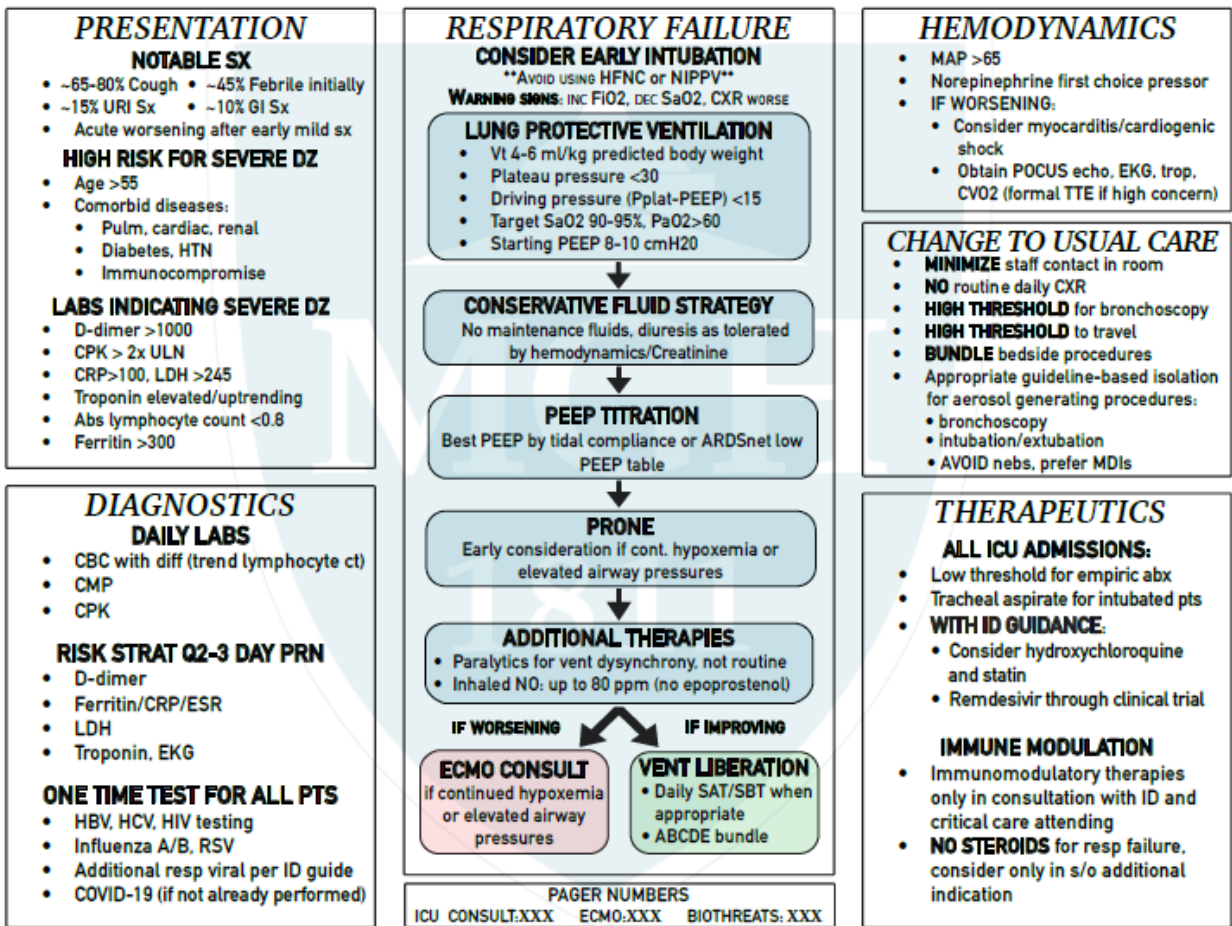**MASSACHUSETTS GENERAL HOSPITAL**
MGH 1811

Massachusetts General Hospital
Treatment Guidance for Critically Ill Patients with COVID-19

- This document was developed by members of the Division of Pulmonary and Critical Care Medicine at MGH, in collaboration with the Department of Anesthesia, Critical Care and Pain Medicine and Respiratory Care, to provide guidance to frontline clinicians caring for patients with COVID-19 in the ICU.
- This is a living document that may be updated as more data emerge (*updated as of 3/24/20*)

Executive Summary:

MGH TREATMENT GUIDE FOR CRITICALLY ILL PATIENTS WITH COVID-19

PRESENTATION

NOTABLE SX
- ~65-80% Cough • ~45% Febrile initially
- ~15% URI Sx • ~10% GI Sx
- Acute worsening after early mild sx

HIGH RISK FOR SEVERE DZ
- Age >55
- Comorbid diseases:
  - Pulm, cardiac, renal
  - Diabetes, HTN
  - Immunocompromise

LABS INDICATING SEVERE DZ
- D-dimer >1000
- CPK > 2x ULN
- CRP>100, LDH >245
- Troponin elevated/uptrending
- Abs lymphocyte count <0.8
- Ferritin >300

DIAGNOSTICS

DAILY LABS
- CBC with diff (trend lymphocyte ct)
- CMP
- CPK

RISK STRAT Q2-3 DAY PRN
- D-dimer
- Ferritin/CRP/ESR
- LDH
- Troponin, EKG

ONE TIME TEST FOR ALL PTS
- HBV, HCV, HIV testing
- Influenza A/B, RSV
- Additional resp viral per ID guide
- COVID-19 (if not already performed)

RESPIRATORY FAILURE

CONSIDER EARLY INTUBATION
Avoid using HFNC or NIPPV
WARNING SIGNS: INC FiO2, DEC SaO2, CXR WORSE

LUNG PROTECTIVE VENTILATION
- Vt 4-6 ml/kg predicted body weight
- Plateau pressure <30
- Driving pressure (Pplat-PEEP) <15
- Target SaO2 90-95%, PaO2>60
- Starting PEEP 8-10 cmH20

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CONSERVATIVE FLUID STRATEGY
No maintenance fluids, diuresis as tolerated by hemodynamics/Creatinine

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PEEP TITRATION
Best PEEP by tidal compliance or ARDSnet low PEEP table

↓

PRONE
Early consideration if cont. hypoxemia or elevated airway pressures

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ADDITIONAL THERAPIES
- Paralytics for vent dysynchrony, not routine
- Inhaled NO: up to 80 ppm (no epoprostenol)

IF WORSENING / **IF IMPROVING**

ECMO CONSULT
if continued hypoxemia or elevated airway pressures

VENT LIBERATION
- Daily SAT/SBT when appropriate
- ABCDE bundle

PAGER NUMBERS
ICU CONSULT:XXX   ECMO:XXX   BIOTHREATS: XXX

HEMODYNAMICS
- MAP >65
- Norepinephrine first choice pressor
- IF WORSENING:
  - Consider myocarditis/cardiogenic shock
  - Obtain POCUS echo, EKG, trop, CVO2 (formal TTE if high concern)

CHANGE TO USUAL CARE
- **MINIMIZE** staff contact in room
- **NO** routine daily CXR
- **HIGH THRESHOLD** for bronchoscopy
- **HIGH THRESHOLD** to travel
- **BUNDLE** bedside procedures
- Appropriate guideline-based isolation for aerosol generating procedures:
  - bronchoscopy
  - intubation/extubation
  - AVOID nebs, prefer MDIs

THERAPEUTICS

ALL ICU ADMISSIONS:
- Low threshold for empiric abx
- Tracheal aspirate for intubated pts
- **WITH ID GUIDANCE:**
  - Consider hydroxychloroquine and statin
  - Remdesivir through clinical trial

IMMUNE MODULATION
- Immunomodulatory therapies only in consultation with ID and critical care attending
- **NO STEROIDS** for resp failure, consider only in s/o additional indication

A living document by Division of Pulmonary and Critical Care in collaboration with the Dept. of Anesthesia,Critical Care, and Pain Medicine and Respiratory Care. May be updated or modified as situation evolves. Version created 3/19/20

Figure 1: Summary of Critical Care Protocol for COVID-19

It is expected that somewhere between 5-15% of hospitalized patients with COVID-19 will develop critical illness. Features of critical illness associated with COVID-19 include hypoxemia, respiratory

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failure, the Acute Respiratory Distress Syndrome (ARDS), shock (both distributive and, in at least in some reported cases, cardiogenic shock and multiple organ dysfunction syndrome (MODS). ICU management should focus on lung protective ventilation, avoidance of fluid overload, and support of organ function while minimizing risk of transmission with Strict Isolation. Additionally, attempts should be made to minimize the number of personnel providing care, avoid low-value diagnostics such as routine daily chest x-rays and aerosol-generating procedures such as bronchoscopy without strong indications. Measures to support organ function include supplemental oxygen, intubation and lung protective mechanical ventilation. Provided adequate resources are available, intubation is currently preferable to high-flow nasal canula or non-invasive positive pressure ventilation. There have been reports of rapid deterioration after the onset of hypoxemia. Therefore, an increasing oxygen requirement in any COVID-19 patient should prompt consideration of ICU transfer and intubation. The decision to intubate should be made early in order to facilitate deliberate planning and minimization of aerosol generation.

The most common severe manifestation of COVID-19 in the ICU is ARDS. Management of ARDS in the setting of COVID-19 does not differ significantly from management of ARDS due to other causes. Ventilation should be provided in the volume control mode with low tidal volumes. PEEP should be titrated according to usual unit protocol. Early consideration should be given to prone ventilation if PaO2/FiO2 is less than ~150 to 200 after 12 hours mechanical ventilation and PEEP titration, depending on illness trajectory (may wish to prone earlier if rapid deterioration). Inhaled pulmonary vasodilators (nitric oxide up to 80 ppm) may be used in the case of refractory hypoxemia. If patients fail to respond to these measures either due to persistent hypoxemia or unacceptably high airway pressures, it is appropriate to consider extra-corporal membrane oxygenation (ECMO).

There are variable reports of a late viral myocarditis that is associated with cardiogenic shock. Sudden deterioration in an ICU patient with COVID-19 should prompt work-up for cardiac dysfunction. Such a workup should include EKG, high-sensitivity troponin, central venous oxygen saturation (if available), lactate and bedside trans-thoracic echocardiography.

No specific treatments for COVID-19 have been conclusively demonstrated to provide benefit. It is appropriate to consider antiviral medication (i.e. remdesivir, chloroquine etc.) in the context of clinical trials or compassionate/off-label use programs. Antiviral medications should be given in consultation with ID and in compliance with the separate MGH protocol for anti-infective therapy in COVID-19. Steroids are not currently recommended for the treatment of viral pneumonia due to COVID-19 in the absence of an additional indication.

Clinical Features

The initial presentation of COVID-19 is non-specific and may include fever, malaise, sore throat, and myalgias. No single symptom is present in a majority of cases. Fever is the most common presenting symptom but is present on presentation in less than half of cases. In published case series, the median time to ICU transfer from symptom onset is approximately 10 days. Mortality is high, with estimates ranging from 20-60% in ICU patients. The most common reason for ICU transfer is hypoxemia and

respiratory failure. Patient characteristics associated with need for critical care include older age (>60), male sex, and presence of comorbidities including cardiac disease, diabetes, and chronic respiratory disease. Laboratory values that are significantly associated with need for mechanical ventilation in published series include lymphopenia, elevated troponin, elevated creatinine, elevated LDH and increased C-reactive protein. Procalcitonin is often normal and total white count can be normal. Most, but not all, patients have abnormalities on chest imaging. These include bilateral patchy opacities and interstitial changes, ground-glass opacities and consolidation.

Triage

ICU patients with COVID-19 who are expected to need aerosol generating procedures are optimally treated with Strict Isolation including Airborne Infection Isolation Room (AIIR) in order to reduce the risk of nosocomial transmission during such procedures as bronchoscopy and intubation, which may have to be performed emergently. Please refer to the triage grid for COVID 19 patients for preferred locations and precautions. There have been reports of rapid decompensation in patients with hypoxemia (P:F < 300, room air O2 saturation < 93%). ICU transfer should be considered in any patient with escalating oxygen requirement. Warning signs of deterioration include lymphopenia, in particular a progressive decline in peripheral blood lymphocytes, increasing lactate, elevated CRP and progression in chest radiograph abnormalities.

General ICU Care

It is important to conduct care in such a way as to minimize the risk to staff and eliminate the possibility of nosocomial transmission. To this end, patients should be treated under appropriate isolation precautions as indicated in separate infection control protocol. Efforts should be made to minimize the number of staff in and out of patient rooms. On rounds, it is not necessary for the entire ICU team to enter the room.

Fluid Resuscitation: Patients with hypoxemic respiratory failure should be managed with a conservative fluid strategy. A conservative fluid strategy includes limiting fluid boluses only to patients in shock who have indications of volume responsiveness, and early initiation of diuresis in those with improving or resolved shock. Positive fluid balance should be avoided in patients who are not volume responsive. Fluid responsiveness in patients with shock can be assessed by a variety of methods including passive leg raise, pulse pressure variation, and ultrasound assessment of IVC distensibility.

Empiric Antimicrobial Therapy: Bacterial superinfection has been reported. Consideration should be given to the early initiation of empiric antibiotics with rapid de-escalation, as outlined in the ATS/IDSA guidelines for severe community acquired pneumonia (or hospital acquired pneumonia if acquired > 48 hours from admission). Invasive diagnostic techniques such as bronchoscopy offer no benefit over blind tracheal suctioning using an in-line catheter and dramatically increases the risk to staff. Diagnostic bronchoscopy should generally be avoided in COVID-19 patients.

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Imaging: Routine daily chest x-rays have been demonstrated to have no effect on outcome in the ICU and should be avoided in the care of COVID-19 patients. Radiographic findings consistent with a diagnosis of COVID-19 are discussed above (See Clinical presentation). Possible indications for chest radiography subsequent to ICU admission include hemoptysis, suspected volume loss consistent with mucous plugging, and rapidly progressive hypoxemia. Various patterns on chest CT have been associated with COVID-19 but these (ground glass consolidation, bilateral opacities and consolidation) are non-specific and are not expected to inform daily management. Transport of patients to the CT scanner presents a risk of viral transmission to staff and other patients, as well as to the critically ill patient undergoing transport, and will also result in the need to temporarily close the scanner after the study for cleaning. For these reasons, chest CT should be reserved for situations in which an alternative diagnosis (i.e. pulmonary embolus) is suspected. Follow usual unit protocols for DVT prophylaxis.

Laboratory Investigation: Recommended daily labs include CBC with diff (in order to trend total lymphocyte count), complete metabolic panel, CPK, and LDH. Progressive elevations in CRP have been associated with poor outcome. In the event of clinical deterioration, studies to consider include EKG, D-dimer, central venous oxygen saturation, CRP, lactate, and LDH. Bacterial and fungal superinfection have been reported in a minority of cases so sputum culture and routine blood cultures on ICU admission are reasonable. Please see the separate ID document for initial laboratory workup for COVID-19 disease.

Aerosol generating therapies: Bronchoscopy, endotracheal intubation, extubation, trach change etc. are associated with a high risk of aerosolization and subsequent viral transmission. Such procedures should be conducted with all staff wearing N95 and other appropriate PPE. The decision to intubate should be made early in the course of clinical deterioration. Avoid routine bronchoscopy and perform only if less invasive tests have not yielded sufficient diagnostic information. Respiratory samples for diagnosis of bacterial superinfection may be obtained by close-loop endotracheal aspirate. Inhaled medications should be given by metered dose inhaler instead of nebulizer whenever possible to decrease the risk of viral transmission. Ventilators should be set up with adaptors in the dry arm of the circuit to facilitate subsequent use of inhalers without opening the circuit.

Non-invasive respiratory support

In published series from China and other countries, significant numbers of patients were treated with High-Flow Nasal Cannula (HFNC) and non-invasive positive pressure ventilation (NPPV). Concerns have been expressed about the potential for HFNC and NIPPV to generated infectious aerosols and recent data indicates viral particles can persist for some time after aerosol generating procedures. . **Where mechanical ventilation is available, it is the preferred means of respiratory support in COVID-19 patients**. In patients with other etiologies of respiratory failure, HFNC and NIPPV should be offered in accordance with usual indications. In particular, we should to continue to offer NIPPV in patients with hypercarbic respiratory failure and known COPD. Should there be a need to employ NIPPV or HFNC in a patient with known or suspected COVID-19 these therapies should only be

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provided to suspected or confirmed COVID-19 patients in the context of Strict Isolation after appropriate consultation with the MICU attending and Respiratory Care leadership.

Decision to Intubate

As above, the decision to intubate should be taken deliberately, in consultation with the intubation team, and should be performed in a negative pressure room with staff adhering to Strict Isolation. Indications for intubation include increased work of breathing (accessory muscle use, tachypnea), persistent hypoxemia and concern for worsening hypoxemia. As noted above, some patients will deteriorate quickly. In the presence of bilateral pneumonia, mechanical ventilation with low tidal volumes may be less injurious than continued vigorous spontaneous breathing with or without non-invasive support, but this benefit has to be weighed against the need for sedation often associated with mechanical ventilation. In the particular case of COVID-19, mechanical ventilation results in the patient breathing in a closed, filtered circuit that may reduce the risk of viral transmission. Additionally, non-emergent intubation allows staff adequate time to don PPE and prepare for the procedure. Therefore, as resources allow, early intubation is preferred in these patients.

Management of Respiratory Failure

The majority of patients with COVID-19 associated hypoxemic respiratory failure develop ARDS. Management of ARDS in the setting of COVID-19 does not meaningfully differ from standard ARDS management. Patients should be initially placed on volume-assist control ventilation with tidal volume of less than or equal to 6cc/kg IBW (ideal body weight, based on height), a set rate up to 35 breaths per minute, and moderate (8-10 cmH_2O) positive end expiratory pressure (PEEP). Plateau airway pressure (P_{plat}, pressure measured during an end-inspiratory pause) should be maintained below 30 cmH_2O and driving pressure (Pplat – PEEP) should be maintained < 15cmH_2O. Hypercarbia is acceptable (*permissive hypercarbia*) if there is no evidence of increased intracranial pressure and the goal should be to maintain arterial pH > 7.25.

Adjustment of ventilator settings

Patients with ARDS may fail to respond to initial ventilator settings, either through persistent high airway pressures (P_{plat} > 30 cmH_2O and/or driving pressure >15 cmH_2O) or persistent hypoxemia. Severity of hypoxemia can be assessed by means of the P:F ratio. Although ideally oxygen saturation should be maintained above 90% it is generally felt to be more important to minimize airway pressures. The following steps may be taken to optimize ventilatory settings:

Airway pressure: If P_{plat} is above 30 cm H_2O and/or driving pressure >15 cmH_2O, consider reducing the Vt below 6cc/kg to as low as 4cc/kg predicted body weight. The lower limit on the ability to decrease tidal volume is determined by the associated decrease in minute ventilation and thus hypercarbia. Respiratory rate can be increased as needed to compensate as long this does not result in significant auto-peep. Auto-peep is indicated by an expiratory flow curve on the ventilator screen that does not return to zero prior the initiation of the next inspiration.

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PEEP Optimization: In the presence of persistent hypoxemia (~Spo2 < 90%) requiring high FiO2 (~0.6 or more) attempts should be made to formally optimize the choice of PEEP. There is no method of PEEP optimization that is clearly superior to any other and PEEP optimization should proceed according to usual ICU protocol.

Lower PEEP/higher FiO2

FiO$_2$	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO$_2$	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24

Figure 2: ARDSnet Low - PEEP High FiO2 Table

If individualized PEEP titration is not available, PEEP may reasonably be set using the ARDSnet Low-PEEP table reproduced above. If time and staffing allow for individualized PEEP titration, PEEP may be set by best tidal compliance. If setting PEEP by best tidal compliance, consider a recruitment maneuver prior to PEEP trial according to usual unit protocol. During the trial, PEEP is adjusted in 2 cm H20 steps every 2-5 minutes with SpO2, driving pressure and hemodynamics recorded at each level. The optimal PEEP is the PEEP associated with the lowest driving pressure, as long as this coincides with hemodynamic stability and acceptable oxygenation (arterial oxygen saturation 90-95%).

Prone Ventilation: Prone ventilation for ARDS is strongly recommended in current clinical practice guidelines and should be implemented early in COVID-19 patients. Current indications for prone ventilation are a persistent hypoxemia defined as P:F < 150 for 12 hours (some clinicians favor < 200 sooner) after optimal PEEP titration as noted above. Prone ventilation results in a host of improvements to lung mechanics and should be instituted via established unit protocol. Prone ventilation can be carried out in the patients' current bed and requires minimal additional equipment. Contraindications to prone ventilation include an inability to turn neck (e.g. fixed or unstable c-spine) and second/third trimester pregnancy. Vascular access lines, chest tubes and CVVH lines are not contraindications to prone ventilation. The patient should be maintained in the prone position, for at least 16 hours. If P:F remains greater than 150 (some clinicians prefer 200) and driving pressure is less than 15 at the end of the 2 period of supine ventilation on PEEP of 10 cm H20 or less, prone ventilation may be discontinued. If returned to the prone position, prone and supine ventilation should be alternated with at least 16 hours prone and 2 hours supine. These time intervals are approximate and can be altered to facilitate staff needs (i.e. to avoid changes in position at shift change, etc.). A flow sheet for lung protective ventilation in the setting of COVID-19 is provided below:

Figure 3: Respiratory failure flow sheet for COVID-19

Ventilator Asynchrony: Patients with ARDS may have a high respiratory drive and attempts to minimize tidal volume and airway pressure can result in ventilator asynchrony. This can manifest in multiple ways including double triggering (see figure):
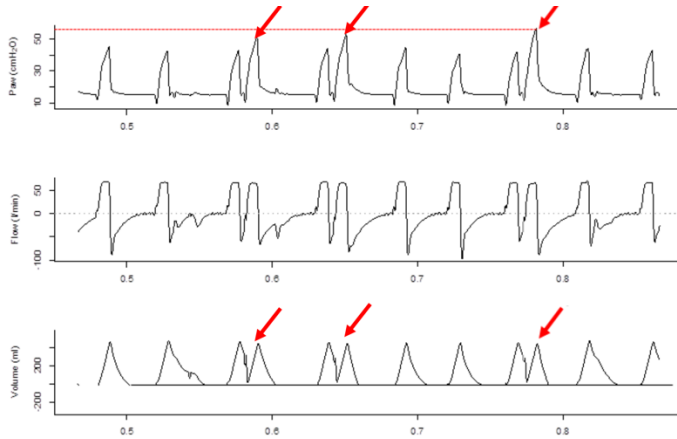
Figure 3: From JAMA. 2017;318(14):1335-1345

Ventilator asynchrony such as double triggering results in high tidal volumes and airway pressures that can be injurious. Increasing inspiratory flow may decrease dyspnea, but if asynchrony is persistent then consider continuous neuromuscular blockade (i.e. cisatracurium). The initiation of neuromuscular blockade should be only undertaken in response to asynchrony or persistent high airway pressures (by eliminating tone of chest wall muscles, neuromuscular blockade can decrease chest wall compliance and thus decreases pressures at any given volume). We do not recommend routine neuromuscular blockade. If double triggering increases with deep sedation, consider the diagnosis of "reverse triggering" or entrainment. This reflex breathing pattern may abate with reducing sedation.

Pulmonary Vasodilators: In case of persistent hypoxemia despite optimization of ventilator settings, patients should be started on inhaled pulmonary vasodilators. This should consist of a trial of inhaled nitric oxide (NO) at 40ppm, with increases in dose up to 80ppm as needed. A successful trial of inhaled NO consists of a 10-15% increase PaO_2. If the patient responds to NO, its use should be maintained and the recommendation is to not switch to inhaled prostacyclin analogues for COVID-19 patients given the increased risk of aerosol generation.

ECMO: Patients with persistent hypoxemia or unacceptable airway pressures despite the optimization of ventilator settings, neuromuscular blockade, prone positioning, and inhaled pulmonary vasodilators are deemed to have refractory ARDS and the team should consider if the patient is appropriate for extra-corporal membrane oxygenation team (ECMO). If determined to be a candidate, and capacity allows, the best way to consult the MGH ECMO team is via the Heart Center ICU phone app.

Hemodynamic Management

Initial reports from China and Italy indicate a predominance of isolated respiratory failure associated with COVID-19. In other words, patients with COVID-19 associated respiratory failure have a lower than expected incidence of associated organ failures such as shock and renal failure. Irrespective of the above, shock and renal failure do occur. It is reasonable to treat these patients with usual protocols

for distributive shock (Norepinephrine titrated to MAP > 65 mm hg with vasopressin (0.04 units/min) as initial pressors, tailored fluid resuscitation, monitoring of CVO_2, lactate and central venous oxygen saturation). There have been variable reports from China and Seattle of patients with cardiogenic shock secondary to myocarditis occurring late in their clinical course. One series from China reported myocarditis in 7% of patients. Therefore, a high index of suspicion must be maintained for the development of cardiogenic shock and viral myocarditis. In addition to exam findings (hypotension, cold extremities, delayed capillary refill) patients in whom cardiogenic shock is suspected should have bedside echocardiography, EKG, lactate and central venous oxygen saturation checked. Such patients may require the addition of inotropes (dobutamine, milrinone) to achieve hemodynamic stability. Confirmed or suspected presence of myocarditis should be discussed with the ECMO team if patients are being considered for extra-corporal support as it may have implications for choice of ECMO therapy (veno-arterial vs veno-venous).

Specific Therapies and Immunomodulation

There are no specific anti-viral therapies that have been proven to be effective in the settings of COVID-19. Investigational agents should be provided in consultation with infectious disease and in accordance with the separate MGH protocol for anti-infective treatment of COVID-19. Both bacterial and fungal superinfection has been reported. Immunomodulatory therapies such anti-IL6ra should be provided in the context of ongoing clinical trials, access to which may be facilitated by infectious disease. In the absence of a secondary indication (exacerbation of COPD, transplant recipients, adrenal insufficiency) corticosteroids should be avoided in the setting of COVID-19.