Review Article

Extracorporeal Membrane Oxygenation for Severe Respiratory Failure During Respiratory Epidemics and Pandemics: A Narrative Review

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Abstract

Introduction: Epidemics and pandemics from zoonotic respiratory viruses, such as the 2019 novel coronavirus, can lead to significant global intensive care burden as patients progress to acute respiratory distress syndrome (ARDS). A subset of these patients develops refractory hypoxaemia despite maximal conventional mechanical ventilation and require extracorporeal membrane oxygenation (ECMO). This review focuses on considerations for ventilatory strategies, infection control and patient selection related to ECMO for ARDS in a pandemic. We also summarise the experiences with ECMO in previous respiratory pandemics. Materials and Methods: A review of pertinent studies was conducted via a search using MEDLINE, EMBASE and Google Scholar. References of articles were also examined to identify other relevant publications. Results: Since the H1N1 Influenza pandemic in 2009, the use of ECMO for ARDS continues to grow despite limitations in evidence for survival benefit. There is emerging evidence to suggest that lung protective ventilation for ARDS can be further optimised while receiving ECMO so as to minimise ventilator-induced lung injury and subsequent contributions to multi-organ failure. Efforts to improve outcomes should also encompass appropriate infection control measures to reduce co-infections and prevent nosocomial transmission of novel respiratory viruses. Patient selection for ECMO in a pandemic can be challenging. We discuss important ethical considerations and predictive scoring systems that may assist clinical decision-making to optimise resource allocation. Conclusion: The role of ECMO in managing ARDS during respiratory pandemics continues to grow. This is supported by efforts to redefine optimal ventilatory strategies, reinforce infection control measures and enhance patient selection.

Ann Acad Med Singapore 2020;49:199–214

Key words: Acute Respiratory Distress Syndrome, Coronavirus disease 2019, ECMO, Infection control, Mechanical ventilation

Introduction

Respiratory viruses resulting in epidemics and pandemics such as the severe acute respiratory syndrome coronavirus (SARS), H1N1 influenza A (H1N1pdm09), Middle East respiratory syndrome coronavirus (MERS-CoV) and the recent novel coronavirus disease 2019 (COVID-19) can lead to severe acute respiratory failure (ARF) that requires intensive care support. In a subset (4–40%) of patients with severe ARF (such as severe acute respiratory distress syndrome [ARDS]) refractory to maximal conventional mechanical ventilation (MV) support, extracorporeal membrane oxygenation (ECMO) may be required.[1,2] Briefly, ECMO uses modified cardiopulmonary bypass technology to provide respiratory or cardio-respiratory support in potentially reversible conditions where maximal conventional intensive care support is failing (Fig. 1). It is broadly categorised into venovenous (VV) and venoarterial (VA) ECMO. In VV ECMO, blood is drained from the venous system, pumped into an artificial lung for addition of oxygen and removal of carbon dioxide, before being returned to a central vein, thus providing respiratory support. In VA ECMO,

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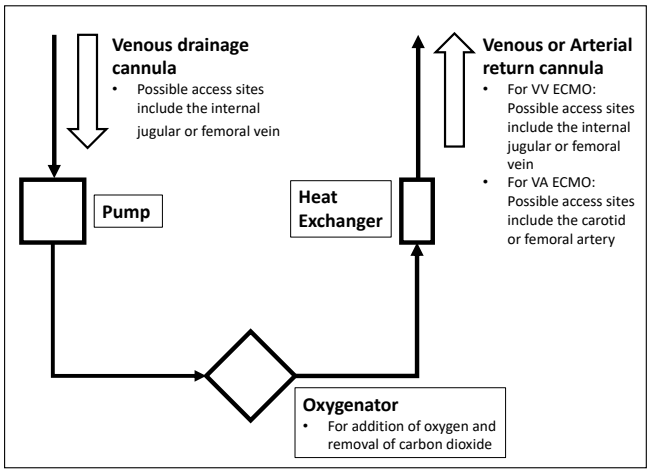

Fig. 1. Schematic representation of an ECMO circuit. Deoxygenated blood is drained from a central vein and pumped to a membrane lung oxygenator, where oxygen is added and carbon dioxide is removed. The oxygenated and decarboxylated blood is passed through a heat exchanger before being returned to the patient, with the site of the return cannulae varying according to the mode of ECMO. Blood in the extracorporeal circuit cools to room temperature and a heat exchanger is necessary for thermoregulation.
ECMO: Extracorporeal membrane oxygenation; VA: Venoarterial; VV: Venovenous

blood is drained from the venous system, pumped into an artificial lung and returned to the aorta or femoral artery, thus providing cardio-respiratory support. Although the evidence for ECMO in ARDS is limited, ECMO remains included in major clinical practice guideline recommendations for management of patients with severe ARDS.

In initial reports of the COVID-19-infected pneumonia epidemic, up to 25% of patients were critically ill, with significant mortality ranging between 10–60% within this group.[3–5] Among patients that required care in the intensive care unit (ICU), ARDS was the most common reason for admission (61–67%) and 8–15% of these patients required ECMO support.[3–5] As such, a review of the use of ECMO during respiratory epidemics and pandemics is timely. In this narrative review, we focus on some pertinent considerations in the use of ECMO during epidemics and pandemics (such as ventilatory strategies during ECMO and infection control considerations). We summarise the experience of the use of ECMO in patients with SARS, H1N1pdm09, MERS-CoV and–COVID-19 with the main aim to outline potential lessons learnt and applications for ECMO deployment for the current COVID-19 and future epidemics/pandemics. For clinical aspects that we did not include, we refer readers to other excellent review articles on the use of ECMO in the ICU.[6,7]

For the purpose of this narrative review, we searched MEDLINE, EMBASE and Google Scholar using the following MESH terms and keywords: ECMO, epidemics, pandemics, SARS, H1N1pdm09, MERS-CoV and COVID-19. Additionally, we examined the references of articles found and included those that we considered appropriate for this focused narrative review.

Ventilatory Strategies During ECMO

MV is life-saving for patients with severe ARF. However, MV results in repetitive stress and strain on diseased lung units with consequent distortion of lung parenchyma and extracellular matrix, leading to ventilator induced lung injury (VILI).[8] The 2 key contributory mechanisms in VILI are repetitive volutrauma (from excessive tidal volumes), and atelectrauma (from repetitive opening and closure of alveoli).[8] Lung protective ventilation (LPV) techniques are recommended for both adults[9] and children[10] with the aim to achieve a delicate balance of adequate alveolar recruitment of non-aerated and injured lung segments while limiting over-distension.

Key determinants of VILI which can be manipulated during MV include tidal volume (TV), positive end expiratory pressure (PEEP), plateau pressure (Pplat) and driving pressure (ΔP). Additionally, increased work of breathing and patient-ventilator dyssynchrony contribute to increases in transpulmonary pressures and lung injury and may be mitigated with sedation and neuromuscular blockade.[11] However, the relative contributions of disease, ventilator and patient factors to the development of VILI and the optimal manipulation of these factors to minimise VILI remains unknown.[8]

In adults, conventional MV with low TV (≤6 mL/kg) is guided by a landmark study which showed a significant reduction in 28-day mortality in adults with ARDS in the patient group that was ventilated with TV ≤6 mL/kg compared to 12 mL/kg.[9] This has since been widely accepted and incorporated into guidelines for the management of ARDS.[12] However, the caveat is that LPV strategies with low TV and airway pressures may result in significant respiratory acidosis. In patients with severe ARDS, this may necessitate the use of high respiratory rates which in turn is hypothesised to contribute to VILI.[13] Thus, there is growing interest and evidence for the use of LPV in conjunction with extracorporeal life support (ECLS) such as VV ECMO or extracorporeal carbon dioxide removal ($ECCO_2R$) to achieve adequate oxygenation and carbon dioxide clearance while implementing lung rest and mitigating VILI.

Although early use of ECMO has not been conclusively shown to be superior to ECMO initiated as rescue therapy,[14] the possibility that it may facilitate mitigating VILI and resultant morbidity and mortality remains of heightened

Table 1. Summary of Mechanical Ventilation Guidelines for ARDS with and without ECLS and Paediatric ARDS

Variable	ARDS	PARDS	During ECLS for ARDS
Recommending body/landmark trials	ATS/ESICM/SCCM[*] ARDSNet[†] PROSEVA[‡] ART[§]	PALICC[¶]	ECMONet[**] EOLIA[††]
Tidal volume	4 – 8 mL/kg	Poor lung compliance: 3 – 6 mL/kg Good lung compliance: 5 – 8 mL/kg	Adjusted to goal Pplat; typically ≤4 mL/kg PBW
PEEP	Higher PEEP with moderate to severe ARDS[‖]	10 – 15 cmH_2O; allowance of ≥15 cmH_2O in severe PARDS	≥10 cmH_2O
Pplat	≤30 cmH_2O	-	≤24 cmH_2O
DP	-	-	≤14 cmH_2O
RR	-	-	≤10 breaths/min
PIP	-	≤28 cmH_2O (≤32 cmH_2O when there is stiff chest wall)	-
Arterial blood gas parameters	-	Allow permissive hypercarbia (pH 7.15 – 7.30) when there are no contraindications[#]	PaO_2 65 – 90 mmHg $PaCO_2$ <45 mmHg
FiO_2	-	-	0.3 – 0.5
SpO_2	-	88 – 92% for severe PARDS	-
Prone positioning	>12 – 16 hr/day for severe ARDS	-	-
HFOV	Routine use in moderate or severe ARDS is discouraged	When Pplat ≥29 cmH_2O	-
Recruitment manoeuvres	Role is controversial	-	-
ECMO	No recommendation for or against	-	-

ΔP: Driving pressure; ARDS: Acute respiratory distress syndrome; ECLS: Extracorporeal life support; ECMO: Extracorporeal membrane oxygenation; FiO_2: Fraction of inspired oxygen; HFOV: High frequency oscillatory ventilation; $PaCO_2$: Partial pressure of arterial carbon dioxide; PaO_2: Partial pressure of arterial oxygen; PARDS: Paediatric acute respiratory distress syndrome; PBW: Predicted body weight; PEEP: Positive end-expiratory pressure, PIP: Peak inspiratory pressure; Pplat: Plateau pressure; RR: Respiratory rate; SpO_2: Peripheral capillary oxygen saturation

[*]Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;195:1253–63.

[†]Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301–8.

[‡]Guerin C, Reignier J, Richard J-C, Beuret P, Gacouin A, Boulain T, et al. PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159–68.

[§] Cavalcanti AB, Suzumura EA, Laranjeira LN, Paisani DM, Damiani LP, Guimaraes HP, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA 2017;318:1335–45.

[‖]Guidelines from the Surviving Sepsis Campaign[91] recommend higher PEEP for ARDS in coronavirus disease 2019 (COVID-19).

[¶]Jouvet P, Thomas NJ, Wilson DF, Erickson S, Khemani R, Zimmerman J, et al. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med 2015;16:428–39.

[#]Contraindications include raised intracranial pressure, severe pulmonary hypertension and certain congenital heart lesions.

[**]Abrams D, Schmidt M, Pham T, Beitler JR, Fan E, Golgher EC, et al. Mechanical ventilation for ARDS during extracorporeal life support: research and practice. Am J Respir Crit Care Med 2020;201:514–25.

[††]Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378:1965–75.

interest, particularly in those with severe ARDS. ECMO support can potentially fully replace the native lung function of gas exchange, allowing for reduction in TV, Pplat and ΔP.[15] Current recommendations for the use of low TV whilst supported on ECMO are based on the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial[14] (Table 1) which demonstrated an improvement in 60-day mortality in those randomised to early ECMO (35%) vs conventional MV with LPV (46%), although this did not reach statistical significance. The potential benefit of further minimising TV is supported by a study from the United States[16] which showed an inverse linear relationship between TV and mortality at two years with no apparent lower limit for the association. A porcine model of ARDS comparing non-protective, protective and near apnoeic ventilation (TV 2.1 mL/kg and respiratory rate of 5 breaths/minute) found the least amount of histological injury associated with the latter, supporting this hypothesis.[17] To test the extent of this benefit in patients supported on ECLS, 2 trials are currently ongoing to assess the role of ultra-low tidal volumes (up to 3 mL/kg) in conjunction with $ECCO_2R$, the SUPERNOVA[29] and REST[30] trials. Although on a different form of ECLS, the outcomes of these trials may be extrapolated to some extent to patients supported on ECMO. However, the benefits of minimising VILI with the use of LPV must be balanced with potential risks of adverse events related to ECLS and the availability of expertise to safely implant, monitor and manage it in addition to the cardiopulmonary interactions and physiological changes that may result from this approach.

There is good evidence for reduction in mortality with lower TV,[9] lower ΔP[20] and plateau pressures.[20,21] However, the role of optimal PEEP and recruitment manoeuvres are less clear and hence feature less prominently in practice guidelines. A database review of ECMO practices in France and Australia from 2007–2013 found an association between improved survival and higher PEEP (12–14 vs 10–12 cmH_2O) with slightly higher TV (4–6 vs 2–4 mL/kg) following ECMO initiation.[15] Hence current guidelines advocate for PEEP between 10–15 cmH_2O in patients with severe ARDS[10,12,14] (Table 1).

In adults, routine high frequency oscillatory ventilation (HFOV) use in severe ARDS is discouraged[12] following 2 large randomised controlled trials (RCTs) of HFOV in critically ill adults: one of which was stopped early[22] as the in-hospital mortality in the HFOV group was significantly higher than the control group (48% vs 35%, relative risk [RR] of death with HFOV, 1.33; 95% confidence interval [CI] 1.09–1.64; $P = 0.005$) and the other which showed no difference between the HFOV and conventional MV arms.[23] In contrast to adult guidelines, HFOV continues to be recommended in children and used as a rescue therapy in critically ill children with severe ARF as some studies suggest benefit while others raise concerns of harm.[10] An RCT comparing HFOV to conventional MV in 112 children with paediatric acute respiratory distress syndrome (PARDS) found a higher incidence of survivors in the HFOV group for children with severe PARDS with a baseline oxygenation index >16 (40% vs 15.8%; $P = 0.004$).[24] Conversely, a large observational study of children in Asia involving 118 pairs of patients matched using genetic matching method, found an association between HFOV and 28-day mortality in PARDS (odds ratio [OR] 2.3; 95% CI 1.3–4.4; $P = 0.01$).[25] While this raises some concerns about the safety of use of HFOV in children, the utility of HFOV in the paediatric ICU remains uncertain. Taking into consideration the data from both adult and paediatric patients, it remains unclear whether patients supported on ECMO should be supported on HFOV in an attempt to reduce VILI. However, the concurrent use of ECMO and HFOV may facilitate HFOV settings akin to LPV or near-apnoeic MV, which would be very different compared to the "rescue" settings that have been studied thus far. This may potentially be superior to LPV in mitigating atelectrauma and should be explored in future studies.

Most recommendations for MV in patients with severe ARDS with or without ECMO support comes from animal and adult studies and these may not extrapolate to children. In children, pressure targeted modes of MV are more frequently used than volume-controlled modes and peak inspiratory pressure (PIP) rather than TV seems to correlate with outcomes.[26,27] No specific range of TV has been shown to impact mortality in PARDS.[28] In a prospective observational multicentre study of the Australian and New Zealand Paediatric Intensive Care Society (ANZPICS) study group, higher TV was associated with reduced mortality even after adjusting for severity of lung disease. In that study, PIP > 25 cmH_2O was associated with increased odds of mortality of 10% (OR 1.1; 95% CI 1.020–1.199).[29] Similarly, in a retrospective review of children with ARF, TV was not associated with mortality and lower median PIP of 26 cmH_2O (interquartile range [IQR] 22–30) was observed in survivors compared with 30 cmH_2O (IQR 24–34, $P < 0.01$) in non-survivors.[27] In addition, a retrospective multicentre cohort of PARDS patients in Asia also showed increased ventilator free days in those supported with PIP ≤28 cmH_2O.[26]

In summary, there is increasing evidence to support the use of LPV in conjunction with ECLS to minimise VILI.

While not recommended routinely, ECMO or $ECCO_2R$ used in conjunction with LPV to manage respiratory acidosis and hypoxia to the extent of allowing near apnoeic ventilation holds promise in the management of severe ARF and a potential for significant reduction in VILI. While the principle of LPV in conjunction with ECMO should also apply for children, it is important to remain mindful that the evidence is extrapolated from adults and that there may be physiological differences when these are applied to children supported on ECMO.

Infection Control Considerations for the Patient on ECMO

The goals for infection control measures for the patient on ECMO support for ARF in the context of a respiratory pandemic are two-fold: 1) mitigation of the risk of co-infections for the patient and; 2) prevention of transmission of novel respiratory pathogens to healthcare workers. Adequate planning and preparation are essential to develop protocols for routine management and in times of crisis. Healthcare staff must also be trained to respond appropriately at various states of emergency. Staff knowledge and competence must be ensured, especially when they are required to function in a stressful, high-risk environment requiring complex and resource-intensive care.

In 2008, the Extracorporeal Life Support Organization (ELSO) created an Infectious Disease Task Force to address the issue of diagnosis, treatment and prevention of infections for ECMO patients. An analysis of the ELSO database reported that the risk of infection on ECMO increased with increasing patient age and with ECMO runs longer than 1–2 weeks.[30] The most common reported organisms include coagulase-negative staphylococci, Candida species, Pseudomonas and Staphylococcus aureus, with smaller numbers of gram-negative organisms such as Enterobacter, Klebsiella, Enterococcus and Escherichia coli species.[30] This should be considered when selecting empirical antibiotic therapy for suspected infections, with a lower threshold for initiating anti-fungal therapy given the high incidence and mortality associated with Candida sepsis.[31] Recommended infection control precautions for patients supported on ECMO include: 1) treating the ECMO circuit as a protected central line, so that "breaking" the line would be avoided as much as possible, with blood sampling preferentially taken from patient sites such as arterial catheters and medication administration through the circuit restricted to continuous infusions rather than intermittent doses; 2) measures to prevent ventilator associated pneumonia such as elevation of the head of the bed, medical treatment of gastroesophageal reflux, pulmonary toilet and oral or gastrointestinal decontamination protocols; 3) initiation of enteral nutrition where possible to maintain gut mucosa, prevent bacterial translocation and reduce the need for parenteral nutrition; 4) administration of parenteral nutrition through a dedicated central venous line rather than directly administering concentrated glucose to the ECMO circuit; 5) administration of blood products or intermittently dosed drugs via peripheral vascular access; 6) avoiding the insertion of new long term tunnelled or cuffed vascular access while on ECMO due the risk of haematoma formation and infection and; 7) removal of all unnecessary lines, tubes and devices once the patient is stable on ECMO.[32] These are summarised in Table 2.

The practice of "surveillance" periodic blood, urine or sputum cultures did not demonstrate benefit and was discouraged, with cultures recommended only if sufficient clinical suspicion arises.[32] However, patients on ECMO receive extracorporeal thermoregulation, with blood in the circuit naturally cooling down and heated to normothermia before returning to the body. This makes it difficult, but not impossible for a patient to mount a fever due to an infection. The extent of ECMO circuit flow should also be considered. Patients with relatively low ECMO flows have a smaller proportion of blood circulating extracorporeally and so can mount a fever, whereas patients with high ECMO flows are subject to a greater degree of extracorporeal thermoregulation and are less likely to generate fever. In such settings, careful clinical examination is required to evaluate for infections and any degree of febrile response while on ECMO should be considered significant. Generally, single dose or 24-hours of prophylactic antibiotic coverage is recommended upon ECMO cannulation, but data did not support longer durations of prophylaxis without specific culture or physiological evidence of ongoing infection or in the absence of risk factors such as transthoracic cannulation, immunocompromised states or pre-existing skin colonisation (such as multidrug resistant organisms or yeast).[30,32] There is a lack of consensus regarding the management of catheter-related infections. Exchanging a catheter at the same site over a guidewire is unlikely to be helpful, given the high likelihood of microbial colonisation of the tract.[33] However, efforts to remove a catheter and replacing it at a new site must be balanced with considerations for the antibiotic susceptibility of the infecting organism, the risk of significant haemorrhage and accessibility of vascular access.

Most respiratory viruses, including SARS, H1N1pdm09, MERS-CoV and COVID-19, are transmitted via respiratory droplets and direct contact with infectious secretions or contaminated fomites.[34,35] However, aerosol-generating

Table 2. Summary of Infection Control Recommendations While on ECMO*

Recommendation	Description
Circuit management	• Treat ECMO circuit as a protected central line to minimise unnecessary accessing or "breaking" of the circuit • Obtaining routine blood samples from patient sites such as arterial catheters rather than from the circuit • Use of needleless hubs for all connection, stopcocks and access sites in the circuit • Use of chlorhexidine preparation solution rather than alcohol • Only allow administration of continuous infusions via the circuit, but not intermittently dosed medications • Avoid pairing care of ECMO patients with other patients with multi-drug resistant organisms or with grossly contaminated wounds or serious infections • Frequent hand washing and easy access to cleansing solutions before handling the circuit
Prevention of systemic infections	• Measures to prevent ventilator-associated pneumonia such as elevation of the head of the bed, oral prophylaxis and medical treatment of gastro-oesophageal reflux • Appropriate pulmonary toilet, suctioning and bronchoscopy when indicated • Early tracheostomy in non-paediatric patients to improve pulmonary toilet, reduce potential for gastrointestinal contamination and reduce sedation requirements • Consider use of oral or gastrointestinal decontamination protocols • Consider early and complete enteral nutrition to maintain gut mucosa, prevent bacterial translocation and to help avoid the use of parenteral nutrition • When parenteral nutrition is necessary, administer it directly to patient via a clean dedicated line rather than expose the circuit to a high glucose concentration which increases risk of infection • Administration of intermittently dosed drugs or blood products via peripheral vascular access • Strict sterile technique when accessing central lines • Avoid insertion of new tunnelled or cuffed vascular catheters while on ECMO due to the risk of haematoma formation and subsequent infection • Removal of all unnecessary lines, tubes and devices once patient is stable on ECMO
Use of prophylactic antibiotics	• There is no data to support the routine use of prophylactic antibiotics for patients on ECMO without specific culture or physiologic evidence of ongoing infection • Single dose or 24-hour prophylactic antibiotic coverage for ECMO cannulation • Prophylactic antibiotics may be considered in patients with risk factors such as transthoracic cannulation, immunocompromised states or with pre-existing skin colonisation with multidrug resistant organisms or yeast • Prophylaxis for surgical procedures while on ECMO should follow standard guidelines • Use of anti-fungal prophylaxis in patients deemed to be at high risk of fungal infection

ECMO: Extracorporeal membrane oxygenation

*Extracorporeal Life Support Organization. Infectious Disease Task Force: Infection Control and Extracorporeal Life Support. Available at: https://www.elso.org/Portals/0/Files/Infection-Control-and-Extracorporeal-Life-Support.pdf. Accessed on 13 February 2020.

procedures within the ICU such as endotracheal intubation, extubation, airway suctioning, bronchoscopy and cardiopulmonary resuscitation may result in airborne transmission via small aerosol spread.[36] Thus, infection control measures for healthcare workers in contact with patients with novel respiratory pathogens in the ICU should include: 1) adequate personal protective equipment (PPE), including a gown, gloves, eye goggles or face shield and N95 respirator; 2) adequate hand hygiene; 3) environmental cleaning and disinfection; 4) measures aimed at containing patient secretions; and 5) dilution and removal of airborne contaminants.[37,38] These apply to any patient receiving MV and are summarised in Table 3.

Of the abovementioned infection control measures, containing patient secretions and removal of airborne contaminants are of particular importance given the nature of care required by patients supported by MV. Specific precautions are required to reduce aerosolisation, contain secretions and reduce duration of exposure to secretions. Endotracheal intubation should be considered early, to allow sufficient time for infection control preparations and be performed in a timely and controlled fashion by the most experienced personnel present, with the least number of assisting staff possible to limit exposure. In addition to other PPE, staff present for intubation (or any other aerosol-generating procedure) should be equipped with powered air-purifying respirators. The patient should be adequately sedated and paralysed to prevent coughing and agitation. If possible, bag-mask ventilation should be avoided and apnoeic oxygenation may be considered. If bag-mask ventilation is necessary, a 2-person technique should be used to ensure tight mask seal at the face and a high-efficiency particulate air (HEPA) filter may be fitted to reduce aerosolised pathogen load.[38] Cuffed endotracheal tubes should be employed to reduce airway leak. Regarding routine care of the ventilated patient, closed system (in-line) airway suctioning should be employed, with a HEPA filter connected to the ventilator expiratory port.[38] In order to reduce condensation within the ventilator tubing and the need to "break" the ventilator circuit to drain

Table 3. Summary of Infection Control Precautions in the Intensive Care Unit During a Respiratory Epidemic/Pandemic

Precaution	Description
Personal protective equipment	• Gown, gloves, eye goggles or face shield and N95 respirator • During aerosol-generating procedures, use powered air-purifying respirator • Provision of antechambers to patient rooms with visual instructions for donning and doffing, with spotter assistance • Sufficient containers for disposal of personal protective equipment, soiled linen and equipment that must be autoclaved
Hand hygiene	• Ensure easy access to alcohol-based hand rub and sinks with anti-bacterial soap and disposable towels inside and outside the patient room • Avoid touching face and environmental surfaces
Environmental cleaning and disinfection	• Trained personnel to clean and disinfect rooms with hospital-grade detergent/disinfectant • Clean frequently touched areas at least daily or once per shift
Containing patient secretions and reducing exposure	• Avoid aerosol-generating procedures if possible (such as bronchoscopy) • Limit the number of staff to essential personnel during aerosol-generating procedures • Consider early intubation by the most experienced personnel, in a timely and controlled manner, using a cuffed endotracheal tube with adequate sedation/paralysis and apnoeic oxygenation • Avoid bag-mask ventilation but if required, consider the 2-person technique to ensure tight mask seal with attached HEPA filter • Use closed system (in-line) airway suctioning • Attach HEPA filter to ventilator expiratory port • Attach HMEF to endotracheal tube • Avoid heated humidifier systems to reduce condensation within ventilator tubing • If ventilator circuit is disconnected, turn ventilator to standby mode with PEEP turned off • If high frequency oscillatory ventilation is required, consider maintaining inflated cuff for endotracheal tube, with HEPA filter and HMEF attached to circuit • Avoid nebulised medications if possible • The use of non-invasive ventilation is controversial and may pose additional nosocomial transmission risk
Dilution and removal of airborne contaminants	• Use of negative pressure isolation rooms • Installation of or provision of portable photocatalytic HEPA filters to reduce airborne pathogen load • Appropriate hospital design to augment ventilation within the ward • Open windows and keep fans running to encourage ventilation within the ward
Others	• Ensure adequate staff education and training • Limit visitors and personnel to those essential for patient care and support • Avoid patient movement/transportation unless absolutely necessary. If required, ensure appropriately trained and equipped transport and receiving teams, with shortest route of movement with minimal exposure to other personnel, measures taken to prevent dispersal of patient respiratory secretions and disinfection of route and destination. • Provision of frequently used equipment/resuscitation equipment in individual rooms

HEPA: High-efficiency particulate air; HMEF: Heat and moisture exchanging filter; PEEP: Positive end-expiratory pressure

water, heated humidifier systems should be removed and replaced with a heat and moisture exchanging filter (HMEF) at the endotracheal tube.[39] However, the medical team must be mindful of the increase in dead space and potential increase in airway resistance with HMEFs and HEPA filters, which may impact on the adequacy of MV and validity of capnography. Thus, the patients' respiratory effort, gas exchange and filter quality must be regularly monitored, with filters replaced when necessary. If end-tidal capnography traces are significantly affected, especially in severe ARF with significant intrapulmonary shunting, transcutaneous carbon dioxide monitoring is a potential alternative for real-time non-invasive carbon dioxide monitoring.[40] If disconnections in the ventilator circuit are required, the endotracheal tube should be clamped, with the ventilator transiently turned to standby mode and positive end-expiratory pressure stopped. The risks of nosocomial transmission of respiratory pathogens with HFOV remains uncertain. If HFOV is deemed clinically necessary for the patient, maintaining cuffed endotracheal tubes with the addition of HMEF and HEPA filters to the HFOV circuit may mitigate transmission risk.

Measures to dilute and remove airborne contaminants include strategies to improve ventilation within the ward and the use of photocatalytic HEPA filtration devices, which ideally should be incorporated in negative pressure isolation rooms. Several studies have linked reduced nosocomial transmission of SARS in hospitals to

augmented ventilation within the ward. In a Vietnamese hospital, there was no transmission of SARS in wards with large spacious rooms, high ceilings, large windows and continuously running ceiling fans.[41] Another hospital in China compared window surface area to room volume and found that rooms without windows had the highest nosocomial transmission rates, whereas rooms with larger window surface area to room volume ratios had the lowest transmission rates.[42] If not already available, addition of photocatalytic HEPA filter units to wards may be considered to remove and deactivate airborne pathogens.

ECMO Experience with the Severe Acute Respiratory Syndrome Coronavirus (SARS)

SARS was a novel coronavirus that first emerged as an outbreak of atypical pneumonia in Guangzhou Province, China, in late 2002.[37] It is phytogenetically diverged from other human coronaviruses and is more closely related to a group of lineage B betacoronaviruses found in civets and Chinese horse shoe bats.[43] Rapid progression to ARDS occurred in 20–25% of infected individuals with a mortality rate of approximately 10%.[44] To our knowledge, there were no reports of ECMO use during the SARS epidemic, likely due to lack of relevant expertise and infrequent use during that particular period.

ECMO experience with the H1N1 Influenza A Pandemic (H1N1pdm09)

Compared to prior epidemics, H1N1pdm09 tended to cause critical illness and mortality among a younger patient population.[1] Although the disease course was mostly mild and self-limiting, up to 20% of hospitalised patients were admitted to ICU, with 80% of these requiring MV.[1] Progression from pneumonia to ARDS was rapid, with a mean duration of 1 day from hospitalisation to ICU admission.[1,45]

The H1N1pdm09 pandemic played an important role in the expansion of ECMO as a rescue therapy in adult ICUs. Prior to 2009, ECMO was primarily utilised in the neonatal and paediatric population, with significant controversy regarding the application of ECMO for adults.[46] Most early data in adults showed poor outcomes, particularly for ARDS, and only a few institutions had established ECMO programs for adult ARF at that time.[46] In 2009, results from the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial demonstrated that patients who received ECMO for severe ARF had improved rates of disability-free survival compared to those who received conventional management (63% vs 47%; RR 0.69; 95% CI 0.05–0.97).[47] This was followed by a publication from the Australia New Zealand ECMO Influenza Investigators group that reported a 21% mortality rate among H1N1pdm09 patients who received ECMO in ICUs across Australia and New Zealand.[48] In comparison, overall mortality rates for ARDS on ECMO at the time were 37–48%[47] and mortality for severe H1N1pdm09 ARDS at institutions where ECMO was not available was 46%.[49] Taken collectively during that period, ECMO seemed to hold promise in the management of the pandemic.

The surge in rapidly progressive, severe ARDS in a generally young population due to H1N1pdm09, paired with promising results from these publications, spurred resurgence in exploring ECMO as a rescue therapy for adults with ARF. Although standard ECMO criteria in H1N1pdm09 was lacking, the CESAR trial was frequently referenced and refractory hypoxemia was the primary indication for cannulation. One-third of patients who required MV have been reported to be supported on ECMO for a duration of 10–18 days.[21,48] There was compelling evidence that while H1N1pdm09 can cause severe illness, the disease process was reversible and transfer to an ECMO centre was associated with improved mortality rates in H1N1pdm09 ARDS compared to non-transfer (24% vs 51%; RR 0.47; 95% CI 0.31–0.72).[50] Favourable H1N1pdm09 ECMO outcomes were associated with fewer days of pre-cannulation MV,[51] rapid wean of MV to low pressure settings once on ECMO support,[21] and early initiation of neuraminidase inhibitor treatment.[45] ECMO complications were largely haemorrhagic, thrombotic, or infectious.[48] Rates of intracranial bleeding were reported at 1–11%.[21,48,50,51]

During this pandemic, institutions with ECMO experience took measures to strengthen their programs to meet the anticipated surge in demand,[52] while others with limited or no prior experience sought to develop their own ECMO capabilities.[53] These efforts were met with varying success.[48] The ability for regional systems and individual institutions to adapt to the surge in demand during a crisis is critical to optimise patient outcomes. Factors that appear to have contributed to successful ECMO expansion during the 2009 pandemic include centralisation of ECMO within designated centres of excellence and interhospital transfer capabilities, the establishment of clear criteria for referral to ECMO centres and ECMO initiation, and a structured simulation-based training program to quickly equip ICUs with varying prior ECMO experience to meet anticipated demand.[51]

ECMO Experience with the Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

MERS-CoV was first described in 2012 in the Middle East and is caused by a novel zoonotic coronavirus postulated to be transmitted from dromedary camels.[54] Mortality in infected individuals is high (35%),[55] likely as a result of virus virulence and lack of definitive therapies. Indeed, the most common complication is that of ARDS. In addition to the hallmark of refractory hypoxemia, patients who progressed to ARDS were prone to multiorgan failure and septic shock,[56] often prompting the need for escalation to ECMO as rescue therapy. For ethical concerns, no RCT has been conducted to assess efficacy of ECMO in this cohort of patients. The use of ECMO in MERS-CoV is also limited due to the presence of contraindicated comorbidities, compounded by a lack of resources and trained personnel especially in rural areas.[54] Median time from symptom onset to invasive ventilation and/or ECMO initiation ranged from 4.5 to 7 days[57] which is earlier than that reported in SARS.[42] Guery et al described the clinical course of 2 adults who required ECMO for MERS-CoV for refractory ARF.[58] Bronchoalveolar lavage samples of both patients showed extremely high viral loads and at time of publication, the index patient had demised while the other one remained on ECMO. A retrospective cohort study (n = 35) performed in Saudi Arabia compared MERS-CoV infected patients who fulfilled ECMO criteria (as defined by the ELSO guidelines) but did not receive ECMO (due to lack of an ECMO service) to patients who received ECMO after the government-implemented national ECMO programme in April 2014.They reported that the use of ECMO was associated with lower in-hospital mortality (65% vs 100%; $P = 0.02$), better oxygenation [mean partial pressure of arterial oxygen/fraction of inspired oxygen ratio (Standard deviation [SD]) at days 7 and 14 of ICU admission: 124 (106.9) vs. 63 (66.1), and 237 (42.1) vs. 85 (31.9); $P < 0.05$] and less norepinephrine use (on days 1 and 14 of ICU admission: 29 vs. 80%, and 36 vs. 93%; $P < 0.05$) compared to historical controls who did not receive ECMO.[2] Whilst the use of ECMO appears to be safe in MERS-CoV patients with refractory hypoxemia and may confer overall benefit, reports on these are only limited to small case series and retrospective studies.

Patient Selection for ECMO—Ethical Considerations and Prediction Scoring Systems in a Pandemic

The considerations behind resource allocation in a mass-casualty environment are complex and challenging.[59–61] In 2006, modelling studies suggested that an event of similar scale to the 1918 Influenza pandemic would require 400% of existing ICU beds and 200% of mechanical ventilators in the United States.[62] Subsequent disasters such as Hurricane Katrina and the H1N1pdm09 pandemic also demonstrated the tremendous strain borne by healthcare systems.[59,63] In the wake of acts of terrorism, natural disasters and infectious outbreaks that have threatened to overwhelm healthcare infrastructure, what has become clear is the need for comprehensive pre-disaster planning and preparation at national and institutional levels, with the goals of developing: 1) guidance for the rights and responsibilities of healthcare workers; 2) healthcare infrastructure, supplies, training and protocols for surge capacity; 3) inter-agency collaboration, communication and workflows; 4) simulation exercises to further test and enhance systems; 5) accepted altered standards of care in resource-deficient circumstances; 6) public acceptance of revised workflows and; 7) post-disaster evaluation, accountability and staff care plans.[59,62,64–6]

As a limited, resource-intensive, potentially life-saving treatment that is not universally available, patient selection for ECMO comes under even greater scrutiny. This challenge is compounded not only by improvements in ECMO and other rescue therapies in critical care, resulting in evolving indications for ECMO,[67] but also by the ongoing examination of the benefit of ECMO compared to conventional therapies in various clinical settings.[63] In addition to employing clinical judgement, there are 2 broad approaches to guide patient selection for ECMO in a pandemic with limited resources; 1) the use of ethical principles and; 2) the use of predictive scoring systems to risk-stratify patients.

Outside of a crisis, standard resource allocation strategies typically adopt the "first-come-first-serve" approach and focus on patients with the greatest potential for benefit. However, in a pandemic where resources and infrastructure cannot meet demand, a commonly adopted strategy is to achieve the "greatest good for the greatest number". While certainly an important overarching principle in resource-limited settings, adopting the "greatest good for the greatest number" as a sole allocation principle does not adequately encompass other ethically relevant considerations, which include: 1) broad social value; 2) instrumental value; 3) maximising life years and; 4) the life cycle principle (Table 4).[59,60]

As no single ethical principle can sufficiently address the diverse moral dilemmas likely to arise in a pandemic, it seems reasonable to adopt a multi-principle allocation system. We believe that this combination of ethical principles will encompass a holistic approach to patient selection for a limited, resource-intensive therapy such as ECMO in a pandemic. Whilst the ideal situation may call for advocacy of combining the principles of "greatest

Table 4. Ethical Principles to Guide Resource Allocation in a Pandemic

Principle	Allocation Strategy
Greatest good for the greatest number	• Shift focus of care from the patient to the community at large • May be interpreted in different ways: ▪ Maximise the number of lives saved ▪ Allocate care to achieve maximal benefit with minimal resources ▪ May result in denying resources to groups of people who are deemed "not worth" saving
Broad social value	• Refers to one's overall worth to society • Involves using summary judgements about an individuals' past to determine potential future contributions to society • Difficult to engage the public to agree upon a criterion to assign societal worth • Negates the egalitarian view that all individuals have a right to treatment
Instrumental value	• Refers to ability of individuals to perform specific functions that are essential in a time of crisis • Also known as the "multiplier effect" where prioritising the care of key individuals leads to preservation of more lives through their work • However, key individuals may not recover in a timely manner to fulfil their roles • Difficult to identify roles and key individuals perceived to have instrumental value in a pandemic
Maximise life years	• Refers to prioritising care for an individual with the greatest chance of surviving for the longest time, thus preserving the greatest number of years of life • Already incorporated into strategies for allocating organs for transplantation, where recipients are selected based both on medical need and their expected duration of survival
Life cycle principle	• Refers to giving each individual an equal opportunity to live through various phases of life • Also known as the "fair innings" argument and "intergenerational equity" • Prioritises the young over the elderly, sacrificing experience for youth • A familiar concept where people believe that the young should be prioritised over the elderly in the face of limited resources

good for the greatest number", "maximising life years" and "the life cycle principle", a more likely scenario is that we are forced to be in a situation where we need to modify our current guidelines, accept less than normal standard of care in some cases and accept a "first-come-first-served" approach.

Scoring systems have long been used in critical and emergency care and multiple attempts have been made to adapt scoring systems to triage patients for critical care, MV and ECMO. While several scoring systems for ECMO in severe ARF have certainly demonstrated promising results, all of them, by their nature, share similar limitations[68–80] (Tables 5 and 6 for Paediatric and Adult scores, respectively). Most scoring systems have been developed in small and restricted derivation cohorts and lack external validation, with variable performance in different cohorts of patients. Their validity may also be challenged over time with further improvements in diagnostic and therapeutic modalities. Ultimately, the intent of these scores are to quantify and analyse cohorts of patients, not to reliably predict outcomes when applied to individual patients.[81] Several studies evaluating the performance of predictive scores when retrospectively applied, have demonstrated that these scores overpredicted mortality.[81] In other words, patients who may have had a significant chance of survival would have been erroneously denied critical care. This does not mean that scoring systems have no place in deciding resource allocation, but that clinicians must remain aware that such scores are imperfect. At present, predictive scores for ECMO in ARDS will likely best serve as an initial screen and adjunct to experienced clinical assessment and decision making. Whether these scores ultimately enhance patient selection for ECMO in a pandemic remains to be determined.

Lessons Learnt to Apply for ECMO in COVID-19

ECMO and MV are not disease-modifying therapies in themselves, but rather, life-sustaining support systems that allow time for other interventions to correct the underlying pathology. In the absence of definitive treatment for ARDS secondary to COVID-19, we are compelled to focus on mitigating risk of further harm and optimising conditions, not just for survival, but for survival with good neurological and functional recovery. Initial steps in this endeavour would involve capitalising on the benefits of ECMO in ARDS to minimise VILI, titrate fluid status, optimise nutrition and initiate early neurorehabilitation in the ICU.[82,83] However, if the natural history of COVID-19 amongst critically ill patients tends to progress towards

Table 5. Summary of Paediatric Predictive Scoring Systems for Survival for ECMO in Acute Respiratory Failure

Score, Year	Cohort Characteristics/ ECMO Mode	PreECMO Variables	Internal Validation (AUROC)	External Validation (AUROC)
PIPER, 2016*	ELSO Registry 2000–10 (n = 1501): <30 days old with respiratory failure, mortality 37%, VA 100%	Age, APGAR at 5 minutes, birth weight, mean arterial blood pressure, PaO_2, pH, inhaled nitric oxide use	0.73 (0.70 – 0.75)	-
Neo-RESCUERS, 2016†	ELSO Registry 2008–13 (n = 3139): <28 days old with respiratory failure, mortality 31%, VA 65%, VV 35%	Age, birth weight, comorbidities, gender, gestational age, PaO_2/FiO_2 ratio, pH, primary diagnosis, renal failure, inhaled nitric oxide use	0.78 (0.76 – 0.79)	-
Ped-RESCUERS, 2016‡	ELSO Registry 2009–14 (n = 1611): 29 days to <18 years old with respiratory failure, mortality 39.8%‖	Diagnosis (of asthma, bronchiolitis, malignancy and pertussis), hours admitted, hours intubated, mean airway pressure, $PaCO_2$, pH, milrinone use, ventilator type	0.69 (0.67 – 0.71)	-
P-PREP, 2017§	ELSO Registry 2001–13 (n = 4352): >7 days to <18 years old with PARDS, mortality 43%, VA 57%, VV 43%	Comorbidities, duration of MV, mode of ECMO, primary pulmonary diagnosis, PaO_2/FiO_2 ratio, pH	0.69 (0.67 – 0.71)	0.69 (0.67 – 0.71)¶

APGAR: Appearance, pulse, grimace, activity and respiration; AUROC: Area under receiver operating characteristic curve; ELSO: Extracorporeal Life Support Organization; ECMO: Extracorporeal membrane oxygenation; FiO_2: Fraction of inspired oxygen; MV: Mechanical ventilation; $PaCO_2$: Partial pressure of arterial carbon dioxide; PaO_2: Partial pressure of arterial oxygen; PARDS: Paediatric acute respiratory distress syndrome; VA: Veno-arterial; VV: Veno-venous

*Maul TM, Kuch BA, Wearden PD. Development of risk indices for neonatal respiratory extracorporeal membrane oxygenation. ASAIO J 2016;62: 584–90.

†Barbaro RP, Bartlett RH, Chapman RL, Paden ML, Roberts LA, Gebremariam A, et al. Development and validation of the Neonatal Risk Estimate Score for Children Using Extracorporeal Respiratory Support. J Pediatr 2016;173:56–61.

‡Barbaro RP, Boonstra PS, Paden ML, Roberts LA, Annich GM, Bartlett RH, et al. Development and validation of the Pediatric Risk Estimate Score for Children Using Extracorporeal Respiratory Support (Ped-RESCUERS). Intensive Care Med 2016;42:879–88.

§Bailly DK, Reeder RW, Zabrocki LA, Hubbard AM, Wilkes J, Bratton SL, et al. Development and validation of a score to predict mortality in children undergoing extracorporeal membrane oxygenation for respiratory failure: Pediatric Pulmonary Rescue with Extracorporeal Membrane Oxygenation Prediction score. Crit Care Med 2017;45:e58–66.

‖Mode of ECMO used was not specified

¶Validation with an independent cohort of 2007 patients by Bailly et al.[71]

distributive shock with refractory multi-organ failure, the role of ECMO may be limited.[84]

At present, there are limited detailed reports on the use of ECMO in COVID-19.[3,4,85] Based on recent clinical data related to COVID-19, previous studies and recommendations from ELSO, the Chinese Society of Extracorporeal Life Support (CSECLS) has recently drafted a series of recommendations for the use of ECLS for critically ill patients with COVID-19[86] (Table 7). While providing clear and objective indications for ECLS, these recommendations lack guidance for optimal MV strategy. Considering that the majority of deaths from ARDS are caused by sepsis and multi-organ failure (MOF)[87] and that there is emerging evidence of VILI contributing to MOF,[88] we should focus on identifying and adhering to the optimal mode of LPV while on ECMO support. Whether this ideal LPV strategy to minimise VILI turns out to be ultra-low TV of <3 mL/kg, apnoeic oxygenation with PEEP or even individualised electrical impedance tomography-guided MV, it is biologically plausible and reasonable to take advantage of the support provided by ECMO to further reduce MV settings from the current accepted standard of LPV.[82] We eagerly await the results of ongoing trials assessing the role of ultra-low TV in ARDS to provide further guidance.[18,19] The need to rely on evidence derived outside of a respiratory pandemic must be recognised, given the numerous challenges of conducting large, multi-centre trials in resource-limited settings. While this might limit the applicability of study findings, we may have no other choice but to extrapolate such findings to patients in future pandemics. Efforts to minimise VILI and consequent MOF should also be coupled with strict adherence to infection control precautions to reduce the incidence of intercurrent sepsis, ventilator-associated pneumonia and nosocomial transmission of COVID-19 to healthcare workers. This is especially important, given that up to 40% of a reported COVID-19 cohort were attributed to nosocomial transmission.[3]

Table 6. Summary of Adult Predictive Scoring Systems for Survival for ECMO in Acute Respiratory Failure

Score, Year	Cohort Characteristics/ ECMO Mode	PreECMO Variables	Internal Validation (AUROC)	External Validation (AUROC)
ECMOnet, 2013[*]	Italian cohort 2009 (n = 60): H1N1 ARDS, mortality 32%, VA 2%, VV 98%,	Bilirubin, haematocrit, hospital LOS, mean arterial blood pressure, serum creatinine	0.86 (0.75 – 0.96)	0.69 (0.56 – 0.83)[**] 0.60 (0.54 – 0.67)[††] 0.51 (0.37 – 0.66)[‡‡] 0.69 (0.59 – 0.79)[§§]
Roch, 2013[†]	French cohort 2009–13 (n = 85): ARDS, mortality 56%, VA 9%, VV 91%	Age, diagnosis of influenza, pneumonia, SOFA score	0.80 (0.71 – 0.89)	0.70 (0.56 – 0.83)[‡‡] 0.55 (0.45 – 0.70)[‖‖] 0.56 (0.45 – 0.68)[§§]
PRESERVE, 2013[‡]	French cohort 2008–12 (n = 140): ARDS, mortality at 6 months 40%, VA 5%, VV 95%	Age, body mass index, immunocompromised status, MV duration, PEEP, plateau pressure, SOFA score, use of prone positioning	0.89 (0.83 – 0.94) [to predict 6-month survival]	0.68 (0.62 – 0.75)[††] 0.80 (0.66 – 0.90)[‡‡] 0.64 (0.51 – 0.77)[‖‖] 0.59 (0.48 – 0.71)[§§]
Enger, 2014[§]	German cohort 2008–13 (n = 304): acute respiratory failure, mortality 38%, VV 100%	Age, haemoglobin, immunocompromised status, lactate, minute ventilation on MV	0.75 (0.69 – 0.80)	–
RESP, 2014[‖]	ELSO Registry 2000–12 (n = 2355): acute respiratory failure, mortality 43%, VA or mixed modes 18%, VV 82%	Acute non-pulmonary infection, acute respiratory diagnosis, age, cardiac arrest, CNS dysfunction, immunocompromised status, inhaled nitric oxide use, MV duration, $PaCO_2$, PIP, use of bicarbonate infusion, use of paralysis	0.74 (0.72 – 0.76)	0.92 (0.89 – 0.97)[¶¶] 0.79 (0.65 – 0.89)[‡‡] 0.69 (0.60 – 0.79)[##] 0.69 (0.58 – 0.81)[‖‖] 0.64 (0.53 – 0.75)[§§]
VV-ECMO mortality score, 2016[¶]	Taiwanese cohort 2007–15 (n = 116): acute respiratory failure, mortality 47%, VV 100%	Immunocompromised status, MV duration, SOFA score	0.76 (0.67 – 0.85)	–
PRESET, 2017[#]	German cohort 2010–15 (n = 108): ARDS, mortality 62%, VV 100%	Hospital LOS, lactate, mean arterial blood pressure, pH, platelet count	0.85 (0.76 – 0.93)	0.70 (0.56 – 0.83)[***]

ARDS: Acute respiratory distress syndrome; AUROC: Area under receiver operating characteristic curve; CNS: Central nervous system; ELSO: Extracorporeal Life Support Organization; ECMO: Extracorporeal membrane oxygenation; FiO_2: Fraction of inspired oxygen; LOS: Length of stay; MV: Mechanical ventilation; $PaCO_2$: Partial pressure of arterial carbon dioxide; PaO_2: Partial pressure of arterial oxygen; PEEP: Positive end-expiratory pressure; PIP: Peak inspiratory pressure; SOFA: Sequential organ failure assessment; VA: Veno-arterial; VV: Veno-venous

[*]Pappalardo F, Pieri M, Greco T, Patroniti N, Pesenti A, Arcadipane A, et al. Predicting mortality risk in patients undergoing venovenous ECMO for ARDS due to influenza A (H1N1) pneumonia: the ECMOnet score. Intensive Care Med 2013;39:275–81.

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[#]Hilder M, Herbstreit F, Adamzik M, Beiderlinden M, Burschen M, Peters J, et al. Comparison of mortality prediction models in acute respiratory distress syndrome undergoing extracorporeal membrane oxygenation and development of a novel prediction score: the PREdiction of Survival on ECMO Therapy-Score (PRESET-Score). Crit Care 2017;21:301.

[**]Validation in an independent cohort of 74 patients by Papparlardo et al.[72]

[††]Validation in a cohort by Enger et al.[75]

[‡‡]Validation in a cohort of 50 patients by Lee et al.[79]

[§§]Validation in a cohort of 108 patients by Hilder et al.[78]

[‖‖]Validation in a cohort of 99 patients by Kang et al.[80]

[¶¶]Validation in an independent cohort of 140 patients by Schmidt et al.[76]

[##]Validation in a cohort of 116 patients by Cheng et al.[77]

[***]Validation in an independent cohort of 59 patients by Hilder et al.[78]

Table 7. Summary of Recommendations for Extracorporeal Life Support for COVID-19 from the Chinese Society of Extracorporeal Life Support*

Recommendation	Description
Indications for ECMO	• Hypoxemia despite maximal conventional mechanical ventilation (FiO_2 ≥0.8, TV 6 mL/kg, PEEP ≥10 cmH_2O) with at least 1 of the following conditions met: ▪ PaO_2/FiO_2 ratio <50 for >3 hours ▪ PaO_2/FiO_2 ratio <80 for >6 hours ▪ PaO_2/FiO_2 ratio <100 when FiO_2 = 1.0 ▪ Arterial pH <7.25, $PaCO_2$ >60 mmHg for >6 hours and RR >35 breaths/min ▪ Arterial pH <7.2 with Pplat >30 cmH_2O and RR >35 breaths/min ▪ Air leak syndrome • Cardiogenic shock or cardiac arrest
Relative contraindications	• Combination of irreversible disease, severe central nervous system damage or advanced-stage malignancy • Coagulopathy • Mechanical ventilation at high settings (FiO2 >0.9, Pplat >30 cmH2O) lasting ≥7 days • Severe multiple organ failure • Moderate to severe aortic regurgitation and acute aortic dissection could be considered contraindications to VA-ECMO support • Pharmacologic immunosuppression (absolute neutrophil count <0.4 × 109/L) • Lack of vascular access to ECMO cannulation due to altered anatomy or vascular pathology • While advanced age was not considered an actual contraindication, it is associated with increased mortality risk
Circuit configuration	• VV-ECMO is preferred in normal cardiac function • VA-ECMO may be considered if cardiogenic shock or cardiac arrest occurs • VAV-ECMO may be considered in differential hypoxia between upper and lower body

COVID-19: Coronavirus disease 2019; ECMO: Extracorporeal membrane oxygenation; FiO_2: Fraction of inspired oxygen; $PaCO_2$: Partial pressure of arterial carbon dioxide; PaO_2: Partial pressure of arterial oxygen; PEEP: Positive end-expiratory pressure; Pplat: Plateau pressure; RR: Respiratory rate; TV: Tidal volume; VA: Veno-arterial; VAV: Veno-arterial-venous; VV: Veno-venous

*Chinese Society of Extracorporeal Life Support. Recommendations on extracorporeal life support for critically ill patients with novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi 2020;43:E009.

The expansion in ECMO use during the H1N1pdm09 pandemic has highlighted the importance of collaboration within and between institutions to establish and strengthen ECMO capabilities to optimise outcomes. Key steps to institute in the COVID-19 epidemic include the preparation of designated high-volume expert ECMO centres, establishment of ECMO transport services with clear criteria for timely referral and transfer of critically ill patients, as well as simulation training to test and enhance knowledge, skill and workflows. However, ECMO transport services should be centrally coordinated, with a dynamic criterion for ECMO based on resource availability, so as to prevent ECMO centres from being overwhelmed.[84] The expanding use of ECMO must also be accompanied by efforts to reduce its associated risks. For example, the use of biocompatible circuits and hollow-fibre oxygenators have contributed to a reduced need for anticoagulation.[7] This is demonstrated by the recent EOLIA trial, where severe bleeding complications were rare, with a 2% incidence of haemorrhagic stroke in the ECMO group, compared to 4% in the non-ECMO group.[14] Finally, national and institutional protocols must be provided to guide physician decisions regarding resource-allocation and patient selection for ECMO for critically ill patients with COVID-19, ideally by considering multiple ethical principles in conjunction with the use of prediction scoring systems and expert clinical judgement.

Conclusion

The role of ECMO for ARDS secondary to respiratory epidemics and pandemics has expanded and continues to grow. While the majority of patients with COVID-19 have had mild disease, a significant proportion become critically ill and develop ARDS and circulatory compromise. Despite equipoise regarding the benefit of ECMO in ARDS and the lack of robust evidence for optimal MV techniques and infection control, recent and emerging research continue to be encouraging, highlighting the importance of capitalising on ECMO support to minimise VILI and MOF, as well as improvements in technology and practices to reduce the risks of ECMO. We may need to rely on evidence for ECMO derived outside of a respiratory pandemic, given the challenges of conducting large, multi-centre trials in resource-limited settings. Moral dilemmas regarding patient selection for ECMO in a resource-deficient setting may undermine various aspects of the healthcare system. Thus, it is critical to prepare and develop protocols and surge capacity for future pandemics, as well as craft

guidelines for patient selection, using multiple ethical principles and prediction scores to complement expert clinical judgement.

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