Anesthesia & Analgesia Journal Publish Ahead of Print

DOI: 10.1213/ANE.0000000000004957

COVID Activated Emergency Scaling of Anesthesiology Responsibilities (CAESAR) ICU

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Disclosure of funding: Each of the authors discloses no conflicts related to this work. This work was prepared as a collaborative effort of the American Society of Anesthesiologists (ASA), the Anesthesia Patient Safety Foundation (APSF), the Society of Critical Care Medicine (SCCM) and the Society of Critical Care Anesthesiologists

(SOCCA). For more details please refer to : https://www.asahq.org/in-the-spotlight/coronavirus-covid-19-information/caesar

Author Contributions

Ricardo E. Verdiner: This author helped to conceptualize the review, perform the literature review, and compose the submission.

Christopher G. Choukalas: This author helped to perform literature review and compose the submission.

Shahla Siddiqui: This author helped to perform literature review and compose the submission.

David L. Stahl: This author helped to perform literature review and compose the submission.

Samuel M. Galvagno Jr.: This author helped to perform literature review and compose the submission.

Craig S.Jabaley: This author helped to perform literature review and compose the submission.

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Ashish Khanna: This author helped to conceptualize the review, perform literature review, and compose the submission.

Abstract Word Count: 100

Word Count (excluding Abstract and References): 5000

Abstract

In response to the rapidly evolving coronavirus disease 2019 (COVID-19) pandemic and the potential need for physicians to provide critical care services, the American Society of Anesthesiologists (ASA) has collaborated with the Society of Critical Care Anesthesiologists (SOCCA), the Society of Critical Care Medicine(SCCM), and the Anesthesia Patient Safety Foundation (APSF) to develop the COVID Activated Emergency Scaling of Anesthesiology Responsibilities (CAESAR) ICU workgroup. CAESAR ICU is designed and written for the practicing general anesthesiologist and should serve as a primer to enable an anesthesiologist to provide limited bedside critical care services.

Glossary of Terms

ACE-2	Angiotensin converting enzyme-2
ACS	Acute coronary syndrome
AKI	Acute kidney injury
APSF	Anesthesia Patient Safety Foundation
ASA	American Society of Anesthesiologists
ATN	Acute tubular necrosis
BIS	Bispectral Index
CAESAR ICU	COVID Activated Emergency Scaling of Anesthesiology Responsibilities in the Intensive Care Unit
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
COVID-19	Corona Virus Disease, 2019
CRRT	Continuous renal replacement therapy
DVT	Deep venous thrombosis
ECMO	Extracorporeal membrane oxygenation
FVC	Forced vital capacity
HFNC	High flow nasal canula
IL-6	Interleukin-6
INF-Beta	Interferon Beta
NIHSS	National Institute of Health Stroke Scale
NIPPV	Non-invasive positive pressure ventilation
NSAID	Non-steroidal anti-inflammatory drugs

PPE	Personal protective equipment
RASS	Richmond Agitation and Sedation Scale
RSBI	Rapid shallow breathing index
SARS-COV-2	Severe acute respiratory syndrome coronavirus 2
SAT	Spontaneous awakening trial
SBT	Spontaneous breathing trial
SCCM	Society of Critical Care Medicine
SOCCA	Society of Critical Care Anesthesiologists
VA	Veno-arterial
VV	Veno-venous
WHO	World Health Organization

INTRODUCTION

The COVID-19 worldwide pandemic presents physicians, other healthcare workers, and healthcare systems with enormous challenges. Among them is the rapid transmissibility of COVID-19 and high level of respiratory severity, which has the potential to overwhelm hospitals and critical care units. Anesthesiologists, with skills in airway management, critical care, and logistics are well-positioned to serve on critical care resuscitation/delivery teams under such conditions .

The CAESAR ICU program is a joint initiative of ASA, SCCM, APSF, and SOCCA and is intended to create a "survival" guide for the practicing anesthesiologist who may be called upon to provide early management and stabilization of COVID-19 patients. This narrative review of COVID-19 is based on work done by the CAESAR ICU group and provides basic critical care management principles for the anesthesiologist with an emphasis on relevant organ system effects impacted by COVID-19

COVID-19 PATHOPHYSIOLOGY AND THE ACE-2 RECEPTOR

COVID-19 is the systemic manifestation of the SARS-COV-2 virus. SARS-COV-2 enters human cells via the ACE-2 receptor. It has a binding affinity 10-15 times greater than the SARS virus responsible for a smaller outbreak in 2003.[1] The ACE-2 receptor is a cell membrane associated protein that can be found in epithelial (cardiac and renal) cells, endothelial (pulmonary and vascular) cells, and cells of the oral mucosa and nasopharynx (see figure 1). When SARS-COV-2 binds to the ACE-2 receptor it reduces intracellular ACE-2 protein activity.[2,3] In the heart, ACE-2 is involved in endothelial regulation, vasoconstriction, and cardiac function. In the renal system, ACE-2 impairment has been implicated in oxidative stress, inflammation, and fibrosis of the renal tissue.[4] The role of

ACE-2 in the lung is incompletely understood but increased activity may possibly reduce lung injury in the adult respiratory distress syndrome (ARDS).[5]

PULMONARY CONSIDERATIONS

Hypoxia and Hypercarbia

Although COVID-19 may have diverse presentations, respiratory failure is the presentation most relevant to critical care management. Patients often present with a dry cough, fever, tachypnea and dyspnea;[6] oxygen saturations less than 90% are common and patients are surprisingly asymptomatic for their degree of desaturation.[7,8] Alternative diagnoses include pneumonia, congestive heart failure (CHF), iatrogenic volume overload, or pulmonary embolism, but these should not rule out COVID-19 without testing; pulmonary embolism occurs commonly in conjunction with COVID-19, [9] even in patients receiving prophylactic or therapeutic anticoagulation, suggesting an underlying hypercoagulable state.[10]

In a suspected COVID-19 patient, personal protective equipment (PPE) should include precautions against contact, droplet, and, in the case of aerosolizing procedures, such as transesophageal echocardiogram examinations, endoscopy, extubation, tracheostomy, chest compressions, and nebulizer treatments,[11] airborne spread. Avoiding bronchoscopies and sputum cultures will reduce aerosolization.

Injured Lungs and ARDS

Although COVID-19 lung injury clinically resembles bilateral pneumonia, the specific pathophysiology remains controversial[12,13] In some patients, lung compliance is low leading to lower tidal volumes for the same inspiratory airway pressure.[14] This reduced compliance is likely due to alveolar exudates that reduce the number of viable alveoli.

Such a presentation resembles the acute respiratory distress syndrome (ARDS), and can be stratified based on PaO2/FiO2 ratio of < 300 = mild disease and <100 = severe).[14-16] In some patients with COVID-19 lung compliance can be normal.[17,18]

Ventilation strategies

Many patients with COVID-19 respiratory failure do not require immediate intubation. Efforts to avoid intubation and mechanical ventilation should be balanced against the risk of nosocomial transmission. The use of high flow nasal canula (HFNC) carries a poorly quantified but likely higher risk of aerosol generation than lower-flow forms of oxygen supplementation;[19] its risk compared to NIPPV[20] or intubation and mechanical ventilation are also unknown. Some healthcare organizations have recommended against noninvasive ventilation due to the risk of COVID transmission[21-24] given these same risks. Self-proning of awake patients receiving oxygen by nasal canula or HFNC, while minimally described in the literature,[25] is low-risk and may improve oxygenation[26]

A core principle of ARDS management is control of fluid balance to reduce the contribution of pulmonary edema to gas exchange abnormalities in the injured lung. Although data in COVID-19 are lacking, limiting fluids has improved outcomes in other forms of ARDS[27] and is used in COVID-19 management to improve gas exchange. Under such conditions, monitoring for adequacy of oxygen delivery and end organ damage due to hypovolemia is needed.

Considerable variability currently exists among centers with respect to when patients with COVID-19 respiratory failure should be intubated. Factors to consider include the time required to don PPE and the rapidity of deterioration in gas exchange. For COVID-19 intubations, video laryngoscopy with appropriate PPE (contact, droplet, and airborne),

ideally in a negative pressure environment, and with the most experienced personnel performing the laryngoscopy may reduce the likelihood of healthcare infection (see figure 2). Bag mask ventilation may also increase the risk of aerosolization. In many centers, central line and arterial line insertion are performed in the same encounter to reduce donning/doffing episodes for clinicians and radiology staff. Once intubated, lung protective ventilation is the cornerstone of ARDS management and ARDSNet-based principles of ventilation should be followed.

Key priorities are as follows:

- Low tidal volumes (6-7 ml/kg of ideal body weight-calculated from a formula using height in meters and gender)
- Preventing barotrauma with a reduced plateau (30 cm H2O or under) and a driving pressure (where driving pressure is plateau pressure minus PEEP) of less than 14 cm H20.
- Preventing repeated alveolar collapse by utilizing appropriate lung recruitment with PEEP.
- Using oxygen and PEEP to target a PaO2 between 55-80.
- Permissive hypercapnia so long as pH remains greater than 7.2. [14,16]

Volume control modes of ventilation are easiest to manage clinically as they deliver a prespecified tidal volume rather than an inspiratory flow and do not allow the patient to increase tidal volumes. Small tidal volumes combined with high PEEP and hypercarbia may contribute to air-hunger and deep sedation may be required (see Neurologic Considerations section for drug choices and strategies). Auto-PEEP can cause severe reductions in cardiac output and may when expiratory gas flow does not reach 0

liters/second before the next breath. In such patients, disconnecting the ventilator can prevent cardiac arrest. If the ventilator must be disconnected for a COVID-19 patient, caregivers should be careful to limit aerosolization as much as is possible (i.e., disconnecting from the circuit in a way that leaves any filtering device in place on the endotracheal tube). Instead, if clinically appropriate, shortening inspiratory time, treating bronchospasm if present, and increasing sedation may resolve the issue.

Rescue strategies

Other than lung protective ventilation and maintaining a negative fluid balance, [27] few therapies have been successful in managing ARDS.[15] Prone positioning may improve outcomes,[28] but should be performed by experienced personnel as proning may dislodge tubes and drains. The benefit of early paralysis with neuromuscular blocking agents for 48 hours remains uncertain.[29,30] Due to low tidal volume ventilation, permissive hypercarbia can occur. Routine supportive care during mechanical ventilation includes stress ulcer prophylaxis, spontaneous awakening trials coupled with spontaneous breathing trials (SAT/SBT) where safe, and the use of bundled care to prevent ventilator associated pneumonia (VAP) and sepsis. The importance of deep venous thrombosis (DVT) prophylaxis deserves emphasis, given the reported hypercoagulable state[10] and high rate of DVT[9] in patients with COVID-19. There is some evidence that elevated D-dimer levels may be associated with poor prognosis[31] It is believed that SARS-COV-2 may facilitate both endothelial activation of von Willenbrand factor and factor VIII as well as complement mediated microvascular injury and thrombosis[32] Both pathways would contribute to a hypercoagulable state. Because of the reduced mortality associated with anticoagulation in severe COVID-19 cases, some authors have recommended therapeutic

doses of anticoagulation[33,34] In the absence of shock, fluid therapy should be managed conservatively to minimize the contribution of pulmonary edema to gas exchange and lung compliance.[35] The inhaled pulmonary vasodilator, nitric oxide, can be trialed to reduce V/Q mismatch and shunt, but can worsen hypotension or hypoxemia.[36] Use of methylprednisone for ARDS, in general, and for COVID-19, specifically, remains controversial.[37-39] In cases of refractory hypoxemia and hypercarbia, extracorporeal membrane oxygenation (ECMO) can be considered (see Extracorporeal Life Support section).[40]

In light of increased mortality in elderly patients and those who require intubation, end-of-life care issues should be addressed.

When the respiratory status improves, the most common approach to ventilator weaning is daily SAT/SBT to assess readiness for extubation. Patients with COVID-19 often require prolonged ventilation and extubation failure can worsen outcomes.[41] A daily SBT is usually coupled with a spontaneous awakening trial and should last for 30-60 mins with institution-specific pressure support settings (usually 5/5 cm H20). Patients with COVID-19 should be extubated with the same PPE required for intubation.[42] Criteria for an extubation attempt typically include:

- An awake and hemodynamically stable patient.
- SBT passed if hemodynamics, RR, ABG or SaO2 are acceptable after 30-60 mins.
- RSBI (rapid shallow breathing index or RR/Vt) is < 105.
- FVC (forced vital capacity) is adequate, ideally double resting Vt.

Although data are lacking in patients with COVID-19, extubating to HFNC can decrease reintubation and should be considered if resources are sufficient.[43,44] The same PPE required for intubation should be utilized by healthcare workers during extubation.

INFECTIOUS DISEASE CONSIDERATIONS

The dramatic spread of COVID-19 has galvanized research institutions to find effective solutions to minimizing the societal impacts of this disease. The Surviving Sepsis Campaign COVID-19 panel composed guidelines based on an extensive review of the literature.[45] The three major principles addressed by the panel were infection control, laboratory diagnosis, and supportive care. Infection control stipulates that COVID-19 patient-to-patient or patient-to-healthcare worker transmission be minimized. In a Feb 24, 2020 study 1,716 (3.8%) of 44,672 COVID-19 cases were health care workers, and 1080 were in Wuhan alone.[46] A March 17, 2020 Italian study documented 2,026 cases (8.9%) among health care workers out of the total 22,512 COVID-19 cases.[47] Without proper infection control, those providing treatment can clearly become transmitters of the disease itself.

Laboratory diagnosis and specimen retrieval enables confirmation of the suspected diagnosis as well as appropriate de-escalation of treatment and resources like broad spectrum antibiotics, airborne precautions, and negative pressure isolation. Typical specimen samples will include nasal swab if the patient is not intubated and tracheal aspirate if intubated.[45]

The last of the principles, supportive care, encompasses a range of issues in patients with COVID-19. With regard to systemic steroids, the panel reserved administration for ventilated patients with severe ARDS, but on a case-by-case basis. Empiric antibiotics were recommended because bacterial co-infection may be difficult to recognize and diagnose (see table 1). Daily assessment for de-escalation, duration, and antibiotic spectrum was recommended based on microbiology specimens. In regard to fever management, acetaminophen was viewed as a patient comfort strategy. For the patient presenting in high output septic shock, conservative and judicious resuscitation with crystalloids was preferred over liberal fluid resuscitation due to lung injury associated with a concomitant capillary leak syndrome and poor outcomes with higher cumulative fluid balances in ARDS. If a vasoactive agent was needed, the panel recommended norepinephrine as the preferred first line vasoactive agent. Vasopressin was the second line agent if norepinephrine alone did not reach the targeted mean arterial pressure goal of 65mmHg. Dobutamine was the recommended inotropic agent when cardiac dysfunction was present. Hydrocortisone at 200 mg/day was recommended in refractory shock. [45] Angiotensin II, though not recommended by the SCCM guidelines, may have a potential therapeutic role beyond supporting the MAP based on the speculative hypothesis of downregulation of ACE-2 receptors, saturation of and competitive inhibition of ACE2 enzyme activity. [48,49] .Insufficient data exist to strongly support any single approach to antiviral therapy. The panel did not recommend IVIG without adequate titers of neutralizing antibodies. Recombinant Interferon (INF-Beta) inhibits SARS-COV-2 in cell cultures and studies by the World Health Organization (WHO) are ongoing. Currently, trials of convalescent plasma are also underway. Lopinavir/Ritonavir is still being investigated by the WHO.

Remdesivir, a pro-drug analog of adenosine, results in premature RNA chain termination, and trials in mild, moderate, and severe COVID-19 patients are ongoing. Hydroxychloroquine has received attention in the lay-press and may be a more potent inhibitor of SARS-COV-2 in vitro compared to chloroquine. Although randomized trial data are lacking, dosing regimens of 400mg BID loading followed by 200mg BID for 4 days. Tocilizumab is an anti-interleukin-6 (IL-6) immunoglobulin. This drug was originally used in both rheumatology and oncology for its effects on hemophagocytic syndrome. Its effects on reducing cytokine concentrations and acute phase reactants has prompted its consideration in severe COVID-19 where a hyper-inflammatory state (cytokine release syndrome) is known to be a prominent feature.[50]

CARDIOVASCULAR CONSIDERATIONS

As previously mentioned, SARS-COV-2 virus' entry target is the ACE-2 receptor. The presence of this receptor in cardiac epithelial cells facilitates myocardial damage by the virus via inhibition of the intracellular activity of the ACE-2 protein.[48,51,52] In the setting of COVID-19, a 7.2% incidence of acute cardiac injury and 16.7% incidence of arrhythmias has been reported.[1]

The presentation of myocardial injury in COVID-19 includes elevated troponin and C-reactive protein, ST changes, T-wave inversion, arrhythmia, heart failure, reduced ejection fraction, angina, and cardiomegaly on chest X-ray. Trending these markers helps plot an overall cardiac course. Additionally, IL-6 levels are used as an indicator of systemic dysregulation of pro-inflammatory mediators (cytokines, oxygen free radical, and coagulation factors). In COVID-19, early detection and mitigation of such a cytokine "storm" may reduce end-organ damage (a clinical trial is ongoing).[52] In the absence of

rapid IL-6 levels, clinicians have also used the H score to assess excessive immune reactivity.[53,54] If elevated, tocilizumab may be used.[54,55]

Electrocardiography not only helps monitor arrhythmias and ST changes, but can also help detect drug related prolongation of QTc.[55] Hydroxychloroquine/Chloroquine and azithromycin are commonly used treatments for COVID-19. Both agents cause prolongation of QTc.[56,57] When the QTc is greater than 500 the risk of Torsade de Pointes (polymorphic ventricular tachycardia) is higher, which can be avoided if the medications are either stopped or the doses reduced.

Echocardiography may also distinguish between COVID-19 related acute coronary syndrome (ACS) and myocarditis. The hypoxia of ARDS, increased metabolic demand, and end organ hypoperfusion can cause myocardial ischemia, which presents on echo as regional hypokinesis. If severe, overall ejection fraction may be depressed and echo may reveal isolated left ventricular or right ventricular dilation. The typical ACS management protocol should be followed with the caveat that the effect of beta blockers such as metoprolol may be enhanced by concomitant use of either hydroxychloroquine and chloroquine due to inhibition of CYP2D6.

In contrast to the regional hypokinesis of myocardial ischemia, hypokinesis due to COVID-19-induced myocarditis is global. Both ventricles are dilated and contractility is reduced (see figure 3). On echocardiography, the ventricles will appear round in the four-chamber view instead of the typical oval shape that tapers at the apex. In the presence of COVID-19 this finding is highly suggestive of myocarditis.[56,58,59] If the left ventricular ejection fraction falls below 20%, anticoagulation should be considered to prevent spontaneous left ventricular thrombus formation. Steroids and non-steroidal anti-inflammatory drugs

(NSAIDs) are not recommended for COVID-19 patients, in general, [60] and particularly those with impending or ongoing myocardial injury and may worsen heart failure.[61,62] Data are insufficient to support stoppage of ACE inhibitors and ACE receptor blockers. [63] If the H score or C-reactive protein level are significantly elevated, an IL-6 inhibitor should be considered.

EXTRACORPOREAL LIFE SUPPORT CONSIDERATIONS

Initiating ECMO is an option for some COVID-19 patients, depending on institutional expertise and resource availability. In the 2018 ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial[64] 60-day mortality was not significantly lower with patients randomized to receive ECMO, but the trial was limited by a high rate of crossover from the control to the ECMO group.[40,64] A recently published pooled analysis of seventeen COVID-19 patients treated with ECMO reported a high mortality (94.1%),[65] although in other emerging reports survivors have been reported.[66]

Given the overwhelming presentation of patients during the COVID-19 pandemic, starting new ECMO centers is not advised and decisions to initiate ECMO must be subject to considerable thought and judgment.[66] and each patient should be considered individually with respect to risks, benefits, and available resources. For both VV and VA approaches, current guidelines[67,68] endorse use of ECMO for patients with severe disease and high predicted mortality. Experience with non-COVID use of ECMO suggests that younger patients with minor or no-comorbidities should remain the highest priority for ECMO.[66,69] Use of ECMO in COVID-19 patients with a combination of advanced age (>60 years old), multiple co-morbidities, or multiple organ failures should be rare. Readers are encouraged to review ECMO management materials available at the ASA CAESAR resource library

(https://www.asahq.org/in-the-spotlight/coronavirus-covid-19-information/caesar) and the Extracorporeal Life Support Organization (https://www.elso.org/Resources/Guidelines.aspx).

NEUROLOGIC CONSIDERATIONS

Many patients in the ICU with COVID-19 will require mechanical ventilation, which typically obligates them to sedation. The ABCDEF Bundle is helpful to determine sedation needs and is implemented in the following fashion: Assess, Prevent, and Manage Pain, Both Spontaneous Awakening Trials (SAT) and SBT, Choice of analgesia and sedation, Delirium: Assess, Prevent, and Manage, Early mobility and Exercise, and Family engagement and empowerment. [70] Delirium screening should be performed daily in patients who are able to participate, as delirium increases mortality and should be prevented.[71] The Confusion Assessment Method for the ICU (CAM-ICU) is commonly used to screen patients for delirium, and is validated for patients receiving sedation and on mechanical ventilation.[72] Sedation should be titrated using a clinical scale such as the Richmond Agitation and Sedation Scale (RASS) score ranges from +4 (combative), 0 (awake and calm), to -5 (comatose), and a reasonable goal would be a range of 0 to -2.[73] Such scales are preferred over EEG monitoring;[74] Deeper sedation is often required to tolerate high-PEEP ventilator settings, and for patients who will require paralysis. Strict ventilator synchrony (e.g., not overbreathing or "double-stacking") is important in order to avoid increased oxygen consumption and barotrauma. Dexmedetomidine should not be used without other amnestic medication in patients requiring neuromuscular blockade, and bispectral (BIS) monitor might be suited to such patients.[74] Of note, sevoflurane and propofol interact with chloroquine and hydroxychloroquine to increase the likelihood of

QTc prolongation. Remdesivir does not have known interactions with any major anesthesia drugs. Propofol infusion syndrome should always be considered if sudden acidosis occurs after prolonged infusion, particularly in younger patients.[75] Furthermore, pain control with IV infusions and enteral regimens are both acceptable. Half of ICU patients will have pain, and multimodal regimens can be used even when patients are mechanically ventilated (e.g., acetaminophen, gabapentinoids, transdermal lidocaine, tramadol, muscle relaxants (methocarbamol, etc.) and opioids). [76]

Although epidemiologic data are lacking, and given noted concerns about hypercoagulability, stroke may be a relatively common complication of COVID-19[77] A sudden change in mental status or acute onset of focal neurologic changes not explained by drugs should trigger a differential diagnosis that includes stroke and hemorrhage. The NIH Stroke Scale (NIHSS) is performed for all patients suspected of stroke, and a head CT should be ordered when a stroke is suspected.[78] In many institutions, a 'CODE STROKE' pathway is present which mobilizes the neurology team and makes the patient a top priority for a rapid, definitive diagnostic evaluation.[79] Ischemic strokes and subarachnoid hemorrhage (after clipping/coiling) may require a higher blood pressure for several days in order to prevent permanent loss of function while hemorrhagic strokes require tighter blood pressure control, commonly with an infusion. Special care should be given to patients with status epilepticus, spinal cord injuries and TBI, and hyperventilation cannot be used for anything beyond short-term, emergent control of catastrophic elevations in intracranial pressure (i.e., during active herniation).

RENAL CONSIDERATIONS

Acute kidney injury (AKI) is common in critically ill adults with an incidence of 57.3% in one large, international epidemiologic study.[80] AKI and the duration thereof are independently associated with poor clinical outcomes.[81,82] Early published COVID-19 data suggest that AKI develops in approximately 15% of inpatients and 50% of non-survivors.[83] In another study examining critically ill adults, 29% had AKI. [84] AKI has likewise been associated with adverse outcomes in patients with COVID-19.[85,86] In one small series of critically ill adults from Washington state, 4 of 21 patients developed acute kidney failure.[87] Anecdotally, the authors have personally found that approximately 20 to 30% of mechanically ventilated COVID-19 patients require renal replacement therapy (RRT) in their institutions.

The pathophysiology of AKI in COVID-19 is not yet definitively established. SARS-CoV-2 binds with ACE-2 receptors, which are expressed in the kidneys. Both podocytes and proximal straight tubule cells have been identified as viral hosts,[88] possibly explaining the high incidence of observed proteinuria.[85] Pathologic findings have been consistent with acute tubular necrosis (ATN).[89] Aside from direct cytopathic effects, ARDS and shock may also contribute to ATN in severely ill patients. Pre-renal etiologies should be considered early in the disease course in patients who have had anorexia or severe GI manifestations.

For critically ill adults with COVID-19, the authors recommend that the routine diagnostic workup include urine analysis, spot urine studies for electrolytes, protein, and microalbumin-to-creatinine ratio in addition to routine serum chemistries. For patients with AKI, urine microscopy may be helpful, and the diagnostic workup should parallel that of

AKI in critically ill adults. Similarly, the care of COVID-19 patients with perturbations in renal function should center around foundational supportive care: avoidance of renal insults (i.e., nephrotoxins and hypotension), resuscitation or diuresis to euvolemia, correction of electrolyte and acid-base perturbations, and nutritional optimization.[90]

Patients with COVID-19 demonstrate hypercoagulability[10] which may increase the risk of clotting of continuous renal replacement therapy (CRRT) filters. Appropriate temporary dialysis catheter placement and position are important from an access quality standpoint, and optimization of the dialysis prescription (e.g., high blood flows and predilution replacement fluid) may help to extend filter life. One potential solution is staged anticoagulation for patients on CRRT: regional citrate anticoagulation, followed by escalation to pre-filter heparin administration with serum monitoring of heparin levels per local protocol, and then finally consideration of alternative systemic anticoagulants (i.e., direct thrombin inhibitors). Potential local or national shortages of citrate, calcium, and/or systemic anticoagulants may influence the optimal approach. Hospitals should also develop staged RRT surge plans, which might include mixed CRRT durations with machine redeployment, various prolonged intermittent renal replacement therapy approaches, and/or acute peritoneal dialysis.[91]

ENDOCRINE CONSIDERATIONS

Glycemic Control

Like other critically ill patients, those with COVID-19 are at risk of dysregulated glucose. Targeting blood glucose levels under 180mg/dL utilizing subcutaneous or intravenous insulin and avoiding oral hypoglycemics are reasonable.[92,93] Aggressive treatment of hypoglycemia with 50% dextrose or continuous infusion of dextrose-

containing crystalloids will avoid complications of hypoglycemia.Severe hyperglycemia may be associated with diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome. Both processes result in osmotic diuresis and electrolyte wasting, and therefore require volume resuscitation and vigilant correction of electrolyte imbalances, along with administration of insulin.[94] Measured sodium values may be falsely low in the presence of hyperglycemia and require corrected calculation. Insulin infusions require hourly glucose checks and are resource demanding so subcutaneous regimens should be used if possible. Nutritional considerations are critical to the management of patients with ARDS, in general, and a detailed resource can be found on the CAESAR-ICU website here: https://bit.ly/2VpcGmI.

Thyroid Function

Critically ill patients may have abnormal thyroid function tests (e.g. decreased T3) in the absence of true thyroid dysfunction (i.e., euthyroid sick syndrome), and thyroid hormone supplementation is not warranted.[95,96] Patients with chronic hypo- or hyperthyroidism should continue their home thyroid medication regimens with minimal interruptions. Rarely, patients with untreated thyroid dysfunction may develop life-threatening thyroid disorders (e.g. myxedema coma, thyroid storm), which warrant immediate consultation with an endocrinologist.

Steroid Use and Adrenal Insufficiency

Patients with primary or secondary (e.g. chronic prednisone use) adrenal insufficiency are at significant risk for adrenal crisis. Empiric stress dose steroid replacement (e.g. hydrocortisone 50mg every 6 hours) should be considered in these patients for the duration of their critical illness.[97] Patients without known adrenal insufficiency may develop relative adrenal insufficiency during critical illness, which presents commonly as refractory hypotension unexplained by sepsis or cardiac dysfunction. Random cortisol levels and ACTH stimulation testing are not routinely recommended; rather empiric use of stress-dose hydrocortisone (as above) should be considered in patients with profound distributive shock and inadequate response to vasoactive medications.[97-99]

Steroids are not recommended for treatment of hypoxia and ARDS precipitated by viral pneumonia, as they may prolong viral clearance and increase mortality.[100] Steroids can be considered for patients with COVID-19 who develop refractory shock or have underlying adrenal insufficiency.

ETHICAL CONSIDERATIONS

Under normal non-pandemic circumstances, the general principles of medical ethics apply, as described by Beauchamp and Childress.[101] These include patient autonomy, beneficence, non-maleficence, and justice. However, under resource-limited circumstances such as in the COVID-19 pandemic, the Utilitarian philosophy of social justice (the most good for the greatest number of people) becomes important. Ethical issues may occur when allocating ICU beds, ventilating patients, withdrawing life-supportive treatment, starting experimental treatments, or resuscitating patients suffering from cardiac arrest.

These decisions will require: 1) a hospital policy, 2) consultations with the broader ICU team, and 3) rapid ethics consultations.[102] Such decisions should consider a) the age and premorbid status of the patient, b) the severity and prognosis of the disease, c) the severity of the shortage of resources (supply/demand proportion), and d) the stage of the pandemic (whether the overburdened phase has been reached).[103]

Ways of moving forward should include the following:

- Instituting goals of care discussions early in the treatment plan
- Communicating frequently and transparently with family members
- Having team/interprofessional meetings often
- Conducting a time-limited trial of therapy in selected patients
- Avoiding therapies that are untested and may lead to harm.

In rapidly evolving clinical scenarios like COVID-19, clinicians should anticipate and plan so sufficient time is available for multi-disciplinary teams to participate in decision making.[104] Clinicians at the bedside should not be left to make triage decisions, such as ventilator allocation, alone, as these can cause extreme moral conflicts and distress. Ideally, hospitals would develop triage officers or teams comprised of individuals not involved in the direct care of the patient to make such ethical decisions.[105]

Other specific strategies may ease the impact of these complex decisions on caregivers and families, but all stem from the underlying recognition that the patients are someone's loved one who may be denied some aspect of care (e.g., an ICU bed or ventilator). The sharing of empathy and compassion and having conversations early in the clinical course may be helpful, particularly for patients that are elderly or at high risk. Emphasizing comfort care measures may allay concerns that caregivers are abandoning patients who are not being

offered other critical care measures, and palliative care teams can be invaluable in this setting. It is also critical for clinicians to make use of available support system resources, as complex end-of-life issues will take a psychological toll on caregivers.

CONCLUSION

The current Coronavirus pandemic is unprecedented in the modern medical era and COVID-19 is an entirely new disease. COVID-19 is remarkably transmissible and can render patients critically ill in a very short period of time. The COVID-19 pandemic may require healthcare systems to adapt to volumes of critically ill patients that exceed their capacity, and non-intensivist anesthesiologists are rapidly being deployed in their critical care management. The respiratory care of these patients should closely mimic the care for ARDS patients without COVID-19, with the caveat that some patients may not have the typical poor compliance of ARDS, and that many patients require extended ventilatory support. Because COVID-19 may affect the heart and affected patients may be hypercoagulable, myocardial injury has been reported and can be severe. In addition to antiviral protocols, the use of broad-spectrum antibiotics to cover coinfection should be considered, particularly for patients in shock. Many critically ill patients with COVID-19 will require sedation for mechanical ventilation, and the 2018 Society of Critical Care Medicine guidelines are appropriate for the care of these patients. Most importantly, sedation should be targeted to a desired effect, including ventilator synchrony, with interruptions daily if possible, and patients will often require deep sedation if they are severely hypoxemic or require neuromuscular blockade. Acute kidney injury is a common consequence of COVID-19, either due to ATN or hypotension. The hypercoagulability of COVID 19 patients may lead to increased clotting of CRRT filters but the nature of this

hypercoagulability is not defined. The need for glycemic control is not unique to patients with COVID-19, but because of the need to limit room entry, patients who might otherwise be managed with an insulin infusion should be first trialed on a subcutaneous regimen. The role of steroids has been raised for both lung injury and hemodynamic aspects of care of COVID-19 patients, but the best evidence for steroids is for the treatment of septic shock refractory to pressors and for adrenal insufficiency. Finally, because of the expected high mortality of critically ill patients, and the possibility that the number of patients will exceed the resources available, ethical considerations must be a part of healthcare systems' response plans. Systems, not individual clinicians, should develop plans for how to triage and ration care requiring limited resources (e.g., ventilators, ICU beds, blood products), and, perhaps more important than many of the medical strategies described above, clinicians must address the end of life concerns of patients who have a high likelihood of dying of this disease.

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Figure Legends

Figure 1. The Role of ACE-2. This figure illustrates the conversion of Angiotensin I and II into Angiotensin (1-7) which has organ protective effects by ACE-2 cleavage. Angiotensin II in the absence of ACE-2 demonstrates increased cytokine release and could lead to end organ injury.

Figure 2. Intubation in COVID. Key features include adequate personal protective equipment, admitted the fewest and most experienced providers possible, utilizing rapid-sequence induction and avoiding mask ventilation whenever possible, and using video laryngoscopy whenever possible. Clinicians should consider performing central and arterial line insertion during the same encounter.

Figure 3. Key features distinguishing between acute coronary syndrome and myocardial injury due to COVID-19.

Table 1. Initial Empiric Therapy for Septic Shock

Source	Common Pathogen	Empiric Therapy	Duration
Pulmonary Community Acquired Pneumonia	S.Pneumoniae, H.Influena, Mycoplasma Presumed MRSA	Vanco+Cefepime	5-7 Days
		Vanco+Piperacillin/Tazobactoam	
Pulmonary Ventilator Associated Pneumonia	S. Aureus, Gram negative rods, Pseudomonas	Vanco+Cefepime	7 Days
		Vanco+Piperacillin/Tazobactam	
Abdomen	Gram negative rods, Enterobacter, Enterococcus, etc.	Piperacillin/Tazobactam	7 Days
Urinary Tract	Community Acquired	Ceftriaxone	7-14 Days
	Hospital Associated Nursing Home	Piperacillin/Tazobactam	
Line or Device Related	S. Aureus	Vancomycin	Up to 4 Weeks or more
	Candida	Fluconazole or Micafungin	

Figure 1

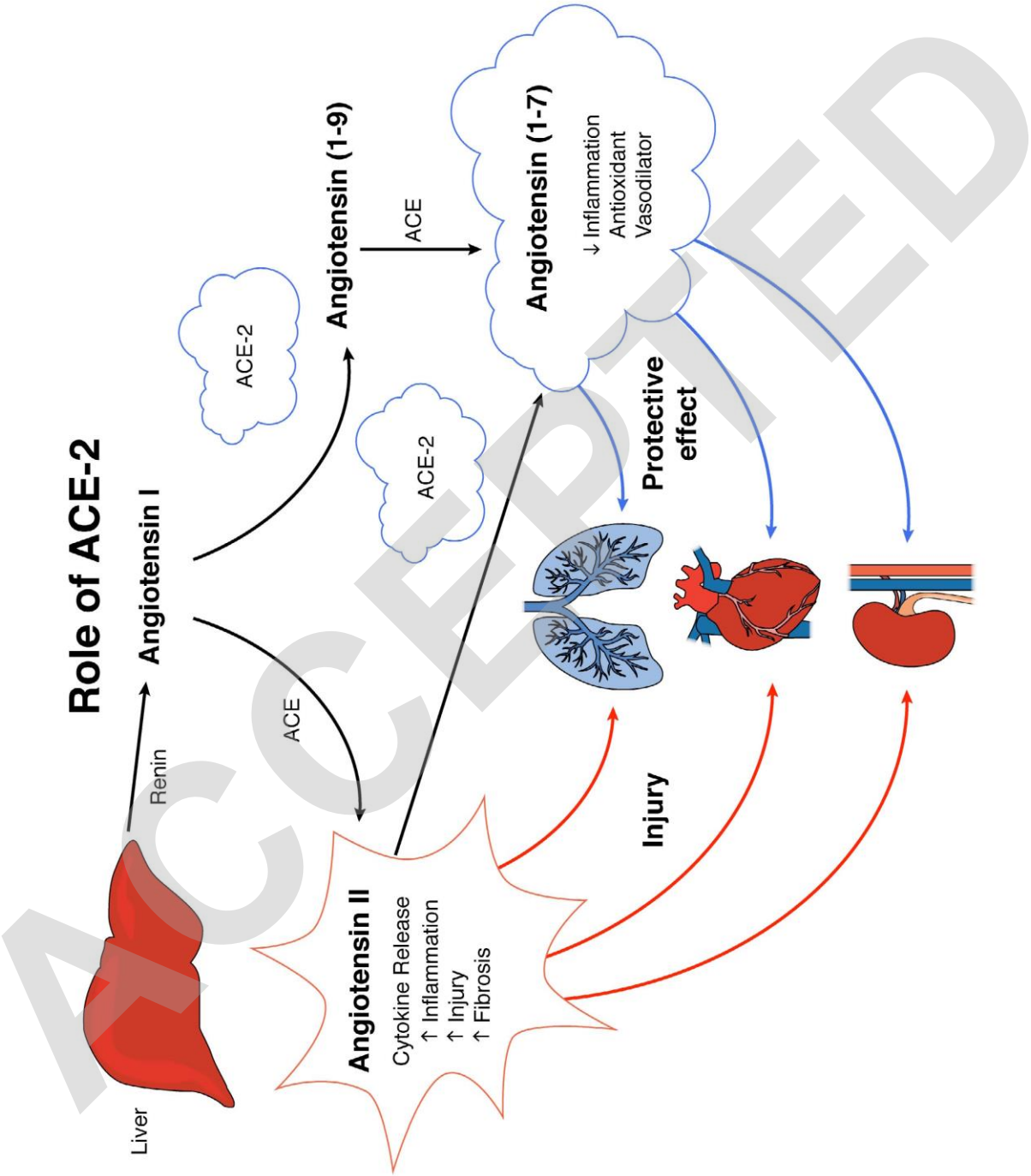

Figure 2

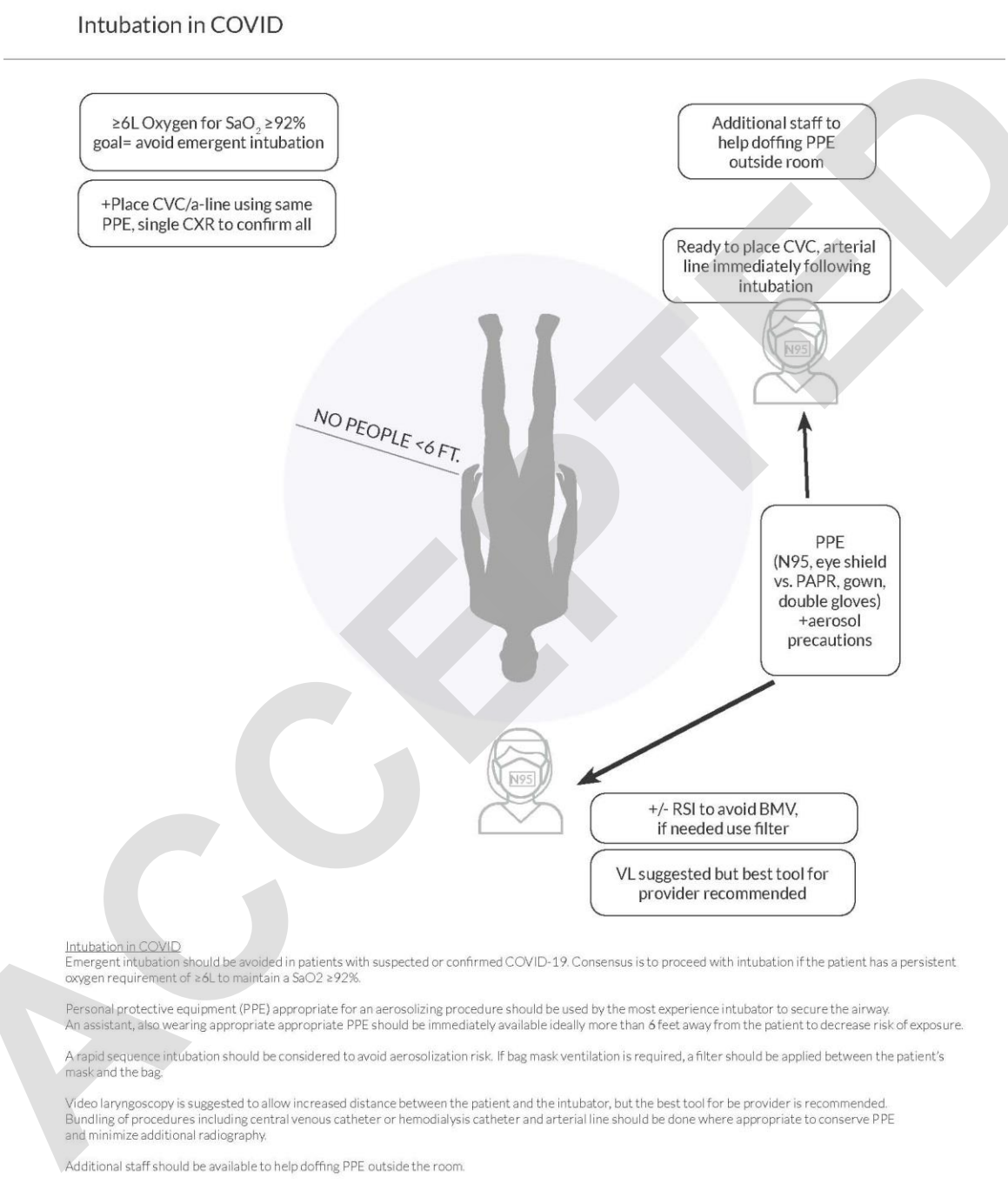

Figure 3