NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of extracorporeal albumin dialysis for acute liver failure

Acute liver failure is a life-threatening condition in which liver function suddenly and rapidly deteriorates. It can affect the ability of the blood to clot and reduce the oxygen supply to the brain, resulting in a sudden deterioration in mental functioning. Acute liver failure is most commonly caused by infection or poisoning following the use of prescription or recreational drugs, or alcohol.

In extracorporeal albumin dialysis blood is pumped through a filter coated in albumin. The filtered blood is then pumped back into the body. The aim is to enable the patient to survive until the liver either repairs itself or is replaced by a transplanted donor liver.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this 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 2009.

Procedure name

- Extracorporeal albumin dialysis for acute liver failure

Specialty societies

- British Association for Study of the Liver
- British Renal Society
- British Society of Gastroenterology – Liver Section
- Intensive Care Society

Description

Indications and current treatment

Acute liver failure (ALF) is an uncommon condition in which liver function deteriorates rapidly. ALF has a high mortality rate and the risk increases with the development of complications. These include cerebral oedema associated with a sudden onset of cognitive dysfunction, renal failure, respiratory distress syndrome, coagulopathy and infection.

ALF may result from poisoning caused by pharmaceutical or recreational drugs, or alcohol, or from a viral infection. Less commonly, the cause may be a vascular disorder, metabolic disease or acute fatty liver of pregnancy.

There are few treatment options for patients with diminishing liver function. Some patients recover liver function with medical therapy, and sometimes heamodialysis/filtration are necessary. Other patients need transplantation; however, there is a shortage of donor livers.

What the procedure involves

Extracorporeal liver support systems can be used as a ‘bridge’ before liver transplantation to return the patient to a state of compensated cirrhosis or as an adjunct to standard medical therapy. The perceived advantage of this procedure is that it uses albumin to remove additional pathogens as opposed to water-based haemodialysis.

This procedure is designed to selectively eliminate toxins bound to albumin in the blood of patients with ALF. It does this by passing the blood through a filter with a thin, albumin-impregnated membrane. The blood is dialysed against an albumin-rich dialysate. Toxic molecules bound to albumin in the blood are adsorbed onto binding sites of albumin in the filter and then onto the binding sites of albumin in the dialysate. The dialysate is passed through an activated charcoal and an anion-exchange resin column (to remove bound toxins from albumin) and through a conventional filter (to remove water-soluble toxins). The albumin is thus regenerated, and is circulated once again through the main dialyser. The pore size of the main dialyser does not allow larger molecules such as essential hormones bound to carrier proteins, growth factors or the patient’s own albumin to be dialysed out. There are a number of different systems available for this procedure.

OPCS code

X43.1 Extracorporeal albumin haemodialysis

List of studies included in the overview

This overview is based on 789 patients from one meta-analysis[1], one randomised controlled trial[2], two non-randomised controlled trials[3,4], three case series[5–7] and one case report[8].

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 appendix A.

Efficacy

A meta-analysis reported that there was no statistically significant difference in 30-day all-cause mortality between patients who had extracorporeal albumin dialysis and those who had standard medical treatment (relative risk [RR] 0.56; 95% confidence interval [CI] 0.28 to 1.14; p = 0.11)[1]. Similarly, there was no statistically significant difference in mortality between the treatment groups in the subgroups of patients with acute-on-chronic liver failure (RR 0.49; 95% CI 0.12 to 2.17; p = 0.35) or acute liver failure (RR 0.49; 95% CI 0.15 to 1.58; p = 0.23).

A randomised controlled trial of 24 patients reported that there was no statistically significant difference in 6-month survival between patients treated with talbumin dialysis (5 of 8 patients survived), the molecular adsorbent recirculating system (MARS) of albumin dialysis (5 of 8 patients survived) and standard haemodialysis (3 of 6 patients survived) (p = 0.40)[2].

A non-randomised controlled trial of 79 patients with acute alcoholic liver disease reported that survival at 3-year follow-up was significantly greater following extracorporeal albumin dialysis (52%; 17 of 33 patients) than following standard medical therapy (17%; 8 of 46 patients) (p = 0.0035)[3]. A non-randomised controlled trial of 159 patients reported no statistically significant difference in overall survival at 6-month follow-up between patients treated with extracorporeal albumin dialysis (75%; 85 of 113 patients) and those who had standard medical therapy (61%; 28 of 46 patients) (p = 0.07)[4]. There was also no statistically significant difference in 6-month survival following liver transplantation between the patients who had extracorporeal albumin dialysis (94%; 31 of 33 patients) and those who had standard therapy (77%; 20 of 26 patients) (p = 0.06).

A case series of 191 patients who had a total of 2027 treatments with extracorporeal albumin dialysis reported that mean arterial pressure improved significantly, from 59 ± 7.7 mmHg at baseline to 79 ± 4.1 mmHg following treatment (0.02). Changes in heart rate and cardiac index were not statistically significant[5].

Safety

In a meta-analysis only one study reported adverse events. In this study there were 17 adverse events in 12 patients during 91 extracorporeal albumin dialysis treatment sessions and 6 adverse events in 4 patients during 11 dialysis treatments in the control group (the total number of patients treated was not reported)[1].

A randomised controlled trial of 24 patients reported no serious adverse events (such as a fall in arterial blood pressure, haemolysis or bleeding requiring therapeutic intervention) in any of the three treatment groups[2]. Of 8 patients in the extracorporeal albumin dialysis group, 1 patient had bleeding 10 hours after termination of treatment.

A case series of 191 patients who had 2027 extracorporeal albumin dialysis treatments reported transitory hypotension in 14% (292 of 2027) of treatments. Transitory hypoglycaemia occurred in 17% (335 of 2027) of treatments, all in patients with scores of 30–40 on the Model for End-stage Liver Disease scoring system, which grades severity of disease from 1(least severe) to 40 (most severe)[5]. Haemorrhage from the catheter requiring a position change occurred in 4% of treatments for patients with fulminant hepatitis change (absolute figures not reported).

A case series of 30 patients reported that 30% (9 of 30 patients) developed positive blood cultures during extracorporeal albumin dialysis treatment at between 2 and 17 days of follow up[7]; all 9 patients died.

A case report of two patients described severe pulmonary oedema in both patients following treatment with albumin dialysis, leading to suspension of therapy in the second patient. The oedema resolved within 24 hours in both patients following aggressive medical treatment, but both died, the first at 9-day follow-up and the second at 201-day follow-up[8].

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to extracorporeal albumin dialysis for acute liver failure. Searches were conducted of the following databases, covering the period from their commencement to 07-11-08, and updated to 01-06-09: 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 appendix C for details of search strategy).

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 acute liver failure (including acute-on-chronic liver failure).
Intervention/test	Extracorporeal albumin dialysis
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.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Living-donor liver transplantation. NICE interventional procedures guidance 194 (2006). Available from www.nice.org.uk/IPG194
- Extracorporeal albumin dialysis for acute-on-chronic liver failure (current guidance). NICE interventional procedures guidance 45 (2004). Available from www.nice.org.uk/IPG45

Technology appraisal guidance

There is currently no NICE technology appraisal guidance related to this procedure.

Clinical guidelines

There is currently no NICE clinical guideline related to this procedure.

Public health guidance

There is currently no NICE public health guidance related to this procedure.

Table 2 Summary of key efficacy and safety findings on extracorporeal albumin dialysis for acute liver failure

Abbreviations used: ALF, acute liver failure; CI, confidence interval; MARS, molecular adsorbent recirculating system; MELD, Model for end-stage liver disease; NS. not significant;

Study details	Key efficacy findings	Key safety findings	Comments
Khuroo MS (2004)[1] **Meta- analysis** Saudi Arabia and India analysis – international studies Study period: not reported Study population: ALF or acute-on-chronic liver failure Age = not reported,Sex = not reported. **n = 128 (62 MARS) from 4 randomised controlled trials and two non-randomised controlled trials** Inclusion criteria: not reported. Technique: MARS in 6- to 8-hour treatment sessions daily until defined end point reached vs. standard medical treatment or haemodialfiltration. **Follow-up: Not reported.** Conflict of interest: Not reported	**30-day all-cause mortality** Randomised controlled trials All studies MARS Control Relative risk (95% CI) p= 12/36 21/31 0.56 (0.28 to 1.14) 0.11 Peer-reviewed studies MARS Control Relative risk (95% CI) p= 10/28 13/22 0.72 (0.37 to 1.40) 0.33 Studies in patients with acute-on-chronic liver failure MARS Control Relative risk (95% CI) p= 7/20 11/17 0.49 (0.12 to 2.17) 0.35 Studies in patients with ALF MARS Control Relative risk (95% CI) p= 5/16 10/14 0.49 (0.15 to 1.58) 0.23 Non-randomised controlled trials In two studies of patients with acute-on-chronic liver failure the MARS group had a statistically significant pooled reduction in mortality compared with the control group (relative risk 0.36 [95% CI 0.17 to 0.76]) (p = 0.007).	**Complications** Only 1 study reported adverse events in both arms. There were 17 adverse events in 12 patients during 91 MARS treatment sessions, and 6 adverse events in 4 patients during 11 dialysis treatments in the control group. Specific complication rates were not reported but included bleeding, coagulopathy, hypotension, fever and anemia.	Well described search strategy using MeSH terms and free text in Medline, Embase, and Cochrane database, and using bibliography cross-referencing. Randomised and non-randomised controlled trials included in analysis. Analysis undertaken on intention-to-treat principle using random effects model Publication bias tested. Three researchers independently evaluated trials for inclusion. Study quality assessed. One study was in abstract form only and not in peer-reviewed journal. No statistically significant heterogeneity between studies in any analysis. Concomitant treatment in the control groups may have varied between studies.

Abbreviations used: ALF, acute liver failure; CI, confidence interval; MARS, molecular adsorbent recirculating system; MELD, Model for end-stage liver disease; NS. not significant;			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Dethloff T (2008)[2] **Randomised controlled trial** Denmark Study period: not reported Study population: Patients with pre-existing liver disease and decompensated cirrhosis on transplant list. Cirrhosis confirmed clinically, biochemically and radiologically. Age = 55 years, Sex = 63% male. **n = 24 (8 MARS, 8 Prometheus)** Inclusion criteria: Patients with ascites, and a history of hepatic encephalopathy or repeated variceal bleeding. No active haemorrhage, systemic infection, extraheapatic cholestasis, necrotic pancreatitis, cardiovascular failure or albumin dialysis within the past 7 days. Technique: Extracorporeal blood treatment using Prometheus, vs. MARS vs. standard heamodialysis in 6-hour treatment session. Patients in all groups treated with identical blood and dialysate flow rates. **Follow-up: 6 months** Conflict of interest: Supported by manufacturer.	**Procedure success** 2 out of 8 patients in the conventional heamodyalisis group dropped out of the study due to repeated clotting of the filters. During MARS treatment there were significant increases in systolic and diastolic blood pressure – 10.5% and 15.2% respectively – compared with baseline (absolute figures and measurement of significance not reported). **Survival** Of the 8 patients in the MARS group 6 were alive at 6-month follow-up (1 of whom had received a liver transplant) and 2 had died. Of the 8 patients in the Prometheus group 5 were alive at 6-month follow-up (3 of whom had received a liver transplant) and 3 had died. Of the 6 patients who completed treatment in the conventional heamodialysis group 3 were alive at 6-month follow up (1 of whom had received a liver transplant) and 3 had died. There was no statistical difference in 6-month survival outcome between the groups(p = 0.397).	**Complications** 1 of 8 patients in the MARS group had bleeding 10 hours after termination of treatment. Both during and after treatment no patient required calcium or citrate supplements, and no correction of pH was necessary. No other serious adverse events were reported from any group	Randomisation by computer-generated sequence, concealment by opaque envelopes. There were two treatment arms using albumin dialysis treatments and one with conventional dialysis. Number of treatment sessions not reported. No statistically significant difference between the three groups at baseline in terms of age, or clinical characteristics. Authors state that choice of treatment will depend on the risk of adverse events, and the possible positive or negative haemodynamic influences of the the available treatment types.

Abbreviations used: ALF, acute liver failure; CI, confidence interval; MARS, molecular adsorbent recirculating system; MELD, Model for end-stage liver disease; NS. not significant;

Study details	Key efficacy findings	Key safety findings	Comments
Hessel P (2006)[3] **Non-randomised controlled trial** Germany Study period: 1999 to 2003 Study population: Patients with acute progressionof alcoholic liver diseaseor known chronic liver disease and documented alcohol abuse for >5 years. Age = 48 years, Sex = 64% male; Mean Child Pugh score 11.6. **n = 79 (33 MARS)** Inclusion criteria: Patients with bilirubin level > 300 mmol/µl and no gastrointestinal bleeding, carcinoma, other comorbidity,or placement on liver transplant list. Technique: Extracorporeal blood treatment using MARS for 5 consecutive days vs. standard medical treatment with every therapeutic option other than MARS. **Follow-up: 3 years** Conflict of interest: supported by manufacturer.	**Survival** MARS (n = 33) / Standard medical (n = 46) Discharge: 67% (22/33) / 63% (29/46) 1 year: 58% (19/33) / 35% (16/46) 2 years: 52% (17/33) / 26% (12/46) 3 years: 52% (17/33) / 17% (8/46) (p = 0.0035)	Safety outcomes were not reported.	Potentially some of the same patients as included in the meta-analysis by Khuroo (2004); however, additional patients reported here. Consecutive patient accrual. Method for treatment allocation not reported. Child-Pugh score is used to assess the prognosis of liver disease. It measures 5 factors producing a score from 5 to 15 points. Higher scores represent worse prognoses. Loss to follow-up well reported. There were no significant differences in baseline demographics or clinical characteristics (including acute-on-chronic liver failure). Cost-effectiveness outcomes also reported but not extracted here, therefore only limited clinical data are available. Quality-of-life outcomes were collected but are not reported here.

Abbreviations used: ALF, acute liver failure; CI, confidence interval; MARS, molecular adsorbent recirculating system; MELD, Model for end-stage liver disease; NS. not significant;			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Kantola T (2008)[4] **Non-randomised controlled trial** Finland Study period: 2001 to 2007 (MARS) Study population: Patients with life-threatening liver failure of various aetiologies evaluated for liver transplant. Age = 43 years, Sex = 39% male. MELD score = 31, encephalopathy grade = 1.9 **n = 159 (113 MARS)** Inclusion criteria: Not reported. All patients considered for placement on liver transplant list. Technique: Extracorporeal blood treatment using MARS 22 hours daily vs. control therapy with renal replacement therapy where necessary and high-volume plasmapherisis in 12 patients **Follow-up: 6 months** Conflict of interest: not reported.	**Survival** At 6-month follow-up survival was 75% (85/113) in the MARS group and 61% (28/46) in the control group (p = 0.07). At 6-month follow-up survival following liver transplant was 94% (31/33) in the MARS group and 77% (20/26) in the control group (p = 0.06). In the MARS group the native liver recovered in 49% (55/113) of patients compared with 17% (8/46) in the control group (p<0.001).	**Complications** There were no serious complications associated with MARS treatment. Mild thrombocytopenia was observed. 2% (1/46) of patients in the control group died from transfusion-related acute lung injury.	Prospective data collection in the MARS group. Retrospective case-note analysis of control patients. Historical control group prior to availability of MARS treatment Consecutive treated patients Concomitant treatment was the same in both groups using standard medical therapy. Liver failure treatment varied significantly between patients included in the control group. The aetiology of disease among patients in the MARS group was significantly different from the control group, with more unknown aetiology in the latter group. Survival results for the different aetiologies of liver failure are also reported but not extracted here.

Abbreviations used: ALF, acute liver failure; CI, confidence interval; MARS, molecular adsorbent recirculating system; MELD, Model for end-stage liver disease; NS. not significant;

Study details	Key efficacy findings	Key safety findings	Comments
Pugliese F (2008)[5] **Case series** Italy Study period: 1999 onwards Study population: Patients with liver failure of various aetiologies. Age = 40 years, Sex = 50% male. ALF n = 83, acute-on-chronic liver failure n =9 4. **n = 191 (2027 treatments)** Inclusion criteria: Patients with bilirubin level > 300 mmol/µl and no gastrointestinal bleeding, carcinoma, other comorbidity or placement on liver transplant list. Technique: Extracorporeal blood treatment using MARS for 6 hours for a mean 11 treatments in patients with acute-on-chronic liver failure, or continuously with a kit change every 8 hours in ALF patients. **Follow-up: Not reported** Conflict of interest: not reported.	**Toxic parameters** ALF patients, mean and standard deviation Baseline / Post treatment / p= Interleukin 6: 42.14 ± 9.1 / 32.36 ± 10.86 / <0.01 Tumour necrosis factor α: 20.33 ± 8.95 / 12.2 ± 4.50 / <0.2 Nitrates (µmol/L): 95 ± 16.8 / 77.6 ± 9.80 / <0.2 Nitrites (µmol/L): 15.04 ± 1.81 / 12.23 ± 8.29 / NS Acute-on-chronic liver failure patients, mean and standard deviation Baseline / Post treatment / p= Interleukin 6: 38.14 ± 11.1 / 23.48 ± 9.68 / <0.001 Tumour necrosis factor α: 15.41 ± 7.85 / 11.5 ± 6.57 / <0.03 Nitrates (µmol/L): 98.14 ± 23.1 / 73.48 ± 8.68 / <0.1 Nitrites (µmol/L): 13.04 ± 1.81 / 9.84 ± 3.36 / 0.4 Acute on chronic liver failure patients treated in ICU, mean and standard deviation (n = 42) Baseline / Post treatment / p= Heart rate (BPM): 105 ± 20 / 86 ± 9.1 / NS Mean arterial pressure (mmHg): 59 ± 7.7 / 79 ± 4.1 / <0.02 Cardiac index (L/min/m^2): 7.9 ± 1.6 / 5.4 ± 4.3 / NS	**Complications** Transitory hypotension occurred in 14% (292/2027) of treatments,and was corrected through parenteral administration of mannitol and cortisone. Transitory hypoglycaemia occurred in 17% (335/2027) of treatments all in patients with MELD scores of 30–40. In the first 3 years of treatment of patients with acute-on-chronic liver failure, infections requiring catheter changes occurred in 29% of patients (absolute figures not stated). However, this was reduced by 20% with a kit change every 10 days. Haemorrhage from the catheter requiring a position change was reported in 4% of treatments for patients with fulminant hepatitis (absolute figures not stated).	Treatment regimen varied depending on type of liver failure. Follow-up period not reported. Efficacy outcomes are measured at end of treatment. Units of measurement not reported for all haemodynamic parameters assessed.

Abbreviations used: ALF, acute liver failure; CI, confidence interval; MARS, molecular adsorbent recirculating system; MELD, Model for end-stage liver disease; NS. not significant;

Study details	Key efficacy findings	Key safety findings	Comments
Steiner C (2002) [6] **Case series** International Study period: 1999 onwards Study population: Patients with liver failure of various aetiologies. Age = not reported, Sex = Not reported. ALF n = 38, Acute-on-chronic liver failure n = 99, graft dysfunction following transplant n = 27. **n = 176** Inclusion criteria: Not reported. Technique: Extracorporeal blood treatment using MARS not otherwise described. **Follow-up: Not reported** Conflict of interest: not reported	**Survival** Acute-on-chronic liver failure patients: 57% (56/99) of patients discharged fully recompensated (50 without liver transplant) Child-Pugh / No / % / In-hospital survival 10 / 1 / 2 / 100% 11 / 7 / 11 / 86% 12 / 17 / 27 / 71% 13 / 20 / 31 / 60% 14 / 11 / 17 / 55% 15 / 5 / 8 / 0% Acute liver failure patients: 50% (19/38) of patients survived (13 without liver transplant) Primary graft dysfunction patients: 57% (15/27) of patients survived (all without liver re-transplant) **Neurological function** Acute-on-chronic liver failure patients: Neurological outcome: 0–4 (where 0 is minimal changes in memory and 4 is coma) Baseline: 2.2 ± 0.9 Post procedure: 0.9 ± 1.2	**Complications** Clinical features complicating the course of liver failure are noted	Part retrospective analysis 'Survival' defined as 'recompensated and discharged from hospital'. 37 hospitals from 11 European and Asian countries. 176 patients included in database from 800 treated. Child-Pugh score is used to assess the prognosis of liver disease. It measures 5 factors producing a score from 5 to 15 points. Higher scores represent worse prognoses.

Abbreviations used: ALF, acute liver failure; CI, confidence interval; MARS, molecular adsorbent recirculating system; MELD, Model for end-stage liver disease; NS. not significant;

Study details	Key efficacy findings	Key safety findings	Comments
Doria C (2005)[7] **Case series** Italy Study period: September 2000 to April 2003 Study population: Patients with cirrhosis awaiting liver transplantation who developed acute-on-chronic liver failure. Age = 52 years, Sex = 57% male. **n = 30** Inclusion criteria: Patients with 2 of the 4 following criteria: worsening encephalopathy despite intensive medical management, rising bilirubin level > 10 mg/dl, worsening renal function despite volume expansion, worsening coagulopathy and no culture-proven sepsis. Technique: Extracorporeal blood treatment using MARS for 6 hours for a mean 7 treatments on consecutive days. A second treatment was initiated in responders. **Follow-up: 2 to 17 days in patients who became infected** Conflict of interest: not reported.	No efficacy outcomes were reported.	**Complications** 30% (9/30) of patients developed positive blood culture during treatment. All died during the same hospital admission. Survival was statistically worse than in patients without infection (p = 0.0002). In the 9 patients who developed positive blood culture the source of infection was sputum in 4, ascites in 3, urine in 1 and purely blood-borne in 1. **Baseline cardiac profile group mean and standard deviations** Cardiac output (l/min): Positive blood culture 10.9 ± 1.4; Negative blood culture 10.9 ± 3.4; p= NS Cardiac index (l/min): 6.9 ± 0.9; 10.1 ± 4.0; NS Vascular resistance (dynesec/cm^5/m^2): 688 ± 170.2; 1060 ± 692; <0.05	Case accrual method not reported. Follow-up of patients who did not develop blood infection not reported. Highly selected patient cohort

Abbreviations used: ALF, acute liver failure; CI, confidence interval; MARS, molecular adsorbent recirculating system; MELD, Model for end-stage liver disease; NS. not significant;			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Doria C (2003)[8] **Case report** Italy Study period: Not reported Study population: Patients with cirrhosis who developed acute-on-chronic liver failure, or pruritus, encephalopathy and worsening renal function. Age = 60 years; Sex = 100% male **n = 2** Inclusion criteria: Not reported Technique: Extracorporeal blood treatment using MARS. Treatment protocol varied. **Follow-up: 9 to 201 days** Conflict of interest: not reported.	**Case 1** Patient with cirrhosis underwent a successful mesocaval shunt. Three months after surgery the patient developed acute-on-chronic liver failure with rapidly worsening encephalopathy, rising bilirubin, and worsening coagulopathy. Throughout MARS treatment the patient had negative blood culture with no signs of infection or sepsis, was haemodynamically stabl and had a normal chest X-ray. Following partial response to MARS a 2nd treatment was started. During the 4th session of the 2nd treatment course the patient developed pulmonary oedema requiring intubation. No blood or blood products were transfused in the 48 hours prior to the development of severe pulmonary oedema, and other known causes could not be identified. MARS treatment was stopped and aggressive medical management of the pulmonary oedema initiated. 24 hours later the oedema resolved. Subsequently the patient became haemodynamically unstable. 9 days after the final MARS session the patient died of end-stage liver failure and multiple organ failure. **Case 2** Patient evaluated for liver transplant and treated with MARS for cirrhosis complicated by intractable pruritis, encephalopathy, and worsening renal failure. Throughout MARS treatment the patient had negative blood cultures with no signs of infection or sepsis, was haemodynamically stable,and had a normal chest X-ray. After the 7th MARS session the patient developed pulmonary oedema. An even fluid balance was maintained throughout the MARS treatment. No blood or blood products were transfused in the 48 hours prior to the development of severe pulmonary oedema, and other known causes could not be identified. MARS treatment was stopped and aggressive medical management of the pulmonary oedema initiated. Pulmonary oedema was considered to be of non-cardiogenic origin. 24 hours later the oedema resolved. Transplant treatment was excluded because of previous treatment for urinary bladder cancer. 6 months after completion of MARS treatment the patient developed renal insufficiency requiring haemodyalysis. The patient died of cardiac arrest at 201-day follow -up.		Denominator number of patients treated at the centre not reported. Clinical experience not reported.

Validity and generalisability of the studies

- Clinical condition (severity of liver failure) of patients at baseline varies considerably between studies.
- Aetiology of liver failure varied within and between studies, and the purpose of liver support varied.
- Follow-up length was often short.

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 does not represent the view of the society.

Professor M Bellamy (Intensive Care Society), Dr J Freeman (British Society of Gastroenterology – Liver Section), Dr A Lee (British Association for Study of the Liver), Dr A Rhodes (Intensive Care Society), Professor R Williams (British Association for Study of the Liver).

- Four Specialist Advisers considered the procedure to be novel and of uncertain safety and efficacy, and one categorised it as the first in a new class of procedure.
- There is no real comparator apart from standard clinical supportive therapy.
- There are no major randomised controlled trials available.
- Reported adverse events related to the procedure include increased variceal bleeding and infection.
- Additional theoretical adverse events may include coagulopathy, shock states, hypotension, electrolyte abnormalities and circuit thrombosis.
- The key efficacy outcomes for this procedure are survival or successful bridge to transplant, reduced intracranial pressure/encephalopathy and improved heamodynamic stability.
- Uncertainty relates more to efficacy than safety.
- The procedure requires familiarity with dialysis, heamofiltration and extracorporeal support, and specific device-related training.

- There is uncertainty about whether this should be implemented by intensivists, renal physicians or hepatologists.
- Additional risk with this procedure is small as most patients will already require an extracorporeal circuit for haemofiltration.
- The procedure is potentially a very important intervention in a small number of patients and might reduce the need for transplantation.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

- Non-English language studies were not included.
- There is potential overlap/double reporting of patients in the studies included in table 2; this is highlighted where known.
- Many studies have been published very recently.

References

1 Khuroo MS, Farahat KLC (2004) Molecular adsorbent recirculating system for acute and acute-on-chronic liver failure: a meta-analysis. Liver Transplantation 10:1099–106

2 Dethloff T, Tofteng F, Frederiksen HJ et al. (2008) Effect of Prometheus liver assist system on systemic hemodynamics in patients with cirrhosis: a randomized controlled study. World Journal of Gastroenterology 14:2065–71

3 Hessel FP (2006) Economic evaluation of the artificial liver support system MARS in patients with acute-on-chronic liver failure. Cost Effectiveness and Resource Allocation 4, Article Number: 16. 4 Kantola T, Koivusalo AM, Hockerstedt K et al. (2008) The effect of molecular adsorbent recirculating system treatment on survival, native liver recovery, and need for liver transplantation in acute liver failure patients. Transplant International 21: 857–66

5 Pugliese F, Novelli G, Poli L et al. (2008) Hemodynamic improvement as an additional parameter to evaluate the safety and tolerability of the molecular adsorbent recirculating system in liver failure patients. Transplantation Proceedings 40:1925–8

6 Steiner C, Mitzner S (2002) Experiences with MARS liver support therapy in liver failure: analysis of 176 patients of the International MARS Registry. Liver 22: Suppl. 5: 20-25

7 Doria C, Marino IR (2005) Bacteremia using the molecular adsorbent recirculating system in patients bridged to liver transplantation. Experimental & Clinical Transplantation: Official Journal of the Middle East Society for Organ Transplantation 3: 289–92

8 Doria C, Mandala L, Scott VL et al. (2003) Noncardiogenic pulmonary edema induced by a molecular adsorbent recirculating system: case report. Journal of Artificial Organs 6: 282–5

Appendix A: Additional papers on extracorporeal albumin dialysis for acute liver failure

The following table outlines the studies that are considered potentially relevant to the 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
Auth MK, Kim HS, Beste M et al. (2005) Removal of metabolites, cytokines and hepatic growth factors by extracorporeal liver support in children. Journal of Pediatric Gastroenterology & Nutrition 40 (1): 54–9	Case report n = 4 Follow-up not reported	Extraction of albumin-bound and water-soluble candidate substances was detected with variable effects on blood levels.	Larger studies are included in table 2
Boyle M, Kurtovic J, Bihari D et al. (2004) Equipment review: the molecular adsorbent recirculating system (MARS). Critical Care (London, England) 8 (4): 280–6	Case report n = 5 Follow-up not reported	Preliminary experience indicates some clinical efficacy	Larger studies are included in table 2
Campli CD, Gaspari R, Mignani V. et al. (2003) Successful ARS treatment in severe cholestatic patients with acute on chronic liver failure. Artificial Organs 27 (6): 565–9	Case series n = 7 Follow-up = 3 months	MARS can represent a safe therapeutic choice to achieve a quick improvement of neurological status, haemodynamic stability, and a better clinical utcome	Larger studies are included in table 2
Camus C, Lavoue S, Gacouin A et al. (2006) Molecular adsorbent recirculating system dialysis in patients with acute liver failure who are assessed for liver transplantation.[see comment]. Intensive Care Medicine 32 (11): 1817–25	Case series n = 23 Follow-up = 1 month	A statistically significant improvement in liver function was observed after MARS therapy	Larger studies are included in table 2
Catalina MV, Barrio J, Anaya F et al. (2003) Hepatic and systemic haemodynamic changes after MARS in patients with acute on chronic liver failure. Liver International 23: (Suppl. 43)	Case series n = 4 Follow-up not reported	MARS decreases portal hypertension and ameliorates hyperdynamic circulation in patients with acute-on-chronic liver failure	Larger studies are included in table 2
Chiu A, Chan LM, Fan ST. (2006) Molecular adsorbent recirculating system treatment for patients with liver failure: the Hong Kong experience. Liver International 26 (6): 695–702	Case series n = 22 Follow-up not reported	Suitable for temporarily supporting patients with liver failure when transplantation is not immediately available	Larger studies are included in table 2
Covic A, Maftei ID, Gusbeth-Tatomir P. (2007) Acute liver failure due to leptospirosis successfully treated with MARS (molecular adsorbent recirculating system) dialysis. International Urology & Nephrology 39 (1): 313–6	Case report n = 1 Follow-up = 3 months	Albumin dialysis may confer a significant survival benefit on patients with leptospirosis-induced acute liver failure	Larger studies are included in table 2

de Naeyer S., Ysebaert, D., van, Utterbeeck M et al (2008) Acute fatty liver of pregnancy and molecular absorbent recirculating system (MARS)-therapy: a case report. Journal of Maternal-Fetal & Neonatal Medicine 21 (8) 587-589.	Case report n=1 FU=?	MARS was started because of failing hepatic and renal function and oedema of the brain. During the 34 days MARS was used the patient's hepatic , renal , and neurological function improved.	Larger studies are included in table 2
Di Campli C, Santoro MC, Gaspari . et al. (2005) Catholic university experience with molecular adsorbent recycling system in patients with severe liver failure. Transplantation Proceedings 37 (6): 2547–50	Case series n = 20 Follow-up= 3 months	Confirms safety and clinical efficacy of MARS treatment with the best results in patients with MELD score 20 to 29.	Larger studies are included in table 2
Ding YT, Xu QX., Qiu YD et al. (2004) Molecular adsorbent recycling system in treating patients with acute liver failure: a bridge to liver transplantation. Hepatobiliary & Pancreatic Diseases International 3 (4): 508–10	Case series n = 8 Follow-up not reported	MARS is effective in bridging patients with acute liver failure to liver transplantation	Larger studies are included in table 2
Donati G, Piscaglia F, Coli L. et al. (2007) Acute systemic, splanchnic and renal haemodynamic changes induced by molecular adsorbent recirculating system (MARS) treatment in patients with end-stage cirrhosis. Alimentary Pharmacology & Therapeutics 26 (5): 717–26	Case series n = 12 Follow-up not reported	MARS significantlyimproves various haemodynamic alterations in cirrhotic patients in the short term	Larger studies are included in table 2
Doria C, Mandala L., Scott VL et al. (2006) Fulminant hepatic failure bridged to liver transplantation with a molecular adsorbent recirculating system: a single-center experience. Digestive Diseases & Sciences 51 (1): 47–53	Case series n = 7 Follow-up not reported	MARS is a safe temporary life support mechanism for patients awaiting liver transplantation or recovering from fulminant hepatic failure.	Larger studies are included in table 2
Evenepoel P, Laleman W, Wilmer A. et al. (2006) Prometheus versus molecular adsorbent recirculating system: comparison of efficiency in two different liver detoxification devices. Artificial Organs 30 (4): 276–84	Non-randomised controlled trial n = 18 (9 MARS) Follow-up = 3 months	Prometheus produces higher blood clearance rates for most toxins which results in higher delivered treatment doses	Comparison of two albumin dialysis techniques Larger studies are included in table 2

Gaspari, R., Cavaliere, F., Sollazzi, L. et al (2009) Molecular adsorbent recirculating system (Mars) in patients with primary nonfunction and other causes of graft dysfunction after liver transplantation in the era of extended criteria donor organs. Transplantation Proceedings 41 (1) 253-258.	Case series n=7 FU=6 months	MARS is a safe, therapeutic option for the treatment of liver dysfunction after transplantation	Larger studies are included in table 2
Hetz H, Faybik P, Berlakovich G. et al. (2006) Molecular asorbent recirculating systems in patients with early allograft dysfunction after liver transplantation: A pilot study. Liver Transplantation 12 (9): 1357–64	Case report n = 12 Follow-up = 1 year	Sustained improvement of renal and neurological function and of mean arterial pressure were observed	Larger studies are included in table 2
Inderbitzin D, Muggli B, Ringger A. et al. (2005) Molecular absorbent recirculating system for the treatment of acute liver failure in surgical patients. Journal of Gastrointestinal Surgery 9 (8): 1155–61.	Case series n = 7 Follow-up not reported	MARS can be an effective treatment of postoperative liver insufficiency in the surgical hepatobiliary ward	Larger studies are included in table 2
Koivusalo AM, Vakkuri A, Hockerstedt K et al. (2005) Experience of Mars therapy with and without transplantation in 101 patients with liver insufficiency. Transplantation Proceedings 37 (8): 3315-3317.	Case series n = 101 Follow-up = to 1 year	Did not observe much benefit of MARS for patients with acute-on-chronic liver failure without liver transplantation.	Larger studies are included in table 2
Krisper P, Haditsch B, Stauber . et al. (2005) In vivo quantification of liver dialysis: comparison of albumin dialysis and fractionated plasma separation. Journal of Hepatology 43 (3): 451–7	Non-randomised controlled trial n = 8 (cross over) Follow-up = 6 hours	Fractionated plasma separation provided higher treatment dose	Larger studies are included in table 2 Studies with longer follow- up are included in table 2
Kurtovic J, Boyle M, Bihari D et al. (2006) An Australian experience with the molecular adsorbent recirculating system (Mars). Therapeutic Apheresis & Dialysis: Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy 10 (1): 2–6	Case series n = 6 Follow-up not reported	Overall survival rate 17% (1/6) was poor	Larger studies are included in table 2

Lahdenpera A, Koivusalo AM, Vakkuri A et al. (2005) Value of albumin dialysis therapy in severe liver insufficiency. Transplant International 17 (11): 717–23	Case series n = 88 Follow-up not reported	Only 23% of patients with acute-on-chronic liver failure survived compared with 80% who had ALF	Larger studies are included in table 2
Lee KH, Lee MK, Sutedja DS et al. (2005) Outcome from molecular adsorbent recycling system (MARS) liver dialysis following drug-induced liver failure. Liver International 25 (5): 973–7	Case series n = 13 Follow-up = 8 days	MARS liver dialysis in a setting without timely liver transplantation is associated with a poor outcome	Larger studies are included in table 2
Lemoine, M., Revaux, A., Francoz, C. et al (2008) Albumin liver dialysis as pregnancy-saving procedure in cholestatic liver disease and intractable pruritus. World Journal of Gastroenterology 14 (42) 6572-6574.	Case report n=1 FU=6 months	Albumin dialysis could be considered as a pregnancy-saving procedure in pregnant women with severe cholestasis and refractory pruritus	Larger studies are included in table 2
Lionte C, Sorodoc L, Simionescu V. (2005) Successful treatment of an adult with Amanita phalloides-induced fulminant liver failure with molecular adsorbent recirculating system (MARS). Romanian Journal of Gastroenterology 14 (3):267–71	Case report n = 1 Follow-up not reported	MARS appears to be a safe and highly effective therapy in adults with amanita phalloides-induced ALF	Larger studies are included in table 2
Javouhey, E., Ranchin, B., Lachaux, A., et al (2009) Long-lasting extracorporeal albumin dialysis in a child with end-stage renal disease and severe cholestasis. Pediatric Transplantation 13 (2) 235-239.	Case report n=1 FU=8 months	MARS dialysis is feasible in children, decreases adverse effects of severe chronic cholestasis	Larger studies are included in table 2
Novelli G, Rossi M, Pugliese F et al. (2005) One Hundred Sixteen Cases of Acute Liver Failure Treated with MARS. Transplantation Proceedings 37: 2557–9	Case series n = 116 Follow-up not reported	MARS can be applied with tolerability for long periods for patients with acute liver failure as a bridge to transplant	Larger studies are included in table 2
Novelli G, Rossi M, Pugliese F et al. (2007) Molecular adsorbent recirculating system treatment in acute-on-chronic hepatitis patients on the transplant waiting list improves Model for End-stage Liver Disease scores. Transplantation Proceedings 39 (6): 1864–7	Case series n = 80 Follow-up = 3 months	MARS treatment improved multiple organ functions	Larger studies are included in table 2

Pares, A., Deulofeu, R., Cisneros, L. et al (2009) Albumin dialysis improves hepatic encephalopathy and decreases circulating phenolic aromatic amino acids in patients with alcoholic hepatitis and severe liver failure. Critical Care 13 (1)	Case series n=9 FU=1 year	Albumin dialysis results in a significant decrease in circulating phenolic aromatic amino acids and improvement of hepatic encephalopathy in patients with severe liver failure	Larger studies are included in table 2 Mixed study population of patients with ALF of pruritus
Penafiel A, Devanand A, Tan HK et al. (2006) Use of molecular adsorbent recirculating system in acute liver failure attributable to dengue hemorrhagic fever. Journal of Intensive Care Medicine 21 (6): 369–71	Case report n = 1 Follow-up = 1 week	MARS led to rapid reversal of biochemical profile and encephalopathy resulting in early extubation and ICU discharge.	Larger studies are included in table 2
Rubik J, Pietraszek-Jezierska E, Kaminski A.et al. (2004) Successful treatment of a child with fulminant liver failure and coma caused by Amanita phalloides intoxication with albumin dialysis without liver transplantation. Pediatric Transplantation 8 (3): 295–300	Case report n = 1 Follow-up = 1 year	Patient avoided scheduled liver transplantation after MARS treatment	Larger studies are included in table 2
Saich R, Collins P, Ala A et al. (2005) Benign recurrent intrahepatic cholestasis with secondary renal impairment treated with extracorporeal albumin dialysis. European Journal of Gastroenterology & Hepatology 17 (5): 585–8	Case report n = 1 Follow-up = 7 weeks	MARS treatment immediately improved symptoms	Larger studies are included in table 2
Sen S, Davies NA, Mookerjee RP et al. (2004) Pathophysiological effects of albumin dialysis in acute-on-chronic liver failure: a randomized controlled study. Liver Transplantation 10 (9): 1109–19	Randomised controlled trial n = 18 (9 MARS) Follow-up = 1 week	In inflammation-related acute-on-chronic liver failure patients albumin dialysis using MARS results in improvement in encephalopathy	Larger studies are included in table 2

Stefoni S, Coli L, Bolondi L et al. (2006) Molecular adsorbent recirculating system (MARS) application in liver failure: clinical and hemodepurative results in 22 patients. International Journal of Artificial Organs 29 (2): 207–18	Case series n = 22 Follow-up = 300 hours	MARS treatment led to an improvement in clinical, haemodynamic, and neurological conditions in all patients	Larger studies are included in table 2
Taccone FS, Lucidi V, Donckier V et al. (2008) Fulminant hepatitis requiring MARS and liver transplantation in a patient with Still's disease. European Journal of Internal Medicine 19 (6): e26–8	Case report n = 1 Follow-up = 1 year	MARS can be an additional therapeutic option to buy time until an organ is available when urgent transplantation is required	Larger studies are included in table 2
Tan HK, Yang WS, Chow P et al. (2007) Anticoagulation minimization is safe and effective in albumin liver dialysis using the molecular adsorbent recirculating system. Artificial Organs 31 (3): 193–9	Case series n = 4 Follow-up not reported	Heparin-minimised MARS did not compromise circuit function and longevity in extended intermittent MARS	Larger studies are included in table 2
Tsai MH, Chen YC., Wu CS et al. (2005) Extracorporeal liver support with molecular adsorbent recirculating system in patients with hepatitis B-associated fulminant hepatic failure. International Journal of Clinical Practice 59 (11): 1289–94.	Case series n = 10 Follow-up = 3 months	MARS can improve multiple organ failure in hepatitis B virus-associated fulminant hepatic failure	Larger studies are included in table 2
Wagholikar GD, Lee KH, Pandey D et al. (2007) Re-transplant optimization by Molecular Adsorbent Recirculating System in patients with severely decompensated chronic liver disease.[see comment]. Indian Journal of Gastroenterology 26 (3): 110– 2	Case series n = 9 Follow-up =27 days	Pre-liver transplantation MARS is well tolerated and results in reduction of jaundice and improvement in renal function	Larger studies are included in table 2
Wang M-M, Chen S-J, Ye Q-F et al (2008) Liver support therapy with molecular adsorbents recirculating system in liver failure: a summary of 252 cases from 14 centers in China	Case series n = 44 Follow-up not reported	Survival rate was 62.5% (including patients bridged to transplant) in patients with acute liver failure	Larger studies are included in table 2
Wai CT, Lim SG, Aung MO.et al. (2007) MARS: a futile tool in centres without active liver transplant support. Liver International 27 (1): 69–75	Case series n = 50 Follow-up not reported	Survival was related to availability of liver transplant and where not available MARS was of little benefit	Larger studies are included in table 2

Wolff B, Machill K, Schumacher D et al. (2007) MARS dialysis in decompensated alcoholic liver disease: a single-center experience. Liver Transplantation 13 (8): 1189–92.	Case series n = 14 Follow-up = 9 days	Experience does not support the indiscriminate use of MARS in acutely decompensated alcoholic liver disease without further controlled studies	Larger studies are included in table 2
Wu BF,Wang MM (2004) Molecular adsorbent recirculating system in dealing with maternal Amanita poisoning during the second pregnancy trimester: a case report. Hepatobiliary & Pancreatic Diseases International 3 (1): 152–4	Case report n = 1 Follow-up = 7 months	MARS appears to be an optimal therapy for patients with acute liver failure secondary to cytotoxic mushroom poisoning during pregnancy.	Larger studies are included in table 2
Yuan JZ, Ye QF, Zhao LL et al. (2006) Preoperative risk factor analysis in orthotopic liver transplantation with pretransplant artificial liver support therapy. World Journal of Gastroenterology 12 (31): 5055–9	Case series n = 50 Follow-up = 1 month	MARS treatment can relieve the preoperative factors that cause early death after transplantation	Larger studies are included in table 2
Zhou XM, Miao JY, Yang Y et al. (2004) Clinical experience with molecular adsorbent recirculating system (MARS) in patients with drug-induced liver failure. Artificial Organs 28 (5): 483-486	Case series n = 14 Follow-up = 6 to 12 months	Overall survival rate was about 79%.	Larger studies are included in table 2

Appendix B: Related NICE guidance for extracorporeal albumin dialysis for acute liver failure

Guidance	Recommendations
Interventional procedures	**Extracorporeal albumin dialysis for acute-on-chronic liver failure (current guidance). NICE interventional procedures guidance 45 (2004)** 1.1 Current evidence on the safety and efficacy of extracorporeal albumin dialysis for acute-on-chronic liver failure (AoCLF) does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to undertake extracorporeal albumin dialysis for AoCLF should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. Use of the Institute's Information for the Public is recommended. • Audit and review clinical outcomes of all patients having extracorporeal albumin dialysis for AoCLF. Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. The Institute may review the procedure upon publication of further evidence. **Living-donor liver transplantation. NICE interventional procedures guidance 194 (2006)** 1.1 Current evidence on the efficacy of living-donor liver transplantation and its safety profile appears adequate to support the use of this procedure for suitable recipients. 1.2 However, current evidence suggests that living-donor liver transplantation carries a significant risk of morbidity and a small risk of death for donors. Therefore clinicians wishing to undertake this procedure should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that donors and recipients undergo thorough physical and psychological screening, and receive counselling about the morbidity and risks associated with this procedure. They should also be provided with clear written information. In addition, use of the Institute's information for patients ('Understanding NICE guidance') is recommended.

	• Audit and review clinical outcomes of all people donating liver tissue for transplantation (see section 3.1). 1.3 Living-donor liver transplantation should only be performed on patients selected using UK Transplant Liver Advisory Group standards in specialist centres and in the context of a multidisciplinary team. 1.4 Clinicians should enter all donors and recipients into the UK & Ireland Liver Transplant Audit (www.rcseng.ac.uk/surgical_research_units/ceu/projects/proj_liver.html).

Appendix C: Literature search for extracorporeal albumin dialysis for acute liver failure

Database	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	10/11/2008	Issue 4, 2008	2
Database of Abstracts of Reviews of Effects – DARE (CRD website)	10/11/2008	N/A	1
HTA database (CRD website)	10/11/2008	N/A	4
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	10/11/2008	Issue 4, 2008	6
MEDLINE (Ovid)	7/11/2008	1950 to October Week 5 2008	275
MEDLINE In-Process (Ovid)	10/11/2008	November 07, 2008	41
EMBASE (Ovid)	10/11/2008	1980 to 2008 Week 45	219
CINAHL (EBSCOhost)	10/11/2008	N/A	9
BLIC (Dialog DataStar)	11/11/2008	N/A	21
National Research Register (NRR) Archive	11/11/2008	N/A	Liver Support With Extracorporeal Albumin Dialysis (mars) in Fulminant Hepatic Failure, Primary Graft Dysfunction and Alcoholic Hepatitis
UK Clinical Research Network (UKCRN) Portfolio Database	11/11/2008	N/A	The predictive utility of the dimethylargninines and ischemia modified albumin as prognostic biomarkers in patients with acute on chronic liver failure
Current Controlled Trials *meta*Register of Controlled Trials - *m*RCT	11/11/2008	N/A	The Effect of Prometheus Liver Support Dialysis on Cerebral Metabolism in Acute Liver Failure
Clinicaltrials.gov	11/11/2008	N/A	Single Pass Albumin

			Dialysis in Patients With Cirrhosis The MARS Albumin Dialysis System in Patients With Fulminant and Subfulminant Hepatic Failure

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

1 Acute Liver Failure/

2 (acute* adj3 liver* adj3 fail*).tw.

3 (liver* adj3 (insufficienc* or diseas* or defect* or deficienc* or fail*)).tw.

4 Hepatic Insufficiency/

5 (hepatic* adj3 insufficien*).tw.

6 exp Liver Diseases/

7 (Acute* adj3 decompen* adj3 liver* adj3 diseas*).tw.

8 Overdose/

9 Liver/

10 8 and 9

11 Cholestasis/

12 Cholestasis*.tw.

13 11 or 12

14 (Drug* adj3 induce*).tw.

15 13 and 14

16 (therapy* adj3 resistant* adj3 pruritius*).tw.

17 6 and 16

18 (extracorporeal* adj3 albumin* adj3 dialysis*).tw.

19 Serum Albumin/

20 (serum* adj3 albumin*).tw.

21 (plasma* adj3 albumin*).tw.

22 19 or 20 or 21

23 extracorporeal*.tw.

24 albumin*.tw.

25 dialysis*.tw.

26 22 and 25

27 MARS.tw.

28 Molecular Adsorbents Recirculating System.tw.

29 (Molecular* adj3 Adsorbent* adj3 Recirculat* adj3 System*).tw.

30 (extracorpor* adj3 support* adj3 therap*).tw.

31 25 and 24 and 23

32 6 or 3 or 7 or 2 or 15 or 1 or 4 or 10 or 5

33 27 or 28 or 18 or 30 or 26 or 31 or 29

34 33 and 32

35 animals/

36 humans/

37 35 not (35 and 36)

38 34 not 37