Refractory ascites



Victor de Lédinghen MD PhD Christophe Bureau MD PhD

CHU Bordeaux France

Paris 14 January 2019







Disclosures

- ✓ AbbVie
- ✓ Gilead
- ✓ MSD
- Intercept Pharma
- ✓ Pfizer
- ✓ Echosens
- ✓ Supersonic Imagine

A 53 yrs old woman with alcoholic cirrhosis

- $\checkmark\,$ With refractory ascites since 6 months
- ✓ Paracenteses > 10 litres every 10 days
- ✓ EV grade 2 in primary prophylaxis NSBB
- ✓ Chronic skin suppuration





What do you think about NSBB in this case?

Refractory ascites in liver cirrhosis



Fig. 1 Interplay between systemic inflammation, refractory ascites, and the development of hepatorenal syndrome

Adebayo D et al. Am J Gastro 2019

Beta-blockers in ascites : good or bad?



NSBB in patients with refractory ascites

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

European Association for the Study of the Liver*

- In patients with cirrhosis and refractory ascites [16] NSBB (propranolol, nadolol) should be used cautiously with close monitoring of blood pressure, serum sodium and serum creatinine (4;C).
 - Until randomized trials are available NSBB should be reduced/discontinued if a patient with refractory ascites develops any of the following events (5;D):
 - Systolic blood pressure <90 mmHg
 - Hyponatremia (<130 mEq/L)
 - Acute kidney injury [17]

A 53 yrs old woman with alcoholic cirrhosis

- $\checkmark\,$ With refractory ascites since 6 months
- ✓ Paracenteses > 10 litres every 10 days
- ✓ EV grade 2 in primary prophylaxis NSBB
- ✓ Chronic skin suppuration





Is it refractory ascites ?

Diagnosis of refractory ascites

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis $^{\rm \! \times}$

European Association for the Study of the Liver*

Recommendations

- The diagnosis of refractory ascites relies on the assessment of the response of ascites to diuretic therapy and salt restriction. Such an evaluation should be done in stable patients without associated complications, such as bleeding or infection, after ascertaining patient compliance to treatment (III;1).
- Patients with refractory ascites should be evaluated for LT (III;1).

A 53 yrs old woman with alcoholic cirrhosis

- ✓ Doppler US : no PVT no HCC
- ✓ Serum sodium 134 mmol/l
- ✓ Albumin 31 g/l
- ✓ Platelets : 135 G/L
- ✓ Bilirubin 20.8 µmol/l
- ✓ INR 1.3
- ✓ Creatinine 86.1 µmol/l



- ✓ Child-Pugh B8
- ✓ MELD 11

What is your option?

1.Large volume paracentesis + albumin infusion

2.TIPS

3.Alfapump

4.Liver transplantation

Long-term albumin administration in decompensated cirrhosis (ANSWER)



Figure 1: Trial profile

For the SMT group, wrong inclusions were one advanced hepatocellular carcinoma, one neoplastic ascites, and two refractory ascites. For the SMT plus HA group, wrong inclusions were one advanced hepatocellular carcinoma and one refractory ascites. HA=human albumin. SMT=standard medical treatment.

Caraceni P et al. Lancet 2018; 391: 2417–29

Not refractory ascites

Long-term albumin administration in decompensated cirrhosis (ANSWER)



Figure 3: Overall survival

Kaplan-Meier estimates for the probability of overall survival in the modified intention-to-treat population of SMT and SMT plus HA groups. The p value was calculated by the log-rank test. HA=human albumin. SMT=standard medical

Long-term albumin administration in decompensated cirrhosis (ANSWER)



Large Volume Paracentesis in refractory ascites

- ✓ Usually performed as an outpatient procedure
- More effective and safer in managing large volume ascites compared to diuretic therapy
- Lower incidence of renal dysfunction, electrolyte abnormalities and much less disturbances to the systemic and hemodynamic status
- ✓ Survival rates no different.

Large Volume Paracentesis in refractory ascites

 Intravenous human albumin (HAS) infusions is recommended after LVP to prevent the development of paracentesis-induced circulatory dysfunction (PICD).

 The AASLD recommends infusion of 6–8 g of albumin/L of ascites removed with a paracentesis of >5 L.

LVP in refractory ascites

Clinical Practice Guidelines



EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis *

European Association for the Study of the Liver*

Recommendations

- Repeated LVP plus albumin (8 g/L of ascites removed) are recommended as first line treatment for refractory ascites (I;1).
- Diuretics should be discontinued in patients with refractory ascites who do not excrete >30 mmol/day of sodium under diuretic treatment (III;1).

TIPS in refractory ascites





Salerno F et al. Gastroenterology 2007;133:825-34

Serum bilirubin and platelet count: A simple predictive model for survival in patients with refractory ascites treated by TIPS

Christophe Bureau^{1,2,*}, Sophie Métivier¹, Mario D'Amico³, Jean Marie Péron^{1,2}, Philippe Otal⁴, Juan Carlos Garcia Pagan³, Valérie Chabbert⁴, Carine Chagneau-Derrode⁵, Bogdan Procopet¹, Hervé Rousseau³, Jaume Bosch³, Jean Pierre Vinel^{1,2}



Fig. 2. Actuarial rates of survival in the 105 patients (TC) with cirrhosis and refractory ascites treated with TIPS according to serum bilirubin concentration and platelet count (number below the graph are patients at risk at each time point).

Serum bilirubin and platelet count: A simple predictive model for survival in patients with refractory ascites treated by TIPS

Christophe Bureau^{1,2,*}, Sophie Métivier¹, Mario D'Amico³, Jean Marie Péron^{1,2}, Philippe Otal⁴, Juan Carlos Garcia Pagan³, Valérie Chabbert⁴, Carine Chagneau-Derrode⁵, Bogdan Procopet¹, Hervé Rousseau³, Jaume Bosch³, Jean Pierre Vinel^{1,2}



Fig. 5. Actuarial rates of survival of the 48 patients of Spanish external validation cohort (EC).

Covered TIPS vs LVP + albumin in refractory ascites

Characteristics of patients	TIPS (n = 29)	LVP + A (n = 33)
Age (yrs)	56	56
Alcohol cirrhosis (%)	90	85
Bilirubin (µmol/l)	17	17
INR	1,39	1,46
Albumin (g/l)	30,7	33,4
Creatinine (µmol/I)	85	86
Na (mmol/l)	134	132
Platelets (G/L)	179	169
Child-Pugh	9,1 ± 1,4	9,0 ± 1,6
MELD	12,1 ± 3,5	13,1± 3,9
Number paracentesis before inclusion	4,5 ± 1,4	4,2 ± 1,3

Bureau C et al. Gastroenterology 2017;152:157-63

TIPS vs LVP + albumin in refractory ascites

	TIPS (n=29)	LVP + A (n=33)	р
Number of paracentesis	32	320	<0.001
Total volume ascites	169 L	2 061 L	<0.001
Total albumin	1 170 g	17 727 g	<0.001

Bureau C et al. Gastroenterology 2017;152:157-63

TIPS vs LVP + albumin in refractory ascites

	TIPS (n=29)	LVP + A (n=33)	р
Variceal bleeding	0	6	0.001
Hospitalization stay (days per year)	17 ± 28	35 ± 40	0.04

TIPS vs LVP + albumin in refractory ascites



liver

Bureau C et al. Gastroenterology 2017;152:157-63

Risk factors for encephalopathy post-TIPS

 Table 2 Risk factors for the development of hepatic

 encephalopathy post-TIPS insertion

Risk factors for post-TIPS encephalopathy:

1. Age over 65

2. Low-arterial pressure (Mean arterial pressure <80 mmHg)

3. MELD score >15

4. Child-Pugh score >12

5. HE prior to TIPS insertion

Low PSPG post-TIPS insertion of <5 mmHg

7. Large diameter stent of >10 mm

Adebayo D et al. Am J Gastroenterol 2019

TIPS in refractory ascites

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis *

European Association for the Study of the Liver*

- Patients with refractory or recurrent ascites (I;1), or those for whom paracentesis is ineffective (*e.g.* due to the presence of loculated ascites) should be evaluated for TIPS insertion (III;1).
- TIPS insertion is recommended in patients with recurrent ascites (I;1) as it improves survival (I;1) and in patients with refractory ascites as it improve the control of ascites (I;1).
- The use of small-diameter PTFE-covered stents in patients is recommended to reduce the risk of TIPS dys-function and hepatic encephalopathy with a high risk of hepatic encephalopathy is recommended (I;1).

TIPS in refractory ascite

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

European Association for the Study of the Liver*

- Diuretics and salt restriction should be continued after TIPS insertion up to the resolution of ascites (II-2;1), as well as close clinical follow-up (III,1).
- Careful selection of patients for elective TIPS insertion is crucial, as is the experience of the centre performing this procedure. TIPS is not recommended in patients with serum bilirubin > 3 mg/dl and a platelet count lower than 75 x 10⁹/L, current hepatic encephalopathy grade ≥2 or chronic hepatic encephalopathy, concomitant active infection, progressive renal failure, severe systolic or diastolic dysfunction, or pulmonary hypertension (III;1).

Alfapump in refractory ascites



Fig. 4 Position of alfapump within the abdominal wall once implanted



FIGURE 1 Alfapump with peritoneal catheter (blue) and pigtail bladder catheter (yellow)

- The programmable and rechargeable pump transports small amount of ascites continuously from the peritoneal cavity into the bladder to be eliminated by miction
- The device is fitted with sensors in the peritoneal cavity and bladder allowing for individualized management of ascites.
- The pump is programmed to work during awake hours so not to interfere with the patient's sleep.

Alfapump® system (Automated Low-Flow Ascites Pump System, Sequana Medical, Zurich, Switzerland)

Stirnimann G et al. Aliment Pharmacol Ther 2017;46:981-91

Alfapump versus large volume paracentesis

Time until the first large volume paracentesis



Alfapump - results

- Reduction in LVP requirement
- Prophylactic antibiotic
- Intermittent albumin as guided by renal function is recommended in the small proportion of patients at risk for renal

✓ dysfunction.

 Alfapump system is currently not approved in North America.

Alfapun

well as close clinical follow-up (III,1).

- Careful selection of patients for elective TIPS insertion is crucial, as is the experience of the centre performing this procedure. TIPS is not recommended in patients with serum bilirubin > 3 mg/dl and a platelet count lower Clinical Practice Guidelines of the patic encephalopathy. Concomitant than 75 x 10 /L, current hepatic encephalopathy, concomitant active infection, progressive remarks fully fully
- At present the addition of clonidine or midodrine to diuretic treatment cannot be recommended (III;1).
- Alfapump[®] implantation in patients with refractory ascites not amenable to TIPS insertion is suggested in experienced centres. However, close patient monitoring is warranted because of the high risk of adverse events including renal dysfunction and technical difficulties (**I**;**2**).

A 53 yrs old woman with alcoholic cirrhosis

- ✓ Doppler US : no PVT no HCC
- ✓ Serum sodium 134 mmol/l
- ✓ Albumin 31 g/l
- ✓ Platelets : 135 G/L
- ✓ Bilirubin 20.8 µmol/l
- ✓ INR 1.3
- ✓ Creatinine 86.1 µmol/l



- ✓ Child-Pugh B8
- ✓ MELD 11





A 53 years old woman with alcoholic cirrhosis

	Baseline	M6
		o / -
Bilirubin (µmol/l)	20.8	21.5
Albumin (g/l)	31	34
INR	1.3	1.3
Creatinine (µmol/l)	86.1	70.3
Serum sodium (mmol/l)	134	139
Child-Pugh Score	8	6
MELD Score	11	12

Main evolution of hepatic and renal function between baseline and month 6

Conclusion





Before TIPS

After TIPS