TITLE: Extracorporeal Membrane Oxygenation for Acute Respiratory Failure: A Review of the Clinical Effectiveness and Guidelines

DATE: 15 December 2014

CONTEXT AND POLICY ISSUES

Respiratory failure can be a life threatening condition. It can be either hypoxemic (i.e. inadequate blood oxygenation) or hypercapnic (i.e excess of circulating carbon dioxide), or a combination of both types of gas exchange abnormalities.[1] It is one of the most common causes leading to patients being admitted to the intensive care unit (ICU).[2] Respiratory failure may occur due to various reasons such as pneumonia, chronic obstructive pulmonary disease, acute respiratory distress syndrome, injury, drug overdose, and smoke inhalation. Treatment for respiratory failure depends on whether the condition is acute or chronic and on disease severity. It also depends on the underlying cause. Standard forms of treatment include mechanical ventilation, oxygen supplementation, and medication. In addition, there are more sophisticated and complex procedures such as extracorporeal membrane oxygenation (ECMO). It is also referred to as extracorporeal life support (ECLS).

Since the 1980s, extracorporeal membrane oxygenation (ECMO) has been proposed as an approach for achieving recovery of pulmonary function in patients with severe acute respiratory failure.[3] However, early studies demonstrated poor results and an unfavourable risk-benefit ratio. With technological advances and the severe acute respiratory distress syndrome that characterized the 2009 influenza A(H1N1) pandemic there was resurgence of interest in the use of ECMO to support the respiratory system.[4] The ECMO system consists of an oxygenator and a pump and allows blood to be drained from the native vascular system, circulated outside of the body and then returned into the circulation via a an arterial or venous route.[5-7] During ECMO, oxygen is added and carbon dioxide is removed from the blood.[6,8] There are primarily two types of ECMO depending on the route of access: venovenous ECMO (VV ECMO) and arterialvenous ECMO (VA ECMO).[7] ECMO is a complex procedure and requires a multidisciplinary team. It is an invasive procedure with inherent complications associated with it. Complications associated with ECMO use include bleeding, pneumonia or sepsis, and renal failure.[9,10]

The purpose of this report is to review the available evidence on clinical effectiveness of ECMO compared to other modalities for patients with acute respiratory failure and in addition to review the evidence based guidelines on use of ECMO for patients with acute respiratory failure.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of extracorporeal membrane oxygenation for patients with acute respiratory failure?

2. What are the evidence-based guidelines regarding the use of extracorporeal membrane oxygenation for patients with acute respiratory failure?

KEY FINDINGS

Study results are inconsistent and it appears that there is no clear mortality benefit with ECMO compared with mechanical ventilation or standard care without the use of ECMO in patients with acute respiratory failure. There appeared to be a statistically significant mortality benefit with venovenous ECMO, when only the three good-quality studies comparing venovenous ECMO with mechanical ventilation, were considered. Bleeding appeared to be statistically significantly higher with ECMO compared to mechanical ventilation. However, little information was available on other adverse events hence it is difficult to judge the risk/benefit ratio of ECMO use.

One evidence-based guidance document recommended that for adults with acute respiratory failure undergoing ECMO, the procedure should be undertaken by clinical teams with specific training and expertise in the procedure. One evidence-based consensus conference report on acute respiratory distress syndrome recommended that initiating of ECMO must be based on a multidisciplinary decision making, weaning from ECMO should be determined based on daily checking of criteria indicative of recovery, and an intensive care unit conducting ECMO should have a team with specific skills.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 11), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 1990 and November 17, 2014.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved. These potentially relevant articles were divided among two reviewers and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Patients in the ICU with acute respiratory failure
Intervention	Extracorporeal membrane oxygenation (may also be called extracorporeal life support)
Comparator	Any
Outcomes	Clinical effectiveness (recovery, survival, bridge to other therapy, quality of life) Safety Evidence-based guidelines (including conduct of ECMO and patient management [including initiation, weaning, ventilation and anticoagulation], personnel required, contraindications/prioritization, and quality assurance)
Study Designs	Health technology assessment (HTA), systematic review (SR) and meta-analysis (MA), randomized controlled trial (RCT). Non-randomized studies to be included only if few HTA/SR/MA/RCTs available

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria, if they were duplicate publications, or were published prior to 1990. Studies on neonates were excluded. Studies without matched controls and non-comparative studies such as case series and case reports were excluded, as these studies are generally considered to be of low quality and observed outcomes are difficult to attribute to the intervention being used. Studies that were included in a selected systematic review were excluded. Systematic reviews that included studies which were already included in a more recent or comprehensive review were excluded.

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on an assessment tool appropriate for the particular study design. The AMSTAR checklist[11] was used for systematic reviews; the Downs and Black checklist[12] for non-randomized studies; and the AGREE checklist[13] for guidelines.

For the critical appraisal, a numeric score was not calculated. Instead, the strength and limitations of the study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 939 citations were identified in the literature search. Following screening of titles and abstracts, 907 citations were excluded and 32 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, 27 publications were excluded for various reasons, while six publications met the inclusion criteria and were included in this report. These six publications comprised of one systematic review,[14] three non-randomized

studies,[9,15,16] one evidence-based guidance report,[17] and one evidence-based consensus conference report.[3] Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references that did not meet the inclusion criteria but may be of potential interest are included in Appendix 2.

Summary of Study Characteristics

Characteristics of the included systematic review and non-randomized studies are summarized below and details are provided in Appendix 3. Both terms, ECMO or ECLS, was used in the included articles and are used in this report to reflect the terminology as it was used by the authors of those articles.

Systematic review

One relevant systematic review[14] comparing ECLS (ECMO or extracorporeal carbon dioxide removal [$ECCO_2R$]) with mechanical ventilation in patients with acute respiratory failure (ARF) was identified. It was published in 2014 from Canada. It included 10 studies, of which four were RCTs and six were non-randomized studies, and were published between 1979 and 2013 from USA and Europe. The total number of patients was 1,248. The total number of patients in the individual studies varied between 18 and 196.The mean age of the patients in these studies varied between 32 years and 52 years. The cause of ARF was H1N1 infection in three studies and pneumonia and other conditions such as sepsis, trauma, and transfusion in seven studies. VV ECMO was used in five studies, both VV ECMO and VA ECMO were used in two studies, VA ECMO was used in one study, and ECCO2R was used in two studies. Outcomes reported included mortality, length of stay (LOS) in the intensive care unit (ICU), LOS in-hospital, and adverse events.

Non-randomized studies

Three relevant non-randomized studies[9,15,16] were identified. Two studies[9,15] were published from the USA in 2014 and 1996, and one study[16] was published from Germany in 2013. The total number of patients in the studies ranged between 34 and 116. One study[9] included adult trauma patients with ARF, one study[16] included both pediatric and adult H1N1 pneumonia patients with acute respiratory distress syndrome (ARDS) and one study[15] included pediatric patients with ARF. All three studies reported on survival or mortality. Two studies[9,16] reported on length of stay (LOS) in ICU and in-hospital and only one study[9] reported on complications.

ECMO guidelines

One evidence-based guidance document[17] on general recommendations for ECMO use in severe acute respiratory failure was identified. It was published from the United Kingdom (UK) in 2011. It is an interventional procedure guidance prepared by the National Institute for Health and Care Excellence (NICE)

In addition, an evidence-based consensus conference report[3] with recommendations for ECLS use in patients with ARDS, was identified. The Société de Réanimation de Langue Française (SRLF) held a Consensus Conference on ECLS and produced the above mentioned report. It was published from France in 2014.

Summary of Critical Appraisal

Strengths and limitations of the systematic review and individual non-randomized studies are provided in Appendix 4.

Systematic review

The systematic review[14] was overall well conducted. The objectives, inclusion and exclusion criteria were described. A comprehensive literature search using multiple databases was conducted. Article selection and data extraction were done in duplicate. Quality assessments of individual studies were performed and the risk of bias was reported to be low in six studies and high in four studies. Methods used to combine findings from individual studies were appropriate. Predefined subgroup analyses were conducted. Sensitivity analyses were also conducted. Publication bias was explored and there was no evidence of significant publication bias. Few procedural details of ECLS used in the individual studies were provided. A list of excluded studies was not provided.

Non-randomized studies

In all three non-randomized studies[9,15,16] the objectives were clearly stated. However, overall the studies were of limited quality. Due to the non-randomized nature of the studies, there is potential for selection bias resulting in groups not being truly comparable and this could impact the observed outcomes either negatively or positively. Although matching of groups was done, there may be unmeasured covariates which could introduce bias and confounding. The number of patients in each treatment group was not large, varying between 17 and 61. Sample size calculations were not conducted, so it is unclear whether the studies had a sufficient size to detect clinically important effects. Study findings were based on registry data hence they were dependent on the extent and quality of data recorded. It was unclear if the criteria for initiation of ECLS/ECMO were uniform across all centres in each study.

ECMO guidelines

One evidence-based guidance document[17] was identified. It was a brief document and did not contain enough information to conduct a formal critical appraisal. However the guidance document was prepared using processes described in the NICE Interventional Procedures Programme methods guide.[18] These processes include identification, selection, and collation of appropriate evidence; assessment of evidence and consideration of the evidence and commentary (including specialist advice and lay input) by a committee. The committee in making the recommendations for ECMO considered evidence of efficacy and safety from published literature and specialist advice.

One evidence-based consensus conference report was identified. This report was the result of a consensus conference report organized by SRLF to determine conditions and procedures for use of ECLS. The report contained an extensive list of recommendations. A systematic review was undertaken to collect relevant evidence and the Grading of Recommendations Assessments, Development and Evaluation (GRADE) was used. The formulation of the recommendations was based on the available evidence and the expert panel's analysis of the risk/benefit ratio. The areas of expertise of the panel that formulated the recommendations were

not stated. It was unclear if patient input was sought or if cost implications were considered. Further details are provided in Appendix 4.

Summary of Findings

The overall findings from the systematic review and non-randomized studies are summarized below and details are available in Appendix 5.

What is the clinical effectiveness of extracorporeal membrane oxygenation for patients with acute respiratory failure?

Systematic review

The systematic review[14] showed that when all 10 studies (i.e. including both RCTs and non-randomized studies) were pooled there was no statistically significant difference in in-hospital mortality for ECLS compared with mechanical ventilation (relative risk [RR] 95% confidence interval [95% CI] 1.02 [0.79 to 1.33]). However, on limiting the pooling to the three good quality studies (RCT and quasi-RCT), with low risk of bias, there was a statistically significant lower risk of in-hospital mortality with VV ECMO compared with mechanical ventilation (RR [95% CI] 0.64 [0.51 to 0.79]). Also, on pooling the three studies on patients with H1N1 associated ARDS, there was a statistically significant lower risk of in-hospital mortality with ECLS compared with mechanical ventilation (RR [95% CI] 0.62 [0.45 to 0.84]). Of these three studies, two studies had low risk of bias and one study had high risk of bias. There was no statistically significant difference between ECLS and mechanical ventilation in most of the other subgroups. Few of the studies reported on adverse events. Bleeding was reported in five studies and was statistically significantly higher with ECLS compared with mechanical ventilation (RR [95% CI] 11.44 [3.11 to 42.06]).

Non-randomized studies

Mortality with ECLS was statistically significantly lower than mechanical ventilation or supportive care without ECMO in two studies and statistically significantly higher in one study (Table 2). LOS in the ICU and hemorrhagic complications were numerically higher in the ECLS group but were not statistically significantly different between the two groups.

Table 2: Outcomes with ECLS/ ECMO versus conventional (mechanical ventilation [MV] or "no ECMO")

Outcome	Effect		
	Guirand[9]	Weber-Carsten[16]	Green[15]
Survival (Kaplan Meier survival curve)	64.7% vs 23.5% P = 0.01	NR	NR
Mortality	NR	54% vs 20% P <0.001	26.4% vs 47.2% P <0.01
LOS (days) in ICU	38.5 vs 18.2 P = 0.064	33 vs 27 P = 0.094	NR
LOS (days) in-hospital	45.9 vs 21.1 P = 0.04	39 vs 32 P = 0.582	NR
Any complications	94% vs 94% P = 1	NR	NR

Outcome	Effect		
	Guirand[9]	Weber-Carsten[16]	Green[15]
Hemorrhagic complications	18% vs 0% P = 0.227	NR	NR
LOS = length of stay; NR = not reported; vs = versus			

What are the evidence-based guidelines regarding the use of extracorporeal membrane oxygenation for patients with acute respiratory failure?

One evidence-based guidance document[17] recommended that for adults with severe acute respiratory failure undergoing ECMO, the procedure should be undertaken by clinical teams with specific training and expertise in the procedure.

The consensus conference report[3] has an extensive list of recommendations for the use of ECMO in patients with ARDS. Some key recommendations with respect to implementation and patient management are presented in this report. The recommendations state that the use of ECMO should be based on a multidisciplinary decision and for implementation and management of ECMO medical and nursing staff trained in setting up the circuit are required. At least 10 ECMO procedures are recommended to be conducted annually to maintain the ECMO skills of an intensive care department. ECMO is contraindicated for cases where anticoagulation treatment is not possible. The conference report further states that daily checking of criteria indicative of recovery from respiratory or cardiorespiratory failure is required to determine initiation of weaning from ECMO. Further details are provided in Appendix 6.

Limitations

Comparison across studies was difficult as there was considerable variation in study population, setting, available technologies and management strategies.

Although in the non-randomized studies efforts were made to match groups to minimize selection bias, hidden bias may still remain due to unmeasured covariates. Two non-randomised studies had a “no ECMO” comparative group but what “no ECMO” consisted of was not described.

Not all studies reported all outcomes. Reporting and definitions of adverse events were often absent and even when present, were heterogeneous among the studies.

Due to paucity of data as well as inconsistencies in the results, definitive conclusions are not possible.

None of the studies were conducted in a Canada hence results may not be applicable to a Canadian setting. There was paucity of evidence-based guidelines on the use of ECMO for respiratory failure.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Study results are inconsistent and it appears that there is no clear mortality benefit with ECMO compared with mechanical ventilation or “no ECMO”, in patients with acute respiratory failure. There appeared to be a statistically significant mortality benefit with VV ECMO when only the three good quality studies comparing VV ECMO with mechanical ventilation were considered.

Bleeding appeared to be statistically significantly higher with ECMO compared to mechanical ventilation. However, little information was available on other adverse events and complications, hence it is difficult to judge the risk/benefit ratio of ECMO use.

Results from the ongoing, multi centre RCT, EOLIA[19] which is examining the use of ECMO compared with conventional mechanical ventilation in patients with ARDS may provide further insights. The estimated study completion date was reported to be January 2015.

One evidence-based guidance document, recommended that for adults with acute respiratory failure undergoing ECMO, the procedure should be undertaken by clinical teams with specific training and expertise in the procedure. One evidence-based consensus conference report on acute respiratory distress syndrome recommended that initiating of ECMO must be based on a multidisciplinary decision making, weaning from ECMO should be determined based on daily checking of criteria indicative of recovery, and an intensive care unit conducting ECMO should have a team with specific skills.

A registry of ECMO use is being maintained by the Extracorporeal Life Support Organization (ELSO). It is an international consortium of health care professionals and scientists and is involved in the development and evaluation of novel therapies for support of failing organ systems and its primary mission is to maintain a registry of, at least, use of ECMO in active ELSO centers.[20] The data are used for the purpose of quality assurance and decision making.[21] Registry data showed that with the use of ECMO, the survival to discharge or transfer, were respectively 57% and 56% in pediatric and adult patients with respiratory conditions.[22]

ECMO is an invasive procedure and as such is associated with inherent adverse events. It is a complex procedure and guidelines recommend a multidisciplinary team with appropriate training and expertise.

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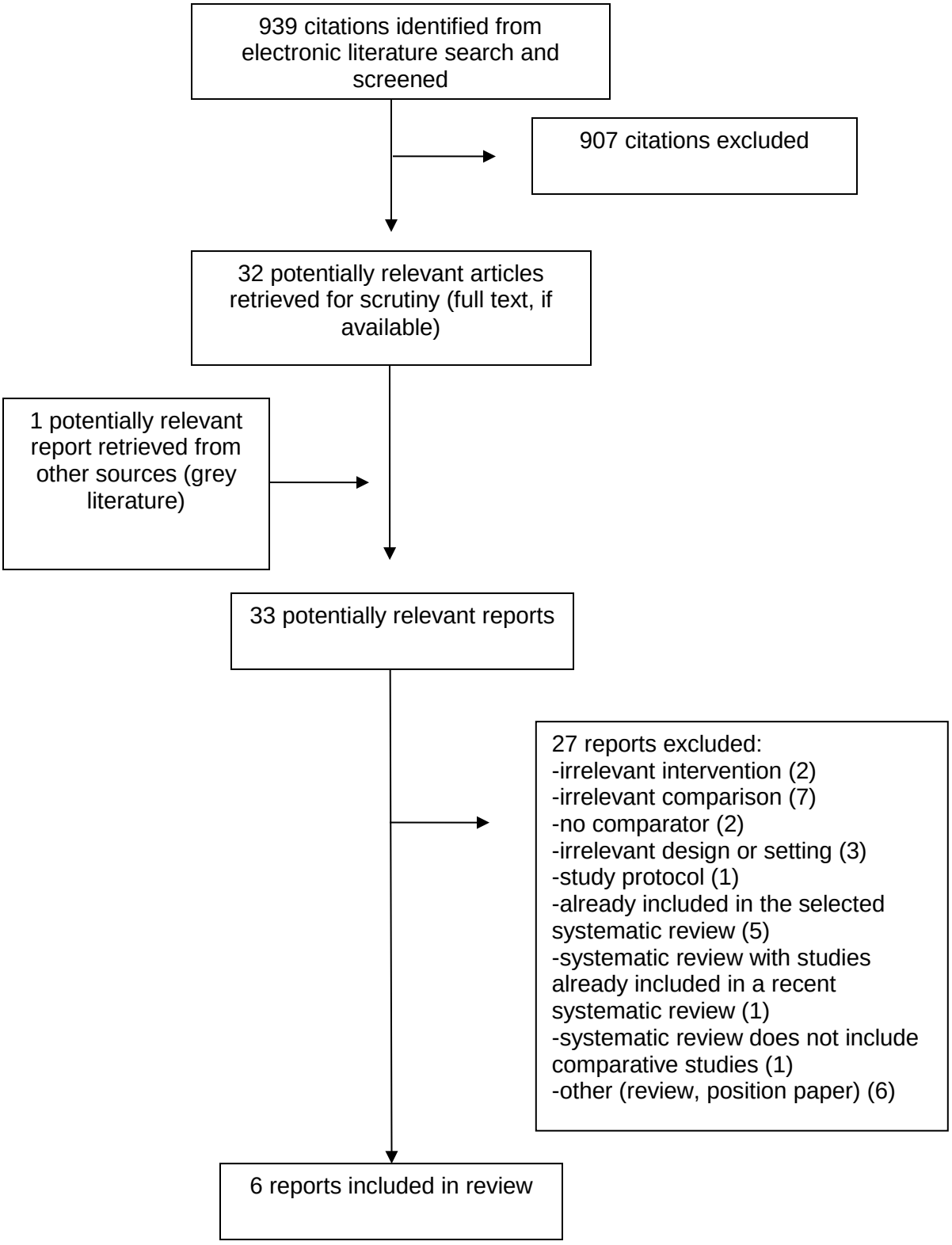
ABBREVIATIONS

ARDS	acute respiratory distress syndrome
ARF	acute respiratory failure
CI	confidence interval
$ECCOR_2$	extracorporeal carbon dioxide removal
ECLS	extracorporeal life support
ECMO	extracorporeal membrane oxygenation
ELSO	extracorporeal life support organization
ICU	intensive care unit
LOS	length of stay
MV	mechanical ventilation
NICE	National Institute for Health and Care Excellence
NR	not reported
OR	odds ratio
RCT	randomized controlled trial
RR	relative risk
SD	standard deviation
SOFA	Sequential organ failure assessment
SRLF	Société de Réanimation de Langue Française
VA	venoarterial
vs	versus
VV	venovenous

APPENDIX 1: Selection of Included Studies



APPENDIX 2: References of potential interest

HTA/SR with studies already included in a more recent SR:

Zampieri FG, Mendes PV, Ranzani OT, Taniguchi LU, Pontes Azevedo LC, Vieira Costa EL, et al. Extracorporeal membrane oxygenation for severe respiratory failure in adult patients: a systematic review and meta-analysis of current evidence. J Crit Care. 2013 Dec;28(6):998-1005.

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APPENDIX 3: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size (n)	Intervention	Outcomes Measured
Systematic review				
Munshi,[14] 2014, Canada	SR (10 studies [4 RCTs + 6 NRSs). MA conducted with all 10 studies Studies published between 1979 and 2013 from USA and Europe	Adult patients with acute respiratory failure. N = 1,248 Age (years) (mean): 32 to 52 % Male: NR	ECLS (ECMO or $ECCO_2R$) versus mechanical ventilation. (8 studies used VV ECMO or VA ECMO and two studies used $ECCOR_2$)	Mortality, LOS in ICU, Adverse events
Non-randomized studies				
Guirand,[9] 2014, USA	Retrospective study: review of ECLS registry, multicentre. Jan 2001 to December 2009	Adult trauma patients with acute hypoxemic respiratory failure N = 34 (=17+17) (propensity score matched) Age(year) (mean ± SD): 30.9 ± 11.4 in ECLS, 34.1 ± 10.7 in MV. % Male: 71 in ECLS, 88 in MV	ECLS versus mechanical ventilation	Survival, LOS in ICU and in hospital, Complications
Weber-Carstens,[16] 2013, Germany	Web-based data from German ARDS Network's registry (data from several hospitals)	H1N1 pneumonia patients with ARDS N = 116 (= 61 ECMO + 55 no ECMO) Age (years) (mean [range]): 42 [13 to 66] in ECMO, 43 [5 to 65] in no ECMO. % Male:	ECMO versus no ECMO	Mortality, LOS in ICU, LOS in hospital

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size (n)	Intervention	Outcomes Measured
		55.7% in ECMO, 58.2% in no ECMO		
Green,[15] 1996, USA	Retrospective study using Acute Pediatric Respiratory Failure database, multicenter	Pediatric patients with acute respiratory failure. N = 82 (=29 ECMO + 53 no ECMO) (matched for diagnosis and severity) Age: NR % Male: NR	ECMO versus no ECMO	Mortality
ECLS = extracorporeal life support; ECMO = extracorporeal membrane oxygenation, LOS = length of stay; MV = mechanical ventilation; NR = not reported;				

APPENDIX 4: Summary of Study Strengths and Limitations

First Author, Publication Year, Country	Strengths	Limitations
Systematic review		
Munshi,[14] 2014, Canada	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases searched, from inception to October 2013 • Study selection described and flow chart presented. • List of included studies provided • Article selection and data extraction were done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted • Methods used to combine the findings of studies were appropriate. Subgroup and sensitivity analyses conducted were decided a priori • Publication bias was explored and there was no evidence of significant publication bias. • Authors' disclosures were reported	• List of excluded studies not provided • Procedural details of ECLS used in the individual studies were limited
Non-randomized studies		
Guirand,[9] 2014, USA	• Objectives were clearly stated. • Inclusion and exclusion criteria were stated but lacked detail. • Patient characteristics, interventions and outcomes were described. • Groups matched by propensity score • P values were provided. • Conflict of interest was reported and there appeared to be none	• Non-randomized, retrospective hence prone to bias • Though propensity score matched analysis was undertaken there is a possibility of unmeasured covariates not being considered which could impact results • Sample size calculations were not reported. • Unclear if the criteria for initiation of ECLS were uniform across all centres. • Generalizability is limited as data pertain to a few centres in California, USA.
Weber-Carstens,[16] 2013, Germany	• Objectives were clearly stated. • Inclusion criteria were stated. • Patient characteristics were described.	• Non-randomized hence prone to bias • Exclusion criteria were not stated. • Propensity score matching was

First Author, Publication Year, Country	Strengths	Limitations
	• P values were provided. • Generalizable to the German population as several hospitals provided data in the registry. • Conflict of interest was reported; it is unclear to what extent this could impact results	not conducted. However, the various patient characteristics appeared to be not statistically significantly different in the two groups, as indicated by P-values. • Details of interventions were not described. It was unclear what comprised “no ECMO” • Unclear if the criteria for initiation of ECLS were uniform across all centres. • Sample size calculations were not reported • Contributing data to the registry was on a voluntary basis. In addition due to time and resource restrictions only data on a few variables could be collected. Hence unlikely to be comprehensive.
Green,[15] 1996, USA	• Objectives were clearly stated. • Inclusion and exclusion criteria were stated but lacked detail. • Groups were matched but details not provided • To some extent may be generalizable as data in the database came from several centres	• Non-randomized, retrospective hence prone to bias • Patient characteristics, interventions and outcomes details were not provided. • Method of matching groups was not presented. • Sample size calculations were not reported • The different ECMO centres did not use uniform criteria for initiation of ECMO. • Conflict of interest was not reported
Guideline		
Richard,[3] 2014, France	• The scope and purpose were clearly stated. • The recommendations development group comprised mostly of individuals from the hospitals but details of areas of expertise were not provided. • The methods used for the development of the guidelines were rigorous. • Recommendations were clear • Conflicts of interest of the recommendation development	• Unclear if patient input was sought • Cost implications or organizational barriers were not discussed.

First Author, Publication Year, Country	Strengths	Limitations
	team members were stated. Three members were involved with the EOLIA trial on ECMO and the remaining members were stated to have no conflicts of interest	

APPENDIX 5: Main Study Findings and Authors' Conclusions

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td colspan="2">Systematic review</td></tr>
<tr><td>Munshi,[14] 2014, Canada</td><td>
Main Findings:
Outcomes with ECLS compared to mechanical ventilation
<table>
<tr><th>Studies</th><th>No. of studies</th><th>No. of patients</th><th>Evidence assessment (GRADE)</th><th>RR (95% CI)</th><th>P value</th></tr>
<tr><td>In hospital mortality</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>All studies</td><td>10</td><td>1,248</td><td>M</td><td>1.02 (0.79 to 1.33)</td><td>0.87</td></tr>
<tr><td>RCT, quasi- RCT[a]</td><td>6</td><td>713</td><td>M-H</td><td>0.80 (0.61 to 1.04)</td><td>0.09</td></tr>
<tr><td>RCT, quasi- RCT (with VV ECMO)</td><td>3</td><td>504</td><td>M-H</td><td>0.64 (0.51 to 0.79)</td><td><0.0001</td></tr>
<tr><td>RCT, quasi- RCT[a] (with lung protective ventilation)</td><td>4</td><td>583</td><td>M-H</td><td>0.65 (0.53 to 0.80)</td><td><0.0001</td></tr>
<tr><td>HINI associated ARDS</td><td>3</td><td>364</td><td>M-H</td><td>0.62 (0.45 to 0.84)</td><td>0.002</td></tr>
<tr><td>Lung protective ventilation</td><td>6</td><td>773</td><td>M-H</td><td>0.82 (0.57 to 1.18)</td><td>0.29</td></tr>
<tr><td>>50% ARDS due to pneumonia</td><td>8</td><td>1,069</td><td>M</td><td>0.91 (0.72 to 1.14)</td><td>0.40</td></tr>
<tr><td>Age < 40 y</td><td>5</td><td>737</td><td>M</td><td>1.08 (0.64 to 1.82)</td><td>0.77</td></tr>
<tr><td>Very severe ARDS (average PF < 50)</td><td>2</td><td>168</td><td>M</td><td>0.63 (0.31 to 1.30)</td><td>0.21</td></tr>
<tr><td>VV ECLS</td><td>7</td><td>1,061</td><td>M</td><td>1.03 (0.98 to 1.57)</td><td>0.87</td></tr>
<tr><td>Length of stay</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>ICU</td><td>6</td><td>162</td><td>L</td><td>8.65 (29.72 to 27.01)</td><td>0.36</td></tr>
<tr><td>Adverse events</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Bleeding</td><td>5</td><td>429</td><td>L-M</td><td>11.44 (3.11 to 42.06)</td><td>0.0002</td></tr>
<tr><td>Barotrauma</td><td>2</td><td>162</td><td>M</td><td>1.46 (1.21 to 1.76)</td><td><0.0001</td></tr>
<tr><td>Sepsis</td><td>3</td><td>333</td><td>L-M</td><td>1.63 (0.82 to 3.26)</td><td>0.16</td></tr>
<tr><td colspan="6">[a]quasi- RCT: studies with matched control based on GenMatch matching</td></tr>
</table>
Authors' Conclusion:
"ECLS was not associated with a mortality benefit in patients with acute respiratory failure. However, a significant mortality benefit was seen when restricted to higher-quality studies of venovenous ECLS. Patients with H1N1–acute respiratory distress syndrome represent a subgroup that may benefit from ECLS. Future studies are needed to confirm the efficacy of ECLS as well as the optimal configuration, indications, and timing for adult patients with respiratory
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>failure." P.802</td></tr>
<tr><td colspan="2">Non-randomized studies</td></tr>
<tr><td>Guirand,[9] 2014, USA</td><td>Main Findings:
Outcomes with veno venous extracorporeal life support (ECLS) compared with mechanical ventilation (MV)
<table>
<tr><th>Outcome</th><th>ECLS
N = 17</th><th>MV
N = 17</th><th>P value</th></tr>
<tr><td>Survival (Kaplan Meier estimate, up to 60 days) (%)</td><td>64.7</td><td>23.5</td><td>0.01</td></tr>
<tr><td>LOS (days) in ICU, mean ± SD</td><td>38.5 ± 36.9</td><td>18.2 ± 22.9</td><td>0.064</td></tr>
<tr><td>LOS (days) in hospital, mean ± SD</td><td>45.9 ± 41.6</td><td>21.1 ± 23.6</td><td>0.040</td></tr>
<tr><td>Any complication, n (%)</td><td>16 (94)</td><td>16 (94)</td><td></td></tr>
<tr><td>Hemorrhagic complication, n (%)</td><td>3 (18)</td><td>0</td><td>0.227</td></tr>
<tr><td>Pulmonary complication, n (%)</td><td>0</td><td>3 (18)</td><td>0.227</td></tr>
<tr><td>Renal complication, n (%)</td><td>16 (94)</td><td>16 (94)</td><td></td></tr>
</table>
Authors' Conclusion:
"VVECLS is independently associated with survival in adult trauma patients with AHRF. ECLS should be considered in trauma patients with AHRF when conventional therapies prove ineffective; if ECLS is not readily available, transfer to an ECLS center should be pursued." P. 1275</td></tr>
<tr><td>Weber-Carstens,[16] 2013, Germany</td><td>Main Findings:
Outcome with extracorporeal membrane oxygenation (ECMO) compared with no ECMO)
<table>
<tr><th>Outcome</th><th>ECMO
N = 61</th><th>No ECMO
N = 55</th><th>P value</th></tr>
<tr><td>Mortality n (%)</td><td>33 (54)</td><td>11 (20)</td><td><0.001</td></tr>
<tr><td>LOS (days) in ICU, mean [95% CI]</td><td>33 [27 to 39]</td><td>27 [20 to 34]</td><td>0.094</td></tr>
<tr><td>LOS (days) in hospital, mean [95% CI]</td><td>39 [31 to 47]</td><td>32 [26 to37]</td><td>0.582</td></tr>
</table>
Authors' Conclusion:
"Even persons without any other accompanying disease developed life-threatening respiratory failure as a result of H1N1 infection, and many of these patients needed ECMO. This study reveals for the first time that the mortality with of H1N1 infection in Germany is comparable to that in other countries. H1N1 patients with acute respiratory failure had a worse outcome if they also had serious accompanying disease." P.543</td></tr>
<tr><td>Green,[15] USA, 1996</td><td>Main Findings:
Outcome with extracorporeal membrane oxygenation (ECMO) compared with no ECMO)
<table>
<tr><th>Outcome</th><th>ECMO
N = 29</th><th>No ECMO
N = 53</th><th>P value</th></tr>
<tr><td>Mortality (%)</td><td>26.4</td><td>47.2</td><td><0.01</td></tr>
</table></td></tr>
</table>

First Author, Publication Year, Country	Main Findings and Authors' Conclusion
	Multivariate analysis showed that survival was not independently associated with care in an ECMO hospital (P= 0.18) or use of high frequency ventilation (P = 0.99)
	Authors' Conclusion: "The use of ECMO was associated with an improved survival in pediatric patients with respiratory failure. The lack of association of outcome with treatment in the ECMO-capable hospital or with another tertiary technology (i.e., high frequency ventilation) suggests that ECMO itself was responsible for the improved outcome. Further studies of this procedure are warranted but require broad-based multi-institutional participation to provide sufficient statistical power and sensitivity to demonstrate efficacy " p. 323
ARDS = acute respiratory distress syndrome; CI = confidence interval; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; L = low; L-M = low-moderate; LOS = length of stay; M = moderate; M-H = moderate-high; VV = venovenous; y = year	

APPENDIX 6: Guidelines and Recommendations

Guideline Society, Country, Author, Year	Recommendations
NICE[17], UK, 2011	"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. 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. Clinicians are encouraged to submit data on all adults undergoing ECMO for severe acute respiratory failure to the international Extracorporeal Life Support Organization register." P.3
SRLF- Consensus Conference report, France, Richard,[3] 2014,	"The indications for ECMO must be based on a collective and multidisciplinary decision, noted in the medical records" p. 2 of 16 "The impossibility of using anticoagulation treatment is a classic contraindication to ECMO" p. 3 of 16 "The risk-benefit ratio of ECMO in ARDS should be considered unfavorable in cases of 1) hemorrhagic or potentially hemorrhagic intracranial lesions, 2) coma following cardiac arrest, 3) ARDS in which mechanical ventilation exceeds seven days, 4) severe immunosuppression, 5) multiorgan failure syndrome (SOFA > 15)" p. 3 of 16 "The setting up, priming and daily management of ECMO should be formalized, and safety check-lists should be used" p. 3 of 16 "For the implementation and management of ECMO, medical and nursing personnel trained in setting up the circuit should be present" p. 3 of 16 "The procedure for weaning from ECMO comprises daily checking of criteria indicative of recovery from respiratory or cardiorespiratory failure" p.4 of 16 "On weaning from ECMO, the absence of acute cor pulmonale should be confirmed" p.4 of 16 "The decision to discontinue ECMO is based on the results of formalized weaning over several hours" p.4 of 16 "for quality and safety of care, a structured national organization is indispensable for optimal management of ARDS patients requiring ECMO" p.4 of 16 "An intensive care department able to perform ECMO in ARDS must: 1) acquire

Guideline Society, Country, Author, Year	Recommendations
	and maintain specific skills, 2) have at least two trained physicians in its medical personnel, 3) have access to emergency vascular and thoracic surgery, 4) implement a regular training program for paramedical staff, 5) formalize the indications and ensure their traceability, 6) enter data in the severe ARDS registry, and 7) at least once a year during morbidity-mortality reviews analyze all the medical records of patients treated with ECMO" p.4 of 16 "Maintenance of the ECMO skills of an intensive care department may be compromised if there are fewer than ten indications for ECMO annually"
ARDS = acute respiratory distress syndrome; NICE = National Institute of Health and Care Excellence; SOFA = Sequential Organ Failure Assessment ; SRLF = Société de Réanimation de Langue Française	