Advanced Pulmonary and Cardiac Support of COVID-19 Patients: Emerging Recommendations From ASAIO—A "Living Working Document"

Keshava Rajagopal,*† Steven P. Keller,‡ Bindu Akkanti,§ Christian Bime,¶ Pranav Loyalka,† Faisal H. Cheema,*†‖ Joseph B. Zwischenberger,# Aly El Banayosy,** Federico Pappalardo,†† Mark S. Slaughter,‡‡ and Marvin J. Slepian‡‡

The severe acute respiratory syndrome (SARS)-CoV-2 is an emerging viral pathogen responsible for the global coronavirus disease 2019 (COVID)-19 pandemic resulting in significant human morbidity and mortality. Based on preliminary clinical reports, hypoxic respiratory failure complicated by acute respiratory distress syndrome is the leading cause of death. Further, septic shock, late-onset cardiac dysfunction, and multiorgan system failure are also described as contributors to overall mortality. Although extracorporeal membrane oxygenation and other modalities of mechanical cardiopulmonary support are increasingly being utilized in the treatment of respiratory and circulatory failure refractory to conventional management, their role and efficacy as support modalities in the present pandemic are unclear. We review the rapidly changing epidemiology, pathophysiology, emerging therapy, and clinical outcomes of COVID-19; and based on these data and previous experience with artificial cardiopulmonary support strategies, particularly in the setting of infectious diseases, provide consensus recommendations from ASAIO. Of note, this is a "living document," which will be updated periodically, as additional information and understanding emerges. *ASAIO Journal* 2020; 66:588–598.

Key Words: COVID-19, coronavirus, mechanical ventilation, extracorporeal membrane oxygenation, mechanical circulatory support, ARDS

The human environment is surrounded by a myriad of viruses, the number, and type increasingly being defined.[1] Many viral species result in serious, if not fatal infections, *e.g.,* Marburg, Hanta, Ebola, although typically remaining contained to specific hosts, circumstances of infections, or geographies, limiting modes, and extent of spread.[2–4] Of viral species, respiratory viruses, in particular, have periodically presented with widespread distribution of virus resulting in pandemics, with often overwhelming morbidity and mortality.[3,5] We presently face such a situation with the emergence of the severe acute respiratory syndrome (SARS)-CoV-2 virus.[6–8] The major viral pandemics of the last century, including those involving 1918 H1N1 and 2009 H1N1 influenza and 2003 SARS-CoV and 2012 middle east respiratory syndrome (MERS)-CoV coronavirus, predominantly manifested as respiratory system illnesses with possible secondary cardiovascular and other end-organ system effects.[9] Although many patients develop a mild to moderate illness, a significant subset of patients develop severe progressive respiratory and occasionally cardiac failure, refractory to conventional therapies, including advanced ventilator management strategies. For these patients, the only plausible treatment strategy is artificial lung or circulatory support. From the initial clinical experience in China and in Italy, it is clear that SARS-CoV-2 infection, also termed coronavirus disease 2019, that is COVID-19, has a disease natural history that results in severe respiratory and circulatory compromise for a significant portion of those infected. It is the specific goal of the present paper to provide a resource document to the clinical community regarding evolving best practice strategies for advanced pulmonary and cardiac support in patients with severe progressive COVID-19. Overall, the philosophy of the present paper is to be a living document—one gathering best practice information of the moment, which will be rapidly and continuously updated as improved strategies emerge. We first provide a brief background on the biology and pathophysiology of COVID-19 infection, evolving modes of diagnosis, and valuable laboratory parameters to follow. We provide evolving information on medical therapies. We then focus on management of the severely compromised patient warranting

From the *Departments of Clinical and Biomedical Sciences, University of Houston College of Medicine, Houston, TX; †Houston Heart, HCA Houston Healthcare, Houston, TX; ‡Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; §Division of Pulmonary and Critical Care Medicine, Department of Medicine, McGovern Medical School, University of Texas-Houston, Houston, TX; ¶Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Arizona College of Medicine - Tucson and Banner Health, Tucson, AZ; ‖HCA Research Institute, Nashville, TN; #Department of Surgery, University of Kentucky College of Medicine and Medical Center, Lexington, KY; **Nazih Zuhdi Transplant Institute, Integris Baptist Medical Center, Oklahoma City, OK; ††Vita-Salute San Raffaele University, Milan, Italy; ‡‡Department of Cardiovascular and Thoracic Surgery, University of Louisville School of Medicine and Jewish Hospital, Louisville, KY; and §§Departments of Medicine and Biomedical Engineering, Sarver Heart Center, University of Arizona, Tucson, AZ.

Submitted for consideration April 2020; accepted for publication in revised form April 2020.

This article has been copublished in ASAIO Journal and Circulation: Heart Failure.

Disclosure: Dr Slepian has research grants from Abiomed and NIH/NIBIB. Dr Keller has research grant from Abiomed and NIH. Dr Bime has a research grant from NIH/NHLBI. Dr Zwischenberger has research grants from Avalon-Maquet and NIH and is an unpaid consultant for Cytosorbents; Dr El-Banayosy has a research grant from Abbott. The other authors have no conflicts of interest to report.

Correspondence: Keshava Rajagopal, Department of Clinical Sciences, University of Houston College of Medicine, Houston Heart, HCA Houston Healthcare, 1200 Binz Street, Suite 900, Houston, TX 77004. Email: krajago2@central.uh.edu, or Marvin J. Slepian, Departments of Medicine and Biomedical Engineering, Sarver Heart Center, University of Arizona, 1501 North Campbell Avenue, Tucson, Arizona 85724. Email: slepian@email.arizona.edu

DOI: 10.1097/MAT.0000000000001180

artificial lung or circulatory support. Recommendations are offered for patient selection and details of appropriate therapeutic pulmonary or cardiac support.

COVID-19 Infection: Background and Molecular Biology

COVID-19 is the result of infection with SARS-CoV-2, a novel coronavirus, causing severe acute respiratory syndrome.[6,10,11] COVID-19 is considered a zoonotic infection, with a natural reservoir most likely in bats, and with a potential intermediate species before the onset of human infection.[12,13] At the time of this writing, it is unclear how human transfer occurred. Moreover, if or when mutations have occurred in SARS-CoV-2, it is unknown whether these may have occurred within nonhuman animal reservoirs, or following human transfer. Recent studies, however, now point to pangolin species as a natural reservoir of SARS-CoV-2-like CoVs.[14]

SARS-CoV-2 is a single (+) stranded RNA virus whose replication is catalyzed by an RNA-dependent RNA polymerase.[15] However, genomic single-stranded RNA also has messenger RNA function, such that it may be translated on ribosomes into a peptide sequence. Similar to the original SARS virus, also a coronavirus, SARS-CoV-2 is capable of binding cell surface-bound angiotensin-converting enzyme 2 (ACE2), which is richly expressed on pneumocytes, as well as endothelial cells.[11,16] This interaction facilitates viral intracellular entry. In addition, the viral spike protein has a polybasic cleavage site at a location between the spike subunits, which may be proteolytically cleaved; this is thought to enhance viral entry and infectivity.[17,18]

Clinical Pathophysiology and Outcomes

Infection with SARS-CoV-2 results in the development of acute pneumonia, with patchy ground-glass opacities.[19] The distribution of this infiltrate appears to be more dominant in lung bases, and is eccentric, with an emerging pattern.[20] This pattern may be appreciated via direct example shared on line.[21] This is a near-universal (>99%) finding in hospitalized patients with COVID-19, based upon data from the original patient cohorts in Wuhan, China. However, clinical manifestations may be quite variable. Fever is a near-universal finding. However, although dyspnea is a common finding both in intensive care unit (ICU)-hospitalized as well as non-ICU-hospitalized patients, it is unsurprisingly significantly and substantially more common in ICU patients. In addition, constitutional symptoms such as anorexia are more common in ICU patients.[22]

Acute hypoxemic respiratory failure of varying severity is the norm in ICU patients. A median P_aO_2/F_IO_2 ratio of <150 was identified in ICU-hospitalized patients, and ratios were worse in non-survivors in comparison to survivors.[23] The documented incidence of acute respiratory distress syndrome (ARDS) was ≈20%. Biochemical evidence of myocardial injury was present in ≈15% of patients; further, overt shock was evident in <10% of patients.[24] As expected, ARDS and shock were more common in ICU-hospitalized patients. Systemic arterial blood pressure did not appear to relate to survival; however, inotrope/vasoconstrictor usage was substantially higher in ICU-hospitalized and non-survivor patients.[25] Moreover, the hemodynamic profiles of shock in these patients are unclear. Finally, as is common in other etiologies of shock and respiratory failure, dysfunction of other end-organs, such as the kidney and the liver, was found to be more common and more severe in ICU-hospitalized and non-survivor patient groups. In particular, acute kidney injury and its severity were highly correlated with poorer outcomes.

Laboratory data consistent with higher-risk COVID-19 subgroups were identified as well.[26] ICU-hospitalized patients and non-survivors tended to have overall leukocytosis yet with lymphopenia, coagulation profiles consistent with disseminated intravascular coagulation (elevated prothrombin time and D-dimer), elevated blood urea nitrogen and creatinine, elevated serum transaminase levels, and elevated procalcitonin.[27,28] These findings are broadly consistent with those of high-risk subsets of sepsis.

Many fail to appreciate the degree of isolation and care that Chinese medical institutions provided their early patients. They were experienced with the SARS epidemic and applied that experience early in the spread of the disease. Likewise, the medical sophistication of Italy appears underappreciated in the lay press. The Italian setup mostly focused on large hospitals with ICU preparedness, lacking a comprehensive plan on community medicine and small healthcare institutions.[29] Indeed, the first patient was diagnosed in a small city, Codogno. Following this, a "Red Zone," with total limitation of social mobility, was instituted for containment of infectious spread. The case was particularly challenging since this patient was a young healthy athlete without any medical or epidemiological (travel to China or contact) risk factors. The first case immediately prompted the development of a task force for managing and limiting the outbreak on a Regional level.[30] The United States is early in its experience with COVID-19, but has per capita fatality rates that are, along with Germany, the lowest of those countries afflicted with a large burden of infected patients. The early German public health experience with COVID-19 is particularly noteworthy for the lowest mortality outcomes within the group of infected patients, but the reasons for this are unclear at this time. Unpublished communications suggest that this may be due, at least in part, to a younger COVID-19-infected population.

COVID-19 Diagnostic Strategies and Monitoring

COVID-19 infection manifests with symptoms typically associated with other respiratory infections, that is, fever, cough, and shortness of breath, which are sensitive but highly non specific. To this end, a basic diagnostic algorithm for "fever clinics," given the high sensitivity of fever as a sign of COVID-19, has been developed.[31] High-fidelity, sensitive, specific, and predictive diagnostic strategies are needed. It should be noted that current Center for Disease Control (CDC) recommendations reiterate that "clinicians are strongly encouraged to test for other causes of respiratory illness" as appropriate. Conversely, COVID testing should be employed for those with a high index of suspicion and for those at increased risk.[32] A hierarchy of "priorities of testing" is provided by the CDC. Current diagnostic strategies include obtaining samples for viral testing from the upper (nasopharyngeal or oropharyngeal swab or wash) or lower (induced sputum, endotracheal aspirates, bronchoalveolar lavage) respiratory tract samples for *via* nucleic acid amplification tests, such as reverse transcriptase-polymerase chain reaction; as well as for bacterial or fungal cultures as is appropriate.[33,34] Confirmation of SARS-CoV-2 may be made *via* follow on nucleic acid sequencing, *via* detection of the specific N, E, S, and RdRP viral genes. For

in-hospital patients, we recommend sending two specimens on two different days to ensure adequate specimen collection. A computed tomography scan of the chest revealing ground-glass opacities or consolidation consistent with the disease increases the clinical suspicion of disease.[19,20] Basic monitoring includes pulse oximetry and telemetry for stable patients outside the intensive care unit, and more invasive monitoring with systemic arterial and central venous/pulmonary arterial (PA) catheters in the intensive care unit. Of note, for inpatients, continued viral detection and shedding has been reported which may also be monitored *via* blood and stool sampling.[35,36]

A baseline transthoracic echocardiogram (see following) can be performed if the patient presents with systemic arterial hypotension or overt shock. PA catheter placement may be useful in patients with shock as well (see following). We do not recommend routine endomyocardial biopsies, due to risks of cardiac structural injury (iatrogenic ventricular septal defect, right ventricular [RV] free wall rupture and cardiac tamponade, and tricuspid valve injury with regurgitation). In patients who have evidence of focal/regional cardiac injury, *via* electrocardiography or echocardiography, diagnostic left-sided cardiac catheterization with coronary angiography is reasonable.

Ultimately it will be important to monitor if a given patient mounts an immune response and develops protective immunity. While the COVID pandemic is just evolving, it is important to mention this here as well. As such, with an eye to the future, early reports examining the serologic response of patients in China reveal that COVID patients generally mount a typical serologic response to viral infection. Specifically, utilizing ELISA, IgM has been detected by day 3 with IgG levels rising subsequently as IgM begins to decline.[37]

Pharmacotherapy

There are currently no specific therapeutics approved by the Food and Drug Administration to treat this patient population. The only randomized-controlled trial done to date was an open-label trial comparing Rotinavir/Lotanavir combination therapy to standard of care in patients with confirmed COVID-19 illness.[38] This study included 199 hospitalized patients with treatment with the study drug failing to show difference in time to clinical improvement or mortality. There was a trend towards better outcomes in patients started on the study drug less than 13 days after symptom-onset and met the study's secondary outcome. The number of severely ill patients needing invasive mechanical ventilation was low in this particular trial. Further studies are required to determine if this drug is efficacious in patients with severe hypoxemic respiratory failure. Remdesivir, an inhibitor of RNA synthesis, developed by Gilead Sciences Inc., is currently enrolling patients for three clinical trials on the basis of their previous data which showed promise in animal models for treating MERS and SARS which are also caused by coronaviruses.[39] Favipiravir is a similar antiviral agent under investigation in Asia.[40] Hydroxychloroquine/chloroquine, reported to inhibit SARS-CoV-2 *in vitro*, is postulated to help with inhibition of viral entry and reduce viral infectivity. Although this has been currently universally recommended given absence of strong data for any other drugs, there is currently no randomized-controlled trial that has proven its efficacy.[41]

With respect to therapies that are not directly antiviral, corticosteroids have been studied in a subset of patients from Wuhan with positive results (HR 0.38, CI, 0.20–072), in a retrospective study cohort of 201 patients.[42] Further prospective randomized-controlled trials are needed to study this further. Tocilizumab, an anti-interleukin (IL)-6 receptor blocking monoclonal antibody, is being studied for patients with cytokine release syndrome. There is limited evidence at present time for this drug. Similarly, other anti-inflammatory agents inhibiting IL-1 receptor signaling, such as anakinra (soluble IL-1 receptor antagonist) and canakinumab (anti-IL-1β monoclonal antibody), are under evaluation. Adoptive transfer of sera from recovered COVID-19 patients also is being undertaken in COVID-19.[43,44] This approach was utilized with some success in Ebola, SARS, and MERS, with enhanced efficacy if utilized early in the disease natural history.[45,46] Conceptually, this technique is logically predicated upon (1) adequate anti-coronavirus antibody titers and (2) that these antibodies are disproportionately neutralizing in character.

From an immunological perspective, solid organ transplant recipients are a group warranting particular attention and careful therapeutic consideration. Consensus presently does not exist as to how to best manage immunosuppressive regimens in the setting of COVID-19 infection. It may be reasonable to use lower levels of immunosuppression in the setting of COVID-19 infection, as is often employed when transplant recipients develop other infections, waged from the perspective of favoring innate immune augmentation. However, as some mortality and morbidity in COVID-19-infected patients may be due to hyperactivation of adaptive or innate components of the immune system, it may be reasonably hypothesized that maintained or even increased levels of immunosuppression may be beneficial in the setting of COVID-19 infection. As such, we urge caution and careful consideration on an individual patient in addressing this issue. Clarity for this issue will emerge as we progress further in the COVID pandemic.

Pharmacotherapies for the cardiopulmonary physiologic effects of COVID-19 are under investigation. Anticoagulation is strongly recommended in patients with persistent D-dimer elevation, due to suspicions of an as-yet-to-be-defined prothrombotic milieu in these patients. The role of inhaled pulmonary vasodilators is unclear in the setting of COVID-19 with refractory acute hypoxemic respiratory failure but is being studied. There is no current available guidance regarding the merits of utilizing inhaled nitric oxide, although it could be postulated that this could be helpful in normal compliance ARDS by reducing hypoxic pulmonary vasoconstriction and improving ventilation-perfusion (V/Q) matching, reducing RV afterload.

Last, with respect to prophylaxis and protection, anti-COVID-19 vaccines are under development by several groups.[47] These include standard peptide/protein-based strategies, as well as RNA-based strategies. Plans for rapid testing are underway.

Mechanical Pulmonary or Cardiac Support and COVID-19: ASAIO Recommendations

The need for pulmonary or cardiac support strategies, and the extent of support required, is inversely proportional to the quality of native pulmonary or cardiac function. In addition, the availability of particular types of support equipment is inversely proportional to their invasiveness, complexity, and extent of support required. The broad recommendations below are in line with these concepts. What is proposed as first-line

therapeutic strategies generally provide lesser degrees of gas exchange or hemodynamic function support, but are clearly more widely available, and are less complex and less invasive (and thus, less dependent upon operator expertise). However, escalation to second- or third-line therapeutic strategies should not be delayed in favor of prolonged trials of first-line support. Decisive determination of whether a strategy is succeeding or failing is essential to achieving optimal outcomes. **Tables 1** and **2** provide a simple reference guide.

Pulmonary Support

COVID-19 results in acute hypoxemic respiratory failure, with severe V/Q mismatch and overt intrapulmonary shunting.[48,49] The recommendations below are based on previous experience with the management of ARDS, especially the 2009 H1N1 influenza pandemic experience.[50–52]

Mechanical ventilation: noninvasive and invasive. Noninvasive mechanical ventilation (MV) strategies, such as continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP), may be appropriate for short durations in patients with hypoxemia suboptimally treated by high-flow supplemental O_2 systems alone. As either a noninvasive or invasive mode of MV, CPAP increases basal (throughout the respiratory cycle, and thus evident even at end-expiration, the invasive analog being positive end-expiratory pressure [PEEP]) intra-alveolar pressure, and thus, lung volume. Globally, this may manifest as an improvement from lower-normal to higher lung volumes in the setting of normal overall lung compliance, or in the setting of low overall lung compliance, from lower- to normal-higher lung volumes. MV recruits under- or non-ventilated alveoli that are otherwise yet perfused, and thus improves O_2 transfer of blood flowing past these alveoli, and the overall V/Q ratio. BiPAP, which is analogous to pressure-support invasive MV, provides CPAP plus additional input airway pressure during inspiration. This not only increases mean alveolar pressure and volume, but does so by augmenting the inspiratory flow rate, and for a fixed inspiratory time, the tidal volume. Noninvasive ventilation (NIV) is a reasonable initial strategy in patients with COVID-19-related respiratory failure, provided that hypoxemia is not profound, and the anticipated duration of NIV support is not long. The issue with NIV is the need for patient cooperation. There is current concern that CPAP and BIPAP modes may potentiate aerosolization of the respiratory viral particles. Some institutional guidelines limit high-flow nasal cannula to <30 L/min, and avoid NIV, due to risk of staff infection, and further suggest that early intubation should be attempted.[53] The timing of such transition from NIV to invasive MV presently remains patient specific.

A variety of invasive MV modes are available to treat acute hypoxemic respiratory failure. Volume-controlled, pressure-controlled, pressure-support, and mixed invasive MV modes may be best suited for individual patients. Based upon data principally best expressed in the ARDSNet studies, it is well established that excess pressure and volume each may contribute to pulmonary injury (barotrauma and "volu"-trauma, respectively).[50,54] Consequently, whether either volume-controlled or pressure-controlled modes of invasive MV are chosen, lung-protective mechanical ventilation should be used in patients with COVID-19-related acute hypoxemic respiratory failure. This consists in: tidal volumes of <6 mL/kg ideal body weight, plateau airway pressures of <30 cm H_2O, and F_IO_2 titrated in order to achieve adequate systemic arterial O_2 saturations. In some patients, paralytic agents may be required.[55,56]

Importantly, individual centers, depending upon availability of invasive and even noninvasive MV, need to make often difficult decisions about resource utilization in the context of potentially more than one individual patient condition. Factors in these considerations include severity of gas exchange derangement, individual patient comorbidities, anticipated survivability of the COVID-19 infection, and availability of resources, all must be considered in determination of MV allocation to an individual patient. These issues are even more acute with respect to advanced lung support strategies, as are discussed below.

Prone position mechanical ventilation. Prone positioning is now the standard of care in ARDS and should be considered in patients with COVID-19 as this would potentially improve lung aeration at the bases of the lung.[57] A prospective multicenter randomized control trial has shown that in patients with P_aO_2/F_IO_2 ratio less than 150 mmHg, with an F_IO_2 ≥0.6, and a PEEP ≥5 cm H_2O, early application of prolonged prone positioning

Table 1. Management of COVID-19-Related Respiratory Failure Before Considerations of Escalation

Pharmacologic Strategies	Ventilatory Strategies	When to Escalate
Monitor systemic arterial oxygen saturation with pulse oximeter	Early intubation with rapid sequence intubation with minimal bagging	If ECMO needed at a hub-hospital: Transport patient early when P_aO_2/F_IO2 ratio >150 and concern for deterioration
If hypoxemic, consider hydroxychloroquine (limited evidence)	Sedation and paralytics as needed to limit ventilator dys-synchrony.	If ECMO available on-site: P_aO_2/F_IO_2 ratio <100 with maximal therapies as noted here (ELSO guidelines)
Consider enrollment in clinical trial for Remdesivir or other experimental drug	Lung-protective ventilation starting at PEEP 8–10 cm H_2O Target systemic arterial oxygen saturation >92%–96% Plateau pressure goal <30cm H_2O	In resource-scarce areas, ECMO should be utilized extremely rarely
Early transition to invasive mechanical ventilation from noninvasive mechanical ventilation to prevent aerosolization.	Conservative fluid management after hemodynamics stabilize If P_aO_2/F_IO_2 ratio still <100, consider early proning (PROSEVA trial) Consider inhaled nitric oxide if worsening hypoxemia despite maximal recruitment strategy	

COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; ELSO, Extracorporeal Life Support Organization; PEEP, positive end-expiratory pressure.

Table 2. Management of COVID-19-Related Respiratory Failure *Via* Artificial Cardiopulmonary Support Strategies

Isolated Respiratory Failure	Cardiopulmonary—RV Support	Cardiopulmonary—LV or BiV Support
V-V ECMO Peripheral cannulation Consider bi-femoral strategy to limit exposure near the endotracheal tube	Single cannula-based RVAD (***e.g.*** Protek Duo) with gas exchanger V-V ECMO plus catheter-mounted RVAD (***e.g.*** Impella RP) If volumetric flow rates low, in highly selected cases, consider surgical RVAD plus gas exchanger In selected case, V-A ECMO (See Right Column; some issues typically not relevant when used for RV dysfunction)	V-A ECMO in highly selected cases with clear evidence of LV dysfunction Similar high threshold for catheter-mounted, percutaneously cannulated paracorporeal, and surgical LVAD support, with or without gas exchanger ("modular" V-A ECMO if gas exchanger) Need to be able to achieve high volumetric flow rates Relative advantages of peripheral cannulation are less, but yet easier LV distension complicating V-A ECMO: LV venting (catheter-mounted LVAD such as Impella is easiest) Differential hypoxemia complicating V-A ECMO: hybrid V-V/V-A ECMO with (or Impella addition may help with mixing)

BiV, biventricular; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; LV, left ventricle; LVAD, left ventricular assist device; RV, right ventricle; RVAD, right ventricular assist device.

sessions significantly decreased the 28-day and 90-day mortality (16% *vs.* 32.8%, 28-day mortality; 23.6% *vs.* 41%, 90-day mortality).[58] We recommend that whenever feasible, all patients with severe hypoxemic respiratory failure with COVID-19 ARDS should undergo either manual or artificial prone positioning, depending upon the resources available. There is a concern that the man-power needed to prone these patients could potentially expose a large majority of staff members to the virus, and this should be taken into consideration before proning.

Other observations and unique considerations with respect to conventional management. Regarding the preliminary experience with COVID-19 which highlighted the discrepancy between gas exchange and lung mechanics (severe hypoxemia with normal compliance) some relevant physiologic and clinical points are noteworthy. First, several groups have (unpublished data) suggested that COVID-19 is associated with microvascular thrombosis in several tissue beds: pulmonary, coronary, and renal. Indeed, high D-dimer is associated with increased severity and mortality of COVID-19, which is indicative of microthrombosis in these arterial/arteriolar/capillary beds.[26] This may a contributory mechanism with respect to why severe hypoxemia is observed in the setting of normal or high lung compliance, since capillary endothelium and alveolar epithelium both may be involved. In addition to hypoxemia, pulmonary vascular microthrombi, when severe, may also contribute to shock.[59] Second, because of refractory hypoxemia, most clinicians increase PEEP. However, high PEEP may result in alveolar overdistension in the setting of normal

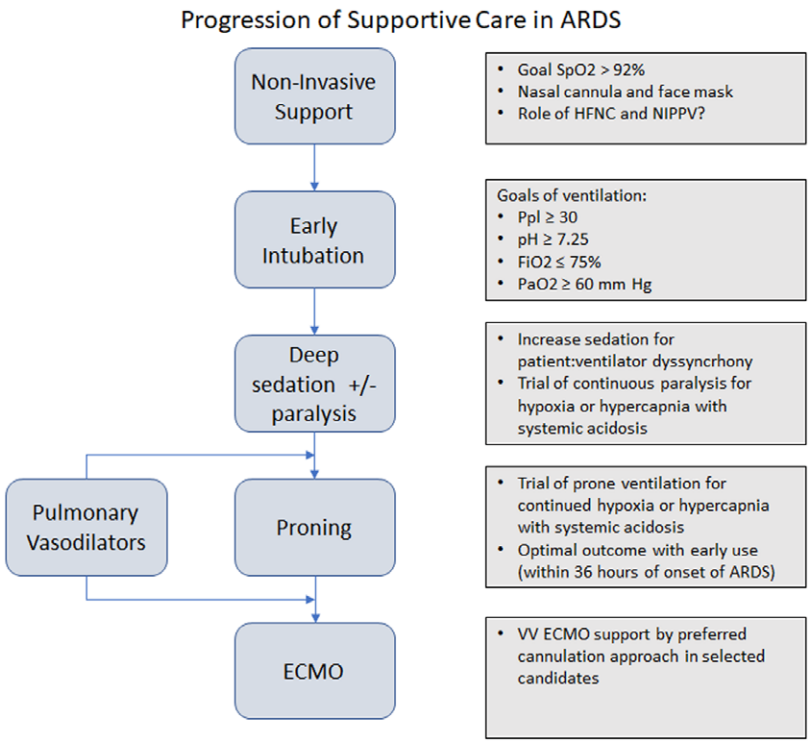

Figure 1. Algorithm for supportive care for ARDS secondary to COVID-19 infection. ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation. full color online

or high compliance. High PEEP also can augment pulmonary vascular impedance (creation of West Zone 1 lung; although if this incidentally happened to occur in unventilated lung zones and pulmonary blood flow were better redistributed to better-ventilated lung zones, this might ameliorate hypoxemia), and reduce systemic venous return, both of which reduce RV stroke volume and cardiac output (CO). Conversely, decreased oscillatory lung loading *via* low tidal volume and distending pressure "lung-protective" ventilation may cause or exacerbate hypercapnia, permissive or otherwise.

Extracorporeal gas exchange: extracorporeal membrane oxygenation. If invasive MV fails, a decision needs to be made quickly as to whether extracorporeal gas exchange is appropriate. Since COVID-19-associated respiratory failure is hypoxemic in nature, extracorporeal membrane oxygenation (ECMO) is almost certainly the most appropriate extracorporeal strategy (in contrast to extracorporeal carbon dioxide removal). The decision to utilize ECMO, similar to that for MV above, relates to (1) anticipated benefit (failure of MV to achieve adequate oxygenation, or requirement of traumatic MV settings in order to achieve adequate oxygenation) in the background of organ systems not directly supported or treated by ECMO, (2) risks (most notably, local cannulation-related complications, and active or biochemical coagulopathy), and (3) ECMO supply availability and other institutional infrastructure, and (4) practitioner expertise. In the case of COVID-19, in particular, but in ECMO deployment in general as well, dysfunction of organ systems other than those that are ECMO-supported (*e.g.*, hematological/immune, renal, hepatic) decreases the anticipated benefit and may even increase the risks of therapy.[60,61] ECMO support has well-recognized local cannulation site vascular risks—that is, both ischemic and bleeding. Preexisting coagulopathy increases the risks of local bleeding complications but also increases systemic bleeding complications—most ominously, intracranial hemorrhage. Additionally, practical considerations, while non-ideal, are real factors that influence the decision to implement ECMO.

With respect to recently published literature, ECMO utilization in the setting of COVID-19 respiratory failure has been associated with poor outcomes (hospital survival well below 50%), although the number of cases has been too small to draw definitive conclusions. Most patients reported in the population from China died.[62] More recent data available to us, as yet unpublished, seem more encouraging, although we do not have data on survival to hospital discharge. Overall, we believe that in a high mortality scenario such COVID-19, ECMO would not significantly impact on the global outcome figures, rather should be discussed on a patient-specific individual basis. Our suggestion is that the decision to implement ECMO should follow a clear failure of invasive MV, paralytic agents, and prone positioning; however, this assessment should be rapid. The latter of these is to avoid dysfunction or failure of other organ systems, and we further recommend that in light of the pandemic status of COVID-19 and the generalized poorer outcomes of ECMO support when other organ system dysfunction occurs, that ECMO implementation generally should be restricted to those with isolated single organ system (pulmonary) dysfunction who are invasively mechanically ventilated ≤7 days. Each institution's experience and resources differ, as do the local and regional epidemiology of COVID-19; consequently, ECMO implementation in the setting of renal or hepatic failure must be assessed on a case-by-case basis (further discussion regarding institution in the setting of cardiac failure follows later in this document). We also mention emerging early experience to combine ECMO with means of modulating or removing cytokines, as yet a further extension of modalities for the sickest of patients with cytokine storm and severe cardiopulmonary compromise.[63]

We now turn to the specific "tactical" aspects of ECMO, focusing on cannulation approaches, since the cannulation approach is one of the few important variables that can be not only controlled, but altered to optimize gas exchange. We initially focus on "right-sided" ECMO used for pulmonary support, that is, ECMO in which the right side of the circulation is exclusively accessed (the most common form of which is veno-venous [V-V] ECMO). **Tables 1** and **2** provide a summary.

Central versus peripheral. Central cannulation, that is, of the great vessels and generally *via* an open surgical approach, has the advantage of providing large cannula, with low resistance and high maximal volumetric flow rates. However, it is invasive and has greater periprocedural (not necessarily longer-term, though) bleeding risks. Moreover, central cannulation requires cardiothoracic surgeons to perform it. Peripheral cannulation generally cannot achieve the fluid mechanics of central cannulation. However, peripheral cannulation is most commonly percutaneous and has lower periprocedural bleeding risks. Finally, practitioners of a variety of specialties can be trained to perform peripheral cannulation procedures—*i.e.* cardiothoracic surgeons, interventional cardiologists, critical care anesthesiologists, and ICU physicians. Although central cannulation is hemodynamically advantageous (with respect to higher flow rates; hemodynamic support is not relevant in pure V-V ECMO), in light of its invasiveness, bleeding risks, and specialized training required, it is more reasonable to propose peripheral cannulation as the initial approach of choice for COVID-19-related respiratory failure.

Percutaneous: single versus two cannula. For right-sided ECMO, either single cannula (dual-lumen) or dual cannula approaches exist. Advantages of the single cannula approach include reduced risks of local bleeding complications and the potential to ambulate. In the case of right atrial/ventricular inflow and pulmonary arterial outflow, lesser degrees of recirculation are present. This latter single cannula approach also provides RV mechanical circulatory support (MCS) (see below). However, overall volumetric flow rates may be lower, and image guidance during cannulation is necessary. In contrast, the two-cannula approach requires two venous cannulation sites and typically precludes the ability to ambulate. Moreover, recirculation is common, although it may occur with the single cannula approach if both inflow and outflow are in the systemic venous compartment. However, higher flow rates are achievable with the two-cannula approach, and image guidance—which often is not present under emergent circumstances—usually is not needed. The lack of need for image guidance means that unlike the single cannula approach, cannulation using the two-cannula technique does not require operating room or catheterization laboratory environments, and potential COVID-19 exposure of these vital spaces and their ancillary staff. Thus, we suggest that the two-cannula technique should be preferred for most institutions and circumstances. Bi-femoral approaches are particularly advantageous in terms of rapidity of deployment, avoidance of cannulating surgeons

and physicians being positioned near the patient's oropharynx and endotracheal tube, and ease of subsequent prone positioning. However, under the current circumstances, we recommend each team use whatever cannulation technique is most familiar and comfortable, to minimize complications.

Cardiac and Mixed Cardiac/Pulmonary Support

Some patients with COVID-19 develop shock.[59,64] The hemodynamic profile of shock (cardiogenic *versus* distributive *versus* hypovolemic), and its coexistence or lack of coexistence with respiratory failure is unclear based upon the available published literature. It is possible that, in highly selected and limited cases, MCS with or without pulmonary support may be appropriate.[65–67] In particular, decision-making regarding implementation of left ventricular (LV) support is complex (see below). These strategic and tactical issues related to MCS in COVID-19-infected patients are reviewed.

When (if at all) should MCS be used in the setting of shock in COVID-19. Based upon the existing data, it is unclear whether shock occurs in a subset of hospitalized COVID-19-infected patients with respiratory failure, or whether it may occur independent of respiratory failure. Unpublished communications to us suggest that shock occurs in a small but noteworthy (due to their dire clinical status) subset of COVID-19 patients with respiratory failure requiring at least mechanical ventilation. Because outcomes are clearly poorer when more organ systems are dysfunctional, we suggest that MCS ought to be highly selectively implemented in COVID-19-infected patients. Yet, some patients, particularly those who are relatively younger, with fewer underlying comorbid conditions and good overall short- and long-term life expectancy, may be appropriate candidates for MCS. Given the range of clinical profiles in patients with COVID-19, we recommend early adoption of an interdisciplinary approach, incorporating advanced heart failure specialists, a lesson learned from ongoing efforts in the arena of complex cardiogenic shock.[68,69]

The immediate discussion is restricted to the left-sided circulation because decision-making here is even more complex. It is first important to determine whether left-sided cardiac dysfunction is present. In patients with shock, echocardiography (see following discussion) is particularly useful, and pulmonary arterial catheters are helpful as well, both for blood flow measurements as well blood gas measurements from different circulatory compartments. Underlying congenital or acquired structural or coronary arterial disease is assumed to be absent for the purposes of this discussion. If the systemic arterial blood pressure (mean arterial pressure [MAP] <60 mmHg) is decreased, or high doses of inotropic and vasoactive agents are required to achieve a normal-range systemic arterial blood pressure, then echocardiography should be undertaken. If the LV ejection fraction (LVEF) is at least moderately reduced (LVEF <40%), this is clearly abnormal, and in the acute setting, with a non-dilated LV and normal-range LV end-diastolic volume (LVEDV), stroke volume would be substantially reduced. In addition, invasive hemodynamic monitoring assessments, such as those provided by pulmonary arterial catheters, often are helpful in discerning whether intrinsic LV dysfunction is present (LV stroke work may be calculated; see discussion below).

However, it is important to note that the LVEF is not a good index of intrinsic LV systolic function or true LV contractility because it is inversely proportional to afterload; indices such as PRSW are superior, but generally are not feasible to obtain in the clinical setting.[70] The LVEF may be reduced if the impedance of the systemic circulation is increased, without decreased LV contractility; however, the systemic arterial blood pressure most commonly is normal-range or increased in such patients (calculations of LV stroke work or power would be required in order to formally assess this), which is not the case in shock. Regardless of whether systemic arterial hypotension is thought to be cardiogenic with LV failure, distributive, or mixed, the LVEF generally is a useful index to use in order to determine whether MCS is reasonable. If LVEF is high or even normal in the setting of systemic arterial hypotension, and the LVEDV and heart rate are normal, then the CO is normal or elevated, and MCS would have to be able (with native output) exceed that in order to have a hemodynamic benefit. In contrast, if the LVEF is low, then for a normal LVEDV and heart rate, the CO is reduced despite optimal LV preload, and MCS may be reasonable. If the LVEF is reduced, and high doses of inotropes are required to treat systemic arterial hypotension, MCS for the LV may be appropriate in highly selected COVID-19 patients. However, with rare exception, shock with a normal LVEF (predominantly distributive) should not be treated with MCS, unless volumetric flow rates well in excess of the native CO can be achieved.

As discussed, although invasive hemodynamic assessment may not be feasible in a timely fashion in patients with COVID-19 whose clinical status is rapidly deteriorating, invasive assessment is the gold standard. If PA catheters can be placed expeditiously in patients with shock, they are recommended for the purposes of definitive diagnostics; from PA catheters, the CO and index, LV power/cardiac power output (CPO), as well as PA pulsatility index,[69] may be obtained. As stated earlier, PRSW or stroke work index[70] is the gold-standard index for the assessment of LV systolic function, being superior to systolic ventricular elastance measures.[69,71] Determination of PRSW requires a range of LVEDVs to be studied, but for a given LVEDV, a particular SW may be used as an isolated data point. LV power (CPO) is the closest clinical correlate to SW (being LV work per unit time) and is clinically calculated as MAP multiplied by CO.[71] This is analogous to electrical power, which for a simple circuit with a single battery and resistor is equal to current (flow) multiplied by voltage (pressure difference), or the square of the current (flow) multiplied by resistance (systemic vascular resistance). An important caveat in using CPO is that it is not a per beat assessment, in that heart rate is incorporated. Tachycardia commonly observed in the majority of shock may limit decreases in CPO, even when per LV dysfunction is evident on a per beat basis.

Modalities for support: veno-arterial ECMO, short-term ventricular assist devices. V-A ECMO: central or peripheral. The relative advantages of central *versus* peripheral cannulation have been discussed above. However, unlike right-sided ECMO, systemic arterial cannulation is employed. Ischemic extremity complications are far more common with peripheral arterial cannulation than central cannulation, which reduces the relative advantages of central cannulation. Perhaps more importantly, lower extremity arterial cannulation may result in differential hypoxemia when hypoxemic respiratory failure is present, wherein the LV ejects hypoxemic pulmonary venous return into the aortic root/coronary arteries/proximal aortic

arch, whereas the lower body is perfused with normoxemic or hyperoxemic postgas exchanger blood flow. Consequently, decision-making with respect to central *versus* peripheral cannulation for V-A ECMO is more complex than for V-V ECMO alone. Hybrid V-V/V-A ECMO approaches may be reasonable under such circumstances. However, hybrid configurations are more complex and resource-intensive, typically requiring continuous bedside attendance by a perfusionist or ECMO specialist.

Short-term paracorporeal left ventricular assist devices with either central or peripheral cannulation; short-term catheter-mounted left ventricular assist devices (Impella). The principal advantages of left ventricular assist devices (LVADs) over V-A ECMO in shock are direct LV unloading, and more homogeneous distribution of blood flow through the systemic arterial circulation. Direct (inflow cannula within the left side of the heart, and particularly the LV) LV unloading is more effective in reduction of LVEDV,[71] and consequently, LV diastolic and systolic pressures (reduction of systolic pressures being a manifestation of the Frank-Starling mechanism); this may be advantageous relative to indirect (inflow cannula proximal to/upstream of the left side of the heart) unloading (*e.g.*, *via* V-A ECMO) vis-à-vis greater reduction of pathologic load-induced signals and resultant mechanotransduction.

It should be noted that the effectiveness of V-A ECMO in unloading the left side of the heart is an area of some controversy. Modeling studies suggest that V-A ECMO should *consistently* result in augmentation of the LVEDV and LVEDP.[72] However, this is demonstrably not so based upon clinical experience in which LV distension and even subclinical LV volume overload only occur in a minority of cases[73,74] as well as recent and even classical controlled animal model studies of V-A ECMO support in acute LV systolic dysfunction.[75–77] Even when LV distension does occur, drainage through a right-sided PA vent catheter[78] can decompress the LV, which runs counter to the aforementioned modeling studies. What is less controversial and clearer, based upon a review of physiologic concepts and the literature regarding LV distension in V-A ECMO, is that MCS approaches which employ left-sided circuit inflow ("direct" unloading) generally are more effective in achieving LV unloading than those which employ right-sided circuit inflow.[71] Consequently, in some patients, LVAD-based approaches may be superior to V-A ECMO.

In addition, when gas exchangers are used in concert, this "modular" approach permits isolated treatment (as well as de-escalation) of cardiac and pulmonary failure. However, these approaches are more technically demanding and require a high level of practitioner and institutional expertise. As is the case for V-A ECMO, we recommend that only highly selected patients with COVID-19 be considered for short-term LVAD support. Because the Impella catheter-mounted micro-axial VADs are substantially different from other pump mechanisms insofar as the pump mechanisms themselves are intracorporeal and miniaturized, we briefly mention two salient features. First, percutaneous transfemoral placement may be performed at the bedside under echocardiographic guidance, rather in than in a cardiac catheterization laboratory. In pandemic conditions, this may be useful. Second, placement *via* an axillary artery approach, using the newest iteration of introducer sheaths and securing devices, results in secure pump position, which may facilitate safer prone positioning. With further reference to the range of Impella devices, a wide range of delivered volumetric flow rates may be achieved. The original Impella 2.5 device generally may not provide adequate flow for the severely compromised shock patient for which robust LV MCS is required. The Impella CP device is better with a peak flow of 4.3 L/m. The Impella 5.0 and 5.5 devices, each of which may be introduced *via* side-grafts on the axillary artery, are capable of providing flows of 5.0 and 5.5 L/m, respectively, that is, levels of flow close to those achievable with surgically implanted LVADs, all *via* a minimally invasive platform. Finally, secure pump positioning achieved with devices inserted *via* axillary artery side-grafts has the advantage of longer-term MCS, in patients with slow recovery of LV function. Experience with Impella in combination with ECMO, that is, "ECPELLA," to enhance unloading and boost support is just beginning to emerge in severly compromised COVID patients.[79]

Right ventricular support. Respiratory failure commonly causes an increase in the pulmonary vascular impedance, increasing RV afterload. In some cases, this can occur to such an extent ("afterload mismatch") that even in the setting of normal intrinsic RV contractility, the RVEF and output may decrease substantially (cor pulmonale). In such patients in the acute setting, attempting to treat the underlying etiology of impaired gas exchange using V-V ECMO alone may not be sufficient. This is because V-V ECMO recirculation is exacerbated by reduced RVEF and tricuspid regurgitation. In cases of cor pulmonale with COVID-19-related respiratory failure, we suggest that strategies to support the RV are appropriate. For patients who may require proning, percutaneous RVADs using femoro-femoral approaches, can be used with an oxygenator. The single cannula (*e.g.*, Protek Duo) approach to this offers the advantages of peripheral cannulation *via* one site, and with minimal recirculation. Central approaches may be reasonable in patients in whom high-flow rates cannot be achieved. If high-flow rates are thought not to be achievable with a single cannula approach, then V-V ECMO plus a device such as the Impella RP may be reasonable.[80]

Guidance From the Extracorporeal Life Support Organization With Respect to ECMO

Our ASAIO recommendations are meant to complement those of the Extracorporeal Life Support Organization (ELSO). The potential role of ECMO, in particular, in COVID-19 is discussed in an overview in *Lancet Respiratory Medicine*.[81] The ELSO Guidance Document: "ECMO for COVID-19 Patients with Severe Cardiopulmonary Failure" describes usage of ECMO in COVID-19 patients intended for experienced ECMO centers. Although the published small number of patients from China who underwent ECMO had poor outcomes, currently unpublished data from Japan and South Korea, with ECMO support in 50+ COVID-19 cases, is communicated at ≈50% recovery and survival; however, other locations have communicated equivalent or worse outcomes.

Accepted ECMO indications, access, and management, are described in the ELSO Guidance for Adult Respiratory and Cardiac Failure on the ELSO web site (elso.org). In general, ECMO is warranted when metrics indicate a high (80%) risk of mortality with conventional management. These notably include P_aO_2/F_IO_2 ratio below 100, despite available optimal

care. ECMO used at the time when patients meet indications (not days later) has better outcomes. As mentioned in a recent article by ELSO leaders in *JAMA*, for inexperienced centers, "ECMO is not a therapy to be rushed to the front lines when all resources are stretched during a pandemic."[82] To supplement general ECMO guidelines a COVID-specific ELSO ECMO Guidance Document has just been published online.[83] A list of experienced ECMO centers is provided on the ELSO web site.[84] The recommendations below are summarized from the ELSO report. During the COVID-19 surge, we propose concentrating the sickest young patients in hospitals where experienced ECMO teams are available.

Because the use of ECMO for COVID-19 is occurring in the midst of a pandemic which can overwhelm hospital resources, important unique strategic issues/questions/considerations for ECMO resource allocation in COVID-19 patients are as follows:

Should ECMO be considered for COVID-19 patients? This is largely a local (hospital and regional) decision based on overall patient load, other events, and policies in the hospital. If the hospital must commit all resources to other patients, then ECMO should not be considered until the resources stabilize. If the hospital feels that ECMO can be safely provided, then it should be offered to patients based on risk/benefit analyses. Understanding hospital resource limitations as above, standard ECMO should continue when that is possible related to overall hospital resources. Patients without comorbid conditions under age 50 are the highest priority while resources are limited. Health care workers are high priority. Standard contraindications apply: terminal disease or otherwise highly limited life expectancy at baseline, active biochemical or clinical coagulopathy (particularly that which is unable to be treated or has failed treatment), major CNS damage, do not resuscitate (DNR status), and the absence of consent. Exclusions for COVID-19 during limited resources are hospital-specific. Because prognosis is worse, patients with major comorbid conditions (of particular note is immunosuppression—either due to disease or iatrogenically), age >70, and mechanical ventilation greater than 7 days, could be reasonably excluded. Anecdotally, renal failure is not an exclusion; however, general outcomes with COVID-19 patients with renal failure is exceedingly poor in the published Chinese experience.

Should ECMO during CPR (E-CPR) be considered for COVID-19 patients? Due to the complexity and extensive team training associated with doing E-CPR, centers who do not currently provide these services, should not initiate programs during times of limited resources. In ECMO centers, consideration should be given to whether to continue developmental programs such as out of hospital E-CPR or off-site cannulation during resource-limited times. If an E-CPR program is also structured for organ donation and shares these personnel, strict cooperation with the transplant allocation system should be maintained, as COVID-19 status has eventually to be thoroughly assessed and evaluated.

What protective measures for the team should be used? Standard COVID-19 precautions as recommended by WHO and national health organizations (*e.g.*, Centers for Disease Control) should be used. There are not special precautions for blood contact. Eventually, health care workers who are immune to COVID-19 (post-convalescent, or vaccinated) may not need protection for themselves (although they could be carriers).

Does V-V ECMO replace the need for mechanical ventilation? It has come to our attention that some groups are considering early adoption of ECMO as a potential alternative to mechanical ventilation. We emphasize that V-V ECMO is NOT an alternative to mechanical ventilation or proning. On a physiologic level utilizing active, appropriate pressure and volume lung inflation, avoiding barotrauma, with low-level PEEP, is vital to maintain pulmonary alveolar inflation, reduce fluid transudation and attempt to maintain a modicum of innate lung physiology, with an aim towards recovery. V-V ECMO should only be considered when mechanical ventilation is failing. Further, from a resource utilization and relative risk perspective, moving to ECMO is a resource-intensive and resource-consuming procedure that should be utilized with careful consideration. To date, survival on ECMO for cardiorespiratory failure is highly variable in COVID patients and significantly less than the previously reported 40% at most centers.[84]

How to approach therapeutic futility for termination? During times of limited resources observing no lung or cardiac recovery after 14 days on ECMO can largely be considered futile, and the patient can be returned to conventional management. Of course, individual patient decisions must be guided by the overall consensus related to a given patient, in a given clinical context, by the treatment team involved. Of note, the "SAVE"—Survival After Veno-Arterial ECMO, scoring system has been developed by ELSO and the Department of Intensive Care at the Alfred Hospital in Melbourne, to provide estimates of survival for adults undergoing V-A ECMO.[85] However, we caution that this was developed based solely on consideration of patients with refractory cardiogenic shock. As of this writing, no data exists as to its translatable utility in compromised COVID patients on ECMO. Further, the bulk of compromised patients with COVID in need ECMO, with pulmonary dominant needs, will require VV, rather than V-A ECMO, to which SAVE does not apply.

Conclusions

The COVID-19 pandemic poses major and possibly unique challenges to physicians and medical institutions. Although a limited number of patients may need artificial lung and/or heart support, these patients are among the most complex and resource-intensive. Consequently, it is important to develop pathways for their optimal care. This document is offered by ASAIO as a starting point of guidance in order to help our community approach these critically ill patients. This document will evolve as our collective experience grows, and as treatment approaches reveal efficacy *versus* limited success. We refer all readers to the ASAIO website "COVID-19 active portal" (in red), to the input tab of "therapeutic and diagnostic suggestion/comments" to provide in the field practical feedback and insight. As our collective experience of what is working *vs.* what is not evolves, this living document will be rapidly updated. Thank you for your participation to improve care for COVID-19 patients, over the spectrum of illness, including the most gravely ill.

References

1. Carroll D, Daszak P, Wolfe ND, *et al*: The global virome project. *Science* 359: 872–874, 2018.
2. Baseler L, Chertow DS, Johnson KM, Feldmann H, Morens DM: The pathogenesis of ebola virus disease. *Annu Rev Pathol* 12: 387–418, 2017.

3. Towner JS, Pourrut X, Albariño CG, et al: Marburg virus infection detected in a common African bat. *PLoS One* 2: e764, 2007.
4. Jonsson CB, Figueiredo LT, Vapalahti O: A global perspective on hantavirus ecology, epidemiology, and disease. *Clin Microbiol Rev* 23: 412–441, 2010.
5. Lyons DM, Lauring AS: Mutation and epistasis in influenza virus evolution. *Viruses* 10: E407, 2018.
6. Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E: A novel coronavirus emerging in China - key questions for impact assessment. *N Engl J Med* 382: 692–694, 2020.
7. Liu SL, Saif L: Emerging viruses without borders: The Wuhan coronavirus. *Viruses* 12: E130, 2020.
8. Wu P, Hao X, Lau EHY, *et al*: Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China, as at 22 January 2020. *Euro Surveill* 25: 1–6, 2020.
9. Zhong NS, Zheng BJ, Li YM, *et al*: Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, people's republic of China, in february, 2003. *Lancet* 362: 1353–1358, 2003.
10. Wu Z, McGoogan JM: Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *JAMA* 323: 1239–1242, 2020.
11. Wang Q, Zhang Y, Wu L, *et al*: Structural and functional basis of SARS-CoV-2 entry by using human ACE2. *Cell* 2020. doi: 10.1016/j.cell.2020.03.045. [E-pub ahead of print]
12. Zhou P, Yang XL, Wang XG, *et al*: A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 579: 270–273, 2020.
13. Calisher CH, Childs JE, Field HE, Holmes KV, Schountz T: Bats: Important reservoir hosts of emerging viruses. *Clin Microbiol Rev* 19: 531–545, 2006.
14. Zhang T, Wu Q, Zhang Z: Probable pangolin origin of 2019-nCoV associated with outbreak of COVID-19. *Curr Biol* 30: 1346–1351, 2020.
15. Khan S, Siddique R, Shereen MA, *et al*: The emergence of a novel coronavirus (SARS-CoV-2), their biology and therapeutic options. *J Clin Microbiol* 2020. doi: 10.1128/JCM.00187-20. [E-pub ahead of print]
16. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q: Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science* 367: 1444–1448, 2020.
17. Wrapp D, Wang N, Corbett KS, *et al*: Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 367: 1260–1263, 2020.
18. Lan J, Ge J, Yu J, *et al*: Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor [published online ahead of print, 2020 Mar 30]. *Nature* 2020. doi: 10.1038/s41586-020-2180-5. [E-pub ahead of print]
19. Shi H, Han X, Jiang N, *et al*: Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: A descriptive study. *Lancet Infect Dis* 20: 425–434, 2020.
20. Zu ZY, Jiang MD, Xu PP, *et al*: Coronavirus Disease 2019 (COVID-19): A perspective from China. *Radiology* 21: 200490, 2020.
21. Bernheim A: *COVID-19 Retrospective Study of Chest CTs from China: What is the Relationship to Duration of Infection?* [Video] United States, VuMedi, 2020. Available at: https://www.vumedi.com/video/covid-19-chest-ct-findings/.
22. Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ: Presymptomatic Transmission of SARS-CoV-2 — Singapore, January 23–March 16, 2020. *MMWR Morb Mortal Wkly Rep* 69: 411–415,2020.
23. Rajgor DD, Lee MH, Archuleta S, Bagdasarian N, Quek SC: The many estimates of the COVID-19 case fatality rate. *Lancet Infect Dis* 2020. doi: 10.1016/S1473-3099(20)30244-9. [E-pub ahead of print]
24. Guo T, Fan Y, Chen M, *et al*: Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020. doi: 10.1001/jamacardio.2020.1017. [E-pub ahead of print]
25. Guan WJ, Ni ZY, Hu Y, *et al*: Clinical characteristics of coronavirus disease 2019 in China. *NEJM* 382:1708–1720, 2020.
26. Zhou F, Yu T, Du R, et al: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 395: 1054–1062, 2020.
27. Lippi G, Lavie CJ, Sanchis-Gomar F: Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis. *Prog Cardiovasc Dis* 2020. doi: 10.1016/j.pcad.2020.03.001. [E-pub ahead of print]
28. Lippi G, Plebani M, Henry BM: Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clinica Chimica Acta* 506: 145–148, 2020.
29. Livingston E, Bucher K: Coronavirus Disease 2019 (COVID-19) in Italy. *JAMA* 323: 1335–1335, 2020.
30. Carinci F: Covid-19: preparedness, decentralisation, and the hunt for patient zero. *BMJ* 368: bmj.m799, 2020.
31. Zhang J, Zhou L, Yang Y, *et al*: Therapeutic and triage strategies for 2019 novel coronavirus disease in fever clinics. *The Lancet Respir Med* 8: e11–e12, 2020.
32. Evaluating and Testing Persons for Coronavirus Disease 2019 (COVID-19). Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-criteria.html. Accessed April 7, 2020.
33. Murthy S, Gomersall CD, Fowler RA: Care for critically ill patients With COVID-19. *JAMA* 323(15):1499–1500, 2020.
34. WHO. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases. *Interim Guidance*, (March), 1–7. 2020. Available at: https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117.
35. Zhang W, Du RH, Li B, et al: Molecular and serological investigation of 2019-nCoV infected patients: Implication of multiple shedding routes. *Emerg Microbes Infect* 9: 386–389, 2020.
36. Ding Y, He L, Zhang Q, Huang Z, Che X, Hou J, Jiang S: Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: Implications for pathogenesis virus transmission pathways. *J Pathol* 203: 622–630.2004.
37. Xiao SY, Wu Y, Liu H: Evolving status of the 2019 novel coronavirus infection: Proposal of conventional serologic assays for disease diagnosis and infection monitoring. *J Med Virol* 92: 464–467, 2020.
38. Cao B, Wang Y, Wen D, *et al*: A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *NEJM* 382:1787–1799, 2020.
39. Kujawski SA: First 12 patients with coronavirus disease 2019 (COVID-19) in the United States. *medRxiv* [pre print] 2020.
40. Delang L, Abdelnabi R, Neyts J: Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. *Antiviral Res* 153: 85–94, 2018.
41. Devaux CA, Rolain JM, Colson P, Raoult D: New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents* 105938, 2020. doi: 10.1016/j.ijantimicag.2020.105938. [E-pub ahead of print]
42. Wu C, Chen X, Cai Y, *et al*: Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020. doi: 10.1001/jamainternmed.2020.0994. [E-pub ahead of print]
43. Shen C, Wang Z, Zhao F, *et al*: Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA* 323(16):1582–1589, 2020
44. Lin Q, Zhu L, Ni Z, Meng H, You L: Duration of serum neutralizing antibodies for SARS-CoV-2: lessons from SARS-CoV infection. *JMicrobiol Immunol Infect* 2020. doi: 10.1016/j.jmii.2020.03.015. [E-pub ahead of print]
45. Garraud O: Use of convalescent plasma in Ebola virus infection. *Transfus Apher Sci* 56: 31–34, 2017.
46. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al; Convalescent Plasma Study Group: The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: A systematic review and exploratory meta-analysis. *J Infect Dis* 211: 80–90, 2015.
47. Cohen J: Vaccine designers take first shots at COVID-19. *Science* 368: 14–17, 2020.

48. Yang X, Yu Y, Xu J, *et al*: Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020. doi: 10.1016/S2213-2600(20)30079-5. [E-pub ahead of print]
49. Wang D, Hu B, Hu C, *et al*: Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 323:1061–1069, 2020.
50. Brower RG, Matthay MA, *et al*; Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *NEJM* 342: 1301–1308, 2000.
51. Fineberg HV: Pandemic preparedness and response — lessons from the H1N1 influenza of 2009. *NEJM* 370: 1335–1342, 2014.
52. Zampieri FG, Mendes PV, Ranzani OT, *et al*: Extracorporeal membrane oxygenation for severe respiratory failure in adult patients: A systematic review and meta-analysis of current evidence. *J Crit Care* 28: 998–1005, 2013.
53. Brigham and Women's Hospital COVID-19 Clinical Guidelines. Available at: https://covidprotocols.org/. Accessed April 7, 2020.
54. Beitler JR, Malhotra A, Thompson BT: Ventilator-induced lung injury. *Clin Chest Med* 37: 633–646, 2016.
55. Cherian SV, Kumar A, Akasapu K, Ashton RW, Aparnath M, Malhotra A: Salvage therapies for refractory hypoxemia in ARDS. *Respir Med* 141: 150–158, 2018.
56. Papazian L, Forel JM, Gacouin A, *et al*; ACURASYS Study Investigators: Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 363: 1107–1116, 2010.
57. Scholten EL, Beitler JR, Prisk GK, Malhotra A: Treatment of ARDS with prone positioning. *Chest* 151: 215–224, 2017.
58. Guérin C, Reignier J, Richard JC, *et al*; PROSEVA Study Group: Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 368: 2159–2168, 2013.
59. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW: Association of Coronavirus Disease 2019 (COVID-19) with myocardial injury and mortality. *JAMA Cardiol* 2020.
60. Millar JE, Fanning JP, McDonald CI, McAuley DF, Fraser JF: The inflammatory response to extracorporeal membrane oxygenation (ECMO): A review of the pathophysiology. *Crit Care* 20: 387, 2016.
61. Schmidt M, Schellongowski P, Patroniti N, *et al*: Six-month outcome of immunocompromised severe ARDS patients rescued by ECMO. An International Multicenter Retrospective Study. *Am J Respir Crit Care Medi* 2018. doi: 10.1164/rccm.201708-1761OC. [E-pub ahead of print]
62. Li X, Guo Z, Li B, *et al*: Extracorporeal Membrane Oxygenation for Coronavirus Disease 2019 in Shanghai. *ASAIO J* 66: 475–481, 2020.
63. Hartman ME, Hernandez RA, Patel K, *et al*: COVID-19 respiratory failure: targeting inflammation on VV-ECMO support. *ASAIO J* 66: 603–606, 2020.
64. Clerkin KJ, Fried JA, Raikhelkar J, *et al*: Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease. *Circulation* 2019. doi: 10.1161/CIRCULATIONAHA.120.046941. [E-pub ahead of print]
65. Morine KJ, Kapur NK: Percutaneous mechanical circulatory support for cardiogenic shock. *Curr Treat Options Cardiovasc Med* 18: 6, 2016.
66. Miller PE, Solomon MA, McAreavey D: Advanced percutaneous mechanical circulatory support devices for cardiogenic shock. *Crit Care Med* 45: 1922–1929, 2017.
67. Kar S: Percutaneous mechanical circulatory support devices for high-risk percutaneous coronary intervention. *Curr Cardiol Rep* 20: 2, 2018.
68. Tehrani BN, Truesdell AG, Sherwood MW, *et al*: Standardized team-based care for cardiogenic shock. *J Am Coll Cardiol* 73: 1659–1669, 2019.
69. Basir MB, Kapur NK, Patel K, *et al*; National Cardiogenic Shock Initiative Investigators: Improved outcomes associated with the use of shock protocols: Updates from the national cardiogenic shock initiative. *Catheter Cardiovasc Interv* 93: 1173–1183, 2019.
70. Glower DD, Spratt JA, Snow ND, *et al*: Linearity of the frank-starling relationship in the intact heart: The concept of preload recruitable stroke work. *Circulation* 71: 994–1009, 1985.
71. Rajagopal K: Left ventricular distension in veno-arterial extracorporeal membrane oxygenation: From mechanics to therapies. *ASAIO J* 65: 1–10, 2019.
72. Uriel N, Sayer G, Annamalai S, Kapur NK, Burkhoff D: Mechanical unloading in heart failure. *J Am Coll Cardiol* 72: 569–580, 2018.
73. Truby LK, Takeda K, Mauro C, *et al*: Incidence and implications of left ventricular distention during venoarterial extracorporeal membrane oxygenation support. *ASAIO J* 63: 257–265, 2017.
74. Kim S, Kim JS, Shin JS, Shin HJ: How small is enough for the left heart decompression cannula during extracorporeal membrane oxygenation? *Acute Crit Care* 34: 263–268, 2019.
75. Solholm A, Salminen PR, Stangeland L, *et al*: Myocardial perfusion and cardiac dimensions during extracorporeal membrane oxygenation-supported circulation in a porcine model of critical post-cardiotomy failure. *Perfusion* 267659120907557, 2020.
76. Bavaria JE, Ratcliffe MB, Gupta KB, Wenger RK, Bogen DK, Edmunds Jr LH: Changes in left ventricular systolic wall stress during left ventricular assistance. *Ann Thorac Surg* 45: 526–532, 1988.
77. Shen I, Levy FH, Vocelka CR, *et al*: Effect of extracorporal membrane oxygenation on left ventricular function of swine. *Ann Thorac Surg* 71: 862–867, 2001.
78. Pommereau A, Radu C, Boukantar M, *et al*: Left ventricle unloading through pulmonary artery in patients with veno-arterial extracorporeal membrane oxygenation. *ASAIO J* doi: 10.1097/MAT.0000000000001179 [E-pub ahead of print]
79. Bemtgen X, Krüger K, Supady A, *et al*: First successful treatment of COVID-19 induced refractory cardiogenic plus vasoplegic shock by combination of pVAD and ECMO – a case report. *ASAIO J.* 66: 607–609, 2020.
80. Kapur NK, Esposito ML, Bader Y, et al: Mechanical circulatory support devices for acute right ventricular failure. *Circulation* 136: 314–326, 2017.
81. Ramanathan K, Antognini D, Combes A, *et al*: Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. *Lancet Respir Med* 2020. doi: 10.1016/S2213-2600(20)30121-1. [E-pub ahead of print]
82. Maclaren G, Fisher D, Brodie D: Preparing for the most critically ill patients with COVID-19: The potential role of extracorporeal membrane oxygenation. *JAMA* 323:1245–1246, 2020.
83. Bartlett RH, Ogino MT, Brodie D, *et al*: Initial ELSO guidance document: ECMO for COVID-19 patients with severe cardiopulmonary failure robert. *ASAIO J.* 66: 472–474, 2020.
84. Extracorporeal Life Support Organization. Available at: https://www.elso.org/. Accessed April 7, 2020.
85. Schmidt M, Burrell A, Roberts L, *et al*: Predicting survival after ECMO for refractory cardiogenic shock: The survival after veno-arterial-ECMO (SAVE)-score. *Eur Heart J* 36: 2246–2256, 2015.