Received: 22 March 2017 | First decision: 17 April 2017 | Accepted: 30 August 2017

DOI: 10.1111/apt.14331

WILEY AP&T Alimentary Pharmacology & Therapeutics

Treatment of refractory ascites with an automated low-flow ascites pump in patients with cirrhosis

G. Stirnimann[1] | T. Berg[2] | L. Spahr[3] | S. Zeuzem[4] | S. McPherson[5] | F. Lammert[6] | F. Storni[1] | V. Banz[1] | J. Babatz[7] | V. Vargas[8] | A. Geier[9] | A. Stallmach[10] | C. Engelmann[2] | C. Trepte[11] | J. Capel[11] | A. De Gottardi[1]

[1]Bern, Switzerland
[2]Leipzig, Germany
[3]Geneva, Switzerland
[4]Frankfurt, Germany
[5]Newcastle, UK
[6]Homburg, Germany
[7]Dresden, Germany
[8]Barcelona, Spain
[9]Würzburg, Germany
[10]Jena, Germany
[11]Zurich, Switzerland

Correspondence
Dr. G. Stirnimann and Dr. A. De Gottardi, University Clinic for Visceral Surgery and Medicine, Bern, Switzerland.
Emails: guido.stirnimann@insel.ch; andrea.degottardi@insel.ch

Funding information
This study was funded in full by Sequana Medical AG, Zurich. The preparation of this paper was funded in part by Sequana Medical AG, Zurich. Writing support for a previous version of this manuscript was provided by Randall Watson and Dr. Diana Shy of medicalwriters.com and funded by Sequana Medical AG, Zurich.

Summary

Background: Refractory ascites (RA) is a frequent complication of cirrhosis, requiring large volume paracentesis or placement of a transjugular intrahepatic portosystemic shunt (TIPSS). The automated low-flow ascites pump (alfapump, Sequana Medical AG, Zurich, Switzerland) is an innovative treatment option for patients with RA.

Aim: To assess safety and efficacy of this treatment in patients with a contraindication to TIPSS.

Methods: Fifty-six patients (43 males; mean age 62 years) from centres in Germany, Switzerland, UK and Spain were included and followed for up to 24 months. Complications, device deficiencies, paracentesis frequency and patient survival were recorded.

Results: At the time of this analysis, 3 patients completed the 24-month observation period, monitoring of 3 was ongoing, 9 underwent liver transplantation, 17 patients were withdrawn due to serious adverse events and 23 patients died. Most frequently observed technical complication was blocking of the peritoneal catheter. Twenty-three pump-related reinterventions (17 patients) and 12 pump exchanges (11 patients) were required during follow-up. The pump system was explanted in 48% of patients (in 17 patients due to serious adverse events, in 9 at the time of liver transplantation and in 1 due to recovery from RA). Median frequency of paracentesis dropped from 2.17 to 0.17 per month.

Conclusions: The alfapump can expand therapeutic options for cirrhotic patients with RA. Continuous drainage of ascites in a closed loop automated system led to significant reduction in paracentesis frequency. Technical and procedural improvements are required to reduce the rate of adverse events and reinterventions.

https://clinicaltrials.gov/ct2/show/NCT01532427

The Handling Editor for this article was Professor Peter Hayes, and it was accepted for publication after full peer-review.
The authors' complete affiliations are listed in Appendix.

1 | INTRODUCTION

Refractory ascites (RA) is a serious complication of cirrhosis, developing in 5%-10% of patients with ascites every year.[1] RA is associated with poor prognosis and a 6-month transplant-free survival of only 65.3%.[2] Treatments for RA are considered short-to-medium term solutions while awaiting potential liver transplantation. Treating tense ascites before transplantation may also prevent further deterioration of a patient's condition, including appetite loss, inadequate nutrition, impaired gut motility or sarcopenia,[3] and relieve discomfort.

Initial RA treatment consists of repeat large volume paracentesis (LVP) in combination with albumin substitution.[1] Although the risk of peri-procedural complications from repeat paracentesis is low,[4-6] and circulatory dysfunction can be prevented with intravenous albumin replacement,[7-9] this treatment option poses a substantial burden on the patient as well as on the medical team and is associated with high economic cost.[10]

The placement of a transjugular intrahepatic portosystemic shunt (TIPSS) offers an alternative to repeat LVP. Four randomised clinical trials, comparing bare TIPSS to repeat paracentesis, have been reported.[11-14] A meta-analysis of these studies[2] showed that TIPSS is an effective treatment and markedly decreased the number of paracenteses required. However, 42% of TIPSS patients experienced recurrence of tense ascites. Additionally, long-term survival benefits and the development of encephalopathy have been debated.[15-17] A recent randomised controlled trial in mostly Child B patients younger than 65 years comparing covered TIPSS with LVP plus albumin showed an improved transplant-free survival in the TIPSS group, without significant difference in the occurrence of hepatic encephalopathy.[18]

However, a significant proportion of patients with RA show indicators of poor post-TIPSS prognosis, namely previous episode of hepatic encephalopathy, higher age, platelet count below 75 × 10E9/L and bilirubin >50 μmol/L.[19] Hence, novel treatment options for RA represent an important requirement in hepatology.

The aim of this study was to prospectively assess safety and efficacy in cirrhotic patients with RA, who had a contraindication to TIPSS and were therefore treated with an alfapump.

The automated low-flow ascites pump (alfapump, Sequana Medical AG, Zurich, Switzerland) (Figure 1) is a fully implantable pump system, developed to transfer ascitic fluid from the abdominal cavity to the urinary bladder via tunnelled peritoneal and bladder catheters that are connected to the subcutaneous pump. The alfapump contains 4 pressure sensors to monitor the abdominal pressure and the bladder pressure and to provide information on flow rate and system behaviour. A pumping cycle is initiated only if the bladder pressure is below a certain threshold. At the same time, pumping is immediately stopped when the pressure in the peritoneal cavity drops significantly which indicates that the alfapump cannot access sufficient fluid.

The pump type used within the alfapump is a so called gear pump where fluid is moved forward in between rotating gears. To transport a desired volume, a dedicated amount of motor turns is necessary. In combination with the motor speed, this leads to the flow rate of the alfapump. When ascites is transported, it moves past several pressure sensors. The changes in pressure sensor values confirm fluid is actually being transported.

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

The physician in charge of following up a patient implanted with the alfapump uses the alfapump Programmer, a computer running FlowControl software. FlowControl allows to program the target daily volume, the pumping times throughout the day, the frequency of pumping and to switch the alfapump on and off.

A wireless induction system is used to charge the pump in general twice daily. Pump parameters including operating time, cycle frequency and daily ascites volume can be set as clinically required for each patient with a wireless controller. Information from the device about the effective ascites volume that has been transferred into the bladder as well as possible dysfunctions is transmitted automatically via the charger docking station to the manufacturer and is periodically reported to the treating physician. Thus, pump status is continuously monitored and updated, and adjustments to the pump programming by the physician are based on actual patient and pump conditions.

The safety and efficacy of the alfapump system were investigated in the PIONEER study.[20] The authors reported a reduction in the median frequency of paracentesis from 3.4 to 0.2 per month and an adequate safety profile, so that this device was approved for commercial use in Europe in 2011. Results of the first randomised clinical trial comparing the effect of the alfapump system with standard of care large volume paracenteses have been published recently.[21] Compared to the standard of care group, the alfapump system significantly reduced the need for LVP and patients in the alfapump group had a significant improvement in health-related quality of life after 3 months as measured with the Chronic Liver Disease Questionnaire. Acute kidney injury in the immediate post-operative phase and pump-related reinterventions were the most prominent adverse events. In both treatment groups, survival was similar.

2 | MATERIALS AND METHODS

Ten European referral centres participated in this prospective observational study. Cirrhotic patients with RA presenting any contraindications to TIPSS received a treatment with the alfapump system. RA was defined as diuretic-resistant or diuretic-intractable or as early recurrence of ascites after paracentesis.[22] Inability to operate the charging system was considered an exclusion criteria. Patients on treatment with the alfapump were followed up for at least 12 months and information about LVP, hepatic decompensations, infections, death, adverse device events and liver transplant were recorded prospectively. Blood chemistry, haematology data and adverse events information was collected as part of standard clinical practice (no study-specific tests were required).

The management of candidates for an alfapump implantation was optimised with respect to nutritional support and screening/treatment of oesophageal varices.[23]

One day prior to the implantation of the pump, a LVP was performed to void the abdominal cavity. Albumin was replaced according to current guidelines.[22] The peritoneal catheter was introduced into the abdominal cavity just above the umbilicus. The entry point into the abdominal cavity was closed using a tight purse-string suture to prevent leakage of ascites. To facilitate positioning of the pigtail bladder catheter, the bladder was filled retrograde with methylene-blue coloured saline. The pigtail catheter was introduced into the bladder with a removable introducer system. A subcutaneous pump pocket was formed in the right upper quadrant of the abdomen to position the pump. The pump pocket was just large enough to hold the pump but small enough to prevent pump migration. Both the bladder and the peritoneal catheter were connected to the pump via subcutaneous tunnelling (Figure 5). Skin sutures were left in place for up to 3 weeks in order to prevent wound dehiscence or ascites leakage.[24]

After implantation of the pump, long-term antibiotic prophylaxis was administered, in most cases norfloxacin, 400 mg daily. Patients were followed up weekly for the first month after implantation and on an individual schedule as determined by the treating physician thereafter. Albumin administration was left to the discretion of the individual investigators, according to the current treatment guidelines.[22,25] The maximum follow-up period for this analysis was set to 24 months, excepting 2 patients who received last follow-up at 26.4 months.

Reintervention was defined as surgical replacement or correction of either one or both alfapump system catheters (pump in situ) or a revision of the pump pocket. Pump exchange comprised the exchange of the alfapump with a new pump system within the same surgical procedure. Explantation was defined as surgical removal of the pump due to serious adverse event (SAE), transplantation or no more need.

2.1 | Statistics

Results are reported as mean (±SD) or as median (interquartile range, IQR), as indicated. For survival analyses, Kaplan-Meier plots were used. The follow-up schedule was at the discretion of the investigator and laboratory data that were closest to the indicated time points (baseline, 1, 3, 6, 12, 18 and 24 months) were analysed. Statistical analyses were performed using SPSS V23.0 Armonk, NY, USA.

"alfapump system survival" was defined as elapsed time from pump implantation to the time of explant for pump-related reasons. Pump replacement due to pump malfunction was counted as an event having occurred at time of replacement. Explant due to an SAE was counted as an event having occurred at time of explant. Explants due to OLT or due to an SAE unrelated to the pump system were censored at time of explant.

This study was approved by the required Independent Ethical Committees and Institutional Review Boards of the participating centres and all patients gave their written consent to participate in this study.

3 | RESULTS

Fifty-six patients (43 men, 13 women, mean age 62 years) were enrolled in this study—30 in Switzerland (Bern, 25; and Geneva, 5), 21 in Germany (Leipzig, 7; Frankfurt am Main, 6; Homburg, 3; Dresden, 2; Würzburg, 2; and Jena, 1), 3 in the United Kingdom (Newcastle) and 2 in Spain (Barcelona). All pumps were implanted under general anaesthesia. Median duration of surgery was 60 min (50-69). Median hospital stay following implantation was 7 days.[3-14]

Patients' baseline characteristics are presented in Table 1. Median MELD score was 13 and mean Child-Pugh score was 8.9 (1.3). Fifteen patients (24.8%) were Child-Pugh class C, 36 (64.3%) were class B, and 5 had an unknown score. The median duration of ascites prior to implantation of the alfapump system was 11.0 months (8.0-19.0) with a median frequency of large volume paracenteses over the previous 3 months of 2.17 per month (1.45-4.34) (Table 2).

3.1 | Outcome

Overall survival is shown in Figure 2. Mean actuarial survival was 12.8 months (95% CI 10.0-15.7) and median survival was 9.8 months. Patient disposition at the end of study (data cut-off) is listed in Table 3. Twenty-three patients (41.1%) died during the study, while 7 patients died after being withdrawn from the study due to pump removal secondary to SAEs. The primary cause of all deaths (during the study and after withdrawal) was progression of cirrhosis with decompensation (Table 4). MELD score and Child-Pugh score over time are summarised in Table S1.

3.2 | Device and procedure-related safety events

The most frequent device related event was clogging of the peritoneal catheter by proteinaceous debris and/or fibrin clots and aspiration of the omentum (21 events in 13 patients). In 5 patients, the peritoneal catheter was either displaced, disconnected, or twisted. The bladder catheter was blocked or displaced in one case each. There were 2 procedure-related problems involving wound dehiscence. Device and procedure-related events are listed in Table S2).

TABLE 1 Baseline characteristics

Number included in analysis	56
Median age in years (range)	62 (50-78)
Gender (%)	43 male (77) 13 female (23)
Body weight (kg), mean (SD)	77 (16.1)
BMI (kg/m^2), mean (SD)	25.9 (4.7)
Aetiology of liver cirrhosis (%)	
Alcohol	39 (69.7)
Hepatitis C	4 (7.1)
Cryptogenic	4 (7.1)
NASH	3 (5.4)
Cardiac	2 (3.6)
Autoimmune hepatitis	1 (1.8)
Drug-induced	1 (1.8)
HBV and AIH	1 (1.8)
HCV and HBV and Alcohol	1 (1.8)
History of hepatic encephalopathy (%)	
Yes	21 (37.5)
No	31 (55.4)
Unknown/missing data	4 (7.1)
History of renal dysfunction (%)	
Yes	26 (46.4)
No	23 (41.1)
Unknown/missing data	7 (12.5)
History of hepatorenal syndrome (%)	
Prior episode of HRS	20 (35.7)
No prior episode of HRS	24 (42.9)
Unknown/missing data	12 (21.4)
History of SBP (%)	
Yes	22 (39.3)
No	30 (53.6)
Unknown/missing data	4 (7.1)
History of urinary tract infection (%)	
Yes	9 (16.1)
No	34 (60.7)
Unknown/missing data	13 (23.2)
Child-Pugh score, mean (SD)	8.9 (1.3)
B (7-9) (%)	36 (64.3)
C (10-15) (%)	15 (26.8)
Unknown/missing data (%)	5 (8.9)
MELD score	
Median (n, range, Q1, Q3)	13 (53, 6-25, 9.5, 16)
Mean (SD)	13.6 (4.4)
Unknown/missing data (%)	3 (5.4)
Blood values	
Bilirubin (μmol l^{-1}), N = 54, mean (SD) Median (IQR)	34.9 (32.9) 24.7 (16.0-40.0)
Creatinine (μmol l^{-1}), N = 56, mean (SD) Median (IQR)	111.0 (47.1) 98.6 (83.4-119.5)
Albumin (g/L), N = 56, mean (SD) Median (IQR)	31.0 (6.7) 31.5 (26.5-36.8)
INR, N = 54, mean (SD) Median (IQR)	1.30 (0.22) 1.27 (1.14-1.42)

Long-term ascites leakage did not occur in any patient, although short-term leakage after implantation was common and not specifically monitored as it usually resolved quickly.

3.3 | Reinterventions, pump exchanges and pump explantations

Seventeen patients (21.4%) required at least on reintervention (23 interventions in total) and 11 patients had a surgical pump replacement (in total, 12 pumps were exchanged). The pump was explanted in 27 cases. In 17 patients (30.4%), the pump was explanted due to a SAE associated either with progressive liver disease, including infection (12 [21.4%]), or for reasons related to device deficiency (5 [8.9%], including pump pocket infection [2], clogged pump [1], and macroscopic haematuria [2]). In 9 of the 27 cases, the pump was explanted because patients received liver transplants. In a single case, the patient was successfully treated for chronic hepatitis C and recovered from RA, so that the pump was explanted, because it was no longer necessary (Table 5). Outcome after surgical revision (1-month survival) is specified in Table 6 and Table S3. One-month recovery after surgical revision was 100%, whereas 1 patient died 2 weeks after the exchange of the pump system. In this patient, the pump had to be explanted 1 week after the exchange of the system due to a pump pocket infection. Survival of the alfapump system after implant is presented in Figure 2. The median pump system survival in this study was 13.6 months (95% CI 10.2-16.9 months).

3.4 | Liver and renal function

Blood chemistry and coagulation parameters are presented in Figure 3 and in Table S4. After the implantation of the pump system, an increase in plasma creatinine could be observed (mean increase of 20.2 μmol l^{-1} at 1 month, 46.6 μmol l^{-1} at 3 months as compared to baseline). At 6 months, a further increase could only be observed in patients with a less favourable outcome (non-long term survivors). Similarly, serum albumin levels decreased slightly over time (mean decrease of 1.4 g/L after 1 month, 2.3 g/L after 3 months and 3.2 g/L after 6 months). This effect was less pronounced in long-term survivors).

3.5 | Efficacy: Large volume paracenteses after the implantation

The frequency of LVP decreased to 0.17 per month (0.00-0.41) after implantation (Table 2).

TABLE 2 Paracentesis requirements and ascites volume removed by paracentesis and by alfapump system

	Pre-implant	Post-implant
Paracentesis frequency per month	48[a] patients	56 patients
Mean (SD, range)	2.88 (1.81, 0.5-10.1)	0.28 (0.34, 0-1.2)
Median (IQR)	2.17 (1.45-4.34)	0.17 (0-0.41)
Paracentesis volume (L per month)	45[a] Patients	51 patients
Litres per month, mean (SD, range)	19.3 (11.6, 3.9-53.2)	1.22 (1.67, 0-5.6)
Litres per month, Median (IQR)	16.3 (10.1-26.1)	0.41 (0-2.1)
Pump data		
Average volume per patient removed by pump (mL/day)	NA	55 patients
Mean (SD, range)	NA	884 (398, 50-2051)
Median (IQR)	NA	935 (625-1081)
Average volume per patient removed by pump per month (L per month)	NA	55 patients
Mean (SD, range)	NA	26.5 (11.9, 1.5-61.5)
Median (IQR)	NA	28.1 (18.8-32.4)

[a]Evaluable patients. Baseline data not complete for all patients.

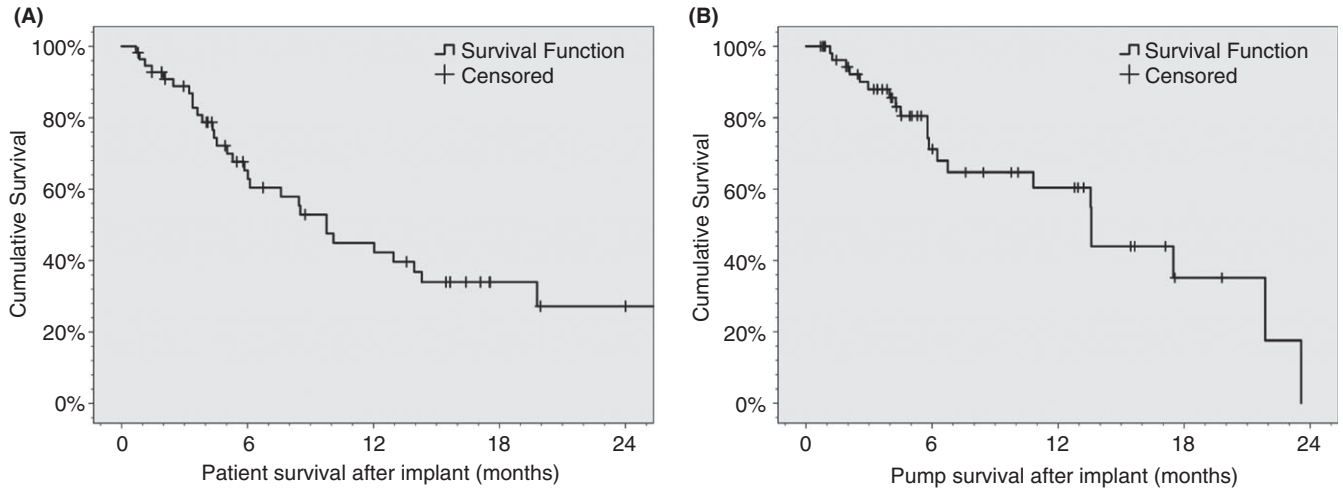

FIGURE 2 A, Kaplan-Meier curve of overall survival (ITT) including known deaths after pump explant or withdrawal from study. B, Kaplan-Meier curve of alfapump system survival

Over a median follow-up of 5.8 months, 37 patients (66.1%) did not require any LVP after the system implantation.

Of 127 post-implant paracenteses, 55 (43%) were related to pump or catheter-related issues, such as clogging of the pump or obstruction of the peritoneal catheter, dislocation or disconnection of the catheters. The remaining LVPs were necessary due to technical issues with the charger or insufficient charging (10%), because the programmed pumping volume was too low (27%), or for unknown reasons in patients with normal pump function (20%) (Table S5). Frequency of LVP per patient is displayed in Figure 4.

4 | DISCUSSION

The management of RA in patients with cirrhosis is challenging and novel therapies are an unmet need in hepatology. The alfapump was first introduced in 2010 as part of the PIONEER trial and has been available commercially since 2011.[20] The outcomes reported in that initial series may have been influenced by the lack of previous experience with this device, potentially increasing the occurrence of preventable adverse events like infections and technical failures. Many of these issues have now been addressed by process improvements and continued development of the pump system.

This is the largest reported series to date of patients implanted with an alfapump. The most frequently observed device deficiency in this series was obstruction of the peritoneal catheter requiring its exchange (21 events). Only 2 reinterventions were required for issues related to the bladder catheter. Battery charging was a minor issue with 2 chargers being replaced due to technical failure. In this study, reintervention procedures were mostly simple, rapidly performed and associated with a good outcome (Table 6).

Of note, that in the follow-up of patients with covered TIPSS, the reintervention rate due to TIPSS dysfunction or hepatic encephalopathy ranges, according to recent reports, from 7% to

TABLE 3 Disposition at data cut-off

Total enrolled (ITT/safety population)	56
Still on core treatment	3
Completed study (24-month follow-up)	3
Received liver transplant	9
Alfapump system no longer required (spontaneous recovery after anti-viral therapy of HCV with SVR)	1
Withdrawn due to SAE[a]	17
Subsequent death[b]	7
Recovered	7
Outcome unknown	3
Deceased on study	23
Deceased overall	30
Median follow-up, months (range, IQR)	5.8 (0.7-26.4, 3.4-12.9)
Mean follow-up, months (SD)	8.31 (6.7)

[a]Infection (all cause), suspicion of infection, macrohaematuria, sepsis.
[b]Complications linked to liver disease; persistent liver insufficiency; multi-organ failure.

TABLE 4 Causes of death in known mortality

	N	%
Progressive liver disease	15	50
Sepsis/infection	6	20
Renal failure	2	6.7
Post-TIPSS bleeding	1	3.3
Hepatocellular carcinoma	1	3.3
Stroke	1	3.3
Ischaemic heart disease	1	3.3
Perforated diverticulum	1	3.3
Unknown/other	2	6.7
Total[a]	30	100

[a]Includes 7 deaths after subject withdrawal.

42%[18,26,27] depending on the duration of follow-up and technical characteristics of the TIPSS. Moreover, patients with repeat LVP due to RA are regularly seen in out-patient clinics or, depending on the respective country, even require short hospitalisations for the treatment of the ascites. The large number of infections, in particular spontaneous bacterial peritonitis (SBP) that occurred earlier prompted the decision to use prophylactic antibiotics in all patients following implantation.[20] Despite this precaution, bacterial infections occurred in roughly one-third of patients included in the present study. The incidence of infections is, however, similar to estimates of infection rates in cirrhotic patients who are hospitalised (25%-35% in recently published series).[28] In this context, it should be underlined that about 25% of patients in this study had a very advanced stage of liver cirrhosis (Child C), in which bacterial infections are known to occur very often even in the absence of any intervention or device.

TABLE 5 Reasons for pump explantation

Pumps explanted	27
Adverse event/device deficiency	17
Clogged pump	1
Macroscopic haematuria	2
Infection	14
Peritonitis	5
Sepsis or suspicion of infection[a]	5
Pump pocket infection	2
Urinary tract infection	1
Perforated diverticulum	1
Other	10
OLT	9
No longer required[b]	1

[a]No infection subsequently found in 2 patients.
[b]Patient stopped producing ascites due to successful treatment for HCV.

TABLE 6 Outcome of revisional procedures

	Number of procedures (patients)
Reinterventions w/o pump exchange or explantation	23 (17)
Recovered[a]	23 (17)
Died	0 (0)
Unknown	0 (0)
Pump exchange	12 (11)
Recovered[a]	11 (10)
Died	1 (1)
Unknown	0 (0)
Explantation	27 (27)
Recovered	18 (18)
OLT	9 (9)
No more need[b]	1 (1)
SAE, recovered[a]	8 (8)
SAE, died	6 (6)
Unknown	3 (3)

[a]One-month survival.
[b]Patient stopped producing ascites due to successful treatment for HCV.

Nevertheless, some infections were clearly related to the presence of the device and prompted explantation of the pump system. In particular, among the 17 pumps explanted due to SAEs, 2 cases were related to pump pocket infections.

The results of this study show that the automated low-flow ascites pump is effective in decreasing the need for LVP in patients with RA by over 10-fold (from a median of 2.17 per month to 0.17 per month). Most patients treated with this system remained free of LVP and the majority of paracenteses performed after the implantation of the pump system were necessary because of charger or programming issues.

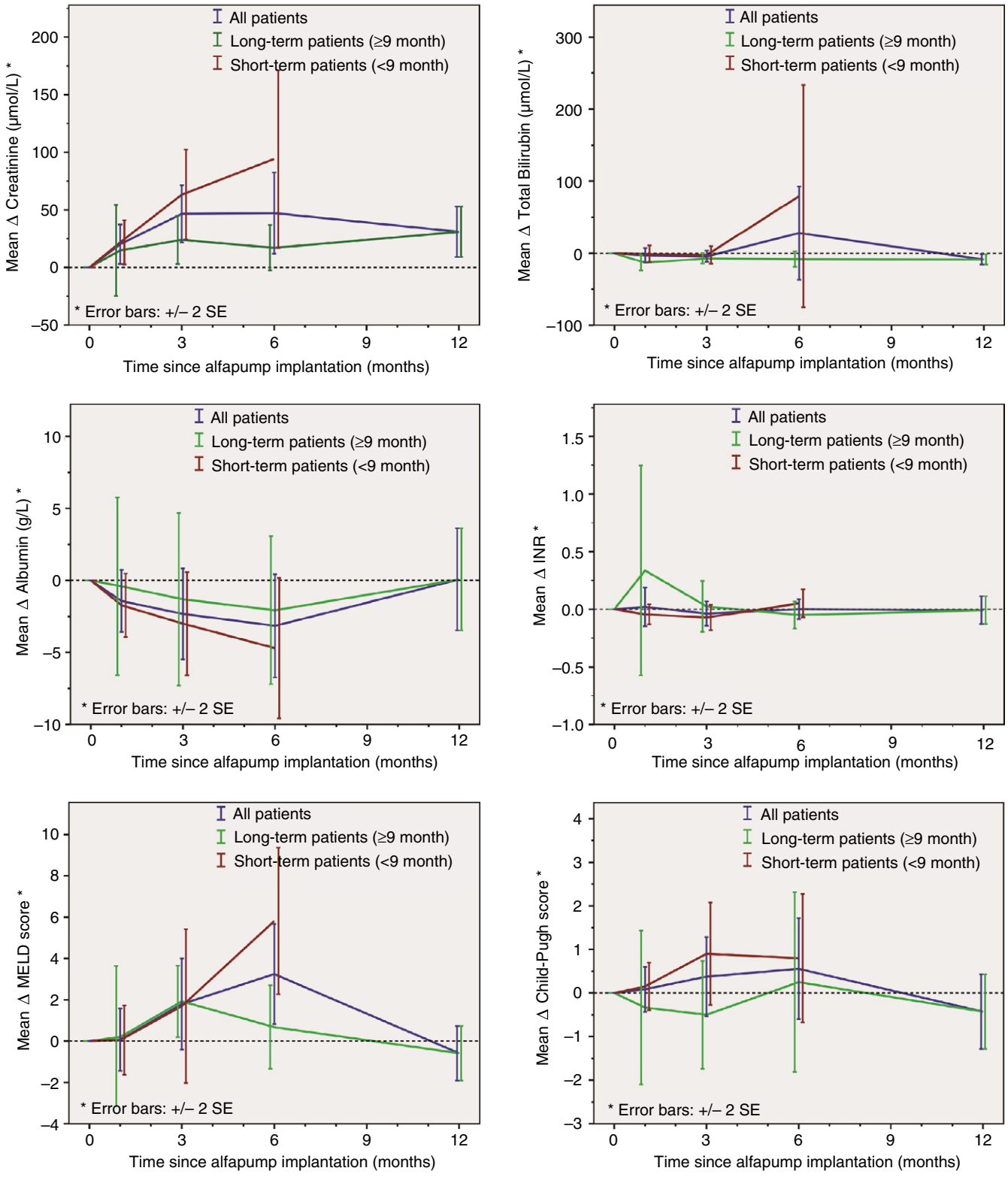

FIGURE 3 Creatinine, bilirubin, albumin, INR, MELD and Child-Pugh scores over time

As for the survival observed in the present study, it is consistent with that of patients undergoing LVP included in recent studies for RA.[2,29,30] To note, our survival data at 6 and 12 months were similar to those of patients treated with LVP in a meta-analysis of trials investigating LVP vs TIPSS for RA.[2] A number of factors associated to a higher risk of mortality may limit the use of TIPSS in patients with RA.[15-17,19,31] They include patient age >60,[32] history of hepatic encephalopathy,[15] and either a platelet count below 75 × 10^9/L or a serum bilirubin >50 μmol l^{-1}, and Child-Pugh C class.[31] The results of a recent study performed by

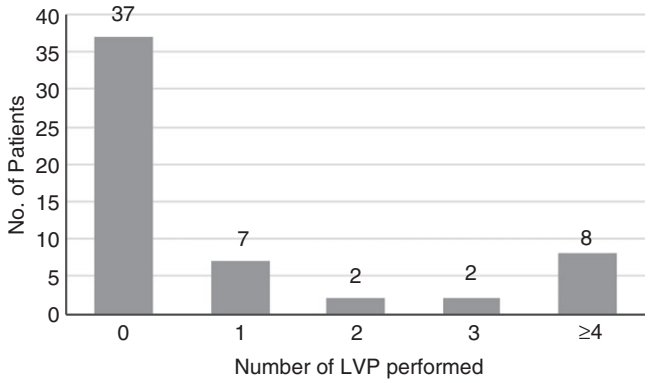

FIGURE 4 Number of LVP performed per patient post alfapump system implant

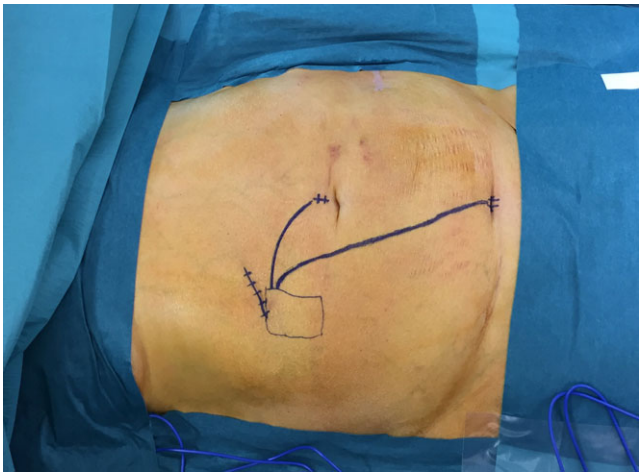

FIGURE 5 Patient with alfapump in situ. For better visibility, pump, catheters and incisions are marked

Luca et al[33] in patients with RA and a MELD score below 12 (associated with a low procedural risk) confirm a high mortality in this population and show that anaemia, MELD score and previous encephalopathy are negative prognostic factors for the use of TIPSS. Therefore, the alfapump may be considered an alternative to LVP in patients with RA for whom TIPSS is contraindicated. In this study, 31 patients (55.3%) were over 60 years old and among those under 60, one-third were Child-Pugh C or had a MELD score of 12 or above.

Clearly, the performance of the alfapump system will require a direct comparison with that of TIPSS. A randomised controlled trial will compare the efficacy and safety of PTFE-covered TIPSS vs alfapump system vs repeated LVP in patients with cirrhosis and RA (NCT02612519).

Regarding the drop of albumin levels after the implantation of the alfapump, it has to be taken into account that prior to the implantation albumin has been replaced on a regular basis in the context of large volume paracenteses. A sub-analysis of albumin levels covering the 6 months prior to the implantation of the pump revealed that 50% of patients with an albumin level greater than 30 g/L at inclusion had levels below 30 g/L during the past 6 months before inclusion (data not shown).

Information on albumin substitution has been collected in the context of paracentesis. Consequently, albumin-related information is restricted to patients with at least 1 paracentesis after the implantation of the alfapump. The decision to administer albumin with the pump system in place was taken on a case by case basis according to the evaluation of each investigator. After the implantation of the pump system, of 31 patients with LVP, 24 received at least one albumin substitution (maximum number of substitutions was 8 in 1 patient), whereas in 7 patients no albumin replacement was reported.

During the follow-up period, we observed a moderate decrease in serum albumin. This decrease can be explained at least partly by the losses through the drained ascites and the gradual reduction in the production of endogenous albumin related to the progression of cirrhosis. Whether this decrease indeed was clinically relevant, cannot be answered based on the available data on albumin.

During the follow-up, we also observed a mild increase in plasma creatinine that was consistent at every time point and had already been reported in the PIONEER study.[20] In the randomised controlled trial reported by Bureau et al,[21] mean creatinine levels were slightly higher in the alfapump treatment arm as well as in the standard of care arm during follow-up compared with baseline, but these differences were neither between nor within groups significant. In the alfapump group, 30 adverse events with acute kidney injury were reported compared to 11 events in the standard of care group. Of the 30 events in the alfapump group, more than 40% occurred during the first week after the implantation of the pump. Kidney function improved over time in more than 70% of patients with acute kidney injury.

The increase in plasma creatinine observed in patients with an alfapump system in place may reflect a decline in glomerular filtration rate, the mechanism of which cannot be ascertained from the current observational study. A combination of a relative depletion of intravascular blood volume in the setting of continuous drainage and hypoalbuminaemia may contribute to explain the findings. The lack of systematic albumin replacement may have aggravated effective hypovolaemia that is known to occur in cirrhosis with ascites. Clearly, future studies should include controlled use of albumin substitution, measurements of plasma renin activity, norepinephrine, and natriuretic peptide to clarify these issues.[34]

For the interpretation of urinalysis, it is crucial to know whether the urine is mixed with ascites or not. A common misinterpretation in patients with an implanted alfapump is severe proteinuria that in facts represents protein originating from the ascitic fluid.

Taking into account that most patients have their pump only during daytime in operation mode, early morning urine can be used for urinalysis. In case of relevant bacteria count in the urine, distinguishing urinary tract infection from bacterial peritonitis might be difficult and diagnostic paracentesis needed for confirmation or exclusion of bacterial peritonitis. In critically ill patients with severely impaired kidney function, the alfapump can be temporarily paused to have a better control of urine output and composition.

The ideal patient for treatment with the alfapump system would be a patient with RA that is otherwise in a relatively good condition, ie presenting in a good nutritional status with normal kidney function, without relevant infection during the last months and a preserved liver function. Taking into account that a contraindication for TIPSS was a prerequisite for this observational study, most patients had more advanced disease with additional cirrhosis-associated complications at baseline like poor nutritional status, a history of SBP, hepatic encephalopathy or hepatorenal syndrome.

Prior to the implantation of the alfapump, the diagnosis of RA should be carefully reviewed by a hepatologist, as many of these patients still have potential for improvement with conservative measures, ie optimisation of nutrition (low salt diet and adequate protein intake, compensation for selective deficits, eg zinc) and diuretic therapy (with a combination of an aldosterone antagonist and a loop diuretic). Optimisation of nutrition is also beneficial for the reduction of perioperative complication what has been shown in several other surgical fields.[35]

Patients with a decreased renal function at baseline are at risk for further deterioration of kidney function after the implantation of the pump system and the decision to implant an alfapump should be taken with caution.

Contraindications for the pump are active infection, especially SBP or urinary tract infection, a life expectancy of less than 3 months, permanent confinement to bed, loculated ascites and urinary outflow tract obstruction, unless treated successfully.

The limitations of this study include its observational design without a direct comparison of the alfapump treatment with other treatments that are considered as the current standard of care. In addition, the long-term management of patients was left to the discretion of the treating physicians and did not follow a predefined protocol that was common for all participating centres, nor did it require that all patients in each centre be enrolled in the registry. However, procedure-related events were collected in a standardised, prospective way. Therefore, the device deficiency data are robust. Quality-of-life data were not collected and the available data on albumin substitution in the context of paracenteses preclude the determination of meaningful correlations with serum albumin. Currently, the pump is marketed in the EU, in Switzerland and in Israel, and the cost for the pump in the EU is 25 000€. Health-related costs, however, were not specifically addressed in this study.

In conclusion, the data presented here show that the alfapump system for the management of patients with RA and contraindications for TIPSS offers good efficacy, leading to an over 10-fold reduction in the need for LVP under real-world conditions. Technical and procedural improvements are required to reduce the rate of adverse events and reinterventions. Optimisation of the system is ongoing, and preliminary results of a new version of the peritoneal catheter show a markedly decreased rate of catheter-related complications. Remaining open issues include the effects on quality of life and liver function and the role of albumin replacement with its effect on relative volume status.

ACKNOWLEDGEMENTS

Declaration of personal interests: Guido Stirnimann has served as a speaker, a consultant and an advisory board member for Sequana Medical AG, Zurich, Switzerland. Thomas Berg has served as a speaker for Sequana Medical AG, Zurich, Switzerland and has received research funding from Sequana Medical AG, Zurich, Switzerland. Andreas Geier has served as a speaker, a consultant and an advisory board member for Sequana Medical AG, Zurich, Switzerland and has received research funding from Sequana Medical AG, Zurich, Switzerland. Cornelius Engelmann has received research funding from Sequana Medical AG, Zurich, Switzerland. Andrea De Gottardi has served as a speaker, a consultant and an advisory board member for Sequana Medical AG, Zurich, Switzerland and has received research funding from Sequana Medical AG, Zurich, Switzerland. Claudia Trepte is an employee of Sequana Medical AG, Zurich, Switzerland. Jeroen Capel is an employee of Sequana Medical AG, Zurich, Switzerland.

AUTHORSHIP

Guarantor of the article: Guido Stirnimann.

Author contributions: ADG, GS, JC: Study concept, design and supervision; GS, TB, LS, SZ, SMP, FL, FS, VB, JB, VV, AG, AS, CE, ADG: acquisition of data; GS, CT, JC, ADG: analysis and interpretation of data; GS, JC, ADG: drafting of the manuscript; TB, LS, SZ, SMP, FL, FS, VB, JB, VV, AG, AS, CE: revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript.

ORCID

G. Stirnimann http://orcid.org/0000-0003-3447-264X
S. McPherson http://orcid.org/0000-0002-5638-2453
A. Stallmach http://orcid.org/0000-0002-6101-5244

REFERENCES

1. Ginès P, Cárdenas A, Arroyo V, Rodés J. Management of cirrhosis and ascites. *N Engl J Med*. 2004;350:1646-1654.
2. Salerno F, Cammà C, Enea M, Rössle M, Wong F. Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data. *Gastroenterology*. 2007;133:825-834.
3. Kim HY, Jang JW. Sarcopenia in the prognosis of cirrhosis: going beyond the MELD score. *World J Gastroenterol*. 2015;21:7637-7647.
4. De Gottardi A, Thévenot T, Spahr L, et al. Risk of complications after abdominal paracentesis in cirrhotic patients: a prospective study. *Clin Gastroenterol Hepatol*. 2009;7:906-909.
5. Pache I, Bilodeau M. Severe haemorrhage following abdominal paracentesis for ascites in patients with liver disease. *Aliment Pharmacol Ther*. 2005;21:525-529.
6. De Pietri L, Bianchini M, Montalti R, et al. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: a randomized, controlled trial. *Hepatology*. 2016;63:566-573.

7. Ruiz-del-Arbol L, Monescillo A, Jimenéz W, Garcia-Plaza A, Arroyo V, Rodés J. Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. *Gastroenterology*. 1997;113:579-586.
8. Ginès A, Fernández-Esparrach G, Monescillo A, et al. Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. *Gastroenterology*. 1996;111:1002-1010.
9. Sola-Vera J, Miñana J, Ricart E, et al. Randomized trial comparing albumin and saline in the prevention of paracentesis-induced circulatory dysfunction in cirrhotic patients with ascites. *Hepatology*. 2003;37:1147-1153.
10. Fagan KJ, Zhao EY, Horsfall LU, et al. Burden of decompensated cirrhosis and ascites on hospital services in a tertiary care facility: time for change? *Intern Med J*. 2014;44:865-872.
11. Rössle M, Ochs A, Gülberg V, et al. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. *N Engl J Med*. 2000;342:1701-1707.
12. Ginès P, Uriz J, Calahorra B, et al. Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. *Gastroenterology*. 2002;123:1839-1847.
13. Sanyal AJ, Genning C, Reddy KR, et al. The North American Study for the treatment of refractory ascites. *Gastroenterology*. 2003;124:634-641.
14. Salerno F, Merli M, Riggio O, et al. Randomized controlled study of TIPS versus paracentesis plus albumin in cirrhosis with severe ascites. *Hepatology*. 2004;40:629-635.
15. Copelan A, Kapoor B, Sands M. Transjugular intrahepatic portosystemic shunt: indications, contraindications, and patient work-up. *Semin Intervent Radiol*. 2014;31:235-242.
16. Garcia-Tsao G. Transjugular intrahepatic portosystemic shunt in the management of refractory ascites. *Semin Intervent Radiol*. 2005;22:278-286.
17. Verna EC. Indications for use of TIPS in treating portal hypertension. *Virtual Mentor*. 2008;10:805-809.
18. Bureau C, Thabut D, Oberti F, et al. Transjugular intrahepatic portosystemic shunts with covered stents increase transplant-free survival of patients with cirrhosis and recurrent ascites. *Gastroenterology*. 2017;152:157-163.
19. Bureau C, Métivier S, D'Amico M, et al. Serum bilirubin and platelet count: a simple predictive model for survival in patients with refractory ascites treated by TIPS. *J Hepatol*. 2011;54:901-907.
20. Bellot P, Welker M-W, Soriano G, et al. Automated low flow pump system for the treatment of refractory ascites: a multi-center safety and efficacy study. *J Hepatol*. 2013;58:922-927.
21. Bureau C, Adebayo D, de Chalret Rieu M, et al. Alfapump® system vs. large volume paracentesis for refractory ascites: a multicenter randomized controlled study. *J Hepatol*. 2017; https://doi.org/10.1016/j.jhep.2017.06.010 [Epub ahead of print].
22. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010;53:397-417.
23. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol*. 2005;43:167-176.
24. Stirnimann G, Banz V, Storni F, de Gottardi A. Automated low-flow ascites pump for the treatment of cirrhotic patients with refractory ascites. *Therap Adv Gastroenterol*. 2017;10:283-292.
25. Angeli P, Ginès P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol*. 2015;62:968-974.
26. Tan HK, James PD, Sniderman KW, Wong F. Long-term clinical outcome of patients with cirrhosis and refractory ascites treated with transjugular intrahepatic portosystemic shunt insertion. *J Gastroenterol Hepatol*. 2015;30:389-395.
27. Hayek G, Ronot M, Plessier A, et al. Long-term outcome and analysis of dysfunction of transjugular intrahepatic portosystemic shunt placement in chronic primary Budd-Chiari syndrome. *Radiology*. 2017;283:280-292.
28. Jalan R, Fernandez J, Wiest R, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. *J Hepatol*. 2014;60:1310-1324.
29. Narahara Y, Kanazawa H, Fukuda T, et al. Transjugular intrahepatic portosystemic shunt versus paracentesis plus albumin in patients with refractory ascites who have good hepatic and renal function: a prospective randomized trial. *J Gastroenterol*. 2011;46:78-85.
30. Gaba RC, Parvinian A, Casadaban LC, et al. Survival benefit of TIPS versus serial paracentesis in patients with refractory ascites: a single institution case-control propensity score analysis. *Clin Radiol*. 2015;70:e51-e57.
31. Lebrec D, Giuily N, Hadengue A, et al. Transjugular intrahepatic portosystemic shunts: comparison with paracentesis in patients with cirrhosis and refractory ascites: a randomized trial. French Group of Clinicians and a Group of Biologists. *J Hepatol*. 1996;25:135-144.
32. Sanyal AJ, Freedman AM, Shiffman ML, Purdum PP III, Luketic VA, Cheatham AK. Portosystemic encephalopathy after transjugular intrahepatic portosystemic shunt: results of a prospective controlled study. *Hepatology*. 1994;20:46-55.
33. Luca A, Miraglia R, Maruzzelli L, D'Amico M, Tuzzolino F. Early liver failure after transjugular intrahepatic portosystemic shunt in patients with cirrhosis with model for end-stage liver disease score of 12 or less: incidence, outcome, and prognostic factors. *Radiology*. 2016;280:622-629.
34. Bernardi M, Ricci CS, Zaccherini G. Role of human albumin in the management of complications of liver cirrhosis. *J Clin Exp Hepatol*. 2014;4:302-311.
35. Abbas N, Makker J, Abbas H, Balar B. Perioperative care of patients with liver cirrhosis: a review. *Heal Serv Insights*. 2017;10:1178632917691270.

SUPPORTING INFORMATION

Additional Supporting Information will be found online in the supporting information tab for this article.

How to cite this article: Stirnimann G, Berg T, Spahr L, et al. Treatment of refractory ascites with an automated low-flow ascites pump in patients with cirrhosis. *Aliment Pharmacol Ther*. 2017;46:981-991. https://doi.org/10.1111/apt.14331

APPENDIX 1

AUTHORS' COMPLETE AFFILIATIONS

Guido Stirnimann and Andrea De Gottardi, Hepatology, University Clinic for Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; Thomas Berg and

Cornelius Engelmann, Section Hepatologie, Department for Gastroenterology and Rheumatology, University Hospital Leipzig, Leipzig, Germany; Laurent Spahr, Department of Medical Specialties, Service of Gastroenterology, Geneva University Hospitals, Geneva, Switzerland; Stefan Zeuzem, Department of Medicine, University Hospital, Frankfurt, Germany; Stuart McPherson, Liver Unit, Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK; Frank Lammert, Department of Medicine II, Saarland University Medical Center, Homburg, Germany; Federico Storni and Vanessa Banz, Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland; Jana Babatz, Medizinische Klinik I, Universitätsklinikum Carl Gustav Carus, Dresden, Germany; Victor Vargas, Liver Unit, Hospital Vall d'Hebron, Universitat Autònoma Barcelona, CIBERehd, Barcelona, Spain; Andreas Geier, Division of Hepatology, Department of Medicine II, University Hospital Würzburg, Würzburg, Germany; Andreas Stallmach, Klinik für Innere Medizin IV (Gastroenterologie, Hepatologie und Infektiologie), Universitätsklinikum Jena, Jena, Germany; Claudia Trepte and Jeroen Capel, Sequana Medical AG, Zurich, Switzerland.