NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of extracorporeal membrane oxygenation for severe acute respiratory failure in adults

Treating severe acute respiratory failure using an artificial 'lung' to oxygenate the blood outside the body

Extracorporeal membrane oxygenation (ECMO) is a temporary life support technique, used to treat respiratory failure (where the lungs do not work effectively) in critically ill patients. The aim is to increase oxygen levels in the blood. During the procedure, a tube carries blood from the right side of the heart then pumps it through an artificial lung where it picks up oxygen. This oxygen-rich blood is then passed back into the person's blood system.

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 May 2010.

Procedure name

- Extracorporeal membrane oxygenation (ECMO) for severe acute respiratory failure in adults

Specialty societies

- British Thoracic Society
- Society for Cardiothoracic Surgery in Great Britain and Ireland
- The Intensive Care Society.

Description

Indications and current treatment

Extracorporeal membrane oxygenation (ECMO) is a supportive therapy for adults with severe acute respiratory failure from a potentially reversible cause. Extracorporeal membrane systems mimic gas exchange in the lungs, by eliminating some carbon dioxide from the blood and adding oxygen.

There are many causes of severe acute respiratory failure, including acute respiratory distress syndrome (ARDS, which may in turn be caused by a range of underlying conditions), pneumonia, chest trauma, pulmonary haemorrhage and neurological injury.

Conventional treatment involves maximum critical care support, including mechanical ventilation (for example, intermittent positive-pressure ventilation). The high airway pressures and oxygen concentrations generated by this form of ventilation may exacerbate lung injury from the primary illness.

Arteriovenous extracorporeal membrane carbon dioxide removal (AV-ECCO_2R), also known as pumpless extracorporeal lung assist (PECLA), has also been used to support gas exchange in patients with severe acute respiratory failure, where hypercapnia is a problem. This procedure is similar to ECMO but the primary aim is to remove excess carbon dioxide.

Extracorporeal membrane oxygenation (ECMO) uses heart-lung bypass technology to provide gas exchange of carbon dioxide and oxygen outside the body, while the failing lungs are kept inflated and resting by mechanical ventilation. The aims are to reduce ventilator-induced lung injuries and improve patient outcomes.

What the procedure involves

There are two main types of ECMO: venovenous ECMO (for respiratory support) and venoarterial ECMO (for cardiac and mixed cardiac and respiratory support). In venovenous ECMO, 2 or 3 single-lumen catheters are used, typically placed via the jugular and femoral veins, alternatively a double-lumen cannula is placed into the right side of the circulation via the jugular vein. Desaturated blood is withdrawn from the superior and inferior venae cavae and pumped through an oxygenator, where gas exchange of oxygen and carbon dioxide takes place. The oxygenated blood is then returned to the venous system. In venoarterial ECMO, blood is usually withdrawn via the jugular or femoral vein and the oxygenated blood is returned to the arterial system, usually via the femoral artery. In both systems patients are given a continuous infusion of an anticoagulant, usually heparin, to prevent blood clotting in the external system.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to ECMO in adults. Searches were conducted of the following databases, covering the period from their commencement to 5 May 2010: 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). 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	Adults with severe acute respiratory failure.
Intervention/test	Extracorporeal membrane oxygenation (ECMO)
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 overview

This overview is based on approximately 2505 patients from 1 randomised controlled trial (RCT), 3 non-randomised comparative studies, 2 case series and 1 case report [1–8].

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.

Table 2 Summary of key efficacy and safety findings on extracorporeal membrane oxygenation (ECMO) for severe acute respiratory failure in adults

Abbreviations used: ARDS, acute respiratory distress syndrome; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; FEV_1, forced expired volume during 1 second; HAD, hospital anxiety depression; IQR, interquartile range; OR, odds ratio; PEEP, positive end-expiratory pressure; RR, relative risk; VAS, visual analogue score; SAPS II, simplified acute physiology score; SOFA, sepsis-related organ failure assessment

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Peek GJ (2009)[1,8]

Randomised controlled trial

UK

Recruitment period: 2001–6

Study population: patients with severe but potentially reversible respiratory failure

n = 180 (90 ECMO vs 90 conventional management)

Mean age: 40 years (range 18–65)
Sex: 58% (104/180) male

Patient selection criteria: aged 18–65 years with severe but potentially reversible respiratory failure and a Murray score of 3.0 or higher (average score of 4 variables: PaO_2/FiO_2 ratio, positive end-expiratory pressure, lung compliance, and chest radiograph appearance), or uncompensated hypercapnoea with pH <7.20 despite optimum conventional treatment. Patients were also considered for inclusion if the Murray score was 2.5 or higher, so that trial entry</td>
<td>Number of patients analysed: 180 (90 vs 90)

75% (68/90) of patients randomised to the consideration for ECMO group went on to receive ECMO (16 patients improved with conventional management, 3 died within 48 hours before transfer, 2 died during transfer, 1 patient could not be heparinised).

Death or severe disability at 6-month follow-up:
• ECMO group = 37% (33/90)
• Conventional management = 53% (46/87) (there was no information about disability for 3 patients)
RR = 0.69 (95% CI: 0.05 to 0.97) (based on 177 patients with known primary outcome)
Death before 6-month follow-up or discharge:
• ECMO group = 37% (33/90)
• Conventional management = 45% (45/90)
RR = 0.73 (95% CI: 0.52 to 1.03)
Severe disability before 6-month follow-up or discharge:
• ECMO group = 0% (0/90)
• Conventional management = 1% (1/90)
Median time between randomisation and death (days):
• ECMO group = 15 (IQR 3–41)
• Conventional management = 5 (IQR 2–14)

Length of stay for all patients (days)
<table>
<tr><th></th><th>ECMO (n = 90)</th><th>Conventional management (n = 90)</th></tr>
<tr><td>Critical care</td><td>24.0</td><td>13.0</td></tr>
<tr><td>Hospital</td><td>35.0</td><td>17.0</td></tr>
</table>
Length of stay for patients who died (days)
<table>
<tr><th></th><th>ECMO</th><th>Conventional</th></tr>
</table>
</td>
<td>2 serious adverse events were reported, both in the ECMO group:

1 mechanical failure of the oxygen supply in the ambulance, resulting in the death of the patient during transfer to the ECMO centre.

1 vessel perforation during cannulation; the perforation was controlled but the clinical team felt that it contributed to the patient's death.</td>
<td>This is the 'CESAR' trial referred to in the original guidance.
Follow-up issues:
• 91% (52/57) of patients in the ECMO group who were eligible for the 6-month follow-up were assessed at 6 months. In the conventional management group, 70% (32/46) of eligible patients were assessed at 6 months.
Study design issues:
• An independent central randomisation service was used to randomly allocate patients in a 1:1 ratio to conventional management or consideration for ECMO.
• The primary outcome was death or severe disability at 6 months after randomisation or before discharge from hospital.
• The primary analysis was by intention to treat.
• Only the researchers who did the 6-month assessment were blinded to treatment allocation.
• Severe disability was defined as confinement to bed and inability to wash or dress alone.
• Patients randomised to the consideration for ECMO group received cannulation and ECMO if they did not respond to a standard acute respiratory</td>
</tr>
</table>

Abbreviations used: ARDS, acute respiratory distress syndrome; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; FEV_1, forced expired volume during 1 second; HAD, hospital anxiety depression; IQR, interquartile range; OR, odds ratio; PEEP, positive end-expiratory pressure; RR, relative risk; VAS, visual analogue score; SAPS II, simplified acute physiology score; SOFA, sepsis-related organ failure assessment

Study details	Key efficacy findings	Key safety findings	Comments

could be accelerated if the patient continued to deteriorate. Patients were excluded if they had: been on high pressure or high FiO_2 ventilation for >7 days; signs of intracranial bleeding; any other contraindication to limited heparinisation; any contraindication to continuation of active treatment.

Technique: Conventional management included intermittent positive-pressure ventilation or high-frequency oscillatory ventilation, or both. All ECMO was done in the **venovenous** mode with percutaneous cannulation. ECMO was continued until lung recovery, or until apparently irreversible multiorgan failure.

Follow-up: 6 months

Conflict of interest/source of funding: funded by UK NHS Health Technology Assessment, English National Specialist Commissioning Advisory Group, Scottish Department of Health, and Welsh Department of Health.

	(n = 33)	management (n = 45)
Critical care	11.0	5.0
Hospital	15.0	5.0

Follow-up assessment at 6 months

	ECMO (n = 90)	Conventional management (n = 90)
Overall health status (VAS, 0–100)*	67.9	65.9
*SF-36 (0–100)**		
Physical functioning	64.5	60.0
Physical role	58.2	46.3
Bodily pain	66.2	62.2
General health	54.1	59.3
Vitality	52.9	47.7
Social functioning	69.5	62.1
Emotional role	72.6	71.4
Mental health	70.5	65.5
St George's respiratory questionnaire (0– 100)#		
Symptom score	32.4	41.2
Activity score	29.5	38.4
Impact score	15.0	18.8
HAD scale (depression) (0–21)#		
Mean score	4.4	5.8
Clinically significant depression	4 (4%)	4 (4%)
HAD scale (anxiety) (0–21)#		
Mean score	5.8	7.4
Clinically significant anxiety	7 (8%)	10 (11%)
Sleep problems score (0–100)#	16.7	18.8

* higher score indicates better condition
# higher score indicates worse condition

distress syndrome treatment protocol within 12 hours or were haemodynamically unstable.

Study population issues:

- Steroids were used in more patients in the consideration for ECMO group than the conventional management group, and molecular albumin recirculating system for liver dysfunction was used in almost a fifth of patients in the consideration for ECMO group compared with none receiving conventional management.

Other issues:

- Most deaths (60%) in the conventional management group were due to respiratory failure, whereas this caused 24% of deaths in patients in the ECMO group. Most deaths (42%) in the ECMO group were due to multiorgan failure.
- Patients randomly allocated to consideration for treatment by ECMO were transferred to a single centre.
- There was no standardised treatment protocol for patients in the conventional management group.
- The outcome for patients in the conventional management group was better than predicted when the study was planned.

Abbreviations used: ARDS, acute respiratory distress syndrome; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; FEV_1, forced expired volume during 1 second; HAD, hospital anxiety depression; IQR, interquartile range; OR, odds ratio; PEEP, positive end-expiratory pressure; RR, relative risk; VAS, visual analogue score; SAPS II, simplified acute physiology score; SOFA, sepsis-related organ failure assessment

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Mols G (2000)[2]

Non-randomised comparative study

Germany

Recruitment period: 1991–9

Study population: patients with acute lung injury or ARDS

n = 245 (62 ECMO, 183 conservative management)

Mean age (years): ECMO = 35, controls = 43, p = 0.001
Sex: 56% (35/62)

Patient selection criteria: patients with PaO_2/FIO_2 ≤ 50 mmHg at a PEEP of at least 10 cm H_2O after a conventional treatment trial of 2 hours were given ECMO. Patients with PaO_2 ≤ 40 mmHg were immediately given ECMO without a treatment trial. The remaining patients received ECMO if FIO_2 >0.6 for several days without substantial improvement of gas exchange despite maximal supportive therapy. Contraindications to ECMO included severe cerebral injury, severe chronic pulmonary disease, relevant</td>
<td>Number of patients analysed: 245

Patients were treated with ECMO for 15 ± 10 days

Survival rate (to hospital discharge):
• ECMO = 54.8% (34/62)
• Controls = 61% (actual figures not given, p = not significant)

In the ECMO group, multiorgan failure, most often associated with sepsis, was the leading cause of death (64%, 18/28).

Characteristics of survivors and non-survivors in the ECMO group
<table>
<tr><th></th><th>Survivors (n = 34)</th><th>Non-survivors (n = 28)</th><th>p value</th></tr>
<tr><td>Mechanical ventilation before ECMO (days)</td><td>13 ± 8</td><td>11 ± 6</td><td>NS</td></tr>
<tr><td>Lung injury score at entry</td><td>3.5 ± 0.3</td><td>3.5 ± 0.3</td><td>NS</td></tr>
<tr><td>Acute renal failure at entry</td><td>9%</td><td>39%</td><td>0.003</td></tr>
<tr><td>Acute hepatic failure at entry</td><td>44%</td><td>75%</td><td>0.026</td></tr>
<tr><td>Duration of ECMO</td><td>12 ± 7</td><td>17 ± 11</td><td>0.013</td></tr>
<tr><td>Fresh frozen plasma/day during ECMO</td><td>3.5 ± 1.4</td><td>5.7 ± 3.2</td><td>0.006</td></tr>
<tr><td>Unit of thrombocytes/day during ECMO</td><td>1.6 ± 1.9</td><td>5.0 ± 5.4</td><td>0.026</td></tr>
</table>
In the control group, logistic regression revealed that age and acute renal failure were the only independent factors associated with survival. Acute renal failure occurred in 57% of non-survivors versus 18% of</td>
<td>ECMO-related complications
• Rupture of tubing system = 4.8% (3/62) (brain death was diagnosed in 1 patient after resuscitation and reinstitution of ECMO).
• Difficulties and/or injuries during cannulation = 8.1% (5/62) (surgical intervention to repair injury of the carotid artery was required in 1 patient).
• Clots in circuit = 3.2% (2/62)
• Massive disseminated intravascular coagulation = 4.8% (3/62)
• Colonisation of catheters = 1.6% (1/62)
• Air in circuit = 1.6% (1/62)

‘Other’ complications
• Severe pleural bleeding = 6.4% (4/62)
• Large bronchopleural fistula = 1.6% (1/62)
• Brain death = 1.6% (1/62)

Surgical interventions during ECMO
• Thoracotomy = 9.7% (6/62)
• Laparotomy = 1.6% (1/62)</td>
<td>This study was included in table 2 of the original overview.

Study design issues:
• Prospective data collection.
Study population issues:
• When compared with the controls, the ECMO patients had a longer history of mechanical ventilation before admission to the study centre ICU (10 vs 2 days, p < 0.0001), they were younger, gas exchange was more severely impaired and the lung injury score was higher (3.2 vs 2.7, p < 0.0001).

Other issues:
• The study includes the first patient treated with ECMO at the study centre.
• The authors note the importance of experience and that all of the first 4 ECMO-treated patients died.</td>
</tr>
</table>

Abbreviations used: ARDS, acute respiratory distress syndrome; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; FEV_1, forced expired volume during 1 second; HAD, hospital anxiety depression; IQR, interquartile range; OR, odds ratio; PEEP, positive end-expiratory pressure; RR, relative risk; VAS, visual analogue score; SAPS II, simplified acute physiology score; SOFA, sepsis-related organ failure assessment

Study details	Key efficacy findings	Key safety findings	Comments
coronary artery disease, chronic heart failure, chronic renal failure, chronic liver failure, malignancy, immunosuppression, sepsis, contraindication for anticoagulation, age >55 years, acute left ventricular failure. Technique: **Venovenous** ECMO. Conventional management included prone positioning, inhalation of nitric oxide, optimisation of haemodynamics and infection control. **Follow-up: to hospital discharge** Conflict of interest/source of funding: not reported	survivors ($p < 0.0001$). Non-survivors were on average older than survivors (48 ± 17 versus 40 ± 15 years, $p = 0.012$).		

Abbreviations used: ARDS, acute respiratory distress syndrome; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; FEV_1, forced expired volume during 1 second; HAD, hospital anxiety depression; IQR, interquartile range; OR, odds ratio; PEEP, positive end-expiratory pressure; RR, relative risk; VAS, visual analogue score; SAPS II, simplified acute physiology score; SOFA, sepsis-related organ failure assessment

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Beiderlinden M (2006)[3]

Non-randomised comparative study

Germany

Recruitment period: 1998–2003

Study population: patients with severe ARDS

n = 150 (32 ECMO, 118 conservative management)

Mean age: 42 years
Sex: not reported

Patient selection criteria: ARDS and lung injury score >2.5; age <70 years; weight >15 kg. Exclusion criteria were malignancy, end-stage lung disease, and intracranial bleeding.

Technique: Venovenous ECMO via the jugular and femoral veins, using a heparin-bonded ECMO circuit (Super Tygon, Medtronic).

Follow-up: not reported
Conflict of interest/source of funding: not reported.</td>
<td>Number of patients analysed: 150
Survival rate:
• ECMO = 53.1% (17/32)
• Controls = 71.2% (84/118), p = 0.059

Baseline variables
<table>
<tr><th></th><th>ECMO (n = 32)</th><th>Controls (n = 118)</th><th>p value</th></tr>
<tr><td>Days on mechanical ventilation prior to admission</td><td>5.5 ± 7</td><td>6.7 ± 8</td><td>0.34</td></tr>
<tr><td>Lung injury score</td><td>3.8 ± 0.3</td><td>3.3 ± 0.4</td><td><0.0001</td></tr>
<tr><td>SAPS II</td><td>52 ± 14</td><td>43 ± 12</td><td>0.001</td></tr>
<tr><td>SOFA</td><td>14 ± 3.3</td><td>10 ± 3.5</td><td><0.0001</td></tr>
<tr><td>PaO_2/FIO_2 ratio(mmHg)</td><td>63 ± 28</td><td>100 ± 36</td><td><0.0001</td></tr>
<tr><td>PEEP (cmH_2O)</td><td>19 ± 3</td><td>15 ± 4</td><td><0.0001</td></tr>
<tr><td>Compliance (ml/cmH_2O)</td><td>21 ± 10</td><td>33 ± 14</td><td><0.0001</td></tr>
<tr><td>$PaCO_2$ (mmHg)</td><td>98 ± 42</td><td>71 ± 25</td><td>0.0002</td></tr>
<tr><td>Mean pulmonary artery pressure (mmHg)</td><td>39 ± 9</td><td>35 ± 8</td><td>0.023</td></tr>
</table>
Multivariate logistic regression excluded ECMO as a predictor of mortality (p = 0.79) and revealed the following risk factors:
• Age, OR = 1.04, 95% CI: 1.01 to 1.08
• Mean pulmonary artery pressure, OR = 1.08, 95% CI: 1.03 to 1.14
• SOFA, OR = 1.15, 95% CI: 1.02 to 1.29
• Days of mechanical ventilation prior to referral, OR = 1.06, 95% CI: 1.01 to 1.12</td>
<td>No safety outcomes were reported.</td>
<td>Study design issues:
• Prospective study, consecutive patients.
• Patients were referred to study centre from external hospitals; staff physicians were dispatched to the referring hospital to optimise the patients' condition prior to transport.
• Patients unresponsive to conservative measures were placed and transported on ECMO.
• The main outcome measure was hospital mortality.
Study population issues:
• The severity of disease was significantly higher in ECMO-treated patients than in those without ECMO treatment.
Other issues:
• The conclusion of the study was that despite the worse baseline variables in the ECMO group, the outcome was no worse for these patients than the fitter control group.</td>
</tr>
</table>

Abbreviations used: ARDS, acute respiratory distress syndrome; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; FEV_1, forced expired volume during 1 second; HAD, hospital anxiety depression; IQR, interquartile range; OR, odds ratio; PEEP, positive end-expiratory pressure; RR, relative risk; VAS, visual analogue score; SAPS II, simplified acute physiology score; SOFA, sepsis-related organ failure assessment

Study details	Key efficacy findings	Key safety findings	Comments
The Australia and New Zealand ECMO Influenza Investigators (2009)[4] **Non-randomised comparative study** Australia and New Zealand Recruitment period: 2009 Study population: patients with 2009 influenza A (H1N1)-associated ARDS **n = 201 (68 ECMO, 133 mechanical ventilation without ECMO)** Median age (ECMO): 34 years (IQR 27 to 43) Sex (ECMO): 50% (34/68) male Patient selection criteria: confirmed or strongly suspected 2009 influenza A (H1N1)-related severe ARDS (all of the patients fulfilled the severity criteria for enrolment in the CESAR study). Technique: The initial mode of ECMO was **venovenous** in 93% of patients. **Follow-up: not reported** Conflict of interest/source of funding: not reported.	Number of patients analysed: 201 Comparison of patients with **confirmed influenza A** who received ECMO (n = 61) and controls who received mechanical ventilation without ECMO Variable / **ECMO (n = 61)** / **Controls (n = 133)** / **P value** Median age (years) / 36 / 44 / 0.02 Mechanical ventilation at ICU admission / 87% (53/61) / 88% (117/133) / 0.80 Vasopressor at ICU admission / 57% (35/61) / 34% (46/133) / 0.02 Renal replacement therapy / 8% (5/61) / 7% (9/133) / 0.95 Median duration of mechanical ventilation (days) / 18 / 8 / 0.001 Median length of ICU stay (days) / 22 / 12 / 0.001 Median length of hospital stay (days) / 28 / 20 / 0.07 Mortality in ICU / 23% (14/61) / 9% (12/133) / 0.01 Mortality in hospital / 23% (14/61) / 13% (17/133) / 0.06 78% (53/68) of patients were weaned off ECMO and 76% (52/68) survived. At the time of the report, 2 patients remained on ECMO, 4 patients were still in the intensive care unit, 16 were still in the hospital and 47% (32/68) patients had survived to hospital discharge. Total mortality rate for ECMO group = 21% (14/68).	**Complications in ECMO group** *Haemorrhagic complications (54% [37/68]):* • Bleeding at cannulation sites = 22% (15/68) • Gastrointestinal tract bleeding = 10% (7/68) • Respiratory tract bleeding = 10% (7/68) • Vaginal bleeding = 9% (6/68) • Intracranial haemorrhage = 9% (6/68) *Infective complications (62% [42/68]):* • Respiratory tract infection = 44% (30/68) • Bloodstream infection = 21% (14/68) • Non-ECMO catheter-related infection = 19% (13/68) • ECMO cannula-related infection = 10% (7/68)	**Study design issues**: • Retrospective study. • Patient population includes all patients admitted to 15 intensive care units with influenza who received mechanical ventilation. • Patient selection is not described. **Study population issues**: • The study population includes 3 children treated with ECMO. • 7 patients in the ECMO group had suspected but unconfirmed influenza. All the remaining patients had confirmed 2009 influenza A (H1N1) or influenza A not subtyped. • 81% (55/68) of patients in the ECMO group had 1 or more rescue therapy before commencement of ECMO (such as recruitment manoeuvres, prone positioning, high-frequency oscillatory ventilation, inhaled nitric oxide, or prostacyclin). The authors note that the patients were young and had ARDS secondary to viral pneumonia, which has been associated with higher survival rates than other causes of ARDS. • **Other:** The authors note that several patients remained in the ICU at the time of reporting.

Abbreviations used: ARDS, acute respiratory distress syndrome; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; FEV_1, forced expired volume during 1 second; HAD, hospital anxiety depression; IQR, interquartile range; OR, odds ratio; PEEP, positive end-expiratory pressure; RR, relative risk; VAS, visual analogue score; SAPS II, simplified acute physiology score; SOFA, sepsis-related organ failure assessment

Study details

Brogan TV (2009)[5]

Case series

USA

Recruitment period: 1986–2006

Study population: adults with severe respiratory failure

n = 1473

Median age: 34 years (range 16–84)
Sex: 53% (563/1066) male

Patient selection criteria: adult patients (age ≥ 16 years) with respiratory failure (including ARDS, pneumonia, acute respiratory failure, trauma, aspiration pneumonitis, sepsis, asthma and miscellaneous). The decision to employ ECMO was made at each centre without standardisation.

Technique: **Venovenous** mode was used in 48% (703/1473) of all patients. Venoarterial mode was used for 20% (297/1473) of all patients. The ECMO mode was unknown for 27% (391/1473) of all patients. In more recent patients (2002–6), the proportion of

Key efficacy findings

Number of patients analysed: 1473

Survival to discharge = 50% (741/1473)

Multiple logistic regression analysis of pre-ECMO variables influencing outcome (probability of fatal outcome)

Variable	Odds ratio	95% CI	p value
Age	1.03	1.02 to 1.04	<0.001
Pre-ECMO duration of mechanical ventilation (days)	1.002	1.001 to 1.003	0.005
Pre-ECMO arterial blood gas pH <7.18 (vs >7.36)	2.50	1.66 to 3.78	<0.001
Race			0.04
White	1.00		
Asian	1.86	1.19 to 2.90	
Black	2.00	0.82 to 4.90	
Hispanic	1.06	0.41 to 2.76	
Other	1.39	0.85 to 2.27	
Diagnostic group			0.01
ARDS	1.00		
Pneumonia	0.71	0.46 to 1.08	
Acute respiratory failure	0.40	0.20 to 0.79	
Trauma	0.69	0.39 to 1.23	
Aspiration pneumonitis	0.62	0.21 to 1.86	
Sepsis	1.36	0.62 to 2.96	
Asthma	0.15	0.04 to 0.56	
Other	0.98	0.65 to 1.48	
ECMO mode			<0.001

Key safety findings

Complications, n (%)

Variable	Survivors (n = 741)	Non-survivors (n = 732)	p value
Circuit complications			
Mechanical problems	186 (25)	265 (36)	<0.001
Circuit rupture	19 (3)	45 (6)	0.001
Circuit clot	124 (17)	132 (18)	0.51
Brain injury			
Seizures	11 (1)	21 (3)	0.07
Central nervous system infarction or haemorrhage	13 (2)	51 (7)	<0.001
Brain death	0	72 (10)	-
Renal complications			
Renal insufficiency	97 (13)	191 (26)	<0.001
Renal failure	73 (10)	135 (18)	<0.001
Renal replacement therapies	258 (35)	390 (53)	<0.001
Haemorrhage			
Surgical haemorrhage	181 (24)	260 (36)	<0.001
Gastrointestinal haemorrhage	15 (2)	54 (7)	<0.001
Pulmonary haemorrhage	24 (3)	79 (11)	<0.001
Metabolic			
Hypoglycaemia	6 (1)	12 (2)	0.147
Hyperglycaemia	109 (15)	157 (21)	0.001
Arterial blood pH <7.20	24 (3)	70 (10)	<0.001
Arterial blood pH >7.60	9 (1)	28 (4)	0.001
Other			
White blood cell count <1500	12 (2)	23 (3)	0.06

Comments

Study design issues:

- Retrospective review (Extracorporeal Life Support Organization [ELSO] registry).
- Data are included from 116 US and 14 international centres.
- Complications occurring only during ECMO support were evaluated.
- Survival was to hospital discharge.

Study population issues:

- Many variables (including patient selection, indication for ECMO, and ECMO mode) were neither included in the database nor standardised.

Abbreviations used: ARDS, acute respiratory distress syndrome; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; FEV_1, forced expired volume during 1 second; HAD, hospital anxiety depression; IQR, interquartile range; OR, odds ratio; PEEP, positive end-expiratory pressure; RR, relative risk; VAS, visual analogue score; SAPS II, simplified acute physiology score; SOFA, sepsis-related organ failure assessment

Study details	Key efficacy findings	Key safety findings	Comments

Study details

venovenous and venoarterial mode ECMO was 66% and 27% respectively.

Follow-up: to hospital discharge

Conflict of interest/source of funding: not reported.

Key efficacy findings

Venoarterial	1.00		
Venovenous	0.56	0.39 to 0.81	
Venovenous to venoarterial	3.45	1.08 to 11.0	
Other	0.77	0.33 to 1.80	

Key safety findings

cells/mm^3			
Cardiopulmonary resuscitation	32 (4)	129 (18)	<0.001
Inotropic medications	345 (47)	511 (70)	<0.001
Documented infections	126 (17)	204 (28)	<0.001
Pneumothorax	78 (11)	133 (18)	<0.001
Arrhythmias	88 (12)	196 (27)	<0.001
Hypertension	44 (6)	45 (6)	0.87

Complications occurred more commonly among patients started on venoarterial ECMO.

Abbreviations used: ARDS, acute respiratory distress syndrome; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; FEV_1, forced expired volume during 1 second; HAD, hospital anxiety depression; IQR, interquartile range; OR, odds ratio; PEEP, positive end-expiratory pressure; RR, relative risk; VAS, visual analogue score; SAPS II, simplified acute physiology score; SOFA, sepsis-related organ failure assessment

Study details

Hemmila MR (2004)[6]

Case series

USA

Recruitment period: 1989–2003

Study population: adults with severe ARDS

n = 255

Mean age: 38.4 years (range 17–69)
Sex: 49% (124/255) male

Patient selection criteria: patients with severe ARDS refractory to all other treatment. The indications for ECMO were based primarily on lung dysfunction measured as PaO_2/FiO_2 ratio <100 on FiO_2 of 1.0, alveolar-arterial gradient >600 mm Hg, or transpulmonary shunt fraction >30% despite and after optimal treatment. Early in the study, contraindications were age >50 years, time on mechanical ventilation >5 days and severe systemic sepsis. As experience grew, the age contraindication advanced to 70 years, time on mechanical ventilation was advanced to 10 days and severe sepsis was no longer

Key efficacy findings

Number of patients analysed: 255

Successful weaning and survival off ECMO = 67.1% (171/255)

Survival to discharge = 51.8% (132/255)

Multiple logistic regression analysis of pre-ECMO variables influencing outcome (probability of fatal outcome)

Variable	OR	95% CI	p value
Age	1.03	1.01 to 1.05	0.01
Gender (male vs female)	0.58	0.34 to 0.996	0.048
pH ≤7.10	8.40	1.55 to 45.5	0.01
PaO_2/FiO_2	0.98	0.96 to 0.998	0.03
Pre-ECMO ventilator days	1.20	1.09 to 1.31	<0.001
Pre-ECMO ventilator days >8	5.53	1.94 to 15.8	0.001

'Almost all surviving patients returned to normal function by 1 year post-discharge. The major abnormalities experienced are neurologic or neuromuscular disorders, including deafness and prolonged weakness or neuropathy. The major disability is psychological, as is common after any life-threatening illness. Approximately 25% of patients have fear of recurrence of illness, nightmares, or even overt depression.'

Key safety findings

Complications

	%	Survival (%)	OR	95% CI
Cannula problems	21.2	40.7	1.76	0.92 to 3.41
Oxygenator failure	20.8	41.5	1.68	0.88 to 3.28
Clots in circuit	20.7	47.2	1.26	0.66 to 2.42
Air in circuit	6.7	52.9	0.95	0.31 to 2.88
Tubing rupture	3.1	25.0	1.77	0.49 to 7.05
Cannulation site bleeding	31.4	41.3	1.86	1.05 to 3.29
Surgical site bleeding	26.7	26.5	4.34	2.27 to 8.50
Haemolysis	11.8	30.0	2.81	1.17 to 7.27
Gastrointestinal haemorrhage	7.1	22.2	4.11	1.24 to 17.6
Disseminated intravascular coagulation	4.7	33.3	2.23	0.58 to 10.3
Cerebral infarction	5.5	21.4	4.22	1.07 to 24.03
Clinical brain death	3.5	0.0		
Cerebral haemorrhage	2.7	14.3	6.72	0.79 to 311.3
Renal replacement therapy	53.7	33.6	5.32	3.00 to 9.46
Pneumothorax	22.0	32.1	2.72	1.40 to 5.43
Pulmonary haemorrhage	14.1	27.8	3.43	1.51 to 8.31
Inotropic medications	71.8	43.2	3.46	1.85 to 6.59

Comments

Study design issues:

- The primary outcome measures were lung recovery (successful weaning and survival off ECMO), survival to hospital discharge and complications.

Study population issues:

- 75% (191/255) of patients were transferred to the study centre from outside. 91 patients were transported on ECMO.

Other issues:

- The authors concluded that >80% of these patients would have died without extracorporeal support.

Abbreviations used: ARDS, acute respiratory distress syndrome; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; FEV_1, forced expired volume during 1 second; HAD, hospital anxiety depression; IQR, interquartile range; OR, odds ratio; PEEP, positive end-expiratory pressure; RR, relative risk; VAS, visual analogue score; SAPS II, simplified acute physiology score; SOFA, sepsis-related organ failure assessment

Study details	Key efficacy findings	Key safety findings	Comments

a contraindication.

Technique**: Venovenous** access was the preferred mode of support for isolated respiratory failure. Venoarterial access was used when systemic arterial perfusion support was necessary in addition to respiratory support.

Follow-up: 1 year

Conflict of interest/source of funding: not reported.

Cardiac arrhythmia	37.3	36.8	2.55	1.47 to 4.47
Hypertension	20.8	60.4	0.64	0.33 to 1.24
Cardio-pulmonary resuscitation	13.3	11.8	10.3	3.44 to 41.4
Tamponade	3.9	40.0	1.64	0.38 to 8.09
Culture-proven new infection	38.0	41.2	1.99	1.15 to 3.43
White blood cell count <1500 cells/mm^3	3.5	33.3	2.21	0.46 to 13.9
Ischaemic bowel	2.0	0.0		
Deep venous thrombosis post-ECMO	7.5	78.9	0.26	0.06 to 0.86
Pulmonary embolus post-ECMO	2.0	0.0		
Glucose ≥ 240 mg/dl	55.3	50.4	1.13	0.67 to 1.92
Hyperbilirubin-aemia	16.1	36.6	1.99	0.95 to 4.29
pH ≤ 7.20	10.6	22.2	4.32	1.60 to 13.5
pH ≥ 7.60	2.4	50.0	0.71	0.06 to 6.32
Glucose ≤ 40 mg/dl	1.2	0.0		

All of the patients who suffered clinical brain death, ischaemic or gangrenous bowel, or glucose ≤ 40 mg/dl died.
Complications associated with deceased survival on multivariate analysis included cannulation site bleeding, surgical site bleeding, cerebral infarction, renal replacement therapy, pulmonary embolism and cardiopulmonary resuscitation on ECMO.

Abbreviations used: ARDS, acute respiratory distress syndrome; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; FEV_1, forced expired volume during 1 second; HAD, hospital anxiety depression; IQR, interquartile range; OR, odds ratio; PEEP, positive end-expiratory pressure; RR, relative risk; VAS, visual analogue score; SAPS II, simplified acute physiology score; SOFA, sepsis-related organ failure assessment

Study details	Key efficacy findings	Key safety findings	Comments
Hermans C (2008)[7] **Case report** Belgium Recruitment period: not reported Study population: patient with acute respiratory failure **n = 1** Age: 39 years Sex: male Technique: Venovenous ECMO was later switched to venoarterial ECMO. Conflict of interest/source of funding: not reported.	**Endogenous carbon monoxide production** A 39-year old patient with end-stage pulmonary fibrosis developed acute respiratory insufficiency due to a spontaneous pneumothorax and was started on venovenous ECMO. Therapy with inhaled nitric oxide was also started. On day 9, the patient developed a cardiogenic shock and ECMO access was switched to venoarterial using an additional cannula in the femoral artery. Carboxyhaemoglobin levels rose up to 4.4% on day 13 and nitric oxide was discontinued. Carboxyhaemoglobin levels continued to rise up to 9.5%. On day 18 the patient was transplanted, still on ECMO, but did not survive the operation because of massive pleural bleeding and haemorrhagic shock. The authors state that the high levels of carboxyhaemoglobin were most likely due to massive mechanical haemolysis in the ECMO circuit.		

Efficacy

Survival

An RCT of 180 patients randomised to consideration for treatment by ECMO or conventional management reported death or severe disability in 37% (33/90) and 53% (46/87) of patients respectively at 6-month follow-up (relative risk [RR] 0.69, 95% confidence interval [CI] 0.05 to 0.97)[1].

A non-randomised comparative study of 245 patients treated by ECMO or conventional treatment reported survival to hospital discharge in 55% (34/62) and 61% (actual figures not given) of patients respectively (p = not significant)[2]. A non-randomised comparative study of 150 patients treated by ECMO or conventional treatment reported survival rates of 53% (17/32) and 71% (84/118) respectively (p = 0.06)[3]. A non-randomised comparative study of 201 patients treated by ECMO or conventional management reported that 23% (14/61) and 13% (17/133) of patients, respectively, died during their hospital stay (p = 0.06)[4]. In these non-randomised comparative studies, it was noted that patients in the ECMO group had more severe disease than those treated by conventional management.

A case series of 1473 patients reported survival to discharge in 50% (741/1473) of patients[5]. A case series of 255 patients reported survival to discharge in 52% (132/255) of patients[6].

Quality of life

The RCT of 180 patients randomised to consideration for treatment by ECMO or conventional management reported similar levels in overall health status scores in both groups of patients at 6 months (67.9 versus 65.9, measured on a visual analogue scale from 0 to 100, where a higher score indicates a better health status)[1].

Safety

Difficulties and/or injury during cannulation

An RCT of 180 patients randomised to consideration for treatment by ECMO or conventional management reported that 1 patient out of 90 in the ECMO group had a vessel perforation during cannulation that was considered to have contributed to their death[1].

A non-randomised comparative study of 245 patients reported difficulties and/or injuries during cannulation in 8% (5/62) of patients; 1 patient required surgical intervention to repair an injury to the carotid artery[2].

Rupture of tubing system

A non-randomised comparative study of 245 patients and 2 case series of 1473 and 255 patients reported rupture of the ECMO tubing system in 5% (3/62), 4% (64/1473) and 3% (actual numbers not given) of patients respectively[2,5,6]. In the non-randomised comparative study, brain death was diagnosed in 1 patient after resuscitation and reinstitution of ECMO[2].

Haemorrhagic complications

A non-randomised study of 201 patients and a case series of 1473 patients reported bleeding as a complication in 54% (37/68) and 42% (613/1473) of patients respectively[4,5].

A non-randomised comparative study of 245 patients and a case series of 255 patients both reported that 5% of patients (3/62 in the comparative study, no actual figures were given for the case series) had disseminated intravascular coagulation[2,6].

Validity and generalisability of the studies

- The evidence presented relates largely to venovenous systems.
- In the RCT, patients randomly allocated to consideration for treatment by ECMO were transferred to a single centre and treated according to a standard protocol. There was no standardised treatment protocol for patients in the conventional management group[1].
- In the RCT, patients were randomised to consideration for ECMO or to conventional management. Some patients in the consideration for ECMO group improved with conventional management and did not actually receive ECMO[1].
- In 1 non-randomised comparative study, some patients were given ECMO immediately and others were treated by ECMO after a trial of conventional management, according to the severity of their condition[2].
- A non-randomised comparative study and a case series reported that ECMO was used for those patients who were unresponsive to conservative measures[3,6]. Another non-randomised comparative study reported that 81% of patients in the ECMO group had received 1 or more rescue therapies before commencement of ECMO[4].

- Patient selection, indication for ECMO and ECMO mode were not included in the database or standardised in the largest case series[5].
- In 2 non-randomised comparative studies, the patients treated by ECMO had more severe disease than the control patients[2,3].
- In 1 non-randomised comparative study, the authors noted that the patients were young and had ARDS secondary to viral pneumonia, which has been associated with higher survival rates than other causes of ARDS[4].

Existing assessments of this procedure

An Ontario Health Technology Assessment on extracorporeal lung support technologies was published in April 2010[9]. The CESAR trial was the only large RCT identified in the literature review. The report recommended that 'any approval for bridge to transplantation or bridge to recovery in adults for ILA or ECMO should be conditional on evidence development, since there is insufficient evidence that either technology improves survival rates.

Given the fact that there is moderate quality evidence that these technologies improve intermediate outcomes, from a social values perspective and in terms of biological plausibility, controlled funding should be considered as there are no alternative technologies for these patients.'

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

- Arteriovenous extracorporeal membrane carbon dioxide removal. NICE interventional procedures guidance 250 (2008). Available from http://www.nice.org.uk/guidance/IPG250
- Extracorporeal membrane oxygenation (ECMO) in adults. NICE interventional procedures guidance 39 (2004). This guidance is currently under review. For more information, see http://www.nice.org.uk/guidance/IPG391
- Extracorporeal membrane oxygenation (ECMO) in postneonatal children. NICE interventional procedures guidance 38 (2004). Available from www.nice.org.uk/guidance/IPG38

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.

Dr M Wise (British Thoracic Society), Mr G Bellingam, Miss J Eddleston (the Intensive Care Society), Mr G Peek, Mr S Tsui (Society of Cardiothoracic Surgeons of Great Britain and Ireland).

- Two Specialist Advisers had never performed the procedure, 1 had performed it at least once and 2 perform it regularly.
- Three Specialist Advisers considered the procedure to be established practice and no longer new. One Adviser stated that although it was established practice, there remains uncertainty with regard to efficacy.
- One Adviser commented that there have been constant improvements in technique and equipment.
- Anecdotal adverse events include vascular complications, air embolism, haemorrhage, thromboembolic events, sepsis, haemolysis, multi-organ failure and mechanical failure.
- Key efficacy outcomes include successful wean from ECMO, successful wean from ventilator, survival to critical care discharge, 28 day survival, survival to hospital discharge, 60 or 90 day survival and quality of life.
- One Adviser stated that there is some uncertainty about whether the procedure improves survival. There could be a role for specific groups, including the very refractory hypoxaemic patients. Another Adviser noted that the success rate depends on the underlying aetiology and reversibility of the pulmonary condition being treated, and pre-existing co-morbidities of the patients.
- Extensive training and expertise are required.
- Three Specialist Advisers thought that the procedure is likely to have a minor impact on the NHS and 1 thought that the impact would be major.

Patient Commentators' opinions

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

Issues for consideration by IPAC

There is an international registry of the Extracorporeal Life Support Organization (ELSO), based at the University of Michigan, USA (www.elso.med.umich.edu), which collects data on neonatal, paediatric and adult cases.

References

1. Peek GJ, Mugford M, Tiruvoipati R et al. (2009) Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 374: 1351–63.

2. Mols G, Loop T, Geiger K et al. (2000) Extracorporeal membrane oxygenation: a ten-year experience. American Journal of Surgery 180:144–54.

3. Beiderlinden M, Eikermann M, Boes T et al. (2006) Treatment of severe acute respiratory distress syndrome: role of extracorporeal gas exchange. Intensive Care Medicine 32: 1627–31.

4. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, Bailey M et al. (2009) Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. JAMA 302: 1888–95.

5. Brogan TV, Thiagarajan RR, Rycus PT et al. (2009) Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multi-center database. Intensive Care Medicine 35: 2105–14.

6. Hemmila MR, Rowe SA, Boules TN et al. (2004) Extracorporeal life support for severe acute respiratory distress syndrome in adults. Annals of Surgery 240: 595–607.

7. Hermans G, Meersseman W, Wilmer A et al. (2007) Extracorporeal membrane oxygenation: experience in an adult medical ICU. Thoracic & Cardiovascular Surgeon 55: 223–8.

8. Peek GJ, Elbourne D, Mugford M et al. (2010) Randomised controlled trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR). Health Technology Assessment 14 (35) 1-73.

9. Extracorporeal lung support technologies – Bridge to recovery and bridge to lung transplantation in adult patients. Ontario Health Technology Assessment Series 10: 1-47 (2010).

Appendix A: Additional papers on extracorporeal membrane oxygenation (ECMO) for severe acute respiratory failure in adults

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
Bermudez CA, Rocha RV, Sappington PL et al. (2010) Initial experience with single cannulation for venovenous extracorporeal oxygenation in adults. Annals of Thoracic Surgery 90: 991–5.	Case series n = 11	3 non-fatal cannulation-related events (including 1 acute thrombosis of the cannula). Single-venous cannulation in venovenous ECMO is a promising technique.	Larger studies are included.
Buckley E, Sidebotham D, McGeorge A et al. (2010) Extracorporeal membrane oxygenation for cardiorespiratory failure in four patients with pandemic H1N1 2009 influenza virus and secondary bacterial infection. British Journal of Anaesthesia 104: 326–9.	Case series n = 4	2 patients died during ECMO support. The 2 survivors had prolonged hospital stays, which were complicated by renal failure and limb ischaemia.	Larger studies are included.
Conrad S A, Rycus PT, Dalton H. (2005) Extracorporeal Life Support Registry Report 2004. ASAIO Journal 51: 4–10.	Case series (registry data) n = 972	Survival to discharge or transfer = 53%	Data from the same registry is included (Brogan TV, 2009).
Cordell-Smith J A, Roberts N, Peek GJ et al. (2006) Traumatic lung injury treated by extracorporeal membrane oxygenation (ECMO). Injury 37: 29–32.	Case series n = 28	ECMO for severe respiratory failure following trauma. Survival = 71% (20/28)	Larger studies are included.
Dahlberg PS, Prekker ME, Herrington CS et al. (2004) Medium-term results of extracorporeal membrane oxygenation for severe acute lung injury after lung transplantation. Journal of Heart & Lung Transplantation 23: 979–84.	Non-randomised comparative study n = 172 (16 ECMO)	ECMO for primary allograft failure after lung transplant. 90-day survival: • ECMO = 60% • Non-ECMO = 90% 2-year survival: • ECMO = 46% • Non-ECMO = 69%	Larger studies are included.
Fischer S, Bohn D, Rycus P et al. (2007) Extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation: analysis of the Extracorporeal Life Support Organization (ELSO) registry. Journal of Heart & Lung Transplantation 26: 472–7.	Case series (registry data) n = 151	Post-lung transplant patients with primary graft dysfunction. Survival to hospital discharge = 42%.	Data from the same registry is included (Brogan TV, 2009).
Freed DH, Henzler D, White CW et al. (2010) Extracorporeal lung support for patients who had severe respiratory failure secondary to influenza A (H1N1) 2009 infection in Canada. Canadian Journal of Anesthesia 57: 240–7.	Case series n = 4	3 out of 4 patients on ECMO survived.	Larger studies are included.

Frenckner B, Palmer P, Linden V. (2002) Extracorporeal respiratory support and minimally invasive ventilation in severe ARDS. Minerva Anestesiologica 68: 381–6.	Case series n = 38	Survival rate = 66% (25/38)	Larger studies are included.
Hermans G, Meersseman W, Wilmer A et al. (2007) Extracorporeal membrane oxygenation: experience in an adult medical ICU. Thoracic & Cardiovascular Surgeon 55: 223–8.	Case series n = 23	16 venovenous, 7 venoarterial ECMO. Survival rate = 48% (11/23) Technical complications were fatal in 2 patients.	Larger studies are included.
Iacono A, Groves S, Garcia J et al. (2010) Lung transplantation following 107 days of extracorporeal membrane oxygenation. European Journal of Cardio-Thoracic Surgery 37: 969–71.	Case report n = 1	Patient underwent bilateral lung transplant after 107 days of ECMO. He survived for 351 days post-transplant.	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Lewandowski K, Rossaint R, Pappert D et al. (1997) High survival rate in 122 ARDS patients managed according to a clinical algorithm including extracorporeal membrane oxygenation. Intensive Care Medicine 23: 819-835	Non-randomised comparative study n = 122	Survival rates: • ECMO = 55% • Controls = 89%, p <0.0001 (groups differed significantly with regard to disease severity and duration of mechanical ventilation prior to admission).	Larger, more recent studies are included. (this study was included in table 2 of the original overview)
Lidegran MK, Mosskin M, Ringertz HG et al. (2007) Cranial CT for diagnosis of intracranial complications in adult and pediatric patients during ECMO: Clinical benefits in diagnosis and treatment. Academic Radiology 14: 62–71.	Case series n = 123 (69 adults, 54 children)	63% (78/123) of patients had cranial CT while on ECMO. 37% (45/123) of patients had intracranial haemorrhage or cerebral infarction.	Study focuses on the use of cranial CT during ECMO.
Linden VB, Lidegran MK, Frisen G et al. (2009) ECMO in ARDS: a long-term follow-up study regarding pulmonary morphology and function and health-related quality of life. Acta Anaesthesiologica Scandinavica 53: 489–95.	Case series n = 21 Median follow-up = 26 months	The majority of patients had good physical and social functioning although most had reduced health-related quality of life due to pulmonary sequelae. The majority of patients had residual lung parenchymal changes suggestive of fibrosis. Pulmonary function tests revealed good restitution with mean values in the lower normal range.	Larger studies are included.
Marasco SF, Preovolos A, Lim K et al. (2007) Thoracotomy in adults while on ECMO is associated with uncontrollable bleeding. Perfusion 22: 23–6.	Case reports n = 4	Four patients on venovenous ECMO required thoracotomy and experienced massive bleeding; 3 patients died as a direct consequence.	Bleeding is already described as a complication.
Mikkelsen ME, Woo YJ, Sager JS et al. (2009) Outcomes using extracorporeal life support for adult respiratory failure due to status asthmaticus. ASAIO Journal 55: 47–52.	Case series (registry data) n = 1257	Status asthmaticus was the primary indication for ECMO in 24 patients. 83% of asthmatics survived to hospital discharge compared with 51% of non-asthmatics (OR 4.86, 95% CI 1.65 to 14.3, p = 0.004). Complications = 79%	Data from the same registry is included (Brogan TV, 2009).
Mitchell MD, Mikkelsen ME, Umscheid C A et al. (2010) A systematic review to inform institutional decisions about the use of extracorporeal membrane oxygenation during the H1N1 influenza pandemic. Critical Care Medicine 38: 1398–404.	Systematic review and meta-analysis 6 articles (3 RCTs)	Moderate, statistically significant heterogeneity in reported risk ratios for mortality. Summary risk ratio for mortality = 0.93 (95% CI 0.71 to 1.22)	Includes RCTs published in 1979 and 1994 as well as the CESAR trial.
Moran JL, Chalwin RP, Graham PL (2010) Extracorporeal membrane oxygenation (ECMO) reconsidered. Critical Care & Resuscitation 12: 131–5.	Meta-analysis (3 RCTs)	Mortality odds ratio = 0.78 (95% CI: 0.25 to 3.04) Weak evidence of efficacy.	Includes RCTs published in 1979 and 1994 as well as the CESAR trial.
Morris AH, Wallace CJ, Menlove RL et al. (1994) Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for Adult Respiratory Distress Syndrome. American Journal of	RCT n = 40	Survival rates: • ECMO = 33% • Controls = 42% , p = 0.8	Larger, more recent studies are included. (this study was

Respiratory & Critical Care Medicine 149: 295-305			included in table 2 of the original overview)
Muller T, Philipp A, Luchner A et al. (2009) A new miniaturized system for extracorporeal membrane oxygenation in adult respiratory failure. Critical Care 13: R205.	Case series n = 60	New miniaturised device Survival to discharge = 45% 62% of patients were weaned from ECMO	Larger studies are included.
Nosotti M, Rosso L, Palleschi A et al. (2010) Bridge to lLung tTransplantation by vVenovenous eExtracorporeal mMembrane oOxygenation: aA lLesson lLearned on the fFirst fFour cCases. tTransplantation pProceedings 42 (4) 1259-1261.	Case series n = 4	ECMO is an adequate bridge to lung transplantation	Larger studies are included.
Oshima K, Kunimoto F, Hinohara H et al. (2010) Extracorporeal membrane oxygenation for respiratory failure: comparison of venovenous versus venoarterial bypass. Surgery Today 40 (3) 216-222.	Case series n = 16	Venovenous ECMO is comparable to with venoarterial ECMO.	Larger studies are included.
Pasquini A, Di Valvasone S, Biondi S et al. (2010) Extracorporeal membrane oxygenation for influenza A (H1N1): Experience in a regional referral center. Critical Care Conference: 30th International Symposium on Intensive Care and Emergency Medicine, ISICEM Brussels Belgium. Conference Publication: S32-S33.2010.	Case series n = 6	All 6 patients on ECMO were successfully weaned from ECMO support, extubated and discharged from ICU.	Larger studies are included.
Peris A, Cianchi G, Biondi S et al. (2010) Extracorporeal life support for management of refractory cardiac or respiratory failure: initial experience in a tertiary centre. Scandinavian Journal of Trauma, Resuscitation & Emergency Medicine 18: 28.	Case series n = 13	62% survival	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Rega FR, Evrard V, Bollen H et al. (2007) pH 48 h after onset of extracorporeal membrane oxygenation is an independent predictor of survival in patients with respiratory failure. Artificial Organs 31: 384–9.	Case series n = 70 Follow-up = 90 days	Survival rate = 42.7% In multivariate analysis, age and pH at 48 hours were independent predictors of survival.	Larger studies are included.
Risnes I, Wagner K, Nome T et al. (2006) Cerebral outcome in adult patients treated with extracorporeal membrane oxygenation. Annals of Thoracic Surgery 81: 1401–6.	Case series n = 28 Mean follow-up = 5 years	Disabilities or sequelae found at clinical examination = 57% (16/28) Impaired neuropsychological performance = 41% Pathologic electroencephalogram = 41% There was a significant correlation between the cognitive outcome and neuroradiological findings. The incidence of neuroradiological findings was significantly higher in the venoarterial group compared with the venovenous group (75% versus 17%)	Small case series with mixed indications (including cardiac failure).
Roch A, Lepaul-Ercole R, Grisoli D et al. (2010) Extracorporeal membrane oxygenation for severe influenzaÂ A (H1N1) acute respiratory distress syndrome: a prospective observational comparative study. Intensive Care Medicine VOL 36: 1899–905.	Non-randomised comparative study n = 18	Patients treated with or without ECMO had the same hospital mortality rate (56%, 5/9).	Larger studies are included.
Wagner K, Risnes I, Abdelnoor M et al. (2008) Is it possible to predict outcome in pulmonary ECMO? Analysis of pre-operative risk factors. Perfusion 23: 95–9.	Case series n = 72	50% (36/72) of patients died within 30 days of ECMO. The only factor that correlated with survival was pre-operative serum creatinine levels.	Larger studies are included.
Wang CH, Chou CC, Ko WJ et al. (2010) Rescue a drowning patient by prolonged extracorporeal membrane oxygenation support for 117 days. American Journal of Emergency Medicine 28 (6) 750-757.	Case report n = 1	Patient recovered after 117 days of ECMO support.	Larger studies are included.
Wigfield CH, Lindsey JD, Steffens TG et al. (2007) Early Institution of Extracorporeal Membrane Oxygenation for Primary Graft Dysfunction After Lung Transplantation Improves Outcome. Journal of Heart and Lung Transplantation 26: 331–8.	Case series n = 22 Follow-up = 3 years	ECMO for primary graft dysfunction after lung transplantation. 30-day survival = 75% 1-year survival = 54% 2-year survival = 36% Multi-organ failure was the predominant cause of death (58%).	Larger studies are included.
Zapol WM, Snider MT, Hill JD et al. (1979) Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA 242: 2193-2196	RCT n = 90	Survival rates: • ECMO = 9.5% • Controls = 8.3% , p = not significant	A larger, more recent RCT is included. (this study was included in table 2 of the original overview)

Appendix B: Related NICE guidance for extracorporeal membrane oxygenation (ECMO) for severe acute respiratory failure in adults

Guidance	Recommendations
Interventional procedures	**Arteriovenous extracorporeal membrane carbon dioxide removal. NICE interventional procedures guidance 250 (2008).** 1.1 Current evidence on the efficacy of arteriovenous extracorporeal membrane carbon dioxide removal (AVECCO2R) is limited. With regard to safety, there are a number of potential complications. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and for audit or research. 1.2 Clinicians wishing to undertake AVECCO2R should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients or their relatives and carers understand the uncertainty about the procedure's efficacy and the risk of complications. In addition, clinicians should provide clear written information. Use of the Institute's information for patients and carers ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/IPG250publicinfo). • Audit and review clinical outcomes of all patients having AVECCO2R (see sections 1.4 and 3.1). 1.3 This procedure should only be used by specialist intensive care teams. Only patients with potentially reversible hypercarbic respiratory failure or those being considered for lung transplantation should be selected for this procedure. 1.4 Clinicians should collaborate in data collection. The establishment of a register is recommended. Data collection and research should aim to provide evidence on thresholds for intervention and criteria for patient selection. The Institute may review the procedure upon publication of further evidence. **Extracorporeal membrane oxygenation (ECMO) in postneonatal children. NICE interventional procedures guidance 38 (2004).** 1.1 Current evidence on the safety and efficacy of extracorporeal

	membrane oxygenation in postneonatal children appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 All children undergoing this treatment, including those treated after cardiopulmonary bypass, should be entered onto the international registry of the Extracorporeal Life Support Organization (ELSO), based at the University of Michigan, USA (www.elso.med.umich.edu).

Appendix C: Literature search for extracorporeal membrane oxygenation (ECMO) for severe acute respiratory failure in adults

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	05/05/2010	Cochrane Library, Issue 1, April 2010
Database of Abstracts of Reviews of Effects – DARE (CRD website)	05/05/2010	N/A
HTA database (CRD website)	05/05/2010	N/A
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	05/05/2010	Cochrane Library, Issue 1, April 2010
MEDLINE (Ovid)	05/05/2010	1950 to April Week 3 2010
MEDLINE In-Process (Ovid)	05/05/2010	May 04, 2010
EMBASE (Ovid)	05/05/2010	1980 to 2010 Week 17
CINAHL (NHS Evidence)	05/05/2010	1981 to Present
Zetoc	05/05/2010	1993 to date

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

1 ECMO.tw.
2 exp Extracorporeal Membrane Oxygenation/
3 Extracorpor* membran* Oxygenat*.tw.
4 Extracorporeal Circulation/
5 (Extracorpor* adj3 Circulat*).tw.
6 Oxygenators, Membrane/
7 (oxygenator* adj3 membrane).tw.
8 Heart-Lung Machine/
9 Hear* Lung* machin*.tw.
10 ECCO2R.tw.
11 Extracorpor* carbon* dioxid* remov*.tw.
12 Extracorp* CO2 Remov*.tw.
13 or/1-12
14 exp Respiratory Insufficiency/
15 Respiratory Distress Syndrome, Adult/
16 (respirat* adj3 (insufficien* or failur* or depress* or distress* or syndrome*)).tw.
17 or/14-16
18 adult/ or aged/ or middle aged/
19 Adult*.tw.
20 (Middle* adj age*).tw.

21	aged*.tw.
22	Elderly*.tw.
23	(Old* adj (people* or Person*)).tw.
24	or/18-23
25	13 and 17 and 24
26	(CESAR adj3 Trial).tw.
27	25 or 26
28	Animals/ not Humans/
29	27 not 28
30	2003*.ed.
31	2004*.ed.
32	2005*.ed.
33	2006*.ed.
34	2007*.ed.
35	2008*.ed.
36	2009*.ed.
37	2010*.ed.
38	or/30-37
39	29 and 38