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Veno-venous extracorporeal membrane oxygenation allocation in the COVID-19 pandemic

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ABSTRACT

Rapid global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resultant clinical illness, coronavirus disease 2019 (COVID-19), drove the World Health Organization to declare COVID-19 a pandemic. Veno-venous Extra-Corporeal Membrane Oxygenation (VV-ECMO) is an established therapy for management of patients demonstrating the most severe forms of hypoxemic respiratory failure from COVID-19. However, features of COVID-19 pathophysiology and necessary length of treatment present distinct challenges for utilization of VV-ECMO within the current healthcare emergency. In addition, growing allocation concerns due to capacity and cost present significant challenges. Ethical and legal aspects pertinent to triage of this resource-intensive, but potentially life-saving, therapy in the setting of the COVID-19 pandemic are reviewed here. Given considerations relevant to VV-ECMO use, additional emphasis has been placed on emerging hospital resource scarcity and disproportionate representation of healthcare workers among the ill. Considerations are also discussed surrounding withdrawal of VV-ECMO and the role for early communication as well as consultation from palliative care teams and local ethics committees. In discussing how to best manage these issues in the COVID-19 pandemic at present, we identify gaps in the literature and policy important to clinicians as this crisis continues.

1. Introduction

Unfettered global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) prompted the World Health Organization to declare the clinical illness known as coronavirus disease 2019 (COVID-19) a pandemic on March 11, 2020. COVID-19 related acute respiratory distress syndrome (ARDS) has affected a wide spectrum of patients. Higher mortality is seen not only more vulnerable populations such as the elderly or chronically ill but also young, otherwise healthy patients [1]. This burden of disease has led to high utilization of healthcare resources, particularly with respect to supportive therapies for critical illness. Veno-venous Extra-Corporeal Membrane Oxygenation (VV-ECMO), a resource-intensive approach to managing severe respiratory failure [2], was utilized with some success during the influenza A (H1N1) pandemic of 2009 [3,4] and presumptively may be of value when managing COVID-19 [3,5,6]. However, given the severity of constraints on healthcare resources, the utilization of VV-ECMO as a therapeutic intervention for COVID-19 requires careful deliberation.

The use of VV-ECMO is indicated in severe hypoxemic respiratory failure refractory to conventional mainstays of medical therapy including mechanical ventilation with optimal positive end expiratory pressure (PEEP) [7], neuromuscular blockade [8], and prone positioning [9]. VV-ECMO differs from veno-arterial ECMO (VA-ECMO) as the latter technology is typically initiated for patients in cardiac or circulatory failure with or without concomitant respiratory failure. Despite a lack of definitive data supporting the use of VV-ECMO, there continues to be substantial optimism surrounding its benefit with widespread ongoing utilization of this therapy [10,11]. Importantly, despite its logistical constraints, patients with severe COVID-19-related ARDS have already been managed with VV-ECMO [12-14]. However, given the rapid spread of COVID-19, many intensive care units (ICUs) have become overwhelmed; allocation of VV-ECMO must be a carefully adjudicated triage decision. Here we outline the ethical and legal aspects pertinent to allocation of this resource-intensive, but potentially life-saving, therapy in the setting of the COVID-19 pandemic.

2. VV-ECMO in COVID-19-associated acute respiratory failure

Early experience with COVID-19 has demonstrated unique features distinguishing the disease from other viral illnesses such as H1N1,

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Severe Acute Respiratory Distress Syndrome (SARS), and Middle-Eastern Respiratory Syndrome (MERS). Two primary "phenotypes" describing the most common features of COVID-19 have been proposed [15]. The Type L phenotype is characterized by low respiratory system elastance. This phenotype has been associated with low lung weight, low ventilation-to-perfusion ratio, and low recruitability. Clinicians have noticed atypical presentations in these COVID-19 patients, including some patients who present with profound desaturation without loss in mental acuity. Such patients have been successfully treated without mechanical ventilation, instead utilizing non-invasive ventilation modalities such as high flow nasal cannula [16]. By contrast, the Type H phenotype is characterized by high elastance, heavier lung weight, more significant right-to-left shunt, and greater lung recruitability. Type H patients more often require mechanical ventilation. The disease may evolve from the Type L phenotype to Type H due to COVID-19-related cytokine storm, stress of injurious mechanical ventilation, and pulmonary edema caused by increased vascular permeability [17,18]. In clinical practice, differentiation of the two phenotypes is challenging. Without large randomized controlled trials to guide clinicians treating this unique disease, there remains no consensus in how to optimally manage critically ill patients with COVID-19-associated respiratory failure [19]. Thus, clinicians must adhere to time-tested therapies for other forms severe ARDS. VV-ECMO is among these therapies, and may be considered for patients displaying profound deoxygenation despite mechanical ventilation with optimized PEEP, neuromuscular blockade, and prone positioning.

Guidelines for the use of VV-ECMO are imprecise. Directives from the Extracorporeal Life Support Organization (ELSO) suggest judicious use of this technology during a pandemic, due to its resource intensive nature [20,21]. VV ECMO is most likely to benefit patients when initiated relatively early in a patient's disease course [22]. Once initiated, VV-ECMO is commonly considered a "bridge" to specific endpoints, such as recovery or lung transplantation. Unfortunately, VV-ECMO may also become a "bridge to nowhere" in patients who become dependent on VV-ECMO though lacking realistic chance of intrinsic recovery. Thus, it is imperative that possible outcomes and goals of care are clearly communicated prior to ECMO initiation.

Early experience with VV-ECMO in COVID-19 was characterized by high mortality rates raising alarm among clinicians [12,13,23]. A more recent pooled analysis of 331 patients placed on ECMO found a combined mortality rate of 46% [24]. This figure is not dissimilar from the overall 40% mortality rate for extracorporeal life support (ECLS) in pulmonary failure [25] and is an improvement upon reported ICU mortality rates exceeding 60% in mechanically ventilated COVID-19 patients [14,26,27].

3. Resource allocation concerns in a pandemic

To maximize benefit to a population suffering from pandemic and to reduce the frequency of "bridge to nowhere" situations, appropriate assessment and triage of VV-ECMO candidates must occur. Triage strategies range from those which focus predominantly on individual benefit to those which prioritize population health, at the expense of some especially-ill persons (Table 1). Unfortunately, evidence supporting any one particular approach is lacking. Of note, ELSO guidelines state that healthcare providers should be given high priority for access to VV ECMO, superseded only by the young with minor or no comorbidities [21]. This triage approach essentially endorses a "societal value" paradigm, prioritizing those who may generate greatest benefit to society at large. However, this approach has not been universally adopted. At Beth Israel Deaconess Medical Center's current critical care resource allocation guideline (created with Massachusetts state government guidance [28]), health care worker status is only used as a tie-breaker between patients with equal prioritization scores. This strategy has already been called into question and may be amended in future versions of this document.

Recent guidance by the Commonwealth of Massachusetts recommends to reserve VV-ECMO for those who would be most likely to benefit and avoid prolonged use if there are no signs of recovery [28]. Ultimately, irrespective of nomenclature of a given triage strategy, the decision to offer VV-ECMO may be best made by multidisciplinary teams at the bedside based on the principle of distributive justice [29]. Broadly, distributive justice refers to the fairness in distribution of finite resources and benefits. Centers should aim to justly distribute the high-intensity, complex modality of VV-ECMO in a manner which prioritizes the needs of the populations they serve, while withholding therapy from individual patients who realistically are unable to benefit from this specific component of care. As healthcare institutions reach escalating levels of surge capacity, distributive justice approaches generally support the idea that increasingly stringent selection criteria be used to prioritize those most likely to benefit and return to an acceptable quality of life (Table 1) [30].

Centers struggling with designing a comprehensive approach to VV-ECMO triage protocols may benefit from ELSO guidelines for ECMO in COVID-19 [30]. In these, specific contraindications for VV-ECMO are listed, which may help tailor the institutional approach. These contraindications are listed in Table 2. Furthermore, a number of VV-ECMO risk prediction models have been created. These may also help guide

Table 1
Allocation strategies and considerations in the COVID-19 pandemic.

Allocation strategy	Definition	COVID-19 pandemic application
Utilitarian	Prioritizing based on likelihood of survival. Saving the most lives.	- Favoring VV-ECMO allocation to patients with lower RESP score or based on another risk calculator. - Ignores other morally relevant considerations
Life stages or QALYs preserved	Saving the most life years QALY.	- No appropriate validated risk tool available. - Introduces subjectivity, consider multidisciplinary approach.
Likelihood of death	Prioritizing individuals of the greatest acuity.	- The sickest patients will naturally have lower survival resulting in worsened outcomes. - Significant resources may be spent in medically inappropriate cases.
Societal value	Prioritizing individuals with particular instrumental or social value.	- Who should be prioritized, to what degree? (Politicians, religious figures, health care workers, military personnel) - May invite controversy.
First come, first served	Prioritizing patients currently on VV-ECMO	- Accounts for no clinically or socially relevant factors. - Significant resources may be spent in medically inappropriate cases. - Disparately impacts those communities with least access to ECMO centers.
Lottery	Prioritizing patients based on random chance.	- Accounts for no clinically or socially relevant factors.
Self-sacrifice	Allowing individuals or surrogate decision makers acting on their behalf to disavow their right to VV-ECMO.	- Potentially coercive or impacted by distressed emotional state in time of crisis. - Potential for conflict.
Combination	Prioritizing patients based on more than one rationing strategy.	- May inform institutional *scoring* rubric established a priori. - Consider multidisciplinary approach, evolving needs.

Abbreviations: QALY, quality adjusted life years; VV-ECMO, veno-venous extracorporeal membrane oxygenation, RESP, Respiratory ECMO Survival Prediction.

decision-making with respect to patient survival [31-36] (Table 3). These risk scoring systems vary widely in inclusive variables and resulting complexity due to methodology and relatively small derivation cohorts expected with this type of therapy. The Respiratory Extracorporeal Membrane Oxygen Survival Prediction (RESP) score [34], developed from a cohort of 2355 patients contained within the ELSO registry, by far the largest derivation and validation study of VV-ECMO to date. As such the RESP score is the most widely used tool for risk stratification prior to initiation, although external validation studies have yielded mixed results [35,37,38]. A noteworthy finding of the derivation and validation of the RESP score is the recognition that viral pneumonia was independently associated with hospital survival (odds ratio, 2.26; 95% CI 1.62–3.14; $P < 0.0001$). Thus, legitimate enthusiasm for use of VV-ECMO in the COVID-19 patients may be more warranted than in other populations.

As a supportive therapy, VV-ECMO does not treat the underlying disease process but instead provides time for potential organ recovery or transplant. Unlike other supportive therapies (such as mechanical ventilation or renal replacement therapy) tremendous resources are required to initiate and manage VV-ECMO, including specialized healthcare workers trained to care for these patients [39].

VV-ECMO is expensive. The estimated cost of VV-ECMO is roughly $30,000 per quality adjusted life year (QALY) [40]. Although this figure compares favorably with some chemotherapeutic regimens expected to prolong life for less than one year [41], predicted pandemic-related economic fallout has led to cost concerns [42]. Hospitals, in particular, are reeling due to widespread cancellations of revenue-generating elective procedures. Thus, in keeping with the principle of distributive justice, individual centers must consider the future implications on population health (including other expensive care modalities) when designing VV-ECMO pandemic policies. Though, VV-ECMO may be resource intensive, it compares favorably to VA-ECMO in terms of cost, resource utilization and risk of adverse events [43,44]. This consideration is relevant when contemplating conversion from VV to VA-ECMO in patients who develop myocardial injury and/or distributive shock related to COVID-19 [45,46]. Such patients should be carefully screened for signs of multiorgan failure or other relative contraindications that may portend poor prognosis (Table 2).

Currently both large academic centers and many community hospitals have VV-ECMO capability, but these institutions have varied initiation practices [47]. Some thought-leaders have suggested creation of a centrally-coordinated regional outbreak system, with referral to high-volume centers when smaller centers reach capacity [48]. This strategy may balance the economic realities of a healthcare network's needs while also limiting disparities in access to VV-ECMO.

Table 2
Recommended contraindications for ECMO in centers facing resource constraints in the COVID-19 pandemic[a].

Relative contraindications
- Age ≥ 65
- Obesity (BMI ≥40
- Immunocompromised status
- No legal medical decision maker available
- Advanced chronic systolic heart failure
- High dose vasopressor requirement (not under consideration for V-A ECMO)
Absolute contraindications
- Advanced age
- Clinical Frailty Scale Category ≥ 3
- Mechanical ventilation >10 days
- Significant co-morbidities including:
o CKD ≥ III
o Cirrhosis
o Dementia
o Baseline neurologic disease precluding rehabilitation potential
o Disseminated malignancy
o Advanced lung disease
o Uncontrolled diabetes with chronic end-organ dysfunction
o Severe deconditioning
o Protein-energy malnutrition
o Severe peripheral vascular disease
o Other life-limiting medical illness
o Non-ambulatory status
- Severe multiple organ failure
- Severe acute neurologic injury e.g. anoxic, stroke
- Uncontrolled bleeding or contraindication to anticoagulation
- Inability to accept blood products
- Ongoing CPR

Abbreviations: BMI, body mass index; V-A, veno-arterial; ECMO extracorporeal membrane oxygenation; CPR, cardiopulmonary resuscitation.

[a] Adapted from Extracorporeal Life Support Organization COVID-19 Interim Guidelines [30]

4. Setting expectations and establishing goals of care

In many cases, patients will be incapacitated prior to initiation of VV-ECMO. Clinicians must therefore rely on advanced directives and/or surrogate decision makers to determine how a patient may wish to proceed with care. One unique circumstance presented by the current pandemic is the separation of hospitalized patients from surrogates due to distancing policies designed to prevent spread of COVID-19, forcing many important discussions to occur via telemedicine. Disrupted physical presence may complicate decision-making and generate significant psychological and emotional stress [49]. Early palliative-care consultation can assist families and clinicians with complex decision-making processes, reduce conflict, and increase family satisfaction [50]. Ethics consultation, while mandatory at some institutions for all VV-ECMO patients, may be warranted to ensure moral, ethically justifiable care is provided [51]. These discussions and consultations should occur before cannulation or as early as possible following VV-ECMO initiation. Ideally, predefined goals can be set, with tentative plans to withdraw care that is no longer meeting the patient's needs and allow for resources to be directed elsewhere.

Unfortunately, although multiple risk stratification instruments are available to guide initiation of VV-ECMO, no such instruments are available to guide withdrawal. Adverse events and suboptimal response to therapy are generally considered appropriate reasons to consider withdrawal of VV-ECMO [52]. This is especially true in patients with COVID-19, as they are uniquely predisposed to bleeding and/or thrombotic complications [53]. These realities should be discussed early, or even before, using VV-ECMO for a given patient. Setting clear goals, including the expectation that accrued complications or medically futility may warrant early discontinuation of therapy (implying a transition to comfort measures), can help families cope such decisions [54].

In periods of resource scarcity, particularly after an institution has activated an allocation policy (sometimes referred to as “Crisis Standards of Care”), communication with patients and surrogate decision makers regarding the process for allocation of any scarce resources is critical. This should include an explanation of the possibility that the patient will not receive a scarce resource or will receive it for a time-limited trial and then have it removed and reallocated prior to recovery. Prior understanding of this situation generally, should help when facing the specific circumstances of scarce VV-ECMO allocation decisions.

5. Legal and ethical precedents

A 2016 survey found that experienced physicians favored paternalistic values over patient autonomy when considering the value of complex care for a given patient. Hypothetically, this finding reflects physicians' unwillingness to cede authority to presumably less-knowledgeable care recipients, while also avoiding dispute over the appropriateness of ongoing medical care [55]. States differ in their attitudes toward this physician-patient relationship. For example, the Texas Advanced Directives Act of 1999 justifies withdrawing life-sustaining therapy against the wishes of surrogate

Table 3
Veno-venous ECMO survival prediction instruments.

Prediction instrument	Primary disease	Patients in derivation cohort	Predictors included	Internal validation (AUROC)	External validation (AUROC)
ECMOnet 2012 [36]	ARDS in suspected Influenza A (H1N1)	60 from 14 Italian hospitals	Pre-ECMO LOS, MAP, Bilirubin, Creatinine, Hematocrit	0.86	0.69 [36] 0.604 [32] 0.695 [35] 0.554 [62]
PRESERVE 2013 [31]	ARDS	140 patients from 3 French hospitals	Age, BMI, Immunocompromise, SAPS II, Prone positioning, MV duration, Plateau Pressure, PEEP	0.89	0.685 [32] 0.75 [63] 0.593 [35] 0.64 [37]
Roch et al. [33]	ARDS	85 patients at single French center	Age, SOFA score, Influenza	0.80	0.564 [35] 0.619 [62]
RESP 2014 [34]	Severe acute respiratory failure	2355 from ELSO database	Age, immunocompromise, diagnosis, CNS dysfunction, Non-pulmonary infection, bicarbonate infusion, Cardiac Arrest, MV duration, NMB, iNO, PaCO2, PIP	0.74	0.92 [31] 0.81 [63] 0.645 [35] 0.835 [62] 0.69 [37]
PRESET 2017 [35]	ARDS	108 from single German center	Pre-ECMO LOS, MAP, Admission, arterial pH, Lactate, Platelet count	0.845 [0.76–0.93]	0.70

Abbreviations: ECMO, extracorporeal membrane oxygenation; AUROC, area under the receiver operating characteristics curve; ARDS, acute respiratory distress syndrome; LOS, length of stay; MAP, mean arterial pressure; MV, mechanical ventilation; PEEP, positive end expiratory pressure; SOFA, sequential organ failure assessment; ELSO, Extracorporeal Life Support Organization; CNS, central nervous dysfunction; NMB neuromuscular blockade; iNO, inhaled nitric oxide; PaCO2, arterial content of carbon dioxide; PIP, peak inspiratory pressure.

decision makers so long as physicians account for patient autonomy, ensure good stewardship of patient resources, and avoid harm to patients [56,57]. This could be considered "informed non-dissent," in which surrogates agree interventions should be limited but prefer to leave the actual decision to continue or withdraw therapy to physicians [58,59]. Informed non-dissent may be a palatable approach for both clinicians and recipients of care, though must be a legally acceptable strategy in an individual institution.

In Massachusetts, in the absence of a legally appointed surrogate decision maker, providers must generally seek approval from surrogate decision makers before withdrawing care from patients unable to vouch for themselves. In cases involving withdrawal of VV-ECMO, agreement among the patient and/or surrogate decision-makers (legally recognized or otherwise) obviates the need for settlement within the court system. Withdrawal despite the objection of one or more family members could be considered battery. To our knowledge, no case has established a legal precedent for consideration of withdrawal of technology as battery. Further, Massachusetts passed legislation during the COVID-19 state of emergency that granted certain liability protections for the acts or omissions of healthcare providers during such state of emergency, so long as the treatment was impacted by the treatment conditions resulting from the COVID-19 outbreak and the providers acted in good faith [60]. Accordingly, during the recent COVID-19 outbreak, any uncertainty regarding the ability of a Massachusetts provider to withdraw VV-ECMO from a patient who was on a "bridge to nowhere" seems to have been resolved.

Importantly, it is commonly considered ethically unacceptable to remove a patient from a life sustaining therapy to make room for another [61]. Value for autonomy necessitates not only informed consent upon initiation, but also upon withdrawal of therapy. It is generally considered legally unacceptable to remove patients from therapy against their will, even if removal would provide greater benefit to another patient. In cases of withdrawal, the principle of nonmaleficence may prompt clinicians to wonder if not receiving an intense intervention, such as VV-ECMO, is better than receiving that intervention when it is inadequate to reverse a patient's demise. VV-ECMO cannulation, even when intended as life-saving therapy, does bear the risk of unintentionally hastening death if complications were to occur. COVID-specific complications related to prothrombotic state and the use of anticoagulation are also pertinent and should be communicated to families.

At our tertiary medical centers, institutional policy dictates that no provider should be forced to provide treatment that is harmful, ineffective, or of no medical benefit. At Beth Israel Deaconess Medical Center, dissenting health care surrogates have the right to a second opinion and may be offered accommodation of patient transfer. If no facility is willing to accept the patient, the surrogate can appeal once more, prompting a committee to deliberate. If the committee reaches a consensus that the requested intervention is harmful, ineffective, or of no medical benefit, then hospital administration generally supports the clinicians' decision not to offer such intervention, even over the surrogate decision-maker's objection.

VV-ECMO is a difficult technology to reconcile under this rubric because it is, at least temporarily, usually effective at prolonging life. However, when a patient's life is sustained with no hope of ever being able to survive independent of the intervention outside the ICU setting (i.e., is receiving therapy as a "bridge to nowhere"), the intervention should be considered to be of no medical benefit. This determination would apply under normal standards of care, as well as crisis standards of care. As mentioned above, the best way to avoid such situations is through discussion of these concepts prior to ECMO initiation. Palliative care consultants and ethics committees can aid in family counseling in situations where families cannot be at the bedside.

In the setting of crisis capacity and activation of scarce resources allocation policies, our institution endorses consideration of odds for survival following a therapeutic trial to guide discontinuation of therapy. If a patient either shows signs of decline despite receiving VV-ECMO or does not show signs of improvement after an appropriate trial period, VV-ECMO may be discontinued in favor of another patient more likely to benefit from VV-ECMO. This is an explicit rejection of the first-come, first-served paradigm which is likely to result in unjust distribution; namely, it is unlikely to save the most lives and life-years (Table 1) and it is likely to have a disproportionately negative impact on individuals from certain ethnic and racial groups, and individuals of lower socio-economic status. In this time of scarcity, the threshold for making this decision may fluctuate with increasing disease burden and it may be reasonable to consider a paradigm valuing the greatest number of life years preserved, while ensuring equitable distribution along racial, ethnic, and socio-economic lines.

6. Conclusion: The future of VV-ECMO allocation

VV-ECMO is a well-established component of support for patients in respiratory failure and has been used successfully in treating COVID-19 associated respiratory disease. However, access to this therapy is dependent on regional disease prevalence, individual hospital expertise, and perceived benefit to the balance between individual patients and the

population as a whole. Prior to the next pandemic, allocation guidelines should be more rigorously defined to prevent injustice in clinical outcomes, and to reduce the stress on healthcare providers who are choosing to use this particular resource. These guidelines may be best sourced from professional medical societies. Medical professionals have the responsibility to inform the public regarding the true risks and benefits of VV-ECMO such that these guidelines can be understood and accepted by affected communities. Regional leadership from centers of excellence should engage communities and form outbreak response systems capable of making allocation decisions guided by distributive justice principles. Nevertheless, allocation decisions should be transparent and clearly communicated to patients and surrogate decision makers. There is clearly a need for clinicians to effectively communicate when VV-ECMO therapy becomes medically inappropriate care in terms of the patient's values. This process begins with establishing expectations before initiation and can be facilitated by consultants from palliative care and institutional ethics committees. Addressing these allocation concerns will facilitate optimal deployment of VV-ECMO within the current pandemic and for the next healthcare catastrophe we may face.

Declaration of Competing Interest

None.

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