NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of extracorporeal carbon dioxide removal for acute respiratory failure

Extracorporeal carbon dioxide removal is used to treat respiratory failure (when the lungs do not work effectively) in critically ill patients. The aim is to remove excess carbon dioxide from the blood. The patient still needs oxygen by mechanical ventilation. Blood is taken from the circulation, out of the body (extracorporeal). It is then passed through a synthetic membrane, where carbon dioxide is removed, before the blood is returned to the body.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) 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 IP overview was prepared by the Birmingham and Brunel Consortium External Assessment Centre (B&BC) in August 2015.

Procedure name

- Extracorporeal carbon dioxide removal for acute respiratory failure

Specialist societies

- Intensive Care Society
- Faculty of Intensive Care Medicine
- Society for Cardiothoracic Surgery in Great Britain and Ireland.

Description

Indications and current treatment

Acute respiratory failure is a life-threatening condition that results in abnormally low oxygen levels (hypoxia) or abnormally high carbon dioxide levels (hypercapnia) in the blood. A particularly severe type of acute respiratory failure is acute respiratory distress syndrome (ARDS), which is a disease process resulting from several conditions including sepsis, pneumonia or chest trauma.

The conventional treatment for acute respiratory failure is mechanical ventilation. However, in some patients, hypoxia or hypercapnia cannot be adequately corrected, despite the maximum mechanical ventilation that the lungs can tolerate, without causing ventilator-induced lung injury. Extracorporeal carbon dioxide removal ($ECCO_2R$) may reduce blood carbon dioxide levels, allowing a reduction in the ventilation settings. It may also be used to support weaning from ventilation and as a bridge to lung transplantation.

What the procedure involves

The aim of extracorporeal carbon dioxide removal ($ECCO_2R$) is primarily to reduce blood carbon dioxide levels and allow a reduction in ventilation settings (such as airway pressures and tidal volume). This may minimise the risk of ventilator-induced lung injury and help to improve the likelihood and speed of lung recovery. The technique may also increase blood oxygen levels.

There are 2 main types of $ECCO_2R$: venovenous and arteriovenous. In both types, cannulae are connected to a low-resistance synthetic membrane device where exchange of carbon dioxide occurs. In venovenous $ECCO_2R$, either a single-access double lumen catheter or a dual-access system using 2 venous catheters is inserted into a large vein or veins (typically the femoral or internal jugular veins) and connected to a venovenous circuit. Flow across the membrane is maintained using a pump. In arteriovenous $ECCO_2R$, an artery and a vein are cannulated (typically the femoral artery and femoral vein). Arterial blood pressure drives blood continuously through the device and it is returned through the vein. Cannulation of the femoral artery may be associated with leg ischaemia.

$ECCO_2R$ can be done using either a true $ECCO_2R$ system or a modified extracorporeal membrane oxygenation system.

Patients may be treated with $ECCO_2R$ support for several weeks, depending on clinical need.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to extracorporeal carbon dioxide removal for acute respiratory failure. The following databases were searched, covering the period from their start to 25 August 2015: 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 selected using evidence hierarchy as the follows: randomised controlled trial; non-randomised controlled trial; comparative cohort study; single cohort study; or case series. Emphasis was placed on identifying good-quality studies. Meta-analyses of primary studies were also included. Reviews without meta-analysis, editorials, or laboratory or animal studies were excluded. Abstracts were also excluded because of the difficulty of appraising study methodology. Only publications in English were included.
Patient	Adults and children, with potentially reversible severe acute respiratory failure or being considered for lung transplantation.
Intervention	1. Extracorporeal carbon dioxide removal ($ECCO_2R$) system including venovenous (VV) and arteriovenous (AV) 2. Extracorporeal membrane oxygenation (ECMO) system: AV mode VV mode for combined hypoxaemia and hypercapnia, where hypercapnia predominates or is the primary condition the system is used for VA mode used in respiratory (with or without cardiac) failure to treat combined hypoxaemia and hypercapnia, where hypercapnia predominates or is the primary condition for which the system is used
Comparator	Other interventional procedures designed to provide respiratory support for these patients
Outcome	Any patient-centred and clinical efficacy and safety outcomes, such as:

measure	• Survival. • Duration of mechanical ventilation post-baseline. • Intensive care unit stay. • Any adverse events including, but not limited to: arterial, venous and device thrombus formation; plasma leakage from gas exchange device; vascular access damage; infections; complications needing surgery including lower limb amputation; gas embolism; haemolysis and heparin-induced thrombocytopenia. • Total hospital stay post baseline. • Reduction in ventilation volume pressure (ventilation litres per minute change) from baseline. • Reduction in ventilation settings from baseline: inspired oxygen concentration, airway pressures and tidal volume. • Carbon dioxide removal (PaCO2 change from baseline). • Ventilator-related morbidity, including ventilator-related lung injury. • Duration on mechanical ventilation from baseline.

List of studies included in the IP overview

This document summarised the 9 best studies (with a total of 1073 patients) identified from the literature (studies 3–9 in table 2), alongside the outline data from the Extracorporeal Life Support Organization (ELSO) register and the most recent systematic review by Fitzgerald et al. (2014) (study 2 in table 2). Of the 9 best studies from the literature, 2 were randomised controlled trials by Bein et al. (2014) and Morris et al.(1994), 1 was a review and meta-analysis by Walles (2007), 1 was a matched comparison study by Kluge et al. (2012), and the remaining were case series studies.

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 carbon dioxide removal for acute respiratory failure

Study 1 Cummins C 2015[2][1]

Details

Study type	**Retrospective study (using UK subset of ELSO register)**
Country	United Kingdom
Recruitment period	2012–15
Study population and number	**N=60** (**22 had AV-ECCO$_2$R; 38 had VV-ECCO$_2$R**) Indications for ECCO$_2$R: • Pneumonia (27). • COPD (5). • Septic shock (5). • Acute respiratory failure (3). • Asthma (2). • Influenza (2). • Lung involvement in other condition (2). • Pneumothorax (2). • Pulmonary insufficiency (2). • Acute URTI, biliary tract condition, bronchiectasis, cardiomyopathy, cerebral oedema. • Coronary atherosclerosis, empyema, flail chest, lower respiratory tract anomaly, tracheoesophageal fistula (1 case each)
Age and sex	Median 58 years (IQR 46–68) 35/60 (58.3%) male
Patient selection criteria	All UK patients who received ECCO$_2$R entered on the ELSO database were included in the analysis.
Technique	AV-ECCO$_2$R (n=22), VV-ECCO$_2$R (n=38)
Follow-up	**Not applicable**
Conflict of interest/source of funding	No conflict of interest declared. The study was funded by the National Institute for Health and Care Excellence.

Analysis

Follow-up issues: None.

Study design issues:

- The study relied on an existing register designed originally to collect information on the ECMO procedure. While agreement was reached to add additional fields to assist in the analysis, the register owner encountered technical issues in updating the register and were unable to make all the needed changes in the study period.
- Dependent on the quality of data entry into the register by NHS Trusts.

[1] Analysis of ELSO Register commissioned by NICE and manuscript for publication in peer review journal in preparation.

Study population issues: Intensive care units (ICUs) were encouraged to enter all cases from 2012 by the Birmingham and Brunel External Assessment Consortium. There was, however, under-reporting of cases by ICUs for a number of reasons including single use of the procedure by an ICU, the need to be a member of ELSO in order to enter case on the register and the register being offline during summer 2014.

Estimates of register coverage were derived from a survey of ICUs and sales and hire data from the company. Both indicated in excess of 200 potential cases could have been entered onto the register.

The register includes relevant cases dating back to 2007 that were included in the analysis.

All patients had an ICD-9 code for primary diagnosis and 23 patients had a second code, with 7 patients having 3 or more diagnosis codes. On inspection, choice of primary diagnosis code did not appear to be consistent across patients, so a primary diagnosis was chosen from all diagnoses to produce a classification consistent with primary diagnoses in those patients who only had a single diagnosis. Some ICD-9 codes cover more than 1 condition, hence in some cases it is not possible to identify a precise indication. Moreover, in some instances there were several comorbidities, and other patients none were specified but plausibly may have been present.

Other issues: None

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 60
Survival
• 27/60 patients did not experience recovery but died.
• 33/60 patients experienced recovery but 6 of these died before discharge.
• The survival to discharge rate was 45% (27/60).
• 13/27 (48.1%) of those discharged, were discharged to home.
• 9/22 (40.9%) receiving AV-ECCO$_2$R and 18/38 (47.4%) receiving VV-ECCO$_2$R were discharged alive (ns).
Ventilator settings pre-ECCO$_2$R and at 24 hours of ECCO$_2$R
<table>
<tr><td></td><td colspan="2">Worst values in 6 hours pre-ECCO$_2$R</td><td colspan="2">Best values at 24 hours of ECCO$_2$R</td><td></td></tr>
<tr><td></td><td>n</td><td>Median, IQR</td><td>n</td><td>Median, IQR</td><td>p (Wilcoxon)</td></tr>
<tr><td>Rate/Hz</td><td>37</td><td>22
17–28</td><td>36</td><td>18
14–24</td><td>0.002</td></tr>
<tr><td>Mean arterial pressure</td><td>21</td><td>16
9–27</td><td>21</td><td>15
10–23</td><td>0.033</td></tr>
<tr><td>FiO2</td><td>54</td><td>70
50–90</td><td>53</td><td>55
38–70</td><td><0.001</td></tr>
<tr><td>PIP/ampl</td><td>49</td><td>30
26.0–33.25</td><td>45</td><td>24
20–28</td><td><0.001</td></tr>
<tr><td>PEEP</td><td>46</td><td>8
5–12</td><td>43</td><td>10
5–12</td><td>0.032</td></tr>
</table>
Blood gases and haemodynamics pre-ECCO$_2$R and at 24 hours of ECCO$_2$R
<table>
<tr><td></td><td colspan="2">Worst values in 6 hours pre-ECCO$_2$R</td><td colspan="2">Best values at 24 hours of ECCO$_2$R</td><td></td></tr>
<tr><td></td><td>n</td><td>Median, IQR</td><td>n</td><td>Median, IQR</td><td>p (Wilcoxon)</td></tr>
<tr><td>pH</td><td>55</td><td>7.1
7.1–7.3</td><td>55</td><td>7.4
7.3–7.4</td><td><0.001</td></tr>
<tr><td>PaCO$_2$ (kPa)</td><td>55</td><td>11.4
9.0–14.0</td><td>55</td><td>7.0
6.1–8.0</td><td><0.001</td></tr>
<tr><td>PaO$_2$ (kPa)</td><td>55</td><td>10.5
9.0–13.0</td><td>55</td><td>9.3
8.1–10.7</td><td><0.004</td></tr>
<tr><td>SBP</td><td>39</td><td>110
96–130</td><td>39</td><td>123
110–135</td><td>0.043</td></tr>
<tr><td>DBP</td><td>39</td><td>57
52–73</td><td>39</td><td>60
55–70</td><td>0.980</td></tr>
<tr><td>MAP</td><td>35</td><td>72
67–95</td><td>35</td><td>84
73–95</td><td>0.301</td></tr>
</table>
</td><td>
19/60 patients experienced complications (31.7%): single complication (11), 2 complications (2), 3 (3), 4 (2) and 7 (1).

• Mechanical complications (7) (Oxygenator failure (1), pump malfunction (2), clots, oxygenator (1), clots, other (2) and cannula problems (1).
• Haemorrhagic complications (10) (GI haemorrhage [1], cannulation site bleeding [7], haemolysis [hgb >50 mg/dl]).
• Seizure (1).
• CNS haemorrhage (1).
• Renal complications (6).
• Cardiovascular complications (6).
• Pneumothorax needing treatment (1).
• Infections (5).
• Metabolic complications (2).

15/38 (39.5%) receiving VV-ECCO$_2$R experienced 1 or more complications.

4/22 (18.2%) receiving AV-ECCO$_2$R experienced 1 or more complications.
</td></tr>
</table>

Abbreviations used: Ampl, pressure amplitude; ARDS, acute respiratory distress syndrome; AV-$ECCO_2R$, arteriovenous extracorporeal carbon dioxide removal; cmH_2O, centimetre of water; CNS, central nervous system; DBP, diastolic blood pressure; $ECCO_2R$, extracorporeal carbon dioxide removal; ELSO, Extracorporeal Life Support Organization; FiO_2, fraction of inspired oxygen; HIT, heparin-induced thrombocytopenia; ICU, intensive care unit; iLA AV, interventional lung assist arteriovenous; IQR, interquartile range; ml/kg, millilitres per kilogram; mmHg, millimetres of mercury; MPA, mean arterial pressure; n, number of patients; ns, not statistically significant; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; PaO_2, partial pressure of oxygen in arterial blood; PEEP, positive end expiratory pressure; PIP, peak inspiratory pressure; SBP, systolic blood pressure; SD, standard deviation; VV-$ECCO_2R$, venovenous extracorporeal carbon dioxide removal.	

Study 2: Fitzgerald M (2014) (1)

Details

Study type	**Systematic Review**
Country	United Kingdom
Recruitment period	Not applicable
Study population and number	**N= 495** patients. The review included 14 studies. (2 randomised controlled trials [RCTs; n=119] and 12 observational studies [n=263]). Adults with ARDS.
Age and sex	Average age across studies not reported 348/485 male (71.8%); 10 recorded (RCT studies 85/119 [71.4%] male; non-RCT 263/366 male [71.8%]).
Patient selection criteria	The selection criteria for included studies in the review was adult patients (>18 years) with ARDS (or acute respiratory failure in studies occurring prior to the American-European Consensus Conference Committee definition of ARDS in 1994).
Technique	Arteriovenous (AV) $ECCO_2R$ was used in 7 included studies, and venovenous (VV) $ECCO_2R$ in the 7 other studies
Follow-up	**Not applicable**
Conflict of interest/source of funding	None declared; study supported by Intensive Care Foundation.

Analysis

Follow-up issues: None.

Study design issues: None.

Study population issues: The population was clearly defined and was relevant to the review's objective.

Other issues: None.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **495** • No mortality benefit to $ECCO_2R$ was found. • Mortality rates for included observational studies that provided data ranged from 27% to 75% (mean 55.5%, standard deviations 74.2 to 60.3). • Post hoc analysis of data from the most recent RCT (Bein et al, 2014) showed an improvement in ventilator-free days in more severe ARDS. • No benefit to $ECCO_2R$ was found in terms of organ failure-free days or length of ICU stay. Carbon dioxide removal was widely demonstrated as feasible.	• Complication rates varied greatly across the included studies from 0 to 25%. Five studies reported rates in excess of 20% [21, 27–30] • In studies examining AV devices, the most common complication was lower limb ischaemia secondary to arterial cannulation. In the majority of studies this was a transient complication, except 5 cases of compartment syndrome and 1 case of lower limb amputation. • In studies where VV $ECCO_2R$ was used, clotting within the circuit was the main complication, with catheter and membrane malfunction also reported. • Studies conducted before 2000 (all using VV $ECCO_2R$ reported higher rates of diffuse bleeding or at sites other than that where cannula insertion had occurred. • Both RCTs described a significant increase in the need for red cell transfusion in the $ECCO_2R$ group compared with the control group.
Abbreviations used: ARDS, acute respiratory distress syndrome; AV, Arteriovenous; $ECCO_2R$, extracorporeal carbon dioxide removal; ICU, intensive care unit; n, number of patients; RCT, randomised control trial; VV, venovenous.	

Study 3 Bein T (2013) [3]

Details

Study type	**RCT**
Country	Germany (8 ICUs) and Austria (2 ICUs)
Recruitment period	2007–10
Study population and number	ARDS Patients receiving AV-$ECCO_2R$, **n=79 (40 low V_T ventilation (≈3 ml/kg) combined with extracorporeal CO_2 elimination vs a ARDSNet strategy (≈6 ml/kg) without the extracorporeal device).**
Age and sex	In the AV-$ECCO_2R$ group: age (mean ±SD) 49.8±12 years, 95% (38/40) male. In the control group: age (mean ±SD) 48.7±17 years, 77% (30/39) male.
Patient selection criteria	(1) Presence of ARDS according to the American-European Consensus Conference defined by bilateral infiltrates on chest X-ray, and a PaO_2/FIO_2 <200 present for at least 2 hours. At the time of screening patients could not have any evidence of left ventricular failure. (2) Age ≥18 years. (3) History of mechanical ventilation <7 days. (4) Plateau pressure [25 cm H_2O at defined ventilator settings (PEEP/FIO_2-table+V_T ≈6 ml/kg). (5) Absence of severe haemodynamic instability with high demand for vasopressors (mean arterial pressure ≥70 mmHg with continuous norepinephrine infusion ≤0.4 µg/kg/min). Exclusion criteria: decompensated heart insufficiency, acute coronary syndrome, severe chronic obstructive pulmonary disease, advanced malignancy with life expectancy <6 months, chronic dialysis treatment, lung transplant patients, proven HIT, morbid obesity (body mass index [40 kg/m2]), cirrhosis of the liver Child Class CB (Child–Pugh scores C7), or acute fulminant hepatic failure, severe peripheral arterial occlusive disease, absence of limb Doppler pulse, and acute brain injury (Glasgow Coma Scale ≤9).
Technique	The intensive care management in both groups followed the 'best clinical evidence' recommended by the European Society of Intensive Care Medicine and the patients received a low V_T ventilation (≈3ml/kg) combined with extracorporeal CO_2 elimination. The control group received a ARDSNet strategy (≈6 ml/kg) without the extracorporeal device.
Follow-up	**60 days**
Conflict of interest/source of funding	T. Bein and A. Slutsky are consultants for Novalung and received honoraria. A. Slutsky is also a consultant to Maquet Medical. The other authors declare no conflicts of interest.

This study is included in the Fitzgerald M (2014) review (study 2) above.

Analysis

Follow-up issues: None.

Study design issues: A sample size was calculated assuming an increase in 28-VFD from 6.0±10 (control group) to 11.0±8 (study group). The authors estimated that 53 patients would be needed per group for a power of 0.8 and an alpha of 0.05. The authors assumed a 'drop-out-rate' of 10 % and calculated that 120 patients would need to be enrolled.

The trial was stopped before the sample size was reached. After an interim analysis with 56 patients by the Data Safety Monitoring Board, it was decided to limit the study period to 3 years, since a statistical significant difference was not expected in a longer study period.

The daily monitoring included the assessment of awakeness / sedation (RASS) and the daily evaluation of the SOFA and the SAPS-II score. After randomization to the treatment group, percutaneous cannulation and initiation of pumpless extracorporeal lung assist (iLA AV, Novalung, Heilbronn, Germany) was performed

Study population issues:

Patients did not differ with respect to age and body mass index, but in the AV-$ECCO_2R$ group there were more patients with secondary ARDS.

Other issues: None.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **79 (40 AV-$ECCO_2R$ vs 39 control)**

Outcome parameters of the study

	AV-$ECCO_2R$ N=40	Control N=39	p value
Ventilator-free days at 28 days *	10.0±8	9.3±9	0.779
Ventilator-free days at 60 days *	33.2±20	29.2±21	0.469
Non-pulmonary organ failure free days at 60 days *	21.0±14	23.9±1.5	0.447
Lung injury score on day 10 *	2.2±0.6	2.1±0.5	0.854
Length of hospital stay (days) *	46.7±33	35.1±17	0.113
Length of stay in ICU (days) *	31.3±23	22.9±11	0.144
In-hospital mortality	17.5% (7/40)	15.4% (6/39)	1.000

* Mean±SD

Post hoc analysis of patients with greater hypoxemia (PaO_2/FiO_2 ≤150) at randomisation

	AV-$ECCO_2R$ N=21	Control N=10	p value
Ventilator-free days at 28 days *	11.3±7.5	5.0±6.3	0.033
Ventilator-free days at 60 days *	40.9±12.8	28.2±16.4	0.033
Non-pulmonary organ failure free days at 60 days *	24.1±7.5	29.0±17.7	0.428
Lung injury score on day 10 *	2.3±0.8	2.2±0.5	0.601
Length of hospital stay (days) *	42.0±16.6	40.3±15.7	0.815
Length of stay in ICU (days) *	25.9±13.1	31.0±12.7	0.258
In-hospitality mortality	4.8% (1/21)	10% (1/10)	0.563

* Mean±SD

Safety

Incidence of AV-$ECCO_2R$ related adverse events 8% (3/40 patients):

- transient ischaemia of the lower limb (n=1).
- developed a 'false' aneurysm as a result of arterial cannulation (n=2).

Abbreviations used: ARDS, acute respiratory distress syndrome; AV-$ECCO_2R$, arteriovenous extracorporeal carbon dioxide removal; cm H2O, centimetre of water; $ECCO_2R$, extracorporeal carbon dioxide removal; FiO_2, fraction of inspired oxygen; HIT, heparin-induced thrombocytopenia; ICU, intensive care unit; iLA AV, interventional lung assist arteriovenous; ml/kg, millilitres per kilogram; mmHg, millimetres of mercury; PaO_2, partial pressure of oxygen in arterial blood; PEEP, positive end expiratory pressure; RASS, Richmond Agitation Sedation Scale; RCT, randomised controlled trial; SAPS-II, Simplified Acute Physiology Score; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

Study 4 Morris AH (1994) [4]

Details

Study type	**RCT**
Country	USA
Recruitment period	1987–91
Study population and number	Patients with severe ARDS, **n=40 (21 low-frequency positive-pressure ventilation and $ECCO_2R$ vs 19 continuous positive-pressure ventilation alone)**.
Age and sex	Mean age: 35 years; 43% (17/40) male
Patient selection criteria	PaO_2 <0.2, bilateral chest radiographic infiltrates, total thoracic compliance less than 50 ml/cmH_2O and no clinical evidence of heart failure; patients who met ECMO entry and exclusion criteria. Exclusion criteria included age <12 and >65 years, and mechanical ventilation >21 days.
Technique	Arterial oxygenation was achieved primarily through the patient's natural lung.
Follow-up	**30 days**
Conflict of interest/source of funding	Equipment was donated from a number of different manufacturers.

This study was included in the NICE overview for IPG428. It is also included in FitzGerald review (study 2 above).

Analysis

Follow-up issues: None.

Study design issues:

- Patients were stratified by age and by the presence or absence of trauma.
- Blinded randomisation with blocking.
- A sample size of 60 was calculated to detect a survival difference between 9 and 40% (power = 0.80).
- The trial was discontinued before the sample size was reached because it was deemed that the difference between the 2 therapies was too small for a significant survival difference to be demonstrated with 60 patients.
- Analysis was by intention to treat.

Study population issues: Of the 21 patients assigned to $ECCO_2R$, 1 patient died before it could be started and another improved without it. There were no statistically significant differences between the 2 patient groups at randomisation.

Other issues: The authors noted that the overall survival rate (38%) was higher than expected; they expected a survival rate of 9% in the control group.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **40 (21 $ECCO_2R$ vs 19 control)** **Survival rate (at 30 days):** $ECCO_2R$=33.3% (7/21) (1 patient died before $ECCO_2R$ could be started and 2 patients died within 1 day of starting it). Control group =42.1% (8/19), p=0.56 There were no statistically significant differences in total hospital length of stay, intensive care unit length of stay or clinical trial time between the 2 groups. Mean PaO_2 (mmHg)±SEM: $ECCO_2R$=58.6 ±0.3 Control group =59.3±0.3 Mean arterial pH: $ECCO_2R$=7.39 Control group=7.36 There were no clinically important differences in blood gas mean values between the 2 groups.	**Major complications:** Cardiac dysrhythmia arrest: • $ECCO_2R$=9.5% (2/21) • Control=10.5% (2/19) Cardiac tamponade: • $ECCO_2R$=4.8% (1/21) • Control=0% (0/19) Intracranial haemorrhage: • $ECCO_2R$=4.8% (1/21) • Control=5.3% (1/19) Cerebral arterial gas embolism: • $ECCO_2R$=0% (0/21) • Control=5.3% (1/19) Cerebral hypoxia depression: • $ECCO_2R$=4.8% (1/21) • Control=5.3% (1/19) Extremity ischaemia: • $ECCO_2R$=0% (0/21) • Control=10.5% (2/19) Arterial embolism: • $ECCO_2R$=0% (0/21) • Control=5.3% (1/19) Venous thrombosis: • $ECCO_2R$=4.8% (1/21) • Control=10.5% (2/19) Intrapulmonic haemorrhage: • $ECCO_2R$=19.1% (4/21) • Control=0% (0/19) • Packed red blood cell transfusion >0.8 l /day: $ECCO_2R$=47.6% (10/21) • Control=0% (0/19) $ECCO_2R$ circuit clotting: 19.1% (4/21) $ECCO_2R$ had to be discontinued in 7 patients because of haemorrhage.
Abbreviations used: ARDS, acute respiratory distress syndrome; CO_2, carbon dioxide; $ECCO_2R$, extracorporeal carbon dioxide removal; ECMO, extracorporeal membrane oxygenation; iLA, interventional lung-assist; IQR, interquartile range; ml/cm H_2O, millimetres per centimetre of water; PaO_2, partial pressure of oxygen in arterial blood; RCT, randomised controlled trial; SEM, standard error of the mean.	

Study 5 Walles T (2007) [5]

Details

Study type	**Review and meta-analysis**
Country	Germany
Recruitment period	Not applicable
Study population and number	Critically ill patients with ventilation-refractory lung failure, **n=225 (8 case series studies, n ranged from 5 to 90).**
Age and sex	Mean age: not reported; sex: not reported
Patient selection criteria	Not reported
Technique	Pumpless arteriovenous $ECCO_2R$ using the iLA device (Novalung, Germany).
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported

This study was included in the NICE overview for IPG428.

Analysis

Follow-up issues: Follow-up was not reported.

Study design issues: All included studies were retrospective. Statistical methods not described.

Study population issues: The author states that there may have been some overlap between patients in the identified studies**.**

Other issues:

- The authors noted that cannula thrombosis was not observed following implementation of modified cannulae after 2001. The problem of plasma leakage disappeared with a new oxygenator membrane in 2003.

- The authors noted that the following are contraindications to treatment: heart failure, septic shock with low mean arterial pressure, severe arterial occlusive disease and history/presence of heparin-induced thrombocytopenia type II. Unfavourable prognostic factors include acute renal failure, high vasopressor demand, long preceding duration of artificial ventilation, high age, obesity and cancer.

Key efficacy and safety findings

Efficacy	**Safety**
Number of patients analysed: **225**	**Complications**
	Total=29%
Mean duration of $ECCO_2R$ ranged from 5 to 16 days	Arterial thrombus formation=2.2% (5/225)
	Venous thrombus formation=4.9% (11/225)
‘Success rate’ (not further defined)=56% (range 41–83)	Oxygenator thrombus formation=2.7% (6/225)
	Limb ischaemia=9.3% (21/225)
	Bleeding at cannulation site=3.6% (8/225)
	Infection=0.4% (1/225)
	Plasma leakage=4.4% (10/225)
Abbreviations used: $ECCO_2R$, extracorporeal carbon dioxide removal; iLA, interventional lung-assist	

Study 6 Flörchinger B (2008) [6]

Details

Study type	**Case series**
Country	Germany
Recruitment period	1996–2007
Study population and number	Patients with severe respiratory insufficiency; n=**159**
Age and sex	44 years (range 7–78) 76% (121/159) male
Patient selection criteria	Severe hypoxia with a PaO_2/FiO_2 ratio less than 80 mmHg or hypercapnia with $PaCO_2$ greater than 70 mmHg (despite aggressive mechanical ventilation therapy). An attempt at conservative mechanical ventilator treatment had to be performed before $ECCO_2R$ was initiated.
Technique	Pumpless arteriovenous $ECCO_2R$ using iLA device (Novalung, Germany).
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported

This study was included in the NICE overview for IP428**.**

Analysis

Follow-up issues: Follow-up not reported.

Study design issues: Consecutive patients.

Study population issues: 70% (112/159) of patients had acute respiratory distress syndrome. In 2 patients, $ECCO_2R$ was used as a bridge to lung transplantation.

Other issues:

- The technology used for $ECCO_2R$ evolved over the 10-year study period. The authors also noted that there was an institutional learning curve with regard to efficacy of $ECCO_2R$ in terms of oxygenation and carbon dioxide removal. Indications for the procedure have changed over the study period.

- There are some discrepancies between results summarised in the abstract and those presented in the main body of the paper. The percentage of patients dying during $ECCO_2R$ was quoted as 48.7% rather than 47.2% (the numerator is stated to be 75).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **159**

Mean $ECCO_2R$ support interval=7 days (range 0–33)

Successful weaning from $ECCO_2R$:

- Overall = 52.2% (83/159)
- By underlying cause of respiratory insufficiency:
  - ARDS and no trauma=47.4% (18/38)
  - ARDS after trauma=64.9% (24/37)
  - ARDS after surgery=41.4% (12/29)
  - ARDS after chemotherapy=25.0% (2/8)
  - Bacterial pneumonia=63.6% (21/33)
  - Viral pneumonia=25.0% (1/4)
  - Other pneumonia (aspiration)=62.5% (5/8)

Overall survival rate=34.6% (55/159)

47.2% (75/159) of patients died during $ECCO_2R$ (main causes of death were multi-organ failure, septic shock and low cardiac output syndrome).

Variable	Death during $ECCO_2R$	Death after $ECCO_2R$	Survivor	p value
Patients (n)	75	29	55	
Age (years) *	45±16	52±17	35±15	0.004
Body mass index *	27.7±4.9	27.1±5.0	25.4± 4.7	0.02
Support (days) *	4.8±5.1	9.4±8.6	8.5±6.3	0.001
Continuous venovenous haemofiltration before $ECCO_2R$	44 (59%)	10 (34%)	13 (24%)	0.007
Mechanical ventilation before $ECCO_2R$ (days) *	6.6±7.2	7.5±13.0	4.2±5.8	0.01

* Mean ± SD

Gas exchange (mean)

	Time on $ECCO_2R$			
	Pre	2 hours	24 hours	Before $ECCO_2R$ termination
FiO_2	0.96	0.89	0.77	0.48*
PaO_2 (mmHg)	66	81	79	91*
PaO_2/FiO_2 (mmHg)	72	95	111	203
$PaCO_2$ (mmHg)	67	40	35*	39

Safety

Complications

Percutaneous femoral cannula placement was unsuccessful in 6 patients who needed an open surgical exposure and insertion.

- Lower limb ischaemia=8.2% (13/159) (In these patients, the arterial cannula was either exchanged with a smaller one or moved to the contralateral femoral vessel.
- Compartment syndrome necessitating fasciotomy=2.5% (4/159) (1 patient needed lower leg amputation).
- Thrombus formation=17.0% (27/159) (needed oxygenator exchange; thrombosis of the entire system developed in 8 patients: 4 were inadequately anticoagulated, 2 had heparin-induced thrombocytopenia type II and there were 2 device failures).
- Plasma leakage=4.4% (7/159).

Arterial saturation of oxygen (%)	86.2	93.6	95.1	96.3
Venous saturation of oxygen	61.8	74.3	74.9	76.5

*p<0.001

Change in mechanical ventilation

	Time on $ECCO_2R$			
	Pre	2 hours	24 hours	Before $ECCO_2R$ termination
Respiration rate (breaths/min)	32	30	29	21
Peak inspiratory pressure (cmH_2O)	37.7	36.0	34.5	29.6
Minute ventilation (l/min)	13.8	11.7	11.6	9.8

Abbreviations used: ARDS, adult respiratory distress syndrome; cmH_2O, centimetre of water; $ECCO_2R$, extracorporeal carbon dioxide removal; $ECCO_2R$, extracorporeal carbon dioxide removal; FiO_2, fraction of inspired oxygen; iLA, interventional lung-assist; l/min, litres per minute; mmHg, millimetres of mercury; $PaCO_2$, partial pressure of CO_2 in arterial blood; PaO_2, partial pressure of oxygen; SD, standard deviation

Study 7 Bein T (2006) [7]

Details

Study type	**Case series**
Country	Germany
Recruitment period	1996–2004
Study population and number	Patients with ARDS **(n=90)**
Age and sex	Median age: 44 years Sex: 77% (69/90) male
Patient selection criteria	Patients with severe respiratory failure considered to be at risk for acute life-threatening hypoxaemia and/or excessive hypercapnia, when other optimised therapies, including mechanical ventilation, have failed. Failure of alternative treatment was defined as insufficient oxygenation (PaO_2 <55 mmHg at FiO_2 =1) and/or when hypercapnia had induced arterial acidosis and haemodynamic instability occurred or distinct deterioration was observed. Contraindication: haemodynamic depression of cardiac origin.
Technique	Pumpless arteriovenous $ECCO_2R$ using iLA device (Novalung, Germany).
Follow-up	**Respiratory variables reported for first 24 hours, plus survival in hospital**
Conflict of interest/source of funding	The authors declared 'no financial arrangements with Novalung GmBH.

This study was included in the NICE overview for IPG428.

Analysis

Follow-up issues: Only covers period while patient in hospital.

Study design issues: Retrospective study.

Study population issues:

The authors stated that the patients included were the most severely critically ill, and in retrospect concluded that some were too ill and haemodynamically unstable to benefit from $ECCO_2R$. They suggest that $ECCO_2R$ should not be used for patients with cancer or refractory shock, or in geriatric patients, very obese patients or those developing multiple organ dysfunction syndrome, who were found to benefit least from the procedure.

Other issues:

The period covered by the case series 1996–2004 may limit the relevance of the study's findings as result of improvements in the technology to deliver $ECCO_2R$.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **90**

Survival

59% (53/90) of patients died in hospital; duration of survival and whether patients died while on $ECCO_2R$ was not stated.

Causes of death: septic shock or persistent systemic inflammatory response syndrome (49%), multiple organ failure (25%), cardiac failure (19%), cerebral injury (7%)

Mean duration of $ECCO_2R$ support =5 days (SD 5)

Changes in arterial blood gases

	Time on $ECCO_2R$		
	Pre	2 hours	24 hours
CO_2 removal (ml/min)	-	141 (85–211)	136 (100–169)
$PaCO_2$ (mmHg)	60 (48–80)	36 (30–44)*	34 (30–39)*
$PaCO_2/FiO_2$ ratio (mmHg)	58 (47–79)	82 (64–103)*	101 (74–142)*

Median (IQR)

*p<0.05 vs Baseline

Change in mechanical ventilation

	Time on $ECCO_2R$		
	Pre	2 hours	24 hours
FiO_2	1.0 (1.0–1.0)	0.9 (0.8–1.0)*	0.8 (0.7–0.9)*
Minute ventilation (l/min)	13.0 (10.0–6.4)	11.0 (8.0–4.1)*	9.9 (8.0–14.8)*
Tidal volume (ml)	430 (360–540)	410 (330–480)*	380 (320–470)*
Respiratory frequency (breaths per min)	27 (21–43)	25 (20–40)	23 (17–23)*
Peak inspiratory pressure (cmH_2O)	38 (325–40)	36 (32–39)	35 (31–39)*
PEEP (cmH_2O)	15 (12–17)	15 (13–18)	14 (12–18)

Median (IQR)

*p<0.05

Safety

Complications:

24% (22/90) of patients experienced a serious complication.

Intracerebral haemorrhage=1% (1/90)

Ischaemia of lower limb=10% (9/90)

(This led to amputation in 1 patient. In the remaining patients, normal perfusion returned after removal of the cannulae).

- Compartment syndrome of lower limb=4% (4/90).
- Haematoma/aneurysm at cannulation site=1% (1/90).
- Haemolysis=1% (1/90).
- Diffuse bleeding/shock syndrome during cannulation=1% (1/90).

Abbreviations used: ARDS, adult respiratory distress syndrome; cmH_2O, centimetre of water; CO_2, carbon dioxide; $ECCO_2R$, extracorporeal carbon dioxide removal; FiO_2, fraction of inspired oxygen; iLA, interventional lung-assist; IQR, interquartile range; l/min, litres per minute; ml, millilitre; mmHg, millimetres of mercury; $PaCO_2$, partial pressure of CO_2 in arterial blood; PEEP, positive end expiratory pressure; SD, standard deviation

Study 8 Liebold A (2002) [8]

Details

Study type	**Case series**
Country	Germany
Recruitment period	Not stated
Study population and number	Patients with severe pulmonary failure; n=**70**
Age and sex	41 years (range 8–72) 79% (55/70) male
Patient selection criteria	'Severest forms of ARDS'; conventional ventilator therapy failing and patient would die without $ECCO_2R$ (physicians' consensus); mean arterial pressure >70 mmHg and cardiac output > 6l/min. Patients with septic shock were only excluded if haemodynamic needs could not be met. Patients with cardiac failure were excluded.
Technique	Pumpless arteriovenous $ECCO_2R$ using the 'Nova Breath Lung Assist Device System' (Jostra, Germany).
Follow-up	**Respiratory variables reported for first 24 hours, plus survival in hospital.**
Conflict of interest/source of funding	Respiratory variables reported for first 24 hours, plus survival in hospital.

This study was included in the original overview for IP428 and was also included in the meta-analysis by Walles T (2007).

Analysis

Follow-up issues: None.

Study design issues: Consecutive patients.

Study population issues: The authors concluded that $ECCO_2R$ was suitable for patients with ARDS arising from sepsis, as long as cardiac output was adequate.

Other issues: None.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 70
Survival
51% (36/70) of patients were weaned; 49% (34/70) died while on $ECCO_2R$. Of those who were weaned, 11 (16% of all patients) died later from unresolved organ failure; 25 (36% of all patients) were eventually discharged from hospital. Overall 64% (45/70) of patients died.
Mean duration of $ECCO_2R$ (days)=6 (range 1–35)

Change in arterial blood gases
<table>
<tr><td></td><td colspan="2">Time on $ECCO_2R$</td></tr>
<tr><td></td><td>Pre</td><td>24 hours</td></tr>
<tr><td>$PaCO_2$ (mmHg)</td><td>59±17</td><td>32±8</td></tr>
<tr><td>PaO_2/FiO_2 ratio (mmHg)</td><td>50 (not stated)</td><td>110 (not stated)</td></tr>
<tr><td>PaO_2 (mmHg)</td><td>46±7</td><td>85±21</td></tr>
</table>
Mean ± SD
p values not stated

Change in mechanical ventilation
<table>
<tr><td></td><td colspan="2">Time on $ECCO_2R$</td></tr>
<tr><td></td><td>Pre</td><td>24 hours</td></tr>
<tr><td>FiO_2</td><td>1.0</td><td>0.8 (0.1)</td></tr>
</table>
Mean±SD
p values not stated
</td><td>
Technical problems occurred in 21.4% (15/70) patients.
Thrombus formation

Arterial cannula=7.1% (5/70)
Venous cannula=2.9% (2/70)
Membrane gas-exchange device=1.4% (1/70)

Cannulae had to be changed for two patients. The patient with thrombosis in the gas-exchange device was later diagnosed with heparin-induced thrombocytopenia.

Ischaemia of lower limb=4.3% (3/70) (needing cannula removal)
Haemolysis=0% (0/70)
Bleeding=0% (0/70)
Plasma leakage from gas-exchange device=7.1% (5/70), device was replaced; 1 patient received 3 modules

The authors stated that none of the deaths was directly attributable to complications with arteriovenous $ECCO_2R$.
</td></tr>
<tr><td colspan="2">Abbreviations used: ARDS, adult respiratory distress syndrome; CO_2, carbon dioxide; $ECCO_2R$, extracorporeal carbon dioxide removal; FiO_2, fraction of inspired oxygen; mmHg, millimetres of mercury; l/min, litres per minute; mmHg, millimetres of mercury; $PaCO_2$, partial pressure of CO_2 in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; SD, standard deviation</td></tr>
</table>

Study 9 Zimmermann M (2009) [9]

Details

Study type	**Case series**
Country	Germany
Recruitment period	2004–08
Study population and number	Patients with ARDS (mostly due to pneumonia, trauma or sepsis); n=**51**
Age and sex	52 years 84% (43/51) male
Patient selection criteria	Persisting impairment in pulmonary gas exchange after a stabilisation period of 12–24 hours (PaO_2/FiO_2 70–200 mmHg with PEEP of 10 cmH_2O or more and/or arterial pH <7.25 because of respiratory acidosis). Contraindications included cardiac insufficiency, severe peripheral vascular disease, and the need for continuous high doses of vasoactive or inotropic agents.
Technique	Pumpless arteriovenous $ECCO_2R$ using interventional lung-assist (iLA) device (Novalung, Germany). Reduced diameter cannulae were used, inserted with the aid of ultrasound.
Follow-up	**To hospital discharge.**
Conflict of interest/source of funding	1 author received 'lecture honorary' from manufacturer.

This study was included in the NICE overview for IPG428.

Analysis

Follow-up issues: None.

Study design issues: Prospective study.

Study population issues: None

Other issues: In more severe cases of hypoxaemia, a pump-driven venovenous extracorporeal membrane oxygenation (ECMO) was preferably initiated.

The authors note that the data in this study resulted from a strict algorithm with defined indications and contraindications, in contrast to their previous study [6]. The procedure was withdrawn from life-threatening 'rescue-situations' towards the support of lung-protective ventilation in acute lung injury or early acute respiratory distress syndrome.

The authors note there is ongoing technical evolution of smaller cannulae, more efficient gas exchange membranes and easy system handling.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **51**

Survival rate=50.9% (26/51)

Non-survivors were statistically significantly older than survivors but there were no differences between the groups for severity of disease and severity of lung injury.

Changes in gas exchange, cardiovascular and respiratory variables before and during $ECCO_2R$

	Time on $ECCO_2R$		
	Pre	2 hours	24 hours
PaO_2/FiO_2	75 (62 to 130)	102* (70 to 127)	110* (86 to 160)
$PaCO_2$ (mmHg)	73 (61 to 86)	44** (36 to 54)	41** (34 to 48)
Arterial pH	7.23 (7.16–7.30)	7.38** (7.32 to 7.16)	7.44** (7.37 to 7.49)
Mean arterial pressure (mmHg)	76 (65 to 80)	83** (75 to 91)	81 (76 to 90)
FiO_2	1 (0.8 to 1.0)	0.8** (0.7 to 1.0)	0.7** (0.6 to 09)
Minute ventilation (l/min)	11.5 (9.3 to 12.5)	8.6** (6.4 to 10.5)	6.6** (5.5 to 8.3)
Tidal volume (ml/kg)	6.6 (5.3 to 7.2)	5.0** (4.0 to 6.4)	4.4** (3.4 to 5.4)
Respiratory rate (breadths per min)	25 (22 to 27)	23 (20 to 30)	21 (18 to 26)
Plateau pressure (cmH_2O)	35 (31 to 38)	34 (30 to 37)	30** (26 to 34)
PEEP (cmH_2O)	17 (14 to 20)	15* (11 to 19)	17 (14 to 20)

Median (IQR)

* p <0.05 in comparison with pre-$ECCO_2R$

** p<0.01 in comparison with pre $ECCO_2R$

Safety

Complications

- Ischaemia of lower limb=5.9% (3/51) (removal of the cannula resulted in normalisation of distal perfusion).
- Cannula thrombosis=1.9% (1/51).
- Bleeding during cannulation=1.9% (1/51).
- Compartment syndrome (limb)=1.9% (1/51) (needed surgical intervention).

Abbreviations used: ARDS, adult respiratory distress syndrome; cmH_2O, centimetre of water; CO_2, carbon dioxide; $ECCO_2R$, extracorporeal carbon dioxide removal; FiO_2, fraction of inspired oxygen; iLA, interventional lung-assist; IQR, interquartile range; l/min, litres per minute; ml/kg, millilitres per kilogram; mmHg, millimetres of mercury; $PaCO_2$, partial pressure of CO_2 in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; PEEP, positive end expiratory pressure

Study 10: Kluge S (2012) [10]

Details

Study type	**Multicentre retrospective matched comparison study**
Country	Germany
Recruitment period	2007–10
Study population and number	Patients with acute hypercapnic respiratory failure, n=**42 (21 non-intubated patients who were treated with PECLA for acute hypercapnic respiratory failure vs 21 patients who had been admitted with acute hypercapnic respiratory failure and were treated with invasive mechanical ventilation after failing NIV)**
Age and sex	Age (years) PECLA 58 (27–80) matched comparator 58 (23–79) Male 48% (10/21) PECLA; 43% (9/21) matched comparators
Patient selection criteria	All non-intubated patients who were treated with PECLA for acute hypercapnic respiratory failure during study period were included. All patients initially received standard treatment including NIV, antibiotic and bronchodilator therapy, nutritional support and physiotherapy, according to international guidelines criteria for initiation of NIV were respiratory acidosis (pH≤7.35) and/or clinical signs of ventilatory pump failure in patients with chronic pulmonary disease. Criteria for failure of NIV and intubation were (1) worsening respiratory acidosis, (2) worsening oxygenation, (3) increasing respiratory rate, and (4) clinical signs suggestive of respiratory muscle fatigue and/or increased work of breathing. The decision to use a PECLA in these patients was always made by at least two senior intensivists. These procedures were applied in patients with potentially reversible respiratory failure when endotracheal intubation carried a high risk of secondary complications because of prolonged invasive mechanical ventilation. Controls were patients who had been admitted with acute hypercapnic respiratory failure and were treated with invasive mechanical ventilation after failing NIV. Cases matched 1:1 based on the following criteria: (1) underlying diagnosis; (2) age±10 years; (3) simplified acute physiology score (SAPS) II, assessed within the first 24 hours after ICU admission, ±6 points; (4) pH±0.05 before PECLA or intubation. If more than one match was available, a random selection was done.
Technique	PECLA device for the intervention group; invasive mechanical ventilation for the control group.
Follow-up	**6 months**
Conflict of interest/source of funding	AN, ME and SR have received lecture honoraria from Novalung GmbH, Heilbronn, Germany. SK is a member of the advisory board of Novalung GmbH and therefore has received advisor honoraria. All other authors declare that they have no conflicts of interest.

Analysis

Follow-up issues: None.

Study design issues: The interpretation of the results is limited by the design. Due to the retrospective nature of the study, data for short- and long-term side effects of ventilator-associated and analgosedation-associated complications are lacking.

The relatively small number of patients reduces the power of the study with respect to an alpha error, not detecting a potential true difference of outcomes between the 2 strategies. Despite all efforts of matching, the PECLA patients had significantly worse respiratory failure with respect to hypercapnia than the controls.

Study population issues: 9 of the 21 patients (43 %) in the PECLA group were listed for and awaiting a lung transplant, as opposed to none in the control group. Although all patients were treated as part of routine care, it needs to be emphasised that this treatment took place in expert centres. Therefore, the results may not be generalisable to other centres.

Other issues: None.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **42**

Comparison of outcomes between the PECLA group and the mechanical ventilation group

	PECLA group (n=21)	MV group (n=21)	p value	p value (Adjusted for baseline)
Intubation, n (%)	2 (10)	21 (100)	<.001	<.001
28 day mortality, n (%)	5 (24)	4 (19)	1	0.845
6 month mortality, n (%)	7 (33)	7 (33)	1	0.897
Time on PECLA/MV (days)	9 (1–116)	21 (1–47)	0.944	0.944
Length of ICU stay (days)	15 (4–137)	30 (4–66)	0.577	0.263
Length of hospital stay (days)	23 (4–137)	42 (4–248)	0.342	0.056
Tracheostomy, n (%)	2 (10)	14 (67)	0.004	0.004

Median (IQR)

Outcome measures reported only for PECLA (median, IQR) (Figures taken from graphs)

	ICU*	NIV§	Baseline‡	21–24hr
$PaCO_2$ mmHg	86 (70–106)	85 (72–99)	87 (73–99)	52 (46–66)
pH	7.3 (7.2–7.3)	7.3 (7.3–7.3)	7.3 (7.2–7.3)	7.5 (7.4–7.5)
Respiratory rate (per min)	30 (25–32)	28 (24–31)	28 (25–31)	21 (17–25)

*admission to ICU

§during NIV

‡ baseline pre PECLA

Safety

Authors stated there were no immediate complications attributed to the implantation of the device. The haemodynamic state was not significantly altered with the institution of the PECLA.

- major bleeding complications (2)
  - major bleed at the insertion site on day 7 needed bedside surgical repair (1);
  - bleeding led to removal of the cannulas on day 5 and to subsequent intubation and invasive mechanical ventilation.(1)
- minor bleeding complications (7)
- pseudoaneurysm of the femoral artery (1)
- heparin induced thrombocytopenia type 2. (1)

Abbreviations used: hr, hour; ICU, intensive care unit; IQR, interquartile range; mmHg, millimetres of mercury; min, minute; MV, mechanical ventilation; n, number of patients; NIV, non-invasive ventilation; $PaCO_2$, partial pressure of CO_2 in arterial blood; PECLA, pumpless extracorporeal lung assist; SAPS, simplified acute physiology score.

Study 11: Lehle K (2014) [11]

Details

Study type	**Retrospective study (using Regensburg ECMO Register)**
Country	Unclear
Recruitment period	2009–13
Study population and number	Adults with severe respiratory failure needing VV-ECMO support recorded in Regensburg ECMO Register N=**317**
Age and sex	50 (37–62) years 218/317 (69%) male
Patient selection criteria	Not describe
Technique	Non-microporous poly-4-methyl-1-pentene (PMP) gas membrane microfibers for oxygenation and CO_2 removal
Follow-up	**Unclear**
Conflict of interest/source of funding	The study was supported by departmental resources without external funding. CS is an adviser to Maquet Cardiopulmonary AG, Rastatt, Germany. ML, AP, and TM received travel support and lecture honoraria from Maquet Cardiopulmonary AG, Rastatt, Germany. None of the other authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

Analysis

Follow-up issues: None

Study design issues: This study was designed to compare the gas exchange performance of four membrane oxygenation systems and not to assess the efficacy of $ECCO_2R$

Study population issues: Uses register data and therefore, there may be potential reporting biases from under-recording of cases.

Other issues: None

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **317** CO_2 removal was more effective than O_2 transfer Outcomes were reported for 4 different systems. Overall outcome measures (range across devices) were: Died on ECMO: 29 % (92/317) (20% to 29%) Died after ECMO: 9 % (28/317) (2% to 21%) Discharged from Hospital: 32% (196/317) (60% to 78%) CO_2 removal depended on the type of ECMO system ($p \leq 0.001$) and non-linearly on both blood flow ($p \leq 0.001$) and gas flow (≤ 0.001)	The study does not report on adverse events or complications.
Abbreviations used: CO_2, carbon dioxide; ECMO, extracorporeal carbon dioxide removal; O_2, oxygen; vvECMO, venovenous ECMO	

Efficacy

Mortality and discharge from hospital alive

In a multicentre randomised controlled trial (RCT) of 79 patients treated by low ventilation (about 3 ml/kg) combined with arteriovenous (AV) extracorporeal carbon dioxide removal ($ECCO_2R$; n=40) or an acute respiratory distress syndrome network strategy without $ECCO_2R$ (about 6 ml/kg; n=39), 18% (7/40) of patients in the AV-$ECCO_2R$ group died in hospital compared with 15% (6/39) in the control group (the difference between the 2 groups was not statistically significant). [3]

In an RCT of 40 patients treated by low-frequency positive-pressure ventilation and $ECCO_2R$ (n=21) or continuous positive-pressure ventilation alone (n=19), survival rate at 30 days was 33% (7/21) in the group treated by $ECCO_2R$ compared with 42% (8/19) in the control group (p=0.56). [4]

In a systematic review including the 2 RCTs listed above and 12 observational studies, mortality rates of patients treated by $ECCO_2R$ ranged from 27% to 75% (mean 55.5%, standard deviations 74.2 to 60.3). [2]

In an analysis of UK patients on the Extracorporeal Life Support Organization register, the survival to discharge rate was 45% (27/60). Of those discharged, 48% (13/27) were discharged to home, and 41% (9/22) of patients receiving AV-$ECCO_2R$ and 47% (18/38) receiving venovenous $ECCO_2R$ were discharged alive (the difference between the groups was not statistically significant). [1]

In an analysis of the Regensburg extracorporeal membrane oxygenation register data comparing the efficacy of different systems used to deliver $ECCO_2R$, 32% (196/317) of patients overall were discharged from hospital (range across devices 60% to 78%). [11]

Changes in concentration of blood gases

Carbon dioxide concentration

Three case series of patients treated by AV-$ECCO_2R$ reported a significant reduction in the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) within 24 hours of initiating $ECCO_2R$ support, compared with baseline.[7,6,9]

In the first case series of 90 patients, $PaCO_2$ decreased from a median of 60 mmHg to 34 mmHg at 24 hours ($p<0.05$). [7]

In the second case series of 159 patients, $PaCO_2$ decreased from 67 mmHg to 35 mmHg at 24 hours (p=0.001). [6]

In the third case series of 51 patients, $PaCO_2$ decreased from 73 mmHg at baseline to 41 mmHg at 24 hours ($p<0.01$).[9]

Oxygen concentration (PaO_2/FiO_2 ratio)

In the case series of 90 patients, there was a significant increase in partial pressure of oxygen (PaO_2)/ fraction of inspired oxygen (FiO_2) ratio from 58 mmHg at baseline to 101 mmHg at 24 hours ($p<0.05$). [7]

In the case series of 51 patients, there was a significant increase in PaO_2/FiO_2 from 75 mmHg at baseline to 110 mmHg at 24 hours ($p<0.05$). [9]

Changes in mechanical ventilation setting

Minute ventilation (MV)

In the case series of 90 patients, median minute ventilation (MV) significantly decreased from 13.0 litres/minute at baseline to 9.9 litres/minute at 24 hours ($p<0.05$).[7]

In the case series of 159 patients, mean MV decreased from 13.8 litres/minute to 11.6 litres/minute (p value not stated). [6]

In the case series of 51 patients, median MV decreased from 11.5 litres/minute to 6.6 litres/minute ($p<0.01$). [9]

Respiratory frequency

In the case series of 90 patients, median respiratory frequency decreased significantly from 27 breaths/min at baseline to 23 breaths/min at 24 hours ($p<0.05$). [7]

In the case series of 159 patients, there was a decrease from 32 breaths/min at baseline to 29 breaths/min at 24 hours (p value not stated). [6]

In the case series of 51 patients, there was a decrease from 25 breaths/min to 21 breaths/min at 24 hours (p value not stated). [9]

In a multicentre retrospective matched comparison study of 42 patients treated by pumpless extracorporeal lung assist (PECLA; n=21) or invasive mechanical ventilation (n=21), there was a decrease from a median number of 28 breaths/min (interquartile range [IQR] 25–31) at baseline to a median number of 21 breaths/min (IQR 17–25) at 21–24 hours for the PECLA group (p value not stated). [10]

Safety

Overall complication rates

An analysis of the Extracorporeal Life Support Organization (ELSO) register data reported that 32% (19/60) patients had complications. Of these 19 patients, 11 had a single complication and 8 had 2 or more complications.[1]

In a multicentre randomised controlled trial (RCT) of 79 patients treated by low ventilation (about 3 ml/kg) combined with arteriovenous (AV) extracorporeal carbon dioxide removal ($ECCO_2R$; n=40) or an acute respiratory distress syndrome (ARDS) network strategy without $ECCO_2R$ (about 6 ml/kg; n=39), 8% (3/40) of patients had $ECCO_2R$-related adverse reactions. [3]

In a meta-analysis of 8 case series (n=225), the complication rate was 29%.[5]

In a case series of 90 patients, serious complications were reported in 24% of patients (22/90). [7]

Ischaemia

Limb ischaemia was reported in 9% (21/225) of patients in the meta-analysis of 8 case series.[5]

$ECCO_2R$-related ischaemia was reported in 1 patient in the RCT of 79 patients treated by low ventilation combined with AV-$ECCO_2R$ (n=40) or an acute respiratory distress syndrome network strategy without $ECCO_2R$ (n=39).[3]

Lower limb ischaemia was reported in 8% (13/159) of patients in a case series of 159 patients treated by $ECCO_2R$; in these patients, the arterial cannula was either exchanged with a smaller one or moved to the contralateral femoral artery.[6]

Bleeding/Haemorrhage

Central nervous system haemorrhage was reported in 1 patient out of 60 in the analysis of UK cases in the ELSO register data.[1]

Intracerebral haemorrhage was reported in 1 patient in the case series of 90 patients.[7]

Intracranial haemorrhage was reported in 1 patient in each arm of an RCT of 40 patients treated by low frequency positive-pressure ventilation and $ECCO_2R$ (n=21) or continuous positive-pressure ventilation alone (n=19). In the same study, intrapulmonic haemorrhage was reported in 19% (4/21) of patients treated by $ECCO_2R$. It was also reported that $ECCO_2R$ had to be stopped in 7 patients because of haemorrhage.[4]

Bleeding at the site of cannulation was reported in 12% (7/60) of patients in the UK patients of the ELSO register, in 4% (8/225) of patients in the meta-analysis of 8 case series, and in 1 patient in the case series of 51 patients. [1,5,9]

Diffuse bleeding and shock during cannulation was reported in 1 patient in the case series of 90 patients (no further details provided).[7]

Aneurysms and false aneurysms

Haematoma/aneurysm at the cannulation site was reported in 1 patient in the case series of 90 patients.[7]

'False' aneurysm was reported in 5% (2/40) of patients treated by $ECCO_2R$ in the RCT of 79 patients treated by low ventilation combined with AV-$ECCO_2R$ or ARDS Network strategy without $ECCO_2R$. [3]

Pseudo aneurysm of the femoral artery was reported in 1 patient treated by pumpless extracorporeal lung assist (PECLA) in a multicentre retrospective matched comparison study of 42 patients treated by PECLA (n=21) or invasive mechanical ventilation (n=21). [10]

Thrombosis

Venous thrombosis was reported in 5% (1/21) of patients in the $ECCO_2R$ arm and in 11% (2/19) of patients in the control arm in the RCT of 40 patients.[4]

The meta-analysis of 8 case series reported arterial thrombus formation in 2% of patients (5/225), venous thrombus formation in 5% (11/225) and oxygenator thrombus formation in 3% (6/225).[5]

Thrombus formation was reported in 17% (27/159) of patients in the case series of 159 patients; the oxygenators were exchanged. In the same study, thrombosis of the entire system developed in 8 patients (4 were inadequately anticoagulated, 2 had heparin-induced thrombocytopenia type II and there were 2 device failures).[6]

$ECCO_2R$ circuit clotting was reported in 19% (4/21) of patients treated by $ECCO_2R$ in the RCT of 40 patients. [4]

Infection

Infection was reported in 8% (5/60) of patients in the analysis of UK patients on the ELSO register.[1]

Infection was reported in 1 patient in the meta-analysis of 8 case series (n=225).[5]

Compartment syndrome

Compartment syndrome needing fasciotomy was reported in 3% (4/159) of patients in the case series of 159 patients; 1 of these patients needed lower leg amputation.[6]

Compartment syndrome was reported in 4% (4/90) of patients in the case series of 90 patients.[7]

Compartment syndrome was reported in 1 patient in the case series of 51 patients; this was surgically treated.[9]

Renal complications

Renal complications were reported in 10% (6/60) of patients in the analysis of UK patients on the ELSO register. [1]

Cardiovascular complications

Cardiovascular complications were reported in 10% (6/60) of patients in the analysis of UK patients on the ELSO register.[1]

Cardiac dysrhythmia was reported in 10% (2/21) of patients in the $ECCO_2R$ group and in 11% (2/19) of patients in the control group in the RCT of 40 patients; cardiac tamponade occurred in 5% (1/21) in the $ECCO_2R$ group and 0% (0/19) in the control group.[4]

Haemolysis

Haemolysis was reported in 1 patient in the case series of 90 patients.[7]

Mechanical complications

Technical problems were reported in 21% (15/70) of patients in a case series of 70 patients treated by $ECCO_2R$. [8]

Mechanical complications were reported on 7 occasions in the analysis of UK patients on the ELSO register: 1 oxygenator failure, 2 pump malfunctions, 1 oxygenator clot, 2 other clots and 1 cannula problem.[1]

Plasma leakage was reported in 4% (10/225) of patients in the meta-analysis of 8 case series. [5]

Validity and generalisability of the studies

- Two RCTs were identified (Morris, 1994; Bein, 2013). Both had small samples with 40 and 79 patients respectively, making it difficult to generalise their findings. The Morris RCT is an old study.
- Much of the evidence identified took the form of case series or case studies, though there were examples of analysis of register data and attempts at retrospective matching of patients (e.g. Kluge 2012 [10]).
- Studies varied in the outcome measures reported and follow-up periods.
- Recent improvements in technology used to deliver $ECCO_2R$ may limit the generalisability of some of the older studies included in this overview.

Existing assessments of this procedure

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

Related NICE guidance

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

Interventional procedures

- Extracorporeal membrane oxygenation (ECMO) for acute heart failure in adults. NICE interventional procedure guidance 482 (2014). Available from https://www.nice.org.uk/guidance/ipg482
- Extracorporeal membrane oxygenation for severe acute respiratory failure in adults. NICE interventional procedure guidance 391 (2011). Available from https://www.nice.org.uk/guidance/ipg391
- Extracorporeal membrane oxygenation in post neonatal children. NICE interventional procedure guidance 038 (2004). Available from https://www.nice.org.uk/guidance/ipg038

NICE guidelines

- Pneumonia: Diagnosis and management of community- and hospital-acquired pneumonia in adults. NICE clinical guideline 191 (2014). Available from https://www.nice.org.uk/guidance/cg191

Specialist advisers' opinions

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

Patient commentators' opinions

Patient commentary was not sought for this procedure.

Issues for consideration by IPAC

Ongoing studies:

- NCT02654327 pRotective vEntilation With Veno-venouS Lung assisT in Respiratory Failure (REST). Location: UK. RCT. Starting in March 2016. Estimated enrolment: 1120. Estimated Completion Date: April 2021.
- NCT02086084 $ECCO_2R$ as an Adjunct to NIV in AECOPD. Location: UK. RCT. Ongoing. Enrolment: 24. Estimated Completion Date: December 2015.
- NCT02282657 Strategy of UltraProtective Lung Ventilation With Extracorporeal CO2 Removal for New-Onset Moderate to seVere ARDS (SUPERNOVA). Location: Belgium. Case series. Ongoing. Enrolment: 100. Estimated Completion Date: December 2015.
- NCT02107222 The PALP-COPD Trial (Low-Flow CO2-Removal ($ECCO_2$-R) in Exacerbated COPD) (PALP-COPD). Location: Germany. RCT. Ongoing. Enrolment: 120. Estimated Completion Date: April 2018.
- NCT01911533 Veno-venous Extracorporeal CO2 Removal in ARDS-patients to Treat Respiratory Acidosis. Location: Belgium. Case series. Recruiting. Enrolment: 10. Estimated Completion Date: December 2015.
- NCT02252094 Ultra-protective Pulmonary Ventilation Supported by Low Flow $ECCO_2R$ for Severe ARDS. Location: Singapore. RCT. Recruiting. Enrolment: 50. Estimated Completion Date: May 2016.
- NCT02260583 Effect of Extracorporeal CO2 Removal in Stable Hypercapnic COPD Patients. Location: Italy. Case series. Recruiting. Enrolment: 15. Estimated Completion Date: October 2015.
- NCT01784367 Extracorporeal Lung Assist to Avoid Intubation in Patients Failing Noninvasive Ventilation for Acute Hypercapnic Respiratory Failure (ECLAIR). Location: Germany. Case series. Ongoing. Enrolment: 30. Estimated Completion Date: April 2015.
- NCT01239966 Pulmonary And Renal Support During Acute Respiratory Distress Syndrome (PARSA). Location: France. Case series. Ongoing. Enrolment: 10. Estimated Completion Date: June 2015.

References

1. Fitzgerald, M., et al., *Extracorporeal carbon dioxide removal for patients with acute respiratory failure secondary to the acute respiratory distress syndrome: a systematic review.* Critical Care, 2014. **18**(3).
2. Cummins, C., *A United Kingdom Register study of patients receiving extracorporeal carbon dioxide removal ($ECCO_2R$).* Report to NICE, 2015.
3. Bein, T., et al., *Lower tidal volume strategy (≈3 ml/kg) combined with extracorporeal CO2 removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study.* Intensive Care Medicine, 2013. **39**: p. 847-856.
4. Morris, A., C. Wallace, and R. Menlove, *Randomized clinical trial of pressure-controlled inverse ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome.* American Journal of Respiratory and Critical Care Medicine, 1994. **149**: p. 295-305.
5. Walles, T., *Clinical experience with the ilA Membrane Ventilator pumpless extracorporeal lung-assist device.* Expert Review of Medical Devices, 2007. **4**: p. 297-305.
6. Florchinger, B., A. Philipp, and K. A;, *Pumpless extracorporeal lung assist: a 10 year institutional experience.* Annals of the American Thoracic Society, 2008. **86**: p. 410-417.
7. Bein, T., F. Weber, and A. Philipp, *A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia.* Critical Care Medicine, 2006. **34**: p. 1372-7.
8. Liebold, A., A. Philipp, and H. Kaiser, *Pumpless extracorporeal lung assist using an arterio-venous shunt. Applications and limitations.* Minerva Anestesiologica, 2002. **68**: p. 387-91.
9. Zimmermann, M., T. Bein, and M. Arlt, *Pumpless extracorpereal lung assist in patients with acute respiratory distress syndrome: a prospective pilot study. .* Critical Care, 2009. **13**(R!)).
10. Kluge, S., et al., *Avoiding invasive mechanical ventilation by extracorporeal carbon dioxide removal in patients failing noninvasive ventilation.* Intensive Care Medicine, 2012. **38**: p. S75.
11. Lehle, K., et al., *Efficiency of gas transfer in venovenous extracorporeal membrane oxygenation: analysis of 317 cases with four different ECMO systems.* Intensive Care Medicine, 2014. **40**(12): p. 1870-1877.

Appendix A: Additional papers on extracorporeal carbon dioxide removal for acute respiratory failure

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.

Venovenous system

Article	Number of patients	Direction of conclusions	Reasons for non-inclusion in table 2
Abrams et al (2013) Pilot Study of Extracorporeal Carbon Dioxide Removal to Facilitate Extubation and Ambulation in Exacerbations of Chronic Obstructive Pulmonary Disease. Ann Am Thorac Soc Vol 10, No 4, pp 307–314, Aug 2013	5	$ECCO_2R$ facilitates early extubation and ambulation in exacerbations of COPD needing IMV and has the potential to serve as a new paradigm for the management of a select group of patients.	Pilot study, small sample size.
Borg UR, Reynolds HN, Habashi NM. (1998) Veno-venous extracorporeal lung assist with concurrent distal aortic perfusion: repair of ruptured aorta in a patient with dense ARDS. International Journal of Artificial Organs 21: 344–347.	1	**Venovenous** $ECCO_2R$ allowed surgical repair of a ruptured descending thoracic aorta to be performed in a patient with profound respiratory failure.	Case report.
Bergantino et al 2012. Extracorporeal carbon dioxide removal: a new flow veno-venous device in lung transplantation. 25th ESICISM Annual Congress, Lisbon, Portugal, 13-17 October 2012.	2	Did not need specialised staff and no adverse events. May be an important aid for patients with mild hypoxia but sever acidosis in association with conventional therapy during perioperative period in lung transplant.	Small sample size.
Brenner et al 2014. Extracorporeal carbon dioxide removal for refractory status asthematicus: experience in distinct exacerbation phenotypes.	2	Early initiation of $ECCO_2R$ should be considered for refractory status asthematicus when optimal ventilator management fails to provide clinical stability, particularly given the improved risk profile of modern extracorporeal technology.	Small sample size.
Brunet F, Mira JP, Belghith M et al. (1992) Effects of aprotinin on haemorrhagic complications in ARDS patients during prolonged extracorporeal CO_2 removal. Intensive Care Medicine 18:	2	**Venovenous** After aprotinin infusion combined with heparin, bleeding vanished until the end of bypass.	Larger studies are included.

364–367.			
Cardenas VJ Jr, Lynch JE, Ates R et al. (2009) Venovenous carbon dioxide removal in chronic obstructive pulmonary disease: experience in one patient. ASAIO Journal 55: 420–422.	1	• **Venovenous** First case using venovenous $ECCO_2R$ – resulted in reduction in minute ventilation to 30% of baseline with improved arterial blood gases, reduction in peak airway pressures and improvement in hyperinflation.	Case report.
Everts P, Franssen T, Schipper R et al. (1989) Venovenous long term extracorporeal CO2 removal with biopump and hollow fiber membrane oxygenator for the failing lung. Journal of Extra-Corporeal Technology 21: 18–22.	1	**Venovenous** The patient died because of irreversible traumatic cerebral damage and $ECCO_2R$ was terminated after 60 hours.	Case report.
Forster et al 2013. Low-flow CO_2 removal integrated into a renal-replacement circuit can reduce acidosis and decrease vasopressor requirements. Critical Care, 2013. 17: p. R154.	10	A hollow-fiber gas exchanger integrated into a conventional renal-replacement circuit with only a little additional trauma could be an useful therapeutic tool on CO_2 removal, acidosis, and haemodynamics for patients with mild to moderate ARDS having invasive ventilation with concomitant respiratory acidosis, as long as no severe oxygenation defects indicate ECMO therapy.	Small sample size cohort study.
Knoch M, Kollen B, Dietrich G et al. (1992) Progress in veno-venous long-term bypass techniques for the treatment of ARDS. Controlled clinical trial with the heparin-coated bypass circuit. International Journal of Artificial Organs 15: 103–108.	18	**Venovenous** There were fewer bleeding complications and more patients survived in the group with a heparin-coated circuit.	Larger studies are included.
Moscatelli A, Ottonello G, Nahum L et al. (2010) Non-invasive ventilation and low-flow veno-venous extracorporeal carbon dioxide removal as a bridge to lung transplantation in a child with refractory hypercapnic respiratory failure due to bronchiolitis obliterans. Pediatric Critical Care Medicine 11: e8–12.	1	**Venovenous** Non-invasive mechanical ventilation and venovenous $ECCO_2R$ were efficacious in managing refractory hypercapnic respiratory failure in a paediatric patient awaiting lung transplantation.	Case report.
Nelson J, Cairns B, Charles A. (2009) Early extracorporeal life support as rescue therapy for severe acute respiratory distress syndrome after inhalation injury. Journal of Burn Care & Research 30: 1035–1038.	1	**Venovenous** By using 'rest' ventilator settings and venovenous $ECCO_2R$, the patient remained stable for a total of 6.5 days and was then successfully transitioned to a conventional ventilator and decannulated.	Case report.

Ruberto F, Pugliese F, D'Alio A et al. (2009) Extracorporeal removal CO2 using a venovenous, low-flow system (Decapsmart) in a lung transplanted patient: a case report. Transplantation Proceedings 41:1412–1414.	1	**Venovenous** No adverse events occurred. From baseline to 48 hours, pH values increased and partial pressure of CO_2 reduced. At the same time ventilatory support was reduced.	Case report.
Ryan DP, Doody DP. (1992) Treatment of acute pulmonary failure with extracorporeal support: 100% survival in a pediatric population. Journal of Pediatric Surgery 27: 1111–1116.	2	**Venovenous** Both children survived and were successfully weaned from the ventilator.	Larger studies are included.

Arteriovenous or 'pumpless' system (including studies where the type of system has not been specified)

Article	Number of patients	Direction of conclusions	Reasons for non-inclusion in table 2
Agerstrand et al 2014. ECMO for respiratory failure: current use and evolving applications.	Literature review	More evidence is needed to define the role of ECMO and $ECCO_2R$ in patients with acute respiratory distress.	Narrative review of the literature
Andresen et al (2013). Catastrophic respiratory failure from tuberculous pneumonia: survival after prolonged membrane extracorporeal oxygenation support. Respiratory Medicine Case Reports 10, 19-22	1	Single case, cannot draw conclusions.	Case report.
Arvantagi et al (2011). Pumpless arteriovenous carbon dioxide removal: a novel simplified strategy for severe asthma in children. Indian Journal of Critical Care Medicine, 15(4), 224-226	1	Single case, cannot draw conclusions.	Case report.
Bartosik W, Egan JJ, Wood AE. (2011) The Novalung interventional lung assist as bridge to lung transplantation for self-ventilating patients - initial experience. Interactive Cardiovascular & Thoracic Surgery 13: 198–200.	2	**Arteriovenous** Self-ventilating patients awaiting lung transplantation. 1 patient was successfully transplanted after 140 days. The other was weaned off $ECCO_2R$ after a short period of time.	Larger studies

Beed M, Jayamaha J, Sherman R et al. (2006) Successful use of portable extracorporeal carbon-dioxide removal in a patient with uncontrollable hypercapnoea. British Journal of Intensive Care 16: 24–26.	1	**Arteriovenous** Successful outcome for patient with pneumonia.	Case report.
Baker et al (2012). Extracorporeal carbon dioxide removal ($ECCO_2R$) in respiratory failure: an overview, and where next? Journal of Intensive Care Society, 13 (3), 232-237	Literature review	Concerns around the potential for AV-$ECCO_2R$ for arterial damage and ischaemic complications caused by arterial cannula make VV-$ECCO_2R$ an attractive alternative.	Narrative review of the literature.
Bein T, Osborn E, Hofmann HS et al. (2010) Successful treatment of a severely injured soldier from Afghanistan with pumpless extracorporeal lung assist and neurally adjusted ventilatory support. International Journal of Emergency Medicine 3: 177–179.	1	**Arteriovenous** $ECCO_2R$ enabled safe transportation and lung protective ventilation.	Case report.
Bein T, Scherer MN, Philipp A et al. (2005) Pumpless extracorporeal lung assist (PECLA) in patients with acute respiratory distress syndrome and severe brain injury. Journal of Trauma 58: 1294–1298.	5	**Arteriovenous** Hypercapnia was eliminated and minute volume of artificial ventilation could be reduced. 4 out of 5 patients survived showing a good neurologic function.	Larger studies are included. (included in table 2 of previous overview)
Bein T, Zimmermann M, Philipp A et al. (2011) Addition of acetylsalicylic acid to heparin for anticoagulation management during pumpless extracorporeal lung assist. ASAIO Journal 57: 164–168.	Non-randomised comparative study (comparing 2 anti-coagulant regimens) n = 30	**Arteriovenous** Supplementation of low-dose acetylsalicylic acid is safe and might preserve the function of oxygen transfer.	Larger studies are included.
Bombino M, Patroniti N, Foti G et al. (2011) Bronchopleural fistulae and pulmonary ossification in posttraumatic acute respiratory distress syndrome: successful treatment with extracorporeal support. ASAIO Journal 57: 336–340.	1	Lung rest, achieved by $ECCO_2R$, allowed weaning from mechanical ventilation, closure of bronchopleural fistula, and resumption of spontaneous breathing.	Case report.

Bonnet et al (2012), Refractory hypercapnia: a simplified technique for extracorporeal CO_2 removal ($ECCO_2R$) in the presence of therapeutic limitations	1	Single case, cannot draw conclusions.	Case report.
Burkle et al (2012). Arterial chimney graft for interventional lung assist. Ann. Thorac Surg, 94, 1355-7	1	Single case, cannot draw conclusions.	Case report.
Brunet F, Belghith M, Mira JP et al. (1993) Extracorporeal carbon dioxide removal and low-frequency positive-pressure ventilation. Improvement in arterial oxygenation with reduction of risk of pulmonary barotrauma in patients with adult respiratory distress syndrome. Chest 104: 889–898.	23	Survival rate = 50% Bleeding was the only complication related to the procedure and was the cause of death in 4 patients.	Larger studies are included.
Brunet F, Mira JP, Belghith M et al. (1994) Extracorporeal carbon dioxide removal technique improves oxygenation without causing overinflation. American Journal of Respiratory & Critical Care Medicine 149: 1557–1562.	11	$ECCO_2R$ with low frequency positive pressure ventilation improves gas exchange without causing lung overinflation in a majority of patients with adult respiratory distress syndrome.	Larger studies are included.
Burki et al (2013). A Novel Extracorporeal CO_2 Removal System Results of a Pilot Study of Hypercapnic Respiratory Failure in Patients With COPD. Chest, 143(3): p. 678-686.	20	The use of very low tidal volume combined with extracorporeal CO_2 removal has the potential to further reduce ventilator-induced lung injury compared with a 'normal' lung protective management. Whether this strategy will improve survival in ARDS patients remains to be determined	Small sample size.
Cole et al (2014). Extracorporeal carbon dioxide removal as an alternative to endotracheal intubation for non-invasive ventilation failure in acute exacerbation of COPD. Journal of Intensive Care Society, 15 (5), 344-346	1	Single case, cannot draw conclusions.	Case report.
Cove et al (2012) Bench to	Literature	There are several novel	Narrative

bedside review: extracorporeal carbon dioxide removal, past present and future	review	strategies that can be used for the removal of CO_2.	review, provided no information on outcomes.
Conrad SA, Zwischenberger JB, Grier LR et al. (2001) Total extracorporeal arteriovenous carbon dioxide removal in acute respiratory failure: a phase I clinical study. Intensive Care Medicine 27: 1340–1351.	8	**Arteriovenous** Applied in conjunction with mechanical ventilation and permissive hypercapnia, $ECCO_2R$ resulted in normalisation of arterial PCO_2 and pH and permitted significant reductions in the level of mechanical ventilation.	Larger studies are included.
Conrad SA, Green R, Scott LK. (2007) Near-fatal pediatric asthma managed with pumpless arteriovenous carbon dioxide removal. Critical Care Medicine 35: 2624–2629.	4	**Arteriovenous** Percutaneous cannulation with a simplified pumpless extracorporeal circuit is capable of removing sufficient carbon dioxide to allow application of a protective ventilatory strategy in severe hypercapnic paediatric respiratory failure.	Larger studies are included.
Cracchiolo et al 2012. CO_2 dialysis in the treatment of patient with ARDS and brain trauma: a case report. 25th ESICM Annual Congress, Lisbon, Portugal, 13-17 October 2012.	1	Single case, cannot draw conclusions.	Case report.
David M, Heinrichs W. (2004) High-frequency oscillatory ventilation and an interventional lung assist device to treat hypoxaemia and hypercapnia. British Journal of Anaesthesia 93: 582–586.	1	**Pumpless $ECCO_2R$** $PaCO_2$ normalised after initiation of $ECCO_2R$, which was discontinued after 13 days without complication.	Case report.
Elliot SC, Paramasivam K, Oram J et al. (2007) Pumpless extracorporeal carbon dioxide removal for life-threatening asthma. Critical Care Medicine 35: 945–948.	2	**Pumpless $ECCO_2R$** The addition of $ECCO_2R$ to mechanical ventilation corrected hypercapnia and acidosis, allowing reduction of other supportive measures.	Larger studies are included.
Featherstone et al (2012). Arteriovenous extracorporeal carbon dioxide removal as a bridge to recovery in patients developing acute respiratory failure following successful weaning from	2	Only two cases, cannot draw conclusions.	Small sample size.

venovenous extracorporeal membrane oxygenation. Anaesthesia, 37, 309-317.			
Fischer S, Simon AR, Welte T et al. (2006) Bridge to lung transplantation with the novel pumpless interventional lung assist device NovaLung. Journal of Thoracic & Cardiovascular Surgery 131: 719–723.	12	**Pumpless $ECCO_2R$** 10 out of 12 patients were successfully bridged to lung transplantation, and 8 are still alive (1-year survival, 80%).	Larger studies are included.
Forster et al (2013). Low-flow CO_2 removal integrated into a renal-replacement circuit can reduce acidosis and decrease vasopressor requirements. Critical Care, 2013. 17: p. R154	10	Hollow-fiber gas exchanger in a renal circuit could be an attractive therapeutic tool for patients with mild to moderate ARDS having invasive ventilation with concomitant respiratory acidosis, as long as no severe oxygenation defects indicate ECMO therapy.	Small sample size.
Gattinoni et al (1986) Low frequency positive-pressure ventilation with extracorporeal CO_2 removal in severe acute respiratory failure. JAMA, 1986. 256(881-6)	43	Unclear.	Included in previous overview, old case series.
Gehron et al (2014). Effect of recirculation on carbon dioxide removal and patient $paCO_2$ during veno-venous extracorporeal membrane oxygenation in adults – preliminary results of an observational clinical trial. Theime E-Journal	19	Unclear.	Does not report patient outcomes.
Gardiner et al (2013). First fixed wing air transfer of the Novalung ILA Activve as a bridge to lung transplantation. Crit Care Med, 41, 12 (suppl)	1	Single case, cannot draw conclusions.	Case report.
Hammell C, Forrest M, Barrett, P. (2008) Clinical experience with a pumpless extracorporeal lung assist device. Anaesthesia 63: 1241–1244.	3	**Pumpless $ECCO_2R$** Arterial CO_2 levels were reduced rapidly with a corresponding increase in pH, reduction in vasopressor needs and reduction in inspiratory pressures. There were no complications associated with use of the device.	Larger studies are included.
Haneya A, Philipp A, Foltan M et al. (2009) Extracorporeal circulatory	38	**Pumpless $ECCO_2R$** Discharge rates were 45% for pumpless $ECCO_2R$, 44% for	Includes a range of extracorporeal

systems in the interhospital transfer of critically ill patients: experience of a single institution. Annals of Saudi Medicine 29: 110–114.		extracorporeal life support and 56% for ECMO.	systems.
Haneya A, Philipp A, Mueller T et al. (2011) Extracorporeal circulatory systems as a bridge to lung transplantation at remote transplant centers. Annals of Thoracic Surgery 91: 250–255.	Case series n = 10 (ECMO and $ECCO_2R$)	Implantation of extracorporeal circulatory systems is a safe method to bridge patients decompensating on the waiting list for transplantation. Support intervals of several weeks are possible.	Larger studies are included.
Hermann et al (2016). First experience with a new miniaturized pump-driven venovenous extracorporeal removal system (iLA Activve): a retrospective data analysis. ASAIO Journal, 60, 342-347.	12	Provided effective CO_2 removal in all patients. However, severe impairment of oxygenation and prolonged mechanical ventilation before $ECCO_2R$ are factors of adverse prognosis.	Small sample size.
Hillmann A, Schmeier U, Sandner A et al. (2008) Recompensation of a therapy-resistant respiratory acidosis in severe sepsis with a pumpless extracorporeal CO_2-elimination system. Applied Cardiopulmonary Pathophysiology 12: 23–26.	1	**Pumpless $ECCO_2R$** Recompensation of a therapy-resistant respiratory acidosis in a septic patient with severe pneumonia by the use of $ECCO_2R$.	Case report.
Hommel M, Deja M, von Dossow V et al. (2008) Bronchial fistulae in ARDS patients: management with an extracorporeal lung assist device. European Respiratory Journal 32: 1652–1655.	4	**Pumpless $ECCO_2R$** Initiation of a pumpless extracorporeal lung assist device enabled a less invasive ventilator management, which may have contributed to healing of surgical bronchial repair.	Larger studies are included.
Hughes et al (2013). Novel uses of arteriovenous extra-corporeal carbon dioxide removal (ECCO2R) – two case studies. Journal of the Intensive Care Society, 14 (2), 169-173	2	Only two cases, cannot draw conclusions.	Case report.
Jandhyala R, Haydon P, Czaplicka C et al. (1994) Successful vaginal delivery of a male infant during extracorporeal carbon dioxide removal: A case report. Journal of Extra-Corporeal Technology 26:	1	Uterine contractions began shortly after $ECCO_2R$ was initiated. Nine hours later the baby was delivered vaginally. Both mother and baby survived.	Case report.

87–90.			
Johnson P, Frohlich S, Westbrook A. (2011) Use of Extracorporeal Membrane Lung Assist Device (Novalung) in H1N1 Patients. Journal of Cardiac Surgery 26: 449–452.	3	**Arteriovenous** Use of pumpless arteriovenous $ECCO_2R$ resulted in reduced CO_2 levels, improved pH, and a reduction in inspiratory pressures, allowing for a less-harmful ventilator strategy.	Larger studies are included.
Jung C, Lauten A, Pfeifer R et al. (2011) Pumpless extracorporeal lung assist for the treatment of severe, refractory status asthmaticus. Journal of Asthma 48: 111–113.	1	**Pumpless $ECCO_2R$** ECMO was used initially and was later replaced by $ECCO_2R$, which was removed after 8 days, and the patient was successfully weaned from mechanical ventilation.	Case report.
Lehle et al (2014), Efficiency of gas transfer in venovenous extracorporeal membrane oxygenation: analysis of 317 cases with four different ECMO systems. Intensive Care Medicine, 40(12): p. 1870-1877	317	Compared four ECMO systems and concluded were more effective at CO_2 removal than oxygenation. There were significant differences in CO_2 removal between systems.	Provided limited information on patient outcomes and mainly reported on technical performance differences.
Liebold A, Reng CM, Philipp A et al. (2000) Pumpless extracorporeal lung assist - experience with the first 20 cases. European Journal of Cardio-Thoracic Surgery 17: 608–613.	20	**Arteriovenous** 15 out of 20 patients were weaned off $ECCO_2R$; 5 patients died while on the system (4 sepsis, 1 ventricular fibrillation). 3 patients died after successful weaning on day 8, 30, and 50, respectively. 12 patients were discharged in a healthy state (overall survival 60%). Technical problems included thrombosis of the venous cannula (n = 5), thrombus formation within the membrane oxygenator (n = 2), membrane oxygenator plasma leakage (n = 2), and membrane oxygenator contamination with *Candida albicans*. No bleeding complication was observed.	Larger studies are included.
Lobaz S, Carey M. (2011) Rescue of acute refractory hypercapnia and acidosis secondary to life-threatening asthma with extracorporeal carbon dioxide removal ($ECCO_2R$). Journal of the Intensive	1	A case of life-threatening asthma associated with profound hypercapnia and acidosis that was refractory to conventional medical therapy was managed successfully using $ECCO_2R$.	Case report.

Care Society 12: 140–142.			
Mallick A, Elliot S, McKinlay J et al. (2007) Extracorporeal carbon dioxide removal using the Novalung in a patient with intracranial bleeding. Anaesthesia 62: 72–74.	1	**Arteriovenous** Requirements for both respiratory and cardiovascular support were reduced. The patient made a complete neurological recovery.	Case report.
McKinlay J, Chapman G, Elliot S et al. (2008) Pre-emptive Novalung-assisted carbon dioxide removal in a patient with chest, head and abdominal injury. Anaesthesia 63: 767–770.	1	$ECCO_2R$ was pre-emptively used without anticoagulation, prior to laparotomy, to remove carbon dioxide and to allow for cerebral and lung protective strategies.	Case report.
Muellenbach RM, Wunder C, Nuechter DC et al. (2007) Early treatment with arteriovenous extracorporeal lung assist and high-frequency oscillatory ventilation in a case of severe acute respiratory distress syndrome. Acta Anaesthesiologica Scandinavica 51: 766–769.	1	**Arteriovenous** After 5 days, the patient was switched back to conventional mechanical ventilation from high-frequency oscillatory ventilation and $ECCO_2R$ was removed after 8 days.	Case report.
Muellenbach RM, Kredel M, Wunder C et al. (2008) Arteriovenous extracorporeal lung assist as integral part of a multimodal treatment concept: a retrospective analysis of 22 patients with ARDS refractory to standard care. European Journal of Anaesthesiology 25: 897–904.	22	**Arteriovenous** Overall complication rate = 23% (predominantly due to reversible lower limb ischaemia). 1 patient needed amputation of a seriously injured lower leg 9 days after initiation of $ECCO_2R$. Overall mortality rate = 27%.	Larger studies are included.
Muller T, Lubnow M, Philipp A et al. (2009) Extracorporeal pumpless interventional lung assist in clinical practice: determinants of efficacy. European Respiratory Journal 33: 551–558.	96	**Arteriovenous** Interventional lung assist eliminates approximately 50% of calculated total carbon dioxide production with rapid normalisation of respiratory acidosis. Despite limited contribution to oxygen transfer it may allow a more protective ventilation in severe respiratory failure.	Same study centre and recruitment period as Bein et al. (2006), which is included in table 2. Fewer patient outcomes are documented.
Nierhaus A, Frings D, Braune S et al. (2011) Interventional lung assist	13	**Arteriovenous** Hypercapnia was significantly ($p < 0.05$) reduced from 80.0 to	Larger studies are included.

enables lung protective mechanical ventilation in acute respiratory distress syndrome. Minerva Anestesiologica 77: 797–801.		48.0 mmHg (day 7), as were minute ventilation and inspiratory pressure. Major complications were 2 inadvertent decannulations in the first 2 patients treated.	
Phillipp A, Behr R, Rengr M et al. (1998) Pumpless extracorporeal lung assist. Journal of Extra-Corporeal Technology 30: 38–41.	1	**Arteriovenous** Under good haemodynamic conditions, an arteriovenous pumpless $ECCO_2R$ was instituted for 10 days, when the patient could be successfully weaned.	Case report.
Ricci D, Boffini M, Del Sorbo L, et al. (2010) The use of CO_2 removal devices in patients awaiting lung transplantation: an initial experience. Transplantation Proceedings 42: 1255–1258.	12	Eight patients died on the device. Three patients were bridged to lung transplantation; 1 recovered and was weaned from the device after 11 days.	Larger studies are included.
Ruettimann U, Ummenhofer W, Rueter F et al. (2006) Management of acute respiratory distress syndrome using pumpless extracorporeal lung assist. Canadian Journal of Anaesthesia 53: 101–105.	1	**Arteriovenous** The $ECCO_2R$ device remained in situ for 10 days without any adverse side effect. During this time, the lung recovered such that mechanical ventilation could be reinstalled cautiously. The device was then removed and, after a prolonged period of intensive care, the patient recovered without any sequelae.	Case report.
Sanchez-Lornete et al (2012). The pumpless extracorporeal membrane provides complete respiratory support during complex airway reconstructions without introducing cellular trauma or a coagulatory and inflammatory response. The Journal of Thoracic and Cardiovascular Surgery, 44 (2), 425-430.	15	The data suggests that iLA provides complete respiratory support in patients who cannot receive conventional intubation/ventilation without relevant effects on cellular trauma, coagulatory response and inflammatory response.	Small sample size.
Schellongowski P, et al (2014). Extracorporeal CO2 removal as bridge to lung transplantation in life threatening hypercapnia. Transplant International, 28, 297-304	20	Bridging to lung transplantation with $ECCO_2R$ is feasible and is associated with high transplantation and survival rates.	Small sample size.

Scott LK, Grier LR, Turnage R et al. (2003) Extracorporeal carbon dioxide removal to control arterial pH and PaCO2 in a heart-beating donor with acute lung injury. Transplantation 76: 1630–1632.	1	**Arteriovenous** The $PaCO_2$ and arterial pH promptly corrected after support was initiated.	Case report.
Stirling SL, Cordingley JJ, Hunter DN et al. (2009) Extracorporeal carbon dioxide removal to "protect" the lung. Thorax 64: 726–727.	3	**Arteriovenous** $ECCO_2R$ facilitated a dramatic reduction in the amount of ventilatory support needed, achieving a 'lung-protective' level. Two of the 3 patients survived to hospital discharge.	Larger studies are included.
Taylor K, Holtby H. (2009) Emergency interventional lung assist for pulmonary hypertension. Anesthesia & Analgesia 109: 382–385.	1	$ECCO_2R$ provided circulatory support with oxygenation obviating the need for ECMO while waiting for lung transplantation.	Case report.
Turani et al (2013). A membrane oxgenator phoshororylcholine coated (ABYLCAP) allows protective ventilation in hypercapnia patients with minimal impairment of coagulation and improvement of right ventricular function. 26th ESICM Annual Congress, Paris, 5-9 October 2013	10	$ECCO_2R$ allows protective ventilation without impairment of coagulation (minimal decrease of platelets, no fibrinolysis).	Small sample size.
Twigg S, Gibbon GJ, Perris T. (2008) The use of extracorporeal carbon dioxide removal in the management of life-threatening bronchospasm due to influenza infection. Anaesthesia & Intensive Care 36: 579–581.	1	$ECCO_2R$ enabled a rapid correction of hypercapnoea and acidosis, allowing a reduction in airway pressures, reducing further barotrauma. The patient was successfully weaned from mechanical ventilation and made a full recovery.	Case report.
Weber-Carstens S, Bercker S, Hommel M et al. (2009) Hypercapnia in late-phase ALI/ARDS: providing spontaneous breathing using pumpless extracorporeal lung assist. Intensive Care Medicine 35: 1100–5.	10	**Pumpless $ECCO_2R$** Median reduction in pCO_2 = 50% Significant reduction in tidal volumes and inspiratory plateau pressures. Sedation requirements were reduced.	Larger studies are included.
Zwischenberger JB, Conrad SA, Alpard SK et al. (1999) Percutaneous extracorporeal arteriovenous CO_2 removal	5	**Arteriovenous** All patients survived the experimental period without adverse sequelae. $ECCO_2R$ can achieve approximately	Larger studies are included.

for severe respiratory failure. Annals of Thoracic Surgery 68: 181–187.		70% CO_2 removal in adults with severe respiratory failure and CO_2 retention without haemodynamic compromise or instability.	

Appendix B: Related NICE guidance for extracorporeal carbon dioxide removal for acute respiratory failure

Guidance	Recommendations
Interventional procedures	**Extracorporeal membrane carbon dioxide removal (current guidance). NICE interventional procedure guidance 428 (2012)** 1.1 Current evidence on the safety of extracorporeal membrane carbon dioxide removal ($ECCO_2R$) shows a number of well-recognised complications. Evidence on its efficacy is limited in quality and quantity. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake $ECCO_2R$ should take the following actions. • Inform the clinical governance leads in their trusts. • Ensure that patients (if possible) and their families or carers understand the uncertainty about the procedure's efficacy and the risk of complications and provide them with clear written information. In addition, the use of NICE's information for patients (Understanding NICE guidance) is recommended. Audit and review clinical outcomes of all patients having $ECCO_2R$ (see sections 1.4 and 3.1). 1.3 $ECCO_2R$ should only be used by specialist intensive care teams trained in its use. Only patients with potentially reversible hypercarbic respiratory failure or those being considered for lung transplantation should be selected for this procedure. 1.4 NICE encourages clinicians to enter patients into ongoing trials and collaborate in data collection initiatives, such as the e (ELSO) register. Studies should specify the type of technique being used. Data collected for research and for other clinical purposes should document patient selection criteria, thresholds for intervention, and the procedure's clinical benefits. NICE may review the procedure on publication of further evidence. **Extracorporeal membrane oxygenation (ECMO) for acute heart failure in adults. NICE interventional procedure**

	guidance 482 (2014) 1 Recommendations 1.1 The evidence on the efficacy of extracorporeal membrane oxygenation (ECMO) for acute heart failure in adults is adequate but there is uncertainty about which patients are likely to benefit from this procedure, and the evidence on safety shows a high incidence of serious complications. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake ECMO for acute heart failure in adults should take the following actions. •Inform the clinical governance leads in their NHS trusts. •Ensure that patients and their carers understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for the public is recommended. •Submit data on all adults undergoing ECMO for acute heart failure to the international Extracorporeal Life Support Organization register. 1.3 ECMO for acute heart failure in adults should only be carried out by clinical teams with specific training and expertise in the procedure. 1.4 NICE encourages further research into ECMO for acute heart failure. This should include clear documentation of patient selection and indications for the use of ECMO. Outcome measures should include survival, quality of life and neurological status. **Extracorporeal membrane oxygenation for severe acute respiratory failure in adults. NICE interventional procedure guidance 391 (2011)** 1 Guidance 1.1 Evidence on the safety of extracorporeal membrane oxygenation (ECMO) for severe acute respiratory failure in adults is adequate but shows that there is a risk of serious side effects. Evidence on its efficacy is inadequate to draw firm conclusions: data from the recent CESAR (Conventional ventilation or extracorporeal membrane oxygenation for severe adult respiratory failure) trial were difficult to interpret because different management strategies were applied among many different hospitals in the control group and a single centre was

	used for the ECMO treatment group. Therefore this procedure should only be used with special arrangements for clinical governance, consent and research. 1.2 Clinicians wishing to undertake ECMO for severe acute respiratory failure in adults should take the following actions. •Inform the clinical governance leads in their Trusts. •Whenever possible, ensure that patients and their carers understand the uncertainty about the procedure's efficacy and its risks and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/IPG391/publicinfo). 1.3 Extracorporeal membrane oxygenation for severe acute respiratory failure in adults should only be carried out by clinical teams with specific training and expertise in the procedure. 1.4 Clinicians are encouraged to submit data on all adults undergoing ECMO for severe acute respiratory failure to the international Extracorporeal Life Support Organization register (www.elso.med.umich.edu). 1.5 NICE encourages further research into the use of innovative technologies for the management of severe acute respiratory failure, and may review this guidance on publication of further evidence. **Extracorporeal membrane oxygenation in post neonatal children. NICE interventional procedure guidance 038 (2004)** 1 Guidance 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.

NICE guidelines	**Pneumonia: Diagnosis and management of community- and hospital-acquired pneumonia in adults. NICE clinical guideline 191 (2014)** 1.1 Presentation with lower respiratory tract infection 1.1.1 For people presenting with symptoms of lower respiratory tract infection in primary care, consider a point of care C‑reactive protein test if after clinical assessment a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed. Use the results of the C‑reactive protein test to guide antibiotic prescribing in people without a clinical diagnosis of pneumonia as follows: •Do not routinely offer antibiotic therapy if the C‑reactive protein concentration is less than 20 mg/litre. •Consider a delayed antibiotic prescription (a prescription for use at a later date if symptoms worsen) if the C‑reactive protein concentration is between 20 mg/litre and 100 mg/litre. •Offer antibiotic therapy if the C‑reactive protein concentration is greater than 100 mg/litre. 1.2 Community-acquired pneumonia Timely diagnosis and treatment 1.2.8 Put in place processes to allow diagnosis (including X‑rays) and treatment of community‑acquired pneumonia within 4 hours of presentation to hospital. 1.2.9 Offer antibiotic therapy as soon as possible after diagnosis, and certainly within 4 hours to all patients with community‑acquired pneumonia who are admitted to hospital. 1.3 Hospital-acquired pneumonia Antibiotic therapy 1.3.1 Offer antibiotic therapy as soon as possible after diagnosis, and certainly within 4 hours, to patients with hospital-acquired pneumonia. 1.3.2 Choose antibiotic therapy in accordance with local hospital policy (which should take into account knowledge of local microbial pathogens) and clinical circumstances for

	patients with hospital-acquired pneumonia. 1.3.3 Consider a 5- to 10-day course of antibiotic therapy for patients with hospital-acquired pneumonia.

Appendix C: Literature search for extracorporeal carbon dioxide removal for acute respiratory failure

Below is the strategy used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

Database: Ovid MEDLINE(R) 1946 to July Week 5 2015

Search Strategy:

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1 extracorporeal membrane oxygenation/

2 ECMO.tw.

3 oxygenators, membrane/

4 respiration, artificial/

5 (extracorp$ adj3 (circulat$ or ventilat$ or membran$ oxygenat$ or carbon$)).tw.

6 (lung adj3 assist$).tw.

7 (CO2 adj3 remov$).tw.

8 (carbon adj3 dioxide adj3 remov$).tw.

9 (protect$ adj3 ventilat$).tw.

10 or/1-9

11 (arterioven$ or arterio-ven$).tw.

12 (venoven$ or veno-ven$).tw.

13 AVCO2R.tw.

14 ECCO2R.tw.

15 PECLA.tw.

16 VVCO2R.tw.

17 AVECCO2R.tw.

18 novalung$.tw.

19 ALung.mp.

20 iLA.mp.

21 Respiratory Dialysis System.mp.

22 respiratory dialysis.mp.

23 Hemolung RAS.tw.

24 hemolung.mp.

25 iLA Membrane Ventilator.mp.

26 Respiratory Assist System.mp.

27 or/11-26

28 10 and 27

29 Animals/ not Humans/

30 28 not 29

31 limit 30 to english language

32 limit 31 to yr="2011 - 2015"