Critical Care Protocols for COVID-19 Patients

As of April 12, 2020
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Guiding Principle: To provide summary recommendations for the management of critically ill patients suspected of having COVID-19 that is translatable and scalable across all adult critical care units at Michigan Medicine.

Disclaimer: Traditional high-level evidence (i.e. RCTs) is not yet available and most recommendations are the result of expert consensus or informed by the reported experience of other institutions affected by the pandemic. Information is changing rapidly and therefore this document will remain dynamic and updated frequently as new data to inform best practice becomes available.

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I. **Pathophysiology**

**Respiratory**

The primary pathology for critically ill patients with COVID-19 is rapidly progressive acute respiratory failure. Patients may quickly progress to acute respiratory distress syndrome (ARDS). Diffuse alveolar damage is noted and pneumocytes with viral cytopathic effect are seen implying a direct, virus induced, injury as compared to a secondary, hyper-inflammatory response. (Xu et al 2/17)

**Inflammatory**

Some patients respond to COVID19 with a severe over expression of inflammatory mediators. This has been described as a “cytokine storm syndrome” (CSS) which is noted to occur in other inflammatory states such as sepsis, hemophagocytic lymphohistiocytosis (HLH), and CAR-T therapy. It is unknown which patients are at risk of developing cytokine storm, and ferritin, CRP and IL-6 are early biomarkers that may predict higher risk of CSS development. These patients have a much higher incidence of developing multi-organ dysfunction, rapid decline and death. Currently there is no specific treatment targeting COVID-19 induced cytokine storm, however Michigan Medicine is developing a biomarker risk stratification strategy and investigational treatment trials are underway.

**Cardiac**

COVID-19 may present with elevated troponin which represents a myocarditis reaction rather than type-I cardiac ischemia. Elevated troponin is strongly associated with mortality, however it’s unclear to the degree of this representing the degree of cardiac contribution vs. a marker of overall severity of illness, since elevated troponin levels have been associated with mortality in a variety of critical illness and injury. Up to 7% of patients die of fulminant myocarditis and 33% of patients may die with myocarditis contributing in some way. (Ruan 3/3/20). Arrhythmias have been reported and Wang et al. reported arrhythmias resulted in 12% of ICU transfers. (Wang 2/7)
II. Diagnosis and Monitoring

Laboratory diagnostics

The only confirmative diagnosis is to test directly for the Novel Corona Virus (severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2). This causes the disease known more commonly as COVID-19. Please review frequently updated testing guidelines for the most up to date process.

Biomarkers associated with inflammation are elevated. (Ruan 3/3/20). Ferritin and C-reactive protein have both been associated with COVID-19 and also track the severity of disease. Young and colleagues noted low CRP levels in patients not requiring oxygen (11 mg/L) compared to patients who became hypoxemic (66 mg/L) (Young 3/3). Ruan also found that survivors had a median CRP level of 40 mg/L compared to non-survivors who had a median CRP level of 125 mg/L (Ruan 3/3/20).

Routine ICU comprehensive lab studies evaluating multi-organ injury are suggested upon presentation and repeated daily with the addition of CRP, LDH, ferritin, d-dimer and procalcitonin. A biomarker risk stratification strategy is currently being developed and will be included in this document once available.

Reported abnormalities include:

- Lymphopenia in about 80% of patients (Guan 2/28, Yang 2/21)
- Mild thrombocytopenia however usually > 100,000. More profound thrombocytopenia is associated with increased mortality (Ruan 3/3).
- Elevated D-dimer. Most coagulation studies are normal, however microthrombosis and associated ischemic events are very common (including stroke). D-dimer levels should be monitored frequently (Gattinoni - unpublished). Disseminated intravascular coagulation may progress over time and is associated with a poor prognosis (Tang et al 2020).
- Elevated transaminases are common. Liver biopsy specimens of the patient with COVID-19 shows moderate microvesicular steatosis and mild lobular and portal activity, reflected in transaminitis. Clinical meaning unknown at this time, intrinsic measures of hepatic function such as coagulation studies have been relatively normal.
- Procalcitonin does not appear to be elevated in isolated COVID-19 infection. Procalcitonin levels were shown to be < 0.5 in 95% of patients (Guan 2/28). If elevated, there is likely another bacterial source or co-infection. Suggest referring to https://www.med.umich.edu/asp/pdf/adult_guidelines/COVID-19-treatment.pdf for incorporation of procalcitonin levels into antibiotic stewardship after the initial presentation.

Radiology

General description of lung findings in both chest x-ray and CT scans is patchy ground glass opacities located usually peripheral and basal. Over time these may coalesce into a
consolidation. (Shi 2/24). Pleural effusions are uncommon and have been reported in 5% of cases. Other uncommon findings are cavitation, lymphadenopathy, or masses.

CT is more sensitive than chest x-ray in identifying early less severe or asymptomatic COVID-19 patients with peripheral lung involvement. One series reported a sensitivity of 86% of CT vs 59% chest x-ray early in mildly or asymptomatic COVID-19 patients. (Guan)

Ultrasound findings are relatively non-specific but include

- Thickening of pleural line, a spectrum of findings ranging from patches of B lines to peripheral consolidations.
- Sensitivity and specificity are not well defined
- Daily Lung Recovery – unclear that we should be using this to monitor progression of daily lung changes/recovery compared to chest x-ray.

The Italian Group for the Evaluation of Interventions in Critical Care (GiViTI) suggests that lung ultrasound may be useful in the early identification of patients likely to respond to high PEEP vs prone ventilation. A pattern of widespread B-lines may identify recruitable patients likely to respond to high PEEP, while a predominantly A-pattern anteriorly with posterior consolidations may identify patients likely to respond to prone ventilation. However, this approach has NOT been systematically evaluated nor validated.

Current recommendations are to use a portable chest x-ray initially to establish a baseline and rule out other causes of dyspnea such as pneumothorax or effusion. Chest CT should be utilized if there are other general concerns for current presentation. However, chest CT should not be routinely used where COVID-19 is the only diagnosis being considered due to the time to clean and risk of personnel exposure without much added benefit in management.

### III. Treatment and Management

There are no specific treatment strategies targeted for COVID-19 patients. However, there are some aspects of standard critical care principles that are more useful in critically ill COVID+ patients. Treatment strategies are based upon World Health Organization and the Society of Critical Care Medicine (SCCM) recommendations based upon a modified Surviving Sepsis Campaign Guideline (see Appendix 1). These have not yet been accepted by the Critical Care Medicine journal. They follow a “best evidence” approach with PICO guided questions and detailed literature review by an international, multidisciplinary panel of critical care experts. This guideline will be updated as more information becomes available.

**Hemodynamic Support**

Reported hemodynamic collapse and shock varies in reports from 1% to 35% in COVID-19 patients. This depends greatly on the patient population, comorbidities, age, severity of
illness and the definition of “shock” being used. Up to 40% of patients had “shock” as a major reason of death and this may be related to the reported fulminant myocarditis (Ruan).

In regard to fluid resuscitation, it is recommended dynamic parameters be used to assess fluid responsiveness (i.e. passive leg lift, lactate, capillary refill, skin temperature) to guide volume resuscitation as opposed to static parameters. During the acute resuscitation phase, it is suggested a conservative vs liberal fluid strategy may be beneficial, where balanced crystalloids (Ringer's Lactate) is the resuscitation fluid of choice.

If goal mean arterial pressure (MAP) cannot be achieved with a limited fluid strategy, vasoactive agents should be added. The vasopressor of choice as a first line agent is norepinephrine to achieve MAP 60-65 mmHg. If there is evidence of cardiac dysfunction, then dobutamine or milrinone may be added. As fulminant myocarditis is generally regarded as a bi-ventricular disease, critical care management principles of cardiogenic shock apply. Consequently, there is little evidence to suggest single ventricle mechanical support like IABP or Impella would be of benefit, however, there may be a role for ECMO in selected patients.

**Ventilatory Support**

The prevalence of hypoxic respiratory failure with COVID-19 is up to 20%. It appears that up to 14% will develop severe enough pulmonary disease to require invasive mechanical ventilation. (Wu Z 2020). There is limited data describing risk factors of developing acute respiratory failure requiring mechanical ventilation and mortality was over 50% in those patients. A reasonable SpO2 target range is between 92% and 96%. Supplemental oxygen should be started once SpO2 is 90%. If persistent hypoxia despite supplemental oxygen, consider a trial of HFNC (heated high flow nasal cannula). HFNC is preferred over NIPPV (non-invasive positive pressure ventilation), however if HFNC is not available and no need for intubation, a brief trial of NIPPV can be attempted as long as patient is rapidly assessed for signs of worsening respiratory failure. In areas where ventilator supply is limited, the use of HFNC may be a safe and effective strategy and does not seem to increase risk of disease transmission. In SARS, healthcare workers exposed to HFNC were not at increased risk of developing the disease. (Raboud J, 2010 PLoS One 5:e10717). However, as airway intervention requires significantly more time in this population due to need for complete PPE and airborne precautions, any worsening of respiratory failure despite use of HFNC or NIPPV, early consideration of need for mechanical ventilation is encouraged.

There are currently no studies addressing the optimal strategy for managing COVID-19 patients requiring mechanical ventilation. Several experts concur that mechanically ventilated patients with COVID-19 should be managed similarly to other patients with acute respiratory failure in the ICU and follow ARDS management when applicable. The main ventilator strategy is to minimize ventilator induced lung injury by using low tidal volume (Vt) ventilation with Vt of 4-8 mL/kg of predicted body weight and keeping plateau pressure below 30 mmH2O. Also, by utilizing a higher positive end expiratory pressure (PEEP)
strategy, mortality was improved in ARDS patients. (Briel M, 2010, JAMA). Recruitment maneuvers should be attempted when applicable. Neuromuscular blockade (NMBA) should be used if moderate to severe ARDS and worsening hypoxemia despite optimizing ventilation strategy and in cases of ventilator dyssynchrony (see Pharmacological agents section). Proning should be considered in moderate to severe ARDS when the above interventions have been attempted without significant improvement. Proning takes a significant amount of training and resource coordination and should only be attempted by personnel competent in its use. If severe ARDS with worsening hypoxia persists, a trial of inhaled pulmonary vasodilator can be attempted but should be rapidly tapered if patient does not respond.

**Pharmacological agents**


Per Pharmacy’s recently developed antiviral treatment recommendations (Michigan Medicine Guidance for Diagnosis and Treatment of COVID-19 in Adults and Children) there is no current evidence from randomized controlled trials to recommend any specific anti-COVID-19 treatment for patients with suspected or confirmed COVID-19 infection. In consultation with Infectious Disease, treatment should be considered in symptomatic patients requiring hospitalization or those with conditions associated with severe disease*. Per the guidelines referenced above, the several agents are considered investigational/for compassionate use, and decision to use these should be made only with close attention to the patient’s clinical status, comorbidities, and interacting medications. These may be considered at Michigan Medicine in consultation with Infectious Disease.

*Risk Factors Associated with Severe COVID-19:*

1. Age > 65 Years
2. Chronic cardiovascular, pulmonary, hepatic, renal, hematologic, or neurologic conditions
3. Immunocompromised
4. Pregnancy
5. Residents of nursing homes or long-term care facilities

**Other Therapeutics**

1. **Antibiotics** – patients presenting with sepsis symptoms should follow surviving sepsis guidelines, including early broad-spectrum antibiotics including atypical pneumonia coverage, until a more specific, targeted diagnosis can be made. See procalcitonin section in Diagnosis and Testing on how it may be utilized to guide antibiotic utilization.
2. **Steroids** – There currently is no evidence supporting routine use of corticosteroids even with hypoxic respiratory failure and on mechanical ventilation. However, if on mechanical ventilation and developing signs/symptoms of ARDS, a trial of corticosteroids is recommended. Additionally, steroids should be continued if necessary, for other chronic disease states (asthma, COPD), or for vasopressor refractory shock (recommend hydrocortisone 200mg daily either as infusion or in divided bolus doses).

3. **Paralytics** – The routine use of paralytics are not recommended and should be reserved for consideration in patients moderate to severe ARDS or with ventilator dyssynchrony and or high plateau pressures > 30 cm H20. In these cases, we suggest using as needed intermittent boluses of neuromuscular blocking agents (NMBA) over continuous NMBA infusion, to facilitate lung protective ventilation strategies.

   In the event of persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation, or persistently high plateau pressures we suggest using a continuous NMBA infusion for up to 48 hours.

   In initial airway management higher doses of paralytics are recommended to optimize intubating conditions and decrease change of coughing/gagging (Rocuronium 1.2-1.6 mg/kg; Succinylcholine 1.5-2.0 mg/kg). See Appendix 2 for comprehensive airway management guidance.

**IV. Suggested system-based management approach:**

*See recent SCCM Surviving Sepsis – COVID-19 (Appendix 1) for additional recommendations*

The overall management of COVID-19 is the management of a severe viral pneumonia leading to respiratory failure, ARDS, and multiorgan dysfunction (Murthy et al, WHO Guideline).

1. **Neurologic:** no specific neurologic targets. Sedation should target a Richmond Agitation-Sedation Scale of 0 to -1, while keeping patients safe and able to tolerate lung protective ventilation and proning.
   a. **Recommend** that myocardial depressants such as propofol be used with caution; based on recent data (Wang et al.), acute cardiac injury and dysrhythmias have been noted. May also see paradoxical myocardial depression with ketamine in patients who are in a catecholamine depleted state.
   b. **Recommend** analgosedation with the use of short acting potent opiate agents such as Fentanyl in the event of arrhythmias and/or hemodynamic instability. Recommend the use of benzodiazepines should patients fail opiate adjuncts.
2. **CV**: acute cardiac injury has been noted in 7.2% with a 16.7% arrhythmia rate (Wang et al).
   a. **Recommend screening for myocardial injury** with ECG, troponin testing. Recommend obtaining transthoracic echocardiography to evaluate LV function, especially in patients with persistent hemodynamic instability, arrhythmias, or with cardiac risk factors.
   b. **MAP Target**: 60-65 mmHg
   c. **Fluid Management**: recommend comprehensive evaluation of patient’s volume status based on physical exam, critical care ultrasound, ventricular function and presence of pulmonary edema. **Recommend** conservative fluid management in patients without evidence of shock, in order to prevent exacerbation of ARDS.
   d. **Vasopressors**: usual management per septic shock guidelines. **Recommend** Norepinephrine as first line pressor, vasopressin as second line pressor.
   e. **Inotropes**: recommend that inotropes be used with caution, as patients that manifest cardiac injury may be prone to arrhythmias. The use of inotropes should be considered after evaluation of LV function with bedside echocardiography, and after weighing the patient’s perfusion status vs risk for arrhythmia. Dobutamine should be first line inotrope but if significant arrhythmias may consider use of milrinone.

3. **Respiratory**: Critically ill patients with COVID-19 are at risk of progressing to ARDS. Typical ARDS management for viral pneumonias (Lung protective ventilation, avoiding excess volume resuscitation) are key.
   a. **Recommend** supplemental oxygen on initial presentation if hypoxic to a goal SpO2 of 92-96%. Escalate to heated high flow nasal cannulae (with flow rates of up to 50 LPM) if worsening hypoxia despite 6L/min. Rapid progression of hypoxemic respiratory failure may become apparent in these patients. Patients have been reported to quickly fail supplemental oxygen therapy; in cases like these, the patients will likely continue their progression of respiratory failure and early endotracheal intubation should be considered.
   b. **Non-Invasive Ventilation** – is not suggested in COVID-19 patients, due to its risk of aerosolizing secretions under high pressure as well as its lack of proven efficacy as a primary treatment strategy in ARDS. However, if HFNC is not available and patient does not require intubation, a brief trial can be attempted but should be closely followed by serial re-evaluation. If evidence of progressive respiratory failure despite NIPPV, progress to endotracheal intubation should be considered.
   c. **Recommend** - MDI with spacer as an alternative to nebulized bronchodilator therapy. Small volume nebulizers can be filtered for use, and Tavis masks (filtered face masks) are being made available on a limited basis.
   d. **Recommend against** “breaking” the ventilator circuit at all costs. Any predicted circuit disconnections should occur with the vent on stand-by and the tube clamped prior to disconnection.
   e. **Endotracheal Intubation**: recommend that an experienced provider with the greatest likelihood of first pass success intubate using airborne precautions. A negative pressure room designated for Aerosol Generating Procedures (AGP)
should be used whenever possible. Refer to ED or Anesthesia Airway Management Guidelines for more information (Appendix 3).

f. **Ventilator Management** – **recommend** lung protective Strategy (4-8 cc/kg ideal body weight, Plateau pressures < 30 cm H2O) of ARDS management as cornerstone of treatment (WHO Guideline).
   i. **Consider** maintaining driving pressure ≤ 12-15 cm H2O
   ii. **Hypercapnea** – permitted if meeting pH goal of 7.30-7.45
   iii. **PEEP** – **recommend** that the ARDSNet PEEP table be used as a guide for PEEP titration. There is limited evidence to suggest that the low PEEP v higher PEEP arm is more beneficial. Anecdotal reports from Singapore and other centers suggest COVID-19 patients benefit from higher PEEP. This suggests that COVID-19’s parenchymal problem may be atelectasis and alveolar edema, and as a result, these patients may require higher PEEPs and higher mean airway pressures for optimal lung recruitment. No RCT evidence is available.
   iv. **Neuromuscular Blockers** – **suggested** in patients with severe ARDS and strong respiratory drive that are at risk for volutrama/barotrauma or with ventilator dyssynchrony. Should be started as intermittent dosing and escalated to infusion if needed.

g. **Proning** – **recommended** in patients with severe ARDS (PaO2:FiO2 ≤100-150). Prone ventilation for >12 hours is recommended (WHO Guidelines). Proning must be balanced with the use of human resources and expertise to be performed correctly.

h. **Fluid Management** – **recommend** conservative fluid management in patients with ARDS without evidence of tissue hypoperfusion, in order to prevent exacerbation of ARDS. This has been shown to shorten the duration of mechanical ventilation.

i. **Bronchoscopy** – **is not recommended** and is relatively contraindicated in patients with suspected and confirmed COVID-19 infections (Wahidi et al. American Association for Bronchology and Interventional Pulmonology Statement). Consider bronchoscopy in patients with post-viral pneumonia, mucus plugging, or unclear diagnosis.

j. **ECMO** – **rarely recommended**, due to the need for significant provider and institutional resources, exposure risk, and limited outcome data showing the success of ECMO in this population. Early reports suggest very high mortality of patients that are placed on ECMO. Discuss with ECMO on call and OCA. See Appendix 3 for further guidance.

4. **Renal**: there is no evidence that COVID-19 predisposes patients to higher rates of renal failure requiring CRRT compared to other viruses.
   a. **Recommend** routine management per KDIGO guidelines.

5. **GI**:
   a. **Recommend** routine enteral nutrition within 7d.
6. Hematological:
   a. **Labs** – recommend obtaining CBC with Diff, CRP, LDH, Ferritin, CPK, PT/PTT/INR.

7. ID:
   a. **Labs** – **Recommend** Blood cultures, respiratory viral panel, CRP, urine strep antigen, legionella antigen, gram stain and culture, procalcitonin.
   b. **Co-Infection** – **recommended** that an RPAN be obtained on these patients, as there are some early unpublished data that suggest COVID-19 patients may be co-infected with other viruses. Bacterial co-infection is possible and procalcitonin elevation may be used as an adjunct to other testing for confirmation.
   c. **Treatment** – **recommend** broad spectrum antibiotics for empiric community acquired and atypical pneumonia coverage (e.g. Unasyn/Azithromycin or Ceftriaxone/Azithromycin, Doxycycline if QTc > 500). Broaden antibiotics to include MRSA or anti-pseudomonal coverage in states of septic shock, or with risk factors for multi-drug resistant organisms.
   d. **Steroids** – suggested only in cases of moderate to severe ARDS, vasopressor-refractory shock (hydrocortisone 200mg IV daily either as intermittent bolus dosing or infusion), adrenal insufficiency, or other chronic condition requiring their use (i.e. COPD exacerbation or asthma exacerbation).
   e. **Anti-viral Agents** - **there is no current evidence** from randomized controlled trials to recommend any specific anti-COVID-19 treatment for patients with suspected or confirmed COVID-19 infection. All anti-virals should be considered in consultation with Infectious Disease. The latest guidance can be found at: [https://www.med.umich.edu/asp/pdf/adult_guidelines/COVID-19-treatment.pdf](https://www.med.umich.edu/asp/pdf/adult_guidelines/COVID-19-treatment.pdf)

8. Endocrinology: No specific issues reported. Patients with diabetes mellitus are at higher risk for infection.
   a. **Recommend euglycemia** (Glu 120-180) with the use of insulin sliding scales or insulin drips as needed.
   b. **Do not recommend** the routine use of corticosteroids.

9. Prophylaxis:

10. Special Considerations:
    a. **CPR**: **Recommend** placement of supraglottic airway with viral filter and ETCO2 in line. Use supraglottic airway device if able to ventilate. If not, chest compressions should be paused during intubation to limit aerosolization of the virus.
       i. **Recommend** the use of the LUCAS mechanical CPR device (where available) for compressions in order minimize the use of PPE during codes.
    b. **Resuscitation Logistics** – for the sake of PPE conservation and for first-pass success, **recommend** a single provider intubate, and place an orogastric tube,
central line, +/- arterial line after intubation when necessary. Use of a video assisted laryngoscope (Glidescope or C-Mac) is recommended to help provide more distance between the patient and intubator. A viral filter should be used on BVM and iGel and a passive pre-oxygenation approach utilized when possible (avoid bagging). See Appendix 2

c. ECMO – current experience is very limited. Call OCA and EMCO attending on call for approval. See Appendix 3

V. References


Wahidi et al. American Association for Bronchology and Interventional Pulmonology (AABIP) Statement on the Use of Bronchoscopy and Respiratory Specimen Collection in Patients with Suspected or Confirmed COVID-19 Infection (unpublished, provided by Pepe de Cardenas)


APPENDIX 1: SURVIVING SEPSIS CAMPAIGN TOP 50 RECOMMENDATIONS


I. Infection Control

Recommendation:

1. For healthcare workers performing aerosol-generating procedures* on patients with COVID-19 in the ICU, we recommend using fitted respirator masks (N95 respirators, FFP2, or equivalent), as opposed to surgical/medical masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles) (best practice statement).

2. We recommend performing aerosol-generating procedures on ICU patients with COVID-19 in a negative pressure room (best practice statement).

3. For healthcare workers providing usual care for non-ventilated COVID-19 patients, we suggest using surgical/medical masks, as opposed to respirator masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles) (weak recommendation, low quality evidence).

4. For healthcare workers who are performing non-aerosol-generating procedures on mechanically ventilated (closed circuit) patients with COVID-19, we suggest using surgical/medical masks, as opposed to respirator masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles) (weak recommendation, low quality evidence).

5. For healthcare workers performing endotracheal intubation on patients with COVID-19, we suggest using video-guided laryngoscopy, over direct laryngoscopy, if available (weak recommendation, low quality evidence).

6. For COVID-19 patients requiring endotracheal intubation, we recommend that endotracheal intubation be performed by the healthcare worker who is most experienced with airway management in order to minimize the number of attempts and risk of transmission (best practice statement).

II. Laboratory Diagnosis and Specimens

Recommendations:

7. For intubated and mechanically ventilated adults with suspicion of COVID-19:

7.1. For diagnostic testing, we suggest obtaining lower respiratory tract samples in preference to upper respiratory tract (nasopharyngeal or oropharyngeal) samples (weak recommendation, low quality evidence).
7.2. With regard to lower respiratory samples, we suggest obtaining endotracheal aspirates in preference to bronchial wash or bronchoalveolar lavage samples (weak recommendation, low quality evidence).

III. Supportive Care

a. Hemodynamic Support

Fluid therapy

Recommendation:

8. In adults with COVID 19 and shock we suggest using dynamic parameters skin temperature, capillary refilling time, and/or serum lactate measurement over static parameters in order to assess fluid responsiveness (weak recommendation, low quality evidence)

9. For the acute resuscitation of adults with COVID 19 and shock we suggest using a conservative over a liberal fluid strategy (weak recommendation, very low-quality evidence)

10. For the acute resuscitation of adults with COVID 19 and shock we recommend using crystalloids over colloids (strong recommendation, moderate quality evidence)

11. For the acute resuscitation of adults with COVID 19 and shock we suggest using buffered/balanced crystalloids over unbalanced crystalloids (weak recommendation, moderate quality evidence)

12. For the acute resuscitation of adults with COVID 19 and shock we recommend against using hydroxyethyl starches (strong recommendation, moderate quality evidence)

13. For the acute resuscitation of adults with COVID 19 and shock we suggest against using gelatins (weak recommendation, low quality evidence)

14. For the acute resuscitation of adults with COVID 19 and shock we suggest against using dextrans (weak recommendation, low quality evidence)

15. For the acute resuscitation of adults with COVID 19 and shock we suggest against the routine use of albumin for initial resuscitation (weak recommendation, moderate quality evidence)

Vasoactive agents

Recommendation:

16. For adults with COVID 19 and shock we suggest using norepinephrine as the first line vasoactive agent, over other agents (weak recommendation, low quality evidence)
17. If norepinephrine is not available, we suggest using either vasopressin or epinephrine as the first line vasoactive agent, over other vasoactive agents for adults with COVID 19 and shock (weak recommendation, low quality evidence).

18. For adults with COVID 19 and shock we recommend against using dopamine if norepinephrine is available (strong recommendation, high quality evidence).

19. For adults with COVID 19 and shock we suggest adding vasopressin as a second line agent, over titrating norepinephrine dose, if target mean arterial pressure MAP cannot be achieved by norepinephrine alone (weak recommendation, moderate quality evidence).

20. For adults with COVID 19 and shock we suggest titrating vasoactive agents to target a MAP of 60-65 mmHg, rather than higher MAP targets (weak recommendation, low quality evidence).

21. For adults with COVID 19 and shock with evidence of cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and norepinephrine we suggest adding dobutamine, over increasing norepinephrine dose (weak recommendation, very low-quality evidence).

22. For adults with COVID 19 and refractory shock we suggest using low dose corticosteroid therapy (“shock reversal”), over no corticosteroid therapy (weak recommendation, low quality evidence).

Remark:
A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200 mg per day administered either as an infusion or intermittent doses.

b. Ventilatory Support

Recommendations

23. In adults with COVID 19, we suggest starting supplemental oxygen if the peripheral oxygen saturation (SPO2) is 92% (weak recommendation, low quality evidence) and recommend starting supplemental oxygen if SPO2 is 90% (strong recommendation, moderate quality evidence).

24. In adults with COVID 19 and acute hypoxemic respiratory failure on oxygen we recommend that SPO2 be maintained no higher than 96% (strong recommendation, moderate quality evidence).

25. For adults with COVID 19 and acute hypoxemic respiratory failure despite conventional oxygen therapy we suggest using HFNC over conventional oxygen therapy (weak recommendation, low quality evidence).

26. In adults with COVID 19 and acute hypoxemic respiratory failure we suggest using HFNC over NIPPV (weak recommendation, low quality evidence).
27. In adults with COVID-19 and acute hypoxemic respiratory failure if HFNC is not available and there is no urgent indication for endotracheal intubation we suggest a trial of NIPPV with close monitoring and short interval assessment for worsening of respiratory failure (weak recommendation, very low-quality evidence).

28. We were not able to make a recommendation regarding the use of helmet NIPPV compared with mask NIPPV. It is an option, but we are not certain about its safety or efficacy in COVID-19.

29. In adults with COVID-19 receiving NIPPV or HFNC, we recommend close monitoring for worsening of respiratory status and early intubation in a controlled setting if worsening occurs (best practice statement).

30. In mechanically ventilated adults with COVID-19 and ARDS, we recommend using low tidal volume (Vt) ventilation (Vt 4-8 mL/kg of predicted body weight), over higher tidal volumes (Vt>8 mL/kg) (strong recommendation, moderate quality evidence).

31. For mechanically ventilated adults with COVID-19 and ARDS, we recommend targeting plateau pressures (Pplat) of < 30 cm H2O (strong recommendation, moderate quality evidence).

32. For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, we suggest using a higher PEEP strategy, over a lower PEEP strategy (weak recommendation, low quality evidence).

   Remark:

   If using a higher PEEP strategy (i.e., PEEP> 10 cm H2O), clinicians should monitor patients for barotrauma.

33. For mechanically ventilated adults with COVID-19 and ARDS, we suggest using a conservative fluid strategy over a liberal fluid strategy (weak recommendation, low quality evidence).

34. For mechanically ventilated adults with COVID-19 and moderate to severe ARDS we suggest prone ventilation for 12 to 16 hours over no prone ventilation (weak recommendation, low quality evidence).

35. For mechanically ventilated adults with COVID-19 and moderate to severe ARDS:

   35.1. We suggest using as needed intermittent boluses of neuromuscular blocking agents (NMBA) over continuous NMBA infusion, to facilitate protective lung ventilation (weak recommendation, low quality evidence).
35.2. In the event of persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation, or persistently high plateau pressures we suggest using a continuous NMBA infusion for up to 48 hours (weak recommendation, low quality evidence).

36. In mechanically ventilated adults with COVID 19 ARDS, we recommend against the routine use of inhaled nitric oxide (strong recommendation, low quality evidence).

37. In mechanically ventilated adults with COVID 19 severe ARDS and hypoxemia despite optimizing ventilation and other rescue strategies we suggest a trial of inhaled pulmonary vasodilator as a rescue therapy if no rapid improvement in oxygenation is observed, the treatment should be tapered off (weak recommendation, very low-quality evidence).

38. For mechanically ventilated adults with COVID 19 and hypoxemia despite optimizing ventilation, we suggest using recruitment maneuvers, over not using recruitment maneuvers (weak recommendation, low quality evidence).

39. If recruitment maneuvers are used, we recommend against using staircase incremental PEEP recruitment maneuvers (strong recommendation, moderate quality evidence).

40. In mechanically ventilated adults with COVID 19 and refractory hypoxemia despite optimizing ventilation, use of rescue therapies and proning, we suggest using venovenous VV ECMO if available or referring the patient to an ECMO center (weak recommendation, low quality evidence).

IV. COVID-19 Therapy

Recommendations

41. In mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS), we suggest against the routine use of systemic corticosteroids (weak recommendation, low quality evidence).

42. In mechanically ventilated adults with COVID-19 and ARDS, we suggest using systemic corticosteroids, over not using corticosteroids (weak recommendation, low quality evidence).

43. In mechanically ventilated patients with COVID-19 and respiratory failure, we suggest using empiric antimicrobials/antibacterial agents, over no antimicrobials (Weak recommendation, low quality evidence).

Remark:
If the treating team initiates empiric antimicrobials, they should assess for de-
escalation daily, and re-evaluate the duration of therapy and spectrum of coverage
based on the microbiology results and the patient’s clinical status.

44. For critically ill adults with COVID-19 who develop fever, we suggest using
acetaminophen/paracetamol for temperature control, over no treatment (Weak
recommendation, low quality evidence).

45. In critically ill adults with COVID-19, we suggest against the routine use of
standard intravenous immunoglobulins (IVIG) (Weak recommendation, very low-
quality evidence).

46. In critically ill adults with COVID-19, we suggest against the routine use of
convalescent plasma (Weak recommendation, very low-quality evidence).

47. In critically ill adults with COVID-19:
   47.1. we suggest against the routine use of lopinavir/ritonavir (weak
recommendation, low quality evidence).
   47.2. There is insufficient evidence to issue a recommendation on the use of other
antiviral agents in critically ill adults with COVID-19.

48. There is insufficient evidence to issue a recommendation on the use of
recombinant rIFNs, alone or in combination with antivirals, in critically ill adults with
COVID-19.

49. There is insufficient evidence to issue a recommendation on the use of
chloroquine or hydroxychloroquine in critically ill adults with COVID-19.

50. There is insufficient evidence to issue a recommendation on the use of
tocilizumab in critically ill adults with COVID-19.
APPENDIX 2 – COVID-19 AIRWAY MANAGEMENT ALGORITHM

Michigan Medicine Emergency Service

COVID-19 AIRWAY MANAGEMENT ALGORITHM

1. PREPARATION

LOCATION AND TIMING
- Negative Pressure Room if possible
- Consider early intubation given time needed for preparation
- If potential difficult airway/sedation/Anesthesia know early given time for response and PPE prep time. Add scapel and 6.0 ETT to COVID table

ASSEMBLE TEAM
- **In-Room**
  - 2 Experienced airway operators
  - 2 Resus/EC3 nurses,
  - 1 RT
- **Out-of-Room**
  - 1 Runner/PPE Monitor
  - (in full PPE)
  - EC3 Team Lead to read off this algorithm

Minimize number of healthcare providers needed to complete procedure safely while maximizing protection

2. PRE-CHECK & PRE-BRIEF

EQUIPMENT CHECK
- COVID glidescope is charged and working
- COVID table is adequately stocked and located directly outside of room
- Two-way communication device is active

PRE-OXYGENATION PLAN
- Determine the optimal pre-oxygenation strategy.
  - Options include:
    - 6L NC O2 with surgical mask on patient
    - OR
      - Bv/M = PEEP valve with 2-hand tight mask seal, viral filter, and 6L/min O2 connected to EtCO2 adaptor and 15L/min inlet O2
        - Use PEEP as needed. DO NOT BAG
      - OR
        - HFNC up to 50L/min using the Drager with surgical mask on patient

3. INTUBATION PLAN

Plan A: RSI with VL
- Provider with best chance for first pass success should intubate

Plan B: Rescue Oxygenation
- iGel with viral filter between iGel and BVM. Bag with minimum flow rate and pressure needed for re-oxygenation.
- If fails, use BVM w/o iGel but must use two-person technique, adequate mask seal, in-line viral filter, and OPA/NPA as needed

Plan C: Front of Neck Access
- Scabel, bougie, 6.0 ETT

4. MEDICATION PLAN

In-Room: RSI With Ketamine (0.5 – 1.0 mg/kg) or Etomidate (0.3 mg/kg) and high dose Rocuronium (1.2-1.6 mg/kg) or Sux (1.5-2.0 mg/kg) to suppress gag/cough and optimize intubating conditions

In-Room: Sedation - Pre-prime Propofol, Fentanyl, and Midazolam gtt. Bring pump into the room

Out of Room: Hemodynamic optimization - Phenylephrine syringe, Norepi gtt, Bicarbonate
3. PROCEDURE

**ORGANIZE**
- Personnel, COVID table, drugs, giscope into the room
- Door closed
- Set up viral filter and ETCO2 in line on BVM and ventilator circuit (see photos)
- Set up closed suctioning system (Yankauer) with tight seal on canister
- BP cuff set for 5 min and opposite arm from pulse ox

**OPTIMIZE**
- Correct hypotension, hypoxemia, and acidosis
- Pre-oxygenate using the pre-determined strategy
- Use Wedge as needed to optimize airway anatomy with ear-to-sternal notch position
- If patient is agitated, consider small dose of ketamine (10-30mg) IV

**PERFORM TIMEOUT**
- Administer RSI meds then wait 1 min. Do not bag during apneic period unless life threatening hypoxemia
- Turn off HFNC if applicable then take of surgical mask. Intubate!
- Inflate cuff FIRST, clamp ETT as stylet removed, attach BVM, then unclamp and bag

4. POST CHECKS

**TUBE SAFE?**
- Confirm ETCO2 waveform and secure ETT
  - Transfer to vent:
    - Clamp ETT -> remove BVM -> connect ETT to vent -> unclamp ETT
  - Ensure ETCO2 monitor is in-line.
  - Planned disconnections:
    - Always put ventilator in Standby Mode and clamp ETT prior to disconnecting

**BRAIN / HEART SAFE?**
- Start analgesedation
- Send ABG/VBG, correct acidosis
- HOB 30 degrees

**LUNGS SAFE?**
- TV < 6-8 mL/kg IBW
- Pplat<30
- Adequate exp time/autoPEEP
- Insert O2 tube

**STAFF SAFE?**

**In Room**
- Place glidescope blade and any soiled equip in red bag. Seal and leave in room
- Remove outer gloves -> hand hygiene -> new outer gloves, Wipe glidescope, COVID table, and unused equipment with Oxivir. Put unused equipment into the "dirty" bin.
- Push glidescope, COVID table w/ "dirty" bin out of room w/ foot or wipe-in-hand
- Doff gown and outer gloves -> hand hygiene (to gloves) -> exit room

**Out-of-Room:**
- Remove inner gloves -> hand hygiene -> new gloves -> remove cap -> hand hygiene -> remove goggle -> hand hygiene -> remove N95 -> hand hygiene -> wash face w/ soap/water
- Glidescope and COVID table wiped down again by PPE monitor

5. DEBRIEF

Updated: 3/24/2020
Airway Table (In Room - Stocked)
Airway Response Guidelines for Outside of OR airways

Please review the material and use appropriate isolation precautions. Plan ahead as it takes time to apply all the barrier precautions.

**BEFORE**

1. Prior to intubation: Don the appropriate respiratory protection, gloves x 2, eye protection, and gown x 2. Pay close attention to avoid self-contamination (buddy system). Before and after all procedures, practice appropriate hand hygiene.

2. Get GlideScope GO & Airway Bag from staging area. (Also take Code GlideScope and Code bag to stay outside pt room.)

**DURING**

3. Clothing: Wear 2 gowns, 2 pairs of gloves, a fit-tested N-95 respirator or a PAPR (for those not fit-tested for or unable to use an N-95 mask) + eye protection. (PAPR: powered air-purifying respirator)

4. Staffing: Anesthesia Faculty and CA-3 (UH) or CRNA/Fellow (C&W)

5. Monitoring: Perform pre-procedure time out. Check standards, access, instruments, drugs, ventilator and suction


7. Plan for rapid sequence induction (RSI): RSI may need to be modified, if patient is unable to tolerate 30 s of apnea, or has a contraindication to succinylcholine. If manual ventilation is anticipated, small tidal volumes should be applied or LMA considered.

8. Oxygenation: 5 minutes of pre-oxygenation with oxygen 100% and RSI to avoid potential aerosolization of virus from airways.

9. Check filter: Ensure hydrophobic HME filter placed between facemask and breathing circuit or between facemask and Ambu bag or circuit.

10. Intubate: Intubate with GlideScope GO and confirm correct position of tracheal tube. Try to avoid ETT suction.


**AFTER**

12. Clean equipment: All airway equipment is discarded except GlideScope GO. GO is disinfected and passed outside the room.

13. Remove protective equipment: Doff all PPE in room except N-95 or PAPR and eye protection.

14. Before and after all procedures: Practice appropriate hand hygiene.
APPENDIX 3: ECMO PLANNING

ECMO Consultation in-hospital:

- ECMO consults will be performed in any location, including the ED and the RICU
- ECMO consult for severe hypoxemia is to Adult Respiratory Cannulation on ECMO paging site
- ECMO consult for cardiovascular collapse is to Adult Cardiac Cannulation on ECMO paging site
- ECMO Charge Specialist (pager 9766) can also be called to facilitate ECMO consults
- All ECMO consults will be discussed with Jonathan Haft (ECMO Director) for review and to ensure awareness of ECMO capacity
- If there is no destination ICU bed available to provide ECMO care, the ECMO attending will discuss with OCA in the moment to make a final decision about whether ECMO will be offered or not

Selection criteria for appropriate ECMO candidates:

- Persistent severe hypoxemia despite maximal MV and rescue approaches (high PEEP, prone position, inhaled nitric oxide) and no absolute contraindications present (irreversible pulmonary disease, severe multiple organ failure, severe comorbidities, contraindication to anticoagulation, anoxic brain injury)
- Cardiovascular collapse, cardiogenic shock with no absolute contraindications present (see above)

ECMO Cannulation in-hospital:

- ECMO cannulation will be performed in any location, including the ED and the RICU
- If the decision is made by the ECMO team to cannulate, and the patient is critically ill and unstable, the cannulation (either VV- or VA-ECMO) will be done on-site with the essential ECMO team who brings the ECMO circuit and cart to the bedside for ECMO cannulation
- In rare cases, if the ECMO team decides that the cannulation should be performed in the SICU and the patient is stable for transfer, the patient could be transferred to the SICU for ECMO cannulation
- Cannulation may be performed in the OR when fluoroscopy is indicated for bicaval ECMO cannulation
- For improved PPE during ECMO cannulation due to increased blood exposure risk, white disposable coverall bunny suits will be used by nonsurgical personnel with all other recommended PPE (N-95 or PAPR, eye goggles, gloves, etc). Surgeons will wear impervious surgical gowns.
- After cannulation outside of the destination ICU, if a SICU bed is not immediately available, the essential ECMO team (ECMO specialists and ECMO Cannulation team –
SICU/CVC-ICU Attending and Fellow(s)) will stay with the patient until transfer is complete

**Patient care after ECMO Cannulation:**

- VV-ECMO patients cannulated for severe hypoxemia will be managed on 5D
- VA-ECMO patients cannulated for cardiogenic shock associated with COVID-19 (suspected/confirmed) will be managed on 5D with assistance of CVC-ICU nursing and CVC-ICU Adult Cardiac Surgery ECMO Attending staff
- SICU Attending, Fellow staff will need to be increased to provide care for these patients
- There are only 2 negative pressure rooms on 5D (Bed 2/40), so ECMO capacity is limited.
- When reverse isolation capacity with negative pressure rooms in the SICU is exceeded, we will take direction from OCA regarding possible use of aerosolization minimization non-negative pressure rooms.

**Transfer requests for ECMO Evaluation for Critical Illness associated with COVID-19 (confirmed or suspected):**

- OSH “ECMO” Transfer Requests come through the Transfer Center to the SICU Fellow/Attending
- All transfer requests for critically ill patients who are COVID-19 PUI will be discussed with OCA
- Decisions will be made jointly between the ECMO attending (re whether appropriate ECMO candidate and ICU staffing issues) and OCA (re ICU bed capacity issues, primary priority to our current inpatients) to accept and to what location (if ECMO extremely high possibility may transfer directly to 5D)
- Transfer requests for patients already on ECMO at OSH will be discussed with Dr. Haft and OCA

Remote cannulation for ECMO will be considered on a case-by-case basis in discussion with Dr. Haft/OCA
Policy and Protocol for obtaining Compression Duplex ultrasonography for diagnosis of VTE during the COVID-19 Pandemic

Obi AT, Barnes GD, Henke PK, Eliason J, Brown S, Arndt E, Wakefield TW

Background and current situation: The diagnosis of venous thromboembolism, encompassing deep venous thrombosis (DVT) and pulmonary embolism (PE) relies upon diagnostic imaging. Currently, the gold standard for PE diagnosis is CT imaging (CT PE protocol), and for DVT is duplex ultrasonography. During the COVID-19 pandemic, CT PE may be difficult to perform due to risk of transmission, co-morbid renal failure (precluding the use of intravenous contrast) and critically ill status lending unacceptable risk during transfer. Duplex ultrasonography of the bilateral lower limbs is anticipated to be difficult to perform during the expected surge of patients due to the expansion of off-site locales without necessary co-located equipment or staff, the overall sheer volume of patients, and a limited workforce within the diagnostic vascular units. We also recognize that registered vascular technicians (RVTs) represent a scarce resource, that if depleted, would inhibit our ability to detect other life and limb threatening conditions that require urgent/emergent treatment such as acute limb ischemia, pseudoaneurysms and carotid disease leading to stroke. The following algorithms were created to be able to recommend diagnostic and treatment approaches to PE and DVT in the face of a surge of COVID-19 patients, recognizing that it may be necessary to compromise upon the gold standard of diagnosis in the setting of extreme scarcity, while still prioritizing treatment that represents that best risk-benefit ratio to the patient with available clinical information. We have made absolute commitment to patients treated at Michigan Medicine to ensure appropriate diagnostic testing and long term therapy once the surge has ceased through referral to our cardiovascular outpatient clinic, with the goal of relieving the burden on the inpatient treatment team or primary care physician.

Critical Guiding Principles

1. All patients with COVID-19 or suspected COVID-19 should be treated with thromboprophylaxis. This statement places value on avoiding the need to reassess VTE risk when a patient has a change in status, and accepts overall low bleeding risk associated with use of anticoagulants used at thromboprophylactic doses.

2. Elevated D-dimer is expected with severe COVID infection and should not be a determinant in the decision to obtain imaging. Negative D-dimer in combination with a low clinical risk score can still safely exclude VTE and may have limited utility for this purpose.

3. Current guidelines recommend empiric treatment of suspected PE if imaging is expected to take > 4 hours, or for DVT if imaging is expected to take > 24 hours. We expect that due to stress on the healthcare system that imaging may be delayed for up to a month or greater, but that patients may be safely empirically treated during this time by determining risk-benefit ratio.

4. Duplex ultrasonography should be utilized when the three following conditions are met simultaneously: (1) bleeding risk is high, (2) the results will change management (3) clinical suspicion of pulmonary embolism is high and CT PE is unobtainable or clinical suspicion of DVT is high (based upon modified Wells and Wells scoring systems).

5. Most patients with confirmed or suspected VTE who are not at high bleeding risk should receive therapeutic doses of anticoagulation
6. In patients with ARDS, low dose non-nomogram heparin infusion may reduce risk of major bleeding while still protecting from thrombotic events. There is no data available for this treatment strategy in intubated patients without ARDS.

7. Patients treated with low dose anticoagulation protocols should be transitioned to full dose anticoagulation when no longer ICU status.

8. Referral for CT PE or duplex may be performed once patient has recovered as an inpatient, however, may need to be completed in the outpatient setting in a resource scarce setting. CVC venous clinics (or hematology, if a consulting service as inpatient) will provide continuity of care in reviewing these outpatient imaging tests and providing long term anticoagulation recommendations to the patient, thereby expediting discharges without the burden of additional testing and relieving inpatient providers of burden of follow up.

9. Upper extremity duplex ultrasonography should be limited to patients with unilateral limb symptoms and criteria as listed in #4 and should not be performed routinely.

**Referenced anticoagulation strategies for the COVID-19 pandemic:**

<table>
<thead>
<tr>
<th>Table 1. Anticoagulation strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thromboprophylaxis</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>Full dose anticoagulation</strong></td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Low dose anticoagulation protocol</strong></td>
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</table>

**VTE Prophylaxis**

All COVID-19 positive hospitalized patients should receive prophylactic anticoagulation for VTE prophylaxis. A study published online at JTH March 27, 2020\(^4\) found a mortality benefit to thromboprophylaxis with subcutaneous unfractionated heparin or low molecular weight heparin amongst COVID-19 positive patients with highly elevated (>3x upper limit of normal) D-dimer and sepsis induced coagulopathy score. This data suggests venous thromboembolism or primary pulmonary thrombi may be an underlying etiology responsible for mortality in severe COVID-19 infections. Other case reports have demonstrated varying incidences of pulmonary embolism or primary pulmonary thrombi, as high as 40% in some, underscoring the need for thromboprophylaxis.\(^4\) In patients who initially present with less severe disease, the risk from failure to reassess and provide timely thromboprophylaxis in an over-capacity healthcare system is much more likely to outweigh the risk of major bleeding from appropriately dosed thromboprophylaxis (~1%).\(^4\)(Gould, ACCP Guidelines 2012)

**Suspected Diagnosis of Pulmonary Embolism**

The existing, published Michigan Medicine faculty practice guidelines recommend utilization of a modified Wells score to determine pretest probability of a PE (Table 2, next page).\(^5\)
If the pre-test probability of the modified Wells PE score is low (score ≤4, mean probably of PE 1.7-2.2% if D-dimer negative; 5.1-7.8% overall, independent of the D-dimer): The current recommendation is thromboprophylaxis for the non-critically ill admitted patient. The critically ill patient who is low risk by the Wells score may qualify for empiric lower dose anticoagulation if their bleeding risk of low (see rationale on page 4). We do not recommend that duplex ultrasonography be performed in patients to exclude the diagnosis of PE. The rationale for this is that the use of DVT imaging in the setting of suspected PE has a low accuracy, a sensitivity of 44%, a specificity of 86%, a positive predictive value 58% and a negative predictive value of 77%. This data has been substantiated in other studies with sensitivities of 25-38% for the diagnosis of thrombosis when being used as a surrogate for PE. Thus, duplex imaging has significant limitations in the diagnosis of PE or pulmonary thrombosis and is not a direct test for PE.

A negative D-dimer in combination with a low modified Wells score is generally sufficient to exclude PE as a diagnosis. However, in the setting of COVID-19 infection, which is associated with elevated D-dimer, the clinical utility of D-dimer is unknown (Zhou, Lancet, 2020). A clinician may draw a D-dimer at their discretion in the setting of a low modified Wells score if a negative result will reassure the patient. However, if positive, which is likely, it may distract from pursuing other, more likely diagnoses.

If the pre-test probability of the Wells PE score is high (score >4): We recommend empiric full dose anticoagulation for the high risk patient with a low risk for bleeding anticoagulation based on bleeding risk (VTE Bleed score <2, no other bleeding risk factors such as thrombocytopenia, cirrhosis, other antithrombotic use). Either empiric full dose anticoagulation or lower dose anticoagulation as clinically appropriate in the critically ill patients, largely based on the potential bleeding risk associated with hemorrhagic pneumonitis. For the patient at high risk of bleeding, the clinician could consider obtaining a CT PE study, if this would alter management. If a CT PE is unable to be obtained, lower extremity duplex ultrasonography would be an alternative option, recognizing limitations in sensitivity and specificity. Prior to obtaining imaging, clinicians should ensure none of the following circumstances apply to the patient.

Table 2. Modified Wells Score for Assessment of Clinical Likelihood for Pulmonary Embolism

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of DVT (objectively measured calf swelling and pain with palpation in the deep vein region)</td>
<td>3</td>
</tr>
<tr>
<td>An alternative diagnosis is less likely than PE</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate &gt; 100 beats per minute</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization or surgery in the previous four weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy (on treatment, treated in the past six months, or palliative care)</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: Total score > 4 = PE-likely, ≤ 4 = PE-unlikely²

Table 3. Under the following circumstances no further studies should be performed:

1. Patient end of life/comfort care.
2. Patient has another indication for anticoagulation.
3. Patient has a previous CT PE or DVT scan this admission without a change in modified Wells risk stratification.
4. Patient would not consent to or be a candidate for anticoagulation or IVC filter if offered.
5. Patient has a diagnosis of VTE from OSH study.
If the diagnostic study is negative, no change in management should occur. If the study is positive, consideration should be given to full dose anticoagulation in the non-intubated admitted patient and lower dose empiric anticoagulation in the intubated critically ill patients due to the bleeding risk, or full dose anticoagulation if felt to be appropriate by the intensivist.

**Rationale for using anticoagulation at lower than full dose but higher than prophylactic dose in those patients with severe ARDS:**

Viral pneumonia associated venous thrombotic events resulting in significant mortality were witnessed during the H1N1 2009 pandemic. Patients meeting the following criteria during this time were treated with an empiric low dose anticoagulation protocol: P/F ratio (PaO_2/FiO_2_ < 200; viral pneumonia suspected or confirmed; no absolute contraindications to anticoagulation. In patients meeting these criteria, the following protocol reduced the risk of VTE and primary pulmonary thrombi without increasing bleeding complications: initiation of non-nomogram heparin infusion with a goal Xa 0.2-0.3; no bolus dose administered. The lower Xa is necessary given the risk of bleeding with hemorrhagic pneumonitis. Of note, this goal Xa does not match with an existing heparin nomogram and will require manual titration by the inpatient team. In intubated patients without severe ARDS, there is a paucity of data regarding risk-benefit ratio of empiric anticoagulation strategies.

**Suspected Diagnosis of DVT**

The existing Michigan Medicine faculty practice guidelines recommend utilization of Wells score to determine pretest probability of a DVT. We recommend use of this score during the COVID-19 pandemic, recognizing that sensitivity and specificity diminishes in the inpatient setting and performance in the setting of pandemic pneumonia is untested.

| Table 4. Wells Score for Likelihood Estimation of Lower Extremity Deep Venous Thrombosis |
|---------------------------------|-----------------|
| **Clinical Characteristic**                | **Score**   |
| Active cancer (patient receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment) | 1 |
| Paralysis, paresis, or recent casting or immobilization of the lower extremities | 1 |
| Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia | 1 |
| Localized tenderness along the distribution of the deep venous system | 1 |
| Entire leg swollen | 1 |
| Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below the tibial tuberosity) | 1 |
| Pitting edema confined to the symptomatic leg | 1 |
| Previously documented DVT | 1 |
| Collateral non-varicose superficial veins | 1 |
| Alternative diagnosis at least as clinically likely as DVT | -2 |

A score of < 2 is considered low likelihood for DVT. From Wells et al., N Eng J Med 2003;349:1227-1235; Wells et al, Lancet 1997; 350:1795-1798

If the pre-test probability of the modified Wells DVT score is low (score <2, mean probably of DVT 3%): The current recommendation is thromboprophylaxis in the non-critically ill admitted patient. The
critically ill patient who is low risk by the Wells score may qualify for empiric lower dose anticoagulation if their bleeding risk of low. Higher consideration should be given to empiric anticoagulation if the P/F ratio is less than 200, given previous benefit of avoiding thrombosis related morbidity in the H1N1 epidemic. The use of duplex ultrasound testing with a risk of only 3% DVT does not warrant the risk to the technologists of performing the tests in COVID-19 positive patients or those PUI. Anticoagulation would not be used unless the Wells scores changes.

**If the pre-test probability of the Wells DVT score is not low (score 2, mean probability of DVT 16.6%-74.6%):** With the higher likelihood of DVT in this group, we would recommend anticoagulation based on bleeding risk (VTE-BLEED score). In the low bleeding risk patient (VTE-BLEED score <2), we suggest empiric full dose therapeutic anticoagulation for the non-critically ill admitted patient. In the critically ill patient, we recommend empiric anticoagulation either at therapeutic or low-moderate doses, largely guided by bleeding risk with hemorrhagic pneumonitis. In the high bleeding risk patient (VTE-BLEED score ≥2), a lower extremity DVT scan may be indicated if the patients meet criteria.

<table>
<thead>
<tr>
<th>Table 5. Under the following circumstances no further studies should be performed:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient end of life/comfort care.</td>
</tr>
<tr>
<td>2. Patient has another indication for anticoagulation.</td>
</tr>
<tr>
<td>3. Patient has a previous CT PE or DVT scan this admission without a change in modified Wells risk stratification.</td>
</tr>
<tr>
<td>4. Patient would not consent to or be a candidate for anticoagulation or IVC filter if offered.</td>
</tr>
<tr>
<td>5. Patient has a diagnosis of VTE from OSH study.</td>
</tr>
</tbody>
</table>
If the DVT scan is negative, then no change in management would occur. If the study is positive, consideration should be given to full dose anticoagulation.

**Upper extremity DVT**

Given the low morbidity of upper extremity line associated DVT in our critically ill population (Underhill, JVS 2017), we do not recommend routine upper extremity venous duplex ultrasound. If a patient has unilateral symptoms and a high risk for bleeding, the need for upper extremity imaging can be considered on a case by case basis.

**Consideration for long term therapy**

In patients who are treated with anticoagulants and are unable to get diagnostic imaging during the COVID-19 surge, we recommend that they be discharged with 1-2 month supply of direct oral anticoagulants or vitamin K antagonists. For patients deemed moderate to high risk for PE, a CT PE protocol within 1 month should be ordered. For patients deemed high risk for DVT, a lower extremity venous duplex ultrasound should be ordered. All patients should be referred to the venous health program (VHP) or hematology clinic, as clinically appropriate. These clinics will review the study and provide patients of recommendations for long term duration of therapy. VHP clinic referral can be found in MiChart by typing “CVC Venous Management Clinic.” For patients treated with lower dose empiric anticoagulation in the ICU setting, standard full dose anticoagulation with heparin, LMWH, or oral agents should be initiated once they become floor status.

<table>
<thead>
<tr>
<th>Table 6. VTE-BLEED Score</th>
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<tbody>
<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td>Active cancer*</td>
</tr>
<tr>
<td>Male with uncontrolled arterial hypertensionb</td>
</tr>
<tr>
<td>Anemia*</td>
</tr>
<tr>
<td>History of bleedingc</td>
</tr>
<tr>
<td>Age ≥ 60 years old</td>
</tr>
<tr>
<td>Renal dysfunctiond</td>
</tr>
</tbody>
</table>

**Classification of patients with the VTE-BLEED score**

| Low bleeding risk | Total score <2 |
| High bleeding risk| Total score ≥2  |

**Other factors that contribute to bleeding:**
- Thrombocytopenia
- Cirrhosis
- Other anti-thrombotic use

*Cancer diagnosed within 6 mos. before VTE (excluding BCC or SCC of the skin), recently recurrent or progressive cancer or any cancer that required anti-cancer Tx within 6 mos. before VTE was diagnosed
*Males w/ SBP ≥ 140 mmHg at baseline
Hgb <13 g/dl in men or <12 g/dl in women
Including prior major or non-major clinically relevant bleeding event, rectal bleeding, frequent nose bleeding, or hematuria
GFR <60 ml/min

**References**


**Anticoagulation for all Critically Ill COVID-19 patients:**
Viral pneumonia-associated thrombotic events including primary pulmonary thrombi resulted in severe hypoxemia and significant mortality during the H1N1 2009 pandemic. Similar autopsy findings have been reported in COVID-19 critically ill patients, with significant hemorrhagic viral pneumonia and concurrent primary pulmonary thromboemboli.

![Image of lung sections](https://www.medrxiv.org/content/10.1101/2020.04.06.20050575v1)

**FIGURE 1: Gross Findings of the Lungs and Heart.** A) Lungs with bilateral pulmonary edema and patches of dark hemorrhage, and B) A heart showing extreme right ventricular dilatation, with straightening of the interventricular septum. C) Cut sections of lung showing thrombi present within peripheral small vessels (white arrows).

For severe hypoxemia/ARDS patients, initiate empiric Non-nomogram Heparin Infusion on ICU admission with goal Xa 0.2-0.3 or PTT 40-50; no bolus dose. The lower Xa/PTT goal is necessary given the significant risk of pulmonary bleeding with COVID-19 viral hemorrhagic pneumonitis. If concern for PE/DVT, increase to full dose systemic heparin anticoagulation.

**When no longer ICU status:**
Patients treated with low dose anticoagulation protocol should be transitioned to full dose systemic heparin anticoagulation when no longer ICU status. Oral anticoagulant therapy (direct oral anticoagulants or vitamin K antagonists) can be initiated, dependent on the patient’s renal function, after extubation or tracheostomy and no further invasive procedure planned.

**Long term Anticoagulation Therapy**
In critically ill patients who are treated with anticoagulants and are unable to get diagnostic imaging during the COVID-19 pandemic, we recommend that they be discharged with a plan for empiric 1-2 months of systemic anticoagulation with either direct oral anticoagulants or vitamin K antagonists. A CT PE protocol and lower extremity venous duplex scan within 1 month should be ordered. The final anticoagulation plan will be modified dependent on the findings of these diagnostic studies. All patients should be referred to the venous health program (VHP) or hematology clinic, as clinically appropriate. These clinics will review the diagnostic studies and provide recommendations for duration of anticoagulation.
Non-Critically Ill, Admitted Patients

Clinical Suspicion for PE

Risk Assessment by Modified Wells

PE Likely (> 4)

Low Risk (< 2)

Assess Bleeding Risk (VTE-BLEED)

High Risk (≥ 2)

Optional D-Dimer

Thrombo Prophylaxis

No Anticoagulation on D/C Unless Modified Wells Score Changes

Full Therapeutic Anticoagulation (UFH, LMWH, or DOAC)

D/C with 1-2 mos. AC; refer for PE CT when clinically appropriate with rapid clinic follow-up

Consider 1) PE CT or 2) LE DVT scan (DVU2501) if CT cannot be performed

Meet COVID Protocol for VTE:
- Pt. is not in end of life or comfort care
- PE CT or DVT Scan would change management
- Pt. would consent to AC
- Pt. does not already have Dx of VTE from another study or other indications for AC

VTE-BLEED Score

Factor
- Active cancer
- Male with uncontrolled arterial hypertension
- Anaemia
- History of bleeding
- Age ≥ 60 years old
- Renal dysfunction

Score
2
1
1
1
1
1

Other factors that contribute to bleeding:
- Thrombocytopenia
- Cirrhosis
- Other anti-thrombotic use

DVT-Scan-COVID@med.umich.edu, which will be reviewed daily.

Questions regarding the algorithms can be directed to DVT-Scan-COVID@med.umich.edu, which will be reviewed daily.

Clinical signs and symptoms of DVT (objectively measured calf swelling and pain with palpation in the deep vein region)

An alternative diagnosis is less likely than PE

Heart rate > 100 beats per minute

Immobilization or surgery in the previous four weeks

Previous DVT or PE

Hemoptysis

Malignancy (on treatment, treated in the past six months, or palliative care)
**Modified Wells Score for Assessment of Clinical Likelihood for Pulmonary Embolism**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of DVT (objectively measured calf swelling and pain with palpation in the deep vein region)</td>
<td>3</td>
</tr>
<tr>
<td>An alternative diagnosis is less likely than PE</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate &gt; 100 beats per minute</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization or surgery in the previous four weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy (on treatment, treated in the past six months, or palliative care)</td>
<td>1</td>
</tr>
</tbody>
</table>

**VTE-BLEED Score**

<table>
<thead>
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<td>Renal dysfunction</td>
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</table>

**Other factors that contribute to bleeding:**
- Thrombocytopenia
- Cirrhosis
- Other anti-thrombotic use

---

**COVID-19 Algorithm for PE Assessment**

Obi AT, Barnes GD, Henke PK, Eliason J, Brown S, Arndt E, Wakefield TW

Revision Date: 4/3/2020, 1:00PM

Questions regarding the algorithms can be directed to DVT-Scan-COVID@med.umich.edu, which will be reviewed daily.
COVID-19 Algorithm for DVT Assessment

Obi AT, Barnes GD, Henke PK, Eliason J, Brown S, Arndt E, Wakefield TW
Revision Date: 4/3/2020, 1:00PM

Questions regarding the algorithms can be directed to DVT-Scan-COVID@med.umich.edu, which will be reviewed daily.

Clinical Suspicion for DVT

Risk Assessment by Wells Score

High Risk (≥ 2)

Low Risk (< 2)

Assess Bleeding Risk (VTE-BLEED)

Low Risk (< 2)

Optimal D-Dimer

High Risk (≥ 2)

Thrombo Prophylaxis

No Anticoagulation on D/C Unless Wells Score Changes

Full Therapeutic Anticoagulation (UFH, LMWH, or DOAC)

Consider LE DVT Scan¹ (DVU2501)

¹Meets COVID Protocol for VTE:
- Pt. is not in end of life or comfort care
- DVT Scan would change management
- Pt. would consent to AC
- Pt. does not already have Dx of VTE from another study or other indications for AC

Full dose AC (UFH, LMWH, or DOAC)

D/C with 3 mos. AC

D/C with 1-2 mos. AC; refer for DVT Scan when clinically appropriate with rapid clinic follow-up¹

DVT-Scan-COVID@med.umich.edu, which will be reviewed daily.

Wells Score for Likelihood Estimation of Lower Extremity Deep Venous Thrombosis

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Active cancer (patient receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment)</td>
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</tr>
<tr>
<td>Paralysis, paresis, or recent casting or immobilization of the lower extremities</td>
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</tr>
<tr>
<td>Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
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<tr>
<td>Entire leg swollen</td>
<td>1</td>
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<td>Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below the tibial tuberosity)</td>
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<tr>
<td>Collateral non-varicose superficial veins</td>
<td>1</td>
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VTE-BLEED Score

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<td>2</td>
</tr>
<tr>
<td>Male with uncontrolled arterial hypertension³</td>
<td>1</td>
</tr>
<tr>
<td>Anaemia²</td>
<td>1</td>
</tr>
<tr>
<td>History of bleeding⁴</td>
<td>1</td>
</tr>
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<td>Age ≥ 60 years old</td>
<td>1</td>
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¹Refer for Clinic Follow-up:
1) Virtual Visit with VHP (“CVC Venous Management Clinic”); or
2) Hematology
Clinical Suspicion for DVT

Risk Assessment by Wells Score

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Wells Score for Likelihood Estimation of Lower Extremity Deep Venous Thrombosis

Low Risk (< 2)

High Risk (≥ 2)

Assess Bleeding Risk (VTE-BLEED)

Low Risk (< 2)

High Risk (≥ 2)

Assess Bleeding Risk (VTE-BLEED)

Low Risk (< 2)

High Risk (≥ 2)

Presumptive VTE Treatment with Heparin:
- "Heparin Nomogram for DVT/PE" without bolus (most patients)
- "Heparin Nomogram for ACS/AF" (Xa target 0.2-0.5)
- Non-nomogram Heparin at discretion of attending (Xa target 0.2-0.3)

Thrombo Prophylaxis

Consider LE DVT Scan¹ (DVU2501)

²Meets COVID Protocol for VTE:
- Pt. is not in end of life or comfort care
- DVT Scan would change management
- Pt. would consent to AC
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VTE-BLEED Score

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Questions regarding the algorithms can be directed to DVT-Scan-COVID@med.umich.edu, which will be reviewed daily.

COVID-19 Algorithm for DVT Assessment

Obi AT, Barnes GD, Henke PK, Eliason J, Brown S, Arndt E, Wakefield TW

Revision Date: 4/3/2020, 1:00PM

Remarks:
- Upon no longer critically ill, follow the COVID-19 Algorithm for DVT Assessment, Non-Critically Ill, Admitted protocol
- If positive for occult DVT, consider CVI or exclude DVT with LE DVT Scan (DVU2501)
- If negative for occult DVT and no change in management, proceed with LE DVT Scan (DVU2501)
- If negative for occult DVT and change in management, proceed with LE DVT Scan (DVU2501)

1) Virtual Visit with VHP ("CVC Venous Management Clinic"); or
2) Hematology

Remarks:
- Refer for Clinic Follow-up:
- Virtual Visit with VHP ("CVC Venous Management Clinic"); or
- Hematology
Overview of ARDS Ventilator Strategies for COVID-19

Appendix 1. COVID Specific Recommendations

I. COVID Phenotypes - Investigators in Italy (Gattinoni et al.) have proposed that COVID patients presenting with viral pneumonia due to COVID-19 present with two distinct phenotypes and should receive invasive mechanical ventilation in accordance with the prevailing phenotype. The L phenotype occurs early in the course of respiratory failure and may evolve into the more severe H phenotype by the mechanism of pulmonary micro-thrombosis.

a. **Type L phenotype** – “L” stands for low elastance, i.e. high pulmonary compliance.
   i. Patchy ground glass opacities on CT scan
   ii. Low lung weight
   iii. Low V/Q
   iv. High lung compliance: \( C_{stat} = \frac{V_t}{(P_{plat} - PEEP)} \)
   v. Poor recruitability with PEEP

b. **Type H phenotype** – “H” stands for high elastance, i.e. low pulmonary compliance
   i. More consolidative findings on chest CT with compressive atelectasis in the dependent lung zones
   ii. High lung weight
   iii. High R to L shunt
   iv. Good recruitability with PEEP

---

c. **Transition from Type L to Type H phenotype** – Unclear. This may be due to then natural disease process or, asGattinoni believes high negative intrathoracic pressure swings due to patient effort.

d. **Reported elsewhere, we have not found the L phenotype to be common at MM.** This may be due to the use of HFNC resulting in intubation later in the patient’s clinical course or some other factor.

II. **Ventilator Management**

a. **H phenotype** – as the vast majority of our patients fall into this category, we recommend using the algorithm outlined in the preceding pages with the following considerations.

i. **PEEP titration using the high PEEP table**
1. Keeping Pplat < 30 and Driving pressure (Pplat – PEEP) < 16

2. **Higher PEEP in specific patients:** Recognition that patients with an abnormally stiff chest wall, such as in obesity, ascites, s/p open abdominal surgery may require higher PEEP levels (up to 24 cm H₂O and sometimes higher) than usual as the lungs are not “seeing” the PEEP level administered.
   a. Can calculate transpulmonary pressure if vent is swapped out to an Avia ventilator and an esophageal balloon is inserted to estimate pleural pressure – Not widely available however.

3. **Sedation** should be relatively deep and asynchrony avoided as this can produce injuriously large tidal volumes.
   a. NMB may be required to prevent asynchrony and improve oxygenation.
      i. Consider relatively tight glycemic control in patients on NMB (target glucose 110 mg/dL) to mitigate muscle weakness later on.

4. **Prone ventilation** is found to be frequently successful in COVID ARDS patients. However, risks to personnel (takes 3-4 people to perform) and requirement for a lot of PPE need to be considered.
   a. We recommend prone ventilation if oxygenation is inadequate despite PEEP values of >18 cm H₂O on NMB. Consider prone position if P/F ratio < 150 (Proseva Trial)
   b. 28-day all-cause mortality 16% in prone vs. 32.8% in supine (P<0.001); adjusted odds ratio 0.42 (0.26-0.66)
   c. Patients should be proned for > 16 hrs/day (4pm – 10 am avoids change of shift, improved oxygenation at night)
   d. NMB may be required to prone patients.
   e. Criteria for stopping prone in Proseva were any of the following:
      i. improvement in oxygenation (defined as Pao2:Fio2 ratio of ≥150 mm Hg and Fio2 of ≤0.6; in the prone group, these criteria had to be met in the supine position at least 4 hours after the end of the last prone session)
      ii. a decrease in the Pao2:Fio2 ratio of more than 20%, relative to the ratio in the supine position, before two consecutive prone sessions
      iii. complications occurring during a prone session and leading to its immediate interruption.
5. **Inhaled pulmonary vasodilators** are believed to be a useful adjunct in COVID positive Berlin severe ARDS patient although have never been shown to decrease mortality in a general ARDS patients
   a. iNO was believed to have an antiviral effect in SARS CoV-1 patients
   b. Optimal iNO dose for severe hypoxemia/ARDS is 10 ppm
   c. Do not consider eporpostenol (Veltri) as a lower cost substitute for iNO as it requires frequent circuit disconnects which is an Aerosol-generating procedure.

b. **L Phenotype**
   i. Can consider Vt up to 8 cc/kg ideal body weight as pulmonary compliance is high and Pplat will remain low at < 30
   ii. Deep sedation to avoid swings in pleural pressure
   iii. PEEP does not improve oxygenation and should be kept < 10 cm H2O
   iv. Prone ventilation is usually unnecessary
   v. Monitor closely for transition to H Phenotype

c. **Weaning PEEP**
   i. Important to wean PEEP slowly in patients with severe hypoxemia.
   ii. Premature decrease of PEEP will result in derecruitment and hypoxemia.
   iii. **Note that in the High PEEP table the PEEP is maintained at 16 cm H2O down to an FiO2 of 0.40**
   iv. PEEP decrease may be made when:
      1. After 24-hour stability, if FiO2 is maintained <0.6, PEEP may be reduced by 1 cm H20 q12 hours.
      2. If FiO2 need increases consistently >0.1 from prior value with PEEP wean, revert back to prior PEEP level.

III. **Ventilator Weaning**
   a. COVID patients are generally believed to be more challenging to liberate from mechanical ventilation.
   b. Consideration should be given to:
      i. Not attempting a spontaneous breathing trial (SBT) until a patient is truly ready as intrathoracic pressure swings in spontaneously breathing patients may worsen lung injury (per Gattinoni, as above).
      ii. Establish readiness for liberation in a more conservative manner than has been advocated by either/both:
      iii. Performing an extended (> 2 hour) SBT(s)
      iv. Using lower levels of partial ventilator support during the SBT trial:
         1. Flow by with automatic tube compensation
         2. CPAP at 5 cm H2O
         3. Higher CPAP (10 cm H2O) if morbid obesity to avoid derecruitment
c. **Post-extubation support:**
   i. HFNC for 24 hours, more if necessary
   ii. Wean FiO₂ slowly, as recurrent hypoxemia post-extubation is common
   iii. Wean supplemental oxygen to 6 L NC prior to transfer to floor
Overview of ARDS Ventilator Management Strategies
University Hospital Respiratory Care
Michigan Medicine, Ann Arbor MI

1: Basic Lung Protective Ventilation
- ARDS Network ventilation strategy:
  a. Use VCV or PCV, targeting VT 6 mL/kg PBW
  b. Maintain Pplat <30 cm H₂O
  c. PEEP/FiO₂ per table (see bottom of page)
- Consider maintaining driving pressure ≤12-15 cm H₂O
- If consolidation is asymmetrical, consider placing ‘good lung’ in dependent position

2: Patient-Ventilator Asynchrony
* Consider minor ventilator adjustments (eg, flow rate & pattern, inspiratory pause)
* Assess potential to treat with pharmacologic agents (eg, sedation, NMB), especially in pt with severe ARDS and strong respiratory drive (double-trigger)
* For double-triggering, consider increasing VT 1 mL/kg (max 8 mL/kg), provided Pplat <30 cm H₂O
* For flow asynchrony, consider a variable flow pressure breath mode of ventilation:
  - Volume targeted PC (PRVC, VC+, Autoflow)
  - Pressure control, pressure support

Prone Positioning
* Consider after initial 12-24 hrs of stabilization
* Use 16 hr/day (generally 4 pm to 10 am)
* Discontinue when:
  - Instability in prone position
  - Supine x 4 hr, PaO₂/FiO₂ >150 on FiO₂ ≤0.60 & PEEP ≤10

Higher PEEP
* For pts with PaO₂/FiO₂ <150, consider higher PEEP table

Recruitment Maneuvers
* Consider for pts with clear de-recruitment, negative Ptp or PaO₂/FiO₂ <150
  * Recommend PCV with: 1) 40/20-25 for 1-3 min (as tolerated) or 2) delta-P of 15 and increase PEEP by 5 up to PIP of 40
  * If CPAP method used, limit to 15-30 seconds
  * Provider should be at bedside if pressures >40 cm H₂O used

Neuromuscular Blockade
* No benefit of routine use of NMB in moderate-severe ARDS.
* Consider use if significant asynchrony and concern for VILI.

Esophageal Pressure (Pes) Guided Therapy
* Informs of transpulmonary end-inspiratory (Ptp-plat) and end-expiratory (Ptp-PEEP) pressures
* Requires AVEA ventilator & placement of Pes catheter

Airway Pressure Release Ventilation (APRV)
* Increases Pmean with lower Pplat; lacks outcomes benefit
* Concern for P-SILI in pt with strong respiratory drive

Inhaled Nitric Oxide (iNO)
* Start at 10 ppm
  * If positive response (improved oxygenation) or brought in by Survival Flight:
    - Maintain at 10 ppm and reduce FiO₂ down to 0.8, then titrate iNO down, or consider Veletri or iloprost, per Respiratory Care policy
  * If no response, discuss with team to consider stopping

NOTE: iNO is a very costly drug compared to alternatives

Extracorporeal Membrane Oxygenation (ECMO)
* Absolute contraindications: irreversible pulmonary process
* Evaluate, but lower survival if on vent 7-10 days pre-ECMO
* Consider if: PaO₂/FiO₂ <50 x3 hrs or <80 x6 hrs, or pH <7.25 wt/ PaCO₂ >60 x6 hrs

High Frequency Oscillatory Ventilation (HFOV)
* Strong recommendation against routine use; may have benefit if PaO₂/FiO₂ <64; goal is to increase Pmean
GENERAL COMMENT
Low VT and minimizing Pplat is the only ventilation strategy with a high level of evidence of mortality benefit in ARDS. Therefore, a lung protective ventilation strategy (LPVS) following the ARDS Network strategy (using pressure or volume ventilation) to limit VT (target 6 mL/kg; reduce to 5 or 4 mL/kg for high Pplat, 7 or 8 mL/kg for double-triggering) and Pplat (<30 cm H2O) should be the initial and primary strategy for all ARDS patients.

RECOMMENDED READING
Guidelines or Reviews on ARDS Management:

Setting VT:
* Standard is targeting 6 mL/kg PBW & limit Pplat <30 cm H2O; drive pressure (ie, keep <12-15) may be more important than VT or Pplat

PEEP
* For most pts the Lower PEEP table should be used. For pts with ARDS and P/F <150 and/or those with high Ppl, the Higher PEEP table should be considered

Prone Positioning (PP)
* PP improves respiratory mechanics and hemodynamics which improve both oxygenation and RV function; is associated with lower inflammatory mediator levels

Respiratory Mechanics (RM)
* Reserved for pts with clear de-recruitment, negative Ptp or P/F <150. A PC RM may be better tolerated than CPAP. Use with caution and NOT routinely on all pts.

Airway Pressure Release Ventilation
* Other than Zhao, over 15 RCTs have NOT shown superiority of APRV vs conventional MV. Concern exists about strong resp drive and P-SII in severe ARDS.

Inhaled Nitric Oxide and Inhaled Prostacyclin
* iNO improves oxygenation, reduces shunt thru PFO, helps safe transport to UM, no mortality benefit, is associated with AKI, costly (>$3,500/day not reimbursed)

ECMO
* Rescue therapy for severe hypoxicem RF (ARDS with P/F <60 on >80% O2) after medical and MV optimized (incl NMB, PEEP, fluid/HLD). Consider early consult.

HFOV
* Harmful in mild and moderate ARDS, may be beneficial in very severe (P/F<64) ARDS

RECOMMENDED READING
Guidelines or Reviews on ARDS Management:
Michigan Medicine Tracheostomy Guidelines in COVID-19 Era:

Based on our current understanding of COVID19, it is spread mainly through from person-to-person either via close contact with one another (within about 6 feet) or through respiratory droplets produced when an infected person coughs or sneezes. Procedures such as tracheostomy and laryngectomy result in significant aerosol generation and lead to increased risk to others.

In cases of airway intervention, the goal is to try minimize aerosolization and thereby minimize the risk of viral transmission to health care providers.

Performance of Tracheostomy is a high risk aerosol generating procedure (AGP). Avoid performing tracheostomy in COVID19/PUI patients if possible to avoid increased aerosolization risks to health care providers.

In an attempt to minimize the exposure to COVID-19 to healthcare workers, the following measures are suggested in tracheostomy (or laryngectomy) patients with either a confirmed diagnosis of COVID-19, persons under investigation (PUI), or unknown/asymptomatic status.

We will continue to follow all guidelines from the Michigan Medicine and Infection Prevention and Epidemiology (IPE). This is a dynamic time and best practices may change, so please defer to updated official communications from Michigan Medicine.

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**Emergency Trach/Airway:**

**Indication:** Emergency with impending loss of airway where transoral ETT placement is unsuccessful and cannot be safely performed. If stable, attempt to transfer to the OR.

**At this time, in patients with unknown COVID19 status, COVID19-positive or PUI, all health care providers performing emergent tracheostomy should wear COVID19 PPE.**

In the setting of an emergency airway, the surgical airway team should don appropriate COVID19 PPE (see Michigan Medicine guidelines for the use of PPE) **before entering the room** and assisting with the airway and patient care.

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**Personal Protective Equipment for COVID19**

Please note that institutional guidelines for PPE use are subject to change. Updated guidance can be accessed at-

http://www.med.umich.edu/i/covid19-careplan/protect.html

- PPE should be at the door/unit of all COVID19 and PUI patients
- **PPE should be donned appropriately PRIOR TO ENTERING THE ROOM before proceeding to assist**

---

**Appropriate PPE is critical based on the Viral Exposure Risk:**

- The Covid-19 virus is found in the respiratory tract and secretions, the GI tract and secretions, as well as blood. Eye protection is critically important.

- Though data are sparse, the virus may potentially be aerosolized during the use of electrocautery and during airway manipulation. **Hence PAPR/N-95 use for all tracheostomy related cases and procedures.** ([http://www.med.umich.edu/i/covid19-careplan/protect.html](http://www.med.umich.edu/i/covid19-careplan/protect.html))

Unprotected healthcare personnel **SHOULD NOT** be allowed in a room where an aerosol-generating procedure is/has been conducted.

4/10/2020 8:30 AM
If COVID19 status is unknown, manage patient as if they are COVID-19 positive. Given respiratory symptoms they will fulfil criteria for suspected COVID-19 and there will not be time for testing in this type of emergency situation.

**End of procedure:**

• **Careful DOFFING is critically important.** This is the moment of highest risk for self-contamination. Proper removal of PPE is critical to avoid cross contamination & potential exposure

http://www.med.umich.edu/i/covid19-careplan/protect.html

In known COVID or PUI patients, the room will need to cleared according to institutional guidelines (see link below) to allow adequate air clearance.

http://www.med.umich.edu/i/ice/resources/coronavirus/air_clearance_by_room.pdf

---

**Elective Tracheostomy in non-ICU setting:**

Elective tracheostomy may be necessary in patients who are not critically ill, (ie: major head and neck cancer/reconstructive cases to bypass potential airway obstruction, non-emergent subglottic/tracheal stenosis, etc)

If possible, avoid tracheostomy or delay the procedure as long as avoidance or delay would not cause undue harm to the patient or require use of other scarce resources (ie ICU bed). Decisions to perform pre-operative COVID testing should be based on institutional guidelines.

Protocol for pre-op testing and algorithm for determination of need to proceed to OR:

http://www.med.umich.edu/i/ice/resources/coronavirus/ppe_or_guidance.pdf

---

**Elective Tracheostomy for Mechanically Ventilated Patients in the ICU:**

Carefully consider timing and indication of tracheostomy in all patients who being considered for tracheostomy, particularly those that are COVID19 positive or PUI. **Given the high risk of aerosol generation both during tracheostomy and after the procedure, defer tracheostomy in the COVID19/PUI population until absolutely necessary.**

1. Confirm improvement of symptoms and stable pulmonary status
2. Wait at least 3 weeks from intubation (allows for optimal viral clearance)
   • Extenuating circumstances may present where tracheostomy may be required earlier than 3 weeks; in these exceptional situations, the clinical benefits of tracheostomy must be carefully weighed against the high transmission risk in COVID-19 tracheostomy patients and should be done in a multidisciplinary fashion.

**Decision for tracheostomy in any ICU patient should be a multi-disciplinary decision as transmission risk in a COVID-19 patient with a tracheostomy is high.**

PPE for Elective Tracheostomy: PPE appropriate for an AGP should be used, per institutional guidelines.

**Type and Location of Tracheostomy Procedures:**

• There is no high quality data on the degree of aerosolization with open versus percutaneous tracheostomy techniques.

• The use of bronchoscopy with percutaneous tracheostomy may increase the risk of aerosolization during the procedure, but the degree of aerosolization and risk to the health care worker is felt to be equivalent to open procedures. **Therefore, can consider either open tracheostomy or percutaneous tracheostomy at the discretion of the faculty performing the procedure.**

• For percutaneous tracheostomy performed with alternate techniques, such as with real-time ultrasound guidance without bronchoscopy, will further minimize risk to providers
• **Location of tracheostomy:** Perform tracheostomy (either percutaneous or open) in the ICU if possible.
  - Tracheostomy is favored to be performed in the ICU
  - **Perform tracheostomy in a negative pressure room;** secondary choice is an externally vented room with HEPA filter if airborne room is unavailable. Avoid performing tracheostomy in neutral pressure rooms
  - In cases not felt to be safe for bedside tracheostomy in the ICU, then transport to the OR is appropriate.
  - If a known COVID or PUI patient is taken to the OR, the room will need to cleared for 20-35 minutes to allow adequate air clearance. ([http://www.med.umich.edu/i/ice/resources/coronavirus/air_clearance_by_room.pdf](http://www.med.umich.edu/i/ice/resources/coronavirus/air_clearance_by_room.pdf))

In previously asymptomatic patients who are deemed COVID-19-NEGATIVE based on testing within 48hours of the planned procedure, standard PPE is appropriate.

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**Unique Steps/Precautions During Tracheostomy Procedure:**

These are unique and critical steps within a standard tracheostomy for COVID19/PUI patients:

- **Preparation:**
  - The most senior/experienced surgeon/proceduralist available should perform the tracheostomy in COVID19/PUI patients
  - Limit personnel in the room to individuals essential for safe completion of the procedure
  - Maintain neuromuscular blockade throughout the procedure
  - Consider IV Glycopyrrolate 0.4mg to reduce secretions
  - Inject with 2% lidocaine with 1:100,000 epinephrine to minimize bleeding and need for suctioning
  - Runner outside room
  - Ensure HEPA viral filter on ventilator and suctioning
  - Double gloving
  - Full draping to minimize contamination of surfaces
  - Impervious sheets around patients
  - Avoid electrocautery if possible; strongly recommend smoke evacuator cautery
  - If possible, use single-use bronchoscope for percutaneous trach

- Use the following steps to minimize aerosolization in open tracheostomy or percutaneous:
  - **During open tracheostomy:**
    - Anesthesia informed of imminent tracheal incision; all team members are prepared
    - Preoxygenation 100% for 3min then apnea
    - Ventilator ‘OFF’
    - Cuff deflated just before incision down to trachea or pushed distal to avoid accidently popping balloon of the endotracheal tube (ETT)
    - ETT Pulled back 3 cm and visualization of tip of ETT at tracheotomy
    - **Minimize tracheal succioning to avoid aerosolization**
    - Resume mechanical ventilation only after the tracheostomy tube balloon is inflated and a closed circuit re-established; confirm HME filter is connected to tracheostomy tube
    - After removal of ETT, place ETT in plastic bag for disposal
  - **During percutaneous tracheostomy:**
    - To minimize aerosolization during withdrawal of the endotracheal tube:
• Confirm that patient has been on FiO2 100% through the procedure
• The proceduralist must notify other members of the team that withdrawal of the tube will commence
• Turn off mechanical ventilation
• Withdraw endotracheal tube under appropriate guidance, consider Doppler to determine airflow as ETT pulled back
• After extubation, place ETT in plastic bag for disposal
• Inflate cuff, then resume mechanical ventilation

To minimize aerosolization during dilation:
• Confirm that patient has been on FiO2 100% through the procedure
• The proceduralist must notify other members of the team that dilatation will commence
• Turn off mechanical ventilation
• Perform dilatation and delivery of tracheostomy tube, cover stoma with gauze between these steps
• Consider performing dilatation and tube delivery under a clear plastic drape
• Resume mechanical ventilation only after the tracheostomy tube balloon is inflated and a closed circuit re-established

• End of procedure:
  o Consider a xeroform trach pants to further seal the tracheostomy incision to prevent leak and aerosolization until the stoma has closed around the tracheostomy tube
  o Need to ensure adequate cuff-pressure immediately to minimize leaks
  o Use the largest tracheostomy tube appropriate for the patient to allow bronchoscopy in ICU patients; do not use fenestrated tracheostomy tube

Care of Tracheostomy Patients:


COVID19/PUI/Symptomatic Patients:
Because tracheostomy and tracheal suctioning is considered an AGP, all COVID19/PUI patients not connected to mechanical ventilation should have an HME (heat and moisture exchanger)/filter fitted to the tracheostomy tube.

- Closed suctioning if available is strongly recommended
  - During suctioning, change of inner cannula, disconnect from ventilator circuit, bronchoscopy through tracheostomy tube, and tracheostomy tube change, the caregiver(s) must wear appropriate COVID19 PPE (as above)
  - Keeping tracheostomy tube inflated to minimize secretions from around the tube
  - Avoid routine tracheostomy tube exchange unless absolutely necessary or planning for decanulation. Tracheostomy tube exchange is considered a high risk AGP.

Laryngectomy patients are a unique group of patients that also have similar AGP risks to health care workers with generation of aerosolized respiratory droplets. Laryngectomy HME should be placed immediately and kept at all times regardless of COVID19 status given many carriers are asymptomatic. In COVID19/PUI laryngectomy patients, the addition of appropriate PPE based on their status should be in place for all suctioning, laryngectomy tube exchange, or airway manipulation.


Untested/Asymptomatic Patients:
In untested/asymptomatic tracheostomy and laryngectomy patients should have an HME/filter on at all times and if possible/available, closed suctioning is recommended. Strongly consider testing these patients if symptoms develop and placement in special pathogen precautions while awaiting testing results; however, unless testing COVID19-positive, follow standard precautions

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with any tracheostomy/stomal interventions (i.e.: suctioning, inner cannula exchange, changing HME/filter).

- **Avoid routine tracheostomy tube exchange** unless absolutely necessary or planning for decannulation
- **Tracheostomy tube exchange is considered a high risk AGP**, thus COVID-19 PPE is recommended (even in asymptomatic/untested patients), limit the number of providers to only those essential for the procedure, and must communicate/coordinate with nursing as the room will need to be cleared for 60 minutes after the tracheostomy tube exchange

Decannulation: Should be done as soon as medically safe and immediately place occlusive dressing. Providers should be aware this can take up to 2 weeks to close and in 1-3% of patients will not close.

Laryngectomy patients cannot be decannulated nor should occlusive dressing be placed.

**Special Category: Care of Untested/Asymptomatic Pediatric Tracheostomy Patients:**

- Pediatric tracheostomy patients who are asymptomatic should be maintained in standard precautions with healthcare providers wearing the appropriate PPE
- Patients should use closed suctioning systems for trach tube suctioning whenever possible to limit circuit disconnection and decrease risk of exposure
- Patients should use HME during the day and if possible at night/naps as much as tolerated
  - If HME is not tolerated, can use of trach mask or tracheostomy covers with the goal to cover the tracheostomy as much as possible to minimize droplet spread
- In pediatric patients, routine tracheostomy tube exchanges should occur every 4 weeks unless there is concern for mucus plugging or emergency situation. **Tracheostomy tube exchange should absolutely be performed if there is concern for airway patency.**
- Tracheostomy tube exchanges performed by health care providers should be done with PPE according to institutional guidelines
- Families can continue to participate in tracheostomy tube care in the hospital as appropriate. Tracheostomy tube exchanges with family caregivers will be coordinated by Peds OTO Trach Team. Per IPE, family caregivers should wear loop mask only when participating in tracheostomy tube exchanges.

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9. icmmanaesthesiacovi-19.org
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These guidelines will focus on the use of sedative, analgesic and neuromuscular blocking agents in critically ill patients with COVID-19 infection as required for the management of pain, agitation and delirium, and to optimize ventilator synchrony and gas exchange in the setting of severe hypoxic respiratory failure. This document will not cover the use of procedural sedation or analgesia, which is addressed in the moderate and deep sedation policies of Michigan Medicine.

PAIN, AGITATION, AND DELIRIUM

Critically ill patients with COVID-19 infection often require the use of sedation, analgesia and medications to manage delirium, for the following reasons-

1. Patient comfort during invasive mechanical ventilation.
2. Synchrony with mechanical ventilation, to optimize oxygenation and ventilation in the setting of severe hypoxemic respiratory failure.
3. Prevention of unplanned device removal, especially unplanned extubation.

Specific challenges with management of pain, agitation and delirium in patients with COVID-19 infection.

1. Early reports and anecdotal experience suggests a high rate of acute encephalopathy and agitated delirium in patients with COVID-19 infection.[2] The presence of acute encephalopathy leads to increased usage of sedative and analgesic agents to prevent unplanned device removal and improve ventilator synchrony.
2. A significant proportion of COVID-19 patients develop the acute respiratory distress syndrome (ARDS), necessitating measures that require sedation and analgesia, such as low tidal volume ventilation, high positive end expiratory pressure (PEEP) and prone ventilation.
3. For the above reasons, consumption of sedative and analgesic agents such as Propofol, Midazolam and Fentanyl is high, leading to medication shortages across the United States.
4. The risk of transmission to healthcare workers requires that room entry by nursing and providers be minimized and tasks consolidated, which impacts the ability to perform frequent re-assessments and medication titration.
5. Anecdotal experience suggests that hypertriglyceridemia may be common in critically ill COVID-19 patients receiving Propofol infusions, including at lower infusion rates.

No specific data exists on the optimal use of sedation, analgesia and agents to control delirium in patients with COVID-19 infection. Recommendations for the use of these agents will therefore be based primarily on consideration of the challenges described above and indirect

**Depth of sedation**

1. Light sedation, defined as a Richmond Agitation Sedation Score (RASS) of 0 to -2 is an appropriate initial goal for depth of sedation in critically ill, mechanically ventilated adults with COVID-19 infection. A goal of light sedation decreases time to extubation.
2. A low threshold should exist to deepen sedation when any of the following conditions exist:
   a. The patient is at risk for unplanned device removal despite light sedation and appropriate use of restraints.
   b. Significant ventilator dys-synchrony exists with evidence of impaired gas-exchange despite light sedation.
   c. There is evidence of significant patient discomfort despite light sedation.
   d. Patients who require a high level of ventilator support following intubation may be less likely to tolerate an initial goal of light sedation.
3. Deep sedation (RASS -4 to -5) should be achieved prior to the use of neuromuscular blocking agents. The sedative infusion should subsequently not be weaned down while neuromuscular blockade is in use.

**Analgo-sedation**

1. The use of analgosedation is appropriate as an initial strategy in critically ill, mechanically ventilated patients with COVID-19 infection. Unrecognized pain is a frequent cause of agitation in mechanically ventilated patients, and a strategy of analgosedation may decrease time to extubation. This may include:
   a. Analgesia-first sedation where a potent opioid analgesic infusion such as Fentanyl is used before a sedative to reach the sedative goal
   b. Analgesia-based sedation where a high-dose infusion of an opioid analgesic such as Fentanyl is used instead of a sedative to reach the sedative goal.
2. Intravenous opioid agents preferred for analgo-sedation include Fentanyl and Hydromorphone. Consult with the clinical pharmacist for updates on drug shortages and medication availability.
3. Consider the use of scheduled enteral opioid agents such as Oxycodone to decrease consumption of intravenous opioids.
4. A low threshold should exist to escalate beyond analgosedation to the use of conventional sedative agents (such as Propofol, Dexmedetomidine or Benzodiazepines) when any of the following conditions exist:
   a. The patient is at risk for unplanned device removal despite the use of analgo-sedation and appropriate use of restraints.
   b. Significant ventilator dys-synchrony exists with evidence of impaired gas-exchange despite the use of analgo-sedation
c. There is evidence of significant patient discomfort despite the use of analgo-sedation.

d. Patients who require a high level of ventilator support following intubation may require the use of conventional sedative infusions (Propofol, Dexmedetomidine or Benzodiazepines) as part of the initial sedation strategy. 

Please note: Once a decision has been made to use conventional sedation (with agents such as propofol, benzodiazepines or dexmedetomidine) as the primary strategy, slowly wean down intravenous opioid agents as tolerated to minimize drug consumption and side effects of opioids.

**Choice of sedative agent**

1. Options for sedative infusions include propofol, midazolam, dexmedetomidine, ketamine and lorazepam. **Consult with the clinical pharmacist for updates on drug shortages and medication availability.**

2. Propofol is preferred as a first line agent for sedation in critically ill, mechanically ventilated adults with COVID-19 infection. Compared to benzodiazepine infusions, propofol may shorten time to light sedation and extubation.
   a. Anticipate hemodynamic instability and the need for vasopressor support. Consider transition to an alternate agent such as midazolam and/or ketamine in the presence of severe hemodynamic instability and vasopressor requirement, such as with septic shock.
   b. Transition to an alternate agent such as a benzodiazepine in the presence of significant hypertriglyceridemia (>750mg/dL) to minimize the risk of acute pancreatitis.[4] Anecdotal experience suggests that hypertriglyceridemia is common in patients with COVID-19 infections on a propofol infusion, including at lower rates of infusion.

3. A dexmedetomidine infusion is appropriate when the goal is light sedation, however, an alternate agent should be considered when deep sedation is required.

4. Midazolam may cause prolonged sedation if administered over a longer duration, particularly in the presence of hepatic or renal dysfunction.

5. Consider using scheduled high-dose enteral lorazepam when long-term sedation is required, to decrease consumption of intravenous agents.

6. A ketamine infusion may be considered either as an adjunct to other agents, or as an initial agent, particularly in the setting of severe hemodynamic instability with high vasopressor requirements or bronchospasm.

7. Transition to an alternate agent when adverse effects occur with the agent in use.

**Bolus dosing**

An order for bolus dosing should be entered for most sedative and analgesic agents at the time of initiation. Episodic agitation and discomfort requires the use of bolus doses from the medication infusion bag, particularly when using agents with slower onset, such as benzodiazepines.
Daily sedation interruption (DSI)

Daily sedation interruption (DSI) should be performed in conjunction with spontaneous breathing trials (SBT) in accordance with Michigan Medicine protocol, with due consideration of exclusions based on the required level of ventilator support.

A DSI is defined as a period of time, each day, during which a patient’s sedative medication is discontinued and patients can wake up and achieve arousal and/or alertness, defined by objective actions such as opening eyes in response to a voice, following simple commands, and/or having a Sedation-Agitation Scale (SAS) score of 4–7 or a RASS score of −1 to +1. A DSI may be performed in the absence of an SBT if clinically appropriate, however, this should be coordinated in advance between the provider and the bedside nurse.

Delirium

1. Patients should be assessed for the presence of delirium per Michigan Medicine protocol (UMHS Prevention, Detection and Management of Delirium Guidelines, 62-01-007) using a validated tool such as the Confusion Assessment Method for the ICU (CAM-ICU).
2. Pharmacological prophylaxis should not be used in patients without objective evidence of delirium.
3. A dexmedetomidine infusion is the preferred agent in critically ill COVID-19 patients with objective evidence of agitated delirium, to decrease the risk of unplanned device removal and optimize respiratory function. The use of a continuous infusion permits more consistent control of agitation and may decrease the frequency of required room entry by the bedside nurse.
4. The use of adjunctive agents such as Quetiapine, Olanzapine and Risperidone is appropriate, however, intermittent electrocardiograms (ECG) may be required to assess the QTc interval.
5. Multi-compartment nonpharmacological interventions are appropriate. These include strategies to reduce or shorten delirium (e.g., reorientation, cognitive stimulation, use of clocks); improve sleep (e.g., minimizing light and noise); improve wakefulness (i.e., reduced sedation); reduce immobility (e.g., early rehabilitation/mobilization); and reduce hearing and/or visual impairment (e.g., enable use of devices such as hearing aids or eye glasses).
NEUROMUSCULAR BLOCKADE

Neuromuscular blockade (NMB) has been studied as an adjunct to treatment of acute respiratory distress syndrome (ARDS) in multi-center randomized controlled trials.

In the ACURASYS trial (NEJM 2010), inclusion criteria included early, severe ARDS (< 48 hrs of P/F ratio < 150 on PEEP of at least 5, low tidal volume ventilation, and clinical diagnosis of ARDS). Pts were randomized to cisatracurium infusions (37.5 mg/hr for 48 hours) vs. placebo. ARDS Network ARMA protocol was used for mechanical ventilation. There was a significant decrease in 90-day mortality in the cisatracurium group (n =340, HR 0.68, 95% CI 0.48-0.98, p=0.04). Possible mechanisms of clinical benefit include a decrease in patient-ventilator asynchrony, a decrease in inflammation, and a decrease in oxygen consumption.

The more recent ROSE-PETAL trial (NEJM 2019) was modeled after ACURASYS but differed in that it emphasized lighter sedation targets in the control group as well as a higher PEEP/FiO2 table and conservative fluid management in both groups. Inclusion criteria were similar but specified a P/F ratio < 150 on PEEP of at least 8. Cisatracurium dosing was unchanged. After enrolling 1006 patients, the trial was stopped for futility with 90-day mortality rates of 42.5% and 42.8% in the intervention and control groups.

Based on these trial results, the current Michigan Medicine ARDS algorithm does not recommend routine use of NMB in ARDS but suggests consideration when there is evidence of persistent patient-ventilator asynchrony despite ventilator adjustments and routine sedation.

NMB is often employed simultaneously with prone positioning (> 80% of patients in both arms of the PROSEVA trial, NEJM 2013) as prone positioning has also been linked to decreased mortality in severe ARDS. It is not however necessary that all patients must have NMB in order to undergo proning.

Of note, both large trials of NMB have used a specific agent (cisatracurium) at a high hourly dose. It is unlikely that the benefits of NMB are limited to this agent or dosing scheme.

Train-of-four (TOF) monitoring is routinely used in the operating room to measure depth of, reversibility of, and recovery from NMB. In the ARDS patient in the ICU, the primary goal of neuromuscular blockade is reduction in patient-ventilator asynchrony as opposed to a specific TOF measurement. Selective TOF measurement after NMB has been discontinued can be used to confirm recovery of neuromuscular function and appropriateness of weaning concomitant sedation. During NMB, deep sedation is recommended to minimize the likelihood of patient awareness.

There will be no reliable spontaneous ventilation in a patient receiving NMB in the event of endotracheal tube dislodgement or ventilator malfunction; such situations demand immediate bag-mask ventilation and re-intubation if tube dislodgement and manual bag ventilation via endotracheal tube if ventilator malfunction.
Proposed MM COVID-19 ARDS Protocol for Neuromuscular Blockade (NMB)

- There is no indication for routine use of neuromuscular blockade in ARDS patients regardless of severity
- For patients demonstrating patient-ventilator asynchrony, NMB can be used to maintain oxygenation as well as facilitate lung-protective ventilation and prone positioning
- Goal to limit NMB to 48 hours or fewer
- Deep sedation is required for all patients receiving NMB; this corresponds to a RASS of -4 to -5 in patients prior to receiving NMB; such sedation must be continued during NMB as it is not possible to meaningfully measure RASS after NMB initiation
- If available, first-line neuromuscular blocker is cisatracurium
- The “ICU Neuromuscular Blocking Agents” order set should be used in MiChart which includes loading and infusion doses for cisatracurium, atracurium, and vecuronium
- Given high demand and shortages, consult with ICU pharmacy support regarding alternative agents (i.e. rocuronium, pancuronium) that may be given intermittently
- Q2H TOF monitoring not recommended
- Consider TOF check with cessation of NMB to confirm recovery; this is especially relevant if agents with less predictable pharmacokinetics than cisatracurium are employed
- Alternative ventilator (i.e. self-inflating bag) must be immediately available at all times
Strategies to address shortages of sedative, analgesic and neuromuscular blocking agents during the COVID-19 pandemic

Nationwide shortages of sedative, analgesic and neuromuscular blocking agents have been reported due to a large increase in demand during the COVID-19 pandemic.

1. Consider the use of intermittent dosing of longer-acting agents to minimize the need for agents with limited availability. For example, consider-
   a. Scheduled high-dose intermittent enteral Lorazepam to minimize the need for propofol or midazolam
   b. Scheduled enteral Oxycodone to minimize the need for intravenous fentanyl or hydromorphone
   c. Intermittent doses of IV Rocuronium, Vecuronium or Pancuronium to minimize the need for Cisatracurium.

2. Clinical pharmacists will provide notification to clinical teams of all known and anticipated shortages of these agents. Frequent communication between providers and the clinical pharmacist is essential.

3. When an agent is identified by the clinical pharmacist as being in shortage, an alternative agent should be preferentially used on the unit. For example, Hydromorphone should be used as the preferred agent on the unit when Fentanyl is in shortage.
REFERENCES


