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Abbreviations:
TIPS: transjugular intrahepatic portosystemic shunt
MELD: Model for End-stage Liver Disease
HE: hepatic encephalopathy
SBP: spontaneous bacterial peritonitis
LT: liver transplantation
SMT: standard medical treatment
RA: recurrent ascites
RCT: randomized controlled trial
PTFE-covered: polytetrafluoroethylene-covered
LVP: large volume paracentesis
AP: Alphapump®
MDRO: multidrug resistant organisms
XDRO: extended drug resistant organisms
ACLF: Acute-on-chronic liver failure

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Abstract

Ascites is the most common complication of cirrhosis, as 5-10% of patients will develop this complication per year. Its management relies on symptomatic measures including restriction of sodium intake, diuretics, and paracentesis. The treatment of the underlying liver disease is always mandatory and may improve ascites. In some patients, ascites is not controlled by medical therapies and has a major impact on quality of life and survival; TIPS placement and liver transplantation have therefore to be discussed. More recently, repeated albumin infusions and Alfapump® have emerged as new therapies in ascites.
In this review, we will analyze current data available on these different options and will suggest an algorithm to help the physician in clinical decision.

Introduction

Ascites is the most common complication of cirrhosis, as 5-10% of patients with cirrhosis will develop this complication per year. Ascites has a major impact on quality of life and is associated with poor outcome. Its management can be dichotomized into 2 different aspects: the first one is symptomatic, and relies on restriction of sodium intake, diuretics, albumin infusion, and paracentesis. These symptomatic methods should always be associated with the treatment of the cause of liver disease, in order to improve liver function. The majority of patients will recover thanks to medical therapy.
In patients in whom ascites is not controlled by these medical therapies, transjugular intrahepatic portosystemic shunt (TIPS) placement is the first line treatment that has to be discussed, as it has been shown that TIPS improves ascites, as well as survival when compared to repeated paracentesis. In patients with the most severe presentation, with a high MELD or a high Child-Pugh score, or with hepatic encephalopathy (HE), TIPS is contraindicated and liver transplantation is the only curative option. An age of more than 65 or 70 years is another important issue, as it may be a contra-indication for both TIPS placement and liver transplantation.
In this review, we will first focus on the pathophysiology of ascites in cirrhosis, and then discuss all different therapeutic options. Last, we will suggest an algorithm to help the physician in different clinical situations. The management of hepatorenal syndrome, a severe complication that has the same pathophysiology than ascites, will not be discussed in this review.

1) Pathophysiology of ascites in cirrhosis

Ascites is defined as an accumulation of fluid in the peritoneal cavity and is due to cirrhosis in about 80% of cases. It can be graded according to its severity: grade 1 (mild ascites) if only detectable by ultrasound, grade 2 (moderate ascites) if moderate symmetrical distension of abdomen and grade 3 (large ascites) if marked abdominal distension (1). Ascites affects 5 to 10% of patients with compensated cirrhosis per year and is then considered as the most common complication of cirrhosis. Moreover, its prognosis is poor (two-year mortality of 40%), appearing later than variceal bleeding in the natural history of cirrhosis, with a more severe outcome (2).
Ascites is known to be multifactorial and seems to result from the combination of portal hypertension and liver insufficiency. Several hypotheses have been suggested to explain its pathophysiology, the main one being that ascites reflects the reorganization of hemodynamics in cirrhosis. Indeed, the reorganization of hepatic structure in cirrhosis is responsible for an increase of hydrostatic pressure in sinusoid capillaries, which leads to an increase of local synthesis of vasodilators substances, such as nitric oxide. As a consequence, there is a decrease in splanchnic arterial resistance (3). Then, compensatory mechanisms occur, especially an increase of cardiac output and activation of metabolic pathways to increase effective volemia (sympathetic nervous system and renin-angiotensin-aldosterone pathway). Synthesis of anti-natriuretic substances is then increased and results in sodium and water retention in proximal tubule, loop of Henle and distal tubule (3). This can result in dilutional hyponatremia, which may worsen prognosis and makes treatment of ascites more difficult. At

a final stage, the severe systemic vasodilation and subsequent renal vasoconstriction are responsible for acute kidney injury by decreasing renal blood flow, defining hepatorenal syndrome. Moreover, hypoalbuminemia due to hepatic insufficiency is responsible for a decrease of oncotic pressure, which facilitates the fluid leakage from intravascular sector to interstitial space (3). Due to the reorganization of hepatic structure in cirrhosis, capillaries are no longer fenestrated and protein concentration is then poor in this fluid.
Finally, some studies suggest a role of bacterial translocation, which is frequent in cirrhosis and responsible for local and systemic inflammation. This mechanism may increase permeability of capillaries and then facilitate the fluid leakage to the peritoneal cavity (3).

2) Optimal management of ascites

We will focus on the treatment of ascites in patients: a) without refractory ascites, b) with refractory ascites, d) with spontaneous bacterial peritonitis (SBP). In patients with complicated ascites, i.e with either refractory ascites or SBP, liver transplantation (LT) has to be envisioned.

a) <u>Patients without refractory ascites</u>

Classical treatments
The treatment of ascites relies on symptomatic therapies, including sodium restriction and diuretics, as patients with ascites have a positive sodium balance. Dietary sodium should be moderately restricted (80-120 mmol/day) in order to avoid a reduced calorie intake, a consequence that may impair nutritional status. The aim regarding diuretic therapy is to lead to a weight loss of less than 0.5 kg/day or 1 kg/day (in the presence of peripheral edema). Patients should receive an anti-mineralocorticoid drug alone, starting at 100 mg/day, with stepwise increase to a maximum of 400 mg/day. In non-responders or in patients developing hyperkaliemia, furosemide has to be added from 40 mg/day to a maximum dosage of 160 mg/day. Other general dispositions or treatment have also been evaluated: (1) it has not been shown that a prolonged maintenance of the supine position improves the resolution of ascites; (2) there is evidence that the treatment of the underlying liver disease may improve ascites, such as alcohol abstinence or viral suppression; (3) the use of several drugs is contraindicated in order to avoid renal impairment, such as non-steroidal anti-inflammatory drugs, angiotensin-converting-enzyme inhibitors or aminoglycosides (except in patients with severe bacterial infections); (4) other treatments such as midodrine, or terlipressine or clonidine are not recommended.

New therapeutics in patients without refractory ascites: albumin and TIPS
Hypoalbuminemia and the synthesis of dysfunctional albumin are increasingly recognized as key factors in the pathophysiology of cirrhosis complications including ascites. Patients with moderate ascites were considered the most appropriate candidates to evaluate the efficiency of repeated albumin infusions in order to improve survival, prevent the occurrence of further complications of cirrhosis including encephalopathy, sepsis, but also reduce ascites. In the ANSWER study (4), patient with ascites under diuretics, thus not considered refractory, received either albumin (40g twice a week for two weeks and then 40g weekly) or standard medical treatment (SMT). Patients in the albumin group showed a 38% decrease of the

mortality hazard ratio, fewer episodes of HE and sepsis, and a delayed need for paracentesis. Finally, during the 18 months follow-up, fewer patients were considered to have developed refractory ascites. Interestingly, a post hoc analysis (ILC 2019 presented data) of the ANSWER study showed that the albumin level after one month of treatment was strongly predictive of survival. In particular, 18 months survival reached 90% when above 40g/L. This suggests that the amount of albumin infused is highly important and may need to be adapted individually. In another RCT, patients awaiting liver transplantation received either midodrine 15-30mg/day and albumin 40g/day or placebo. There was no difference between both groups, neither in terms of survival on the waiting list, nor in terms of occurrence of cirrhosis complications or ascites control (5). A very quick access to LT (median treatment duration of 80 days in both groups) may however have precluded this trial to show more significant results.

TIPS placement induces a decompression of the portal circulation by shunting an intrahepatic portal branch into a hepatic vein. Its indications in the treatment of refractory ascites are better defined and will be discussed further away in this manuscript. The benefit of TIPS insertion in less severe patients, such as those with recurrent (or recidivant) ascites (RA) remains however uncertain. RA was first defined in a 1996 consensus as ascites that recurs at least three times within 12 months in spite of sodium restriction and diuretic treatment (6). Recently, EASL guidelines defined early RA as ascites that recurs earlier than one month after initial control (1). None or few of these patients were included in initial RCTs comparing TIPS using bare metal stents versus standard medical treatment (SMT). Recently, a study by Bureau *et al.* compared the prognosis of patients with RA receiving either TIPS with PTFE-covered stents or SMT (7). These patients were however more severe than according to the previous definition of RA. In order to be included, they needed to have required at least 2 LVPs within a minimum 3 weeks interval. Noteworthy, about 30% of patients had a history of variceal bleeding, and about 20% had a history of renal failure, highlighting the severity of their circulatory dysfunction. There was a significant increase of the one-year survival without transplantation rate (93% vs 52% p=0.003) in the TIPS group, which was the primary endpoint of the study. Interestingly, hepatic encephalopathy (HE) did not occur more frequently in the TIPS group. These results, obtained in patients with RA, moderate hepatic insufficiency and absence of previous overt HE, illustrate the importance of defining which patients will be the best candidates for TIPS and those more severely ill who should be listed for transplantation.

b) Patients with refractory ascites

Definition of refractory ascites

According to the International Ascites Club, refractory ascites is defined as “ascites that cannot be mobilized or the early recurrence of which cannot be satisfactorily prevented by medical therapy” (6). This definition includes diuretic-resistant ascites, i.e ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to sodium restriction and diuretic treatment, and diuretic-intractable ascites, i.e. ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic-induced complications that preclude the use of an effective

diuretic dosage. From a practical point of view, it is very difficult to reach the maximal doses of diuretics and 90% of patients display intractable ascites. HE, renal failure, hyponatremia, hypo- or hyper-kaliemia and muscle cramps are the main reasons for diuretics withdrawal (1).

Large-volume paracentesis

Large volume paracentesis (LVP) is the first line treatment of refractory ascites (6). Plasma volume expansion is required in order to prevent a post-paracentesis dysfunction. In a meta-analysis of randomised controlled trials, albumin infusion has shown to be more effective than other plasma expander in the prevention of post-paracentesis dysfunction (8). Albumin infusion should therefore be performed in patients undergoing LVP of more than 5L (8 g/L of ascites removed) (1).

Albumin

Long-term administration of albumin has also been shown to reduce mortality in patients with refractory ascites. The single center, non-randomized study by Di Pascoli *et al.,* evaluated the prognosis of patients of patients with refractory ascites treated with albumin 40g twice weekly versus SMT (9). Two-year mortality, which was the primary endpoint, was significantly lower in the albumin group (41.6% vs 65,5%, p=0.032). This study has many limitations including TIPS as an alternative therapeutic for these patients. However, a survival benefit of long-term administration of albumin in more severe patients, such as those with refractory ascites, may be particularly interesting in selected patients, especially liver transplantation candidates.

Transjugular intrahepatic portosystemic shunt

Transjugular intrahepatic portosystemic shunt (TIPS) placement induces a decompression of the portal circulation by shunting an intrahepatic portal branch into a hepatic vein. In the setting of refractory ascites, 6 prospective randomized controlled trials (RCT) compared non-covered TIPS and LVP in terms of ascites recurrence, hepatic encephalopathy, and survival (Table 1) (10-15). The results were analysed in several meta-analysis, the later showing the more satisfactory methodology (meta-analysis of individual data): in this meta-analysis, ascites recurrence and transplant-free survival were better in the TIPS group, when compared to LVP (16). However, the average number of HE episodes was higher in the TIPS group. It seems important to underline that those results were published before the use of PTFE-covered stents. One can hypothesise that results would be better using covered stents, when extrapolating results obtained in recurrent ascites (7). To date, no prospective controlled trial has been published using covered stent in refractory ascites. In the study published by Bureau and colleagues, patients were included in case of recurrent ascites, defined by 2 LVP within a minimum of 3 weeks, excluding those who had required >6 LVP within the previous 3 months. These criteria were quite different from both the historical definition of recurrent ascites and those of refractory ascites, as previously discussed.

TIPS is contraindicated in patients with heart failure, advanced liver failure, defined by a Child-Pugh score >13 or a MELD score >19, and significant HE. It seems crucial to carefully select patients for TIPS placement. Exclusion criteria were indeed heterogeneous amongst RCT, but some of them were similar, such as age >70 or 75 years, HE on the day of TIPS placement, Child-Pugh >11, HCC out of Milan criteria, and heart failure.

There are 3 main complications that have a negative impact on prognosis after TIPS placement: 1) liver failure and death; 2) refractory HE; and 3) heart failure. First, a simple

survival predictor has been described, combining platelets count and total bilirubin level (17): the actuarial 1-year survival rate in patients with both a platelets count above 75×10^9/L and a total bilirubin level lower than 50 µmol/L [3mg/dl] was 73.1% as compared to 31.2%, in patients with a platelets count below 75×10^9/L or a total bilirubin level higher than 50 µmol/L. Second, several risk factors of further development of HE have been described: older age, a poor liver function, a previous episode of HE, sarcopenia, and minimal hepatic encephalopathy. Nevertheless, there is no predictive model to apply to select effectively patients according to their risk to develop HE. Very recently, we recommended excluding TIPS as a non-urgent option in patients with a history of at least 2 bouts of HE, or with HE on the day of TIPS placement (18). Moreover, we suggested TIPS placement to be discussed case by case in patients older than 70. Last, regarding heart failure, a very recent prospective study has shown that cardiac decompensation occurs in about 20% of patients (19). The authors described that a combination of a BNP<40 pg/mL and a NT-proBNP<125 pg/mL before TIPS and the exclusion of diastolic dysfunction at echocardiography ruled out the risk of cardiac decompensation.

Alfapump®

Alfapump® (AP) is a fully implantable, programmable, and rechargeable pump system that automatically diverts ascitic fluid from the peritoneal cavity to the urinary bladder, allowing fluid removal by micturition (Table 1) (20, 21). A recent multicenter RCT conducted in patients with refractory ascites, AP significantly reduced the number of LVP and improved the quality of life as well as nutritional parameters (22). Quality of life has shown to be improved by AP in another study (23). As the device may provoke acute renal failure-even if reversible-it is currently contra-indicated in patients with chronic renal failure. Moreover, some patients, especially with HE, will experience technical difficulties. Therefore, it seems reasonable not to consider AP as an alternative therapy for patients with HE without any involved relative that could take care of the device.

Liver transplantation

As survival is poor in patients with refractory ascites, LT should be discussed in all of them. Nevertheless, despite the poor prognosis of this clinical situation, some patients will present with a low MELD score that may delay LT. In these latter patients, liver transplantation could be prioritized based on a MELD score exception. Nevertheless, prioritisation will be only considered in patients with a strict contra-indication for TIPS placement (24). That's the reason why TIPS should first be envisioned in those patients.

Summary of available therapeutics, indications (Figure 1)

As previously mentioned, LVP should be performed in patients with refractory ascites. If LVP is the first line treatment, a second line therapy has to been envisioned as soon as the diagnosis is made in order to improve prognosis. A careful clinical, biological examination and morphological is required: 1) clinical history, including age, systematic search for a previous episode of HE or heart decompensation; 2) physical examination with screening for confusion, flapping, sarcopenia, left or right signs of heart failure; 3) biological evaluation including routine blood exams, hepatic function, renal and cardiac function with BNP and NT-proBNP; 4) morphological evaluation including abdominal ultrasound exam, CT scan, and echocardiography. TIPS seems to be the best therapeutic option in patients <65 years,

without any previous episode of HE, with a Child-Pugh score <13 and a MELD score <19, a total bilirubin level <50 µmol/L, a platelets count >75×10^9/L, a normal value of BNP/NT-proBNP, and a normal echocardiography. TIPS should be contraindicated in patients >70 years, with history of more than 2 episodes of HE. AP can be envisioned in the latter patients unless they present a correct renal function (Cl Creat ≥ 50 ml/min). A case-by-case discussion is required for patients considered at high risk, according to liver function, cardiac function, and the risk of HE after TIPS. As there is always a theoretical risk after TIPS in all patients, we believe that a liver transplantation needs to be discussed at the same time in all patients, as they are prone to develop either liver failure or refractory HE requiring LT.

c) Patients with spontaneous bacterial peritonitis

SBP represents the most frequent site of bacterial infection in cirrhotic patients. SBP still carries a high mortality and may trigger worsening of liver function and other complications of cirrhosis such as HE, renal failure, and bleeding. Concerning the treatment of SBP, concern has raised about the increasing prevalence of multidrug resistant organisms (MDRO). They are mainly represented by extended spectrum beta lactamases producing Enterobacteriaceae and beta lactams resistant gram-positive bacteria. The emergence of extended drug resistant organisms (XDRO), in hospitalized patients but also in the community in some parts of the world emphasizes this concern and the need for data concerning the use of newly developed antibiotics in cirrhotic patients. European data support a high prevalence of MDRO infections in decompensated or ACLF patients. About 29% of the strains isolated in the 264 culture positive infections among the 1146 patients with decompensated cirrhosis or ACLF followed in the CANONIC cohort (2011) were MDRO (25). Wide discrepancies existed among centres and countries, with a higher prevalence in western European countries in these almost 10 years old data. The only factors significantly associated with the occurrence of MDRO were nosocomial infections, hospitalization within the previous 3 months and intensive care unit admission. Noticeably, long-term exposure to norfloxacin was not identified as a risk factor. More recent data (2017-2018) concerning 883 European patients with decompensated cirrhosis showed that 39.7% of culture positive infections among the 284 patients who developed infection were MDRO. It represents an almost 10% increase compared to 2011 data. Interestingly, there was a shift towards a higher prevalence in Eastern and Southern European countries. At a worldwide level, the study by Piano *et al.* reported 1302 infections in hospitalized cirrhotic patients (26). MDRO were isolated in 34% of cases. Risk factors were nosocomial or heath care associated infections, antibiotic exposure within the previous 3 months but also geographical origin and in particular India where the rate of MDRO and XDRO was the highest. Interestingly, the sites most concerned by MDR infections were pneumonias and urinary tract infections. Prevalence was lower in SBP (27%), in accordance with the CANONIC cohort (13.9% for SBP vs 29.3% all sites included). An Italian RCT has compared an initial antibiotic therapy with meropenem plus daptomycin versus ceftazidim to treat nosocomial SBP. There was a significantly higher response to treatment in terms of decrease of neutrophils count in ascites in the meropenem plus daptomycin group, but 90 days transplant free survival was similar in both groups. In multivariate analysis, an ineffective first line treatment was however a significant predictor of mortality, as described in the previously reported studies. Recommendations about antibiotic therapy for SBP are for these

reasons very difficult and of paramount clinical importance. They must depend on local bacterial ecology and individual risk factors such as previous antibiotic therapy, health care-associated, or nosocomial infections. Concerning community acquired SBP, EASL guidelines recommend third generation cephalosporins or piperacillin plus tazobactam (1). Concerning nosocomial SBP, meropenem is recommended, in association with linezolid or daptomycin when prevalence of drug resistant Gram-positive bacteria is high. Administration of 20% albumin is also recommended during SBP at the dose of 1.5g/kg at day 1 and 1g/kg at day 3. Indeed, in the study by *Sort et al.*, such treatment, compared to antibiotic therapy with cefotaxime alone, allowed a significant decrease of in hospital mortality (10% versus 29%, p=0.01) and occurrence of renal failure (10% versus 33%, p=0.02) (27). Severe patients (serum creatinine ≥ 88µM or total bilirubin ≥ 68µM) seemed to take most advantage of this treatment. Whether it should be administrated to all cirrhotic patients thus remains a matter of debate.

Prophylaxis of SBP is another clinically relevant issue. Norfloxacin is the only drug recommended and concern is growing about its safety and efficacy regarding the increasing prevalence of MDRO. Frequent neurologic and osteo-articular side effects have led drug-regulating agencies to issue warnings about this drug and advise to limit its use when no alternative is available. In primary prophylaxis, norfloxacin is recommended when ascites fluid protein level is below 15g/L is association with severe cirrhosis (Child-Pugh score ≥ 9 and total bilirubin level ≥ 3mg/L, with either impaired renal function or hyponatremia) (1). A French RCT compared norfloxacin versus placebo in Child Pugh C patients without previous SBP (28). Six-months mortality was only significantly lower in patients with low ascitic fluid protein level (<15g/L), confirming that primary prophylaxis should be restricted to the most severe patients. These data are however not recent enough (2010-2014) to take account of the change in susceptibility to fluoroquinolones of Gram negative bacteria, which may affect the effectiveness of this prophylaxis. Norfloxacin use in secondary prophylaxis is an even greater issue, given the high prevalence of recurrent SBP after a first episode. It has proven its effectiveness in a single RCT published in 1990, significantly decreasing the rate of recurrent SBP from 68% in the placebo group to 20% in the norfloxacin group. Such results have not been reproduced more recently. However, recent German observational data on patients under primary or secondary prophylaxis with norfloxacin are in favour of a significantly greater risk of SBP in patients carrying quinolones resistant Gram-negative bacteria. Such results, in a population with a 50% rate of baseline carriage of MDRO highlight the issue about resistance to fluoroquinolones and suggest that screening patients for MDRO could be relevant in routine practice. Finding an alternative to oral fluoroquinolones also appears to be an important question. Preliminary results and a recent meta-analysis support the effectiveness of rifaximin in primary or secondary prophylaxis of SBP (29). However, the results of a RCT including a larger number of patients, comparing rifaximin and oral fluoroquinolones are still expected.

Conclusion

Prognosis is poor in patients with complicated ascites, including refractory ascites or SBP. In these situations, TIPS placement and liver transplantation have to be discussed at the same time, as TIPS may be either contraindicated or of uncertain evolution in patients at high risk of developing further liver failure, HE or cardiac decompensation. The recent study of Bureau et al. conducted in recurrent ascites suggests that TIPS placement could be indicated at an

earlier stage, i.e. before the development of refractory ascites. We do believe that a multidisciplinary discussion has to be organised in order to better select patients for the best therapeutic option.

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Figure 1. Algorithm for the management of refractory ascites in patients with cirrhosis

Table 1 Main studies comparing LVP and other therapeutics in patients with refractory or recurrent ascites (Table 1a with TIPS, Table 1b with Alfapump®)

Table 1a.

			Enrolled patients (n)		Improvement of ascites (%)		Development of hepatic encephalopathy (%)		Survival (%)	
			TIPS	LVP	TIPS	LVP	TIPS	LVP	TIPS	LVP
		Randomised controlled studies								
Bare TIPS	Refractory ascites	Lebrec et al. 1996	13	12	38	0	15	6	29	60
		Gines et al. 2002	35	35	51	17	60	34	26	30
		Sanyal et al. 2003	52	57	58	16	38	21	35	33
		Narahara et al. 2011	30	30	87	30	20	5	20	5
	Refractory + recurrent ascites	Rössle et al. 2000	29	31	84	43	23	13	58	32
		Salerno et al. 2004	33	33	79	42	61	39	59	29
		Meta-analysis for refractory ascites								
		Salerno et al. 2007	149	156	58	11	58	38	56	50
Covered TIPS	Recurrent ascites	**Randomised controlled study**								
		Bureau et al. 2017	29	33	89	29	34	33	93	52

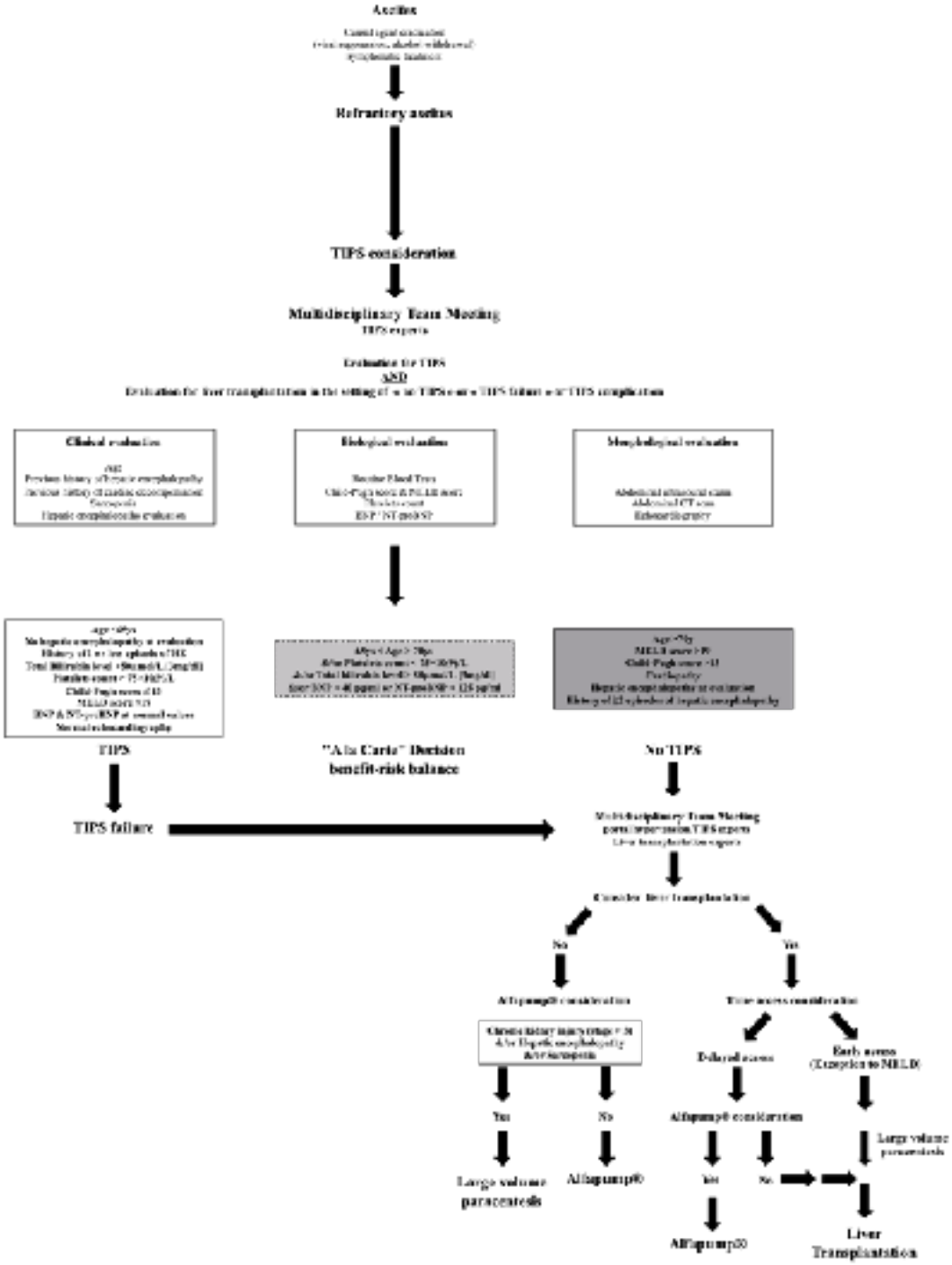
LVP: large volume paracentesis; TIPS: tranjugular intrahepatic portosystemic shunt

Table 1b. Outcome of Alfapump® for patients with cirrhosis and refractory ascites

	Enrolled patients (n)	Length of follow-up (months)	Number of LVP per patient per month (median)		Development of adverse effects (n)				Child-Pugh score (mean)			MELD score (mean)			Death, n (%)	Improvement of Quality of life (HRQoL score)	
			At baseline	At the end of follow-up	Infections	Catheter issues	Pump malfunction	Alfapump® explant	At baseline	At 6 months	At the end of follow-up	At baseline	At 6 months	At the end of follow-up		Abdominal symptoms	Activity scores
Observational studies																	
Bellot et al. 2013	40	6	3.4	0.2	24 (60%)	10 (25%)	2 (5%)	3 (7.5%)	8.5	8.6	8.6	12.6	11.7	11.7	9 (22%)		
Stirnimann et al. 2017	56	24	2.2	0.2		28 (50%)	11 (20%)	27 (48%)	8.8	9.8	7.5	13.42	17.04	9.11	23 (41%)		
Randomised controlled study																	
Bureau et al. 2017	27	6	1.6	0.3	25 (93%)	5 (9%)	4 (7%)	3 (5.4%)	8.2			12.2			15 (56%)	+1.25	+0.80

LVP: large volume paracentesis

Figure 1


Ascites
Refractory ascites
TIPS consideration
Multidisciplinary Team Meeting
Clinical evaluation
Biological evaluation
Morphological evaluation
TIPS
"A la Carte" Decision
benefit-risk balance
No TIPS
TIPS failure
No
Yes
No
Yes
No
Yes
No
Yes
Large volume paracentesis
Alfapump®
Alfapump®
Liver Transplantation