

Palliative Long-term Abdominal Drains Versus Repeated Drainage in Untreatable Ascites Due to Advanced Cirrhosis: A Randomised Controlled Trial REDUCe 2 Study

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Conflict of Interest

- Support from Rocket Medical plc for REDUCe and REDUCe 2 Study

Ascites: Irrefutable Facts !!



- Ascites most common cirrhosis complication requiring hospitalisation, develops in ~ 40% within 5 years
- Ascites is one of the main drivers of impaired HRQoL in advanced cirrhosis in patients and caregivers
- Many patients will not tolerate high dose diuretics
- Refractory ascites helpful prognostic guide as median transplant free survival 6 -12 months: many will NOT receive a liver transplant/TIPS
- Palliative interventions for refractory ascites remains an unmet need: most common option is repeated LVP

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PERITONEOVENOUS SHUNTING AS COMPARED WITH MEDICAL TREATMENT IN PATIENTS WITH ALCOHOLIC CIRRHOSIS AND MASSIVE ASCITES

1x 400 + 320

MALCOLM M. STANLEY, M.D., SHIGERU OCHI, PH.D., KELVIN K. LEE, PH.D.,
BERNARD A. NEMCHAUSKY, M.D., HERBERT B. GREENLEE, M.D., JOHN I. ALLEN, M.D.,
MELODY J. ALLEN, M.D., RICHARD A. BAUM, M.D., THOMAS R. GADACZ, M.D., DANIEL S. CAMARA, M.D.,
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ARUN K. SAMANTA, M.D., AHMAD Z. NAJEM, M.D., MICHAEL E. GLICK, M.D., GEORGE L. JULER, M.D.,
NABEEL ADHAM, M.D., J. DENNIS BAKER, M.D., G. DOUGLAS CAIN, M.D., PAUL H. JORDAN, M.D.,
DOUGLAS C. WOLF, M.D., J. TIMOTHY FULENWIDER, M.D., KENNETH E. JAMES, PH.D., AND THE VETERANS
ADMINISTRATION COOPERATIVE STUDY ON TREATMENT OF ALCOHOLIC CIRRHOSIS WITH ASCITES

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- In the largest ever study in patients with ascites due to cirrhosis (n= ~2000), at the time of discharge, mean diuretic units varied from 2.5±0.2 to 2.7±0.3 units
- One unit being 40 mg furosemide and 100 mg spironolactone

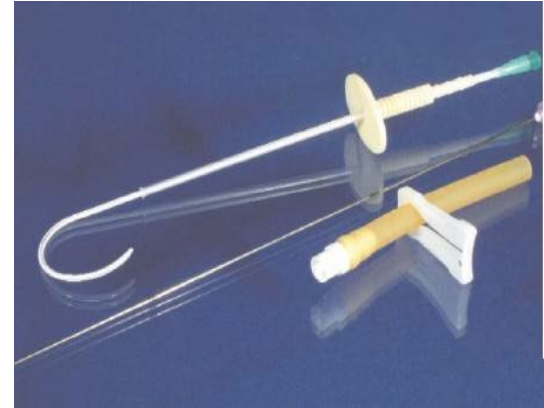
Cirrhosis with ascites in the last year of life: a nationwide analysis of factors shaping costs, health-care use, and place of death in England



Benjamin Hudson, Jeff Round, Brendan Georgeson, Andrew Pring, Karen Forbes, Catherine Anne McCune, Julia Verne

**Lancet Gastroenterol Hepatol
2018; 3: 95-103**

- 2013-2015: of the ~45000 liver-related death, 31% (~13,000) undergoing LVP in last year of life, mean overall healthcare costs > 21K/person
- 75% of deaths in those undergoing LVP occurred in hospital



CARE OF PATIENTS WITH END STAGE LIVER DISEASE AND REFRACTORY ASCITES REMAINS SUBOPTIMAL: NEED FOR EARLIER INPUT FROM PALLIATIVE CARE

Lucia Macken^{1,2} Ahmed Hashim^{1,2} Sumita Verma^{1,2}

¹ Brighton and Sussex Medical School

² Brighton and Sussex University Hospitals NHS Trust



Jan 2013-Dec 2015

- N=138
- 38% (n=51) initiating LVP developed refractory ascites
- N=7(14%) underwent/listed for transplant/underwent TIPS
- Median survival from refractory ascites diagnosis 190 days (42-483)
- 31% had documented end of life discussions; 22% referred to palliative care; 16% had advance care plans

Transjugular Intrahepatic Portosystemic Shunts With Covered Stents Increase Transplant-Free Survival of Patients With Cirrhosis and Recurrent Ascites

Christophe Bureau,^{1,2} Dominique Thabut,³ Frédéric Oberti,⁴ Sébastien Dharancy,⁵

Characteristic	TIPS (n = 29)	LVP+A (n = 33)	P value
Sex, male/female, n	17/12	27/6	.06
Age, y	56.7 ± 5.7	56.4 ± 7.9	.868
Weight, kg	67 ± 15	72 ± 15	.152
BMI, kg/m ²	23.6 ± 4.3	24.3 ± 3.3	.465
Etiology, %			
Alcohol	90	85	1.00
Stopped alcohol use	70	80	1.00
Chronic hepatitis C	3	9	.616
Other	7	6	1.00
History of SBP, %	7	15	.432
History of OHE, %	0	3	1.00
History of variceal bleeding, %	28	30	1.00
History of renal failure, %	21	18	1.00
No. of paracentesis, last 3 mo	4.5 ± 1.4	4.2 ± 1.3	.377
Duration of cirrhosis, y	3.7 ± 4.1	2.9 ± 3.4	.364
Trail making test A, s	71 ± 33	66 ± 44	.614
Bilirubin, μmol/L	17.8 ± 12.7	17.5 ± 16.4	.938
INR	1.39 ± 0.27	1.46 ± 0.30	.382
Albumin, g/L	30.7 ± 5.5	33.4 ± 5.4	.06
Serum creatinine, μmol/L	84.6 ± 30.1	85.6 ± 21.4	.888
Serum sodium, mmol/L	134 ± 4	132 ± 4	.06
Hemoglobin, g/dL	11.5 ± 1.7	11.8 ± 1.7	.543
Platelets, 10 ³ /mm ³	179 ± 94	169 ± 90	.687
ASAT, UL/N	1.69 ± 0.79	1.63 ± 0.85	.771
ALAT, UL/N	1.09 ± 0.28	1.12 ± 0.38	.711
Child-Pugh score	8.7 ± 1.4	8.6 ± 1.6	.922
Child-Pugh class: B/C, n	19/10	22/11	1.00
MELD score	12.1 ± 3.5	13.1 ± 3.9	.289

Randomised clinical trial: palliative long-term abdominal drains vs large-volume paracentesis in refractory ascites due to cirrhosis

Lucia Macken¹ | Stephen Bremner¹ | Heather Gage² | Morro Touray² |

	n	Mean/med (%)	SD/IQR	n	Mean/med (%)	SD/IQR
Age (years)	17	66.3	10.4	19	67.9	12
Female		4/17 (24%)			5/19 (26%)	
White British		16/17 (94%)			19/19 (100%)	
BMI (kg/m ²)	16	28.4	22.2-32.5	15	24.6	22.1-28.9
Serious comorbidity		11/17 (65%)			14/19 (74%)	
Prescribed furosemide		5/17 (29%)			6/19 (32%)	
Prescribed spironolactone		12/17 (71%)			11/19 (58%)	
Ongoing alcohol/drug use		5/17 (29%)			2/19 (11%)	
Child Pugh A		0/17 (0%)			1/18 (6%)	
Child Pugh B		14/17 (82%)			13/18 (72%)	
Child Pugh C		3/17 (18%)			4/18 (22%)	
MELD Score	17	13.8	4.5	18	16.3	7.3
ORELD score	17	34	4.5	18	34.1	8.2
Bilirubin (μmol/L)	17	22	15-37	18	23	17-48
Bilirubin >33 μmol/L	17	6/17 (35%)		18	7/18 (39%)	
Albumin (g/L)	17	33	32-36	18	31	27-33
Albumin <35 g/L	12	12/17 (71%)		16	16/18 (89%)	
Serum creatinine (μmol/L)	17	109	79-141	18	113.5	89-135

Long-term Abdominal Drains (LTADs)

- Tunnelled drains, SOC in malignant ascites: community nurses/caregivers remove 1-2 L of fluid at home 2-3 times/week
- Potential advantages over LVP
 - ★ Symptom guided drainage with potential for improved symptom control
 - ★ Avoids frequent hospitalisations with care in community
 - ★ NICE: clinically effective, low complication rates, could improve HRQoL cost effective and recommended in refractory malignant ascites
- National survey largely amongst BASL members (n=210): almost all (90%) willing to consider palliative LTAD: main deterrents were community management and perceived infection risk



Challenges in Conducting Palliative Trials in Advanced cirrhosis

- Vulnerable and under researched cohort: uncertainty around appropriate outcomes and assessment tools
- High attrition (dealing with missing data)
- Recruitment challenges:
 - ✳ “Gatekeeping”- when clinicians/caregivers assume that palliative care research is intrusive, upsetting and even unethical and unlikely to be of benefit
 - ✳ Inability to have timely palliative care discussions: REDUCe study ~50% of those eligible not recruited as died rapidly and ~40% of those recruited died within 4 weeks

Randomised clinical trial: palliative long-term abdominal drains vs large-volume paracentesis in refractory ascites due to cirrhosis

Lucia Macken¹ | Stephen Bremner¹ | Heather Gage² | Morro Touray² |
Peter Williams² | David Crook¹ | Louise Mason^{1*} | Debbie Lambert¹ |
Catherine J. Evans^{1,3} | Max Cooper¹ | Jean Timeyin¹ | Shani Steer¹ |
Mark Austin¹ | Nick Parnell¹ | Sam J. Thomson⁴ | David Sheridan⁵ | Mark Wright⁶ |
Peter Isaacs⁷ | Ahmed Hashim¹ | Sumita Verma¹ 

- 3 mth feasibility RCT, n= 36 recruited, all received prophylactic antibiotics for study duration
- Community nurses did home drainage, home visits for **ALL** participants for safety monitoring and questionnaire- based assessments
- >85% with LTAD successfully managed in community with ~15% lower total costs
- ≥80% questionnaire uptake
- No SAR due to LTADs – peritonitis incidence LVP vs. LTAD 6% vs. 11%, self limiting cellulitis/leakage higher in LTAD group (41% vs. 11%)
- Qualitative data: acceptability of LTAD by patients and nurses

AASLD Practice Guidance: Palliative care and symptom-based management in decompensated cirrhosis

Shari S. Rogal^{1,2} | Lissi Hansen³ | Arpan Patel^{4,5} | Nneka N. Ufere⁶ |

Guidance statements

33. Abdominal drains may be an alternative to serial LVP for patients with refractory ascites who are transplant and TIPS ineligible and whose goals are comfort focused. However, more comparative effectiveness research is needed before recommending this approach.



OPEN ACCESS

Guidelines on the management of ascites in cirrhosis

Guruprasad P Aithal^{1,2}, Naaventhana Palaniyappan^{1,2}, Louise China³,
Suvi Härmälä⁴, Lucia Macken^{5,6}, Jennifer M Ryan^{3,7}, Emilie A Wilkes^{2,8},
Kevin Moore³, Joanna A Leithead⁹, Peter C Hayes¹⁰, Alastair J O'Brien³,
Sumita Verma^{5,6}

13.8. Effectiveness and safety of long-term abdominal drains should be assessed in RCTs for the palliative care of patients with cirrhosis and refractory ascites.

Tunnelled peritoneal drainage catheter insertion for treatment-resistant, recurrent ascites due to cirrhosis

In development [GID-IPG10194]Expected publication date: TBC

[Register an interest](#)

- [Project information](#)

[Register an interest in this interventional procedure](#)

NICE has been notified about this procedure and it is part of its work programme. The Interventional Procedures Advisory Committee (IPAC) will consider this procedure and NICE will issue an interventional procedures consultation document about its safety and efficacy for 4 weeks' public consultation. IPAC will then review the consultation document in the light of comments received and produce a final interventional procedures document, which will be considered by NICE before guidance is issued to the NHS in England, Wales, Scotland and Northern Ireland.

Status

In progress

Frontline Gastroenterology

Palliative Long-term Abdominal Drains for the Management of Refractory Ascites due to Cirrhosis: A Consensus Document

Journal:	<i>Frontline Gastroenterology</i>
Manuscript ID	Draft
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Date Submitted by the Author:	n/a
Complete List of Authors:	Macken, Lucia; University Hospitals Sussex NHS Foundation Trust CORRIGAN, Margaret; Liverpool University Hospitals NHS Foundation Trust Prentice, Wendy; King's College Hospital NHS Foundation Trust, Department of Palliative Care Medicine Finlay, Fiona; Queen Elizabeth University Hospital Campus, McDonagh, Joanne; Queen Elizabeth Hospital Birmingham, Liver Unit Rajoriya, Neil; Queen Elizabeth Hospital, The Liver Unit Salmon, Claire; Sheffield Teaching Hospitals NHS Foundation Trust, Hepatology Donnelly, Mhairi; Freeman Hospital, Liver Unit Evans, Catherine; King's College London Ganai, Bhaskar; University Hospitals Sussex NHS Foundation Trust Bedlington, Joan; LIVERNORTH Steer, Shani; Patient and Public involvement Wright, Mark; University Hospital Southampton, Hepatology Hudson, Ben; Royal Devon and Exeter NHS Foundation Trust, Hepatology Verma, Sumita; Brighton and Sussex Medical School, Clinical and Experimental Medicine; Brighton and Sussex University Hospitals NHS Trust, Gastroenterology and Hepatology

Current Status of LTAD in Cirrhosis

- Preliminary evidence of safety, efficacy, acceptability and reduced health resource utilisation
- Cannot be considered standard of care: evidence needed from larger trials !!

Definitive trial LTAD vs. LVP

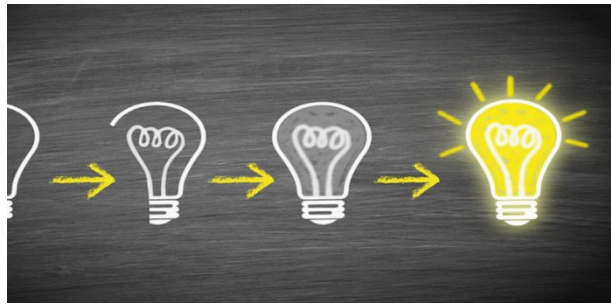
- After extensive discussions amongst research team/PPI group and feedback from HTA Committee and LiverHope Consortium recommendations, two potential primary outcomes considered
 - Peritonitis incidence (6% peritonitis incidence with a 10% non inferiority margin)
 - Health related quality of life

HTA Project: NIHR133889 - Palliative Long-term Abdominal Drains Versus Repeated Drainage in Untreatable Ascites Due to Advanced Cirrhosis: A Randomised Controlled Trial (REDUCe 2 Study)

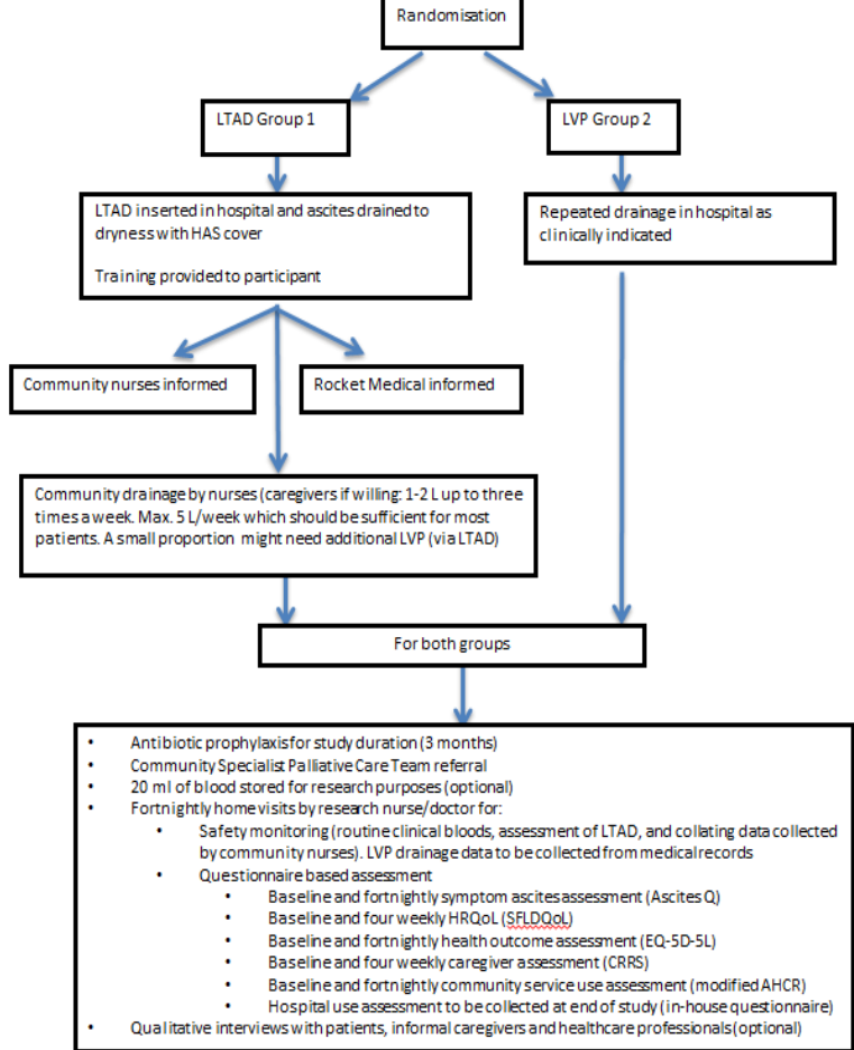
- National 57-mth trial, 18 mth internal pilot (STOP/GO criteria), sample size n=310
- Primary outcome: HRQoL (SFLDQoL) assessed at 3 months
- Questionnaire- based assessments (Ascites Q, SFLDQoL, EQ-5D-5L, AHCR/Hospital use questionnaire), cost effective analysis/QALYs
- Optional: research bloods and interviews with patients, caregivers and healthcare professionals
- 35 sites to be opened in three phases
- Still need to identify about 10 more sites
- Recruitment commences Sept-Nov 2022



- Adults with refractory ascites due to cirrhosis and need for recurrent LVPs
- Not a candidate for liver transplant and or TIPS
- Absence of loculated or chylous ascites



- Hepatic encephalopathy no longer to be exclusion criteria
- Communication skills training for research staff
- All research costs funded including home visits by research staff
- 1K funding/site to facilitate hospital and community trust engagement
- Strategies to reduce LTAD related complications



Key challenges:

- Identifying patients in timely manner
- Engaging with community trusts and interventional radiology to allow timely site set up

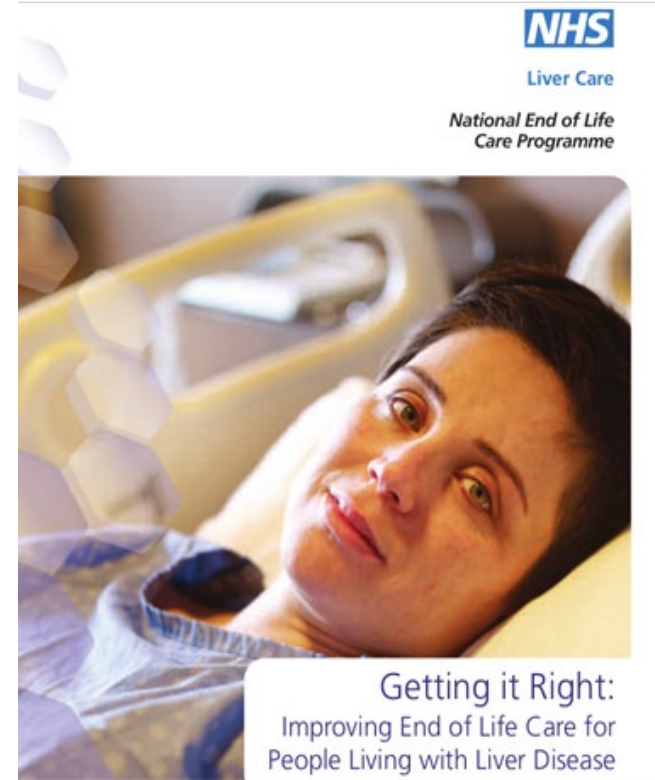
REDUCe 2: Strategies to reduce LTAD related complications



- Haemostatic function and ascitic fluid analysis within 7 +/- 3 days of LTAD insertion
- LTAD to be inserted by experienced clinicians under ultrasound guidance in hospital; antibiotic prophylaxis for study duration
- Fortnightly home visits for safety monitoring and ensuring engagement between hospital and community teams
- LTAD patients provided written information about LTAD management if of hours hospital admission
- Reduce leakage/cellulitis risk by
 - ✳ Draining ascites to dryness following insertion
 - ✳ Ensuring incisions are of appropriate size (may require a suture if too large)
 - ✳ Ensuring tunnelled portion of LTAD not under undue tension

Take Home Messages

- Palliative interventions for refractory ascites due to advanced cirrhosis remains a clear unmet need
- LTADs maybe a potential palliative option for some patients
- REDUCe 2 study first national palliative interventional trial in advanced cirrhosis
 - ✦ Provide evidence base for an under researched disenfranchised cohort
 - ✦ Contribute to the evolution of validated patient reported outcomes enabling conduct of future trials



- Sumita Verma (BSMS/UHS) Chief Investigator
- Co Principal Investigators
- Alastair O'Brien (University College London)
 - Mark Wright (Southampton University Hospitals)
 - Ben Hudson (Devon and Exeter Trust)
 - Lucia Macken (University Hospitals Sussex))
 - Stephen Bremner and Nicky Perry (BSCTU)
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 - Alison Richardson (University of Southampton)
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 - Helena Harder and Rachel Starkings (SHORE-C)
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