MANAGEMENT OF THE CRITICALLY ILL ADULT PATIENT WITH COVID-19 CLINICAL GUIDELINE

The intent of this guideline is to provide clinicians at The Ohio State University Wexner Medical Center (OSUWMC) and with best practices based on latest evidence to optimize the care for the critically ill COVID-19 patient. It is based on pertinent published medical literature, national and state guidelines, and/or expert consensus, which continues to evolve relative to COVID-19. It is neither an attempt to substitute for the practice of medicine nor as a substitute for the provision of any medical professional services. Furthermore, the content is not meant to be complete, exhaustive, or a substitute for medical professional advice, diagnosis, or treatment. This document will be updated regularly to reflect the rapid progression of knowledge regarding the management of patients COVID-19.

Current as of April 8, 2020

I. Background
   a. Coronavirus disease 2019 (COVID-19) is a respiratory illness caused by a novel coronavirus (SARS-CoV-2). COVID-19 was first described in Wuhan, China in December 2019 and is now a global pandemic. After evaluating the cases seen in China, the Centers for Disease Control and Prevention (CDC) had noted that most of those affected have milder illness (80%), 15% will be severely ill (require oxygen) and 5% will require ICU care. Of those who are critically ill, most require early intubation and mechanical ventilation. Other complications include septic shock and multi-organ failure, including acute kidney injury and cardiac injury.1 Patients who were infected were more likely to be of older age and have comorbid diseases, such as COPD, hypertension, coronary artery disease and diabetes.2 One report out of China demonstrated with a multivariate regression that there was an increasing odds of in-hospital death associated with older age, higher Sequential Organ Failure Assessment (SOFA) score and d-dimer greater than 1µg/mL on admission .3 The virus is highly contagious and spread via respiratory droplets, direct contact, and if aerosolized, airborne routes. The most common symptoms include fever, fatigue, dry cough, and shortness of breath.

II. Infection Control
   a. Clinical Course of COVID-19
      i. Clinical Presentation and Disease Course
         1. The initial presentation is non-specific. Frequently reported symptoms for further information of patients admitted to the hospital include: fever, cough, dyspnea, myalgias, GI Symptoms.2,4–7 See the Inpatient Clinical Guidelines for Novel Coronavirus (COVID-19) for further information.
2. Clinical presentation among reported cases of COVID-19 varies in severity from asymptomatic infection to mild illness to severe or fatal illness. Several reports suggest the potential for clinical deterioration during the second week of illness. In one report out of China, among patients with confirmed COVID-19 and pneumonia, just over half of patients developed dyspnea a median of 8 days after illness onset (range: 5–13 days). In another report out of the United States (U.S.), the mean time from illness onset to hospital admission with pneumonia was 9 days.

3. It is expected that approximately 5% of hospitalized patients with COVID-19 will develop critical illness. Features of critical illness associated with COVID-19 include hypoxemia, respiratory failure, acute respiratory distress syndrome (ARDS), and shock (including distributive, cardiogenic, and multiple organ dysfunction syndrome (MODS)). The median time to ICU transfer from symptom onset is approximately 10 days. Mortality is high, with estimates approximating 50-78% in ICU patients. The most common reason for ICU transfer is hypoxemia and respiratory failure.

4. ARDS developed in 17–29% of hospitalized patients with the median time from symptom onset to ARDS was 8-10 days.

Figure 1. Clinical Courses of Major Symptoms and Outcomes and Duration of Viral Shedding

ii. Risk Factors
1. Risk factors for severe illness are not yet clear; however, elderly patients and those with chronic medical conditions may be at higher risk for severe or critical illness.
2. Early U.S. epidemiologic data suggests that the case fatality was highest in persons aged ≥85 years (range 10%-27%), followed by 3%-
11% for ages 65-84 years, 1%-3% for ages 55-64 years, and <1% for ages 0-54 years.\(^9\)

3. Patients with no reported underlying medical conditions had an overall case fatality of 0.9%, but case fatality was higher for patients with comorbidities: 10.5% for those with cardiovascular disease, 7.3% for diabetes, and approximately 6% each for chronic respiratory disease, hypertension and cancer.\(^1,3,5,8,10,11\) Heart disease, hypertension, prior stroke, diabetes, chronic lung disease, and chronic kidney disease have all been associated with increased illness severity and adverse outcomes.\(^10\)

iii. Incubation Period
   1. The median incubation period for COVID-19 is approximately 4 days (interquartile range: 2 to 7 days).\(^11\)

iv. Transmission
   1. According to current evidence, COVID-19 virus is primarily transmitted between people through respiratory droplets and contact routes.\(^2,12,13\)
   2. Droplet transmission occurs when a person is in close contact (within 1 meter) with someone who has respiratory symptoms such as coughing or sneezing and is therefore at risk of having his/her mucosae or conjunctiva exposed to potentially infective respiratory droplets.
   a. In the context of COVID-19, airborne transmission may be possible in specific circumstances and settings in which procedures or support treatments that generate aerosols are performed; i.e., endotracheal intubation, bronchoscopy, open suctioning, administration of nebulized treatment, manual ventilation before intubation, turning the patient to the prone position, disconnecting the patient from the ventilator, non-invasive positive-pressure ventilation, tracheostomy, and cardiopulmonary resuscitation.
   3. Transmission may also occur through fomites in the immediate environment around the infected person.\(^14\) Therefore, transmission of the COVID-19 virus can occur by direct contact with infected people and indirect contact with surfaces in the immediate environment or with objects used on the infected person (e.g., stethoscope or thermometer).
   4. There is some evidence that COVID-19 infection may lead to intestinal infection and can be present in feces. However, to date only one study has cultured the COVID-19 virus form a single stool specimen.\(^15\) There have been no reports of fecal-oral transmission of the virus to date.

b. Isolation and Personal Protective Equipment (PPE)
   i. Link Employee Exposure Guidelines, PPE Instructions and PPE Guidance
   ii. Link Isolation Recommendation Guidance
   iii. Link Discontinuation of Isolation Guidance
   iv. Link Medication Administration Bundling
   v. Link Code Blue Protocol

c. Shortages and Procurement
   i. Ordering PPE
ii. Short acting bronchodilator MDI and Nebulization Guidance
iii. Shortage Updates relevant to COVID Management
d. Inpatient Initial Workup and Screening
   i. Link to COVID-19 Suspect Patient Workflow for Admitted Patient
   ii. Link to Inpatient Clinical Decision Guide
   iii. Link to Symptom Stratification

III. Antiviral Treatment Guideline for SARS-CoV-2
   a. See the Infectious Diseases and Antimicrobial Stewardship Program treatment recommendations for SARS-CoV-2

IV. Respiratory Support for COVID-19 Patients
   a. Introduction to Mechanical Ventilation
   i. Providers can access lecture from Dr. Allen and Dr. Quaney on Management of the COVID-19 Patient with Respiratory Failure: https://ccme.osu.edu/WebCastDetail.aspx?ID=876
   ii. See Appendix A for additional information on mechanical ventilation
   iii. Weaning Strategies
       1. Patients reaching minimal ventilator settings (generally FiO2 of 40% and PEEP 6) are ready for spontaneous breathing trial
       2. Recommend using PEEP 0, PS 0 for the SBT settings based on anecdotal experience of patients with COVID-19 being sensitive to positive pressure.
   b. Sedation and Analgesia in Mechanically Ventilated Patients
      i. Utilize the MICU Sedation Algorithm
      ii. General Principles
         1. To assess level of sedation, use the Richmond Agitation Sedation Scale (RASS):

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Description</th>
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<tbody>
<tr>
<td>+4</td>
<td>Combative</td>
<td>Overtly combative, violent, immediate danger to staff</td>
</tr>
<tr>
<td>+3</td>
<td>Very Agitated</td>
<td>Pulls or removes tube(s) or catheter(s); aggressive</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated</td>
<td>Frequent non-purposeful movement, fights ventilator</td>
</tr>
<tr>
<td>+1</td>
<td>Restless</td>
<td>Anxious but movements not aggressive vigorous</td>
</tr>
<tr>
<td>0</td>
<td>Alert and Calm</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy</td>
<td>Not fully alert, but has sustained awakening to voice (≥10 seconds)</td>
</tr>
<tr>
<td>-2</td>
<td>Light Sedation</td>
<td>Briefly awakens with eye contact to voice (&lt;10 seconds)</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate Sedation</td>
<td>Movement or eye opening to voice (but no eye contact)</td>
</tr>
<tr>
<td>-4</td>
<td>Deep Sedation</td>
<td>No response to voice, but movement or eye opening to physical stimulation</td>
</tr>
<tr>
<td>-5</td>
<td>Unarousable</td>
<td>No response to voice or physical stimulation</td>
</tr>
</tbody>
</table>
2. Assess and treat pain using multimodal therapies prior to sedative initiation.

3. Maintain light sedation in mechanically ventilated patients (Richmond Agitation-Sedation Scale -1 to +1). Some patients with ARDS may require deeper sedation goals (RASS -3 to -4).

4. Non-benzodiazepine based sedation regimens are preferred to prevent delirium in critically ill patients, unless deep sedation is desired. Selection of analgesic and sedative therapies should also take into consideration drug shortages.

5. Perform daily Sedation Awakening Trial (SAT) paired with Spontaneous Breathing Trial (SBT) in patients meeting criteria.

iii. Common Analgesic and Sedative Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Continuous Infusion Rate</th>
<th>Adverse Effects</th>
<th>Clinical Pearls</th>
</tr>
</thead>
</table>
| Propofol    | 5-50 mcg/kg/min (May increase range if unable to achieve goal RASS, maximum 80 mcg/kg/min) | • Hypotension  
• Respiratory depression  
• Hypertriglyceridemia  
• Propofol-related infusion syndrome (PRIS) | • Formulated in a lipid emulsion  
• Quick onset and short duration |
| Dexmedetomidine | 0.2-1.4 mcg/kg/hr       | • Bradycardia  
• Hypotension  
• Heart block | • Does not cause respiratory depression  
• Option for non-intubated patients  
• Only produces light sedation  
• Longer duration of action |
| Fentanyl    | 50-150 mcg/hr (May increase range if unable to achieve goal RASS) | • Constipation  
• Hypotension | • May cause chest wall rigidity  
• Can accumulate with hepatic impairment |
| Hydromorphone | 0.2-1.5 mg/hr (May increase range if unable to achieve goal RASS) | • Constipation  
• Hypotension | • Accumulation with hepatic/renal impairment |
| Ketamine    | 0.5-2 mg/kg/hr (May increase range if unable to achieve goal RASS, maximum 4 mg/kg/hr) | • Psychological Disturbances/Emergence Reactions  
• Hypertension  
• Tachycardia | • Both analgesic and sedative properties  
• Use with caution in patients with cardiomyopathy or pulmonary hypertension |
| Midazolam   | 1-6 mg/hr (May increase range if unable to achieve goal RASS) | • Respiratory depression  
• Hypotension | • Active metabolites  
• Consider for deep sedation |
| Lorazepam   | 1-3 mg/hr (May increase range if unable to achieve goal RASS) | • Respiratory depression  
• Hypotension | • Formulation contains propylene glycol diluent which can cause metabolic acidosis and acute kidney injury  
• Occurs with high doses and longer durations (generally doses >6mg/hr period >48 hours). |

iv. Propofol monitoring in patients with COVID-19

1. There are case reports showing hypertriglyceridemia at baseline in patients with COVID-19. Obtain triglyceride and CK at baseline prior to initiating propofol and monitor every 48 hours due to concerns of propofol-related infusion syndrome (PRIS).

2. Monitor for other signs of PRIS characterized by abrupt onset of myocardial failure (bradycardia or arrhythmias), renal failure, fatty liver, metabolic acidosis, rhabdomyolysis, and myoglobinuria.
3. Link to Propofol IV Guideline for general guidance on when to consider alternative sedation based on triglyceride and CK levels. With known hypertriglyceridemia in the COVID-19 patient population, propofol continuous infusions may be continued with triglyceride levels up to 800 if CK remain within normal limits and no other signs of symptoms of PRIS are present. If triglycerides are >400 and patient remains on propofol, then recommend checking triglycerides and CK every 24 hours.

c. Management of Refractory Hypoxemia in Mechanically Ventilated Patients with ARDS
   i. Proning
      1. Patients with severe hypoxemia (defined as a PaO2/FiO2 ratio of <150) benefit from proning. The OSUWMC Clinical Practice Guideline on Refractory Hypoxemia contains the proning algorithm. Patients being considered for proning should be discussed with the critical care fellow or attending prior to initiation of proning.
      2. Complete the Proning Checklist (Appendix B).
      3. Use the OSUWMC Standard Operating Procedure to perform CPR in the proned patient: Standard of Practice CPR in the Prone Patient
   ii. Fluid Management in ARDS
      1. Fluid management an important component of ARDS management. Following initial resuscitation and in the absence of shock, a conservative fluid management strategy is recommended to achieve a negative fluid balance of 0.5 to 1.0 liters per day.\textsuperscript{16–18} This may be achieved through de-resuscitative strategies utilizing IV diuretics.
      2. In the presence of shock, fluid balance might be achieved with renal replacement therapy, especially if there is associated acute kidney injury and oliguria.\textsuperscript{18}
      3. Although a conservative fluid strategy has not been evaluated specifically in COVID-19 ARDS patients, it has been shown to increase ventilator free days and decrease ICU length of stay in ARDS patients when compared with a liberal fluid strategy. With cardiac failure found to be the cause of death in a large portion of COVID-19 patients in currently available literature, in addition to the concerns for myocardial injury, prevention of volume overload and pulmonary edema through a conservative fluid strategy is recommended.
   iii. Neuromuscular Blockade
      1. There have been conflicting studies published regarding the benefit of continuous neuromuscular in patients with moderate to severe ARDS. Most recently, the ROSE trial failed to show a mortality benefit when patients with a PaO2/FiO2 ratio of <150 received cisatracurium for 48 hours.\textsuperscript{19}
      2. Patients with severe/refractory hypoxemia, hypercarbia, or ventilator dyssynchrony may benefit from neuromuscular blockade.
Neuromuscular blockade should be considered in patients with persistent ventilator dyssynchrony despite deep sedation (RASS -4 to -5), prone ventilation, or persistently high plateau pressures.

a) Using intermittent IV push doses of neuromuscular blocking agents (NMBA) is preferred when able to conserve drug supply of neuromuscular blocking agents with severe drug shortages. Recommend vecuronium or rocuronium if using intermittent IV push due to longer duration of action than cisatracurium or atracurium.

b) Refer to the [Continuous Pharmacologic Neuromuscular Blockade of the Critically Ill Patient Policy](#) and [Continuous Neuromuscular Blocking Agent Pharmacy Checklist](#) when initiating.

   a. NMBA do not possess any amnestic or analgesic properties. Therefore, a continuous amnestic and analgesic must be initiated (or continued) whenever a continuous NMBA is ordered.
   
   b. Prior to initiation of NMBA, patient must be deeply sedated (RASS -4 to -5).

c) NMBA may be on severe shortage during the COVID-19 pandemic, please refer to [drug shortage database](#) for current shortages and assess patients daily for appropriateness of trialing off continuous neuromuscular blockade to limit to the shortest duration.

iv. Pulmonary Vasodilators

   1. For the treatment of ARDS pulmonary vasodilators have not shown to improve clinical outcomes. Despite this, they have proven to increase oxygenation and reduce pulmonary arterial pressure. Inhaled vasodilators may be considered as rescue therapy in patients with refractory hypoxemia despite lung protective ventilation. If patients don’t have clinical improvement within 6 hours of therapy, it should be discontinued, as continued therapy will likely not provide benefit.

      a. Inhaled epoprostenol

         i. Refer to [Inhaled Epoprostenol Policy](#) for general considerations

         ii. For patients who are COVID positive/suspected, inhaled epoprostenol should ONLY be initiated if the patient is requiring mechanical ventilation. While inhaled epoprostenol is able to be administered with NIPPV it is not recommended in PUI/Confirmed COVID-19 patients to decrease aerosolization and spread of COVID-19.

         iii. Even in intubated patients, there is a risk of aerosolization when the circuit is broken during
administration and practitioners should take appropriate precautions when administering.

b. Inhaled nitric oxide (NO)
   i. Inhaled nitric oxide should be reserved for severe refractory hypoxemia. Typical starting dose is 20ppm and titrate to lowest effective dose to avoid methemoglobinemia. Refer to inhaled nitric oxide policy for more information.
   ii. Try to limit potential for methemoglobinemia by using lowest effective dose possible. Recommend monitoring for methemoglobin daily while on therapy.
   iii. Inhaled NO has not been studied in patients with mild ARDS. However, NIPPV is not needed for the administration of inhaled nitric oxide like it is for inhaled epoprostenol. In addition, inhaled nitric oxide may decrease viral replication leading to theoretical benefit. If the decision to start inhaled nitric oxide is made to prevent intubation of a COVID positive or suspected patient with mild ARDS attending approval must be obtained and/or enrolled in a study.

v. Extracorporeal Membrane Oxygenation (ECMO)
   1. It has become increasingly clear that Ventilator-induced lung injury (VILI) associated with mechanical ventilation is a major source of mortality in patients with ARDS. This is why lung protective ventilation is such an important component in early management. In severe ARDS for patients that have failed conventional management, ECMO may have a role in improving oxygenation and gas exchange while also allowing for further reduction of intensity of mechanical ventilation, thereby further reducing risk of VILI.
   2. Refer to the OSUWMC Clinical Practice Guideline on Refractory Hypoxemia for patients who remain hypoxic despite lung protective ventilation.
      a. ECMO is a finite resource compounded in the setting of this pandemic. Further limits on selection criteria may be forthcoming if there is concern of depletion of equipment or personnel with training to care for patients on ECMO.
   4. Early initiation of ECMO facilitates a positive outcome. If patients fail conventional management, consider use of the rescue therapies listed above but they should not delay ECMO consults. ECMO will not be considered if patient has been intubated for greater than 7 days.
5. If ECMO is considered, immediate evaluation is required. For ECMO evaluation use ‘Inpatient consult to ECMO’. Direct physician-to-physician communication is required.

vi. Corticosteroids in ARDS
1. There limited literature available evaluating outcomes in patients with COVID-19 pneumonia or ARDS who received corticosteroids. Current, guideline recommendations from the WHO and CDC extrapolates experience from SARS and MERS to patients with COVID-19.16 The CDC recommended avoiding corticosteroids unless for other clinical indications (e.g. COPD exacerbation, septic shock) due to potential for prolonged COVID-19 viral replication.
   a. To date, there have been 2 small, single-center retrospective studies, limited by sample size and inability to control for confounding variables:
      i. Wu and colleagues’ reported outcomes for 201 patients with COVID-19 pneumonia (41.8% of which had ARDS).21 In the subset of patients with ARDS, the use of methylprednisolone correlated with reduced mortality. Doses and durations were not reported.
      ii. Wang and colleagues’ evaluated 46 patients with severe COVID-19 pneumonia.22 Twenty-six of the 46 patients received methylprednisolone 1-2 mg/kg/day for 5-7 days. The group treated with methylprednisolone had faster improvement in SpO2, faster absorption of lung focus on chest CT, and quicker resolution of fever.

2. The Society of Critical Care Medicine (SCCM) suggests corticosteroids in mechanically ventilated COVID-19 patients with ARDS (weak recommendation, low quality evidence).16 Corticosteroids unlikely to be beneficial and may be harmful in late ARDS (>7 days from ARDS onset).
   a. Recommend avoiding corticosteroid administration for ARDS due to concerns from WHO and CDC of prolonged viral replication.
   b. Discussion of risk vs. benefit should occur between intensivist/pulmonologist and infectious disease attending on a patient-by-patient basis prior to initiating corticosteroids until further literature is available.
   c. If steroids are given, suggest either methylprednisolone 1-2 mg/kg/day for 5-7 days OR dexamethasone 20mg daily for 5 days followed by 10 mg daily for 5 days.16,23,24

vii. Vitamin C in ARDS
1. There is insufficient evidence to recommend the use of Vitamin C in patients with ARDS with or without COVID-19. If vitamin C is given,
a dose of 50mg/kg (maximum of 5,000mg) every 6 hours for 4 days should be used.

V. Shock Management

a. Differentiating Shock Type:

<table>
<thead>
<tr>
<th>Types of Shock</th>
<th>MAP</th>
<th>CVP (Preload)</th>
<th>PCWP (Preload)</th>
<th>CO or CI</th>
<th>SVR (Afterload)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distributive</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
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</tr>
<tr>
<td>Cardiogenic</td>
<td>↓</td>
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<tr>
<td>Hypovolemic</td>
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</tbody>
</table>

b. Antibiotic Selection for Superinfection

i. The incidence of bacterial superinfection in patients with COVID-19 is unknown due to limited utilization of high-quality respiratory samples in areas of early outbreaks. It is known that other viral pneumonias (influenza, MERS) can be associated bacterial superinfections, and it can be difficult to clinically identify concomitant bacterial pneumonia due to similar symptoms to COVID-19 infection. In addition, data from pandemic influenza demonstrates a significant increase in mortality with bacterial superinfection. Therefore, the SCCM guidelines recommend empiric antimicrobials in mechanically ventilated patients with COVID-19. Antibiotic selection should be based upon recommendations for treatment of community acquired pneumonia (CAP), hospital acquire pneumonia (HAP), or ventilator-associated pneumonia (VAP) depending on which risk factors are present. Utilize the following resources to guide diagnosis and antibiotic selection:

1. Link to: OSUWMC Clinical Practice Guideline on CAP
2. Link to: OSUWMC Clinical Practice Guideline on HAP/VAP
3. Link to: MICU algorithm for empiric antibiotics in CAP/HAP/VAP

ii. Procalcitonin

1. For patients in whom antimicrobials are initiated, de-escalation should be based on available culture data and clinical status. Based on current data with COVID-19 patients, procalcitonin can be utilized according to the Procalcitonin Guideline to guide duration of antibacterial agents in patients with sepsis and/or respiratory infections. See below for additional information about procalcitonin in COVID-19 infections.

2. In a description of 1099 COVID-19 patients in China, procalcitonin was negative (<0.5 ng/mL) in 94.5% of all patients, 95.8% of patients with non-severe disease, and 86.3% of patients with severe disease. This is consistent with data from previous viral epidemics (influenza H1N1, SARS, MERS) which demonstrates
that procalcitonin is typically low in hospitalized patients with pure viral infection and more likely to be elevated with bacterial coinfection. A meta-analysis of 4 studies demonstrated that increased procalcitonin values are associated with a nearly 5-fold higher risk of severe COVID-19 infection (OR, 4.76; 95% CI, 2.74–8.29) and the authors suggest that serial procalcitonin measurement may play a role in predicting progression to more severe disease.

c. Fluid Therapy in Septic Shock

i. In a dataset of 1099 patients with COVID-19 infection in China, shock was less common than ARDS, with septic shock being noted in 6.4% of severe cases compared to ARDS in 15.6% of severe cases. Because there is no specific data regarding fluid resuscitation in patients with COVID-19 and shock, and because ARDS is a frequent complication of COVID-19 infection, fluid should be administered according to standard septic shock guidelines with particular attention paid to the potential development of ARDS and the potential need to adjust fluid goals to a more conservative strategy.

ii. Patients with septic shock should receive 30mL/kg of crystalloid fluid within 1 hour of identification of sepsis.

iii. Balanced fluids, such as lactated ringers or plasmalyte, are preferred over 0.9% sodium chloride due to concerns for hyperchloremic metabolic acidosis and AKI with the use of 0.9% sodium chloride.

iv. Colloids should be avoided as there is no evidence of improved outcomes over crystalloids and they may cause harm.

v. Additional fluid administration should be guided by frequent reassessment of hemodynamic status with common goals of MAP ≥ 65mmHg and normalization of serum lactate levels.

vi. Refer to the OSUWMC Clinical Practice Guideline for Initial Sepsis Management for additional details.

vii. Care must be taken to avoid excess fluid resuscitation, as ARDS is a common cause of death amongst COVID-19 patients and may be exacerbated by fluid overload. Therefore, the recommendations for acute resuscitation is to use a conservative fluid strategy. Consider earlier use of vasopressors in patients with tenuous respiratory status.

d. Vasopressor Choice and Management

i. There is no direct evidence on vasoactive agents for patients with COVID-19 and shock. Vasopressor selection and management should follow standard ICU care. For patients with septic shock, norepinephrine should be considered first-line for vasopressor therapy. Patients with COVID-19 are at increased risk of cardiovascular complications, including cardiogenic shock, and should be closely monitored. Initial vasopressor selection and ongoing management should be tailored to individual patient characteristics and response, and guided by drug shortages.

ii. Considerations in COVID-19
1. Angiotensin II (Giapreza)
   a. Angiotensin-converting enzyme 2 (ACE2) has been shown to be a co-receptor on human cells for viral entry for COVID-19.\(^{36}\) Additionally, ACE2 is a key enzyme in degrading angiotensin II to angiotensin(1-7), a conversion which limits angiotensin II's effects on vasoconstriction, sodium retention, and fibrosis.\(^{37}\) In the presence of COVID-19, ACE2 is down-regulated, allowing for uninhibited angiotensin II activity and worsening of lung injury. Given this proposed mechanism, the use of exogenous angiotensin II (Giapreza) for vasopressor therapy in patients with COVID-19 and shock has potential to further exacerbate these effects and is not recommended.
   b. Patients with COVID-19 have also been shown to be at higher risk for cardiovascular complications, including venous thromboembolism.\(^{3,38}\) Angiotensin II has been associated with increased risk of thrombotic events, therefore providing further evidence against the use of angiotensin II in this population.\(^{39}\)

2. Angiotensin Receptor Blockers
   a. Controversy exists over the role of angiotensin receptor blockers (ARB) in patients with COVID-19. Animal models have shown increased expression of ACE2 receptors after ARB administration, which some theorize can worsen disease by providing additional binding sites for COVID-19.\(^{36}\) However, new evidence has proposed increased ACE2 expression can offer therapeutic benefit by counteracting the deleterious effects of angiotensin II on lung and cardiac tissue.\(^{37,40}\) Due to the potential of ARBs to worsen hemodynamic instability without clear evidence of therapeutic benefit, we do not recommend the initiation of ARB therapy for patients with sepsis or septic shock at this time.

e. Adjunctive Agents
   i. Corticosteroids
      1. While current guidelines recommend against using corticosteroids as treatment for COVID-19 infection in patients without ARDS, it is recommended to use low-dose corticosteroid therapy (hydrocortisone IV 50mg every 6 hours) in patients with refractory septic shock.\(^{16}\) Refer to the OSUWMC Clinical Practice Guideline for Initial Sepsis Management for an algorithm regarding corticosteroid use in septic shock.
   ii. Vitamin C
      1. There is insufficient evidence to recommend vitamin C as supportive care in patients with COVID-19 and shock.
2. A phase II randomized, placebo-controlled trial in China is enrolling patients to evaluate high-dose IV vitamin C in critically ill patients with severe COVID-19 infection. Estimated completion date is September 2020.

f. Temperature Control
i. Concerns regarding the use of non-steroidal anti-inflammatory drugs (NSAIDs) to treat patients with COVID-19 are based on theoretical and anecdotal reports rather than clinical outcomes data specific to COVID-19.
ii. NSAIDs are linked to a number of adverse effects, which may be worse among the patient populations at an increased risk of poor outcomes from COVID-19 (e.g., elderly, those with comorbidities such as cardiovascular disease including heart failure and coronary artery disease).
iii. Additionally, COVID-19 has been associated with increased risk of acute cardiac injury.
iv. **NSAIDs should be avoided** in patients with documented/suspected COVID-19 and any cardiovascular comorbidities that would normally preclude NSAID use.
v. At this time, **acetaminophen may be considered as first-line** for temperature control in patients with COVID-19.

VI. Cytokine Storm Syndrome
a. **Tocilizumab**
   i. Proposed Therapeutic Effect:
      1. Recombinant humanized monoclonal IL-6 antibody, approved for certain rheumatological diseases and Chimeric Antigen Receptor (CAR) T cell-induced cytokine release syndrome.
      2. The role of IL-6 in COVID-19 induced cytokine release and acute respiratory distress syndrome is unclear. Other adaptive/innate immune cells and cytokine factors may be implicated.
      3. No specific IL-6 cut-off has been established to predict illness severity. In an open-label study of 21 patients with severe/critical disease, mean IL-6 levels were 132.38 ± 278.54 pg/ml. Tocilizumab reduced body temperatures and supplemental oxygen requirements, as well as improved CT findings in most patients. In another report, IL-6 levels averaged 25.2 pg/ml in severe cases compared to 13.3 pg/ml in non-severe cases.
   ii. OSUWMC Clinical Use:
      1. Due to the lack of data from controlled studies, routine use of tocilizumab is not recommended. Randomized controlled trials are presently underway and results may help determine role in therapy for COVID-19 infection.
      2. Following discussion with the intensivist / pulmonologist and Infectious Diseases attending, tocilizumab may be
considered on a case-by-case basis if there is evidence of worsening oxygenation after trialing first line therapies.

3. Laboratory Monitoring:
   a. Prior to administration, IL-6, CRP, D-dimer, fibrinogen, and ferritin should be obtained and trended daily.
   b. If these tests are ordered over the weekend, the provider should contact the flow cytometry manager to ensure the IL-6 test is performed if therapy is immediately necessary.

4. Therapy-Related Considerations:
   a. Dosing: 4 mg/kg (max 400 mg) IV recommended OR 8 mg/kg (max 800 mg) IV based on clinical judgment. 2nd dose may be repeated 8-12 hours later based on clinical response. Not to exceed 2 doses.

5. Black box warning for severe infection; long half-life with potential for ongoing immunosuppression

6. Hepatotoxicity has been described. Consider avoiding therapy in patients with ALT or AST greater than 5x the upper limit of normal.

7. Expensive medication with limited supply on hand

b. SeaStar Filter with NxStage CRRT Machines
   i. The SeaStar filter is a high-cut off membrane filter used for continuous renal replacement therapy (CRRT). When compared to standard CRRT filters, the SeaStar filter removes larger molecules with a size of 0.5-0.6 kilo Daltons. This allows filtration of inflammatory cytokines such as IL-6, IL-8 and TNF-a.45
   ii. Currently, no studies evaluating the role of the SeaStar filter in patients with COVID-19 have been published, but theoretically removal of cytokines in this population may be beneficial. The Italian Society of Nephrology has also endorsed the use of cytokine filters in COVID-19 patients requiring RRT.46
   i. The SeaStar filter can be used with the NxStage CRRT machine to allow cytokine filtration using the OSUWMC SeaStar CRRT Protocol in patients with COVID-19 (Appendix C)

VII. Cardiac Complications of COVID-19
   a. See the COVID-19 and Cardiovascular Guide

VIII. Renal Manifestations
   a. Pathophysiology of Acute Kidney Injury
      i. The risk of acute kidney injury (AKI) in unclear based on current available literature. In an evaluation of 116 patients with COVID-19, no patients were reported with AKI.47 However, another larger study of 760 patients reported that 15.5% of hospitalized patients presented with an elevated serum creatinine, and AKI was observed in ~3% of patients during hospital admission.48
      ii. COVID-19 is felt to utilize the ACE2 receptor for entrance into cells. Due to the high expression of ACE2 in the kidneys, the virus may cause damage through direct infiltration of these cells. In addition, inflammatory mediators may lead to
direct and indirect damage to the renal cells due to hypoxia. Rhabdomyolysis has also been noted at an increased rate in patients presenting with COVID-19 infection. The elevation in creatine kinase has been linked to an increase AKI in this population.48

b. Continuous Renal Replacement Therapy
i. Patients physically in University Hospital or the Ross will receive CRRT using the NxStage machine and patients physically located in the CCCT or East will receive CRRT using Prismaflex. Additional information about the CRRT modalities can be found here: https://mediasite.osu.edu/Mediasite/Play/56c8758ab3c743edaf5d8f2e0d6091871d
ii. Antibiotic dosing recommendations in CRRT can be found at: CRRT dosing link
iii. Frequent clotting and/or clogging of the CRRT circuit has been anecdotally noted in patients with COVID-19. A modified scale systemic heparin drip or regional anticoagulant citrate dextrose may be considered.
iv. No replacement fluid or dialysate solution contains phosphorus, therefore patients will often require phosphate replacement.
v. SeaStar Cytokine Filter
   1. The SeaStar filter can be used with the NxStage CRRT machine to allow filtration of inflammatory cytokines such as IL-6, IL-8, and TNF-a using the OSUWMC protocol (Appendix C).

IX. Gastrointestinal Manifestations
a. Pathophysiology of Liver Impairment49
i. Pathophysiology of COVID-19 associated liver injury still under investigation, however, possible mechanisms may include direct virus-induced cytopathic effects; ACE2 receptor expression is enriched in cholangiocytes, therefore SARS-CoV-2 may directly bind to ACE2-positive cholangiocytes to dysregulate liver function
ii. Drug induced liver injury
iii. Immune-mediated inflammation and pneumonia-associated hypoxia
iv. The interaction between chronic and acute liver impairment associated with COVID-19 is not well described

b. Incidence
i. 2–11% of patients with COVID-19 had liver comorbidities and 14–53% cases reported abnormal LFTs50
ii. Confounded by potential drug induced liver injury, ischemia/shock induced liver injury, and chronic liver disease

c. Clinical Course
i. Liver injury associated with higher severity of illness and worse outcome3
ii. ALT>40 associated with increased admission to the ICU, need for mechanical ventilation, or death11

d. Management
i. Assessment and monitoring
   1. Baseline LFTs, INR, CK
2. If baseline normal, monitor every 3 days
3. If on hepatotoxic therapies (e.g. hydroxychloroquine, chloroquine, lopinavir/ritonavir, tocilizumab), monitor daily

ii. Therapy modifications/adjustments
1. Currently recommended therapies for the treatment of COVID-19, including lopinavir/ritonavir, ribavirin, and chloroquine/hydroxychloroquine, are all metabolized by the liver.
2. Consider reduced metabolism
3. Consult pharmacy for dosing adjustment recommendations
4. Monitor patients closely for adverse drug effects
5. Discontinue hepatotoxic medications, as able

e. Statin therapy
   i. Do not initiate if LFTs > 3x ULN
   ii. If continuing home statin therapy, obtain daily LFT monitoring; discontinue if > 5x ULN

f. Analgesedation
   i. Consider prolonged half-lives due to reduced metabolism in liver impairment
   ii. Use caution with agents extensively affected by liver impairment, such as midazolam, dexmedetomidine, hydromorphone, morphine; if needed, consider dose reduction.
      1. Propofol preferred for sedation; fentanyl preferred for analgesia; titrate to goal RASS and CPOT

g. Other considerations
   i. GI Involvement
      1. Although data are still evolving, approximately 10% of COVID-19 positive patients present with GI symptoms (nausea, vomiting, diarrhea, abdominal pain).5
      2. A recently study detected COVID-19 in over 50% of infected hospitalized patients51; data evolving regarding fecal-oral method of transmission; practice contact precautions per epidemiology recommendations
   ii. Stress Ulcer Prophylaxis
      1. Administer stress ulcer prophylaxis to critically ill patients with risk factors for GI bleeding per OSU guidelines
      2. Consider once daily regimens to reduce nursing exposure and PPE use, if appropriate

X. Nutrition Support52
   a. Nutrition support of critically ill patients including those with COVID-19 should be initiated early with 24-36 hours of admission if hemodynamically stable.
   b. Enteral nutrition (EN) is preferred:
      i. EN should be withheld in hemodynamically instability requiring high dose vasopressors, escalating dosages, multiple vasopressor agents or rising lactate concentrations.
**ii. Administration Considerations:**

1. **EN is preferred into the stomach.** If intolerance occurs then use of prokinetic agents (watch for drug interactions with macrolides) may be indicated. Proceed to post-pyloric if these strategies fail, however please note, placement of post-pyloric feeding tubes may take longer to place than gastric tubes, increasing exposure time of the healthcare practitioner.
   
   a. Early parenteral nutrition (PN) **should be considered** when concern for viral transmission to the healthcare provider precludes ability to safely obtain post-pyloric access.

2. **EN should be administered continuously** (avoid bolus feeds) targeting 15-20 kcal/kg/day and protein goal of 1.2-2 g/kg/day. Propofol can be a significant source of calories, with each mL containing 1.1 kcal. Contact dietitian for recommendations for patients receiving high rates of propofol.

**iii. Formulations:**

1. High Protein EN formulas (Vital AF, Vital High Protein, Pivot 1.5) **should be used** when applicable to minimize the need for protein modulars. This decreases steps and time to administer supplemental protein modulars, decreases room for error and decreases risk for exposure.

**iv. EN Intolerance**

1. EN intolerance is common in early and late stages of critical illness. Gastric residual volume **should not be utilized** to monitor feeding intolerance as it is not reliable for detection of delayed gastric emptying and risk of aspiration. This recommendation is also relevant to decrease the risk of SARS-CoV2 transmission to the healthcare provider. Patient should be monitored by daily physical exam, as well as confirmation of passage of stool and gas.

**c. Special populations**

i. **Prone Positioning:** Most patients can be fed in the stomach while in prone position. It is recommended to keep the head of bed elevated (reverse Trendelenburg) to at least 10-25 degrees to decrease risk of aspiration of gastric contents, facial edema, and intra-abdominal hypertension.

ii. **ECMO:** It is recommended to start early low dose (trophic) EN with close monitoring for intolerance and slow advancement.

**d. Refeeding Syndrome:**

i. **Risk of refeeding syndrome should be considered** if it is suspected that energy/calorie intake has been limited for greater than 7 days, in chronic alcohol use/abuse and/or with physical signs of malnourishment.

ii. In patients with risk of refeeding syndrome, advance feeds slowly (every 8-12 hours) with frequent monitoring of serum phosphate, magnesium and potassium levels.

**e. Metabolic Studies:**
i. Use of metabolic studies to measure resting energy expenditure for mechanically ventilated patients should be avoided in the subset of SARS-CoV2 patients due to potential aerosolization during the test. This is subject to change pending further information regarding safety to the healthcare provider.

f. All feeding pumps should be allocated to critical care patients. In the event of feeding pump shortages, tube feeds may be administered using gravity bags. Please contact the dietitian for recommendations regarding flow rates. The use of gravity bags should be designated to stable floor patients first before implementing this practice in the ICU.

XI. The Role of Palliative Care
   a. A fundamental goal of medicine is to relieve human suffering, and while saving lives is crucial it may not be the only way to achieve this goal.  
   b. In times of humanitarian emergencies and crises, such as the current COVID-19 pandemic, palliative care is crucial to care. Palliative care and symptom control should be integrated as much as possible to life-saving treatment.
   c. The most common severe type of suffering in humanitarian emergencies and crisis is pain and it should be treated aggressively in any patients. When the decision is made to switch from life-saving therapy to end-of-life care not only pain should be assessed and treated, but also dyspnea, delirium, constipation, and secretions.
      i. Anecdotally, patient with COVID-19 may experience dyspnea and agitation to greater proportion than others at end-of-life (EOL).
      ii. In order to achieve an adequate level of comfort these patients may require proportional sedation.
   d. See the OSUWMC Palliative Medicine EOL guidelines for additional information.
Appendix A

Additional Mechanical Ventilation Information
## Appendix B

### Prone Huddle Checklist

<table>
<thead>
<tr>
<th>Prior to turning patient prone, all team members should huddle and discuss the following:</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explain process to patient/ family</td>
<td></td>
</tr>
<tr>
<td>Prepare the patient for pronation per OSUWMC clinical standards</td>
<td></td>
</tr>
<tr>
<td>Will the patient remain prone for 16 hours</td>
<td>Time to return to supine:__________</td>
</tr>
<tr>
<td>Draw ABG when pt. has been in prone position for 30 minutes</td>
<td></td>
</tr>
<tr>
<td>Wean ventilator settings per protocol to titrate FiO2 ( \leq 0.6 ) PEEP ( \leq 10 ) to maintain SpO2 &gt; 88-%</td>
<td></td>
</tr>
<tr>
<td>Maintain sedation to target a RASS of -4 to -5</td>
<td></td>
</tr>
<tr>
<td>Will tube feedings be restarted?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior to turning patient supine, all team members should huddle and discuss the following:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Will the patient remain in the supine position for at least 6 hrs?</td>
<td>Time to return prone:__________</td>
</tr>
<tr>
<td>Draw ABG when pt. has been in supine position for 30 minutes</td>
<td></td>
</tr>
<tr>
<td>What criteria would prompt re-proning?</td>
<td></td>
</tr>
<tr>
<td>Can sedation be weaned after supination?</td>
<td></td>
</tr>
<tr>
<td>If paralyzed, will the patient stay paralyzed after supination?</td>
<td></td>
</tr>
<tr>
<td>Omit spontaneous awakening trial (SAT) or spontaneous breathing trial (SBT)?</td>
<td></td>
</tr>
<tr>
<td>Sandbag at bedside (for use during cardiac arrest)</td>
<td></td>
</tr>
</tbody>
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Approved by MICU Operations Council
March 12, 2019

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Revision Date 04.08.2020
Appendix C

OSUWMC SeaStar NxStage CRRT Filter Protocol

What is it?

The SeaStar filter is a high-cut off membrane filter used for CRRT. When compared to standard CRRT filters, the SeaStar filter removes larger molecules with a size of 0.5-0.6 kilo Daltons. This allows filtration of inflammatory cytokines such as IL-6, IL-8 and TNF-α.

Evidence for its use:

SeaStar's filter has been used in cytokine filtration for brain-dead organ donors. It has FDA approval “for use in patients with fluid overload, uremia and/or electrolyte disturbances associated with oligoanuria acute renal failure. It may also be used when removal of excess fluid is indicated, such as patients in pulmonary edema or congestive heart failure refractory to diuretic therapy.”

COVID-19 Specific Use:

With the COVID-19 pandemic, numerous reports have cited IL-6 and a cytokine cascade as a potential pathogenesis for COVID induced ARDS, myocarditis and multi-organ failure. In addition, an IL-6 blocker (tocilizumab) has been described as a therapeutic option for patients with ARDS secondary to COVID-19. Use of the SeaStar filter would attenuate this cascade and potentially assist with recovery. The Italian Society of Nephrology has also endorsed the use of cytokine filters in COVID patients requiring RRT.

OSUWMC Protocol:
Inclusion Criteria:
1. Confirmed COVID-19 infection
2. Intubation and either:
   a. Moderate to Severe ARDS: defined by Berlin criteria and a P:F ratio <200
   b. Mild ARDS + evidence of multi-organ failure: P:F <300 + shock, renal failure, etc.

Procedure for use:
1. Contact Anesthesia Critical Care service (Pager #9714, 614-293-ECMO)
2. Place Nephrology consult
3. Obtain baseline inflammatory markers (IL-6, ferritin, ESR, CRP, procalcitonin, troponin, BNP, albumin and D-dimer) prior to initiation and at a daily interval afterwards
4. Obtain vascular access with a hemodialysis catheter (RIJ preferred over LIJ)
5. Initiate SeaStar therapy:
a. Therapy is performed for at least 6 hours per day. Optimal therapy is 12 hours per day. (See below for the C2Rx CRRT prescription)
b. Consider ultrafiltration if necessary to augment volume removal 

6. Discontinue SeaStar therapy once P:F ratio is >250 or if inflammatory markers have normalized (CRP/IL-6)

OSU Clinical and Nursing Implications:
1. The SeaStar filter runs on our current NxStage CRRT machines. Patient must be located in the Doan or Ross in order to initiate therapy.
2. Patients requiring CRRT can receive therapy with SeaStar filters. They do not need to be transitioned to other filters.
3. Filter clotting is diminished using a predilution delivery, but given the hypercoagulable state of COVID-19, citrate anticoagulation or heparin infusion may need to be initiated.
4. With time, high-cutoff filters can leak albumin. Continue to monitor daily levels and consider supplementation if necessary.
5. Antibiotic dosing is adjusted as is customary for CRRT.

CLR 2.0 Hemofiltration Treatment (C2Rx) Prescription

1. C2Rx hemofiltration dose is indexed to patient admission body weight.
   a. Therapy Fluid Rate (TFR)1 will index to the patient’s hospital admission body weight at a dose of 35 ml/kg/hr.
      • Example: in a 75 kg patient, TFR = 75 kg x 35 ml/kg/hr = 2625 ml/hr
   b. Blood flow rate (BFR) will index to TFR to maintain Filtration Fraction (FF) ≤0.1.
      • FF = TFR (in ml/min) / BFR (in ml/min), or BFR = TFR /0.10
      • Example: 87 kg patient
        o TFR = 87 kg x 35 ml/kg/hr = 3,045 ml/hr
        o TFR ml/min = 3045 ml/hr / 60 min/hr = 51 ml/min
        o BFR = 51 ml/min / 0.1 = 510 ml/min

2. On the NxStage System One platform the Therapy Fluid Rate is set in the Therapy Fluid window (top window, green arrows) and the machine automatically matches filtrate output rate to Therapy Fluid input rate to provide a neutral balanced treatment by default.
3. If net fluid removal is desired, the desired hourly Ultrafiltration Rate is set in the middle window (yellow arrows).

For any questions or concerns, please contact Omar Al-Qudsi MD, Ravi Tripathi MD or Bryan Whitson MD
References


8. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the


