Evidence check

20 March 2020

Rapid evidence checks are based on a simplified review method and may not be entirely exhaustive, but aim to provide a balanced assessment of what is already known about a specific problem or issue. This brief has not been peer-reviewed and should not be a substitute for individual clinical judgement, nor is it an endorsed position of NSW Health.

ECMO and COVID-19

Rapid review question

Question 1: What evidence and expert advice is emerging regarding the use of ECMO for COVID-19 patients?

Question 2: What evidence is available about the use of ECMO in the context of emerging respiratory disease outbreaks?

In brief

- The World Health Organization currently recommends for patients with acute respiratory distress syndrome (ARDS), in settings with access to expertise in extracorporeal membrane oxygenation (ECMO), referral of patients who have refractory hypoxemia despite lung protective ventilation should be considered (WHO, 2020) (1)
- Data emerging from China show that among the 28 patients who received ECMO, there was a 50% case mortality, (14 died, 5 weaned successfully, and 9 were still on ECMO at the time of publication (2 March 2020)) (Xie et al, 2020) (2)
- We lack knowledge about incidence of complications, viral persistence or prognoses in different subsets of patients. If the mechanism of death in COVID-19 is shown to be septic shock or refractory multi-organ failure then ECMO is unlikely to be appropriate (Maclaren et al, 2020) (3) (3)
- There is some emerging evidence about factors associated with poorer outcomes which could be considered alongside established ECMO selection criteria (see ACI, 2020). These include older age and comorbidities (hypertension, diabetes or ischaemic heart disease) (Xie et al, 2020); lymphopaenia (Henry, 2020)(4)
- There is little evidence from previous ARDS / respiratory disease outbreaks that ECMO is beneficial.

Definitions

In late 2019, a novel coronavirus, now designated SARS-CoV-2, was identified as the cause of an outbreak of acute respiratory illness in Wuhan, China. the World Health Organization (WHO) designated the disease COVID-19 In February 2020; and characterised the outbreak as a pandemic in March 2020.

Background

A range of clinical syndromes are associated with COVID-19 (Appendix 1). Descriptive case series account of the COVID-19 pandemic are emerging from China (Wang, et al 2020; Wu et al, 2020) (5) and Italy (Grasselli et al, 2020) (6).

Acute respiratory distress syndrome (ARDS) is a major complication in patients with severe disease. In a study of 138 patients, ARDS developed in 20% after a median of eight days, and mechanical ventilation was implemented in 12.3% (Wang et al, 2020). Another study of 201 hospitalised patients with COVID-19 in Wuhan, 41% developed ARDS; Risk factors were age greater than 65 years, diabetes mellitus, and hypertension (Wu et al, 2020).(7)

While mortality among all infected patients is thought to be in the range of 0.5% to 4%, preliminary estimates are that among patients who require hospitalisation, mortality is between 5% and 15%; and for those who become critically ill, between 22% and 62% (Chen et al, 2020; Yang et al, 2020)(8, 9). The exact cause of death is unclear, with progressive hypoxia and multiorgan dysfunction being the presumed causes (Murthy et al 2020)(10). If the cause of death is refractory multi-organ failure then ECMO is of limited use (Maclaren et al, 2020)(3).

Methods

PubMed was search to identify the peer reviewed literature using the following search strings.

((Extracorporeal Membrane Oxygenation[Mesh] OR "Extracorporeal Membrane Oxygenation"[tiab] OR ECMO[tiab] OR "Extracorporeal Life Support"[tiab] OR ECLS[tiab]))

AND ((((("pandemics"[MeSH Terms]) OR (pandemic[Title/Abstract])) AND (respiratory[Title/Abstract])) OR ((2019-nCoV[title/abstract] or nCoV[title/abstract] or covid-19[title/abstract] or covid19[title/abstract] or "covid 19"[title/abstract] OR "coronavirus"[MeSH Terms] OR "coronavirus"[title/abstract])))

Supplementary searches in Google used the search string: ECMO and COVID-19

Inclusion criteria:

- ECMO in patients with COVID-19
- ECMO in pandemic
- Observation studies

Exclusion criteria:

- ECMO in non- pandemic / outbreak contexts
- No ECMO described
- Opinion papers

Results

Question 1: What evidence and expert advice is emerging regarding the use of ECMO for COVID-19 patients?

There is limited evidence about the use of ECMO in COVID-19 patients. According to WHO, patients with acute respiratory distress syndrome (ARDS), can be considered as candidates for ECMO (WHO, 2020). The CDC advises prompt implementation of recommended infection prevention and control measures and supportive management of complications, including advanced organ support if indicated.

Many experts counsel caution in instituting ECMO in the context of the COVID-19 pandemic (Maclaren et al, 2020(3)).

There is some emerging evidence about patient characteristics and outcomes from ECMO in the COVID-19 cohort (Table 1). However, there is insufficient evidence to formulate robust indication criteria.

Table 1: Studies and publications discussing ECMO and COVID-19, (search conducted 20 March 2020)

Study	Study design	Results
Xie et al 2020	Case series, China	Analysed data from 135 patients who died before Jan 30, 2019, in Wuhan city. Older age and male were common in non-surviving patients. More than 70% patients had one or more comorbidities. Hypertension (48.2%) was the most common comorbidity in non-surviving patients, followed by diabetes (26.7%) and ischemic heart disease (17.0%), similar to data reported by others. The study reported high mortality among patients who received ECMO: of 28 patients who received ECMO up to the present, 14 died, 5 weaned successfully, and 9 were still on ECMO at the time of publication (2 March 2020) . Lack of ventilators, fear of becoming infected during the intubation procedure, and unclear need for intubation were the main reasons for delaying invasive ventilation.
Wang et al, 2020	Retrospective observational study, China	Of 138 hospitalized patients with COVID-19, the median age was 56 years (interquartile range, 42-68; range, 22-92 years) and 75 (54.3%) were men. Thirty-six patients (26.1%) were transferred to the intensive care unit (ICU) because of complications, including acute respiratory distress syndrome (22 [61.1%]), arrhythmia (16 [44.4%]), and shock (11 [30.6%]). Of the 36 cases in the ICU, 4 (11.1%) received high-flow oxygen therapy, 15 (41.7%) received noninvasive ventilation, and 17 (47.2%) received invasive ventilation (4 were switched to extracorporeal membrane oxygenation). As of February 3, 47 patients (34.1%) were discharged and 6 died (overall mortality, 4.3%), but the remaining patients are still hospitalized. Among those discharged alive (n = 47), the median hospital stay was 10 days (IQR, 7.0-14.0).
Zhou et al, 2020	Multicentre cohort study, China	191 patients (135 from Jinyintan Hospital and 56 from Wuhan Pulmonary Hospital) were included in this study, of whom 137 were discharged and 54 died in hospital. Three patients received ECMO, all died.
Yang et al, 2020	Retrospective, observational study, China	Of 710 patients with SARS-CoV-2 pneumonia, 52 critically ill adult patients were included. 32 (61·5%) had died at 28 days. Compared with survivors, non-survivors were more likely to receive mechanical ventilation (30 [94%] patients *vs* 7 [35%] patients), either invasively or non-invasively.
Maclaren et al, 2020	Viewpoint	The role of ECMO in the management of COVID-19 is unclear at this point. It has been used in some patients in China but detailed information is unavailable. ECMO is not a therapy to be rushed to the frontline when all resources are stretched in a pandemic.
Murthy et al, 2020	Viewpoint	Management of severe COVID-19 is not different from management of most viral pneumonia causing respiratory failure. The principal feature of patients with severe disease is the development of ARDS: a syndrome characterized by acute onset of hypoxemic respiratory failure with bilateral infiltrates. Evidence-based treatment guidelines for ARDS should be followed, including conservative fluid strategies for patients without shock following initial resuscitation, empirical early antibiotics for suspected bacterial co-infection until a specific diagnosis is made, lung-protective ventilation, prone positioning, and consideration of extracorporeal membrane oxygenation for refractory hypoxemia.
Henry, 2020	Letter	Patients who died from COVID-19 are reported to have had significantly lower lymphocyte counts than survivors. The immunological status of patients should be considered when selecting candidates for ECMO. During ECMO, substantial decreases in the number and function of some populations of lymphocytes is commonplace .The repletion of lymphocytes could

		be key to recovery from COVID-19, and lymphocyte count should be closely monitored in these patients receiving ECMO.

Question 2: What evidence is available about the use of ECMO in the context of emerging respiratory disease outbreaks?

A systematic review of the effect of ECMO on survival in adults with acute respiratory failure associated with H1N1 found insufficient evidence to provide a recommendation (Mitchell et al, 2010).

During the H1N1 pandemic in the spring of 2009, contraindications to ECMO included preexisting comorbidities, weight > 120 kg, pulmonary hypertension, and cardiac arrest (NSW Health; Réseau Européen de Recherche en Ventilation Artificielle) (Combes and Pellegrino, 2011)(11).

There is mixed evidence from previous ARDS / respiratory disease outbreaks that ECMO is beneficial for a select group of patients (Table 2). None of the papers described changes to eligibility criteria.

Table 2: Evidence on the role of ECMO in non-COVID-19 pandemics

Study	**Study design**	**Results**
Mitchell et al 2010 (12)	Systematic review (of H1N1)	Investigated the effect of ECMO on survival in adults with acute respiratory failure to help inform institutional decisions about implementing an extracorporeal membrane oxygenation program or transferring patients to experienced extracorporeal membrane oxygenation centres during the H1N1 influenza pandemic. There was insufficient evidence to provide a recommendation.

Table 3: Studies of the use of ECMO in emerging respiratory disease outbreaks.

Organism	Setting	Number of patients (ECMO and comparator)	Mortality	ref
Middle East respiratory syndrome (MERS)	Saudi Arabia: 5 ICUs April 2014 to December 2015	17 (ECMO) and 18 (conventional)	65% (ECMO) and 100% (conventional)	Alshaharani et al 2018 (13)
Influenza A H1N1	Australia and New Zealand: 15 ICUs June 1 and August 31, 2009.	68 (ECMO)	29% (ECMO)	(Davies et al 2009 (14) Sidebotham, 2011 (15)
Influenza A H1N1	France 114 ICUs 2009-11 .	123 (ECMO) (matched cohort study)	No difference (Before matching: ECMO 36% and non-ECMO 34% After matching: ECMO 50% and non-ECMO 40%)	Pham et al, 2013 (16)

Organism	Setting	Number of patients (ECMO and comparator)	Mortality	ref
Influenza A H1N1	ELSO Registry	256 (ECMO)	34% (ECMO)	Combes and Pellegrino, 2011 (11)
Influenza A H1N1	Sweden July 2009 – January 2010	13 (ECMO)	8% (ECMO)	Holzgraefe et al, 2010 (17)

Appendix 1: Clinical syndromes associated with COVID-19 (WHO, 2020)

Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance

Table 2. Clinical syndromes associated with COVID-19

Mild illness	Patients uncomplicated upper respiratory tract viral infection may have non-specific symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhoea, nausea, and vomiting (3, 11-13). The elderly and immunosuppressed may present with atypical symptoms. Symptoms due to physiologic adaptations of pregnancy or adverse pregnancy events, such as dyspnea, fever, GI-symptoms or fatigue, may overlap with COVID-19 symptoms.
Pneumonia	**Adult** with pneumonia but no signs of severe pneumonia and no need for supplemental oxygen. **Child** with non-severe pneumonia who has cough or difficulty breathing + fast breathing: fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40, and no signs of severe pneumonia.
Severe pneumonia	**Adolescent or adult:** fever or suspected respiratory infection, plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO_2 ≤ 93% on room air (adapted from *14*). **Child** with cough or difficulty in breathing, plus at least one of the following: central cyanosis or SpO_2 < 90%; severe respiratory distress (e.g. grunting, very severe chest indrawing); signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions *(15)*. Other signs of pneumonia may be present: chest indrawing, fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40 *(16)*. While the diagnosis is made on clinical grounds; chest imaging may identify or exclude some pulmonary complications.
Acute respiratory distress syndrome (ARDS) *(17-19)*	**Onset:** within 1 week of a known clinical insult or new or worsening respiratory symptoms. **Chest imaging** (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. **Origin of pulmonary infiltrates:** respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factor present. **Oxygenation impairment in adults** *(17, 19)*: • Mild ARDS: 200 mmHg < PaO_2/FiO_2[a] ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH_2O, or non-ventilated) • Moderate ARDS: 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg (with PEEP ≥ 5 cmH_2O, or non-ventilated) • Severe ARDS: PaO_2/FiO_2 ≤ 100 mmHg (with PEEP ≥ 5 cmH_2O, or non-ventilated) • When PaO_2 is not available, SpO_2/FiO_2 ≤ 315 suggests ARDS (including in non-ventilated patients). **Oxygenation impairment in children:** note OI = Oxygenation Index and OSI = Oxygenation Index using SpO_2. Use PaO_2-based metric when available. If PaO_2 not available, wean FiO_2 to maintain SpO_2 ≤ 97% to calculate OSI or SpO_2/FiO_2 ratio: • Bilevel (NIV or CPAP) ≥ 5 cmH_2O via full face mask: PaO_2/FiO_2 ≤ 300 mmHg or SpO_2/FiO_2 ≤ 264 • Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5 • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3.
Sepsis *(5, 6)*	**Adults:** life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection.[b] Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output (5, 20), fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinemia. **Children:** suspected or proven infection and ≥ 2 age- based systemic inflammatory response syndrome criteria, of which one must be abnormal temperature or white blood cell count.
Septic shock *(5, 6)*	**Adults:** persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L. **Children:** any hypotension (SBP < 5th centile or > 2 SD below normal for age) or two or three of the following: altered mental state; tachycardia or bradycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or feeble pulse; tachypnoea; mottled or cool skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia (21).

[a] If altitude is higher than 1000 m, then correction factor should be calculated as follows: PaO_2/FiO_2 x barometric pressure/760.

[b] The SOFA score ranges from 0 to 24 and includes points related to six organ systems: respiratory (hypoxemia defined by low PaO_2/FiO_2); coagulation (low platelets); liver (high bilirubin); cardiovascular (hypotension); central nervous system (low level of consciousness defined by Glasgow Coma Scale); and renal (low urine output or high creatinine). Sepsis is defined by an increase in the sepsis-related SOFA score of ≥ 2 points. Assume the baseline score is 0 if data are not available *(22)*.

Abbreviations: ARI acute respiratory infection; BP blood pressure; bpm beats/minute; CPAP continuous positive airway pressure; FiO_2 fraction of inspired oxygen; MAP mean arterial pressure; NIV non-invasive ventilation; OI Oxygenation Index; OSI Oxygenation Index using SpO_2; PaO_2 partial pressure of oxygen; PEEP positive end-expiratory pressure; SBP systolic blood pressure; SD standard deviation; SIRS systemic inflammatory response syndrome; SOFA sequential organ failure assessment; SpO_2 oxygen saturation.

https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200301-sitrep-41-covid-19.pdf?sfvrsn=6768306d_2

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