagen, two byproducts of liver cirrhosis. In addition to distorting the liver's architecture, microthrombi development within the intrahepatic vasculature might cause parenchymal extinction in certain places [6]. Collateral vascular formation is another mechanism that leads to the worsening of portal hypertension in cirrhosis. The portal hypertension is maintained due to angiogenesis induced by vascular endothelial growth factor, which increases the splanchnic capacitance and, in turn, the portal flow [7].

Numerous secondary consequences result from the onset of portal hypertension. Firstly, the distension of the splanchnic arteries increases the shear stress on the vessels, and this leads to the formation of several vasodilators including nitric oxide. Vasodilatation of the splanchnic vessels follows. Systemic vasodilation can occur when some of these extra splanchnic vasodilators are transported to the systemic circulation through portosystemic shunts. In response to relatively low effective arterial blood volume (EABV), the body activates a cascade of vasoconstrictor mechanisms, which aim to limit systemic and splanchnic vasodilation and encourage the kidneys to retain more sodium and water, so increasing the volume inside the blood vessels. However, central circulation is relatively inadequate in EABV due to portal hypertension, which preferentially localizes the extra fluid into the peritoneal cavity as ascites.

Disruption of the gut vascular barrier due to venous congestion caused by splanchnic vasodilatation and splanchnic neo-angiogenesis is another downstream impact of portal hypertension. The increased permeability of the gut results in a rise in the translocation of gut bacteria. In addition to aiding in splanchnic vasodilatation, several of these bacterial byproducts also possess vasodilatory characteristics. There are additional components of bacterial products that can trigger systemic inflammation by stimulating the innate immune system. The hemodynamic alterations related to portal hypertension are perpetuated because the pro-inflammatory milieu in the liver promotes further fibrosis and inflammation promotes splanchnic thrombosis in the splanchnic circulation [7,8].

The aforementioned alterations, sodium retention, and vasoconstriction of the renal circulation all worsen with the advancement of the cirrhotic process and the elevation of portal hypertension. In the end, abnormal renal blood flow occurs [9], renal hypoperfusion follows, chronic renal insufficiency (formerly called type 2 hepatorenal syndrome) develops, and diuretic treatment is no longer effective in treating the ascites..

Management OF ERA

Patients with RA should be managed in a systematic manner, with sodium restriction and LVP being the first steps. Careful medicine administration may prevent additional problems. Transjugular intrahepatic portosystemic stent shunts (TIPS) are a potential treatment option for certain patients. There needs to be a liver transplant evaluation for all RA patients.

Dietary sodium and fluid restriction

All patients with ascites, including those with RA, must adhere to a salt restriction diet since it slows the buildup of ascites. A daily sodium consumption of no more than 88 mmol, or 2 g, is advised [10]. In individuals who are rapidly developing ascites, it is helpful to consult with a dietician and evaluate their food diary frequently. Other techniques that can enhance compliance with sodium limitation include providing information on where to obtain reduced sodium food items and offering guidance on low sodium dishes. After

adhering to their sodium restriction, some patients with RA who have previously been diagnosed with ascites may begin to respond to diuretics again. This is particularly true for patients whose daily renal sodium excretion exceeds 88 mmol/day.

Restriction of fluid intake is unnecessary for RA patients. It lacks practicality and is hard to enforce. Patients with RA typically excrete about 500 mL of fluid daily, therefore fluid restriction is only effective when fluid consumption is lower than urine production. It is advised to implement some fluid restriction in individuals with hyponatremia and blood sodium levels of 125 mmol/L or lower [11]. Unfortunately, there is currently no consensus on what serum sodium level should be used to begin fluid restriction.

Calculating the sodium balance

Patients who are quickly putting on weight following an LVP would benefit greatly from this information when trying to gauge their level of compliance with dietary salt restriction. A weight chart and a 24-hour urine collection are necessary to measure the renal sodium output. The accuracy of a 24-hour urine sample far outweighs that of a spot urine sample. The daily sodium buildup in patients who are prescribed a sodium restriction diet of 88 mmol/day and are not excreting any sodium in their urine is 616 mmol/week, or 88 mmol/day. Since the ascitic sodium concentration is the same as serum sodium concentration, the weekly ascites accumulation is 616 mmol/week ÷ 140 mmol/L or 4.4 L/week. Dietary counselling should be repeated for any patient who requests an LVP of more than 4.4 L weekly, as this indicates clear non-compliance with sodium reduction in the diet. A little less ascites builds up because sodium is insensibly lost through the respiratory tract. Many patients mistakenly believe that "simply not adding salt at the table" constitutes sodium restriction, failing to realise that numerous prepared foods include a significant amount of sodium. As a result, a meal record can often provide valuable insights. Patients with sodium excretion rates more than 88 mmol/day should be losing weight on a sodium intake of 88 mmol/day in order to achieve a negative sodium balance. Dietary reeducation is necessary if this isn't occurring [12].

Albumin infusions

Patients with decompensated cirrhosis have been recommended to have albumin infusions on a regular basis. Regular albumin infusions, starting at 40 g twice weekly for two weeks and continuing at 40 g weekly for a total of 18 months, improve overall survival in patients with uncomplicated ascites who are still responding to diuretic therapy [13]. This is particularly true for patients whose serum albumin levels are maintained at a minimum of 40 g/L [14]. On the other hand, midodrine and 40 g of albumin every two weeks had no effect on the risk of complications or survival for patients on the liver transplant waiting list with advanced cirrhosis [15]. Half of the 70 patients in the sole randomised controlled trial of cirrhosis and RA were assigned to receive 40 g of albumin twice weekly [16]. Hospitalizations due to cirrhosis complications and death decreased significantly within 24 months. It appears that these people might benefit from albumin infusions administered on a regular basis. Before routine albumin infusions are suggested as the gold standard for cirrhosis and RA patients, additional supportive randomised controlled trials are required. Positive outcomes may also depend on the dosage and frequency of infusions.

Using beta-blockers that aren't selective (NSBBs)

The treatment of portal hypertension in cirrhosis relies on NSBBs. Heart rate and cardiac output are lowered by 20% when β1 adrenergic action is blocked. Portal inflow, including that from collateral veins, is reduced by approximately 15% when β2 adrenergic action is blocked in the splanchnic vasculature, leading to splanchnic vasoconstriction. Accordingly, using NSBB results in a total reduction of about 35% in portal venous flow. Labetalol and carvedilol are 2 NSBBs that also have α1 adrenergic blocking properties, and so can cause intra-hepatic vasodilatation, with further reduction in portal pressure. According to research, the risk of decompensation or death is greatly reduced when patients with compensated cirrhosis and clinically significant portal hypertension (hepatic venous pressure gradient ≥10 mmHg) get NSBB treatment [17]. Nevertheless, there is greater debate about the use of NABBs in individuals suffering from ascites. Use of NSBBs in ascites patients, particularly those with RA, was linked to an increased risk of morbidity and death in the early trials [18–21]. Patients with ascites, including those with RA, who used NSBB did not experience an increase in renal impairment or death, according to subsequent investigations [22,23]. Additionally, fewer

bacterial infections were observed when NSBBs were used [24]. Variceal haemorrhage, bacterial infections, renal failure, hospitalisation, and death were all more common after NSBB discontinuation [25]. Patients with acute-on-chronic liver failure (ACLF), a common complication of RA, were believed to have a lower ACLF grade when administered NSBB [26]. Possible explanations for these apparently contradicting results include substantial study heterogeneity.

A new study that looked at the effects of NSBB on the cardiovascular system in advanced cirrhosis patients has given us some clues about how to employ these devices with RA patients [27]. Due to their severely dilated blood vessels, these patients must have sufficient heart systolic function and sympathetic hyper-activity to keep their kidneys supplied with blood. Consequently, NSBB may decrease renal perfusion pressure below the threshold for renal blood flow autoregulation and compromise cardiac systolic performance. To rephrase, when perfusion pressure drops, the kidneys can no longer regulate renal perfusion. Thus, renal impairment, including hepatorenal syndrome, can develop in RA patients on NSBB [28]. Patients with hemodynamic abnormalities, such as a low systolic blood pressure of less than 90 mmHg, hyponatremia with serum sodium levels less than 130 mmol/L, or acute kidney injury, may not be given NSBBs, according to the 2021 American Association for the Study of the Liver guidelines on the treatment of ascites. If the circulatory dysfunction improves with the correction of these parameters, NSBBs might be reintroduced [11]. Due to its additional adrenergic blocking effects, carvedilol creates increased systemic hypotension, making it unsuitable for individuals with RA [29].

Large volume paracentesis (LVP)

Ascites removal of more than 5 L has been arbitrarily designated as LVP. Recurrence of ascites is common following LVP since the procedure does not address the pathophysiology that leads to the production of ascites in the first place. This is due to the fact that when ascites is removed with LVP, the intra-abdominal pressure drops. This, in turn, increases the pressure differential between the abdominal cavity and the cirrhotic liver, which prompts the abdominal cavity to quickly refill. Because of this, it is common practise to administer LVPs again when treating these patients. Research has demonstrated that repeat LVPs are a safe and effective way to control RA in cirrhosis. Compared to ongoing diuretic administration, they are associated with a decreased incidence of electrolyte abnormalities, renal dysfunction, and hemodynamic instability [30]. There is a danger of developing further renal failure, dilutional hyponatremia, and death due to the redistribution of circulatory volume to refill the abdominal cavity, which is termed as post-paracentesis circulatory dysfunction (PPCD) [31]. For this reason, after LVP, it is advised to prevent PPCD by replacing volume with colloid solutions such albumin [32]. Patients are more likely to develop PPCD when their LVP volume is larger. Despite reports of using varying amounts of albumin with LVP in the literature, no dosage response studies have examined this combination. Although a lower dosage of 4 g of albumin/L of removed ascites was just as beneficial in preventing PPCD [33], expert opinion advises a higher dose of 6-8 g/L of removed ascites [11]. Renal impairment can be prevented, even in the presence of PPCD, according to another study [34], by administering a greater albumin concentration of 9.0±2.5 g/L of evacuated ascites and restricting LVP to 8 L. Those who had PPCD did not have any impact on survival over a mean follow-up of 2 years.

According to a suggestion, minor paracenteses (<5 L) do not cause a major disruption to systemic and renal hemodynamics, thus there's no need to restore intravascular volume with these procedures [35]. Nevertheless, research has demonstrated that reducing the frequency of PPCD and related consequences, including acute renal injury, hyponatremia, and high mortality, in patients with ACLF can be achieved by using albumin with small volume paracentesis [36]. This is due to the fact that albumin can considerably alleviate the acute inflammatory response and profoundly abnormal hemodynamics frequently seen in ACLF patients due to its volume-expanding, anti-inflammatory, and immune-modulatory characteristics.

Lastly, it should not be disregarded as a reason to avoid LVP if coagulopathy is present. In fact, minimal bleeding was observed with LVP in patients with PT-INR values greater than 1.5 and platelet counts lower than 50×109/L [37]. Plaque or clotting factor infusion is thus unnecessary for LVP.

TIPS

An extremely efficient prosthesis for lowering portal pressure is a transhepatic intrahepatic shunt (TIPS), which connects two branches of the portal vein. In a physiological sense, the EABV fills up gradually when the splanchnic volume returns to the central circulation as a result of a decrease in portal pressure [38]. As a result, the sympathetic nervous system and the activated renin-angiotensin-aldosterone pathways are progressively dampened, and the severity of renal sodium retention in these patients is progressively reduced [39]. Ascites will drain away as the neurohormonal systems' activity levels drop below the levels at which they retain sodium. Three to six months is the typical time frame for this [40]. Half of RA patients experience full remission six months after TIPS implantation, and two-thirds experience partial remission [41]. About 80% of patients experience successful ascites control with TIPS in the long run. Ascites will progressively decline till it disappears after TIPS, thus it is crucial to moderate patient anticipation. The ascites will not clear instantaneously. Dietary sodium restriction must be maintained until the ascites is completely cleared, even if it is still present. Since diuretics lower the EABV and may conceivably postpone ascites clearance, their use after TIPS is contentious.

When it comes to managing ascites, TIPS is far superior to LVP, according to multiple randomised controlled trials that compared the two methods [42–47]. Although careful patient selection is essential, the survival benefit of TIPS over LVP in RA patients was only recently proven [48]. Great transplant-free survival at 3 years is common among younger patients with low Model of End-stage Liver Disease (MELD) scores [50]. If portal hypertension, rather than liver disease, is the patient's primary concern, this is particularly the case. Patients' chances of surviving without a transplant drop dramatically for every year that their age, MELD score, or hemodynamic parameters go up [50]. The first patient can use TIPS to finally put an end to their RA, while the second patient can use it to get them through the time it takes for a liver transplant to take effect. Patients with recurrent ascites (requiring three or more LVPs within a 12-month period with a gap of more than four weeks between each LVP) may benefit from a TIPS insertion rather than an LVP, according to a recent study [51]. The study found fewer side effects and better survival rates overall (93 percent vs. 52 percent, P=0.003). In particular, the incidence of hepatic encephalopathy (HE) after a TIPS insertion was comparable in both groups. At this time, we cannot advise TIPS implantation at the stage of recurrent ascites as standard of care as this study has not been reproduced.

There are a lot of potential problems with inserting TIPS. Arrhythmia, hemoperitoneum, and rupture of the liver capsule are immediate risks of the treatment; nevertheless, these consequences are uncommon in skilled hands. Shunt migration, shunt kinking, ischemic hepatitis (shown by a sharp increase in liver enzymes and hemolytic anaemia), and other problems might occur in the early post-TIPS period. Consequently, jaundice may persist in patients for a few weeks to months after TIPS. Shunt stenosis was common when metal stents were the norm. These are associated with a decrease in neointima thickness and are currently infrequent with PTFE-covered stents [52]. Regardless of the type of stent utilised, the greatest clinical consequence is HE, which can occur in 30–50 percent of patients [53,54]. This can be either newly onset or worsening of existing HE. Age, higher Child-Pugh and MELD scores, history of spontaneous HE episodes, sarcopenia, and a smaller portal systemic pressure gradient after TIPS are all risk factors for the development of HE [55]. The latter is commonly linked to a TIPS that is fully dilated. Without affecting variceal bleeding, ascites recurrence, or the frequency of stent thrombosis, a recent study confirmed that patients whose PTFE stents were intentionally under-dilated to 6 mm had a lower incidence of HE (27 percent) compared to those whose stents were dilated to 8-10 mm (54%). Hence, it seems that stents with smaller diameters or under-dilation are better options to decrease the risk of post-TIPS HE. There is evidence that preemptive administration of lactulose and rifaximin improves HE management after TIPS [57,58]. Cardiac failure following TIPS insertion is another possible consequence of the procedure. The cardiac output can rise by as much as 50% after TIPS implantation, which restores a substantial volume to the systemic circulation from the splanchnic circulation [38]. This means that post-TIPS cardiac decompensation can occur in patients who already have pulmonary hypertension, systolic incompetence, or aberrant diastolic relaxation. Electrocardiograms, echocardiograms, and measurements of brain natriuretic peptide (BNP) are the suitable cardiac investigations

to be performed before to TIPS [59]. In order to rule out cardiac decompensation after TIPS, a normal cardiac evaluation with a BNP level of less than 40 pg/mL and a pro-N-terminal BNP of less than 125 pg/mL have been documented [60].

Locating potential infection sites is another pre-TIPS inquiry, with a focus on the biliary and oral systems. Endotipsitis can occur after a TIPS has been implanted if any infection can enter the TIPS through the bloodstream. Rare as it may be, endotipsitis can cause bacteremia to return, which may not go away no matter how long you take antibiotics [61].

To maximise the effectiveness of TIPS in clearing ascites and minimise the risk of complications, it is crucial to choose patients appropriately. There are certain medical conditions that should not be treated with a TIPS, including being over the age of 70, having a MELD score greater than 18, having a history of spontaneous HE grade 2 or higher, or having cardiac failure, pulmonary hypertension, liver cancer, sepsis, or occlusive portal vein thrombosis [11,62]. Ascites clearance with TIPS is linked to better nitrogen balance [64], substantial muscle development [65], enhanced quality of life [63], and improved survival [48,66,67]. To determine who would be at high risk for death after TIPS, a newly validated index called the Freiburg Index of Post-TIPS Survival (FIPS) took age, bilirubin, albumin, and creatinine into account. The median post-TIPS survival for patients in the high-risk category was 5 months, while the low-risk group had 48 months ($P<0.001$) [68]. Having said that, FIPS's prognostic ability isn't as good in patients who have gotten an early TIPS for non-refractory ascites. A further study showed improved post-TIPS survival in patients who received an 8 mm covered stent compared to those who received a 10 mm covered stent [69].

The automated low flow ascites pump (alfapump)

The alfapump is a programmable and rechargeable device that is implanted subcutaneously. It gradually removes the ascites from the abdominal cavity by use of a peritoneal catheter and then releases it into the bladder as urine using a bladder catheter. Continuous small volume paracentesis is being done effectively. Therefore, the patient won't have to worry about getting up in the middle of the night to urinate the ascites because the device is set to pump the fluid for up to 16 hours while the patient is awake. A number of sensors in the bladder and peritoneum allow the device to cease pumping in the absence of significant ascites. It is also possible to modify the ascites discharge rate based on the sodium intake of the patient's diet. Thus, ascites care is tailored to each patient's unique needs. In most cases, albumin infusions are not necessary while using the alfapump system.

A meta-analysis [77] and other investigations (randomised controlled trial [70], prospective [71–75], and retrospective [76]) have demonstrated that the alfapump effectively reduces the frequency and volume of paracenteses, making it a viable tool for ascites control. Infection of the alfapump system, pump failure, and catheter dislodging were among the several problems that were found in the first trial [71]. These issues have become less common as a result of improvements in implantation techniques, refinements to pump design, and the usage of prophylactic antibiotics. Despite the gradual and constant drainage of ascites, some patients nevertheless experience renal impairment. Although the volume is minimal, the various vasoconstrictor systems are nevertheless activated during continuous paracentesis, according to a physiological research [78]. It has been proposed that patients should be closely observed for the onset of renal impairment and administered albumin intermittently as needed. Hence, patients suffering from renal failure who have a blood creatinine level above 132 μmol/L (1.5 mg/dL) or an estimated glomerular filtration rate below 30 mL/min/1.32 m2 should probably not have an alfapump implanted [79]. The following are additional reasons why alfapump insertion is not recommended: a history of bladder cancer, bilirubin levels >85 μmol/L, recent intra-abdominal surgery, at least two systemic or local abdominal infections in the past six months, and any other medical conditions [79].

After their ascites is under control, patients notice a marked improvement in their mobility and overall well-being [75,80]. Although formal studies on the alfapump's effects on survival have not been conducted, it has been demonstrated that they are at least equivalent to those of patients who receive standard LVP [66].

Liver transplantation

For patients suffering from both rheumatoid arthritis and liver impairment, the gold standard therapy option is a liver transplant. Nevertheless, patients whose primary liver cirrhosis issues are due to portal hypertension without substantial liver damage are not given high priority for liver transplantation. Patients with ascites and a MELD score below 15 were shown to have an infectious cause-related mortality risk of 47.5% one year after not receiving a liver transplant, according to a recent report [81]. When calculating a patient's MELD, it is necessary to add 4.5 MELD [82] or 3.5 MELD-Na [83] points for persistent ascites. This is particularly true for patients with a MELD score below 21 [83,84]. Thus, even though the MELD score is quite low, liver transplantation should still be considered for individuals with RA as the sole sign of cirrhosis. Liver transplantation will be given more priority to patients with RA and hyponatremia who also have a high MELD-Na score. Ascites may linger for weeks or months following a liver transplant because the systemic and renal hemodynamics need time to normalise, particularly in cases where excessive portal input continues [85]. Patients should continue to follow a sodium-restricted diet after a transplant until the ascites goes away.

Midodrine

Midodrine, an alpha-1 agonist acting directly on the peripheral alpha-receptors, has been widely used in the therapy of orthostatic hypotension and various secondary hypotensive disorders. It has recently been shown that single dose administration of midodrine leads to a significant improvement in systemic and renal hemodynamics in non-azotemic cirrhotic patients with ascites, the beneficial effects of midodrine have been attributed to its modulating effects on autonomic function and increased peripheral blood vessel resistance [86].

Midodrine has been found to decrease nitrite and nitrate activity in patients with ascites with or without HRS who had decreased plasma renin activity and decreased levels of antidiuretic hormone [87]. This could be a possible mechanism for decreasing portal pressure and decreasing ascitic fluid accumulation. There is also evidence that a similar reduction in fluid accumulation may occur with use of vasoconstrictors in patients with end-stage liver disease without a significant renal function improvement [88].

Angeli et al. reported that 15 mg of oral midodrine increased renal plasma flow by 40%, GFR by 21% and urinary sodium excretion by 28%. When combined, the studies by Villeneuve et al. and Angeli et al. suggest that diuretic resistance in cirrhotic patients with ascites is possibly due to diminished GFR, and orally administered midodrine could significantly improve GFR in non-azotemic cirrhotics with ascites [88; 89].

Midodrine along with octreotide and albumin, has been shown to better control of ascites in a short-term pilot study in patients with refractory ascites [88].Summary of Select Studies Using Midodrine for Various Indications in Patients with Liver Cirrhosis showed in the next table.

Table 1 Summary of Select Studies Using Midodrine for Various Indications in Patients with Liver Cirrhosis HRS=hepatorenal syndrome; IV=intravenous; LT=liver transplantation; MELD=Model for End-Stage Liver Disease; PICD=paracentesis-induced circulatory dysfunction; RF=renal function; SH=systemic hemodynamic [90].

Indication	Reference	Concomitant drugs	Results
Type 1 HRS	Angeli P, et al10 [91]	Octreotide, albumin	Effective
	Wong F, et al11 [38]	Octreotide, albumin	Reduction of serum creatinine level
Type 2 HRS	Angeli P, et al9 [91]		Modest effect on SH No effect on RF
Natriuretic effect	Kalambokis G, et al5 [20]		Improved SH and sodium excretion
	Misra VL, et al13 [92]	IV furosemide	No increase in natriuretic response to furosemide
PICD	Singh V, et al6 [93]		As effective as albumin
	Appenrodt B, et al12 [94]		Not as effective as albumin
Refractory ascites	Tandon P, et al [88].	Octreotide, albumin	Reduction in the volume of ascites removed No effect on RF Reversible deterioration in MELD score
Post-LT renal outcomes	Rice JP, et al14 [95].	Octreotide, albumin	Pre-LT treatment did not have superior post-LT renal function

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