NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of subcutaneous automated low-flow pump implantation for refractory ascites caused by cirrhosis

Long-term liver damage (cirrhosis) can cause fluid build-up in the abdomen (ascites). This can lead to poor appetite, fatigue, difficulty in breathing and infection. In this procedure, a battery-powered low-flow pump is put under the skin. It is connected to the abdomen and bladder by 2 tubes, and the battery is charged using wireless technology. The aim is to pump excess fluid from the abdomen to the bladder where it is passed in the urine.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in March 2018.

Procedure name

- Subcutaneous automated low-flow pump implantation for refractory ascites caused by cirrhosis.

Specialist societies

- British Society of Gastroenterology (BSG)
- Association of Upper Gastrointestinal Surgeons (AUGIS)
- BASO - The Association for Cancer Surgery
- Royal College of Surgeons
- The Royal College of Physicians.

Description of the procedure

Indications and current treatment

Ascites is a common complication of cirrhosis of the liver. Build-up of fluid causes the abdomen to swell and may lead to discomfort, difficulty breathing, fatigue, nausea and poor appetite.

Treatment is usually diuretics and advice about dietary sodium restriction. For refractory ascites, treatment options include large-volume paracentesis, albumin infusion and insertion of a transjugular intrahepatic portosystemic shunt. These procedures may be used to support a patient who is waiting for a liver transplant.

What the procedure involves

Subcutaneous automated low-flow pump implantation for refractory ascites is usually done with the patient under general anaesthesia, typically through 3 small incisions in the abdominal wall. A battery-powered pump with internal pressure sensors is implanted on the right side above the belt line. One catheter connects the pump to the peritoneal cavity, and another connects it to the urinary bladder. The pump and both catheters are secured with sutures to prevent migration. The pump removes fluid from the peritoneal cavity through the first catheter, and puts it into the bladder through the second catheter. The fluid is eliminated through normal micturition. The pump is programmed to remove pre-set daily volumes of fluid, and the pressure sensors prevent it from over-distending the bladder.

A clinician programs the pump wirelessly using an external handheld charging device, according to the needs of the patient (based on previous large-volume paracentesis requirements, observed

accumulation of ascites and body weight). The hand-held device is also used by the patient to charge the pump wirelessly, by holding it above the pump for about 30 minutes each day. The hand-held device collects data sent by the pump, which are downloaded to a computer for review by the clinician. Anonymised data are sent to the manufacturer, which sends a report to the clinician with a detailed analysis of the data and any recommendations.

The aim of the procedure is to avoid the accumulation of fluid, abdominal swelling and accompanying complications.

Outcome measures

Chronic Liver Disease Questionnaire (CLDQ)

The CLDQ is a disease-specific questionnaire that was designed and validated to measure health-related quality of life in patients with chronic liver disease. It has 29 items, grouped into 6 domains: abdominal symptoms, activity, emotional function, fatigue, systemic symptoms, and worry. The total CLDQ score is the average of the 6 domain scores, which all range from 1 to 7. Higher scores indicate a better quality of life.

Efficacy summary

Reduction in need for large volume paracentesis

In a randomised controlled trial (RCT) of 58 patients, the time to first large volume paracentesis (LVP) was statistically significantly longer in patients who had a low-flow pump implanted compared with patients who had standard of care. Median time to first LVP was not reached after 6 months in the low-flow pump group compared with 15 days in the standard of care group (hazard ratio 0.13, 95% confidence interval [CI] 0.06 to 0.28, p<0.001). The median number of LVPs was statistically significantly higher in the standard of care group compared with the pump group (risk ratio 7.7, 95% CI 3.6 to 16.7, p<0.001). During the 6 months of follow-up, 37% (10/27) of patients with a pump needed LVP compared with 90% (28/31) in the standard of care group. [1] In a case series of 56 patients, the mean number of LVPs decreased from 2.88 per month at baseline to 0.28 per month after a pump was implanted. 66% (37/56) of patients did not need any LVP after the procedure, with a mean follow-up of 8 months. [3] In a case series of 40 patients with 6-month follow-up, there was a statistically significant decrease in the median number of LVPs, from 3.4 at baseline to 0.24 after the pump was implanted (p<0.01). 40% of patients did not need LVP after the procedure. [4] In a case series of 10 patients, 4 did not need LVP after a pump was implanted. The mean number of LVPs per patient decreased from 7.5 in the 3 months before the pump was implanted to 1.8, 3.7, 3.2 and 2.4 at 0 to 3 months, 3 to 6 months, 6 to 9 months and 9 to 12 months after the procedure respectively. [5] In another case series of 10 patients, the mean number of LVPs per month was 3.36 before the pump was implanted and 0.45 at 60-day follow-up (p<0.0001). [6]

Quality of life

In the RCT of 58 patients there were improvements in some aspects of health-related quality of life in patients who had a pump, including statistically significant improvements in the Chronic Liver Disease Questionnaire (CLDQ) abdominal symptom and systemic symptom scores ($p<0.05$ at 1-month follow-up compared with baseline). There were statistically significant deteriorations in the short-form 36 (SF-36) score for bodily pain and physical component summary and the CLDQ score for fatigue in patients who had standard of care ($p\leq0.05$ at 1-month follow-up compared with baseline). At 3-month follow-up, the mean change in the total CLDQ score was statistically significantly higher in the pump group compared with standard of care (0.5 compared with -0.1, $p<0.05$). In multivariate analysis, pump implantation was independently associated with higher health-related quality of life scores, after adjustment for baseline level and other predictors. The scores that were statistically significantly higher ($p\leq0.05$) in the pump group included bodily pain (SF-36), vitality (SF-36), abdominal symptoms (CLDQ), activity (CLDQ), fatigue (CLDQ) and systemic symptoms (CLDQ). [1,2]

Survival

In the RCT of 58 patients, there was no statistically significant difference in overall survival between the patients who had a pump implanted and those who had standard of care ($p=0.355$). [1] In the case series of 56 patients, mean actuarial survival was 12.8 months (95% CI 10.0 to 15.7) and median survival was 9.8 months.[3]

Duration of function

In the RCT of 58 patients with 6 months of follow-up, 67% of implanted pumps functioned without reintervention until study completion, withdrawal or death.[1] In the case series of 56 patients, 21% (17/56) of patients needed at least 1 reintervention during a mean follow-up of 8 months and 11 patients had a surgical pump replacement.[3] In 1 of the case series of 10 patients, long-term follow-up data (1 year or more) were available for 3 patients; in all these patients, the pump stopped working between 2 and 3 years after implantation.[5] In the other case series of 10 patients, 5 pumps were functioning at the end of follow-up (median 165 days, range 23 to 379) and 5 were non-functioning or explanted because of technical failure (n=1), death with functioning pump (n=3), or transplantation (n=1).[6]

Safety summary

Renal and urinary

Serious renal and urinary adverse events were reported in 52% (14/27) of patients who had pump implantation and 10% (3/31) of patients who had standard of care ($p<0.001$) in an RCT of 58 patients. 41% (12/29) of acute kidney injury adverse events in the pump group occurred in the first 7 days after implant, and were transient (10 patients fully recovered and 2 improved).[1] Renal dysfunction was reported in 33% (13/40) of patients in a case series of 40 patients; all were treated successfully except 1 patient who died of acute renal failure on day 54 and 1 patient who died of hepatorenal syndrome on day 147.[4] Acute kidney injury was reported in 40% (4/10) of patients within the first 7 days after pump implantation and in 60% (6/10) of patients during follow-up in a case series of 10 patients. This included 1 patient with urinary peritonitis because of bladder perforation. [5] Acute

renal failure and hepatic-renal syndrome were reported in 30% (3/10) and 20% (2/10) of patients respectively in another case series of 10 patients. [6]

Macroscopic haematuria was reported in 2 patients in a case series of 56 patients: the pump was removed in both patients.[3] Haematuria because of catheter friction with the bladder wall was reported in 1 of 3 patients who had a working system for a year or more in 1 of the case series of 10 patients; the pump was removed.[5]

Decrease in serum albumin

The fall in albumin over time was statistically significantly greater in the pump group than the standard of care group at days 60, 90, and 180 in the RCT of 58 patients. Patients in the pump group received less total albumin during the study than the standard of care group; it was given predominantly for renal insufficiency.[1] The mean decrease in serum albumin was 1.4, 2.3 and 3.2 g/litre at 1, 3 and 6 months respectively in the case series of 56 patients; this effect was less pronounced in long-term survivors.[3] Serum albumin decreased from 31.9 g/litre at baseline to 28.2 g/litre at 3-month follow-up (n=31) and 27.2 g/litre at 6-month follow-up (n=14) in the case series of 40 patients.[4]

Hepatic encephalopathy

Hepatic encephalopathy was reported in 43% (17/40) and 60% (6/10) of patients in the case series of 40 and 10 patients respectively.[4,5] Hepatobiliary disorders were reported in 15% (4/27) of patients who had a pump implanted and 10% (3/31) of patients who had standard of care (p=0.694) in the RCT of 58 patients.[1]

Infection

Infections were reported in 33% (9/27) of patients who had pump implantation and 26% (8/31) of patients who had standard of care (p=0.574) in the RCT of 58 patients. One patient in the pump group, with a severely infected diabetic foot needing amputation, developed septic shock and died 52 days after pump implantation. Three patients needed to have the pump removed because of infection: 1 spontaneous bacterial peritonitis, cellulitis and urinary tract infection, 1 pocket haematoma and abscess and 1 urinary tract infection and wound dehiscence.[1] Infection needing pump removal was reported in 25% (14/56) of patients in the case series of 56 patients (5 peritonitis, 5 sepsis or suspicion of infection, 2 pump pocket infections, 1 urinary tract infection and 1 perforated diverticulum). One patient died 2 weeks after a pump was exchanged because of a pump pocket infection.[3] Infection was reported in 60% (24/40) of patients in the case series of 40 patients: 7 patients had their pumps removed because of difficult-to-treat infections and 1 patient had an emergency removal because of wound dehiscence. There were 3 deaths caused by sepsis.[4] Urinary tract infection and persistent bacterial peritonitis were reported in 50% (5/10) and 20% (2/10) of patients respectively in 1 of the case series of 10 patients. Spontaneous bacterial peritonitis, ascitic fluid colonisation by *Candida glabrata*, catheter-associated bacteraemia, septic shock, pseudomembranous colitis and abdominal skin infection around the subcutaneous pocket were each reported in 1 patient in the same study. Six patients were admitted to hospital because of bacterial infections, with a mean stay of 48 days per patient, and 2 patients had their pumps removed because of infection.[5] Surgical site infection was reported in 2 patients (treated by surgical wound

debridement) and pump pocket infection was reported in 1 patient (pump was removed) in the other case series of 10 patients.[6]

Subcutaneous abscess in the hypogastric area in relation to the bladder catheter was reported in 1 of the 3 patients who had a working system for 1 year or more in the case series of 10 patients; the pump was removed.[5]

Mortality

Mortality was 19% (5/27) in patients who had pump implantation and 13% (4/31) in patients who had standard of care in the RCT of 58 patients.[1] Overall mortality was 54% (30/56) in the case series of 56 patients. Causes of death were progressive liver disease (n=15), sepsis or infection (n=6), renal failure (n=2), bleeding after transjugular intrahepatic portosystemic shunt (n=1), hepatocellular carcinoma (n=1), stroke (n=1), ischaemic heart disease (n=1), perforated diverticulum (n=1) and other or unknown (n=2).[3] Mortality was 20% (8/40) in the case series of 40 patients. Causes of death were sepsis (n=3), progressive liver insufficiency (n=2), acute renal failure (n=1), hepatorenal syndrome (n=1) and unknown (n=1).[4] Mortality during the 12-month study period was 50% (5/10) in 1 of the case series of 10 patients (3 acute-on-chronic liver failure, 1 refractory gastrointestinal bleeding and 1 liver failure). In addition, 1 patient died 4 months after the end of the study period because of acute-on-chronic liver failure associated with sepsis.[5] Mortality was 30% (3/10) in the other case series of 10 patients: 1 patient died from acute pancreatitis on postoperative day 235 and 2 patients died from hepatorenal failure on postoperative days 30 and 119.[6]

Gastrointestinal disorders

Serious gastrointestinal adverse events were reported in 26% (7/27) of patients who had pump implantation and 7% (2/31) of patients who had standard of care in the RCT of 58 patients (p=0.068).[1]

Metabolism and nutrition disorders

Metabolism and nutrition disorders were reported in 15% (4/27) of patients who had pump implantation and in 1 patient who had standard of care in the RCT of 58 patients (p=0.173).[1] Hyponatraemia was reported in 50% (5/10) of patients in 1 of the case series of 10 patients.[5]

Device malfunction

System component replacement or repositioning was reported in 22% (6/27) of patients who had a pump implanted in the RCT of 58 patients.[1] Device removal because of a clogged pump was reported in 1 patient in the case series of 56 patients. Bladder catheter dislocation and peritoneal catheter issues were each reported in 13% (5/40) of patients in the case series of 40 patients. Prolapse of the bladder catheter into the urethra was reported in 8% (3/40) of patients and 1 bladder catheter became kinked and needed repair. Pump malfunction was reported in 5% (2/40) of patients in the same study.[4] Device-related complications were reported in 70% (7/10) of patients in 1 of the case series of 10 patients. These included: replacement of peritoneal catheter (n=2), pump removal because of infection (n=2), reposition of migrated peritoneal catheter (n=1), pump replacement (n=1), peritoneal catheter migration without replacement (n=1), skin erosion because of peritoneal catheter (n=1),

transient pump dysfunction (n=2), smart charger dysfunction (n=1) and technical problems with device charging (n=1).[5] Kinking of the bladder catheter was reported in 1 patient in the other case series of 10 patients.[6]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers described the following anecdotal adverse events: sepsis, leakage when pumps are put in using a radiological insertion technique, and the need for periodic albumin infusions to maintain renal function long-term. They considered that the following were theoretical adverse events: intraperitoneal erosion of the pump and bladder leaks.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to subcutaneous automated low-flow pump implantation for refractory and recurrent ascites. The following databases were searched, covering the period from their start to 1 March 2018: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy for details). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with refractory ascites caused by cirrhosis.
Intervention/test	Subcutaneous automated low-flow pump implantation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 177 patients from 1 randomised controlled trial (included as 2 studies because the quality of life data were reported separately in a later publication) and 5 case series.[1–7]

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in the appendix.

Table 2 Summary of key efficacy and safety findings on subcutaneous automated low-flow pump implantation for refractory ascites caused by cirrhosis

Study 1 Bureau C (2017) and Study 2 Stepanova M (2018)

Details

Study type	**Randomised controlled trial**
Country	UK, France, Austria, Spain, Italy
Recruitment period	2012 to 2016
Study population and number	**n=58** (27 automated low-flow pump, 31 large volume paracentesis) **Patients with refractory ascites caused by cirrhosis.**
Age and sex	• Automated low-flow pump: mean age 61 years; 78% (21/27) male • Large volume paracentesis: mean age 63 years; 81% (25/31) male
Patient selection criteria	Males and non-pregnant females age 18 years or over with liver cirrhosis (based upon histological features, ultrasound, or clinical signs including ascites, hepatic encephalopathy, thrombocytopaenia, and splenomegaly) and refractory ascites needing periodic large volume paracentesis (5 litres or more) and albumin administration. Patients needed to demonstrate willingness to comply with study procedures and the ability to operate the device. Centres were advised not to enrol patients who were eligible for transjugular intrahepatic portosystemic shunt (TIPS).
Technique	• Automated low-flow pump: The alfapump system (Sequana Medical, Switzerland) was used. Pump parameters such as the targeted daily pump volume and the time of day during which the pump is active were adjusted as necessary. Fluid transport by the pump was monitored remotely. Initial pump settings were estimated from the patient's paracentesis history and subsequently modified based on patient weight and volume of ascitic fluid present. Patients were offered antibiotic prophylaxis throughout the study period. Diuretic therapy was discontinued after pump implantation and restarted at the investigator's discretion if needed. 44% (12/27) of the procedures were laparoscopic and 56% (15/27) were open. • Large volume paracentesis: procedure was carried out as required. Patients maintained their diuretic therapy regimen; changes to dosages were allowed at investigator discretion, but were reduced or stopped in case of diuretic-related complications. Abstinence from alcohol and controlled salt intake were recommended in both groups throughout the study.
Follow-up	**6 months**
Conflict of interest/source of funding	Study was sponsored by Sequana Medical, Switzerland.

Analysis

Follow-up issues: An additional 2 patients were randomised and allocated to the low-flow pump group, but they did not have the allocated treatment (1 patient had obstructive uropathy and 1 had a left inguinal hernia). One patient in the control group was lost to follow-up. 37% (10/27) of patients in the low-flow pump group discontinued treatment (2 because of adverse events, 3 patients had liver transplants and 5 patients died). 29% (9/31) of patients in the control group discontinued their intervention (4 patients died, 2 withdrew consent and 3 patients had liver transplants).

Study design issues: Prospective, multicentre, open-label, randomised controlled trial. Patients were randomised to a treatment group by a centralised computer-generated method. A sample size of 56 patients was calculated to give 90% power. The primary endpoint was time to first large volume paracentesis. Secondary endpoints included overall paracentesis requirement, overall safety including renal injury and infections, a disease-specific health-related quality of life instrument (Chronic Liver Disease Questionnaire), and survival. A sub-study of 18 randomly selected patients assessed nutrition, haemodynamics and renal injury biomarkers at 3 months.

Study population issues: There were no statistically significant differences between the 2 treatment groups with regard to baseline characteristics and patient demographics.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **58 (27 versus 31)**

The time to first large volume paracentesis (LVP) was statistically significantly longer in the low-flow pump group compared with standard of care. Median time to first LVP was not reached after 6 months in the low-flow pump group compared with 15 days in the standard of care group (hazard ratio 0.13, 95% CI 0.06 to 0.28, p<0.001).
The median number of LVPs was statistically significantly higher in the standard of care group compared with the low-flow pump group (risk ratio 7.7, 95% CI 3.6 to 16.7, p<0.001).

Proportion of patients who needed LVP:

- Low-flow pump=37% (10/27)
- Standard of care=90% (28/31)

Nutritional parameters (sub study)

Parameter	Baseline		Day 30		Day 90	
	Pump	control	Pump	control	pump	control
Hospital general assessment, n (%)						
Adequately nourished	2 (25.0)	4 (50.0)	4 (50.0)	4 (50.0)	4 (66.7)	3 (50.0)
Moderately malnourished	5 (62.5)	2 (25.0)	4 (50.0)	2 (25.0)	2 (33.3)	1 (16.7)
Severely malnourished	1 (12.5)	2 (25.0)	0 (0)	2 (25.0)	0 (0)	2 (33.3)
p value				0.099		0.090
BMI (kg/m^2), n			7	8	6	7
Adjusted change*			1.237	-0.145	1.992	-0.650
p value				0.056		<0.001
TSF (mm), n			7	8	6	6
Adjusted change*			0.466	-0.432	1.898	-0.848
p value				0.137		0.003
MAMC (cm), n			7	8	6	6
Adjusted change*			0.89	-0.24	1.80	0.16
p value				0.010		0.008
Hand grip (kg), n			7	8	6	6
Adjusted change*			2.44	0.84	4.03	-1.69
p value				0.447		0.044

* mean change from baseline adjusted for the baseline mean by an analysis of covariance

Survival
There was no statistically significant difference in overall survival between the groups (p=0.355). 6 patients in the pump group and 4 in the

Safety

Treatment emergent adverse events (TEAE)

	Pump n=27	Control n=31	p value
Patients with ≥1 TEAE, n (%)	26 (96.3)	24 (77.4)	0.057
Total number of TEAEs, n	199	97	
Mean number of TEAEs/patient	7.4	3.1	
Patients with ≥1 serious TEAE, n (%)	23 (85.2)	14 (45.2)	0.002
Number of serious TEAEs, n	64	27	
Mean number of serious TEAEs/patient	2.4	0.9	

Summary of patients with treatment emergent serious adverse events, n (%)

	Pump n=27	Control n=31	p value
Blood and lymphatic system	1 (3.7)	0	0.466
Cardiac	0	1 (3.2)	1.0
Gastrointestinal	7 (25.9)	2 (6.5)	0.068
General disorders and administration site conditions	4 (14.8)	1 (3.2)	0.173
Hepatobiliary	4 (14.8)	3 (9.7)	0.694
Infections and infestations	9 (33.3)	8 (25.8)	0.574
Injury, poisoning and procedural complications	3 (11.1)	0	0.095
Investigations	0	1 (3.2)	1.0
Metabolism and nutrition disorders	4 (14.8)	1 (3.2)	0.173
Nervous system	6 (22.2)	1 (3.2)	0.042
Psychiatric	1 (3.7)	0	0.466
Renal and urinary	14 (51.9)	3 (9.7)	<0.001

control group died during the 6-month study period. Causes of death were consistent with advanced liver disease.

Overall, 66.6% of implanted systems functioned without reintervention until study completion, withdrawal or death.

Health-related quality of life

Mean changes in health-related quality of life scores from baseline to 1 month follow-up (n=55, values estimated from graphical presentation)

Mean change in Short-Form-36 (SF-36) version 2 scores (range 0 to 100)			
	Pump	control	p
Physical functioning	3	-4	NR
Role physical	4	-3	NR
Bodily pain	2	-10*	≤0.05
General health	7	-1	<0.10
Vitality	3	-2	NR
Social functioning	2	1	NR
Role emotional	12	1	NR
Mental health	-2	3	NR
Physical summary	2	-3*	≤0.05
Mental summary	2	2	NR
Mean change in Chronic Liver Disease Questionnaire scores (CLDQ, range 1 to 7)			
	Pump	control	p
Abdominal	1.0*	-0.05	<0.05
Activity	0.2	-0.4	<0.10
Emotional	0.05	0.25	NR
Fatigue	0.1	-0.6*	≤0.05
Systemic	0.6*	-0.3	<0.05
Worry	0.3	0.2	NR
Total CLDQ	0.4	-1.5	<0.10

*p<0.05 compared with baseline

Mean changes at 3 month follow-up (n=49)

Mean change in SF-36 version 2 scores (range 0 to 100)			
	Pump	control	p
Physical functioning	0.05	-4	NR
Role physical	10	-3	<0.05
Bodily pain	11	-9	<0.05
General health	3	-2.5	NR
Vitality	7.5	-5	NR
Social functioning	5	0	NR
Role emotional	7.5	-5	NR
Mental health	-3	-1	NR
Physical summary	3	-2	NR
Mental summary	1	0	NR
Mean change in CLDQ scores (CLDQ, range 1 to 7)			
	Pump	control	p
Abdominal	1.25	0.15	<0.05
Activity	0.8	-0.5	<0.05
Emotional	-0.05	0.25	NR
Fatigue	0.35	-0.6	<0.05
Systemic	0.4	-0.05	NR
Worry	0.3	0.15	NR
Total CLDQ	0.5	-0.1	<0.05

Respiratory, thoracic and mediastinal	1 (3.7)	0	0.466

Summary of acute kidney injury (including renal insufficiency and hepatorenal syndrome)

	Acute kidney injury all		Acute kidney injury >7 days after implant	
	Pump	control	pump	control
Total events	30*	11	17	11
Events/ patient, mean	1.07	0.35	0.63	0.35
Events/ patient, range	0 to 3	0 to 5	0 to 3	0 to 5
p value		0.007		0.281

*There is a discrepancy in the reported number of total events in the paper (the text reports 29 events and the table reports 30 events).

The paper states that 41.3% (12/29) of acute kidney injury adverse events in the pump group occurred in the first 7 days after implant, and were transient (10 patients fully recovered and 2 improved).

One patient in the pump group with alcoholic liver disease and a history of hepatic encephalopathy died of end-stage liver disease and liver failure 52 days after implantation. This was caused by septic shock and consequent acute kidney injury that occurred on the background of a severely infected diabetic foot needing amputation.

Infection (number of events)

- Pump=25 (23 fully recovered, 1 recovered with sequelae, 1 died [sepsis])
- Control=30 (26 fully recovered, 3 were ongoing or outcome unknown, 1 died [spontaneous bacterial peritonitis]).

One patient had the pump removed on day 8 because of infection and needed 7 post-explant LVPs.

Serum albumin

The fall in albumin over time was statistically significantly greater in the low-flow pump group than standard of care at days 60, 90, and 180. Patients in the pump group received less total albumin during the study than the standard of care group; it was given predominantly for renal insufficiency.

In multivariate analysis, low-flow pump implantation was independently associated with higher health-related quality of life scores, after adjustment for baseline level and other predictors. The scores that were statistically significantly higher (p≤0.05) in the pump group included bodily pain (SF-36), vitality (SF-36), abdominal symptoms (CLDQ), activity (CLDQ), fatigue (CLDQ) and systemic symptoms (CLDQ). There were not enough patients left in the study to reliably report health-related quality of life at 6 month follow-up (n=28).	**Reintervention** Of the 27 patients who had a low-flow pump implanted, 12 (44.4%) had at least 1 device deficiency. 6 patients needed system component replacement or repositioning and 3 needed system explant (1 spontaneous bacterial peritonitis, cellulitis and urinary tract infection, 1 pocket haematoma and abscess, and 1 urinary tract infection, pocket abscess and wound dehiscence). All recovered fully.
Abbreviations used: CI, confidence interval; CLDQ, chronic liver disease questionnaire; LVP, large volume paracentesis; MAMC, mid arm muscle circumference; NR, not reported; SF-36, short-form 36; TEAE, treatment emergent adverse events; TSF, tricipital skin fold thickness.	

Study 3 Stirnimann G (2017)

Details

Study type	**Case series**
Country	Germany, Spain, Switzerland, UK (10 centres)
Recruitment period	Not reported
Study population and number	**n=56** **Patients with cirrhosis and refractory ascites.**
Age and sex	Mean 62 years; 77% (43/56) male
Patient selection criteria	Patients with cirrhosis and refractory ascites, with contraindications to transjugular intrahepatic portosystemic shunt. Refractory ascites was defined as diuretic-resistant or diuretic-intractable or as early recurrence of ascites after paracentesis. Inability to operate the charging system was considered an exclusion criteria.
Technique	The alfapump system (Sequana Medical, Switzerland) was used. The day before pump implantation, a large volume paracentesis was done to void the abdominal cavity. Long-term antibiotic prophylaxis was offered to all patients after the procedure. Albumin administration was left to the discretion of the individual investigators, according to current treatment guidelines.
Follow-up	**Mean 8 months (range 0.7 to 26.4)**
Conflict of interest/source of funding	Study was funded in full by Sequana Medical, Switzerland. The preparation of the paper was funded in part by Sequana Medical, Switzerland. Writing support for a previous version of the manuscript was provided by 2 people from medicalwriters.com and funded by Sequana Medical, Switzerland.

Analysis

Follow-up issues: Patients were followed up for at least 12 months. At the time of analysis, 3 patients had completed the study to 24 month follow-up, 3 patients were still on core treatment, 9 patients had a liver transplant and 17 patients had been withdrawn because of serious adverse events.

Study design issues: Prospective, multicentre, observational study. Information about large volume paracentesis, 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 quality of life data were collected.

Study population issues: The median duration of ascites before the procedure was 11 months (range 8 to 19) with a median frequency of large volume paracenteses over the previous 3 months of 2.17 per month.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 56

Mean actuarial survival=12.8 months (95% CI 10.0 to 15.7)
Median survival=9.8 months

Paracentesis requirements and ascites volume removed
<table>
<tr><th></th><th>Baseline</th><th>After procedure</th></tr>
<tr><td colspan="3">Paracentesis frequency per month, mean (SD, range), n=48</td></tr>
<tr><td>Mean (SD, range)</td><td>2.88 (1.81, 0.5 to 10.1)</td><td>0.28 (0.34, 0 to 1.2)</td></tr>
<tr><td>Median (IQR)</td><td>2.17 (1.45 to 4.34)</td><td>0.17 (0 to 0.41)</td></tr>
<tr><td colspan="3">Paracentesis volume (litres per month), n=45</td></tr>
<tr><td>Mean (SD, range)</td><td>19.3 (11.6, 3.9 to 53.2)</td><td>1.22 (1.67, 0 to 5.6)</td></tr>
<tr><td>Median (IQR)</td><td>16.3 (10.1 to 26.1)</td><td>0.41 (0 to 2.1)</td></tr>
</table>
Average volume removed by pump per patient=mean 884 ml/day (range 50 to 2051)

Average volume removed by pump per month=mean 26.5 litres per month (range 1.5 to 61.5)

66.1% (37/56) of patients did not need any large volume paracentesis after the procedure.

Of 127 paracenteses after the procedure, 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 paracenteses were necessary because of technical issues with the charger or insufficient charging, because the programmed pumping volume was too low, or for unknown reasons in patients with normal pump function.

Reinterventions and pump exchanges
21.4% (17/56) of patients needed at least 1 reintervention (23 interventions in total) and 11 patients had a surgical pump replacement.
</td><td>
Adverse event or device deficiency needing pump explantation (n=17)

Clogged pump=1
Macroscopic haematuria=2
Infection=14

Peritonitis=5
Sepsis or suspicion of infection=5 (no infection subsequently found in 2 patients)
Pump pocket infection=2
Urinary tract infection=1
Perforated diverticulum=1

Of the 17 patients who had their pumps removed because of serious adverse events, 8 recovered (1-month survival), 6 died and the outcome for 3 patients was unknown.

One patient died 2 weeks after a pump exchange. The pump had to be explanted 1 week after the exchange because of a pump pocket infection.

Overall mortality=53.6% (30/56) (15 progressive liver disease, 6 sepsis or infection, 2 renal failure, 1 bleeding after transjugular intrahepatic portosystemic shunt, 1 hepatocellular carcinoma, 1 stroke, 1 ischaemic heart disease, 1 perforated diverticulum, 2 other or unknown).

Pump explantations
The pump was explanted in 48% (27/56) of patients for the following reasons: 17 patients had serious adverse events, 9 had liver transplants, and 1 patient recovered from refractory ascites after successful treatment for chronic hepatitis C.

Mean decrease in serum albumin (g/litre)

1 month=1.4
3 months=2.3
6 months=3.2

The paper states that this effect was less pronounced in long-term survivors.
</td></tr>
<tr><td colspan="2">Abbreviations used: CI, confidence interval; IQR, interquartile range; SD, standard deviation</td></tr>
</table>

Study 4 Bellot P (2013) – included in original overview for 2014 guidance

Details

Study type	**Case series**
Country	Belgium, Bulgaria, Germany, Spain
Recruitment period	2010 to 2011
Study population and number	**n=40** **Patients with cirrhosis and refractory ascites.**
Age and sex	Age range 34 to 80 years; 70% (28/40) male
Patient selection criteria	Patients aged 18 years or over with recurrence of ascites within 4 weeks of paracentesis, despite treatment with a maximum of 160 mg/day of furosemide and 400 mg/day of spironolactone (or equivalent doses of loop-acting and distal-acting diuretics) or intolerance related to diuretic-induced complications; expected survival of more than 6 months; serum creatinine levels ≤2.0 mg/dl for at least 7 days before study entry; total bilirubin levels ≤5 mg/dl. The procedure was offered to patients who were not considered to be candidates for transjugular intrahepatic portosystemic shunt (TIPS), because of their Child-Pugh Class C status (25%), previous hepatic encephalopathy (35%), previous failed TIPS, portal thrombosis, inadequate anatomy for TIPS placement or if the patient had rejected TIPS as therapy for refractory ascites. Exclusion criteria: active systemic or local infection, such as spontaneous bacterial peritonitis, urinary tract infection or cellulitis; malignancy, including hepatocellular carcinoma; evidence of extensive ascites loculation; portal hypertension-related gastrointestinal bleeding or hepatic encephalopathy in the 2 weeks before inclusion into the study; obstructive uropathy or any contraindication for general anaesthesia.
Technique	The alfapump system (Sequana Medical, Switzerland) was used. Minimally invasive surgical techniques were used to implant the pump system. All patients were offered antibiotic prophylaxis with amoxicillin/ clavulanic acid before the procedure and for 2 to 3 days afterwards. Later in the study, patients were also offered norfloxacin prophylaxis.
Follow-up	**6 months (124±57 days)**
Conflict of interest/source of funding	Financial support was provided by Sequana Medical, Switzerland. One of the authors (the principal investigator of the trial) has been a scientific adviser of Sequana Medical.

Analysis

Follow-up issues: No losses to follow-up were described.

Study design issues: Prospective, multicentre observational study. The primary outcome was safety, as evaluated by the incidence and severity of device and procedure-related serious adverse events. Secondary outcomes included the need for paracentesis, pump system function and incidence of haemodynamic derangement. An independent Data Safety Monitoring Board reviewed all serious adverse events and made recommendations that were incorporated into the protocol. Patients were then divided into 2 subgroups (cohort I and II) depending on whether they had the procedure before or after the recommendations of the board.

Study population issues: The aetiology of cirrhosis was alcohol in 43% (17/40) of patients, hepatitis in 25% (10/40), nonalcoholic steatohepatitis in 5% (2/40), cryptogenic in 15% (6/40) and other (not specified) in 12% (5/40). The median number of paracentesis procedures in the month before the pump was implanted was 3.38. Comorbidities included oesophageal varices (68% [27/40]), diabetes mellitis (48% [19/40]), history of hepatic encephalopathy (35% [14/40]), history of renal dysfunction (35% [14/40]), history of spontaneous bacterial peritonitis (23% [9/40]), history of gastrointestinal haemorrhage (20% [8/40]) and history of urinary tract infection (13% [5/40]).

Other issues: The bladder catheter implant procedure was modified during the study to reduce the rate of bladder catheter dislodgments. Other modifications included the use of norfloxacin antibiotic prophylaxis, avoiding nonsteroidal anti-inflammatories and albumin infusion for any large volume paracentesis done immediately before or during implantation.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **40**

Mean volume of fluid removed per patient per day=0.99 litres

Median number of large volume paracentesis (LVP) per month

- Before pump implantation=3.4 (range 1 to 6)
- After pump implantation=0.24 (range 0 to 5), p<0.01

40% of patients did not need a LVP after the pump was implanted.

The need for LVPs was statistically significantly lower in patients from cohort II compared with cohort I, because of the reduced number of technical problems (2 LVPs in 2/19 patients compared with 30 LVPs in 9/21 patients, p=0.034).

5 patients stopped the study early because they had liver transplants (mean implant duration 137 days).

Safety

Number of patients with cirrhosis and device-related adverse events within 6 months of pump implantation

Serious adverse events	Number of patients		
	Cohort I (n=21)	Cohort II (n=19)	p value
Cirrhosis related			
Total	17	13	NS
Hepatic encephalopathy	8	9	NS
Renal dysfunction	9	4	NS
Infections			
Total			
1 occurrence	12 (57%)	7 (37%)	
>1 occurrence	4 (19%)	1 (5%)	0.09
Spontaneous bacterial peritonitis			
1 occurrences	6 (29%)	4 (21%)	
>1 occurrence	2 (10%)	0 (0%)	0.48
Systemic inflammatory response syndrome			
1 occurrence	6 (29%)	0 (0%)	
>1 occurrence	0 (0%)	1 (5%)	0.02
Urinary tract infection			
1 occurrence	1 (5%)	0 (0%)	
>1 occurrence	2 (10%)	0 (0%)	0.49
Other infections			
1 occurrence	1 (5%)	3 (16%)	
>1 occurrence	0 (0%)	1 (5%)	0.21
Bladder catheter dislocations			
Total	5 (24%)	0 (0%)	0.04
Peritoneal catheter issues*			
Total	3 (9.5%)	2 (10.5%)	NS
Other			

Wound dehiscence	1 (5%)	1 (5%0	NS
Bladder perforation	1 (5%)	0	NS
Pump malfunction	2 (10%)	0	NS

*The peritoneal catheter migrated towards the perihepatic space in 2 patients; it was relocated through laparoscopy in 1 patient but the second patient withdrew from the study after reoperation failed to relocate the catheter. Two peritoneal catheters became blocked after 26 days and 62 days and were replaced.

In addition to the above events, there were 4 cases of prolapse of the bladder catheter into the urethra in 3 patients (7.5%) and 1 bladder catheter became kinked and needed repair (2.5%). Leakage of ascitic fluid through the implant wounds was reported in 3 patients (7.5%).

Pump pocket infections refractory to antibiotic therapy were reported in 2 patients: the pumps were explanted in both patients.

In 4 patients with renal dysfunction, there had been inappropriate use of nonsteroidal anti-inflammatories. All the episodes of renal dysfunction were reversible with treatment with the exception of 1 patient who died of acute renal failure on day 54 and 1 patient who died of hepatorenal syndrome on day 147.

Pump explantation

The pump was removed in 13 patients (7 difficult-to-treat infections, 3 withdrawn consent after bladder or peritoneal catheter dislodgement issues, 2 withdrawal of patient consent, 1 emergency removal because of wound dehiscence).

Mortality

In total, there were 8 deaths (mean implant duration 116 days, 3 deaths were caused by sepsis, 2 progressive liver insufficiency, 1 acute renal failure, 1 hepatorenal syndrome and 1 patient unexpectedly died at home and no cause of death was determined).

Effects on renal, circulatory and liver function (number of patients)

	Baseline (40)	Month 1 (37)	Month 3 (31)	Month 6 (14)
Mean arterial pressure (mmHg)	85.1±10.3 (40)	83.7±12.4 (36)	80.1±20.3 (29)	86.8±12.0 (14)
Model for End-Stage Liver Disease score	12.6±4.0 (40)	13.5±5.2 (23)	13.2±6.3 (28)	11.7±4.0 (11)
Child-Pugh score	8.5±1.1 (40)	9.0±1.0 (34)	9.0±0.8 (26)	8.6±0.8 (10)
International normalised ratio*	1.37±0.26 (40)	1.33±0.22 (35)	1.36±0.29 (29)	1.24±0.16 (12)
Serum bilirubin (micromoles/litre)	31.9±16.6 (40)	30.1±18.5 (34)	26.2±20.3 (28)	25.3±23.7 (11)
Serum albumin (g/litre)^	31.9±5.0 (40)	30.0±3.9 (36)	28.2±4.6 (28)	27.2±4.9 (11)
Serum sodium (milliequivalents/litre)	136±5 (40)	133±6 (35)	133±7 (29)	134±5 (12)
Serum creatinine (micromoles/litre)	106±33 (40)	123±63 (35)	127±59 (29)	105±27 (12)

* $p<0.01$, ^$p<0.05$

Abbreviations used: NS, not significant

Study 5 Solà E (2017)

Details

Study type	**Case series**
Country	Spain
Recruitment period	2011 to 2013
Study population and number	**n=10** **Patients with cirrhosis and refractory ascites.**
Age and sex	Median 59 years; 60% (6/10) male
Patient selection criteria	Patients aged 18 years or over with cirrhosis and refractory ascites, needing 2 or more large volume paracentesis (LVP) during the previous 3 months. Exclusion criteria: bacterial infections or gastrointestinal bleeding during the last 7 days, serum creatinine ≥2 mg/dl, serum bilirubin >5 mg/dl, severe coagulopathy defined as platelet count <40,000 or prothrombin time <40%, recurrent spontaneous bacterial peritonitis or urinary tract infections defined as 2 or more episodes during the last 6 months, evidence of loculated ascites, hepatocellular carcinoma exceeding Milan criteria, previous liver transplant, obstructive uropathy or bladder abnormalities that could contraindicate the implantation procedure.
Technique	The alfapump system (Sequana Medical, Switzerland) was used. A LVP with albumin infusion was done in all patients the day before implantation of the pump. All patients were offered antibiotic prophylaxis with ceftazidime plus teicoplanin before and 8 hours after surgery. After the procedure, paracetamol was offered for pain relief if needed. The device was kept off for the first 24 hours after surgery and was then activated on day 2 if there were no complications. All patients were kept in hospital for 7 days, for close monitoring of kidney and circulatory function. All patients were offered antibiotic prophylaxis with norfloxacin. Diuretic medication was withdrawn in all patients during the first week after implantation and was only offered afterwards to patients with leg oedema. A moderately low-sodium diet was recommended to all patients before discharge. During follow-up, albumin was only offered if patients needed a LVP or in case of spontaneous bacterial peritonitis or development of acute kidney injury with serum creatinine of >1.5 mg/dl.
Follow-up	**12 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: There were no losses to follow-up.

Study design issues: Prospective, proof-of-concept, single centre observational study. The primary endpoint of the study was to investigate the effect of treatment with the low-flow pump system on kidney and circulatory function. Secondary endpoints included the need for LVPs during treatment and adverse events.

Study population issues: The aetiology of cirrhosis was alcohol in 6 patients, hepatitis C in 3 patients and nonalcoholic steatohepatitis in 1 patient. The mean number of paracentesis procedures in the 3 months before the pump was implanted was 7.5 (median 9). All patients had been on treatment with LVP for more than 1 year before study inclusion.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **10**

Median daily ascitic fluid volume extraction during the study, ml (IQR)

- Day 7=500 (500 to 500)
- Month 1=700 (500 to 900)
- Month 3=950 (325 to 1,850)
- Month 6=1,000 (600 to 1,700)
- Month 12=800 (375 to 1,450)

Mean number of large volume paracenteses (LVPs) per patient after the procedure

- 0 to 3 months=1.8
- 3 to 6 months=3.7
- 6 to 9 months=3.2
- 9 to 12 months=2.4

40% (4/10) of patients did not need LVP after the procedure.

40% (4/10) of patients needed diuretic treatment for oedema during the study period. In all patients, treatment was effective and the dose of diuretic used was relatively low.

Data on long-term follow-up (1 year or more) with the low-flow pump system working properly were only available for 3 patients. In all these patients, the pump stopped working between 2 and 3 years after implantation.

Safety

Adverse events

Cirrhosis-related adverse events during the 12-month study period

Complication	Number of episodes (number of patients)
Total	68 (8)
Acute kidney injury	
Within the first 7 days	4 (4)
During follow-up	14 (6)
Infectious complications	
Urinary tract infection	8 (5)
Persistent bacterial peritonitis	2 (2)
Spontaneous bacterial peritonitis	1 (1)
Ascitic fluid colonisation by *Candida glabrata*	1 (1)
Catheter-associated bacteraemia	1 (1)
Septic shock	1 (1)
Pseudomembranous colitis	1 (1)
Abdominal skin infection (around subcutaneous pocket)	1 (1)
Hyponatraemia	15 (5)
Hepatic encephalopathy	14 (6)
Spontaneous falls causing bone fractures	3 (3)
Portal hypertension-related bleeding	1 (1)

The aetiology of acute kidney injury was hypovolemic (n=3), nephrotoxicity associated with nonsteroidal anti-inflammatory use (n=2), hepatorenal syndrome associated with bacterial infection (n=3), acute tubular necrosis (n=1) and urinary peritonitis because of bladder perforation (n=1), and unknown (n=8). 14 (78%) episodes were stage 1.

6 patients were admitted to hospital because of bacterial infections, with an average stay of 47.8 days/patient.

Adverse events related to the device during the 12-month study period

Complication	Number of episodes (number of patients)
Total	15 (7)
Surgical reinterventions	
Replacement of peritoneal catheter	2 (2)
Reposition of migrated peritoneal catheter	1 (1)
Pump replacement	1 (1)
Pump removal because of infection	2 (2)
Peritoneal catheter migration without replacement	1 (1)
Urinary bladder leakage	1 (1)
Abdominal wall haematoma	1 (1)
Surgical wound infection	1 (1)
Skin erosion because of peritoneal catheter	1 (1)
Transient pump dysfunction	2 (2)
Smart charger dysfunction	1 (1)
Technical problems with device charging	1 (1)

In the patient with catheter migration without replacement, the low-flow pump system stopped working after 5 months.

Kidney and haemodynamic variables, activity of endogenous vasoconstrictor systems, and proinflammatory cytokines, median (IQR)

	Baseline	Day 7	Month 1	Month 6	End of study period	p value
Glomerular filtration rate, ml/minute/1.73m^2	67 (41 to 90)	58 (47 to 88)	60 (35 to 84)	37 (31 to 72)	45 (36 to 74)	0.04
Serum creatinine, mg/dl	1.1 (0.7 to 1.6)	0.9 (0.8 to 1.4)	1.1 (0.9 to 1.6)	1.4 (0.8 to 2.4)	1.2 (0.9 to 1.8)	0.06
Mean arterial pressure, mmHg	80 (64 to 93)	81 (56 to 90)	79 (58 to 104)	76 (66 to 85)	81 (73 to 104)	0.16
Cardiac output, litres/minute	6.0 (3.4 to 10.2)	5.7 (3.1 to 7.8)	5.7 (3.7 to 9.9)	-	5.7 (3.7 to 9.9)	0.50
Panel reactive antibody, ng/ml*h	3.1 (1.6 to 6.4)	3.2 (2.1 to 6.5)	9.1 (5.7 to 16.8)	17.6 (8.9 to 19.1)	13.5 (8.0 to 21.1)	0.01
Norepinephrine, pg/ml	278 (224 to 358)	320 (116 to 358)	410 (248 to 656)	545 (150 to 615)	516 (336 to 677)	0.01
Aldosterone, ng/dl	103 (66 to 231)	190 (79 to 358)	261 (123 to 358)	229 (191 to 446)	220 (175 to 429)	0.23
Vasopressin, ng/litres	1.7 (1.4 to 2.1)	1.6 (1.3 to 2.0)	2.0 (1.4 to 2.6)	2.0 (1.4 to 3.3)	2.2 (1.5 to 2.7)	0.12
Interleukin 6, pg/ml	48 (33 to 137)	79 (49 to 144)	76 (36 to 193)	-	76 (36 to 193)	0.15
Tumour necrosis factor-alpha, pg/ml	11 (6.5 to 15)	11 (5 to 20)	10 (8 to 13)	-	10 (8 to 13)	0.58

Mortality

In total, there were 5 deaths during the study period (3 acute-on-chronic liver failure, refractory 1 gastrointestinal bleeding and 1 liver failure). In addition, 1 patient died 4 months after the end of the study because of acute-on-chronic liver failure associated with sepsis.

Long-term follow-up

2 of the 3 patients who had a working system for a year or more developed adverse events during the long-term follow-up. One patient developed a subcutaneous abscess in the hypogastric area in relation to the bladder catheter and the other patient had hypogastric pain and haematuria because of catheter friction with the bladder wall. The pump was removed in both patients.

Abbreviations used: IQR, interquartile range; LVP, large volume paracentesis.

Study 6 Thomas MN (2015)

Details

Study type	**Case series**
Country	Germany
Recruitment period	2013 to 2104
Study population and number	**n=10** **Patients with advanced alcoholic liver cirrhosis and refractory ascites.**
Age and sex	Age not reported; 40% (4/10) male
Patient selection criteria	All patients had been evaluated for transjugular intrahepatic portosystemic shunt (TIPS) but had either contraindications (n=8) or TIPS was insufficient (n=2) in controlling the ascites. Ascites treatment before the procedure consisted of diuretics and high volume paracentesis.
Technique	The alfapump system (Sequana Medical, Switzerland) was used. All patients were offered perioperative antibiotic prophylaxis with moxifloxacin, which was continued for 14 days after the procedure. Primary fluid transport volume was set to 1,000 ml/day and successively adapted to the individual need of each patient. Diuretic treatment was continued, and a bladder catheter was left in place until postoperative day 5, to measure urinary function and relieve bladder pressure.
Follow-up	**Median 165 days (range 23 to 379)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: There were no losses to follow-up.

Study design issues: Single-centre observational study, consecutive patients. Clinical outcomes were extracted either from the patient's electronic chart or by personal communication with the patient.

Study population issues: Four patients were treated as a bridge to transplant and 6 patients had the procedure as a destination therapy. All but 1 of the patients had oesophageal varices and 7 had at least 1 episode of gastrointestinal haemorrhage. Seven patients had a history of spontaneous bacterial peritonitis, renal dysfunction or hepatic encephalopathy and 5 patients had diabetes.

Other issues: Includes the first 10 patients to have the procedure in the study centre.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 10

At the end of follow-up, 5 pumps were functioning in situ and 5 were non-functioning or explanted because of technical failure (n=1), death with functioning pump (n=3), or transplantation (n=1).

Median time of pump in situ=165 days (range 23 to 379)
Median pump volume per day=1,000 ml (range 450 to 2,000)

Mean number of paracentesis per month
• Before pump implantation=3.36±0.8
• 60 day follow-up=0.45±1.0, p<0.0001</td><td>Postoperative complications
• Surgical site infections=20% (2/10) (treated by surgical wound debridement and subcutaneous application of gentamicin impregnated foam)
• Kinking of the bladder catheter=10% (1/10) (treated by surgical revision and shortening the catheter)
• Acute renal failure=30% (3/10)
• Hepatic-renal syndrome=20% (2/10)
• Pump pocket infection=10% (1/10) (pump needed to be removed)

Mortality
30% (3/10) of patients died during follow-up (1 from acute pancreatitis on postoperative day 235 and 2 with increasing hepatorenal failure on postoperative days 30 and 119).

Liver and kidney functional parameters
<table><tr><th></th><th>Baseline</th><th>60 day follow-up</th><th>p value</th></tr><tr><td>Serum bilirubin (mg/dl)</td><td>1.8 (0.5 to 2.4)</td><td>0.7 (0.6 to 6.0)</td><td>0.50</td></tr><tr><td>Serum albumin (g/dl)</td><td>3.0 (2.7 to 3.8)</td><td>3.2 (1.8 to 3.7)</td><td>0.40</td></tr><tr><td>Serum sodium (millimoles/litre)</td><td>134 (127 to 138)</td><td>133 (123 to 139)</td><td>0.42</td></tr><tr><td>Serum creatinine (mg/dl)</td><td>1.9 (1.0 to 2.8)</td><td>2.5 (1.2 to 4.8)</td><td>0.17</td></tr><tr><td>International normalised ratio</td><td>1.3 (1.1 to 1.5)</td><td>1.3 (1.2 to 1.7)</td><td>0.16</td></tr><tr><td>Model for End-Stage Liver Disease score</td><td>16 (10 to 21)</td><td>18 (10 to 31)</td><td>0.22</td></tr></table></td></tr>
</table>

Study 7 Karkhanis S (2017)

Details

Study type	**Case series**
Country	UK
Recruitment period	Not reported
Study population and number	**n=3** **Patients with medically refractory ascites and cirrhosis caused by alcoholic liver disease.**
Age and sex	Mean 57 years; 3/3 female
Patient selection criteria	Not reported.
Technique	The alfapump system (Sequana Medical, Switzerland) was used. In all 3 patients, the systems were implanted in an interventional radiology suite under conscious sedation and local anaesthesia, using minimally invasive techniques. Diuretics were discontinued for at least 7 days before the procedure and antibiotic prophylaxis with ciprofloxacin was offered on the morning of the procedure and for 1 week afterwards. Patients were admitted overnight and reviewed the following day.
Follow-up	**Mean 208 days** (duration pump in situ)
Conflict of interest/source of funding	Not reported

Key efficacy and safety findings

- Case 1: 63 year old woman with medically refractory ascites who did not wish to be considered for liver transplant or transjugular intrahepatic portosystemic shunt. The patient tolerated the implantation procedure well. The pump was switched off 224 days after implantation and explanted immediately afterwards, because the patient's overall nutrition had improved significantly and pump volume was decreasing.
- Case 2: 54 year old woman with medically refractory ascites who was not a candidate for transjugular intrahepatic portosystemic shunt because of previous encephalopathy. She was placed on the active liver transplant waiting list and offered the low-flow pump system as a bridge-to-transplant. The patient tolerated the implantation procedure well. There were several episodes of ascites leaking from the peritoneal incision, which was managed by increasing the pump output and aspirating the subcutaneous fluid pocket. The patient also had 1 episode of cellulitis near the skin incision, which responded to oral antibiotic therapy. The patient had a successful liver transplant 112 days after the pump was implanted and the pump was explanted at the same time.
- Case 3: 54 year old woman with medically refractory ascites. She tolerated the implantation procedure well, with no complaints of discomfort. There was an improvement in serum albumin on day 15 but a persistent acute kidney injury was noted. The patient had 2 episodes of cellulitis (day 32 and 64) and 1 episode of urinary tract infection (month 8), which needed antibiotics and hospital admission. She had small volume ascitic fluid leakage through the pump wound at day 30 and moderate to large volume leakage again after 4 months, with a large subcutaneous fluid pocket forming around the pump. This was caused by a migrated bladder tube; both bladder and peritoneal tubings were changed on day 120. The patient continued to have persistent ascites and needed 3 large-volume paracentesis in a 6-month period. She chose to have the pump removed 289 days after implantation. The patient died 315 days later because of sequelae of background liver pathology.

Validity and generalisability of the studies

- There are some data from the UK.
- Most patients included in the studies had alcoholic liver cirrhosis.
- Several studies specifically excluded patients with cancer.
- Although most patients had the procedure under general anaesthesia, there is a recent report that describes 3 patients having the system implanted under conscious sedation and local anaesthesia.[7]
- The studies include the first patients to be treated by this procedure.
- The original implantation technique was modified to overcome problems with insertion or function of the device and catheters.
- Some patients had the treatment as a bridge to transplant and others had it as a destination therapy.

Existing assessments of this procedure

The European Association for the Study of the Liver published guidelines on the management of patients with decompensated cirrhosis in April 2018.[8] It made the following recommendation with regard to subcutaneous automated low-flow pump implantation:

'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.'

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Subcutaneous implantation of a battery-powered catheter drainage system for managing refractory and recurrent ascites. NICE interventional procedures guidance 479 (2014). Available from http://www.nice.org.uk/guidance/IPG479 *[current guidance for this procedure]*

Medical technologies guidance

- PleurX peritoneal catheter drainage system for vacuum-assisted drainage of treatment-resistant, recurrent malignant ascites. Medical technologies guidance 9 (2012, last updated 2018). Available from https://www.nice.org.uk/guidance/mtg9

NICE guidelines

- Cirrhosis in over 16s: assessment and management. NICE guideline 50 (2016). Available from http://www.nice.org.uk/guidance/NG50
- Alcohol-use disorders: diagnosis and management of physical complications. NICE clinical guideline 100 (2010, last updated 2017). Available from http://www.nice.org.uk/guidance/CG100

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two Specialist Advisor Questionnaires for subcutaneous automated low-flow pump implantation for refractory and recurrent ascites were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 1 company who manufactures a potentially relevant device for use in this procedure. NICE did not receive a completed submission.

Issues for consideration by IPAC

Ongoing trials (recruitment status and estimated study completion date as reported on *Clinicaltrials.gov* on 3 April 2018):

- Alfapump System Versus Transjugular Intrahepatic Portosystemic Shunt and Paracentesis in the Treatment of Ascites. A Multicentre Randomised Controlled Study (NCT02612519); Germany; estimated enrolment: 260; estimated study completion date: November 2019. Recruitment status: recruiting.
- ALFApump System Post Marketing Surveillance Registry (NCT01532427); observational study; Germany, Spain, Switzerland and UK; actual enrolment: 100; estimated study completion date: August 2017. Recruitment status: active, not recruiting (NB some results from this trial have been published by Stirnimann G et al., 2017 [study 3]).
- Retrospective Study in the Use of the Alfapump and the Treatment of Malignant Ascites (NCT03200106); observational, retrospective study; Germany, Switzerland and UK; estimated enrolment: 20; estimated study completion date: March 2018. Recruitment status: not yet recruiting.
- A (M)Ulti-center, Prospective, (O)Pen Label, Uncontrolled Feasibility (S)Tudy to Assess the Safety and Effectiveness of an Automatic Low Flow (A)Scites (Alfa) Pump (I)n Patients With (C)Irrhosis and Refractory or Recurrent Ascites (MOSAIC) (NCT02400164); interventional study, single group assignment; US and Canada; actual enrolment: 30; estimated study completion date: September 2018. Recruitment status: active, not recruiting.
- Study Into the Effects of Albumin Replacement Therapy on Renal and Circulatory Function in Patients Implanted With the Alfapump

(NCT02448160); interventional study, single group assignment; UK; estimated enrolment: 10; estimated study completion date: December 2017. Recruitment status: active, not recruiting.

References

1. Bureau C. Adebayo D, Chalret de Rieu M et al. (2017) Alfapump system vs. large volume paracentesis for refractory ascites: A multicenter randomized controlled study. Journal of Hepatology 67: 940–49
2. Stepanova M, Nader F, Bureau C et al. (2018) Patients with refractory ascites treated with alfapump system have better health-related quality of life as compared to those treated with large volume paracentesis: the results of a multicenter randomized controlled study. Quality of Life Research 19
3. Stirnimann G, Berg T, Spahr L et al. (2017) Treatment of refractory ascites with an automated low-flow ascites pump in patients with cirrhosis. Alimentary Pharmacology & Therapeutics 46: 981–91
4. Bellot P, Welker MW, Soriano G et al. (2013) Automated low flow pump system for the treatment of refractory ascites: a multi-center safety and efficacy study. Journal of Hepatology 58: 922–27
5. Sola E, Sanchez-Cabus S, Rodriguez E et al. (2017) Effects of alfapumpTM system on kidney and circulatory function in patients with cirrhosis and refractory ascites. Liver Transplantation 23: 583–93
6. Thomas MN, Sauter GH, Gerbes, AL et al. (2015) Automated low flow pump system for the treatment of refractory ascites: a single-center experience. Langenbecks Archives of Surgery 400: 979–83
7. Karkhanis S, Jones R, Willis A et al. (2017) Radiological insertion of automated low flow ascitic pump (alfapump®) system for management of medically refractory ascites. BJR Case Reports 2: 20170025
8. The European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. Journal of Hepatology (2018), https://doi.org/10.1016/j.jhep.2018.03.024

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	01/03/2018	Issue 2 of 12, February 2018
HTA database (Cochrane)	01/03/2018	Issue 4 of 4, October 2016
Cochrane Central Register of Controlled Trials (Cochrane)	01/03/2018	Issue 2 of 12, February 2018
MEDLINE (Ovid)	01/03/2018	1946 to Present with Daily Update
MEDLINE In-Process (Ovid) and MEDLINE Epubs ahead of print (Ovid)	01/03/2018	February 28, 2018
Embase	01/03/2018	1974 to 2018 Week 09
BLIC (British Library)	01/03/2018	n/a

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Ascites/
2	ascit*.tw.
3	dropsy.tw.
4	Ascitic Fluid/
5	((ascitic or peritoneal or abdom*) adj4 (fluid* or effusion*)).tw.
6	or/1-5
7	"Prostheses and Implants"/
8	(implant* or prosthe*).tw.
9	Catheters/

10	Catheterization/
11	(catheter* adj4 drain*).tw.
12	or/7-11
13	Drainage/
14	(remov* or drain* or shunt or manage* or transport* or excess* or pump* or suction).tw.
15	(recirculating adj4 device*).tw.
16	wireless.tw.
17	batter*.tw.
18	or/13-17
19	(refractory or recurren* or cirrho* or symptomatic or neoplasm* or cancer* or metastas* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or lump* or masses* or sarcoma*).tw.
20	(treatment adj4 resist*).tw.
21	Neoplasm Metastasis/
22	exp Liver Cirrhosis/
23	((liver or hepatic) adj4 (fibros* or cirrhos* or disease*)).tw.
24	subcutaneous.tw.
25	non-transvenous.tw.
26	(non adj1 transvenous).tw.
27	or/19-26
28	6 and 12 and 18 and 27
29	ALFApump.tw.
30	(ALFA adj4 pump).tw.
31	((low-flow or low flow) adj4 pump*).tw.
32	28 or 29 or 30 or 31
33	animals/ not humans/
34	32 not 33

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Stirnimann G, Banz V, Storni F et al. (2017) Automated low-flow ascites pump for the treatment of cirrhotic patients with refractory ascites. Therapeutic Advances in Gastroenterology 10: 283–92	review	The alfapump is an innovative treatment option for patients with refractory ascites and has shown excellent efficacy so far in the reduction in the need for large volume paracentesis in clinical trials. To date, it is not clear, whether the alfapump has a significant survival benefit. However, quality of life may be improved because of a significantly decreased need for paracentesis and the avoidance of tense ascites. Further research is needed to better define the role of the alfapump in the management of refractory ascites. Pump implantation should be restricted for the moment to tertiary referral centres. Complications, such as infections and catheter obstruction, may occur and need treatment. Data for other indications, such as malignant ascites or pleural effusion) is scarce and no conclusion can be drawn about the use of alfapump in these patient populations at this time.	The cited published studies are already included in table 2.