Duke University School of Medicine
Department of Medicine
Division of Pulmonary, Allergy and Critical Care Medicine

SARS-CoV-2 Management Guidelines

INTRODUCTION

This document is meant to serve as internal guidance for the identification and management of patients ***admitted to Duke University Hospital*** with COVID-19 who progress to shock or respiratory failure. When possible, the recommendations made here are based on published literature specific to patients with COVID-19. When data specifically regarding COVID-19 patients is not available, the recommendations will be based on a synthesis of institutional guidelines from academic institutions that have experience taking care of large numbers of COVID-19 patients, as well as published guidelines from relevant national and international medical bodies (e.g. SCCM, CDC, WHO).

The following guidelines took into consideration previously published guidelines from the Society of Critical Care Medicine (SCCM) and Brigham and Women's Hospital (BWH). Some modifications were considered based on recently published clinical trials regarding COVID-19 specific therapies.

This serves as a living document and will change regularly as additional evidence, policies/guidelines, and clinical experience emerges. It is not intended to replace good clinical judgement personalized for each unique patient. This document is not intended to replace any information available on the Duke COVID-19 Intranet but to provide practical clinical guidance for providers.

Contact Dr. Anne Mathews (anne.mathews@dm.duke.edu) with any further suggestions regarding this document.

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GENERAL

Teamwork and morale are extremely important. At minimum, teams should participate in Tier 1 huddle with MDs, RNs, RT, and pharmacy. During this time recent system updates can be reviewed along with a global plan for the unit for the day as well as patients at high risk for certain issues (intubation, coding, etc.) and questions/concerns can also be addressed. Every team member should feel comfortable to openly participate.

A level playing field should exist across all parties in the unit when it comes to recognizing stress and overload. It is okay for anyone to call out anyone else as needing to take a break and step off the unit for a short time.

Every member of the ICU team should be familiar with the general framework of care for COVID patients as detailed on the Duke COVID-19 Intranet and this document. Additional cheat sheets/quick guides will be added as available.

Proper hand hygiene, doffing and donning of PPE are absolutely critical in every circumstance.

Please see the Duke COVID-19 intranet for additional guidance regarding PPE use, reuse and conservation.

Every COVID-19 patient who is admitted should have a code status and HCPOA discussion. Palliative care consult should be considered for patients with high risk of in-hospital mortality or disability. This includes patients over the age of 60 and significant chronic comorbidities such as cardiac disease, pulmonary disease, malignancy, or other significant comorbidities. There is little data about COVID-19 outcomes in medically complex populations in the US, but given evidence of prolonged respiratory failure, we can assume an increased mortality and morbidity.

COVID-19 TESTING AND GENERAL CONSIDERATIONS

Incubation periods

- Incubation period appears to be variable, however based on data from Wuhan, median incubation period was 4-5 days with an interquartile range of 2-7 days as measured from epidemiologically traced exposure to first fever. Additionally, 97% of infected patients who had fever developed fever within 11 days of exposure.

Symptoms

- Based on data from Diamond Princess cruise ship, where patients were comprehensively tested and screened for symptoms, approximately half were asymptomatic at the time of molecular diagnosis, but many developed symptoms after. Overall rate of truly asymptomatic infection appears to be about 20%, with half of the asymptomatic patients demonstrating radiographic abnormalities.
- Common clinical features
    - Fever 95-99%
    - Fatigue 70%
    - Cough 60%
    - Dyspnea 30%

- Myalgia 11-44%
- Loss of taste or smell (potential sign in early infection)

Common laboratory findings

- Lymphocytopenia (35-83%), elevated inflammatory markers (IL-6, ESR, CRP, LDH or ferritin), 38-86%, elevated transaminases 28-38%, and coagulation abnormalities are common.
- Respiratory viral co-infections have been reported in ~25% of cases.

Complications

- Median time to ARDS is 8-12 days after symptom onset
- Median time of onset of sepsis 9 days
- Cardiac complications have been reported in 10-33% of patients with variable time of onset
- AKI, secondary infection
- 5-10% will become critically ill

RNA Testing

- This section will evolve with both availabilities to testing and changes in pretest probability that will occur with increasing prevalence of SARS-CoV-2 within our population.
- Review of the most recent guidelines from Duke Infectious Disease on the the Duke COVID-19 Intranet.
  - NP swab for spontaneously breathing patients and intubated patients first. Repeat testing for intubated patients may include endotracheal aspirate (pending validation as of 4/11/2020) and bronchoalveolar lavage.
  - Bronchoscopy is not generally indicated for diagnosis of COVID-19. Because it is an aerosol generating procedure that poses risk to patients and staff, bronchoscopy has a limited role in diagnosis in COVID-19 and should only be considered in intubated patients if upper respiratory samples are negative and the results would significantly change clinical management.
- As number of cases increase, it may be helpful to consider any patient admitted with acute or acute-on-chronic hypoxic respiratory failure, or fever without a clear non-pulmonary source, as a PUI.
- For high-risk patients, in particular those where an alternative diagnosis is note available who had negative testing, consider ID consultation or repeat testing. There is an algorithm from Duke Infectious Disease on the Duke COVID-19 Intranet offering guidance in these scenarios. Please be careful to not let your inquiry to find an unlikely COVID-19 diagnosis delay diagnosis or treatment of a more likely diagnosis!!!

DIAGNOSTIC INVESTIGATIONS

- On Admission:
  - CBC with differential, CMP or BMP with LFTs, Magnesium, hsTnT & CPK, NT-proBNP, procalcitonin (not available at DUH), CRP, ESR, LDH, coagulation profile (PT/INR and PTT), d-dimer, fibrinogen and ferritin can be considered on COVID-19 positive patients or high risk PUI particularly those who are critically ill.
  - Baseline EKG, Review QTc.
  - TTE should not be ordered routinely in all patients. Consider TTE particularly in patients with concern for new onset heart failure, arrhythmia, shock, rising troponin, dynamic EKG changes or abnormal POCUS if it will change management of the patient.

- Urinalysis and random urine studies, (protein, and microalbumin).
- Sputum or tracheal aspirate cultures, eRVP, blood cultures, and urine cultures/legionella & strep antigens if clinically indicated or if critically ill.

- Serial Labs:
  - Consider daily: CBC with differential, BMP or CMP, Magnesium. ***Can be QoD in stable floor patients***
  - Consider QoD day or Q3days: CRP, NT-proBNP, LDH, d-dimer, DIC panel and/or ferritin in particular if a patient is not clinically improving or worsening. Consider triglycerides Q2 or Q3 days if receiving propofol.
- Procalcitonin (Not available at DUH):
  - Recommendation: The value of procalcitonin is unclear in COVID-19 infected patients, and should be used with caution. There is suggestion that escalating levels of procalcitonin may indicate worse prognosis or bacterial superinfection in these patients, and the clinical context should be considered.

RADIOLOGY

General considerations

- In order to both use resources efficiently, limit patient transport, and limit exposure of equipment and radiology personnel to infection, radiological studies should only be ordered if they will change management. This is a good practice in general for medical care. An excellent resource regarding imaging findings from COVID-19 is available on Radiopaedia.

Chest x-ray

- CXR is neither sensitive nor specific for SARS-CoV-2. The chest xray may be normal in mild or early disease. The chest xray may support an additional diagnosis such as bacterial super infection, pneumothorax etc.
- Do not order daily chest x rays unless there's a specific indication. Routine monitoring of ARDS with CXR does not add value to clinical assessment and oxygen requirements.
- The most common findings are peripheral, bilateral lower lobe predominant infiltrates. Effusions have been reported to be uncommon.

Chest CT

- CT chest used primarily to rule out other superimposed processes, such as pulmonary embolisms, aortic dissection, etc.
- CT may have a limited use to detect multifocal ground glass opacities in high-risk patients with a negative initial COVID-19 PCR but is not necessary nor advised.
- Most common findings are ground-glass, crazy paving, and/or consolidative opacities usually bilateral, peripheral, and basal in distribution.
- Radiology at DUH has specific protocols for most studies. Please contact Duke radiology for further information and be sure they are aware the patient is a PUI prior to transport to radiology.

Point of Care Ultrasound

- Requires and experienced provider to perform and interpret. For the novice may be most useful to identify pneumothorax and pleural effusion. Experience providers have noted focal or diffuse B lines with sparing of uninvolved areas, irregular thickened pleural line with

"scattered discontinuities", subpleural consolidations, alveolar consolidations with air bronchograms

GUIDANCE FOR SPECIFIC AREAS CARING FOR COVID-19 POSITIVE PATIENTS & PUIs

- DUH has outlined recommended PPE for healthcare workers to wear and preferred rooms for patients with known or suspected COVID-19 infection. Specific clinical guidance is provided for inpatient wards, ED (high acuity patient), ED (outpatient and low acuity patient), procedural areas, and outpatient/inpatient radiology departments.
- Guidelines can be found under documents section on DUHS COVID-19 resource page. Duke COVID-19 Intranet

ADMISSION TO ICU

- COVID-19 patient population has a high rate of respiratory failure requiring mechanical ventilation, as well as significant rate of AKI, and shock, particularly cardiogenic shock due to new cardiomyopathy.
- Any provider concern for their patient should be taken seriously by the ICU/RRT and evaluated accordingly.
- Recommend ICU transfer for any patient that has developed significant dyspnea/tachypnea with concerning radiographic abnormalities ***even in the absence of hypoxemia*** given concern for rapid deterioration. This should involve a discussion with the primary team and ICU consultant to discuss early transfer to the ICU for closer monitoring.
- Recommend ICU transfer for any patient with progressive hypoxic respiratory failure worsening despite 6-8 L NC.
- Increase in oxygen requirements to beyond 6-8L NC should lead to consideration of diuresis if clinical exam permits. Avoid severe hypovolemia.
- Any patient in respiratory distress should lead provider to consider anesthesia airway consultation at 115 for assessment. Stable patients may transfer without intubation. ***MICU consultation is available for discussion at **919-385-1320** or **970-3801**.***
- Any evidence of shock.
- Any patient with evidence of new cardiomyopathy and either atrial arrhythmias unresponsive to medical management or any new ventricular arrhythmia.

RESPIRATORY SUPPORT

Prevalence of Hypoxemia

- True prevalence is still unclear, but it appears that up to 10-50% of hospitalized patients with COVID-19 will develop hypoxemic respiratory failure requiring supplemental oxygen. Additionally, it has been reported that 3-17% develop ARDS.

Management of COVID-19 hypoxia on the floor

- Oxygen should be titrated to a goal SpO_2 of 92-96%.
- Given prevalence of both primary viral myocarditis and worsening of the patient's underlying cardiomyopathies, would consider a trial of diuresis in any hypoxic COVID-19 patient.

High flow oxygen

- There is significant previous evidence that heated humidified high-flow nasal cannula (HHHFNC) use reduces rates of intubation in ARDS and reduces mortality compared to NIV and facemask use.
- There appears to be little evidence that at moderate flow rates (40LPM or less) HHHFNC causes increased aerosolization of virus particles when cannulas are appropriately fitted.
- HHHFNC should be offered if available to patients who cannot maintain SpO2>90% (or >88% for patients with chronic hypoxemia or COPD using conventional oxygen therapy at >8LPM).
- HHHFNC may be titrated up to 60%/40L. FiO2 ≥60% or respiratory distress should prompt reassessment of the patient and a conversation regarding the appropriateness of intubation versus further close clinical monitoring.
- Avoid titrating HHHFNC to flow rates >40LPM as this may increase aerosolization of virus particles.
- HHHFNC should prompt transfer to an ICU. Patients receiving HHHFNC require airborne/contact isolation precautions. If available, negative pressure rooms and/or HEPA Filter can be utilized but are not required.
- Additional information is available that the Duke COVID-19 Intranet under "Guidance for Procedural Areas for Suspected or Confirmed COVID-19 patients."

Other oxygen modalities

- Nasal cannula (NC): Consider Humidified nasal cannula (NC) or high-flow nasal cannula (HFNC) 1 to 6 LPM for target SpO2 92-96%. If a patient requires > 6-8 LPM via NC or HFNC, initiate dry Venturi mask (non-humidified to reduce aerosolization risk).
- Venturi mask: Start Venturi mask at 8 LPM and FiO2 about 35%. Up-titrate FiO2 to goal SpO2 of 92-96% (not exceeding FiO2 60%). Consider ICU transfer in this scenario.
- Avoid using a Face Tent or Trach Collar for oxygen delivery to minimize aerosolization risk. If patients with tracheostomy require supplemental oxygen please consult RT and review their **COVID Instructions for Therapeutic Delivery to COVID PUI and COVID guidelines.**
- Non-rebreather mask (NRB): If a non-rebreather mask is necessary due to hypoxemia reassess the patient as well as the need for intubation
- If a surgical mask is placed over any oxygen delivery mask the exhalation ports should be covered but must not be obstructed.

Non-invasive positive-pressure ventilation (NIPPV)

- There is evidence that NIPPV use in ARDS may result in increased mortality. It certainly has not been shown to reduce intubation rates in PNA, except in patients with severe obstructive lung disease. Furthermore, NIPPV was shown to result in increased transmission rate to healthcare workers in SARS-CoV patients.
- NIPPV should **NOT** be offered to COVID-19 positive or suspected patients ***except*** if they have a pre-existing condition that necessitates daily NIPPV use such as central apnea or chronic hypercarbic respiratory failure and fail other modalities as detailed below.
- If you are considering using NIPPV for acute respiratory failure in a COVID-19 patient, please consult the ICU and transfer.
- Patients with OSA who do not have concurrent hypercarbia should trial supplemental oxygen instead.

- For patients who require the use of NIPPV according to above criteria, they should use full face masks with hospital equipment and be treated as if at increased risk of aerosol generation with an emphasis on appropriate special airborne/contact precautions. Negative pressure room and/or HEPA filter should be utilized as available.

Proning Spontaneously Breathing Patients Prior to Intubation

- For patients with hypoxemia, there are many physiologic benefits to the prone, as opposed to the supine position.
- These include better matching of pulmonary perfusion to ventilation, better recruitment of dependent areas of the lung and improved arterial oxygenation. In addition, there is evidence that the prone position results in a more homogenous distribution of stresses in the lung and thus may prevent patients with hypoxemia from developing frank respiratory failure.
- For these reasons, patients admitted with hypoxemia should be encouraged to adopt the prone position where practical and prone positioning may be used as a rescue therapy in patients with escalating oxygen needs.

Contraindications:

- Spinal instability
- Facial or pelvic fractures
- Open chest or unstable chest wall
- Relative contraindications: delirium, confusion, inability to independently change position, recent nausea or vomiting, advanced pregnancy

Equipment:

- Pillow
- Supplemental oxygen, as needed
- Foam Dressings to protect pressure points (if indicated)
- Continuous O2 monitor

Prone position as rescue therapy

- A patient who develops increasing oxygen need (an increase of > 2L/min in the amount of oxygen needed to maintain SpO_2 > 90%) is at risk for respiratory failure.
- If the patient is in the supine position, and it is safe to do so, place the patient in the prone position.
- Work with the medical team to notify nursing supervisors and medical senior of worsening hypoxemia.
- If patient stabilizes (decreased RR, increased SpO_2, decreased L/min O2), reassess with nursing supervisors and medical senior provider after 1 hour, consider transfer to ICU if monitoring is needed.

MANAGEMENT OF OBSTRUCTIVE LUNG DISEASE

- Use of nebulizers appears to increase risk of viral aerosolization. Therefore, all COVID-19 confirmed or suspected patients should receive a trial MDI therapy or a Respimat first.

- Nebulizers may be used if MDIs are not effective and only following consultation/discussion with respiratory therapy. Nebulizers will require airborne precautions in this case.
- Filtered nebulizer delivery is available on a limited basis.
- Avoid standing MDI/nebulizer therapy when PRN is adequate.
- Patients who are on mechanical ventilation should receive nebulized medications if closed circuit system is available.
- For patients with severe obstructive lung disease, some tips for optimizing medical therapy in the absence of nebulizers:
    - Use MDI meds via spacer only
    - Can use MDI albuterol, ipratropium at same intervals as nebulizers (q6h)
    - Symbicort is on the hospital formulary and provides ICS/LABA that can be administered via spacer
- For patients with pre-existing COPD or severe asthma, early and aggressive use of systemic corticosteroids is encouraged given limitations in use of nebulized medications. Steroids would not be considered contraindicated in this case even in a COVID-19 positive patient.

AIRWAY CLEARANCE

- There are reports from other academic centers that patients with COVID-19 pneumonia appear to have disproportionately copious secretions, even in the absence of bacterial pneumonia. There are anecdotal attempts at off-label use of a number of therapies to mitigate this.
    - Dornase is not recommended in non-CF patients given poor outcomes, including increased hospitalizations in non-CF bronchiectasis patients and limited efficacy.
    - Mucomyst is not recommended due to frequency of administration.
    - Hypertonic Saline can be considered
    - For COVID-19 patients, self-administered therapies are preferred over those which require RT, RN, or MD to administer.
    - Manual percussion may be performed using appropriate PPE. Consult RT to discuss.
    - Acapella device, other flutter valve, or IPV should only be provided under appropriate PPE with RT guidance.

ACUTE LUNG INJURY/ARDS & REFRACTORY HYPOXEMIA:

Acute Respiratory Distress Syndrome

- ARDS is a clinical syndrome defined by acute onset hypoxemia (PaO2:FiO2 ratio < 300) and bilateral pulmonary opacities not fully explained by cardiac failure or volume overload.
- The Berlin definition groups patients with ARDS into categories of mild, moderate, and severe on the basis of the ratio of arterial blood partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO 2) (P:F ratio).
    - mild: 200 < P:F ratio ≤ 300
    - moderate: 100 < P:F ratio ≤ 200
    - severe: P:F ratio ≤ 100
- Histological examination of patients with COVID-19 shows bilateral diffuse alveolar damage with cellular fibromyxoid exudates, desquamation of pneumocytes, pulmonary edema, and hyaline membrane formation.
- The median time to development of ARDS is 8-12 days. Reported time to mechanical ventilation is 10.5-14.5 days in COVID-19 positive patients.

Intubation

- Emergent intubations should be avoided if at all possible.
- Intubation should be performed by the most qualified practitioner with adequate PPE.
- Anesthesia will perform intubations and can be consulted at 115. Make the team aware this is a COVID-19 PUI or confirmed patient.
- A protocol for intubation of patients in the ICU has been completed and should be made available outside of all ICU rooms.
- When anesthesia is called, please prepare drugs/supplies as soon as possible per protocol. Assume it will take at least 30 minutes for anesthesia to prepare for intubation.
- Have a bag mask valve (BVM) with viral filter prepared.

Ventilator Management

*****Remember, mechanical ventilation is not curative. It only buys time and potentially harm the lungs and the patient!*****

Determine the phenotype of ARDS that the patient has. **Follow standard respiratory care protocol for ventilation management initially in ALL patients**:

- Use low PEEP Table if chest imaging is not severely opacified and/or driving pressure <15 cmH_2O Hand/or lung compliance is > 40 mL/cmH_2O. This would be more like management of mild ARDS with P:F > 200. Some have described this as a hypoinflammatory ARDS for COVID-19 patients. Be aware of the risks for possible over distension in these patients lungs with higher PEEP.
    - *Driving Pressure or ΔP = Plateau Pressure – PEEP*
    - *Lung Compliance = Delivered breath volume/(Plateau Pressure-PEEP) or ΔV/ΔP*

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP ($cm H_2O$)	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

- Use high PEEP settings if severely opacified lungs on chest imaging and/or driving pressure ≥15 cmH_2O and/or lung compliance is < 40 mL/cmH_2O. This would be more like moderate to sever ARDS with P:F ≤ 200. Some have described this as hyperinflammatory ARDS for COVID-19 patients.

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5-0.8	0.8	0.9	1.0
PEEP ($cm H_2O$)	5	8	10	12	14	14	16	16	18	20	22	22	22-24

- PEEP flexibility between these two extremes allowable based on clinical judgment of rounding team, RT and consultants being aware of the risk for over distension and alveolar derecruitment. A stress index measurement may be considered.

- Practice lung protective ventilation
    - Tidal volume (Vt): A tidal volume around 4-8 mL/kg of **ideal body weight** should be used in all mechanically ventilated patients. See ardsnet.org

- Respiratory rate (RR): To control potentially deleterious increases in $PaCO_2$ (which raise pulmonary arterial pressure), a relatively high respiratory rate of between 25 and 30 cycles/min should be adopted first. Do not excide 35 cycles/min. Monitor patients for hyperinflation/air trapping with assistance of RT.
- Plateau pressure: Maintain a plateau pressure < 30 cm H_2O; this may be liberalized in some cases such as obesity.
- Driving pressure: We recommend at driving pressure under 15 cm H_2O when possible.
- Positive end-expiratory pressure (PEEP): For mechanically ventilated patients with COVID-19 and moderate to severe ARDS, we suggest using a higher PEEP strategy, over a lower PEEP strategy from the ARDS Network PEEP tables

- Oxygenation goal is PaO_2 55-80 mmHg or SpO_2 90-95%.
- Permissive hypercapnia is acceptable with a limit of pH 7.15; consider ECMO if unable to meet lung protective goals.

Refractory Hypoxemia

- Refractory hypoxemia = P:F ratio < 100-150 despite lung protective ventilation
  - P:F ratio = partial pressure of arterial oxygen/FiO2
  - *If the below interventions are not helpful or with any concerns, consider a MICU/pulmonary consultation.*
- Neuromuscular blockade
  - A neuromuscular blocking agent may be considered in ARDS patients with a PaO2/FiO2 ratio < 150 mmHg if ventilator dyssynchrony persists despite above management and a trial of deep sedation.
  - Ensure the patient is adequately sedated prior to paralysis.
  - Consider intermittent neuromuscular blockade with boluses before infusions.
  - A protocol for a continuous infusion of cisatricurium in ARDS is available in Maestro.
  - If a patient requires multiple boluses of neuromuscular blocker, consider continuous infusion early (within 48 h after the start of ARDS), for no more than 48 h, with at least daily evaluation.
  - Following paralysis, consider measuring a stress index with assistance of RT or intensivist to titrate PEEP.

- Prone positioning
  - Consider reviewing indications and contraindications for proning if P:F remains < 150 for 12 hours or more.
  - A video is available for review on the Duke MICU website to demonstrate how to do this and/or the MICU charge nurse can be contacted for assistance. Videos are available under the clinical care section of the Duke MICU website.
  - DUH proning protocol is also available via the Critical Care Box or contact your unit medical director and nurse manager.
  - Sessions of at least 16 consecutive hours should be performed.

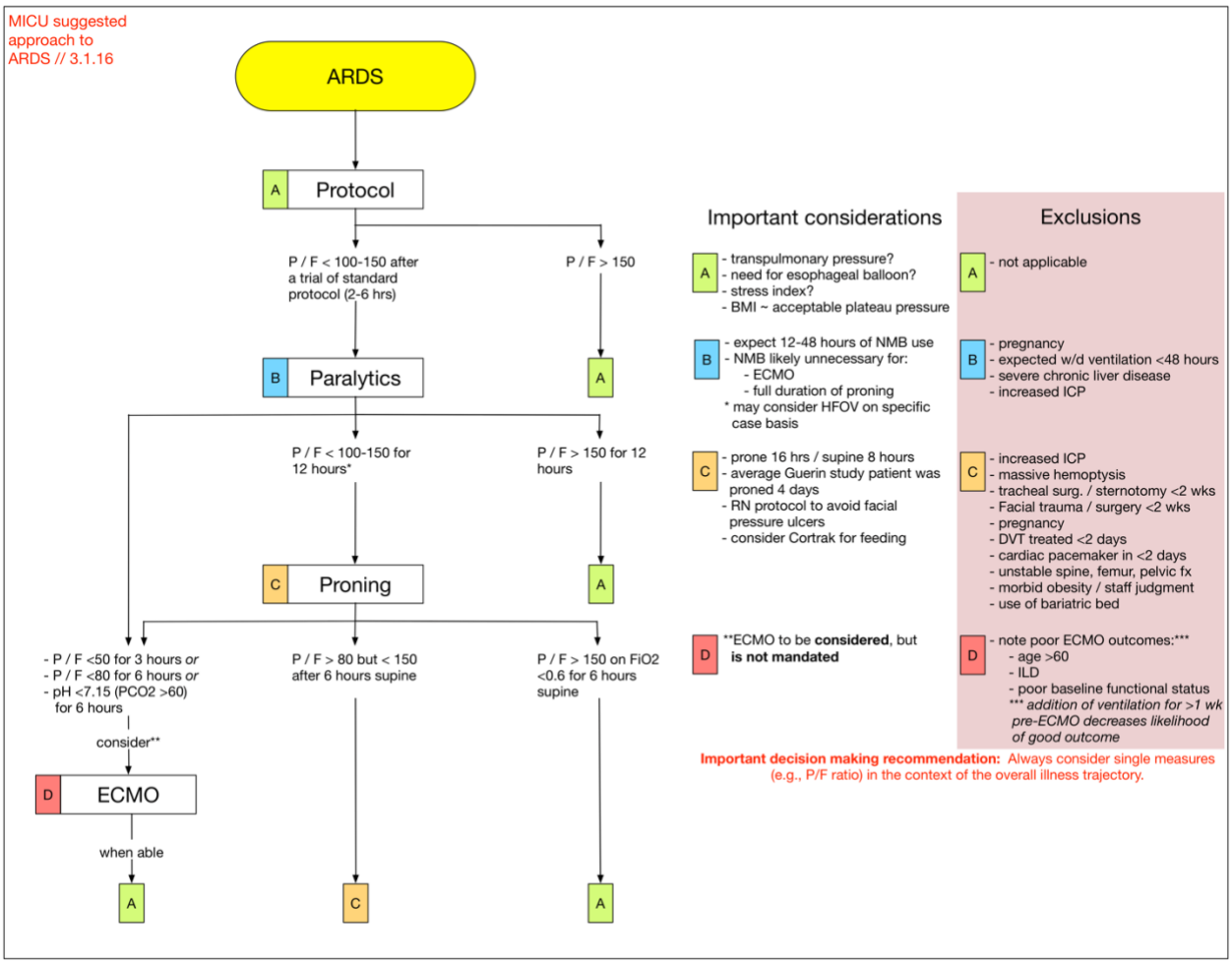
- Inhaled Nitric Oxide (iNO)
  - There has been much debate around the use of inhaled NO for COVID-19 related refractory hypoxemia and ARDS.
  - Pulmonary vasodilators have not been shown to improve mortality in ARDS.

- Consider iNO with severe refractory hypoxemia and/or right heart failure on a case by case basis. At this point, we ***do not recommend*** routine use and would suggest a trial of proning first. There is a strong mortality benefit for proning in ARDS, which is not present for iNO.
- If iNO is initiated, we recommend weaning off if no improvement in oxygenation after 2 hours for ARDS, or hemodynamics in 6 hours for RV failure.

Extracorporeal Membrane Oxygenation (ECMO)

- Consider ECMO for the following
  - If P:F < 50 for 3 hours
  - If P:F < 80 for 6 hours
  - If pH < 7.15 ($PaCO_2$ > 60mmHg) for 6 hours complicated by hemodynamic instability
- Consider interventions such as paralysis, proning, etc. as described above prior to initiation of ECMO.
- DO NOT contact 115 or 970-ECMO to initiate ECMO for COVID-19 patients.
- Consult the MICU for ECMO COVID-19 consults. Cases will be reviewed in a multidisciplinary fashion.
- Patients with suspected or confirmed COVID-19 MUST be located in MICU/CTICU or PICU/PCICU for ECMO consideration and cannulation.
- ECPR cannot be supported in COVID-19 rule-out or confirmed cases.

A standard approach that we have used over the years to manage ARDS is detailed below. Please note it has not been modified entirely for COVID-19 patients yet.



Fluid Management in ARDS

- For mechanically ventilated adults with COVID-19 and ARDS, we suggest using a conservative fluid strategy over a liberal fluid strategy.
- "Dry lungs are happy lungs"
- Consider a trial of diuresis if patient not in shock or with prerenal acute renal failure.
  Diuresing critical ill patients requires the team to be attentive and deliberate.

Sedation Management

- Target sedation: Initially target RASS -2 to -3 until clinically stable post intubation but would target RASS 0 to -2 as tolerated using PAD protocol available in Maestro preferable 0 to -1. RASS Calculator. Excessive sedation prolongs duration of mechanical ventilation.
- Maintain deep sedation immediately post-intubation and while paralyzed (assume 60 minutes for Rocuronium, 10 minutes for succinylcholine)
- Preferred initial sedation regimen:
  - Fentanyl or Hydromorphone (boluses +/- infusion) + Propofol: optimize analgesia first while decreasing sedative requirements as tolerated
  - Measure triglycerides on ICU admission day (for baseline) and then every third day on Propofol or earlier if other reasons for hypertriglyceridemia.
  - Discuss sedation options with pharmacist if unable to continue Propofol

- Consider transition to our **PAD protocol** when patient is stable to allow sedation to be weaned in a controlled manner. In this setting, target a RASS goal of 0 to -1.
- Excessive sedation will prolong the need for mechanical duration, ICU length of stay, and nosocomial infections.
- ***Special Considerations*** – For patients with alcohol withdrawal, would consider lorazepam and/or dexmedetomidine if unable to use Propofol. However, you should discuss options with pharmacist if concerns.
- **The PAD protocol is NOT intended for the following populations:** neuromuscular blockade, oscillation ventilation, targeted temperature management, refractory intracranial hypertension, status epilepticus, severe alcohol withdrawal or any other indication where deep sedation may be warranted as determined by provider.
- Haldol is preferred for hyperactive delirium for patients without history of QTc prolongation or malignant arrhythmia.

Extubation and Liberation from the Ventilator

- Readiness for extubation should follow standard practice of performing SBT/SAT per concurrently if patient qualifies per DUH protocol.
- Patients who pass their SBT should be discussed between MD, RT, and RN with plan for decision to extubate no greater than 2 hours after onset of SBT.

RENAL MANAGEMENT

- The overall strategy is focused on keeping patients as appropriately "dry" as possible. Hypovolemia may however lead to shock, acute renal failure, and worsening VQ mismatch exacerbated by positive pressure ventilation.
- Given concerns for cardiac/arrhythmia issues, we recommend robust electrolyte repletion (K>4.0, Mg >2.0).
- Strict I/Os with all cases
- Estimates for RRT range from 1 to 5% of hospitalized patients. Among critically ill patients, need for CRRT ranges from 5 to 23%
- Indications for dialysis in COVID-19 patients are the same as the indications for all patients.

MANAGEMENT OF SHOCK

The reported prevalence of shock in COVID-19 patients is variable but appears to be a major cause of death (40-50% of cases) and has been linked with both secondary infection and fulminant myocarditis. Considering profound hypoxemia and ARDS, as well as prevalence of cardiomyopathy, we recommend the following strategies based on SCCM guidelines.

- Conservative fluid management. Recommend assessment of intravascular volume using ultrasonography and/or pulse pressure variation, straight leg raise.
- Obtain dynamic measures of perfusion using capillary refill, lactate clearance, and ScVO2
- Use norepinephrine as first line vasoactive
- Use vasopressin or epinephrine as second-line agents
- Add dobutamine for management of poor forward flow in patients with cardiomyopathy
- Add stress dose steroids for patients that require a second-line vasopressor or have a history of adrenal suppression or chronic systemic steroid use. Wean aggressively as soon as able when patient hemodynamically improved.

- A cardiogenic shock team or the CCU is available for consultation via the Duke Paging Website for assistance of cardiogenic shock.
- Advanced mechanical support will require transfer to MICU or CTICU in COVID-19 patients and will require discussion with this service as well.

TABLE: CLASSIFICATION OF SHOCK

Exam findings	**CVP** JVP (RH preload)	**PCWP** - (LH preload)	**CO** - (pump function)	**SVR** "cool" or "warm" (CO distribution)	**SVO_2** - (tissue O_2 use)
Hypovolemic	↓↓	↓↓	↓	↑	↓
Cardiogenic					
↓ LVEF	↑	↑	↓↓	↑	↓
RV infarct	↑↑	nml –↑	↓↓	↑	↓
Obstructive					
PE	↑↑	nml–↓	↓↓	↑	↓
Tamponade	↑↑	↑↑	↓	↑	↓
Distributive	nml– ↓	nml–↓	↑↑	↓	↑

RH = right heart; LH = left heart; CVP = central venous pressure; PWCP = pulmonary capillary wedge pressure; CO = cardiac output; SVR = systemic vascular resistance; SVO_2 = mixed venous saturation of oxygenation

Adapted from Kumar A, et al. Circulatory shock. In: Parillo JE & Dellinger P, eds. *Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 4th Edition.* Philadelphia, PA. Elsevier Saunders. p. 299-324.e9.

CYTOKINE ACTIVATION SYNDROME

- A subgroup of patients with severe COVID-19 may have cytokine activation syndrome and secondary HLH characterized by rapid progression to ARDS, shock, and multiorgan failure.
- CBC with diff, PT/INR, PTT, fibrinogen, d-dimer, ferritin, liver function test, triglycerides, c-reactive protein (CRP) should be ordered for evaluation.
- An HScore (MDcalc online calculator) may be helpful in estimating the probability of secondary HLH in these patients
- Expert consultation with ID or Hematology should be considered in these cases.

CARDIOVASCULAR COMPLICATIONS AND MANAGEMENT

General considerations:

- Cardiovascular complications, including cardiac injury, worsening of pre-existing cardiovascular disease, cardiomyopathy/heart failure, and arrhythmias, seem to be common in patients with COVID-19 infection. The prevalence seems to be varied but has been reported to occur in 10-33%.
- Development of myocarditis or cardiomyopathy can be rapid, fulminant, and can occur at any stage in the disease.
- CHF with pulmonary edema can greatly contribute to worsening hypoxic respiratory failure.

Initial screening and baseline testing

- All COVID-19 *suspected* patients should have a baseline EKG, TnI, CKMB.

- All COVID-19 *confirmed* patients should consider a baseline TTE in particular if previous history of cardiac comorbidities, supportive labs, abnormal POCUS, or with any significant unexplained hemodynamic change.

Daily management goals

- Strict I/O and daily weights for all COVID-19 patients.
- "Dry lungs are happy lungs" – Diurese patients with ALI/ARDS as tolerated.
- When managed on the floor, we recommend considering telemetry monitoring for COVID-19 patients. This need should be reviewed daily by the care team. Given increased incidence of malignant arrhythmias and unexpected codes in this patient population, increased use of telemetry may help mitigate these risks.
- For confirmed or suspected COVID-19 patients with clinical concern for shock, or evidence of undifferentiated shock, or pre-existing history of cardiomyopathy and/or arrhythmia, we recommend telemetry monitoring.
- For patients with normal renal function, daily comprehensive electrolyte assessment should include maintaining K>4.0, Mg>2.0. For patients that are being diuresed, electrolytes should be checked at q12h or more frequently.

ICU management

- All critically COVID-19 ICU patients should have central access and baseline ScVO2 measurements, as well as arterial line placed for ongoing invasive monitoring at least initially. The need to maintain this, as well as, any invasive device should be evaluated at least daily.
- Any evidence of development of shock should include at a minimum repeat ScVO2 measurement, POCUS and physical exam. If there is any concern for change in systolic function, repeat formal TTE should be considered if it will change management.
    - Norepinephrine should be used as first-line vasopressor.
    - In patients with new systolic dysfunction that contributes to shock development, dobutamine should be preferable to dopamine for inotropic support.
- ALL ICU patients have better outcomes with the utilizations of standard protocols and checklists. We recommend utilization of the FASTHUGMBID acronym as a way to assure quality measures should as nutrition, DVT prophylaxis and delirium management are maintained.
- Additionally, ICU patients do better when rounds are completed in a multidisciplinary fashion and line of communication are clear. Make every effort to have the patient's bedside nurse, RT and pharmacy available when possible.

HEMATOLOGIC COMPLICATIONS AND MANAGEMENT **Pending**

NEUROLOGIC COMPLICATIONS AND MANAGEMENT

Introduction

- The incidence of neurological manifestation of COVID-19 is currently unknown however. studies out of Wuhan, China have shown that they are common. The most common of which is headache (1). Other serious presentations have included impaired consciousness/coma, stroke, seizures, and encephalopathy (1).

Cerebrovascular Accident

- In patient with severe COVID-19 infections ischemic strokes have been reported in about 5% of patient and 1% in patient with non-severe infections (1). Older patients with cardiovascular risk factors are at a higher risk (2).
- Activate CODE STROKE. Single team member, doning PPE, should perform focused H&P including NIHSS. CT head without contrast should be performed and reviewed by Neurology. While patient is still in CT scanner, CTA and CT perfusion should be considered to minimize contamination events and expediate care. If ischemic stroke, Neurology will decide upon tPA and/or mechanical thrombectomy.
- Ischemic stroke patients may be considered for Step-Down status if they do NOT: receive tPA, undergo thrombectomy, have AMS, cerebellar involvement, or a large hemispheric stroke. All others should be considered for NICU admission. Low risk patients should undergo q4h neuro assessments. Neurology will determine need for repeat CT head or MRI brain, but they must be informed immediately for change in neuro status. Patients who undergo mechanical thrombectomy should be admitted to Neuro ICU as soon as possible. The patient should stay intubated after intervention. Extubation should occur in ICU. Neuro assessments following thrombectomy should occur q1h x 6 hours, q2h x 6 hours, followed by q4 hours. Alters may occur for patient acuity. Lipid panel, HgA1c, and thyroid studies should be ordered with initial labs. Neurology will determine need for TTE with bubble or Carotid Duplex US.
- The NICU Attending (970-0842) should be called for all patients found to have an ICH. Typical systolic blood pressure (SBP) parameters are <140 for the first 6 hours after an ICH. If patient is stable can be liberalized to <160. Repeat imaging if neuro status changes or if needed to determine intervention. Neurosurgery to be called at discretion of NICU.
- Early intubation should be considered in any patient with a CVA and Glasgow Coma Scale <7. If sedation cannot be safely weaned (such as for respiratory compromise), hourly pupil checks should occur.

Convulsive Seizures

- Metabolic and non-COVID-19 infectious pertubations should be evaluated and corrected. Toxidromes should be assessed for. For acute generalized tonic clonic seizures or convulsive status epilepticus follow the standard protocol included below. Neurology should be consulted.

Electroencephalograph and Non-Convulsive Status Epilepticus

- In patients being RULED OUT for COVID-19 that the ordering team feels that the EEG cannot wait for COVID-19 test results or if the patient tests positive, the EEG fellow (adult or pediatric) will screen the case and discuss the necessity of doing the EEG with the ordering team as well as the EEG attending. A prolonged EEG should only be performed if absolutely necessary. In patients POSITIVE for COVID-19, please discuss with EEG fellow to determine necessity of study. If deemed necessary, EEG lab to follow established protocol.

Meningitis & Encephalitis

- Metabolic and toxic etiologies should be considered. Only perform lumbar puncture if necessary to change management. Otherwise, treat empirically.

References

1. Mao L, Wang M, Chen S, et al. Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study. medRxiv 2020).
2. Li Y, Wang M, Zhou Y, et al. Acute cerebrovascular disease following COVID-19: A single, retrospective, observational study. The Lancet 2020

LINES AND ACCESS

General considerations

- Duration of ICU stay appears to be longer on average than other causes of ARDS
- Anyone admitted with ARDS and/or shock who is COVID-19 positive or PUI should have an arterial and central line placed on arrival to the ICU
- A central line is preferred to a PICC in this case.
- The needs for all invasive devices should be evaluated at least daily and removed when no longer necessary.

Central lines

- Left IJ is preferred line site in order to preserve Right IJ for consideration of RRT or ECMO

Arterial lines

- Perform Allen testing for radial arterial lines considering lines will likely be in for an extended period
- Avoid very distal radial arterial lines which will be affected by wrist positioning
- In patients with significant soft tissue edema or high BMIs, consider femoral or axillary arterial lines using 5F micropuncture
- Avoid brachial arterial lines given prolonged line dwell time increases risk of thrombosis

INTENSIVE CARE UNIT CODE PROCESS

- *Please note that this is different than the process for the RRT/Floor teams given differences in resources and facilities.*

MICU Code Blue for COVID (+) and PUI

Goals: Excellent patient care, minimize exposure and PPE use

In-Room Team

All members of the team who are ACLS certified may be able to run code. MD/RT may intubate.

1. RN #1 (primary RN)
2. RN #2
3. MD/PA
4. RT

Support staff outside of room:

1. RN code manager: Positioned outside of anteroom at door. Ensures each code team member has appropriate materials before entering patient room. Control traffic and noise outside of room.
2. Time Keeper/Recorder: Positioned at window. Knocks on window every 2 minutes for code team. Records if able.

Gray bucket medications/materials

- 3 epinephrine abbojects
- 2 sodium bicarbonate
- 1 calcium chloride
- 3-5 Flushes

Additional Notes

- No apneic bagging to minimize risk of aerosolization of virus.
- Oxygen must be removed with any defibrillation.
- Plastic sheet/poncho must be removed with any defibrillation.
- Alternative scenario:
  - Patient already intubated → leave patient on ventilator during code

Procedure

Step	Actions by Code Blue Team	Actions by Support Staff	Materials
Step 1. Code Blue called, emergency assistance requested		Position code cart outside of room (NOT in anteroom)	
Step 2**. RN #1** on-site dons PPE and enters patient room	**RN #1:** ○ Bring backboard and stool *if able* ○ Place mask + towel over pts face ○ Proceed to chest compression only CPR	**RN code manager:** ○ Assist with donning RN **#1** ○ Gather defibrillator, gray medication bucket and contents of bucket	**RN #1:** stool + backboard *if able*
Step 3. **RN #2** dons PPE and enters patient room	**RN #2:** ○ Bring in defibrillator and gray medication bucket ○ Take over chest compressions **RN #1** ○ Attach defibrillator ○ Prepare EPI	**RN code manager:** ○ Assist with donning **RN #2** ○ Ensure **RN #2** has materials	**RN #2:** ○ Defibrillator + pads ○ Gray medication bucket
Step 4. **MD** and **RT** don PPE and enter room	**MD or RT** ○ Bring in intubation materials ○ Set up materials inside room ○ No apneic ventilation ○ Defibrillate under MD order if shockable rhythm immediately	**RN code manager:** ○ Ensure MD/RT has intubation materials **Time keeper:** ○ Alert team every 2 minutes	**Intubation Materials:** ○ Glidescope + blade ○ Intubation kit ○ Patient drape
Step 5. Prepare to intubate patient	○ **MD/RT** communicate to team that intubation materials are ready ○ Team pauses compressions ○ *Option*: Place patient table over bed to tent plastic drape ○ Team drapes patient with plastic	**RN code manager:** ○ Running for additional needs **Time keeper:** ○ Alerts team every 2 minutes	
Step 6. Intubate patient	○ **MD/RT** intubate patient ○ Secure ETT ○ Attach Ambu bag with filter in place and confirm position		
Step 7. Plastic sheet removed and discarded (fire risk)	○ Resume CPR when sheet remove		

Step 8. Continue ACLS	○ Team continues chest compression, defibrillation, med administration		
Step 9. Post code	○ Post-code medications, care, access ○ Ventilator set up ○ Team debriefing: process, materials, emotions w/ communication to ICU leadership		

THERAPEUTICS AND CLINICAL TRIALS

General Considerations

- The mainstay of treatment for COVID-19 is supportive therapy including excellent evidence based critical care.
- All therapeutics with potential activity against COVID-19 are experimental with limited or no known clinical efficacy data.
- Discussions with patients and/or family regarding experimental or off-label treatment should include clear discussions of unknown benefits and known potential harms.
- Antibiotics for secondary bacterial infections, which are not common, should include agents outlined in Hospital-acquired/Ventilator-acquired Pneumonia or Community-acquired Pneumonia guidance. The principles of antibiotic de-escalation still apply.
- Consider ID Consultation for the following:
    - For assistance with management of secondary infections
    - For management of inpatients who meet ALL of the following criteria:
        - Have a positive COVID-19 test
        - Express desire to discuss experimental or off label treatment
        - Are not enrolling in a clinical trial of COVID-19 therapeutics
        - Have moderate to severe disease OR risk factor for disease progression.

COVID-19 directed pharmaceuticals

- Visit Duke's CustomID.org for the most recent and additional information including clinical trials which are updated frequently.
- Please consult ID for availability of clinical trials and consideration of inclusion for each COVID-19 confirmed positive patient
- Chloroquine/Hydroxychloroquine
    - Given paucity of evidence for either effectiveness or safety in critical care settings, would discuss with ID on an individual basis in severe cases only.
- Antivirals (i.e. Remsedivir)
    - Can be obtained as part of 2 clinical trials at DUH. Compassionate use is limited to pediatric and pregnant patients.
    - Visit CustomID.org for inclusion, exclusion criteria
- Anti-IL6: No clincal data exists to support this medication in COVID-19 patients. Anti-IL6 therapy should only be offered in discussion with ID consultant and in the context of a clinical trial.
    - As of 4/11/2020 – A clinical trial from Roche comparing tocilizumab versus placebo is pending at Duke. Consult ID or CustomID.org for the most recent updates.

- Convalescent plasma: As of 4/11/2020 – A trial regarding this therapy is pending. Consult ID or CustomID.org for the most recent updates.

Additional Clinical Therapeutic Trials

- Mesenchymal Stem Cell Trial:
  - Remestemcel-L, ex-vivo cultured adult human mesenchymal stromal cells (MSCs), is an investigational treatment being evaluated in adult patients with moderate to severe Acute Respiratory Distress Syndrome (ARDS) due to COVID-19 Infection.
  - Inclusion Criteria: Patients are eligible for participation in the treatment protocol if they meet all of the following criteria: 1. 18 years or older 2. Patient has SARS-COV 2 confirmed by RT-PCR or other diagnostic test 3. Patient requiring mechanical ventilatory support with moderate to severe ARDS 4. High sensitivity C-Reactive Protein (hs-CRP) serum level >4.0 mg/dL 5. Acute Physiologic and Chronic Health Evaluation (APACHE IV) score >5 6. The patient or his/her LAR is able to provide informed consent
  - Exclusion Criteria 1. Currently receiving extracorporeal membrane oxygenation (ECMO) or high frequency oscillatory ventilation (HFOV) 2. Females who are pregnant or lactating 3. Patients with established positive bacterial blood cultures prior to enrollment or suspicion of superimposed bacterial pneumonia 4. Patients with untreated HIV infection 5. Patients who have been intubated for more than 72 hours 6. Creatinine clearance less than 30 ml/minute 7. LFTs > 5x normal 8. Known hypersensitivity to dimethyl sulfoxide (DMSO) or to porcine or bovine proteins 9. 2 options: Moderate to severe pulmonary disease defined as known hypercapnia or use of home oxygen therapy prior to becoming ill OR History of prior respiratory disease with requirement for supplemental oxygen 10. Any end-stage organ disease which in the opinion of the investigator may possibly affect the safety of remestemcel-L treatment 11. On another trial of an investigational agent for ARDS
  - Contact Christina Barkauskas, MD (christina.barkauskas@dm.duke.edu) for additional information.

Antibiotics

- Secondary bacterial infection (both community and hospital acquired) has been demonstrated in hospitalized patients with COVID-19 infection.
- For known COVID19 infections and PUIs AND clinical concern for secondary bacterial infection, empiric antibiotics should be initiated to treat all likely pathogens causing respiratory infection and/or sepsis within 1 hour of initial patient assessment.
- For non-critically ill patients, consider rapid de-escalation of antimicrobial therapy if all cultures are negative within 48 hours and clinical status is not deteriorating.
- SCCM recommends empiric antimicrobials for all critically ill patients with COVID19 infection. The principles of antibiotic de-escalation still apply.
- Consider the following for patients with clinical evidence of pneumonia or secondary bacterial respiratory infection are also available from ATS or Duke Custom ID
  - For patients presenting from the community and no risk factors for health care associated infection regardless of whether critically ill or not, consider Ceftriaxone + Azithromycin or doxycycline as empiric antimicrobial regimen.

- For patients at risk for health care/hospital acquired infection, immunosuppressed state, or h/o MDR organisms, consider Vancomycin + anti-Pseudomonal agent (Zosyn, Cefepime).
- Duration of antibiotics therapies should be 5-7 days based upon clinical response and de-escalating with negative cultures.

- Sputum samples, tracheal aspirates, and blood cultures should be collected when safe and possible. Induced sputum should be avoided.
- Bronchoscopy should be avoided and is not recommended.
- See CustomID.org for further Duke Health recommendations or consider ID consultation.

ACE-I and ARBs

- Review of evidence
  - It has previously been shown that SARS-CoV binds to the ACE-II receptor via its spike (S) protein, and subsequent proteolytic cleaving of the S protein via TMPRSS2 allows fusion of viral and cellular membranes. No clinical studies of ACE-I or ARB have been conducted in COVID-19 patients or other models.
- Guidelines**:** The 2020 ACC/AHA and HFSA joint statement recommends against discontinuing ACE-I and ARBs for patients with COVID-19.
- Recommendation: Continue patient's home medication unless otherwise indicated (e.g. renal impairment, hypotension). Additionally new ACE-I, ARBs can be initiated if indicated such as a persistently reduced ejection fraction.

NSAIDs

- Review of evidence: COVID-19 binds to cells via ACE-2 which is upregulated by ibuprofen in animal models. There is a suggestion that NSAIDS could increase mortality, but no studies have been published at this time.
- Recommendation: Tylenol should be used as first line in fever.

Systemic Corticosteroids

- Review of evidence: There has been insufficient and conflicting data regarding the use of systemic corticosteroids in COVID-19. Most studies have shown no benefit or negative effects on similar viruses. There is also mixed data regarding the use of systemic corticosteroids in COVID-19 patients with ARDS.
- Recommendation: We recommend avoiding the use of systemic corticosteroids in patients with COVID-19 with or without ARDS unless there is a secondary indication (COPD/Asthma exacerbation, shock) or the use of steroids is associated with a clinical trial.