NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of extracorporeal whole liver perfusion for acute liver failure

Acute liver failure is when the liver stops working within days or weeks. The patient often dies if they do not get a liver transplant. In this procedure blood is diverted from a large vein, usually in the leg, to a whole liver (perfusion) outside the body (extracorporeal) and returned to the patient through another large vein, usually in the neck. The liver may be a donor human liver that is unsuitable for transplantation or from an animal such as a pig. The aim is to keep the patient alive until their liver starts working again or they get a liver transplant.

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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 professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in April 2020 and updated in November 2020.

Procedure name

- Extracorporeal whole liver perfusion for acute liver failure

Professional societies

- British Association for the Study of the Liver
- British Liver Transplant Group
- Intensive Care Society
- Society of Clinical Perfusion Scientists of Great Britain and Ireland
- College of Clinical Perfusion Scientists of Great Britain and Ireland

Description of the procedure

Indications and current treatment

Acute liver failure is characterised by a rapid decline in liver function, usually less than 4 weeks. Causes include poisoning because of alcohol, pharmaceutical or recreational drugs, and viral infection. Less common causes are metabolic disease and acute fatty liver of pregnancy.

Untreated, acute liver failure can have a high mortality. Current treatment options include medication (to reverse poisoning and to prevent complications caused by acute liver failure), temporary liver support therapies (such as haemodialysis or filtration, plasma exchange, and bioartificial liver support), hepatocyte transplantation and liver transplantation.

What the procedure involves

In this procedure a veno-venous circuit is usually used to perfuse the patient's blood through an extracorporeal whole liver. The aim is to provide metabolic support and prolong survival, to allow time for the patient's liver function to recover or to find a suitable donor liver for transplantation.

Blood is pumped from a catheter inserted into the femoral vein through an oxygenator and the hepatic artery and portal vein of an extracorporeal whole liver. The liver may be a human liver not suitable for transplantation or a xenogeneic liver (typically a pig liver). Effluent blood from the extracorporeal liver, which is maintained at a normal temperature with a normal pH and electrolytes, is returned to the patient through a subclavian or jugular venous cannula. The literature describes modifications to the technique, such as isolating the patient's immune system from the extracorporeal liver and using different sites for venous access. Extracorporeal perfusion is continued for up to 5 days until either the patient has a liver transplant or their liver function recovers.

Efficacy summary

Survival

In a systematic review of 131 patients with acute liver failure, after extracorporeal whole liver perfusion 59% (77/131) of patients survived longer than 48 hours and 28% (37/131) survived long term (duration was not reported)[1].

In a case series of 5 patients with acute liver failure (6 liver perfusions), 2 patients were alive and well at 13 and 8 months after extracorporeal whole liver perfusion (perfusion no longer than 5.5 hours)[6].

Bridge to transplantation

In a case series of 14 patients with acute liver failure, 64% (9/14) of patients were successfully bridged to transplantation with the longest perfusion being 111 hours, and 50% (7/14) were alive at a median of 47 months (range 11 to 80) after liver transplantation[2].

In a case series of 2 patients with acute liver failure, both patients were successfully bridged to liver transplantation after 6.5 and 10 hours of perfusion. They continued to be clinically well at 19 and 6 months respectively after transplantation[3].

In a case series of 4 patients with acute liver failure, 1 patient was successfully bridged to liver transplantation after 16 hours of perfusion, and 18 months later he was well and working full time[4].

In a case series of 3 patients with acute liver failure, 2 patients were successfully bridged to transplantation after 48 and 20 hours of perfusion[5]. Of these 2 patients, 1 remained well 15 months after transplantation and 1 was discharged 2 months after transplantation, without neurologic or pulmonary sequelae.

Improvement in neurological status

In the systematic review of 131 patients, after extracorporeal whole liver perfusion a partial neurological improvement (a decrease of coma stage) was achieved in 67% (88/131) of patients, and temporary or sustained reversal of hepatic coma (regain of consciousness) in 40% (52/131)[1].

In the case series of 4 patients, all patients temporarily improved neurological status from stage 5 hepatic encephalopathy to stage 4 or 3 after extracorporeal whole liver perfusion (range 2 to 16 hours)[4].

In the case series of 5 patients in clinical stage 5 coma, after extracorporeal whole liver perfusion 2 patients improved neurological status to grade 0, 2 improved to grade 3 and 1 improved to grade 4[6].

In a case report of 1 patient with acute liver failure (3 liver perfusions with a total of 6 hours 23 minutes), the patient improved neurological status from stage 4 hepatic coma to stage 0 at 3 days after the final perfusion and then declined to stage 1 on the day she died (8 days after the final perfusion)[7].

Change in biochemical parameters

In the case series of 14 patients, the median plasma ammonia level statistically significantly fell from 146 micromol/litre at baseline to 83 micromol/litre within 12 hours of perfusion (p=0.003) and to 55 micromol/litre (p=0.005) within 48 hours of perfusion[2]. In the same study, the median serum bilirubin level statistically significantly decreased from 385 micromol/litre at baseline to 198 micromol/litre over the first 12 hours (p=0.014) of perfusion and to 216 micromol/litre at 24 hours (p=0.016) but then increased to 272 micromol/litre at 48 hours.

In the case series of 2 patients, after extracorporeal whole liver perfusion both patients had decreased bilirubin levels from baseline (1 patient from 18.6 to 14.0 mg/dl and 1 from 43.0 to 25.5 mg/dl)[3]. In the same study, 1 patient's ammonia rose from 136 to 162 micromol/litre and 1 fell from 140 to 95 micromol/litre.

In the case series of 4 patients, after extracorporeal whole liver perfusion all had temporarily decreased total bilirubin levels from baseline (patient 1 from 21.3 to 12.4 mg/dl; patient 2 from 11.9 to 12.8 mg/dl; patient 3 from 16.3 to 10.4 mg/dl; patient 4 from 24.2 to 22.3 mg/dl) and ammonia levels (patient 1 from 128 to 70 microg/dl; patient 2 from 108 to 42 microg/dl; patient 3 from 176 to 132 microg/dl; patient 4 from 269 to 176 microg/dl)[4].

In the case series of 3 patients, after extracorporeal whole liver perfusion, serum bilirubin levels fell from baseline (patient 1 from 27.3 to 4.5 mg/dl at 40 hours; patient 2 from 23.8 to 2.5 mg/dl at 72 hours; patient 3 from 23 to 12 mg/dl at 20 hours)[5]. In the same study, arterial ammonia levels decreased from baseline (patient 1 from 128 to 54 mmol/litre at 40 hours; patient 2 from 169 to 32 mmol/litre at 72 hours; patient 3 from 112 to 38 mmol/litre at 20 hours).

In the case series of 5 patients, serum bilirubin levels fell from baseline by 28% to 63% during 3.5 to 5.5 hours of perfusion, and within 48 hours the pre-perfusion values of serum bilirubin were regained in 3 patients[6].

Safety summary

Embolism or thrombosis

Acute pulmonary oedema and cardiac arrest were reported in a case report of 1 patient with acute liver failure who had 3 liver perfusions[7]. The patient died from a pulmonary embolism 8 days after the final perfusion.

Septic thrombi in the major hepatic veins and global hepatic infarction were reported in 1 patient in the case series of 4 patients[4].

Haemorrhage

Increased bleeding from the gastrointestinal tract and haematuria were reported in 4 patients during and after perfusion in the case series of 5 patients; and of these 4 patients, 2 died (1 died from uncontrollable gastrointestinal haemorrhage and 1 from widespread bleeding)[6].

Thrombocytopenia

Thrombocytopenia was reported in all patients after each perfusion in the case series of 4 patients, resulting from sequestration of platelets within the membrane oxygenator and of a small number within the perfused liver. All patients received transfusions of platelets during each procedure[4].

Oliguria or anuria

Anuria and marked acidosis were reported in 1 patient after 2 perfusions in the case series of 4 patients[4].

Oliguria was reported in 2 patients in the case series of 5 patients[6]. In 1 of these patients urinary output improved after the second perfusion and the other excreted only 175 ml of urine during the 36 hours before death.

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts 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, the professional expert did not list any anecdotal adverse events but considered that bleeding caused by the heparin used to maintain the dialysis circuit was a theoretical adverse event.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to extracorporeal whole liver perfusion for acute liver failure. The following databases were searched, covering the period from their start to 13 November 2020: 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). 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 acute liver failure.
Intervention/test	Extracorporeal whole liver perfusion.
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 139 patients from 1 systematic review, 5 case series and 1 case report.

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

Table 2 Summary of key efficacy and safety findings on extracorporeal whole liver perfusion for acute liver failure

Study 1 Pascher A (2002)

Details

Study type	**Systematic review**
Country	Included patients from 13 countries (Australia, Canada, Denmark, Finland, France, FRG, GB, Hungary, India, Italy, Japan, Norway, Poland, SA, Spain, Switzerland, USA and USSR; 49 medical centres)
Recruitment period	Search: literature published from 1964 to 2000
Study population and number	n=131 Patients with acute liver failure
Age and sex	Median 37.6 years (range 5 to 79 years); 51% (101/198) female (based on the data from 198 patients: 131 acute liver failure, 6 subacute liver failure and 61 chronic liver failure)
Patient selection criteria	Inclusion criteria: Articles with a clear description of methodology and outcome of patients were included. Patients in whom xenogeneic or allogeneic extracorporeal liver perfusion was performed for hepatic assist in acute liver failure. Patients for whom precise data of ECLP, such as perfusion characteristics, donor species and perfusion time as well as time of discharge, survival time and cause of death were identified and for whom the clinical follow-up status could be allocated to 1 of the following categories were considered: no improvement, neurologic improvement, complete recovery, long term survival, death in ALF or death from other cause.
Technique	Extracorporeal liver perfusion was done with 6 different species (pig, transgenic, baboon, man, calf/cow and combinations). Different technical features of ECLP devices included simultaneous arterial and portal perfusion versus portal perfusion alone, use of an oxygenator versus none as well as perfusion of the liver while floating in saline or any other fluid versus just lying on gauze or anything else.
Follow-up	**Median perfusion duration: 5 hours** (based on the data from 198 patients)
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: This systematic review of the world experience defined the role of discordant and concordant xenogeneic as well as allogeneic ECLP in comparison with other modern therapeutic options in artificial liver support. An internet-based search was conducted in several databases. Additional data were obtained from several authors who provided reprints of their original articles or their personal experience.

Information regarding age, gender, cause of liver failure, onset of ALF, coma stage, species of organ donor, technical details of perfusion (i.e. portal vs. combined portal/arterial perfusion, perfusion time, use of oxygenator, simultaneous dialysis), change in coma stage, time and cause of death, complications during ECLP, subsequent liver transplantation and survival was extracted from the published reports. Patients who were included in multiple reports were deduplicated. The criteria of a proper meta-analysis could not be met but statistical analysis was done.

Depth of coma was classified according to the commonly used 4-stage scheme. Data from publications based on a 5-stage score were transposed into the 4-stage scheme according to the clinical definitions of hepatic coma.

Study population issues: A total of 270 patients with acute, subacute or chronic liver failure were treated by 572 extracorporeal liver perfusions in 49 medical centres with livers from 6 different species. Of these patients, 198 patients were considered having complete data (131 acute liver failure, 6 subacute liver failure and 61 chronic liver failure).

Aetiology included viral hepatitis (n=93), drugs and toxins (n=21), cryptogenic (n=36), alcohol (n=16), infection (n=9), miscellaneous 1 (n=9) and miscellaneous 2 (n=14).

Of 198 patients, 177 were in coma stage IV when ECLP commenced, 21 in stages III to IV or lower. In terms of the number of perfusions, 121 patients had 1 ECLP application, 50 had 2 ECLP applications and 27 had more than 3 ECLP applications.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 131 (patients with acute liver failure)

Outcomes of ECLP
<table>
<tr><th></th><th>No. of patients</th><th>Long-term survival</th><th>Neurologic improvement</th><th>Complete recovery**</th><th>Survival >48 hours</th></tr>
<tr><td>Acute liver failure</td><td>131</td><td>28% (n=37)</td><td>67% (n=88)</td><td>40% (n=52)</td><td>59% (n=77)</td></tr>
<tr><td>Before 1980</td><td>81</td><td>20% (n=16)</td><td>59% (n=48)</td><td>28% (n=23)</td><td>54% (n=44)</td></tr>
<tr><td>1980-90</td><td>28</td><td>32% (n=9)*</td><td>79% (n=22)*</td><td>65% (n=15)*</td><td>68% (n=19)*</td></tr>
<tr><td>After 1990</td><td>22</td><td>56% (n=12)*</td><td>82% (n=18)*</td><td>64% (n=14)*</td><td>64% (n=14)*</td></tr>
</table>
*p<0.05
**Regained consciousness

Multivariant analysis showed that age below 40 years (p<0.029), coma stage lower than III to IV (p<0.003), total perfusion time over 10 hours (p<0.024), hepatitis B as cause for acute liver failure (p<0.05) as well as use of baboon and human livers (p<0.02) were identified as independent positive prognostic markers for improved survival. Gender, number of perfusions and different technical features had no impact on survival rates.
ECLP in acute liver failure turned out to have significantly better prognosis in the last 2 decades compared with the experience before and with chronic liver failure.
ECLP as bridging therapy to liver transplantation was successful in 12 of 14 patients who had liver transplantation after ECLP.
However, these outcomes were based on 198 patients with acute, subacute and chronic liver failure; so, detailed data were not extracted.</td><td>Safety outcomes based on 198 patients

Complications: 54% (n=107)
• Bleeding: 33% (n=66, with 58 ECLPs were accompanied by disturbances of coagulation)
○ Death caused by fulminant gastrointestinal bleeding: 10% (n=18)
• Cardiorespiratory problems: 39% (n=78)
○ Death caused by cardiorespiratory problems: 16% (n=32)
• Death caused by infections (such as aspergillus pneumonia) or multiorgan failure: data not reported

Immunologic complications: n=5
• Anaphylactic reactions: n=3
• Low platelet counts (happened frequently but data not reported)
• Infectious complications: n=21
○ Systemic aspergillus infections: n=3</td></tr>
<tr><td colspan="2">Abbreviations used: ALF, acute liver failure; ECLP, extracorporeal liver perfusion.</td></tr>
</table>

Study 2 Horslen SP (2000)

Details

Study type	**Case series**
Country	USA (single centre)
Recruitment period	1992 to 1999
Study population and number	n=**14 (16 livers with 18 perfusions using 8 human and 8 porcine livers)** Patients with acute liver failure
Age and sex	Median 16 years (range 6 to 44); sex was not reported.
Patient selection criteria	Inclusion criteria: Patients with acute liver failure who were candidates for liver transplantation were considered for ECLP when, despite conventional supportive care, their encephalopathy progressed to grade IV coma, endotracheal intubation was required, and intracranial pressure monitoring had been instituted and indicated marginal CPP. In each case no human liver suitable for implantation was available.
Technique	Extracorporeal liver perfusion was done with human (cadaveric human livers rejected for transplantation) or porcine (miniature swine) livers. The patient was connected to the circuit through percutaneous femoral or subclavian venous cannulae and had continuous perfusion until liver transplantation or withdrawal of support. Two perfusion circuits were used: direct perfusion of patient blood through the extracorporeal liver and indirect perfusion with a plasma filter between the patient and the liver. The direct perfusion circuit included a reservoir, a centrifugal pump and an oxygenator. The indirect perfusion circuit used a haemodialysis filter or ultrafiltration membranes in addition to the direct circuit.
Follow-up	**Perfusion duration using human livers: median 55 hours (range 20 to 92)** **Perfusion duration using porcine livers: median 36 hours (range 7 to 68)** **Follow-up after transplantation: median 47 months (range 11 to 80)**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: This case series reported the experience of extracorporeal liver perfusion using human and porcine livers, as a method of 'bridging' to transplantation, in 14 patients with acute liver failure. A total of 18 liver perfusions were carried out because on 2 occasions the filtered circuit was changed to a direct perfusion circuit because of poor efficacy - hepatic artery and portal vein resistance began to increase significantly and bile flow from the perfused livers deteriorated.

Study population issues: Of 14 patients, aetiology included non-A non-B hepatitis (n=7), acetaminophen (n=2), primary nonfunction post-OLT (n=2), hepatic artery thrombosis post-OLT (n=1), drug induced (n=1) and non-Hodgkin's lymphoma (n=1). Prior to extracorporeal liver perfusion all patients had grade IV hepatic encephalopathy. The median peak prothrombin time was 36.7 sec (range 27.3 to 78.3) which corresponded to an INR of 8.5 (range 5.4 to 50.1).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **14 (16 livers in 18 perfusion circuits using 8 human and 8 porcine livers)**

Bridge to transplantation and survival

Outcomes	n=14	%
Had liver transplantation	9[a]	64%
Support withdrawn	4[b]	29%
Herniated	1[c]	7%

[a]Of the 9 patients who were carried through ECLP, the longest for 111 hours, to transplantation, 7 were alive with a median survival of 47 months (range 11 to 80 months) and 2 died (1 died 3 months after transplantation of sepsis secondary to aplastic anaemia and 1 after a catastrophic bleed after paracentesis about 1 month after transplantation).

[b]After commencing ECLP, it was decided that transplantation was contraindicated, and support was withdrawn after 7, 38, 39 and 70 hours.

[c]The patient who died while receiving ECLP support had been in advanced coma for more than 5 days and died only after being changed from a pig liver that was failing to a human liver that never appeared to function adequately.

Cerebral perfusion pressure (n=11), mean

	Baseline	48 hours
Using human livers, mmHg	70	72
Using porcine livers, mmHg	58	69

Two had very poor CPP at initiation of ECLP, demonstrated no improvement and were withdrawn from support; and 1 did not have an ICP monitor placed.

Intracranial pressure: ECLP was associated with no deterioration of ICP for up to 110 hours.

Human and pig liver perfusions appeared to control CPP and ICP equally well.

Biochemical parameters between baseline and during ECLP, median (range)

	Baseline	12 hours	p	24 hours	p	48 hours	p
Plasma ammonia level, µmol/litre							
All patients	146 (31 to 327)	83 (23 to 239)	0.003	-	-	55	0.005
Using human livers	124 (50 to 300)	83 (31 to 110)	0.043	-	-	50	0.028
Using porcine livers	156 (31 to 327)	82 (23 to 239)	0.048	-	-	90	0.049
Serum bilirubin level, µmol/litre							
All patients	385 (46 to 780)	198 (54 to 498)	0.014	216	0.016	272	-
Using human livers	401 (121 to 464)	-	-	175	-	171	-
Using porcine livers	333 (46 to 780)	196	-	377	-	394	-

Safety

Not reported

Abbreviations used: CPP, cerebral perfusion pressure; ECLP, extracorporeal liver perfusion; ICP, intracranial pressure.

Study 3 Levy MF (2000)

Details

Study type	**Case series**
Country	USA
Recruitment period	Not reported
Study population and number	n=2 Patients with acute liver failure
Age and sex	Mean 17.5 years; 50% (1/2) female
Patient selection criteria	Not reported
Technique	Extracorporeal liver perfusion was done with transgenic pig livers (for human CD55 and human CD59). The patient was percutaneously connected to the circuit through left femoral vein for venous outflow and through right internal jugular vein for venous return. The perfusion circuit included a pump, an oxygenator and a warmer. In addition, a roller pump was incorporated into the circuit in the event gravity return to the patient would have been insufficient.
Follow-up	**Perfusion duration: 6.5 hours for patient 1 and 10 hours for patient 2.** **Follow-up after transplantation: 19 months for patient 1 and 6 months for patient 2.**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: This study reported the first 2 cases of patients who were successfully bridged to liver transplant by extracorporeal liver perfusion using transgenic porcine livers. This study also reported the results of surveillance testing for PoERV in these patients over an intermediate follow-up period.

Study population issues: Patient 1 (17 years; male) had idiopathic fulminant hepatic failure for consideration of liver transplantation. He was approved for transplantation and placed on the waiting list. Forty-eight hours after hospital admission, he required endotracheal intubation for airway protection and for oxygenation. He was deeply comatose but with reactive pupils and a respiratory drive.

Patient 2 (18 years: female) had Wilson's disease and fulminant hepatic failure. Within days of her admission, her clinical course rapidly deteriorated to the point of metabolic coma, mechanical ventilation and full medical support. She was also placed on the liver transplant waiting list.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 2

Biochemical parameters for each perfusion
<table>
<tr><th>Patient no.</th><th>Ammonia (µmol/L)</th><th>Bilirubin (mg/dl)</th><th>Protime (sec)</th></tr>
<tr><td>Patient 1</td><td></td><td></td><td></td></tr>
<tr><td>Preperfusion</td><td>136</td><td>18.6</td><td>23.4</td></tr>
<tr><td>Nadir</td><td></td><td></td><td>20.3</td></tr>
<tr><td>Postperfusion</td><td>162</td><td>14.0</td><td>21.4</td></tr>
<tr><td>Patient 2</td><td></td><td></td><td></td></tr>
<tr><td>Preperfusion</td><td>140</td><td>43.0</td><td>18.3</td></tr>
<tr><td>Nadir</td><td>55</td><td></td><td>17.9</td></tr>
<tr><td>Postperfusion</td><td>95</td><td>25.5</td><td>24.6</td></tr>
</table>
Allotransplantation:
• Patient 1 was perfused for 6.5 hours, after which time a human liver arrived and the procedure was aborted in favour of allotransplantation. At 19 months after transplant, he continued to be clinically well. He developed inflammatory colitis and inflammatory bowel disease but had no signs or symptoms of opportunistic infection.
• Patient 2 was perfused for 10 hours, with cessation upon evidence of decreased function of the porcine liver. Function of the transgenic liver was assessed by clinical parameters and by portal vein pressure and the oxygen extraction of the organ. She went on to allotransplantation 14 hours after perfusion. At 6 months after transplant, she continued to be clinically well, free of signs and symptoms of opportunistic infection.

Indirect immunofluorescence studies: IgG anti-porcine antibody was detected in the sample from posttransfusion days 31 and 65 and no evidence of IgM anti-porcine antibody was detected in any of patient 1’s sera samples.

Porcine endogenous retrovirus (PoERV) surveillance results:
• Patient 1: At days 30, 60, 90, 120, 150, 180, 210, 240, 270 and 300 after transplantation, he had no detectable circulating PoERV or circulating porcine DNA by DNA-PCR of human peripheral blood mononuclear cells.
• Patient 2: She was negative for PoERV at days 30, 60, 90 and 120 after transplantation.

Panel-reactive antibodies (PRA)
• Patient 1: PRA screening performed before transplant and monthly after transplantation showed no anti-HLA antibodies (17 months after perfusion).
• Patient 2: Monthly PRA testing of the patient (3 months after perfusion) continued to show no anti-HLA antibodies.
</td><td>Not reported</td></tr>
<tr><td colspan="2">Abbreviations used: PCR, polymerase chain reaction; PRA, panel-reactive antibodies; PoERV, porcine endogenous retrovirus.</td></tr>
</table>

Study 4 Chari RS (1994)

Details

Study type	**Case series**
Country	UK (single centre)
Recruitment period	Not reported
Study population and number	n=**4 (8 liver perfusions)** Patients with fulminant hepatic failure
Age and sex	Mean 35 years (range 22 to 56); 50% (2/4) female
Patient selection criteria	Inclusion criteria: Patients with irreversible hepatic failure and no other therapeutic options.
Technique	Extracorporeal liver perfusion was done using pig livers. The patients were connected to the circuit through left femoral vein for outflow and through the right internal jugular vein for return. The circuit included a pump, a membrane oxygenator-heat exchanger, and circuit and liver bridges.
Follow-up	**Perfusion duration: 2 to 16 hours** **Follow-up after transplantation: 18 months**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: This study reported the use of a veno-venous circuit for ex vivo pig-liver perfusion for diagnostic and therapeutic purposes in 4 critically ill patients. In assessing patients' clinical status, hepatic encephalopathy was graded using the scale of Sherlock. Stages of hepatic encephalopathy used the scale of Sherlock. On this scale, stage 1 indicated confusion or altered mood or behaviour, stage 2 drowsiness or inappropriate behaviour, stage 3 inarticulate speech but with the ability to obey simple commands, stage 4 responsiveness only to painful stimuli, and stage 5 unresponsiveness to painful stimuli.

Study population issues:

Patient 1: On admission, she had jaundice but no fever and had stage 2 hepatic encephalopathy. Seven days later, her condition progressed to stage 5 hepatic encephalopathy.

Patient 2: On admission, he had a distended abdomen and moderate tenderness in the right upper quadrant, with stage 3 hepatic encephalopathy. Within 6 hours of admission, his neurological status deteriorated to stage 5.

Patient 3: Her fulminant hepatic failure was due to hepatitis B. On admission, she had stage 5 hepatic encephalopathy and a distended abdomen; she also had seizure activity on electroencephalography and computed tomography and markedly elevated intracranial pressure.

Patient 4: He had primary graft nonfunction after liver transplantation for cryptogenic cirrhosis, received another liver transplant 5 days later but his mental status deteriorated rapidly, with stage 5 hepatic encephalopathy.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 4 (8 liver perfusions)

Neurological improvement and survival after perfusion:
• Patient 1: ECLP was terminated when oxygen extraction and bile production decreased. Her neurologic status improved from stage 5 hepatic encephalopathy to stage 3. Improvement lasted for 1 to 2 hours and she died within 24 hours. Her ongoing intraabdominal infection contributed to sepsis and multisystem organ failure.
• Patient 2: His neurological status improved from stage 5 hepatic encephalopathy to stage 3. Four days after the final perfusion, he underwent orthotopic liver transplantation and remained well after 18 months of transplantation and returned to full-time work.
• Patient 3: Her intracranial pressure decreased from 72 to 45 mm Hg during perfusion and she temporarily became responsive to deep pain. Although a human liver became available for transplantation, her intracranial pressure increased again to 110 mm Hg and her pupils became fixed and dilated before transplantation could be performed.
• Patient 4: His neurologic status improved from stage 5 hepatic encephalopathy to stage 4, but he died.

Biochemical parameters for each perfusion
<table>
<tr><th rowspan="2">Patient no.</th><th rowspan="2">Procedure no.</th><th rowspan="2">Duration of perfusion (hour)</th><th colspan="2">Total bilirubin (mg/dl)</th><th colspan="2">Ammonia (µg/dl)</th><th colspan="2">Platelet count (x10^{-3}/mm^3)</th></tr>
<tr><td>before</td><td>after</td><td>Before</td><td>After</td><td>Before</td><td>After</td></tr>
<tr><td>1</td><td>1</td><td>3.5</td><td>21.3</td><td>12.4</td><td>128</td><td>70</td><td>97</td><td>30</td></tr>
<tr><td rowspan="4">2</td><td>1</td><td>0.5</td><td>11.9</td><td>11.6</td><td>108</td><td>95</td><td>282</td><td>181</td></tr>
<tr><td>2</td><td>4.5</td><td>14</td><td>10.1</td><td>131</td><td>79</td><td>208</td><td>28</td></tr>
<tr><td>3</td><td>6</td><td>19.8</td><td>13.8</td><td>137</td><td>75</td><td>75</td><td>28</td></tr>
<tr><td>4</td><td>3.5, 5</td><td>20.3</td><td>12.8</td><td>50</td><td>42</td><td>105</td><td>78</td></tr>
<tr><td>3</td><td>1</td><td>5</td><td>16.3</td><td>10.4</td><td>176</td><td>132</td><td>114</td><td>45</td></tr>
<tr><td rowspan="2">4</td><td>1</td><td>2</td><td>22.3</td><td>20.5</td><td>107</td><td>83</td><td>104</td><td>70</td></tr>
<tr><td>2</td><td>2.5</td><td>24.2</td><td>22.3</td><td>269</td><td>176</td><td>100</td><td>91</td></tr>
</table>
</td><td>Thrombocytopenia: n=4 resulted from sequestration of platelets within the membrane oxygenator and of a small number within the perfused liver. All patients received transfusions of platelets during each procedure.

Anuria and marked acidosis developed in patient 4 and the patient died within 24 hours. An autopsy showed that septic thrombi in the major hepatic veins and global hepatic infarction.</td></tr>
<tr><td colspan="2">Abbreviations used: ECLP, extracorporeal liver perfusion.</td></tr>
</table>

Study 5 Fox IJ (1993)

Details

Study type	**Case series**
Country	USA (single centre)
Recruitment period	Not reported
Study population and number	n=**3** Patients with acute liver failure
Age and sex	Mean 20 years (range 6 to 38); 67% (2/3) female
Patient selection criteria	Inclusion criteria: patients had terminal hepatic disease secondary to acute or subacute hepatic failure; were in stage III or IV hepatic coma (stuporous or responsive only to painful stimuli), with an intracranial pressure monitor in place; had a prothrombin time greater than 15 s; had a serum bilirubin greater than 15 mg/dl; and no suitable donor liver for transplantation at the time ECLP was considered.
Technique	Extracorporeal liver perfusion was done with human livers. The patient was connected to the circuit through percutaneous femoral vein for outflow and through hepatic vein for return. The perfusion circuit included a membrane oxygenator, cardiotomy reservoir, heat exchanger, in-line blood gas monitor and pressure transducers.
Follow-up	**Perfusion duration: range 20 to 72 hours** **Follow-up after transplantation: 15 months for patient 1 and 2 months for 1 patient 3**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: This study examined the utility of extracorporeal liver perfusion as a bridge to transplantation in 2 patients with acute, fulminant hepatic failure, and in 1 patient to determine whether he would benefit from improved hepatic function.

Study population issues: On admission, patient 1 had a serum bilirubin of 30.8/19.8 mg/dl, a prothrombin time of 39.2 s, and an arterial ammonia of 128 mmol/L. Within 36 hours, the patient's condition deteriorated to stage IV hepatic coma. Initial ICPs were within normal range but eventually became elevated to greater than 20 mm Hg, and a brain CT scan showed no cerebral oedema. Patient 2 was obtunded and unresponsive to deep pain, and initial ICPs and head CT scans were normal, but EEGs showed diffuse slowing. For patient 3, the patient was in stage IV hepatic come, with an arterial ammonia of 112 mmol/L, and an uncorrectable prothrombin time. Head CT scan and ICP pressures initially indicated no evidence of cerebral oedema. Within 12 hours of admission, the patient's mental status deteriorated to decorticate posturing, pupillary responses became sluggish, and the ICP began to rise despite the use of hyperventilation and mannitol.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **3** **Bridge to transplantation and survival:** **Patient 1:** ECLP was discontinued at 48 hours and the patient was then successfully bridged to transplantation. The patient was discharged 4 months after transplantation and remained well 15 months post transplantation. **Patient 2:** The patient's mental status failed to reverse, ICPs remained in the high normal range and ECLP was discontinued because seizure activity and neurologic abnormalities were believed to be irreversible and unaffected by ECLP. The patient died 7 days later from multiple organ system (pulmonary and renal) failure. **Patient 3:** After 20 hours of ECLP, the patient was successfully bridged and discharged 2 months after transplantation, without neurologic or pulmonary sequelae. **Change in ICP and CPP following ECLP:** the neurologic examination improved dramatically, with clear clinical improvement in patients 1 and 3 (patient 1: during 40 hours of ECLP, ICPs fell from 70 to 2 mmHg and CPPs rose from 20 to 103 mmHg; no data were shown for patients 2 and 3). **Neurological improvement:** **Patient 1:** During 40 hours of perfusion, the patient improved clinically from being completely unresponsive to having spontaneous movements between pentobarbital doses. **Patient 3:** Toward the end of extracorporeal support, the patient began to respond to painful stimuli and pupillary responses normalised. **Change in serum bilirubin levels after ECLP** • Patient 1 from 27.3 to 4.5 mg/dl at 40 hours • Patient 2 from 23.8 to 2.5 mg/dl at 72 hours • Patient 3 from 23 to 12 mg/dl at 20 hours) **Change in arterial ammonia levels after ECLP** • Patient 1 from 128 to 54 mmol/L at 40 hours • Patient 2 from 169 to 32 mmol/L at 72 hours • Patient 3 from 112 to 38 mmol/L at 20 hours	Not reported
Abbreviations used: CPP, cerebral perfusion pressure; ECLP, extracorporeal liver perfusion; ICP, intracranial pressure.	

Study 6 Parbhoo SP (1971)

Details

Study type	**Case series**
Country	UK
Recruitment period	Not reported
Study population and number	n=**5** (6 liver perfusions) Patients with acute liver failure
Age and sex	Mean 32.6 years (range 20 to 50); 60% (3/5) female
Patient selection criteria	Inclusion criteria: Patients had a diagnosis of acute liver failure; in deep coma; not responded to at least 24 hours standard medical treatment; and less than 60 years old.
Technique	Extracorporeal liver perfusion was done using pig livers. The priming fluid consisted of fresh heparinised compatible human blood. The circuit included pumps, an oxygenator, bubble traps and a heat exchanger.
Follow-up	**Perfusion duration: 3.5 to 5.5 hours** **Follow-up after perfusion: 8 months for patient 1 and 13 months for patient 3**
Conflict of interest/source of funding	This work was supported by the Royal Free Hospital Endowment Fund, the Ingram Trust, the David Fund, a Ministry of Health development grant (E.E.G.), a Peter Samuel Trust grant to 1 author, and a Medical Research Council grant to 1 author.

Analysis

Study design issues: This study examined the efficacy of extracorporeal pig-liver perfusion, with the detailed presentation of long-term survivors in the United Kingdom. In every case recovery was considered unlikely. Corticosteroids and exchange transfusion were not used as part of the routine treatment.

The depth of coma was graded: (I) confused, (II) drowsy, (III) stuporous but speaking and obeying simple commands, (IV) coma and (IV) deep coma with no response to painful stimuli and no spontaneous movements.

Study population issues: All patients were in clinical grade V coma. The duration of symptoms before the onset of coma varied from 3 to 21 days. One patient was in coma for 31 hours and 4 in coma for more than 64 hours before perfusion. The electroencephalograph before perfusion was grade 4 (severe abnormalities) in case 3, grade 6 (moribund) in case 1, and grade 5 (very severe abnormalities) in the remaining 3 patients.

All patients showed bruising at sites of venepuncture and bleeding from the gastrointestinal tract. One patient was bleeding per vaginam. On admission, the thrombotest varied from less than 50% to 22%. The platelet count ranged from 24,000 to 510,000 per µl. Aetiology included viral hepatitis (n=3), fatty liver of pregnancy (n=1) and paracetamol necrosis (n=1). One patient was admitted in renal failure while another 2 developed it during the course of treatment.

Before liver perfusion 3 patients received between 1 and 5 litres of blood and 2 of these patients were also given fresh-frozen plasma and cryoprecipitate.

Key efficacy and safety findings

Efficacy and safety

Number of patients analysed: **5 (6 liver perfusions)**

Clinical and biochemical parameters

Patient no.	Perfusion	Depth of coma clinical grade		EEG grade		Serum-bilirubin (mg/100ml)		Thrombotest (%)		Platelet-count (1000 per µl)		Blood-urea (mg/100 ml)			Survival after procedure
		Before	Lightest	Before	Best	Before	After	Before	After	Before	After	Before	After	Highest	
1	1	V	0	6	1	13.6	5.8	15	<10	87	19	27	35	50	13 months
2	1	V	III	5	4	15.0	5.5	22	-	34		95	85	128	2 hours
3	1	V	0	4	1	10.5	6.5	15	35	106	30	15	19	48	8 months*
4	1	V	IV	5	4	19.6	14.2	<5	30	162	280	24	31	-	10 days
	Exchange transfusion	IV	IV	5	5	27.0	15.0	7	22	160	104	35	38	-	7 days
	2	V	IV	5	4	27.5	18.5	10	9	78	28	67	85	133	4 days
5	1	V	III	5	4	33.2	19.8	8	26	13	27	25	24	90	2 days

*The patient's liver function tests were normal at a 6-month follow-up examination.

In 3 patients (patients 3, 4 and 5) the serum bilirubin regained its pre-perfusion values within 48 hours.

Patient 1: cerebral metabolism

Date	Cerebral blood-flow (ml/100g/min)	Cerebral oxygen consumption (ml/100g/mins)	Cerebral glucose consumption (ml/100g/min)	Oxygen/glucose index (%)
Normal	45 to 55	3.0 to 3.6	3.0 to 5.5	100
28 Jan. 1970	30	0.7	12	7
29 Jan. 1970	42	0.8	11	8.5
Liver perfusion				
29 Jan. p.m.	52	2.4	13	22
30 Jan. a.m.	50	2.8	12	27
30 Jan. p.m.	51	2.3	8	34
2 Feb	51	3.0	3	117
6 Feb	51	3.0	3	117

She has since (13 months later) been completely free from symptoms, living a normal life and taking a normal diet, including pork. In particular, no rashes, joint pains, or food allergy have been noted. In September 1970, haematological and biochemical findings were normal, and a liver biopsy showed a few thin fibrous septa but otherwise normal histology, and liver scan was normal.

Safety:

- **Bleeding** from the gastrointestinal tract increased and haematuria developed: n=4 (2 died: patient 2 died from massive gastrointestinal haemorrhage and patient 4 died from widespread bleeding). Generalised bleeding was aggravated by heparinisation.
- **Acute haemorrhagic pancreatitis:** n=1 (in patient 5, the pancreas showed acute haemorrhagic pancreatitis, causing death.)
- **Oliguria:** n=2

  The blood urea rose after perfusion but returned to normal within 48 hours except in 2 patients (patients 4 and 5), who became oliguric. In patient 4 urinary output improved after the second perfusion but patient 5 excreted only 175 ml of urine during the 36 hours before death. Patients 1 and 3 had a large diuresis after liver perfusion.

Abbreviations used: ALF, acute liver failure; EEG electroencephalograph.

Study 7 Lempinen M (1971)

Details

Study type	**Case report**
Country	Finland
Recruitment period	1969
Study population and number	n=1 (3 liver perfusions) Patient with acute liver failure
Age and sex	26 years; female
Patient selection criteria	Not reported
Technique	Extracorporeal pig-liver perfusion was done. The patient was connected to the circuit through femoral artery for outflow and through femoral vein for return. The circuit included a venous reservoir, a heat exchanger, a pump and a reservoir.
Follow-up	**Perfusion duration: a total of 6 hours and 23 minutes**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: This case report described 3 extracorporeal heterologous pig-liver perfusions performed on a patient with acute liver failure.

Study population issues: The patient had acute liver failure because of necrosis, probably induced by halothane sensitivity. When the first signs of liver failure appeared, she became lethargic and jaundiced and her temperature rose to 40˚C. Two days later she became comatose and an exchange transfusion was performed with no improvement in her condition.

On admission, she was deeply jaundiced and in grade IV come. The cardiovascular, respiratory and renal functions were normal. According to an open liver biopsy, the liver was seen to be enlarged, oedematous and a salmon red colour. Microscopically widespread centrilobular necrosis could be seen and those cells surviving were oedematous and vacuolated.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **1 (3 liver perfusions)** **Three liver perfusions** I. 13 November 1969: perfusion for 3 hours II. 15 November 1969: perfusion for 3 hours III. 17 November 1969: perfusion for 23 minutes - this perfusion had to be stopped after 23 minutes, owing to an increase in liver vascular resistance, first on the arterial and then on the portal side. **Changes in the degree of coma after perfusions** The patient improved neurological status from stage 4 hepatic coma to stage 0 at 3 days after the final perfusion and then declined to stage 1 at the day she died (8 days after the final perfusion). **Degree of liver regeneration** In the pre-perfusion biopsy, 65% of dots fell on necrotic areas, the corresponding figure in the autopsy specimen being 29%. Post-mortem specimens were cut from 3 different sites in the livers and these had a uniform appearance.	**Acute pulmonary oedema and cardiac arrest** was developed on 25 November and the patient died of a pulmonary embolism. Autopsy showed 2 small pulmonary infarcts, 1 in each lung. Embolisms were seen in the corresponding pulmonary arteries. No peripheral venous thrombosis was found.
Abbreviations used: Not applicable	

Validity and generalisability of the studies

- Studies 1 to 7 were published between 1971 and 2002.
- Studies 2, 3 and 5 were conducted in the US, studies 4 and 6 in the UK, study 7 in Finland, and study 1 included patients from 13 countries.
- Studies 2, 3, 4 and 7 were included in study 1 but the total sample of 139 patients was derived from removing duplications.
- Age ranged from 5 to 79 years and, where reported, 50% or more were female.
- Post-perfusion follow up ranged from 2 to 80 months.
- There was variation in the following aspects, so affecting the outcomes of the procedure; this was coupled with advances in critical care over time.
  - Perfusion durations with the longest perfusion being 111 hours.
  - Designs of the perfusion circuit and different components used.
  - Types and quality of extracorporeal liver used and associated preparation process.
- In some cases, it was unclear whether complications were specifically related to the procedure or caused by acute liver failure, so the safety outcomes provide an indication of complications potentially relating to the procedure.

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.

Interventional procedures

- Ex-situ machine perfusion for extracorporeal preservation of livers for transplantation. NICE Interventional procedures guidance 636 (2019). Available from https://www.nice.org.uk/guidance/ipg636
- Living-donor liver transplantation. NICE Interventional procedure guidance 535 (2015). Available from https://www.nice.org.uk/guidance/ipg535
- Extracorporeal albumin dialysis for acute liver failure. NICE Interventional procedures guidance 316 (2009). Available from https://www.nice.org.uk/guidance/ipg316

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional 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 professional experts, 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. One professional expert questionnaire for extracorporeal whole liver perfusion for acute liver failure was submitted and can be found on the NICE website.

Patient commentators' opinions

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

Company engagement

A structured information request was not sent to any companies because the perfusion circuit used in this procedure consists of multiple individual components from different manufacturers. When preparing this overview there was no single company that produces a perfusion circuit using a whole liver.

References

1. Pascher A, Sauer IM, Hammer C et al. (2002) Extracorporeal liver perfusion as hepatic assist in acute liver failure: a review of world experience. Xenotransplantation 9(5): 309-324
2. Horslen SP, Hammel JM and Fristoe LW (2000) Extracorporeal liver perfusion using human and pig livers for acute liver failure. Transplantation 70(10): 1472-1478
3. Levy MF, Crippin J, Sutton S et al. (2000) Liver allotransplantation after extracorporeal hepatic support with transgenic (hCD55/hCD59) porcine livers. Transplantation 69: 272-280
4. Chari RS, Collins BH, Magee JC et al. (1994) Brief report: treatment of hepatic failure with ex vivo pig-liver perfusion followed by liver transplantation. The new England journal of medicine 331: 234-237
5. Fox IJ, Langnas AN, Fristoe LW et al. (1993) Successful application of extracorporeal liver perfusion: A technology whose time has come. The American Journal of Gastroenterology 88: 1876-1881
6. Parbhoo SP, Kennedy J, James IM et al. (1971) Extracorporeal pig-liver perfusion in treatment of hepatic coma due to fulminant hepatitis. The Lancet 1: 659-665
7. Lempinen M, Collan Y, Sivula A et al. (1971) Pig-liver perfusion: extracorporeal pig-liver perfusion in a patient with acute hepatic failure. Scandinavian journal of gastroenterology 6: 377-383

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	13/11/2020	Issue 11 of 12, November 2020
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	13/11/2020	Issue 11 of 12, November 2020
MEDLINE (Ovid)	13/11/2020	1946 to November 12, 2020
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	13/11/2020	November 12, 2020
EMBASE (Ovid)	13/11/2020	1974 to 2020 November 12
International HTA database (INAHTA)	13/11/2020	-

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)

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

1 exp Liver Failure, Acute/ (6253)
2 Hepatic Encephalopathy/ (10413)
3 ((acute or fulmina*) adj4 (hepat* or liver*) adj4 (fail* or disease* or injur* or necros* or impair* or cirrhos*)).tw. (18380)
4 (hepat* adj4 (encephalopath* or coma*)).tw. (9028)
5 (ALF or ACLF or FHF).tw. (4029)
6 or/1-5 (32033)
7 Perfusion/ (49307)

8 Extracorporeal Circulation/ (12943)
9 ((extra corpor?al or extracorpor?al or extra-corpor?al or external) adj4 (perfusion* or assist* or device* or support* or system* or circulat* or machine* or circuit* or apparat* or equip* or mechani* or appliance*)).tw. (28375)
10 ((hepat* or "portal system*" or portal-system* or portosystem* or porto-system* or "porto system*" or portalsystem*) adj4 (encephalopath* or coma* or stupor*)).tw. (9525)
11 (ECLP or ELAD or ELSD).tw. (855)
12 or/7-11 (93631)
13 Swine/ (210520)
14 Liver/ (435002)
15 13 and 14 (9750)
16 ((porcine or pig* or swine*) adj4 liver*).tw. (8514)
17 ((non-transplant* or non transplant* or nontransplant* or unsuitab* or non-viab* or non viab* or nonviab*) adj4 liver*).tw. (164)
18 (bridg* adj4 (transplant* or donor* or donat*)).tw. (4059)
19 ((temporar* or interim or short-term or "short term" or transient or transitory) adj4 (support* or circulat* or function* or prolong*)).tw. (13065)
20 or/15-19 (31854)
21 6 and 12 and 20 (368)
22 animals/ not humans/ (4722437)
23 21 not 22 (287)
24 limit 23 to ed=20200409-20201130 (1)

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
Abouna GM, Garry R, Kirkley J et al. (1969) Hepatic coma due to fulminating hepatitis treated with extracorporeal pig-liver perfusion. British journal of surgery 56: 223-225	Case report n=1 (47 years; male)	Following ECLP using pig liver, the patient regained full consciousness. The biochemical improvement was also striking. His recovery was interrupted by a severe haematemesis 48 hours after perfusion and then relapsed into coma. He died from a further haematemesis.	This study was included in Pascher et al. (2002) in table 2.
Abouna GM, Kirkley JR, Hull CJ et al. (1969) Treatment of hepatic coma by extracorporeal pig-liver perfusion. The Lancet: 64-68	Case series n=4 (range 6 to 47 years; 25% [1/4] female)	The results of 7 perfusions were complete recovery of consciousness in 1, lightening of coma in 5 and neurological improvement in 1. There was a notable reduction in toxic metabolites and significant rise in essential substances.	This study was included in Pascher et al. (2002) in table 2.
Chalstrey LJ and Parbhoo SP (1971) Circuitry and technique of extracorporeal porcine liver perfusion for the treatment of hepatic coma. British Journal of Surgery 58: 522-524	Case series n=3	Three patients in coma owing to acute liver failure had ECLP using pig livers. Improvement in the level of consciousness happened in all 3 patients and 2 were alive and well 8 months and 4 months respectively.	Limited efficacy outcomes were reported.
Eiseman B, Liem DA and Raffucci F (1965) Heterologous liver perfusion in treatment of hepatic failure. Annals of Surgery 162: 329-344	Case series n=8 (terminal liver coma)	Clinical improvement varied from dramatic return of consciousness during perfusion to only slight neurologic improvement. None of these moribund patients with far advanced hepatic failure thus far selected for perfusion	This study was included in Pascher et al. (2002) in table 2.

		had a long-term survivor.	
Eiseman B, van Wyk J and Griffen WO (1966) Methods for extracorporeal hepatic assist. Surg Gynecol Obstet 123: 522-530	Case series n=16	Patients with reversible hepatic failure could be improved by extracorporeal pig liver perfusion.	This study was included in Pascher et al. (2002) in table 2.
Fristoe LW, Merrill JH, Kangas JA et al. (1993) Extracorporeal support with a cadaver liver as a bridge to transplantation. The journal of extracorporeal technology 25: 133-139	Case series n=3	All 3 patients were successfully weaned from ECLP. Two patients received successful orthotopic liver transplantation and the third died of complications unrelated to ECLP after support was discontinued. ECLP has been shown to be an effective treatment for supporting the comatose patient with fulminant hepatic failure prior to transplantation.	The sample was included in Fox et al. (1993) and limited efficacy outcomes were reported.
Ham JM, Pirola RC, Davidson GM et al. (1968) Pig liver perfusion for the treatment of acute hepatic coma. Surg Gynecol Obstet 127: 543-549	Case report n=1 (5 years; female)	The patient who had ECLP using pig liver improved neurology.	This study was included in Pascher et al. (2002) in table 2.
Harris MJ and Beveridge J (1969) Problems associated with survival after pig-liver perfusion. The medical journal of Australia, 2: 348-351	Case report n=1 (10 years; male)	The case presented a probable immunological reaction characterised by fever, cardiomegaly and heart failure, lung involvement and myalgia, which was severe, progressive and potentially fatal, occurring 11 weeks after heterologous liver perfusion. It seems likely that this reaction was a direct consequence of the procedure.	This study was included in Pascher et al. (2002) in table 2.
Henricus BAC, Stockmann MD, Coen A et al. (2000) Extracorporeal perfusion for the treatment of acute liver failure. Annals of surgery, 231: 460-470	Review	Although the results of extracorporeal whole liver perfusion were encouraging, a controlled study has not yet been performed to predict conclusively the outcome. Also, the	This was a review article.

		immunologic implications of human blood perfused through hepatic endothelial tissue are unknown.	
Hickman R, Saunders SJ, King JB et al. (1971) Pig liver perfusion in the treatment of fulminant hepatic necrosis. Scandinavian journal of gastroenterology 6: 564-568	Case series n=4 (mean 22 years; 75% female)	None of the patients survived but 2 shoed a response to the treatment, in that there was an improvement in the level of consciousness. All patients died of haemorrhagic complications.	This study was included in Pascher et al. (2002) in table 2.
Margulis MS, Rosenthal RL, Daugulis EC et al. (1975) Intensive therapy for hepatic coma. Clinical care medicine 3: 226-230	Case series n=45 (perfusion using pig liver n=10)	Improvement of blood chemistries, particularly bilirubin and ammonia, was noted in all patients. this was especially marked in 10 patients who had received pig liver perfusion. Perfusion using pig liver should be included in the combined treatment, as it was quite possible that the irreversible changes in the brain and other organs arise because of the presence of toxins cleared by the liver or the absence of a sufficient amount of substances secreted by the liver.	Limited efficacy outcomes for perfusion using pig livers were reported.
Parbhoo SP, Chalstrey LJ, Ajdukiewicz AB et al. (1971) Extracorporeal perfusion of pig liver in the treatment of acute liver failure. British journal of surgery 58: 746-748	Case series n=5 (6 perfusions; 60% male)	An exchange of 48 to 94 litres from pig liver to patient was achieved during the procedure. All patients showed neurological improvement after perfusion. Three patients died 2 hours to 10 days after liver perfusion and 2 made a full recovery and were leading a normal life 9 and 14 months after perfusion.	The key efficacy outcomes were covered by Parbhoo (1971) in table 2.
Pascher A, Sauer IM and Neuhaus P (2002) Analysis of allogeneic versus xenogeneic	Review n=198 (142 patients had ECLP using porcine livers, 29 used baboon	Pig liver perfusions resulted in a 20% long-term-survival whereas the use of human livers	This study was part of Pascher et al. (2002) in table 2 and did not separate patients with

auxiliary organ perfusion in liver failure reveals superior efficacy of human livers. The international journal of artificial organs 25(10): 1006-1012	livers, 14 used human livers, and 13 used other or mixed species)	was significantly more successful (survival rate (SVR) 43%, p<0.05). Baboon livers also revealed superior success (41%; p<0.05). Twenty-three patients were treated after 1991, 12 surviving long-term (52%). The latter all belonged to a group of 14 patients who received combined treatment consisting of ECLP and LTx (SVR-86% in this subgroup).	acute liver failure from patients with subacute or chronic liver failure.
Watts JM (1969) The treatment of acute hepatic failure by porcine liver perfusion. The medical journal of Australia 1: 324-326	Case series n=5	Although heterologous liver perfusion is effective in improving the clinical state of many patients, it is only 1 part of the treatment of a seriously ill patient who is at risk from a wide variety of potentially lethal complications. Supportive measures such as liver perfusion can only be temporarily effective and the ultimate outcome for any patient with liver failure depends on the ability to regenerate functioning liver parenchyma within a relatively short time.	Limited efficacy outcomes were reported in this study.