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Clinical Course, Prognosis, and Epidemiology

Clinical presentation


   1. Fever, 44-94%
      1. No clear consensus definition, with numerous criteria used in different studies.
      2. Recommendation, based on Washington State data (Arentz et al, *JAMA*, 2020), would be to use >= 38°C (of note, they used solely > 38°C but we would advocate for >= 38°C).
      3. Must also take into account: patient’s immune status, medication regimen (steroids, chemotherapy, etc.), and recent use or administration of antipyretics.

   2. Cough, 68-83%
   3. Sore throat, 14-61%
   4. Shortness of breath, 19-40%
   5. Fatigue, 43%
   6. Headache 14%
   7. Muscle aches, 11%
   8. Upper respiratory symptoms (sore throat, rhinorrhea, nasal or sinus congestion), 5-25%
   9. GI symptoms (nausea, vomiting, diarrhea), 4-9%, can present before respiratory symptoms
   10. Anosmia up to 30% (Anecdotal reports summarized by ENT groups in USA, UK) (https://www.entuk.org/sites/default/files/files/Loss%20of%20sense%20of%20smell%20as%20marker%20of%20COVID.pdf)

      1. The majority of patients present with more than one sign/symptom on admission (Chen et al, *Lancet*, 2020).


   1. Lymphopenia, 35-83%
   2. Mild hepatocellular injury pattern with elevated AST / ALT (~200s), 28-38%

3. Anemia, 51%
4. Increased D-dimer, 36%
5. Elevated CK, 13%
6. Elevated LDH, 76%
7. Low/normal procalcitonin, 94%
8. Elevated inflammatory markers (IL-6, ESR, CRP, or ferritin), 38-86%

1. Compared to those with less severe disease, patients presenting with severe disease have been noted to have more significant laboratory aberrations (Guan et al, *N Engl J Med*, 2020; Zhang et al, *Lancet Gastroenterol Hepatol*, 2020)

3. Abnormal diagnostic imaging findings are common. See “Chest Imaging”
4. Respiratory viral co-infection can be found in up to ~25% (Qingdao, China: Xing Q et al, unpublished 2020; Stanford, CA, USA: Shah N et al, unpublished 2020).

1. This is necessarily going to vary greatly with local epidemiology and season

**Disease course and progression**

1. Duration of symptoms:

   Fever, median 12 days (interquartile range 8-13 days) in survivors.
   Dyspnea, median 13 days (interquartile range 8-13 days)

   Cough, median 19 days (interquartile range 12-23 days) in survivors. Still present in 45% of survivors on discharge and 72% of non-survivors on death (Zhou et al, *Lancet*, 2020).

   **Incubation Period:** Average of 5.1 days. 97% of patients will develop symptoms by day 12. Among those who are infected and will develop symptoms, we expect 101 in 10 000 (99th percentile, 482) will do so after the end of a 14-day monitoring period (Lauer SA, Grantz KH, Bi Q, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med. 2020; [Epub ahead of print 10 March 2020]. doi: https://doi.org/10.7326/M20-0504)


   1. Sepsis, median 9 days (range 7-13 days)
   2. ARDS, median 12 days (range 8-15 days)

2. 53% of vented, critically-ill patients developed ARDS within 72 hours of initiation of mechanical ventilation (Arentz et al, *JAMA*, 2020).

3. A Report from ICNARC showed out of 165/775 ICU patients that had their status “resolved” 60% of them required advanced respiratory care (ventilators or similar).
   1. Of the 60% requiring advanced respiratory care, 34% survived and were discharged, 66% died. (https://ricochet.com/742120/covid-19-data-survival-rates-for-patients-on-ventilators/)

3. Acute cardiac injury, median 15 days (range 10-17 days)

4. AKI, median 15 days and need for HD occurs during the second week (range 13-19.5 days)
   1. Incidence rates as high as 15% (data from Wuhan)
   2. Reports of albuminuria and hematuria in the setting of COVID-19, along with isolation of viral RNA from the urine, further supports potential viral tropism for the kidney (https://www.ajkd.org/article/S0272-6386(20)30618-1/pdf)

5. Secondary infection, median 17 days (range 13-19 days)

3. Severity of disease:
   1. 81% have mild to moderate symptoms (mild symptoms to mild pneumonia)
   2. 14% have severe symptoms (hypoxemia, or >50% lung involvement)
   3. 5% have critical symptoms (respiratory failure, shock, multiorgan dysfunction) (Wu, *JAMA*, 2020)

**ICU admission and critical illness**

1. Median time from symptom onset to ICU transfer, 12 days (Zhou et al, *Lancet*, 2020). Hypoxemic respiratory failure is the most common indication for ICU. 60–70% of patients admitted to the ICU (https://doi.org/10.1016/S2213-2600(20)30161-2)

2. Presentation with shock rare; however, vasopressors used in 67% of critically-ill patients (Arentz et al, *JAMA*, 2020).

Death and hospital discharge

1. Case Fatality Rates 1-7%, but is based primarily on the level of screening. Higher screening leads to lower case fatality rates because of changes in the denominator. (https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30165-X/fulltext)

2. Cause of death (Ruan et al, Intensive Care Med, 2020):
   1. Respiratory failure alone, 53%
   2. Circulatory failure alone (in the setting of myocardial damage), 7%
   3. Mixed respiratory and circulatory failure, 33%
   4. Unknown cause, 7%

2. Time from illness onset:
   1. To discharge, median 22 days (interquartile range 18-25 days) (Zhou et al, Lancet, 2020)
   2. To death, median 18.5 days (interquartile range 15-22 days) (Zhou et al, Lancet, 2020), though has been noted to have two peaks at ~14 days and ~22 days (Ruan et al, Intensive Care Med, 2020).

3. Duration of hospitalization, median 12 days (Guan et al, N Engl J Med, 2020)

Prognostic indicators


Testing for COVID-19 Recommendations

Testing for COVID status in the hospital follows the CDC recommendations.
It is important to note that these recommendations are constantly being re-evaluated and updated.

**PRIORITY 1**
Ensure optimal care options for all hospitalized patients, lessen the risk of nosocomial infections, and maintain the integrity of the healthcare system

- Hospitalized patients
- Symptomatic healthcare workers

**PRIORITY 2**
Ensure that those who are at highest risk of complication of infection are rapidly identified and appropriately triaged

- Patients in long-term care facilities with symptoms
- Patients 65 years of age and older with symptoms
- Patients with underlying conditions with symptoms
- First responders with symptoms

**PRIORITY 3**
As resources allow, test individuals in the surrounding community of rapidly increasing hospital cases to decrease community spread, and ensure health of essential workers

- Critical infrastructure workers with symptoms
- Individuals who do not meet any of the above categories with symptoms
- Health care workers and first responders
- Individuals with mild symptoms in communities experiencing high COVID-19 hospitalizations


**How Are we Testing Currently?**

**RT-PCR** tests currently being used globally to diagnose cases of COVID-19 can only indicate the presence of viral material during infection and will not indicate if a person was infected and subsequently recovered. [https://mbio.asm.org/content/11/2/e00722-20](https://mbio.asm.org/content/11/2/e00722-20)


Data supporting the use of naropharyngeal swab over oropharyngeal swab is limited, but drawn from two small studies. 

The mechanism in which we are collecting these specimens is through nasopharyngeal swab.
[https://www.youtube.com/watch?v=7g4aeMD_e_tc&feature=youtu.be](https://www.youtube.com/watch?v=7g4aeMD_e_tc&feature=youtu.be)

**Serology Based Testing** are those that detect IgM, IgA, IgG, or total antibodies (typically in blood). Development of an antibody response to infection can be host dependent and take time; in the case of SARS–CoV-2, early studies suggest that the majority of patients seroconvert between 7 and 11 days postexposure to the virus, although some patients may develop antibodies sooner. [https://mbio.asm.org/content/11/2/e00722-20](https://mbio.asm.org/content/11/2/e00722-20)

We currently do not have serology based testing at this time but will likely have this available in the future. The only FDA approved serology tested lab is produced by Cellex. [https://www.fda.gov/media/136625/download](https://www.fda.gov/media/136625/download)
Epidemiology

Background and geographic distribution

1. Initially recognized in December 2019 by Chinese authorities in the setting of cases of a pneumonia of unknown origin that seemed to be clustered in relation to a seafood market in Wuhan, Hubei Province (Wuhan Municipal Health Commission, 2019).

2. Bronchoalveolar lavage samples collected from affected patients in late December 2019 yielded evidence of a novel betacoronavirus, genetically-distinct from previously identified SARS-CoV and MERS-CoV but genetically-similar to previously-published coronavirus strains collected from bats from southwestern China (Zhu et al, N Engl J Med, 2020), yielding hypotheses of potential zoonotic origin.

3. The first confirmed case in the United States was documented on January 20, 2020, in Snohomish County, Washington, in a traveler who had returned from Wuhan, China, five days prior (Holshue et al, N Engl J Med, 2020).

4. The virus has spread broadly. Worldwide case counts are published by teams at the World Health Organization, Johns Hopkins University, and others.

5. Viral genomes have been published to GenBank from diverse geographies. Reports on real-time phylogenetic tracking of the viral genome can be found at NextStrain (Hadfield et al, Bioinformatics, 2018).

Transmission dynamics

1. Transmission of SARS-CoV-2 is incompletely understood, and new data continue to emerge. Many of the studies cited below are based on limited data from the early phase of the pandemic.


Viral particles shown to survive < 24h on cardboard, < 72h on plastic or steel; aerosolized (droplet nuclei, < 5 µm) particles appear to last at least 3h (van Dorelmalen et al, New Engl J Med, 2020). The conditions in this study were “highly artificial”, there is probably “a non-zero risk of longer-range spread through the air.

https://www.nature.com/articles/d41586-020-00974-w

1. Aerosolizing procedures are proposed to include intubation, nebulization, non-invasive positive pressure (CPAP, BiPAP), high-flow nasal cannula.

2. Virus has been detected in stool and whole blood (Young et al, JAMA, 2020); however, significance for transmission is unclear (Chen et al, Emerg Infect Dis, 2020).
1. Viral shedding and symptoms: Nasopharyngeal viral load peak within days of symptom onset followed by decline (Young et al, *JAMA*, 2020).

2. Symptomatic and asymptomatic patients can transmit the virus (Bai et al, *JAMA*, 2020; Rothe et al, *N Engl J Med*, 2020), though symptoms are likely associated with increased frequency of transmission.


7. Basic reproduction number (R0): Measure of transmissibility, denoting the theoretical expected number of secondary cases from any given case. An R0 > 1 is consistent with ongoing outbreak potential.


10. Super-spreading, referring to events in which individuals directly spread an infection to a large number of (> 10) others, was noted in the 2002-2003 SARS outbreak (Lipsitch et al, *Science*, 2003).

11. It is thought that there may be a similar role in the spread of COVID-19 given population dynamics, but specific events are not yet known to have been identified (Li et al, *N Engl J Med*, 2020).

12. Case fatality rate: Approximately 2.3% in Italy (Porcheddu et al, *J Infect Dev Ctries*, 2020) and China (Feng et al, *China CDC Weekly*, 2020), though estimates range from 1-7% depending on


2. Case fatality necessarily depends on the availability of health care services, and may increase as hospital systems become saturated and the number of people being tested.

6. Reinfection and immunity: Possibility or risk of reinfection in humans is not yet known nor are details around development of immunity.


**Vulnerable populations and special settings**

1. Skilled nursing facilities (SNF): A single SNF in Kirkland, WA, USA had 167 COVID-19 confirmed cases (101 residents, 50 health care staff, 16 visitors) with respective hospitalization rates of 55%, 6% and 50%; and case-fatality rate of 34% for residents (McMichael et al, *N Engl J Med*, 2020).

2. Homeless populations: Homeless populations less than 65 years old have all-cause mortality 5-10 higher than the general population at baseline (Baggett et al, *JAMA Intern Med*, 2013). Living conditions, higher rates of comorbidities (including substance abuse and mental illness), difficulty for public health agencies to trace homeless individuals and limited connection with medical services are all likely challenges (Tsai and Wilson, *Lancet Public Health*, 2020) but data on the COVID-19 pandemic in the homeless remains limited.

3. Pet owners, zoonotic spread: Preprint data reports evidence of viral replication in inoculated ferrets and cats, with viral transmission between cats; dogs showed low susceptibility, and pigs, chicken, and ducks were deemed not susceptible (Chen et al, *bioRxiv*, 2020 preprint).


Personal Protective Equipment and Infection Control

1. PPE General Guidance

Extended Use of N-95 Respirators
Extended use refers to the practice of wearing the same N95 respirator for repeated close contact encounters with several patients, without removing the respirator between patient encounters. Extended use may be implemented when multiple patients are infected with the same respiratory pathogen and patients are placed together in dedicated waiting rooms or hospital wards. Extended use has been recommended as an option for conserving respirators during previous respiratory pathogen outbreaks and pandemics.

(https://www.cdc.gov/niosh/topics/hcwcontrols/recommendedguidanceextuse.html)

Risks of Extended Use and Reuse of Respirators
Although extended use and reuse of respirators have the potential benefit of conserving limited supplies of disposable N95 respirators, concerns about these practices have been raised. The most significant risk is of contact transmission from touching the surface of the contaminated respirator. One study found that nurses averaged 25 touches per shift to their face, eyes, or N95 respirator during extended use.

https://www.cdc.gov/niosh/topics/hcwcontrols/recommendedguidanceextuse.html#risksextended

Respiratory pathogens on the respirator surface can potentially be transferred by touch to the wearer’s hands and thus risk causing infection through subsequent touching of the mucous membranes of the face (i.e., self-inoculation). While studies have shown that some respiratory pathogens remain infectious on respirator surfaces for extended periods of time, in microbial transfer and reaerosolization studies more than ~99.8% have remained trapped on the respirator after handling or following simulated cough or sneeze.

https://www.cdc.gov/niosh/topics/hcwcontrols/recommendedguidanceextuse.html#risksextended

The risks of contact transmission when implementing extended use and reuse can be affected by the types of medical procedures being performed and the use of effective engineering and administrative controls, which affect how much a respirator becomes contaminated by droplet sprays or deposition of aerosolized particles. For example, aerosol generating medical procedures such as bronchoscopies, sputum induction, or endotracheal intubation, are likely to cause higher levels of respirator surface contamination, while source control of patients (e.g. asking patients to wear facemasks), use of a face shield over the disposable N95 respirator, or use of engineering controls such as local exhaust ventilation are likely to reduce the levels of respirator surface contamination.

https://www.cdc.gov/niosh/topics/hcwcontrols/recommendedguidanceextuse.html#risksextended
**Reuse** refers to the practice of using the same N95 respirator for multiple encounters with patients but removing it (‘doffing’) after each encounter. The respirator is stored in between encounters to be put on again (‘donned’) prior to the next encounter with a patient. For pathogens in which contact transmission (e.g., fomites) is not a concern, non-emergency reuse has been practiced for decades. For example, for tuberculosis prevention, CDC recommends that a respirator classified as disposable can be reused by the same worker as long as it remains functional and is used in accordance with local infection control procedures. Even when N95 respirator reuse is practiced or recommended, restrictions are in place which limit the number of times the same FFR is reused. Thus, N95 respirator reuse is often referred to as “limited reuse”. Limited reuse has been recommended and widely used as an option for conserving respirators during previous respiratory pathogen outbreaks and pandemics.  
https://www.cdc.gov/niosh/topics/hcwcontrols/recommendedguidanceextuse.html

**Safe Practices of Donning PPE and Doffing PPE:** [https://www.cdc.gov/hai/pdfs/ppe/ppe-sequence.pdf](https://www.cdc.gov/hai/pdfs/ppe/ppe-sequence.pdf)

Consideration for just in time training can also be watched at this website:  
[https://www.youtube.com/watch?v=bG6zISnenPg&feature=youtu.be](https://www.youtube.com/watch?v=bG6zISnenPg&feature=youtu.be)

2. **OSU Location-specific PPE guidance:** There are location-specific differences.

   **Non-Patient Facing Areas** are permitted to wear non-medical grade face masks.  
   **Clinical Personnel** that are patient facing but not on designated COVID units, should be using a surgical grade mask at all times and are encouraged to re-use masks.

3. South ICU (COVID designated Unit/PUI and Confirmed Positive): All providers are to wear N-95 mask gown and gloves while interacting with any patient. Providers on this floor are also required to wear eye protection (goggles or face shield).  

   North ICU: All providers are to wear basic surgical mask and gloves while interacting with any patient.  

   5E: All providers are to wear basic surgical mask and gloves while interacting with any patient.  

   6E: All providers are to wear basic surgical mask and gloves while interacting with any patient.  

   7E (COVID designated Unit/PUI and Confirmed Positive): All providers are to wear N-95 mask, gown and gloves while interacting with any patient. Providers on this floor are also required to wear eye protection (goggles or face shield). In addition.
ED: All providers are to wear N-95 mask or equivalent, face shield/eye protection, gown and gloves while interacting with any patient.

**For aerosol generating procedures:** Strict isolation (aerosol) PPE (including N95 masks) are needed during nebulized treatments, NIPPV, high flow oxygen, nasotracheal suctioning, intubation/extubation, CPR, Bronchoscopy. These procedures are preferentially done in negative airflow rooms.

All providers should be educated in appropriate protocols for donning and doffing PPE as described by the CDC [https://www.cdc.gov/hai/pdfs/ppe/ppe-sequence.pdf](https://www.cdc.gov/hai/pdfs/ppe/ppe-sequence.pdf)

**OSU Specific Reprocessing N-95 Respirators for Extended Use**
[https://www.cdc.gov/niosh/topics/hcwcontrols/recommendedguidanceextuse.html](https://www.cdc.gov/niosh/topics/hcwcontrols/recommendedguidanceextuse.html)

OSU is utilizing the Sterrad Sterilization System for N-95’s

1. Staff on COVID designated units will receive a respirator for 1st time use. On the inside of their mask, they will write their last name, first initial and department inside the respirator.
2. After the 1st use (i.e. end of shift), the respirator is to be placed individually in a brown paper bag (1 mask/bag).
3. Clean brown paper bags will be stocked in the clean area the department nursing manager has designated.
   1. Unit Clean Bin Delivery Area
      1. ED: ED Breakroom
      2. MCH: MCH Breakroom
      3. ICUS: Room behind Nutrition
      4. 5E: Conference Room
      5. 7E: Conference Room
      6. RT: TBD
      7. OR: TBD
4. Staff should label the bag with their last name, first initial and department.
5. Each department will have a dedicated dirty bin where brown bags should stored at the end of a shift.
   1. Dirty bins will be kept in soiled utility rooms for all departments.
6. A designated staff member from each department will bring the dirty bin to Central Sterile (CS) daily, at the end of each shift.
   1. Wipe down the outer parts of the bin with a purple top wipe before transporting to CS.
2. Enter CS through the door adjacent to the underground tunnel in the basement. A sign will be posted that contains the pin for the keypad. The sign states “Drop off for Dirty N95 Masks”. The pin to the keypad will be printed on the bottom part of the sign.

3. Leave dirty bins in the wire rack shelf on the left as you enter CS.

4. CS staff will wipe down the dirty bins and return to the soiled utility rooms for each department.

7. Packaging
   1. Respirators can be only be processed two times.
   2. CS staff will remove respirator from paper bag and write “x1” inside the respirator to designate it is the first reprocessing or “x2” to designate the 2nd reprocessing.
   3. After writing the reprocessing count inside the respirator, CS staff will place each individual respirator in a self-seal pouch (peel pack).
   4. CS staff will label the outside of the peel pack with the employee’s name and department.
   5. Peel packs will be loaded, upright into the STERRAD Sterilizer.

8. Sterilization Systems, Cycles and Loads
   1. 40-50 respirators can be processed per load with each load taking 55 minutes.
   2. After processing through the sterilizer is complete, respirators must aerate for one hour.
   3. Approximately 200 respirators can be processed per day.

9. Delivery
   1. Once processed, CS staff will place peel packs in clean bins.
   2. Each department will have a dedicated clean bin.
   3. CS staff will return the clean bins to the appropriate department.
   4. Clean bins will be left in a clean area designated by the department manager. See table above.

10. Discardment process
    1. Respirators cannot be identified (i.e. no name on respirator or paper bag)
    2. Respirators that come to CS have already been reprocessed twice (i.e. x2)
    3. Respirators appear damaged, crushed, or visibly soiled.

Re-use of PPE (specific instructions)

Re-Use of Surgical Masks

1. Perform hand hygiene
2. Remove the procedure mask by holding the ear loops or ties.
3. The front is contaminated, so remove slowly and carefully.
4. After removing facemask, visually inspect for contamination, distortion in shape/form. If contaminated or wet the mask should be discarded.
5. If the facemask is NOT visibly contaminated or distorted, carefully store in the paper bag to avoid destroying the shape of the mask.
6. The facemask should be stored in a well-ventilated container (i.e., paper bag with handles) with user name & date.
7. A disposable facemask can be worn for several hours if not wet or distorted, and not touched while delivering patient care.

Re-Use of N-95 (You can continue to wear the N95 respirator and eye protection for your entire shift. N95 and eye protection may be removed and stored appropriately for re-use later)

1. Perform hand hygiene
2. Remove the procedure mask by holding the ear loops.
3. The front is contaminated, so remove slowly and carefully.
4. After removing N-95, visually inspect for contamination, distortion in shape/form. If contaminated or wet the mask should be discarded.
5. If the facemask is NOT visibly contaminated or distorted, carefully store in the paper bag to avoid destroying the shape of the mask.
6. The facemask should be stored in a well-ventilated container (i.e., paper bag with handles) with user name & date.

Re-Use of Face Shields

1. Full face shields are dedicated to individual healthcare personnel as foam piece and elastic head band cannot be adequately disinfected between personnel.
2. Don gloves and adequately disinfect inside then outside surfaces, avoid using PDI Sani wipe on foam and elastic band.
3. Store reused full face shield alongside your labeled paper bag containing your re-used N95

When Re-Donning N-95 and Face Shield

1. Remove N95 mask from ventilated area and visually inspect for distortion.
2. If creased or bent do not re-use.
3. Perform hand hygiene.
4. Don gown and gloves.
5. Don the N-95 respirator.
6. Perform hand hygiene over gloves.
7. Perform a negative/positive seal check by doing the following
   - No air should be felt around the perimeter while blowing out.
   - If you feel air coming out it is not a tight seal.
   - When taking a small breath in, the mask should pucker in slightly.
   - If it does not, it is not re-usable.
   - If not a tight seal, the respirator cannot be re-used.
Ensure the mask is breathable, if unable to breathe in the mask, the respirator cannot be re-used.

8. PERFORM HAND HYGIENE over gloves following seal check as the mask has been previously used.

Don full face shield over N95

**Under investigation**

Use of TRU-D/UVC decontamination of other PPE including gowns

*Link to a PDF document saved in COVID file*
Diagnostic Testing in COVID positive Patients for Prognostic Prediction

COVID testing

1. This is an area that is actively changing and varies widely by hospital, test availability, and local epidemiology.

Laboratory studies and EKGs

| On admission | CBC with differential  
| If not obtained in ED, draw following morning | CMP  
| | Troponin, CK, BNP  
| | LDH, CRP, Procalcitonin  
| | PTT/INR, Ferritin, fibrinogen  
| | Baseline EKG  
| Daily | CBC with differential  
| Can change to every other day in stable floor patients | CMP  
| If ICU: | If ICU: CMP, CBC with differential, LDH, Ferritin, CK  
| | Every third day on wards, and day of discharge | CPK  
| | LDH, CRP, Ferritin  
| If clinical worsening | CBC with differential  
| | CMP  
| | Troponin & CPK  
| | LDH, CRP, Procalcitonin  
| | PTT/INR, Fibrinogen, Ferritin  
| | ABG preferred over VBG  
| | Repeat EKG  

Chest imaging

1. Findings:

1. Primary features are of atypical pneumonia or organizing pneumonia.

1. Distribution is typically bilateral, peripheral, and basal

1. Bilateral findings in about 85% of patients; 33 - 86% predominantly peripheral and 70 - 80% predominantly posterior (Chung, RSNA, 2020; Song, RSNA, 2020)

2. Parenchymal imaging findings are variable and depend on time course (Wang, RSNA, 2020, American Journal of Roentgenology: 1-7. 10.2214/AJR.20.23034)
1. Days 0-5: ~65% pure GGOs, 24% GGOs with intralobular lines
2. Days 6-11: ~40% pure GGOs, 22% pure GGO with intralobular lines, 28% GGO with irregular lines and interfaces (can see crazy paving)
3. Days 12 - 17: combination of the above, with more consolidations (38% show “mixed” pattern of consolidation, GGOs, and reticular opacities with architectural distortion)
4. Late findings may include fibrotic changes

3. Small bilateral effusions can be seen in <10% of patients; large effusions are not. (American Journal of Roentgenology: 1-7. 10.2214/AJR.20.23034)

1. Large effusions, cavitations, discrete nodules, lymphadenopathy suggestive of another process (i.e., superimposed bacterial infection)

1. **Portable CXR:** Sufficient in most cases. Avoid routine daily CXR (unlikely to change management, evaluate case-by-case).

   1. Findings: Bilateral peripheral and basilar patchy opacities are most common
   2. May be initially normal in up to ~30% of hospitalized COVID patients, particularly in early disease (Wong, *Radiology*, 2019).

   1. Sensitivity 59% in one study, as compared to 86% for CT scan (Guan, *NEJM*, 2020)

2. **CT Chest:** Often will not change management and is associated with potentially unnecessary risk (staff and time required to transport, risk of transmission in transit, decontamination of radiology equipment).

   1. Avoid unless otherwise indicated: e.g. for abscess or empyema, or other causes of hypoxemia like pulmonary embolism Approximately 50% of CT scans are normal up to 2 days after symptom onset. ACR guidelines indicate CT should not be used to screen for or as a first-line test to diagnose COVID-19. CT should be used sparingly and reserved for hospitalized, symptomatic patients with specific clinical indications for CT. Appropriate infection control procedures should be followed before scanning subsequent patients. ([https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection](https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection))

   1. If chest CT obtained, non-contrast scan (or contrast and non-contrast phases) recommended to optimally image GGO patterns.

3. **Point of Care Ultrasound:** Can be used by experienced providers, but is operator-dependent. For experienced providers, sensitivity is likely superior to portable chest X-ray.
1. Recommended to use convex or linear probe to image pleural & subpleural spaces, use intercostal scans to cover wide swaths of surfaces, and image multiple areas in both lungs.

2. Findings: Focal or diffuse B lines with sparing of uninvolved areas, irregular thickened pleural line with “scattered discontinuities”, subpleural consolidations (relatively avascular on Doppler), alveolar consolidations with air bronchograms

3. Multiple limitations including non-universal screening protocols, multiple zone differentiations, no ability to determine chronicity, ability to detect cine loops. (https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30166-1/fulltext)

1. May help distinguishing cardiogenic pulmonary edema from ARDS. See table:

<table>
<thead>
<tr>
<th>Table 1 Lung ultrasonography findings of ACPE and ARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical setting</td>
</tr>
<tr>
<td>B lines</td>
</tr>
<tr>
<td>Distribution of B lines</td>
</tr>
<tr>
<td>Pleural line abnormalities</td>
</tr>
<tr>
<td>Reduction or absence of lung sliding</td>
</tr>
<tr>
<td>Lung pulse</td>
</tr>
<tr>
<td>Consolidations</td>
</tr>
</tbody>
</table>

ACPE acute cardiogenic pulmonary edema, ARDS adult respiratory distress syndrome

Other studies

1. Avoid other studies unless really necessary due to PPE limitations and transmission risk associated with transport.

   1. Avoid routine TTEs (for cardiac studies, see: “Cardiac Complications of COVID” chapter).
   2. Avoid routine CXR as this will unlikely change management unless acute change in clinical condition
Patients that need further evaluation are then sent to their appropriate designation for COVID risk. If the patient is suspected to need any type of aerosolized procedure, they are moved to the negative pressure rooms in the ED (rooms 13-17 at OSU). Less than 20% of the patients in their system are found to need admission to the emergency department after completing this process. 

The Centers for Medicare and Medicaid Services (CMS) has issued guidance for hospitals on their EMTALA obligations during this public health emergency, which includes allowing medical screening examinations (MSEs) to be delivered via telehealth. During this declared emergency, physicians (or other qualified medical persons [QMPs]) can
perform MSEs and meet the MSE requirement without having extensive contact with the patient.

In addition to telehealth options, CMS has also issued a limited blanket waiver of EMTALA sanctions, allowing for patients to be redirected to another location offsite to receive an MSE, as long as the redirection is consistent with a state emergency preparedness or pandemic plan.

Patients presenting to OSU with possible symptoms of COVID-19 and meeting certain criteria (ie, vital sign parameters) are sent to a tent, where they are seen by an in-person nurse and a physician via telehealth (video and audio) who determines if the patient can be discharged from the tent or needs admission to the emergency department. [https://www.cms.gov/files/document/qso-20-15-hospital-cah-emtala-revised.pdf](https://www.cms.gov/files/document/qso-20-15-hospital-cah-emtala-revised.pdf)

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category 1</strong></td>
<td><strong>Consider Discharge to Home</strong></td>
</tr>
<tr>
<td>Symptomatic patient with following clinical presentation</td>
<td></td>
</tr>
<tr>
<td>Clinically well appearing,</td>
<td></td>
</tr>
<tr>
<td>Resting O₂ Sat &gt;94% on room air</td>
<td></td>
</tr>
<tr>
<td>No desaturation with ambulation</td>
<td></td>
</tr>
<tr>
<td>No tachypnea, RR</td>
<td></td>
</tr>
<tr>
<td><strong>Category 2</strong></td>
<td><strong>Consider Admission to COVID Stepdown</strong></td>
</tr>
<tr>
<td>Symptomatic patient,</td>
<td></td>
</tr>
<tr>
<td>Resting O₂ sat &lt; 93% on room air</td>
<td></td>
</tr>
<tr>
<td>Desaturation on ambulation,</td>
<td></td>
</tr>
<tr>
<td>Patients requiring bronchodilator treatment</td>
<td></td>
</tr>
<tr>
<td>OR, Any two (or even one criterion based on clinical presentation):</td>
<td></td>
</tr>
<tr>
<td>Age &gt;60</td>
<td></td>
</tr>
<tr>
<td>Existing conditions such as Diabetes Mellitus, HTN, CHF, CAD, COPD (or any chronic or severe lung disease), CKD, Cancer, Immunosuppression</td>
<td></td>
</tr>
<tr>
<td>Change in mentation</td>
<td></td>
</tr>
<tr>
<td>Respiratory Rate &gt;20/min</td>
<td></td>
</tr>
<tr>
<td>Pulse &lt;120 bpm but &gt; 100</td>
<td></td>
</tr>
<tr>
<td>Systolic BP is normal</td>
<td></td>
</tr>
<tr>
<td><strong>Category 3</strong></td>
<td><strong>Consideration Admission to COVID ICU</strong></td>
</tr>
<tr>
<td>Patient appears toxic and in distress</td>
<td></td>
</tr>
<tr>
<td>O₂ Saturation is &lt; 93% on 6 Liters</td>
<td></td>
</tr>
<tr>
<td>Patient is requiring vasopressors</td>
<td></td>
</tr>
<tr>
<td>Patient is on mechanical ventilation</td>
<td></td>
</tr>
</tbody>
</table>
Patient has arrhythmia on 12 lead or telemetry

Who should be tested in the ED (Guidance)

Currently, testing in the US is only performed for individuals when a positive result will change treatment. Testing is also prioritized for people who have a high risk for bad outcomes from COVID-19 infection, such as elderly or immunosuppressed patients, and those with high risk of exposure and transmission of the disease to other people, such as health care workers.

https://jamanetwork.com/journals/jama/fullarticle/2764238
Respiratory Escalation Pathway and Intubation

For persons NOT under investigation for COVID-19

1. Nasal Cannula
   1. Continue standard practices

2. Noninvasive ventilation, high flow nasal cannula:
   1. Indications remain the same (including OSA)
   2. Because rates of asymptomatic carriage in the community are unknown, and aerosolization risk is unknown, wherever possible:
      1. Consider alternate options as available (e.g., nocturnal nasal cannula.)
      2. Use airborne precautions (Strict isolation, N95, negative pressure room)
      3. Use a closed circuit: BWH NIPPV machine with dual limb with a HEPA filter and BWH mask without anti-asphyxia valve.
      4. Ensure masks/devices fit well and there is minimal air leak
      5. Avoid use of home NIV devices (particularly if single limb with anti-asphyxia valve)
   3. Treat as though this person is a PUI (see below)

3. Cardiac Arrest:
   1. Treat as though this person is a PUI (see below)

For Persons Under Investigation (PUI) or with confirmed COVID-19

1. Nasal Cannula:
   1. Use humidified nasal cannula (NC) 1 to 6 LPM for target SpO2 92-96%.

   If a patient requires >6L, consideration for ICU transfer. We recommend trial of proning with the need for 3-6 liters of oxygen if the patient is able to tolerated. If possible, utilize a protocol that the patient (if able to do independently) uses oxygen supplied by nasal canula and independently prones themselves for 30 minutes-3 hours at least three times daily. They should be monitored. This patient does not necessarily needs to be intubated at this or needs immediate ICU transfer. ([https://rebelem.com/covid-19-hypoxemia-a-better-and-still-safe-way/](https://rebelem.com/covid-19-hypoxemia-a-better-and-still-safe-way/))
In addition, consideration can be given to the ROX score for closer monitoring. Although this was validated for high flow nasal canula, an indication of improvement or failure may be acquired by utilizing similar parameters in COVID-19 patients.
(https://www.atsjournals.org/doi/10.1164/rccm.201803-0589OC)

The calculator can be found at the following website:

2. **High Flow Nasal Cannula:**

HFNC should be used if the patient can tolerate and monitored closely for decompensation as a mechanism to delay intubation. There is evidence that intubating early in these patients based on the physiology of the disease may cause more harm.


1. We recommend trial of proning with HFNC with the need for >6 liters of oxygen, in the ICU if there is bed availability, if the patient is able to tolerate. We are utilizing a protocol that the patient (if able to do independently) uses oxygen supplied by high flow nasal canula and independently prones themselves for 30 minutes-3 hours at least three times daily. They should be monitored.

2. In addition, consideration can be given to the ROX score for closer monitoring. Although this was validated for high flow nasal canula, an indication of improvement or failure may be acquired by utilizing similar parameters in COVID-19 patients.
(https://www.atsjournals.org/doi/10.1164/rccm.201803-0589OC)

3. The calculator can be found at the following website:


2. **BIPAP/CPAP (NIVV)**

1. Consideration for BIPAP/CPAP as a means to avoid intubation
2. Has a risk for aerosolization
   1. If using, should be used with appropriate filter
3. Select DNI patients as a bridge to family arrival or intervention
3. If NIPPV/HFNC is used, it should be under strict airborne precautions including a negative pressure room with providers in PPE for aerosolized procedures
4. Patients utilizing CPAP/BIPAP at home for established OSA should be considered for other modalities as the risk of asymptomatic COVID is present. If necessary, they should be quarantined. (https://aasm.org/covid-19-resources/covid-19-faq)

3. **Intubation:**

   1. Contact the airway team (30 minutes prior to intubation to provide ample time for preparation)
      1. Anesthesia 0700-1900
      2. ED 1900-0700
      1. If appropriate provide ROX score if it was completed

   2. Rapid Sequence Induction (RSI) should be performed, avoiding bagging
      1. By the most experienced airway provider

A dedicated video laryngoscope is available in the COVID ICU. If an acrylic box is unavailable attempt to use a drape.
https://www.youtube.com/watch?v=oROw6VgOpD8
https://www.youtube.com/watch?v=8tgfqOgK7ns

**Intubation in Emergency Department, ICU, or Floor Preparation**

1. Rapid Sequence Induction (RSI) should be performed by the most experienced airway provider using a video laryngoscope (SCCM COVID19 Guidelines) (APSF Considerations for Airway Manipulation, 3/20/2020)

2. Limit providers in room to **3 if at all possible**: 1 airway team member(s), respiratory therapist, and registered nurse
   1. Assign roles and airway plan (who will “hold/do” what)

3. Perform a “pre-induction” checklist prior to starting:
   1. Suction available
   2. Audible pulse oximetry
   3. NIBP cycling
4. Ventilator setup and ready with quantitative EtCO2 monitor in-line and ready (avoid color change device if possible)

5. Acrylic Box or plastic drape to protect airway team and reduce aerosolization
   2. [https://www.youtube.com/watch?v=oROw6VgOpD8](https://www.youtube.com/watch?v=oROw6VgOpD8)
   3. [https://www.youtube.com/watch?v=8tgfqOgK7ns](https://www.youtube.com/watch?v=8tgfqOgK7ns)

6. Free-flowing IV access
7. Post-intubation sedation ready
8. HEPA filter in-line
9. Medications ready
10. Non-rebreather, flow “OFF” until ready to preoxygenate
11. If no ventilator is available, ambu bag post intubation with HEPA filter, +/- CO2 detector. Flows turned down during circuit changes

4. Ensure patients are in negative pressure rooms for all intubations/extubations (SCCM COVID19 Guidelines).

**Procedure**

1. Don appropriate PPE via “read/do” checklist, gather supplies and review airway plan
2. Preoxygenate the patient: maintain preoxygenation technique until neuromuscular blockade has set in
   1. Option 1: 3-5 minutes of tidal breathing 1.0 FiO₂ on non-rebreather at 15L/min flow
   2. Option 2: facemask attached to AMBUbag with HEPA filter (2 hand technique to maintain seal)
   3. Option 3: if patient already on BiPAP then maintain BiPAP with tight seal until ready to intubate (turn “OFF” BiPAP flow prior to removing mask)
3. Intubate the patient with an RSI technique/video laryngoscopy
4. Use awake intubation only when absolutely necessary
5. If mask ventilation becomes necessary:
   1. use 2-hand technique with oral airway to create tight seal
   2. use AMBUbag with HEPA filter in-line with high frequency/low tidal volume
   3. do not remove mask for 2nd attempt intubation until end exhalation
5. After successful intubation:
1. Inflate cuff
2. Connect patient directly to ventilator with HEPA filter with Et\textsubscript{CO}_2 gas sampling line post-filter or use an infrared CO\textsubscript{2} analyzer with no gas sampling
3. Confirm via quantitative in-line Et\textsubscript{CO}_2 (gold standard > 3 breaths), bilateral chest rise, “fogging” of ETT, cuff palpation and possibly increasing Sp\textsubscript{O}_2
4. Avoid listening bilaterally for risk of contamination (touching ears with stethoscope/hands)
5. Secure ETT per hospital policy

6. Clean the laryngoscope:
   1. Remove soiled gloves and replace with clean gloves
   2. Clean the video laryngoscope and allow it to dry - 3 minutes if PURPLE Sani-Cloth (Sani-Cloth Technical Sheet).
   3. Push video laryngoscope out of room with clean gloves on

7. Follow “read/do” instructions for doffing of PPE per hospital protocol
Other Management Principles

Medical management:

1. Management is largely supportive. Antiviral and immune-modulating therapies are investigational. Further details in COVID therapies section.
2. Fluid management should be conservative due to risk of hypoxia/CHF. Further details in fluids section.

Early Advance Care Planning:


1. Educate patient and family on disease course and prognosis
   
   Focus on desired quality of life and tolerance for ICU measures

Triage to ICU

Considerations for transfer to ICU:

1. Provider concern
2. Respiratory distress
   
   1. Need O2 > 6 LPM to maintain SpO2 > 90% or PaO2 > 65.
   2. Rapid escalation of oxygen requirement.
   3. Significant work of breathing.
3. Hemodynamic instability after initial conservative fluid resuscitation
   
   1. SBP < 90, Mean arterial pressure < 65, or Heart rate > 120.
4. Persistent Acidosis
   
   1. VBG with pH < 7.3 or PCO2 > 50 or above patient’s baseline.
   2. Lactate > 2.
5. Need for intensive nursing care or frequent laboratory draws requiring arterial line.
6. Severe comorbid illness / high risk for deterioration.
7. Altered mental status that cannot be adequately managed on the GMF
**Transfer Process**

**Floor / ED to ICU:**

1. ICU RN/designee brings ICU bed to the floor for transfer (to avoid bed transfer in COVID precautions room and subsequent bed cleaning).
2. Patient wears surgical mask (unless ventilated), with an extra clean gown and sheet on top.
   1. If the patient is on HFNC, a surgical mask should be over this device
   2. If the patient is NIV, the patient should have the appropriate viral filter
4. Security facilitates the shortest and fastest transfer route, walks 6 ft away from patient and providers, required to wear surgical mask
5. Necessary tests (*e.g.* CT), should be obtained during transfer if possible.

**ICU to floor:**

1. ICU-RN/designee wears standard PPE
2. Patient travels in wheelchair or stretcher and should have a surgical mask
3. Security facilitates the shortest and fastest transfer route, walks 6 ft away from patient and providers, required to wear surgical mask

**Floor to discharge:**

1. RN/designee wears standard PPE
2. Patient travels in wheelchair with a mask
3. Security facilitates the shortest and fastest transfer route, walks 6 ft away from patient and providers, required to wear surgical mask and exists at the backside of the building (through GI center), to avoid interactions with individuals and allow for facilitated pick up
4. Patient is escorted directly into vehicle; contact case management if patient does not have access to a personal vehicle
   1. If this is a COVID PUI, they are still required to wear a mask

**Discharge Planning (Emergency Department)**

1. RN/designee wears standard PPE
2. Patient travels in wheelchair with a mask
3. RN/designee facilitates the shortest and fastest discharge route.
4. Patient is escorted directly outside of the building through the triage tent
   1. If this is a COVID PUI, they are still required to wear a mask
Discharge Planning (Inpatient)

Discharge criteria

1. Consider discharge for patients’ who meet the following clinical criteria:
   
   1. Resolution of fever >48 hours without antipyretics
   2. Improvement in illness signs and symptoms (cough, SOB, and oxygen requirement)

Confirmed COVID-19 Discharge Checklist

1. If unable to complete any components of checklist: review community resources, discuss transportation and post-acute care options with care coordination and consider ongoing hospitalization

Discharge contingencies

- Verify and document contact number for patient and primary support person; ensure active phone service, voicemail functioning, and language preference correctly documented
- Verify residence with private room, ability to adhere to home isolation instructions and risk of transmission to persons with immunocompromising conditions in the home
- Confirm ability to manage ADL/iADLs with degree of support at home
- Confirm that patient has resources/social support to receive 1-2 weeks of food and other necessary supplies while under quarantine
  - For those in the Tulsa Areas
    - Wheels online - they can deliver 7 frozen meals 1 x per week
    - Grocery Delivery -> Victory Christian Church: Pt need to send a text to: 28950 and then text message "FOODHELP". They will respond to this message and will deliver groceries to the pt.
    - There is an individual thru Life Senior Services that is providing grocery shopping and delivery for free. Her name is Cheryl Fritts: 918-289-9051
    - https://www.reasors.com/shipt-home-delivery

- Perform DME needs assessment and consider sponsorship from hospital if item unable to be delivered or obtained by primary support person

Discharge medications/supplies

- Consider 30-day supply of medications to cover duration of home isolation, recommend meds-to-bed delivery if available
• Provide a surgical mask as available to infected patients who are discharging home (instructions for use in discharge instructions)

Transportation

• Verify patient has a ride by private vehicle or arrange transportation via ambulance (infected person should wear mask in vehicle)
  • Health Ride: They are transporting COVID + & Pending COVID pts if they are not actively having symptoms (fever, cough). Currently the hospitals that they have worked with are providing their driver and the patient with appropriate PPE to be protected during the transport. St. Francis is providing N95 mask; gloves & gown (This service would bill the hospital directly for transport)
  • EMS Services: Can/should be told pts status when scheduling transport; must still have a physician medical necessity form completed; They will transport COVID + and potential COVID pts; At this time they do not have any funding and if patient does not have a payer or insurance denies then patient will receive the bill for the transport.
  • City Bus: They are limiting passengers and have blocked off seating to ensure social distancing. Capacity is limited to 8-12 passengers. All buses sanitized nightly

Discharge instructions

• Ensure that you are using the stock discharge instructions at OSU through Meditech
• There is a canned text in discharge instructions that provide further instruction on self-quarantine and when individuals can be released from quarantine

Ambulatory follow-up plan

• Verify and document patient’s primary care provider
• Provide warm handoff via phone or in-basket message to patient’s primary care provider and confirm that they are able/willing to answer questions post-discharge
• If patients do not have a primary care provider, or their primary care provider cannot get them in for an extended period of time, or do not have virtual capacity, consider the following:
  o Virtual visit through OSU Internal Medicine
    • Cortext Melissa Cox
      • Patient name
      • DOB
      • Phone Number
      • COVID status (Positive or Pending Result)
    • If it is a new patient, fax new patient paperwork to 918-382-3589
    • Melissa will send date, time and doxy information to requester
- Information for doxy.me/drsname will need to be provided to patient and then can access through smart phone, tablet or laptop at designated time and date. The physician will link them to the virtual visit.


1. Fever-free for 72 hours without the use of fever-reducing medications

2. Respiratory symptoms improving

3. At least 7 days since original onset of symptoms

Note that typically for viruses, patients with compromised immune systems have prolonged viral shedding. The CDC guidelines state to extend the patient’s isolation for the duration of symptoms based on the clinical judgement of the provider.

**Test Based Strategy**

1. Resolution of fever without the use of fever-reducing medications **and**

2. Improvement in respiratory symptoms (e.g., cough, shortness of breath), **and**

3. Negative results of an FDA Emergency Use Authorized molecular assay for COVID-19 from at least two consecutive nasopharyngeal swab specimens collected ≥24 hours apart (total of two negative specimens)

**Ongoing Restrictions if release from quarantine occurs prior to 14 days**

1. Wear a facemask at all times while in the healthcare facility until all symptoms are completely resolved or until 14 days after illness onset, whichever is longer

2. Be restricted from contact with severely immunocompromised patients (e.g., transplant, hematology-oncology) until 14 days after illness onset

3. Adhere to hand hygiene, respiratory hygiene, and cough etiquette (e.g., cover nose and mouth when coughing or sneezing, dispose of tissues in waste receptacles)

4. Self-monitor for symptoms, and seek re-evaluation from occupational health if respiratory symptoms recur or worsen
Respiratory and Pulmonology

Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)

Pathophysiology

1. Histology of COVID-19 associated lung disease shows bilateral diffuse alveolar damage with cellular fibromyxoid exudates, desquamation of pneumocytes, pulmonary edema, and hyaline membrane formation.
   1. Autopsy findings such as diffuse alveolar damage and airway inflammation reflect true virus-related pathology; other findings represent superimposed or unrelated processes. (American Journal of Clinical Pathology, \textit{aqaa062}, \url{https://doi.org/10.1093/ajcp/aqaa062})
2. There is also some evidence of direct viral injury to lung tissue. (Xu et al, \textit{Lancet Respir Med}, 2020).

Definition of Acute Respiratory Distress Syndrome (ARDS)

1. Many patients with COVID-19 who require ICU level of care will develop bilateral lung infiltrates.
2. The Berlin definition of ARDS requires the following four criteria:
   1. Acute (onset over 1 week or less)
   2. Bilateral opacities detected on CT or chest radiograph
   3. PF ratio <300mmHg with a minimum of 5 cmH2O PEEP (or CPAP)
   4. Must not be fully explained by cardiac failure or fluid overload

<table>
<thead>
<tr>
<th>Severity</th>
<th>PaO2/FiO2 (on PEEP/CPAP &gt;5)</th>
<th>Mortality (all cause, cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>200-300</td>
<td>27%</td>
</tr>
<tr>
<td>Moderate</td>
<td>100-200</td>
<td>32%</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;100</td>
<td>45%</td>
</tr>
</tbody>
</table>

Time course

1. Anecdotally, many report that progression of hypoxemic respiratory failure occurs rapidly (within ~12-24 hours).
2. From onset of symptoms, the median time to:

Management of Hypoxemia for COVID PUI/ Confirmed Cases

Supplemental Oxygen Escalation

If a patient requires >6L, consideration for ICU transfer. We recommend trial of proning with the need for 3-6 liters of oxygen if the patient is able to tolerated. If possible, utilize a protocol that the patient (if able to do independently) uses oxygen supplied by nasal canula and independently can prone themselves for 30 minutes-3 hours at least three times daily. They should be monitored. *This patient does not necessarily needs to be intubated at this or needs immediate ICU transfer.* ([https://rebelem.com/covid-19-hypoxemia-a-better-and-still-safe-way/](https://rebelem.com/covid-19-hypoxemia-a-better-and-still-safe-way/))

In addition, consideration can be given to the ROX score for closer monitoring. Although this was validated for high flow nasal canula, an indication of improvement or failure may be acquired by utilizing similar parameters in COVID-19 patients. ([https://www.atsjournals.org/doi/10.1164/rccm.201803-0589OC](https://www.atsjournals.org/doi/10.1164/rccm.201803-0589OC))

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High Flow Nasal Cannula:

HFNC should be used if the patient can tolerate and monitored closely for decompensation as a mechanism to delay intubation. There is some evidence that intubating early in these patients based on the physiology of the disease may cause more harm. ([https://www.atsjournals.org/doi/pdf/10.1164/rccm.202003-0817LE](https://www.atsjournals.org/doi/pdf/10.1164/rccm.202003-0817LE))

We recommend trial of proning with HFNC with the need for >6 liters of oxygen, in the ICU if there is bed availability, if the patient is able to tolerate. We are utilizing a protocol that the patient (if able to do independently) uses oxygen supplied by high flow nasal canula and independently prones themselves for 30 minutes-3 hours at least three times daily. They should be monitored. ([https://rebelem.com/covid-19-hypoxemia-a-better-and-still-safe-way/](https://rebelem.com/covid-19-hypoxemia-a-better-and-still-safe-way/))

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BIPAP/CPAP (NIVV)

Consideration for BIPAP/CPAP as a means to avoid intubation

Has a risk for aerosolization

If using, should be used with appropriate filter

Select DNI patients as a bridge to family arrival or intervention

If NIPPV/HFNC is used, it should be under airborne precautions including a negative pressure room with providers in PPE for aerosolized procedures

Patients utilizing CPAP/BIPAP at home for established OSA should be considered for other modalities as the risk of asymptomatic COVID is present. If necessary, they should be quarantined. ([https://aasm.org/covid-19-resources/covid-19-faq])
STEPWISE APPROACH TO WORSENING HYPOXIA AT OSU
1. For patients with progressive O2 requirements consider awake proning


1. Have them self-prone for at least 30 minutes at a time increasing up to 3 hours with a goal of 3 times a day (https://www.youtube.com/watch?v=HCrSUwqoX0I)
2. Encourage proning for as long as they will tolerate it (ideally 16 hours a day)
3. Make sure that you have the patient to a form of oxygen monitoring (continuous pulse ox or continuous cardiac monitoring)

**Intubation:**

1. Contact the airway team (30 minutes prior to intubation to provide ample time for preparation)
   1. Anesthesia 0700-1900
   2. ED 1900-0700
   2. If appropriate provide ROX score if it was completed

2. Rapid Sequence Induction (RSI) should be performed, avoiding bagging

3. By the most experienced airway provider


**3. If HFNC or NIPPV are used:**

1. For HFNC, patient wears surgical mask and us least amount of flow rate to reduce concerns of aerosolization Measured exhaled air distances are minimally increased with CPAP pressures up to 20 cm H2O and HFNC up to 50 LPM; importantly device/interface leaks cause significant lateral air travel (Hui et al, *Eur Respir J*, 2019)
2. For BiPAP, use BWH NIPPV machine with dual limb with a HEPA filter and BWH mask without anti-asphyxia valve Ensure masks/devices fit well and there is minimal air leak
3. Use both under airborne precautions, including N95 and strict isolation

**Initial Mechanical Ventilation**
Checklist following intubation and patient is demonstrating ARDS type physiology (low compliance)

1. Set the initial ventilator settings:
   1. Initiate ARDS ventilation as described below
   2. Determine PEEP and mechanics as described below
   3. Assure adequate sedation as described below

2. Obtain STAT portable CXR to confirm endotracheal tube location
   1. Prioritize CXR and vent settings over procedures (such as central venous catheter placement) if possible.

3. Obtain an ABG (preferred) or a VBG within 30 minutes
   1. Calculate P/F ratio from initial post-intubation ABG. Adjust oxygenation as described below
   2. Goal pH 7.25 to 7.45 adjust ventilation as described below

Use of Single Ventilator Multiple Patients

1. The ASA, SCCM, APSF, AARC, AACN, and CHEST societies have issued a joint consensus statement against using single ventilator for multiple patients (Joint Statement On Multiple Patients Single Ventilator).

Initial ARDS Ventilation Settings

1. Set mode to volume control (AC/VC)
2. Set Initial tidal volume (Vt):
   1. \( V_t = 6 \text{ ml/kg} \) (based on ideal body weight [IBW] from ARDSnet table, see table below)
      1. IBW men (kg) = 50 + 2.3 (height in inches – 60)
      2. IBW women (kg) = 45.5 + 2.3 (height in inches – 60)
3. **Set Initial respiratory rate**

1. Typical starting rates will be 16-24 titrated to goal minute ventilation of 5-8 L/min
2. Consider starting rates of 24-28 titrated to goal minute ventilation of 8-12 L/min in setting of acidosis (pH < 7.25) pre-intubation

4. **Set an Initial PEEP based on BMI (empirically chosen targets):**

1. BMI < 35: PEEP 5
2. BMI > 35: PEEP 10

5. **Initial FiO2:** 100% on intubation then rapidly wean to SpO2 92-96% (Barrot et al, *N Engl J Med*, 2020)

**Determining PEEP and mechanics**

1. **Titrate FiO2 and PEEP for oxygenation**

   1. Initiate PEEP based on BMI, per above, and then titrate PEEP and FiO2 to target oxygenation SpO2 92-96% as per the following guidelines:
1. **BMI < 35**: titrate PEEP and FiO2 as per the ARDSnet LOW PEEP table

<table>
<thead>
<tr>
<th>FiO2</th>
<th>0.3</th>
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<tr>
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<td>14</td>
<td>16</td>
<td>18</td>
<td>18-24</td>
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</tbody>
</table>

2. **BMI ≥ 35**: titrate PEEP and FiO2 as per the ARDSnet HIGH PEEP table

<table>
<thead>
<tr>
<th>FiO2</th>
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<td>22</td>
<td>24</td>
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</table>

2. If SpO2 < 92% or > 96% then titrate PEEP and FiO2 according to the ARDSnet table as per BMI

3. **Special consideration**: anecdotal reports of COVID-19 patients describe a compliant, highly PEEP dependent phenotype in which PEEP management may not strictly adhere to specified ARDSnet tables (e.g., FiO2 0.4 - 0.5 but does not tolerate PEEP <10)

   1. Poor tolerance to high PEEP is likely as the result of the direct and severe lung damage by the virus and inflammatory reactions. The plateau pressure reaches 40 to 50 cm H2O when the PEEP is set at 18 cm H2O, FiO2 at 100%, and the tidal volume at 6 ml/kg according to the FiO2 and PEEP table. The widely used practice in Wuhan, after lung recruitment maneuvers, is to set PEEP at 20 cm H2O and titrate down in a decrement of 2 to 3 cm H2O each time until the goals of oxygenation, plateau pressure, and compliance are all achieved. The commonly used PEEP in this patient population is less than 10 cm H2O.


4. Avoid elevated plateau pressures (with goal < 30), particularly if using the higher PEEP table.

2. **Obtain respiratory mechanics**:

   1. Plateau pressure (goal ≤ 30)
   2. Static compliance
Sedation and Ventilator Synchrony

1. **If unparalyzed, target sedation to ventilator synchrony or RASS -2 to -3 (see table below):**

1. Ventilator-induced lung injury (VILI) is more likely in patients who are not synchronous with the ventilator and can cause lasting damage. After paralytics have worn off, assess patient synchrony with the ventilator (e.g., signs of breath-stacking, double triggering, other ventilator alarms).

   1. Titrate sedatives/analgesics to ventilator synchrony allowing for deeper RASS.
   2. If patient remains dyssynchronous despite deep sedation (RASS -5), initiate continuous paralytics (ensure BIS 40 to 60 prior to initiating and during paralysis).

2. **If paralyzed, target sedation to BIS 40 to 60 and titrate level of neuromuscular blockade to ventilator synchrony:**

1. Maintain deep sedation immediately post-intubation while paralyzed (assume 60 minutes for Rocuronium, 10 minutes for succinylcholine)

   1. Preferred initial sedation regimen:

      1. Fentanyl (boluses +/- infusion) + Propofol: target analgosedation and optimize analgesia first while decreasing sedative requirements

      1. Recommend to obtain baseline triglycerides, lipase and CK if the patient is on propofol. While the patient continues on propofol would recommend checking triglyceride levels daily (if triglycerides are elevated may check lipase and CK q24 or q48h depending on trends).

      1. Patients with severe respiratory failure secondary to COVID may have elevated triglyceride levels, however if lipase and CK remain normal to slightly elevated would continue propofol before switching to an alternative form of sedation if needed for ventilator synchrony (i.e. midazolam) until triglycerides reach > 1000 or elevated CK, lipase and/or concern for pancreatitis

2. Adjunct agent: Midazolam

3. Use dexmedetomidine only when nearing extubation
Ventilator Adjustments and Daily Management

General management of ventilated patients

1. Consider whether patient requires daily CXR:

   1. CXR clearly indicated for:
      
      1. Clinical change
      2. Concern for displaced ET tube:
         
         1. Sudden increase in peak inspiratory pressure or resistance
         2. Decreased, unilateral breath sounds (usually on the right)
         3. RN or RT concern for change in depth of ET tube at teeth

3. Ventilator consults:

   1. If you need additional assistance managing ventilator choices, you can request a pulmonary phone/in-person consult

Changing ventilation parameters (respiratory rate and tidal volume)

1. Follow ARDSnet ventilation where possible:
1. Starting tidal volume of 6 cc/kg (Tidal volumes should be 4-6 cc/kg using IBW (see table above) to excessive pressures and ventilator injury).

2. **Minute ventilation (respiratory rate x tidal volume) typically drives pH and PCO2:**

   1. Titrate ventilatory parameters to pH and not PCO2.

      1. To achieve low tidal volumes will tolerate hypercapnia (functionally no limitation unless clinical sequelae) and acidemia (pH > 7.2).
      2. Because tidal volumes are low, the respiratory rate often has to be high to accommodate; typical RR is 20-35 breaths/minute.


      1. If pH > 7.45, decrease respiratory rate
      2. If pH 7.15-7.30, then increase respiratory rate until pH > 7.30, or PaCO2 < 25 (maximum RR= 35 breaths/minute)
      3. If pH < 7.15, then increase respiratory rate to 35 breaths/minute
      4. If pH still < 7.15, then perform the following:

         1. Tidal volume may be increased by 1 mL/kg until pH > 7.15 (until plateau pressure reaches 30 cm H2O or tidal volume reaches 8 cc/kg)
         2. Deep sedation advancing to RASS -5 if needed
         3. If no improvement, initiate continuous paralysis
         4. If still no improvement, initiate prone ventilation (may improve V/Q matching and better ventilation)

**Changing oxygenation parameters**

1. **Minimize oxygen toxicity:** PEEP and FiO2 drive oxygenation


   2. Extensive mammalian animal data demonstrates that hyperoxic injury occurs at an FiO2 ≥ 75% (at sea level) with the rate of injury increasing as FiO2 exceeds that threshold. In multiple mammalian models, an FiO2 of 100% for 48 to 72 hours is associated with nearly 100% mortality rate. In these models, FiO2 < 0.75 appears to be a key threshold for injury. For a review of hyperoxic acute lung injury, see Kallet and Matthay, *Respir Care*, 2013.
2. **PEEP Optimization:**

   1. PEEP should be set and titrated as explained above using the ARDSNET PEEP tables to guide FiO2 and PEEP determination.

   2. In other contexts, some patients in severe, fibrotic stage ARDS require very low PEEP (even <5 occasionally). Anecdotally, this very low compliance phenotype may be less common in COVID-19, but should not be missed (e.g., by tracking respiratory mechanics).

3. **COVID-specific data.** Preliminary anecdotal reports suggest a common phenotype of high compliance with PEEP-sensitive hypoxia. The pathophysiology of this phenotype has yet to be determined but it may reduce the efficacy of the ARDSNET PEEP tables to guide FiO2 and PEEP management.

3. **Adjust FiO2:**

   1. Goal FiO2 < 60%; if FiO2 >60%; patient requires ventilator optimization. If you need assistance, pulmonary consultation is available (pager 11957)

   1. It is reasonable to put a desaturating patient temporarily on 100% FiO2, but remember to wean oxygen as rapidly as possible.

4. **Check plateau pressure:**

   1. Check plateau pressure with every change in tidal volume, PEEP, or clinical deterioration (worsening oxygenation) but not as part of routine practice.

   2. If plateau pressure is >30 cm H2O, then decrease tidal volume by 1 mL/kg (minimum 4 mL/kg).

   3. If plateau pressure is < 25 H2O and tidal volume < 6 mL/kg, then increase tidal volume by 1 mL/kg until plateau pressure is > 25 cm H2O or tidal volume = 6 mL/kg.

   4. If plateau pressure is < 30 cm H2O and patient is breath stacking or dyssynchronous, then increase tidal volume in mL/kg increments to 7 mL/kg or 8 mL/kg while plateau pressure is < 30 cm H2O.

**BILEVEL Ventilatory Modes**

1. OSU current practice is to trial use of bilevel ventilation either as salvage therapy in patients with persistent hypoxemia not responsive to advanced conventional therapy who are also not ECMO candidates or in patients with persistent ventilator dyssynchrony that is impairing weaning and lightening of sedation.

2. There may be a role for bilevel-type ventilatory support for patients with COVID who require high PEEP pressures but at present, our preference is to use bulk flow ventilation methods.
based on local experience and lack of definitive evidence of superiority of bilevel methods for general use.

3. BILEVEL ventilation will required consultation with pulmonary medicine and require deep sedation with RAAS -4 or -5 in addition to paralytic therapy.

Refractory hypoxemia

1. Refractory Ventilator Hypoxemia pathway:

   1. If patient is hypoxic (PaO2 <75) on individualized PEEP setting from PV tool (or PEEP based on ARDSnet table

      and FiO2 >= 0.6 or PaO2 / FiO2 ratio < 150

      Perform the following in this order:

      1. Optimize volume status by diuresing;

      if no improvement then:

      2. Deep sedation, advancing to RASS -5 if needed;

      if no improvement then:

      3. Initiate continuous paralysis (cisatracurium bolus 0.2mg/kg followed by infusion at 0-5 mcg/kg/min titrated to patient-ventilator synchrony);

      if no improvement then:

      Initiate prone ventilation early: Discuss proning when PaO2/FiO2 < 150 and a requirement of 12 hours of FiO2 of > 75%.

      For adults receiving mechanical ventilation who have moderate to severe ARDS, prone ventilation for 12 to 16 hours is suggested over no prone ventilation

      Use as-needed neuromuscular blocking agents (NMBAs) instead of continuous NMBA infusion to facilitate protective lung ventilation is suggested (Poston JT, Patel BK, Davis AM. Management of Critically Ill Adults With COVID-19. JAMA. Published online March 26, 2020. doi:10.1001/jama.2020.4914)

      if no improvement then:
Consideration for use of lung recruitment maneuvers (intended to open otherwise closed lung segments, such as 40 cm H2O inspiratory hold for 40 seconds) (Poston JT, Patel BK, Davis AM. Management of Critically Ill Adults With COVID-19. *JAMA.* Published online March 26, 2020. doi:10.1001/jama.2020.4914)

if no improvement then:

6. Consider ECMO consultation (see below) if, despite the above steps:
   1. Persistent PaO2 < 75 requiring FiO2 > 0.75
   2. Plateau pressure >30
   3. Refractory hypercapnia and pH < 7.2
   4. Absence of contra-indications (see ECMO section)

**Prone Ventilation**

1. **Prone early:**

   1. We recommend early proning in severe ARDS prior to vasodilator trial (a departure from our typical practice for ARDS not due to COVID-19): < 36 hours from ARDS onset, start discussion of prone when P:F < 150, prone within 12 hours of FiO2 > 75% (Guérin et al, *N Engl J Med*, 2013).

2. **Eligibility criteria for proning:**

   1. The only absolute contraindications to prone ventilation are spinal cord injury, open chest or abdomen, and unstable airway; BMI and patient size are not absolute contra-indications
   2. For tracheostomy, prior COVID-19 patients would typically have their tracheostomy replaced by oral endotracheal intubation (ETT). In the setting of COVID-19, this intubation procedure would be higher risk. The ICU team and anesthesiology should carefully discuss the ability to prone with tracheostomy versus the risks of replacing tracheostomy with ETT.
   3. RRT can be performed while prone (e.g, by femoral vein catheter) but should be discussed with renal consultation prior to proning

3. **Managing a prone patient:**

   1. The proning protocol that is being utilized will be the one that is offered by the DOD. [file:///Users/mousumisom/Downloads/DoD%20COVID19%20Practice%20Management%20Guide%20V10%20%283%29.pdf](file:///Users/mousumisom/Downloads/DoD%20COVID19%20Practice%20Management%20Guide%20V10%20%283%29.pdf)
   2. Prone >16 hrs per 24 hrs. Supine >4 hrs per 24 hrs.
   3. 1 hour post-initiation of prone ventilation:
1. Adjust oxygen parameters: re-assess lung mechanics (plateau pressure and re-optimize PEEP, see above)

2. Assess tidal volume and adjust ventilation parameters as in section 6

   1. Preferred tidal volume is 6 ml/kg (range 4-8)
   2. Goal plateau pressure < 30

4. If patient demonstrates improvement on proning then recommend:

   1. Discontinue neuromuscular blockade while maintaining deep sedation to limit risk of extubation. Resume neuromuscular blockade in setting of patient:ventilator dyssynchrony.
   2. Consider discontinuing further proning if patient meets these goals after supine for >4 hrs:

      1. PaO2 / FiO2 ratio > 200
      2. Ppl < 30
      3. pH > 7.25
      4. FiO2 < 60%

5. In mechanically ventilated adults with COVID-19, severe ARDS and hypoxemia despite optimizing ventilation and other rescue strategies, the society of critical care medicine does 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.

**ECMO consultation**

The use of ECMO in COVID-19 is unknown. In one report, out of 28 patients who received ECMO, 14 died, nine were still on ECMO, and only five were successfully weaned (DOI: [https://doi.org/10.1016/S2213-2600(20)30161-2](https://doi.org/10.1016/S2213-2600(20)30161-2))

1. **OSU ECMO guidelines**

   1. **Indications:**

      1. Persistent PaO2 / FiO2 ratio < 75 mmHg despite optimized ARDS management (optimized PEEP, neuromuscular blockade, proning).
      2. Plateau pressure > 30 cm H2O on ARDSnet ventilation.
      3. pH < 7.2
4. No potentially reversible causes (e.g., pulmonary edema, mucus plug, abdominal compartment syndrome)

2. **Contra-indications**: Each patient is assessed on a case-by-case basis.

   Absolute or relative contra-indications can include:

   5. Advanced age
   6. Active malignancy
   7. Severe shock; high cardiac output state
   8. Multi-system organ failure
   9. Prolonged ventilation or ARDS with poor chance of pulmonary recovery or severe chronic lung disease.
   10. Severe neurologic injury or intra-cranial hemorrhage
   11. Overall poor life expectancy (e.g., < 6 months); poor functional status at baseline; poor potential to recover functional status.
   12. Active hemorrhage or inability to anti-coagulate
   13. Thrombocytopenia (plt < 50)
   14. Neutropenia (ANC < 500)
   15. BMI > 35 / total body weight > 300 pounds

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**Ventilator Weaning and Extubation**

1. Clinical goal is to liberate patients from mechanical ventilation as soon as safe and feasible.

   1. Prolonged intubation is associated with ventilator-associated pneumonia (VAP) with median-time to VAP onset of 8 days in retrospective study of 191 COVID patients in Wuhan (Zhou et al, Lancet, 2020).

2. All patients with improving or stable respiratory disease should be considered for weaning from sedation and mechanical ventilation when they meet the following criteria:

   1. Improving or stable respiratory disease
   2. FiO2 ≤ 50%, PEEP ≤ 10 with SpO2 >92%
   3. Hemodynamically stable (minimal to no vasopressor requirements to maintain target MAPs)

3. Assess patient readiness for weaning at least once daily
1. A daily spontaneous breathing trial (SBT), consisting of temporary cessation of sedatives until a RASS of 0 is achieved, is be considered for all patients who meet the following criteria:

1. Patients are in supine position
2. Continuous paralytics discontinued for a minimum of 6 hours prior to SAT and has evidence of spontaneous motor activity and/or train of fours is 4/4 for neurostimulator test
3. Hemodynamically stable (defined as HR < 120, MAP > 65, and vasopressor requirement of levophed gtt < 10 mcg/min)
4. SpO2 > 92% or PaO2 > 75 with an FiO2 ≤ 50% and PEEP ≤ 10 (and most recent Ppl < 30)

2. A daily spontaneous breathing trial (SBT) is considered for all patients who meet the requirements for a daily SAT

1. SBT consists of Pressure Support ventilation mode with a PS = 5 and PEEP = 5
2. SBT discontinued if the patient develops
   1. Evidence of increased work of breathing with RR > 30
   2. Hypoxia (SpO2 < 92%)
   3. Hemodynamic instability
   4. Rapid shallow breathing index (RSBI) = RR/TV > 105
3. Terminate all SBTs after 30 minutes and return to prior VC settings if patients are deemed not ready to extubate

4. Extubation readiness:

1. Extubation should be considered if patients meet the following criteria
   1. Breathing spontaneously
   2. RASS 0 to -1
   3. Able to follow commands
   4. Intact cough and able to protect airway
   5. Requiring airway suctioning for secretion < q2h

2. Other considerations include:
   1. FiO2 < 40% at the time of extubation
   2. Optimization of volume status prior to extubation
5. Weaning can fail in the setting of the following conditions (address appropriately) from Boles et al, ERJ, 2007:

1. Respiratory factors:
   1. Ongoing pneumonia or pulmonary inflammation
   2. Bronchoconstriction
   3. Glottic and airway edema, sputum production, impaired cough

2. Cardiac factors:
   1. Cardiac dysfunction or shock

3. Neuromuscular factors
   1. Weakness and prolonged immobility
   2. Effects of steroids or neuromuscular blockade

4. Neuropsychological factors
   1. Delirium
   2. Sedating medications

5. Metabolic factors
   1. Malnutrition
   2. Electrolyte disturbances (hypophosphatemia, etc)
Therapeutics and Clinical Trials:
There are no proven therapies for COVID-19. All therapies are based off of small trials that do not have large numbers to definitively identify risks or benefits. However, during this period where there is not ample time to run double blinded placebo controlled trials, all attempts are being focused at determining if there are effective treatment strategies to help contain the pandemic.

Overview

Therapeutics summary

1. The anti-viral and anti-inflammatory section is meant to provide a summary of the literature. As this data is continuously evolving, we recommend consultation with the COVID taskforce in addition to infectious disease and pulmonary critical care when implementing therapies.
2. The following link is connected to ASHP (American Society of Healthcare Pharmacists). This provides an overview of medications being reviewed for their use for COVID patients:
   https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx?la=en&hash=B414CC64FD64E1AE8CA47AD753BA744EDF4FFB8C&hash=B414CC64FD64E1AE8CA47AD753BA744EDF4FFB8C

Infectious Diseases Consultation

1. The inpatient Infectious Diseases (ID) team may be consulted for patients with +COVID-19 PCR as well as patients with both clinical history and any chest imaging suspicious for COVID-19.
2. Re-consultation should occur if the patient develops ARDS (mechanically-ventilated with P/F ratio < 300) or shock/cytokine activation syndrome.
3. Consultations will be telephonic to minimize health care exposure to ensure that they will be able to participate in ongoing care of COVID positive patients. Infectious disease will work in close collaboration with the Clinical Pharmacy Team to ensure that protocols are being followed.

Antibiotics

**Give oral antibiotics when possible to reduce volume load, unless concerns for poor oral absorption.**
Choice of agent


2. Antibiotics should reflect IDSA guidelines, presumed source, and MDRO risk.

   1. For empiric coverage for a presumed pulmonary source of infection:

      1. In patients without risk factors for MRSA or *Pseudomonas* (*i.e.*, living in community, no prior MDROs), start with ceftriaxone + azithromycin. (Metlay et al, Am J Respir Crit Care Med, August 2019.)

      2. In patients with risk factors for MRSA or *Pseudomonas* (*i.e.*, chronic hospitalization, prior MDR infections), start with vancomycin + cefepime + azithromycin. (Metlay et al, Am J Respir Crit Care Med, August 2019.)


3. For coverage of potential coinfections:

   1. If concurrent influenza, treat with oseltamivir.

Discontinuation
1. Unnecessary antibiotics should be discontinued as soon as possible (ideally, within 48 hours). *Clinical judgement should prevail over any specific lab value*, but we suggest discontinuing when the following criteria are met:

1. Clinical status is not deteriorating.
2. Cultures do not reveal pathogens at 48h and/or Procalcitonin and WBC are relatively stable from 0 to 48h

**Metered-Dose Inhalers (MDIs) vs. Nebulizers**


**Non-intubated patients**

1. If COVID-19 is confirmed or suspected:
   1. Use metered dose inhalers (MDIs), NOT nebulizers, due to increased aerosol risk associated with nebulization. Because MDI supply is limited, only prescribe when needed.
   2. Ask patients / families to bring in their home inhalers if possible.

2. In patients WITHOUT suspicion for COVID-19:
   1. Use nebulizers even if on droplet precautions (*e.g.*, influenza) because MDI supply is limited.
   3. If COVID-19 is ruled out (and no patient is longer on COVID precautions per infection control):
      1. Continue patient’s current inhalers until they run out, then switch to nebulizers.

**Intubated patients**

1. At OSU, an in-line nebulizer container is part of a closed ventilator circuit, so nebulizers can be used without opening the circuit and increasing aerosol risk.
1. Other hospitals may need to add this setup or add other options, such as a Heat-Moisture-Exchanger that allows MDI delivery into a closed circuit.

**Airway Clearance**

**Management principles**

1. Anecdotal reports from Wuhan and Italy indicate that some patients develop very thick secretions causing dangerous mucus plugging. However, use of nebulizers and airway clearance techniques may aerosolize secretions.

1. Airway clearance should be used only in selected ventilated patients (closed-circuit) with extremely thick secretions, to avoid mucus plugging that would require bronchoscopy.

**Secretion thinning**

1. Nebulized treatments

   1. **Only use in ventilated patients on strict airborne precautions in a negative-pressure room.**
   2. Options include:

      1. Normal (0.9%) saline nebulizer BID.
      2. Avoid N-acetylcysteine due to bronchospasm and frequent dosing requirements.

**Mechanical airway clearance**

1. Avoid oscillating positive expiratory pressure devices (Aerobika or Acapella) and cough assist (MIE) devices, due to aerosolization risk and unclear benefit in COVID-19.

2. Avoid routine use of chest PT, but can continue chest PT vests if the patient uses at home (e.g., CF patients) with appropriate isolation precautions. Patients with bronchiectasis may be considered on a case-by-case basis.

**Systemic Corticosteroids**

**Corticosteroids**
Pathophysiology:

1. Potent anti-inflammatory and antifibrotic properties; low doses of corticosteroids may prevent an extended cytokine response and may accelerate resolution of pulmonary and systemic inflammation in pneumonia

2. May improve dysregulated immune response caused by sepsis (possible complication of infection with COVID-19) and increase BP when low

Recommendations

At this time, we do not recommend steroids for COVID-19 treatment unless in the case of patients who have severe ARDS and the treatment is then for severe ARDS. This is in line with WHO guidance (WHO, COVID-19 Interim guidance, March 2020) Surviving Sepsis Campaign COVID-19 Guidelines, Intensive Care Med, March 2020)

If treating another indication, use corticosteroids at a low dose for a short duration:

1. **For asthma or COPD exacerbation**, treat with either 1mg/kg or 40mg prednisone PO (whichever dose is less) or 30mg methylprednisolone IV, once daily x 3-5 days.

2. **For shock with history of chronic steroid use in excess of 10mg prednisone daily**, treat with 50mg hydrocortisone IV Q6H until improvement in shock.

3. **For multipressor shock without history of chronic steroid use**, treat with 50mg hydrocortisone IV Q6H until improvement in shock.

Evidence


No randomized controlled clinical studies with corticosteroids for COVID-19 or other coronaviruses have been conducted; however, indirect evidence from studies in patients with community-acquired pneumonia, ARDS, and other viral infections has been used to inform treatment decisions for COVID-19 patients. (Russell CD, Millar JE, Baillie JK. Clinical evidence

A retrospective cohort analysis of patients with COVID-19 who developed ARDS (n=84) noted that methylprednisolone treatment was associated with a decreased risk of death (Wu et al, *JAMA Int Med*, 2020). The SCCM does support using systemic corticosteroids if a COVID positive patient develops ARDS, over not using corticosteroids. There was an additional remark that the majority of their panel support a weak recommendation (i.e., suggestion) to use steroids in the sickest patients with COVID-19 and ARDS. However, because of the very low-quality evidence, some experts on the panel preferred not to issue a recommendation until higher quality direct evidence is available. (Surviving Sepsis Campaign COVID-19 Guidelines, *Intensive Care Med*, March 2020)

An earlier, non-blinded randomized controlled trial of patients with ARDS (not COVID-19) suggested a benefit to dexamethasone treatment (Villar et a, *Lancet Resp Med*, 2020) but this has not been replicated as of yet.

**Remdesivir**

1. If treatment of COVID-19 is being considered, remdesivir through clinical trials, compassionate care or Expanded Access Program should be discussed with the infectious diseases study team for key inclusion and exclusion criteria (NCT04323761) [https://rdvcu.gilead.com/](https://rdvcu.gilead.com/)

**Evidence**

1. Remdesivir is a nucleotide prodrug metabolized to an analog of adenosine triphosphate, which inhibits viral RNA-dependent RNA polymerase, causing premature termination of RNA transcription.
3. There is not yet adequate evidence for remdesivir against SARS-CoV-2 *in vivo*
   1. One case report has been published on the use of remdesivir in a 35-year-old male who improved one day after remdesivir was initiated, but it is unclear if the use of remdesivir resulted in this improvement (Holshue, *N Engl J Med*, 2020)
4. For the treatment of Ebola, remdesivir did not show favorable outcomes compared to other investigational agents (MAb114 and REGN-EB3) in a randomized controlled trial (Mulangu et al, *N Engl J Med* 2020)

Compassionate use of remdesivir has showed some amount of success in a small trial. No viral load data to confirm the antiviral effects of remdesivir or any association between baseline viral load and viral suppression, if any, and clinical response. Moreover, the duration of remdesivir therapy was not entirely uniform in the study, largely because clinical improvement enabled discharge from the hospital. There was also a lack of a controlled randomized control group. (Grein J, et al. Compassionate use of remdesivir for patients with severe COVID-19. NEJM 2020; DOI: 10.1056/NEJMoa2007016.)

**Recommendations**

1. If eligible, patients should be enrolled in the remdesivir clinical trials for COVID-19 moderate or severe disease

**Dosing Regimen**

1. Remdesivir is only available as an investigational agent through clinical trials, compassionate use or expanded access program.
2. 200 mg IV loading dose, followed by 100 mg IV daily for a total of 5 or 10 days, depending on the clinical trial arm

**Monitoring and Toxicity**

1. Elevated liver function tests (AST, ALT), phlebitis, constipation, headache, nausea
2. Remdesivir is co-formulated with sulfobutyl ether β-cyclodextrin (SBECD), so there is a theoretical risk of accumulation in renal failure promoting further renal injury, similar to intravenous voriconazole

**Hydroxychloroquine and Chloroquine**

**Pathophysiology**

2. HCQ is thought to act through multiple mechanisms (Devaux et al, Int J Antimicrob Agent, 2020):

1. **Inhibition of viral entry.** HCQ inhibits synthesis of sialic acids and interferes with protein glycosylation, which may disrupt interactions necessary for viral attachment and entry (Vincent et al, Virol J, 2005; Olofsson et al, Lancet Infect Dis, 2005).

2. **Inhibition of viral release into the host cell.** HCQ blocks endosomal acidification, which activates endosomal proteases. These proteases are required to initiate coronavirus/endosome fusion that releases viral particles into the cell (Yang et al, J Virol 2004).

3. **Reduction of viral infectivity.** HCQ has been shown to inhibit protein glycosylation and proteolytic maturation of viral proteins. Studies on other RNA viruses have shown a resulting accumulation of non-infective viral particles, or an inability of viral particles to bud out of the host cell (Savarino et al, J Acquir Immune Defic Syndr, 2004; Klumperman et al, J Virol, 1994).

4. **Immune modulation.** HCQ reduces toll-like receptors and cGAS-STING signaling. It has been shown to reduce release of a number of pro-inflammatory cytokines from several immune cell types (Schrezenmeier and Dorner, Nat Rev Rheum, 2020).

**Evidence**

1. An expert consensus group out of China suggests that chloroquine improved lung imaging and shortened disease course (Zhonghua et al, CMAPH, 2020). Chloroquine is included in the treatment guidelines from the National Health Commission of the People's Republic of China, but the specific data on which this is based is not available yet (Gao et al, Biosci Trends, 2020).

2. Hydroxychloroquine was found to be more potent than chloroquine in inhibiting SARS-CoV-2 in vitro (Yao et al, Clin Infect Dis, 2020).

3. A small French study has received international attention over the potential of hydroxychloroquine and azithromycin in combination for the treatment of COVID-19 (Gautret, Int J Antimicrob Agents, 2020). This study lacks a control arm.

1. This study is limited and until more studies are done, the risks of QTC prolongation and torsades de pointes outweigh the potential benefits

2. At this time, there is not enough supporting evidence to use azithromycin for COVID-19, unless concomitant community-acquired pneumonia is suspected and atypical coverage is desired
**Recommendations**

1. **Consideration should be given for use of hydroxychloroquine** in patients who:

   1. Inpatient requiring supplemental oxygen OR are inpatients not on supplemental oxygen but at high risk for progression to severe disease
   2. At this time, there is not enough supporting evidence to use azithromycin for COVID-19, unless concomitant community-acquired pneumonia is suspected and atypical coverage is desired.
   3. Optimal dosing is not yet known about hydroxychloroquine for the treatment of COVID-19 positive patients.

**Dosing regimens**

1. **Hydroxychloroquine**: 400mg PO BID on the first day, followed by 200mg q12h for 5 days. This can be administered to either positive RT-PCR COVID patients or PUI.

   1. May extend up to 10 days depending on clinical response, with ID recommendation.
   2. The half-life of HCQ is over 7 days, so a 5-day treatment course should still yield therapeutic HCQ levels past day 10 (Yao et al, *Clin Infect Dis*, 2020).

**Monitoring and Toxicity**

1. Hydroxychloroquine is contraindicated in epilepsy and porphyria. Known adverse effects include:

   1. Bone marrow suppression
   2. Cardiomyopathy and retinopathy

   1. Case series and reports have found this to be a long-term (years) and dose-dependent phenomenon. Given the anticipated short duration in COVID-19, it is not an expected risk (Nord et al, *Semin Arthritis Rheum*, 2004; Yusuf et al, *Eye*, 2017).

   3. QT-segment prolongation and therefore torsades de pointes, especially if administered in combination with azithromycin or other QT-prolonging medications.

   4. For a full list of interacting medications, please visit [https://www.crediblemeds.org/](https://www.crediblemeds.org/)
2. Given this, the following monitoring is required for patients being treated with hydroxychloroquine:

1. Obtain baseline ECG, ECG 3.5 hours after first dose, and daily ECG thereafter.
2. Discontinue all other QT-prolonging agents if at all possible.
4. Do not start if QTc > 500 msec (or 550 msec with pacing or BBB).
5. Discontinue if there is an increase in PVCs or non-sustained polymorphic VT.

The ACC has published a risk score for drug associated QTc prolongation which may help in determining those patients in whom these drugs may be dangerous. ACC and HCQ Risk Assessment [https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19](https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19)

**Lopinavir/ritonavir**

**Pathophysiology**

1. Lopinavir/ritonavir (Kaletra, LPV/r) has been available since 2000 as an antiretroviral agent in the treatment of human immunodeficiency virus (HIV)
2. Lopinavir and ritonavir are both protease inhibitors, which by inhibiting HIV-1 protease, leads to the formation of immature, noninfectious viral particles. Ritonavir specifically is a CYP3A4 inhibitor that is used to decrease metabolism of lopinavir (via CYP3A4 inhibition), thereby increasing serum lopinavir levels.
3. Lopinavir may theoretically work against coronaviruses like SARS-CoV-2 by inhibiting 3-chymotrypsin-like protease (3CLpro)

**Evidence**

1. Lopinavir was shown to have *in vitro* activity against both SARS-CoV-1 and MERS-CoV in some studies (Chu et al, *Thorax*, 2004; de Wilde et al. *Antimicrob Agents Chemother*, 2014), but not in others (Chan et al, *J Infect*, 2013)
2. Against SARS-CoV-1, LPV/r use (n=75) was associated with a lower overall mortality and intubation rate in one study. A subgroup analysis showed no difference in overall mortality or intubation rate however when lopinavir/ritonavir was used as rescue therapy at a median of 18 days after symptom onset (n=31) (Chan et al, *Hong Kong Med J*, 2003)
3. A recent randomized, controlled, open-label trial assessed lopinavir-ritonavir (n=99) vs. standard of care (n=100) in SARS-CoV-2 patients (Cao et al, *N Engl J Med*, 2020)
1. Treatment with LPV/r was **not** associated with a difference in time to clinical improvement or mortality

2. Randomization didn’t occur until a median of 13 days after symptom onset however, so the window for benefit may already have already closed, as seen in the Chan et al paper in SARS-CoV-1

4. There are still many ongoing trials for the use of LPV/r in COVID-19, but other results are not yet available (Yao et al, *J Med Virol*, 2020)

**Recommendations**

1. Lopinavir/ritonavir is **not** recommended as overall evidence is lacking.

**Dosing Regimen if recommended by Infectious Disease**

1. If LPV/r were to be used, the dosing regimen is 400/100 mg by mouth twice daily for up to 10 days

**Monitoring and Toxicity**

1. **Interactions** are an incredibly important aspect of LPV/r use as ritonavir is a potent CYP3A4 inhibitor, so will interact with CYP3A4 substrates (i.e. apixaban, tacrolimus, amiodarone)

2. Diarrhea, nausea, and transaminitis are common. Other adverse effects include hyperlipidemia, pancreatitis, asthenia, and hyperglycemia

**Anti-IL6 Agents (Tocilizumab, Siltuximab, Sarilumab)**

**Pathophysiology**

1. Elevated levels of IL-6 strongly associated with the need for mechanical ventilation (p=1.2.10^{-5}). In addition, the maximal IL-6 level (cutoff 80 pg/ml) for each patient during disease predicted respiratory failure with high accuracy (p=1.7.10^{-8}, AUC=0.98). The risk of respiratory failure for patients with IL-6 levels of ≥ 80 pg/ml was 22 times higher compared to patients with lower IL-6 levels [https://www.medrxiv.org/content/10.1101/2020.04.01.20047381v2](https://www.medrxiv.org/content/10.1101/2020.04.01.20047381v2)

2. IL-6 activates T cells and macrophages, among other cell types (see “Cytokine Activation Syndrome” section in “Shock” chapter). IL-6 inhibitors are approved for cytokine activation
syndrome complications related to Chimeric Antigen Receptor T cell (CAR-T) therapy (Brudno and Kochenderfer, Blood Rev, 2019; Rubin et al, Brain, 2019).

3. IL-6 levels are reported to correlate with severe COVID-19 (Ruan et al, Intensive Care Med 2020; Liu et al, unpublished report). While patients have peripheral lymphopenia, BAL fluid is often lymphocytic, suggesting that IL-6 inhibition and prevention of T cell activation may be protective.

**Recommendations**

1. **We do not recommend routine use of anti-IL-6 agents unless part of a clinical trial or recommended by ID.** There are anecdotal reports of benefit of tocilizumab in COVID-19 patients but no rigorous studies are available (Anecdotal reports from Italy; National Health Commission & State Administration of Traditional Chinese Medicine, Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia [Trial Version 7], March 2020).

2. **For severe cases of COVID-19 with suspicion of cytokine activation syndrome** (see “Other Guidance” chapter), consider use in conjunction with Infectious Diseases consultation.

   1. Retrospective reviews in patients with rheumatological disease suggest a possible increase in serious bacterial infection, so use caution if secondary infection is clinically suspected.

**Dosing regimens if recommended by Infectious Disease**

1. **Tocilizumab** (anti-IL6R mAb): 4-8mg/kg (suggested dose 400mg) IV x1. Dose can be repeated 12h later if inadequate response to the first dose. Total dose should be no more than 800mg. Tocilizumab should not be administered more than twice.

   1. Common adverse effects of tocilizumab include:
      1. Transaminitis (AST, ALT), >22%
      2. Infusion reaction, 4-20%
      3. Hypercholesterolemia, 20%
      4. Upper respiratory tract infection, 7%
      5. Neutropenia, 2-7%

2. **Siltuximab** (anti-IL6 mAb): 11mg/kg IV x1.

   1. Common adverse effects of siltuximab include:
      1. Edema, >26%
2. Upper respiratory infection, >26%
3. Pruritus / skin rash, 28%
4. Hyperuricemia, 11%
5. Lower respiratory tract infection, 8%
6. Thrombocytopenia, 8%
7. Hypotension, 4%

3. **Sarilumab** (anti-IL6R mAb): New intravenous formulation and dosing, available only as part of a clinical trial (NCT04315298).

   1. Common adverse effects of sarilumab include:

      1. Transaminitis (AST, ALT), 28-47%
      2. Neutropenia, 7-10%
      3. Infusion reactions, 7%
      4. Upper respiratory tract infections, 4%
      5. Urinary tract infections, 3%

4. **Tocilizumab and sarilumab** have black box warnings for a risk of serious infections, including tuberculosis and other opportunistic infections. Patients treated with either agent should be tested for latent tuberculosis prior to discharge from the hospital and followed up in the TB clinic if that testing is positive.

**Convalescent Plasma (Clinical Trial)**

**Pathophysiology:**

Passive immunization is a technique to achieve immediate short-term immunization against infectious agents by administering pathogen-specific antibodies. Since its introduction, it has proven to be lifesaving. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4781783/pdf/blt-16-152.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4781783/pdf/blt-16-152.pdf)

**Recommendations:**

1. OSU has developed a relationship under the Mayo Clinic Institutional Research Board, and recommend patient that have severe or critical illness related to COVID-19 be considered for
plasma infusion per Mayo Clinic Protocol. This will be done in conjunction with the PI listed for
the Mayo Clinic.

If patient is age > 18, has laboratory confirmed COVID, admitted to an acute care facility and is
determined to have severe to critical COVID infection, they will qualify for receiving CPP.

Severe COVID: Dyspnea, RR > 30/min, O2 saturation < 93%, PaO2/Fio2 < 300 or lung infiltrates
> 50% within 24 to 48 hours.

Life-Threatening COVID: Respiratory failure, septic shock or multiple organ dysfunction
syndrome.

Additional information can be obtained at:

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-
exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

2. OSU is also working with OBI to develop a protocol for donation of convalescent patients, in
order to be able to transfuse plasma to patients with moderate to severe disease associated
with COVID illness. Patients should have a positive RT-PCR diagnosis of COVID-19.

Evidence:

1. Uncontrolled case series of 5 critically ill patients with COVID-19 and acute respiratory
distress syndrome (ARDS), administration of convalescent plasma containing neutralizing
antibody was followed by an improvement in clinical status.
https://jamanetwork.com/journals/jama/fullarticle/2763983

2. Results from 10 severe adult cases showed that one dose (200 mL) of CP was well tolerated
and could significantly increase or maintain the neutralizing antibodies at a high level, leading
to disappearance of viremia in 7 d. Meanwhile, clinical symptoms and paraclinical criteria
rapidly improved within 3 d. Radiological examination showed varying degrees of absorption of
lung lesions within 7 d. https://www.pnas.org/content/early/2020/04/02/2004168117

3. In a threatened outbreak of measles in a group of preparatory school boys, 66 of whom had
not had measles, convalescent measles serum was used prophylactically. Only 3 cases of
measles, all decidedly attenuated, subsequently developed in this group.

4. A higher day-22 discharge rate was observed among patients who were given convalescent
plasma before day 14 of illness (58.3% vs 15.6%; P<0.001) and among those who were PCR
positive and seronegative for coronavirus at the time of plasma infusion (66.7% vs 20%; P=0.001). [https://www.ncbi.nlm.nih.gov/pubmed/15616839](https://www.ncbi.nlm.nih.gov/pubmed/15616839)

5. Ninety-three patients with severe H1N1 2009 infection requiring intensive care were recruited. Twenty patients (21.5%) received plasma treatment. The treatment and control groups were matched by age, sex, and disease severity scores. Mortality in the treatment group was significantly lower than in the nontreatment group (20.0% vs 54.8%; P = .01). [https://www.ncbi.nlm.nih.gov/pubmed/21248066](https://www.ncbi.nlm.nih.gov/pubmed/21248066)

**Angiotensin Converting Enzyme Inhibitors (ACE-I) and Angiotensin II Receptor Blockers (ARB)**

**Pathophysiology**

1. SARS-CoV-2, the virus that causes COVID-19, enters via the same cell-entry receptor as SARS-CoV, namely angiotensin-converting enzyme II (ACE2) (Paules et al, *JAMA*, 2020). SARS-CoV-2 is thought to have a higher affinity for ACE2 than SARS-CoV.

2. ACE2 is expressed in the heart, lungs, vasculature, and kidneys. ACE-inhibitors (ACEi) and angiotensin-receptor blockers (ARBs) in animal models increase the expression of ACE2 (Zheng et al, *Nat Rev Cardiol*, 2020), though this has not been confirmed in human studies. This has led to the hypothesis that ACEi and ARBs might worsen myocarditis or precipitate ACS. It has also been hypothesized that the upregulation of ACE2 is therapeutic in COVID-19 and that ARBs might be protective during infection (Gurwitz D, *Drug Dev Res*, 2020).

**Recommendations**

1. For outpatients, we recommend **against discontinuing** outpatient ACEi/ARBs.

2. For inpatients, we recommend **against routine discontinuation** of ACEi/ARBs, unless otherwise indicated (*e.g.*, acute kidney injury, hypotension, shock, etc).

**Evidence**

This remains an area of investigation and it is unclear how these medications affect patients with COVID-19. However, the evidence that currently exists favors continuing these medications unless otherwise indicated to stop them because their abrupt discontinuation, particularly in those who have heart failure or have had a myocardial infarction, may lead to clinical instability and adverse outcomes (Vaduganathan et al, NEJM 2020).

Non-steroidal anti-inflammatory drugs (NSAIDs)

Pathophysiology

1. SARS-CoV-2 binds to cells via ACE2. ACE2 is upregulated by ibuprofen in animal models, and this might contribute to increased pathology (see “Angiotensin Converting Enzyme Inhibitors (ACE-I) and Angiotensin II Receptor Blockers (ARB)” section of this chapter).

Recommendations

1. Concern has been raised that NSAIDs may worsen COVID-19 disease. This has not been proven clinically to-date, so we cannot make a recommendation for or against their use at this time.

Evidence


Vitamin C

Pathophysiology:

Antioxidant and cofactor for numerous physiologic reactions; may support host defenses against infection and protect host cells against infection induced oxidative stress

Presence of infection may decrease vitamin C concentrations

Recommendations:

Reasonable to implement 1.5 g orally every 6 hours until shock resolution or for up to 10 days as used in VITAMINS study

Evidence

While this idea has been popular in mainstream media, there is currently no evidence to support low- or high-dose vitamin C in COVID-19 patients. There is a trial currently recruiting
for high-dose vitamin C trial in COVID-19 patients in China slated to be complete in the fall of 2020.

The use of Vitamin C as a treatment for sepsis is beyond the scope of this document. A 96-hour infusion of vitamin C did not demonstrate significant improvement of organ dysfunction, vascular injury or alter inflammatory markers in sepsis patients with ARDS, although a reduction in 28-day mortality was exhibited (Difference -0.17, p=0.03). (Fowler, et al. JAMA, 2019). This study does not look at COVID-19 ARDS patients.

Zinc

Pathophysiology

Zinc is involved in a variety of biological processes, as a structural, catalytic, and intracellular and intercellular signaling component. Thus zinc homeostasis is tightly controlled at the whole body, tissue, cellular, and subcellular levels by a number of proteins, with zinc transporters being particularly important. (01 JUL 2015 https://doi.org/10.1152/physrev.00035.2014)

Recommendations

It is reasonable to consider adding zinc to a regimen that includes chloroquine.

It is reasonable to consider adding zinc to a treatment regimen as there is limited risk to implementing zinc for a short course.

Evidence

Zinc administered within 24 hours of onset of symptoms reduces the duration of common cold symptoms in healthy people but some caution is needed due to the heterogeneity of the data. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001364.pub4/full

Zinc may increase the intracellular Zn(2+) concentration with zinc-ionophores like pyrithione (PT) can efficiently impair the replication of a variety of RNA viruses, including poliovirus and influenza virus. https://www.researchgate.net/publication/47794995_Zn_Inhibits_Coronavirus_and_Arterivirus RNA_Polymerase_Activity_In_Vitro_and_Zinc_Ionophores_Block_the_Replication_of_These_Viruses_in_Cell_Culture

Chloroquine enhanced zinc uptake by A2780 cells in a concentration-dependent manner, as assayed using a fluorescent zinc probe. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4182877/)

Recombinant Erythropoieten (Under development)
Pathophysiology

Erythropoietin (EPO) is a hormone/cytokine produced mainly by the kidneys via hypoxia inducible factor-2 as its primary transcription factor, and through inhibition of RBC precursors’ apoptosis, increases the red cell mass. However, EPO has other beneficial cytoprotective effects including anti-ischemic, regenerative and anti-apoptotic effects in a variety of tissues including lung, kidney, cardiac muscle, nervous system, retina, pancreas, and endothelial cells (Nekoui A, Blaise G. Erythropoietin and Nonhematopoietic Effects. Am J Med Sci. 2017;353(1):76-81.)

Recommendations

Evidence

One anecdotal study that showed improvement in dyspnea and anemia in a COVID positive patient. This patient was concomitantly treated with other therapy for COVID-19. [https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25839](https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25839)

HBOT

Physiology

Hyperbaric oxygen therapy employs a special airtight chamber to increase the atmospheric pressure surrounding a patient (ambient pressure). The pressure may be increased several times above normal atmospheric pressure. The chamber is compressed with air while the patient breathes 100 percent oxygen. With a normal cardiovascular system, this increases the total amount of oxygen delivered to the cells by the blood stream (Henry’s law). In addition, increases in pressure result in a decrease in the size of bubbles (Boyle’s Law).

Recommendations

For patients with moderate COVID-19 symptoms (those requiring 3-6 LPM of Oxygen), with no evidence of respiratory distress, cardiac arrhythmia, or altered mentation, COVID positive patients can be considered to be treated with HBOT. This patients will most likely be entered in a clinical trial that is being sponsored by OSU.

Evidence

No randomized controlled trials. All evidence is anecdotal. The first application of hyperbaric medicine to a Spanish Flu victim was likely also the first application to a human being in the United States. In 1918 Dr. Orval Cunningham of Kansas City was brought a dying friend of a fellow physician. The patient was moribund and blue. Before Cunningham could perform his planned animal experiments he was asked to treat this dying patient. With just a one-hour treatment with compressed air at 1.68 atmospheres absolute the patient experienced...
improvement. Combined with additional hyperbaric treatments over the next 3 days this patient’s life was saved.

There is a clinical trial underway by NYU Hyperbaric oxygen therapy (HBOT) treatment will be provided to patients as an adjunct to standard therapy for a cohort of 40 COVID19-positive patients with respiratory distress at NYU Winthrop Hospital. All patients prior to the clinical application of HBOT will be evaluated by the primary care team and hyperbaric physician. After the intervention portion of this study, a chart review will be performed to compare the outcomes of intervention patients versus patients who received standard of care.

Ivermectin

Pathophysiology


Recommendations

Ivermectin is not recommended for use at OSU Medical Center

Evidence

Currently no known published data regarding efficacy or safety in the treatment of COVID-19 Only data available to date are results of a single in vitro study

Blood Products

Red blood cells

1. Restrictive transfusion strategy (Hct > 21, Hgb > 7) is recommended.

   1. If hemodynamically stable, transfuse 1 unit at a time and reassess needs.
   2. Transfusion thresholds for pRBCs are recommended as follows:
2. Oncology patients: transfuse for Hgb < 7.
3. All others: transfuse for Hgb < 7.

2. Parsimony is encouraged given:

1. Limited supply (blood drives are limited by social distancing).
2. Volume overload is of particular concern in COVID patients.


**Other blood products**

1. In general, treat bleeding not numbers.
2. FFP or 4 factor-PCC (lower volume) should be given for active bleeding in the setting of known or suspected coagulation abnormalities.
3. For warfarin reversal, use 4 factor-PCC given longer effect and lower volume.
4. Platelets should be transfused for platelet count < 10K unless actively bleeding. Transfuse 1 unit at a time.
5. Tranexamic acid: only for ongoing oozing/bleeding with over DIC and hyperfibrinolysis.
6. Procedures: If the patient is at high bleeding risk, the *most experienced operator* should perform the procedure to minimize trauma. Below is a table of the procedure and recommended transfusion thresholds for relevant blood products:

<table>
<thead>
<tr>
<th>Procedure or trauma scenario</th>
<th>Platelets</th>
<th>FFP or 4F-PCC</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central venous catheter</td>
<td>Transfuse for plt &lt; 10 K</td>
<td>Transfuse if INR &gt; 3</td>
<td>Avoid subclavian</td>
</tr>
<tr>
<td>Arterial line</td>
<td>Transfuse for plt &lt; 10 K</td>
<td>Transfuse if INR &gt; 3</td>
<td></td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>Transfuse for plt &lt; 50 K</td>
<td>Transfuse if INR &gt; 1.4</td>
<td></td>
</tr>
<tr>
<td>Trauma, no intracranial bleed</td>
<td>Transfuse for plt &lt; 50 K</td>
<td>Transfuse if INR &gt; 2</td>
<td></td>
</tr>
<tr>
<td>Trauma with intracranial bleed</td>
<td>Transfuse for plt &lt; 75 K</td>
<td>Transfuse if INR &gt; 1.7</td>
<td></td>
</tr>
</tbody>
</table>

**Blood donation**
1. We encourage all staff who are healthy and eligible to donate to make an appointment to donate blood or platelets at the Kraft Family Blood Donor Center at DFCI and BWH, either by phone (617.632.3206) or online.
Cardiology

Acute Cardiac Injury

Definition and incidence

1. **Definition**: The definition differs in studies and is non-specific. More recent studies define as troponin > 99\textsuperscript{th} percentile; earlier studies include abnormal ECG or echocardiographic findings (Zhou et al, *Lancet*, 2020; Shi et al, JAMA Cardiology, 2020).


Pathophysiology

1. The mechanism is unknown, though several have been proposed, based on very limited data outside of case series and reports (Ruan et al, *Intensive Care Med*, 2020; Hu et al, *Eur Heart J*, 2020; Zeng et al, *Preprints*, 2020; Inciardi et al, JAMA Cardiology, 2020)

   1. Possible direct toxicity through viral invasion into cardiac myocytes (*i.e.*, myocarditis)
   2. Acute coronary syndrome and demand ischemia
   3. Stress cardiomyopathy (*i.e.*, Takotsubo’s)

Time course and prognostic implication

1. Troponin rise and acute cardiac injury may be late manifestations of COVID-19.


   2. Among non-survivors, a steady rise in troponin I levels was observed throughout the disease course from day 4 of illness through day 22 (Zhou et al, *Lancet*, 2020).

2. ACI is associated with ICU admission and mortality

2. ACI is higher in ICU patients (22%, n=22) compared to non-ICU patients (2%, n=2) (Wang et al, *JAMA*, 2020)

3. In hospital cardiac arrest is associated with 13% success of ROSC with a 30 day survival of 2.9%, and 1% favorable neurological outcome. ([https://www.sciencedirect.com/science/article/pii/S0300957220301428](https://www.sciencedirect.com/science/article/pii/S0300957220301428)

**Consultation of Cardiovascular Medicine**

1. **Cardiology Consultation**

   1. The following clinical scenarios should prompt cardiology consultation, but may transpire through thorough chart review and telephonic means if possible to reduce exposure:

      1. Malignant and unstable arrhythmias
      2. A marked rise in cardiac biomarkers
      3. Concern for myocarditis
      4. Concern for ACS
      5. New heart failure or new reduction in LVEF
      6. Undifferentiated or suspected mixed or cardiogenic shock

**Cardiovascular Testing**

1. **Cardiac Biomarkers:**

   1. All patients: check Trop, BNP and CPK on admission
   2. Check 12 lead EKG on admission
   3. Consideration for performing point-of-care US (POCUS) to assess for gross abnormalities in LV or RV function; upload to centricity/PACs

      1. If either are abnormal, obtain virtual or bedside cardiology consultation. Consider formal echocardiogram in discussion with cardiology consultation.
      2. If no new ECG or echocardiographic abnormalities, continue to monitor Trop, BNP,

1. **Telemetry:**

   1. Telemetry should be used for all patients if available. Priority will go to those with moderate to critical illness as defined by their oxygen need and overall clinical appearance.
   2. If patients are receiving plaquenil, they should be on telemetry
3. For hospitals, with resource-limitations, telemetry is most important for patients who meet AHA criteria (Sandau et al, *Circulation*, 2017).

2. **ECGs:**

1. Daily ECGs are reasonable for individuals who are receiving treatment for COVID-19.
   
   1. When possible, print ECGs from the in-room monitor to minimize contamination of equipment

3. **TTE:**

1. Do not order routine TTEs on COVID-19 patients.
2. Indications for POCUS:
   
   1. Marked elevation in troponin or BNP
   2. Shock
   3. New heart failure (not pre-existing heart failure)
   4. New persistent arrhythmia
   5. Significant ECG changes

4. If abnormalities are identified on POCUS (e.g. new reduction in LVEF < 50%), a formal TTE should be obtained and cardiology consulted. Although some recommendations favor limited TEE, we believe formal TTE should be performed in order to reduce the likelihood of having to return at a later time for a complete TTE.

5. **Advanced CV Imaging (Stress Testing, TEE, CT, CTA, MRI, Invasive Coronary Angiography)**

1. All testing should be limited to cases where the information is thought to be critical to patient care. Consideration of all advanced imaging should be discussed with cardiology consultation or individual imaging teams.
2. Specific considerations:
   
   1. Stress testing is likely not expected to be commonly indicated in individuals with active COVID. If needed, consider pharmacologic nuclear stress testing or coronary CTA.
   2. TEE
      
      1. Only for absolute necessity
      2. Consider alternative noninvasive imaging modalities (e.g. cardiac CT to rule out left atrial appendage thrombus, cardiac CT or PET/CT for endocarditis complications).
**Arrhythmias**

**Incidence**

1. Case series report the occurrence of unspecified arrhythmias in 17% of hospitalized patients with COVID-19 (n=23 of 138), with higher rate in ICU patients (44%, n=16) compared to non-ICU patients (7%, n=7) (Wang et al, *JAMA*, 2020). In one study of 189 hospitalized patients in Wuhan, China, the rate of VT/VF was 5.9% (n=11) (Guo et al, *JAMA Cardiology*, 2020).

**Workup**

1. Telemetry, 12-lead EKG, cardiac troponin, BNP
2. POCUS to assess LV and RV function with uploaded images
3. Obtain formal TTE and consider cardiology consultation if abnormalities of any of the above

**Management**

1. Atrial fibrillation/atrial flutter
   1. Beta blockade if no evidence of heart failure or shock
   2. If significant heart failure or borderline BPs, use amiodarone. There is no known increased concern for amiodarone lung toxicity
   3. If unstable, synchronized DCCV with 200 Joules biphasic

2. Ventricular tachycardia (VT)
   1. Unstable/pulseless: initiate ACLS
   2. Stable:
      1. **Cardiology consult** (may represent evolving myocardial involvement)
      2. Amiodarone 150mg IV x 1

**Acute Coronary Syndromes**

**Incidence**

1. There is no current available data on the incidence of ACS in COVID. However, we presume that due to the presence of ACE2 receptors on the endothelium, and the known increased risk of ACS in influenza that there is a possible increased incidence of ACS among COVID-19 patients.
1. The incidence of ACS is about 6 times as high within seven days of an influenza diagnosis than during the control interval - incidence ratio 6.05 (95% CI, 3.86 to 9.50) (Kwong et al, NEJM, 2018).

2. Type II Coronary Syndromes are increasingly prevalent as severe increase in myocardial demand triggered by infections can precipitate myocardial injury or infarction. Circulating cytokines released during a severe systemic inflammatory stress could lead to atherosclerotic plaque instability and rupture. Similarly, patients with heart failure are also prone to hemodynamic decompensation during the stress of severe infectious illnesses. https://jamanetwork.com/journals/jamacardiology/fullarticle/2763844

**Workup**

1. Elevated troponin/ECG changes alone may not be able to discriminate between:
   
   1. Coronary thrombosis
   2. Demand-related ischemia
   3. Myocarditis
   4. Toxic myocardial injury (e.g. sepsis)

2. Determination of ACS will rely on all evidence available:
   
   1. Symptoms (if able to communicate): New dyspnea, chest pain, anginal equivalents
   2. Regional ECG changes
   3. Rate of change of Troponin changes (*i.e.*, steep rise suggests ACS)
   4. Echo findings (*e.g.*, new RWMA): When in doubt, request a cardiology consult.

3. **When in doubt, request a cardiology consultation**

**Management**

Medical management of ACS should be **coordinated with cardiology and recommendations should be reviewed**


1. Treat with full dose aspirin, clopidogrel (if not bleeding), heparin, oxygen (if hypoxemic), statin, nitrates (if hypertensive), and opioids (if persistent pain during medical management).
2. Beta blockers should be used with caution given possible concomitant myocarditis/decompensated heart failure.

2. As of the time of this writing, the cath lab will take COVID-19 patients, even if ventilated.

1. If resources become constrained and door-to-balloon time is no longer adequate, cardiology may decide to use lytic medications for COVID-19 STEMI patients in lieu of PCI.
2. ACC guidelines recommend the following (if cardiac catherization cannot be performed)
   1. If lytics infused, a safe and efficient medical environment should be ensured
   2. Emergency intravenous thrombolysis is considered the first choice for acute ST-segment elevation myocardial infarction (STEMI)
      1. However each case will be considered on a case by case situation in conjunction with the cardiology team. The reasoning behind this frame of thought is secondary to the need for revascularization after fibrinolytics that may require return intervention. *(OSU Specific)*
   3. For STEMI patients with confirmed COVID-19, strict isolation should start immediately, and thrombolytic contraindications should be evaluated. Patients with thrombolytic contraindications should be transferred to the local designated infectious medical institution immediately for further treatment through the first-aid transport mode designated by the government.
4. Patients without thrombolytic contraindications should first start intravenous thrombolysis and then transfer to the local designated medical institution of infectious disease for further treatment.
5. If COVID-19 could be excluded by the expert group within ≤1 hour, and the possibility of having COVID-19 was clinically small, cardiologists should evaluate the following two schemes:
   2. Proceed with onsite thrombolysis, make the treatment decision after comprehensive consideration of the benefit to risk ratio. During thrombolysis, review electrocardiogram, bedside echocardiography, and chest radiography. After thrombolysis, check the recanalization status of myocardial perfusion and perform chest computed tomography (CT) immediately.

   o For AMI with non-STEMI (NSTEMI), treatment strategy should be based on the GRACE risk stratification while waiting for the results of novel coronavirus nucleic acid detection.

**Pericarditis and Myocarditis**

**Incidence**

**Workup**

1. Likely no role for endomyocardial biopsy

**Management**

1. Supportive for heart failure and direct viral treatments
2. The use of steroids and anti-inflammatory medications such as Colchicine and Ibuprofen should be discussed with the cardiology consult team as this literature is evolving.
Shock: Septic, Cardiogenic, and Cytokine
Undifferentiated Shock in COVID

Overview

1. Definition:

   1. Acute onset of new and sustained hypotension (MAP < 65 or SBP < 90) with signs of hypoperfusion requiring IVF or vasopressors to maintain adequate blood pressure

2. Time course:

   1. Patients rarely present in shock on admission

      1. Natural history seems to favor the development of shock after multiple days of critical illness.

3. Etiology:

   1. The range of reasons for shock is wide and more variable than for most patients and may includes:

      1. Myocardial dysfunction
      2. Secondary bacterial infection
      3. Cytokine storm

Workup

1. Assess for severity of end organ damage:

   1. UOP, mental status, lactate, BUN/creatinine, electrolytes, LFTs

2. Obtain a FULL infectious/ septic workup, which includes all of the following:

   1. Labs: CBC with differential. Note that most COVID patients are lymphopenic (83%). However, new leukocytosis can occur and left-shift can be used as a part of clinical picture (Guan et al, N Engl J Med, 2020). Two sets of blood cultures, LFTs (for cholangitis/acalculous cholecystitis), urinalysis (with reflex to culture), sputum culture (if safely obtained via inline suctioning, do not perform bronchoscopy or sputum induction), procalcitonin at 0 and 48h (do not withhold early antibiotics on the basis of procalcitonin), urine Strep and legionella antigens
   2. Portable CXR (avoid CT unless absolutely necessary)
3. Full skin exam

3. Assess for **cardiogenic shock**

1. Assess extremities: warm or cool on exam
2. Assess patient volume status: JVP, CVP, edema, CXR
3. Assess pulse pressure: If < 25% of the SBP, correlates highly with a reduction in cardiac index to less than 2.2 with a sensitivity of 91% and a specificity of 83% (Stevenson and Perloff, *JAMA*, 1989)
4. Perform POCUS, if able, to assess for gross LV/RV dysfunction (upload to PACS/Centricity)
5. Labs: Obtain an SCVO2 or MV02 if the patient has central access, troponin x2, BNP, lipid profile, TSH
6. EKG (and telemetry)
7. **Obtain cardiology consultation** if any suspicion of cardiogenic shock

4. Assess for **other causes of shock**:

1. Vasoplegia:
   1. Run medication list for recent cardiosuppressive medications, vasodilatory agents, antihypertensives
2. Adrenal insufficiency:
   1. Unless high pretest probability of adrenal insufficiency, we recommend against routine cortisol stimulation testing
3. Obstruction:
   1. PE with elevated risk of thrombosis. VERY limited observational data suggest up to 5-10% of patients with COVID 19 who required mechanical ventilation have acute VTE. [https://www.hematology.org/covid-19/covid-19-and-pulmonary-embolism](https://www.hematology.org/covid-19/covid-19-and-pulmonary-embolism)
   2. Tamponade (given elevated risk of pericarditis)
   3. Obstruction from PEEP
4. Cytokine storm (see “Cytokine Activation Syndrome” section in this chapter below)
5. Allergic reactions to recent medications
6. Neurogenic shock is uncommon in this context
7. Hypovolemia:
   1. Bleeding
   2. Insensible losses from fever
   3. Diarrhea/vomiting

Differentiating Shock

This video is a helpful tutorial.

<table>
<thead>
<tr>
<th>Type of Shock</th>
<th>Cardiac Output</th>
<th>SVR</th>
<th>CVP/Wedge</th>
<th>ScvO2, MvO2</th>
<th>Other features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic</td>
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<tr>
<td>Distributive (sepsis, cytokine, anaphylaxis)</td>
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<td>Obstructive</td>
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<td>Hypovolemic</td>
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<tr>
<td>Neurogenic</td>
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<td>Decreased HR</td>
</tr>
</tbody>
</table>

Septic Shock and Secondary Infections

Incidence

1. The reported rates of sepsis and septic shock are not reported consistently in currently available case series

1. Secondary bacterial infections are reported:
   1. 20% of non-survivors (Zhou et al, Lancet, 2020)
   2. 16% of non-survivors (Ruan et al, Intensive Care Med, 2020)
3. 12-19% In H1N1 epidemic (MacIntyre et al, BMC Infect Dis, 2018)

Management

1. Antibiotics:
   1. Early empiric antibiotics should be initiated within 1 hour (see “Antibiotic Stewardship” section within “COVID-19 Therapies and Clinical Trials” chapter)
   2. 22.1% of a sample population showed that each hour of delay in initiating effective (proven or adjudicated) antimicrobial therapy was associated with a 7.6% decrease in survival (https://www.atsjournals.org/doi/full/10.1164/rccm.201703-0621ED)

2. Pressors and Fluid Management:
   1. Goal MAP > 65mmHg
      1. While there is emerging data that lower MAP thresholds may be beneficial, we recommend following this threshold for now. https://jamanetwork.com/journals/jama/fullarticle/2763879
   2. Pressors
      1. Start Norepinephrine while determining the etiology of undifferentiated shock https://jamanetwork.com/journals/jama/fullarticle/2763879
      2. Unless new evidence emerges, standard choices for distributive shock (i.e., norepinephrine then vasopressin) are recommended, with high vigilance for the development of cardiogenic shock, addressed in the next section

3. Conservative fluid management:
   1. Do not give conventional 30cc/kg resuscitation
      1. COVID-19 clinical reports indicate the majority of patients present with respiratory failure without shock. ARDS is mediated in part by pulmonary capillary leak, and randomized controlled trials of ARDS indicate that a conservative fluid strategy is protective in this setting (Grissom et al, Crit Care Med, 2015; Famous et al, Am J Respir Crit Care Med, 2017; Silversides et al, Int Care Med, 2017) https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30161-2/fulltext#fig2
      2. Conservative fluid management is also part of the most recent WHO guidelines. WHO, COVID-19 Interim guidance, March 2020).
2. **Instead, give 250-500cc IVF and assess in 15-30 minutes** for:

1. Increase > 2 in CVP
2. Increase in MAP or decrease in pressor requirement

1. Use isotonic crystalloids; Lactated Ringer’s solution is preferred where possible. Avoid hypotonic fluids, starches, or colloids

3. **Repeat 250-500cc IVF boluses; Use dynamic measures of fluid responsiveness**

1. Pulse Pressure Variation: can be calculated in mechanically ventilated patients without arrhythmia; PPV >12% is sensitive and specific for volume responsiveness, although these calculations are typically measured with those individuals who have 8ml/kg VT which may not be applicable to patients who are receiving 6ml/kg


2. Straight Leg Raise: raise legs to 45° w/ supine torso for at least one minute. A change in pulse pressure of > 12% has sensitivity of 60% & specificity of 85% for fluid responsiveness in mechanically ventilated patients; less accurate if spontaneously breathing [https://pulmccm.org/critical-care-review/passive-leg-raise-offers-promise-in-predicting-fluid-responsiveness-chest/](https://pulmccm.org/critical-care-review/passive-leg-raise-offers-promise-in-predicting-fluid-responsiveness-chest/)

3. Ultrasound evaluation of IVC collapsibility should only be undertaken by trained personnel to avoid contamination of ultrasound [https://www.youtube.com/watch?v=j5aboEF2-qo](https://www.youtube.com/watch?v=j5aboEF2-qo)

4. For further guidance, Conservative Fluid Management protocols are available from FACCT Lite trial (Grissom et al, *Crit Care Med*, 2015).

4. **Corticosteroids**

1. See “Systemic Corticosteroids” section
2. Stress dose hydrocortisone should still be considered in patients on > 2 vasopressors.

---

**Cardiogenic Shock**

**Incidence and clinical course**

1. **Etiology:** See “Acute Cardiac Injury” pathophysiology section.
1. Mechanism is unknown, potentially direct viral toxicity, ACS, stress or inflammatory cardiomyopathy

2. Incidence:
   1. Heart failure or cardiogenic shock was observed
      1. In 23% (n=44 of 191) of hospitalized patients in one case series (Zhou et al, Lancet, 2020).
      1. There were higher rates in non-survivors (52%, n=28) compared to survivors (12%, n=16),
      2. In 33% of patients admitted to an ICU in Washington State 33% (n=7 of 21) (Arentz et al, JAMA, 2020).
      1. These patients tended to be older with more comorbidities and had a high mortality (11 of the 21 died).

3. Prognostic implication:
   1. Heart failure or myocardial damage contributed to death
      1. In 39% (n=29) of deaths in a series of 68 patients in Wuhan. Most (n=22 of 29) had concomitant respiratory failure (Ruan et al, Intensive Care Med, 2020).

4. Time course:
   1. Cardiogenic shock may present late in the course of illness even after improvement of respiratory symptoms, and manifest as a precipitous clinical deterioration in the setting of an acute decline in LVEF (see “Acute Cardiac Injury” section)

Workup
1. All cardiogenic shock cases require cardiology consult
2. Consideration for cardiogenic shock if any of the following are present with evidence of hypoperfusion (e.g., elevated lactate):
   1. Elevated BNP
   2. POCUS or echocardiogram with depressed LV and/or RV function
3. Rule out ACS and complete the initial work up as described in “Cardiac Complications” chapter.
4. Ongoing monitoring:
1. Labs: Trend troponins to peak, SCvO2 (obtained by upper body CVC) or MvO2 q8-12h or with clinical change, Lactate q6h, LFTs daily (for hepatic congestion)
2. Daily EKGs or prn with clinical deterioration
3. Trend troponin to peak

Management

1. Close collaboration with the cardiovascular medicine consultation service is recommended. Consideration for pulmonary artery catheter placement.

1. Goals: MAPs 65-75, CVP 6-14, PCWP 12-18, PAD 20-25, SVR 800-1000, SCvO2 > 60%, CI > 2.2
   1. Note: Achieving MAP goal is first priority, then optimize other parameters
2. How to achieve goals:
   1. Continue titration of norepinephrine gtt for goal MAP 65-75
   2. Initiate diuretic therapy for CVP > 14, PCWP >18, PAD > 25
   3. Initiate inotropic support:
      1. Dobutamine gtt for SCvO2 < 60%, CI < 2.2 and MAP > 65. Start at 2mcg/kg/min. Up-titrate by 1-2mcg/kg/min every 30-60 minutes for goal parameters. Alternative strategies should be considered once dose exceeds 5mcg/kg/min. Maximum dose is 10mcg/kg/min.
      4. Ensure negative inotropes such as beta blockers, calcium channel blockers and antihypertensives are discontinued.

Mechanical Support

1. The benefit of mechanical circulatory support in COVID-19 is not yet clear.
2. Patients who experience the following should prompt an immediate call to the cardiovascular medicine consult service for consideration of mechanical support:
   1. Dobutamine gtt at 5mcg/kg/min (or unable to tolerate dobutamine due to tachyarrhythmias) and ScvO2 < 60% or CI < 2.2
   2. Lactate > 4 after medical therapy
3. The criteria for ECMO and other mechanical circulatory support varies among centers and are
difficult to develop even under typical circumstances. The unclear trajectory of the COVID-19
pandemic makes these evaluations even more difficult.

1. Consideration for ECMO consultation for cardiogenic shock can be considered if the
following are met

   1. Younger age
   2. Expected life expectancy >6 months pre-hospitalization
   3. No evidence of solid or liquid malignancy
   4. Able to tolerate anticoagulation
   5. Platelets >50,000
   6. Absence of severe peripheral arterial disease
   7. No evidence of irreversible neurological injury
   8. Able to perform ADLs at baseline prior to illness
   9. Cannot have profound respiratory failure (defined as requiring prone ventilation at time
      of consult for MCS or having PaO2:FiO2 ratio < 150) (for MCS other than ECMO)

Cytokine Activation Syndrome

Pathophysiology

1. A subgroup of patients with severe COVID-19 may have cytokine activation syndrome and

   1. Patients who had cytokine activation developed rapid progression to ARDS, shock, and
      multiorgan failure (Chen et al, Lancet, 2020)

2. Pathophysiology:

   1. Neutrophil activation likely contributes to the pathogenesis of cytokine storm and ARDS (Wu
      et al, JAMA Intern Med, 2020). Wu et al found that COVID-19 confirmed patients with ARDS
      have higher neutrophil counts, average 7.04 (95% CI: 3.98 to 10.12) vs. those without ARDS,
      average 3.06 (2.03 to 5.56)

   2. Similar patterns of cytokine storm and ARDS have been seen with SARS, MERS (Kim et al, J
      Korean Med Sci, 2016)

   3. Other studies have suggested that increased proinflammatory cytokines in the serum are
      associated with pulmonary injury in SARS, MERS, and COVID-19 (Wong et al, Clin Exp
      Immunol, 2004)
**Workup**

1. Suspect if clinical deterioration with shock and multiorgan failure.

   1. CBC with diff, PT/INR, PTT, fibrinogen, d-dimer, ferritin, liver function test, triglycerides, c-reactive protein (CRP) (Ruan et al, *Intensive Care Med*, 2020)


   2. An HScore (MDcalc online calculator) may be helpful in estimating the probability of secondary HLH in these patients

**Management**

1. If high suspicion, discussion with ID about the use of IVIG, steroids, cytokine blockade, particularly IL-6 pathway can be considered. While steroids have been implicated with worse lung injury and outcomes, they may be beneficial in the hyperinflammatory state.
Cardiac Arrest in the COVID patient

Preparation

Minimizing Healthcare Worker Risk of Exposure

Code Responses to COVID-19 patients are high-risk events for healthcare worker exposure due to the aerosolization that occurs with chest compressions and intubation

1. Use PPE:
   1. CDC guidelines recommend N95 respirator, face shield, gown and gloves be used by all code responders during code events (CDC Guidelines, 2020) as well as Face Shield, Gown and Gloves).

2. Minimize personnel:
   1. Use an automated compression device where available to minimize personnel.
   2. If not available, minimize the number of individuals doing compressions

3. Prepare code equipment:
   1. To limit transmission of virus while passing meds/supplies into the patient’s room from the code cart, consider creating Code Bags inside the Code Cart pre-packed with necessary code meds (Epinephrine, Bicarbonate, Calcium etc.) and IV/lab supplies.
   2. Use of video laryngoscopy should be primary mode of intubation

Early goals of care conversations

1. To avoid unnecessary codes in patients with an irreversible underlying condition, patients who are at high-risk for acute decompensation should be identified early and appropriate steps should be taken to confirm code status and initiate early goals of care conversations with the patient and family.

Code Management
https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.120.047463

1. Efforts should be made to minimize the total number of Code responders in the room to 7-8.

   1. Code responders inside the patient’s room who should don full PPE prior to entering the patient’s room:
      1. Code Leader/Physician (1)
2. Code RN, one of which will be administering medications, and one which will be compressing (2)  
3. Nurse tech (1) which will also serve as a compressor  
4. House Supervisor, which should be located 6 feet away from the patient (1)  
5. Respiratory Therapist (1)  
6. Airway team (1)  

2. Code responders outside the patient’s room should not don PPE unless called upon in the room:  
   1. Additional unit nurses (2-3) (supplies, meds from omnicell, code cart)  
   2. Code Cart  
   3. Pharmacist (1)  
   4. Additional medical resident (2) (Medical resident on computer outside the room placing orders, calling consults, and providing code leader with patient information)  
   5. Security to manage personnel that do not need to be involved in the code blue setting  

2. **Circulation**  
   1. Until a definitive airway is obtained, compression-only CPR should be performed. Multiple studies have shown that compression-only CPR is non-inferior to standard CPR (Svensson et al, *NEJM*, 2010).  
   2. If patient has shockable rhythm (VF/VT), defibrillate as soon as possible.  

3. **Airway**  
   1. **Initial Airway Management, Prior to Intubation:**  
      1. If the patient is connected to the ventilator, DO NOT DISCONNECT VENTILATOR  
         1. Increase the FIO2 to 1.0.  
         2. Change mode to Pressure Control Ventilation (Assist Control) and limit pressure as needed to generate adequate chest rise (6 mL/kg ideal body weight is often targeted, 4-6 mL/kg for neonates)  
         3. Adjust the trigger to Off to prevent the ventilator from auto-triggering with chest compressions and possibly prevent hyperventilation and air trapping.  
         4. Adjust respiratory rate to 10/min for adults  
         5. Assess the need to adjust positive end-expiratory pressure level to balance lung volumes and venous return.  
         6. Adjust alarms to prevent alarm fatigue.  
         7. Ensure endotracheal tube/tracheostomy and ventilator circuit security to prevent unplanned extubation.
2. Prior to securing a definitive airway, oxygen should be applied via a non-rebreather mask at 15L/min without humidification


4. If passive oxygen is not available, place a surgical face-mask and a blanket over the patient’s face prior to chest compressions.

5. If the patient does not have a shockable rhythm, proceed with Rapid Sequence Intubation as early as possible to limit aerosolization

2. **Endotracheal Intubation**

   1. Endotracheal intubation is the procedure that subjects the rescuer to the highest risk of infection during resuscitation. To maximize the success rate for intubation, airway interventions should be carried out by experienced individuals and chest compressions should be stopped (Cheung, Lancet Resp Med, 2020). This may deviate from usual cardiac arrest care leading to a pause in chest compressions, however this is acceptable to maintain the safety of code responders.

   2. Chest compressions should resume once the endotracheal tube (ETT) cuff is inflated and the ETT is connected to the ventilator.

   3. If the pause in chest compressions is excessive and endotracheal intubation does not seem likely, consider LMA or other extraglottic airway device.

   4. Code responders should distance themselves from the head of the bed during the intubation procedure (6 ft distance).

   5. Continuous capnography device should be used to monitor ventilation (Cheung, Lancet Resp Med, 2020).

   6. Depending on institutional policies, anesthesia and respiratory therapy may don higher levels of PPE including PAPR hoods for the intubation procedure.

4. **Etiologies to Consider**

   1. Data from a retrospective study in Wuhan (Ruan et al, Intensive Care Med, 2020) revealed cause of death to be:

      1. Respiratory failure (53%)
      2. Heart failure with respiratory failure (33%)
      3. Myocardial damage (7%)
      4. Unknown cause (7%)

   2. It is important to attempt to identify and treat reversible causes (5H’s, 5T’s) before stopping the code.
5. **Terminating Resuscitative Efforts**

1. Avoid prolonged resuscitation if there is no easily reversible etiology identified.
2. No one factor alone, or in combination, is predictive of outcome during cardiac arrest, however it is reasonable to stop resuscitation efforts if return of spontaneous circulation (ROSC) has not been achieved within 30 minutes.
3. In intubated patients, failure to achieve an ETCO2 of greater than 10 mm Hg by waveform capnography after 20 minutes of CPR should be considered as one component of a multimodal approach to decide when to end resuscitative efforts (Mancini et al, *Circulation*, 2015).

6. **Post-Resuscitation Care**

1. Dispose of, or clean, all equipment used during CPR. Any work surfaces used for airway/resuscitation equipment will also need to be cleaned.
2. After the resuscitation has ended adhere to strict doffing procedure to limit exposure.
3. If ROSC is achieved, provide usual post-resuscitation care consistent with current recommended guidelines including targeted temperature management when appropriate (Donnino et al, *Circulation*, 2015).
Hematology
Thrombotic Disease

Incidence:

1. Unclear incidence, though case reports suggest there may be increased venous thromboembolism (VTE) in COVID-19 patients (Xie et al, *Radiol Cardiothoracic Imaging*, 2020; Danzi et al. *Eur Heart J* 2020)
2. One study suggests COVID-19 patients at increased risk for thrombosis and bleeding (Xu et al, *Pulmonology* 2020 [preprint, under review]).

Pathophysiology:

1. The mechanism for VTE are unknown and likely multifactorial:
   1. Systemic inflammatory response as seen in sepsis
   2. Stasis/critical illness
   3. Possibly direct endothelial damage from viral injury/ACE2 binding

2. Colleagues from Wuhan have reported finding microthrombi in pulmonary vasculature on autopsy (Luo et al, *Preprints*, 2020 preprint), which could contribute to local V/Q mismatch or hydrostatic changes causing edema. However these mechanisms remain entirely hypothetical and may indicate more cellular debris than microthrombi.

   1. One theory: SARS-CoV Spike protein can be cleaved by FXa and FIIa. Cleavage of the Spike protein activates it which promotes infectivity. By extension, it is hypothesized that anticoagulation might inhibit SARS-CoV-2 replication. There is a small case series suggesting dipyridamole may be useful, though anticoagulation and antiplatelet agents require further investigation prior to being used therapeutically (Liu et al, *medRxiv*, 2020 preprint; Lin et al, *Emerging Microbes & Infections*, 2020).

Management:

1. Preliminary data from Wuhan suggest that prophylactic LMWH or UFH may be of benefit in those patients with severe COVID-19 and D-dimer levels > 6 times the upper limit of normal (Tang et al, *JTH*, Mar 27, 2020)
2. Initiate prophylactic anticoagulation therapy for all COVID-19 patients unless otherwise contraindicated
   1. If CrCl > 30: Lovenox 40 mg SC daily
2. If CrCl < 30 or AKI: Heparin 5000 units SC TID
3. Hold if Platelets <30,000 or bleeding, start TEDs and SCDs

3. If the patient is on direct oral anticoagulants (DOACs) or Warfarin for Afib or VTE, switch to full dose anticoagulation (LMWH or UFH, as indicated based on renal function or clinical scenario).

Speculative use of therapeutic anticoagulation or tissue plasminogen activator (TPA)

1. While therapeutic anticoagulation has been used empirically in some severe COVID-19 patients in Wuhan given the possible microthrombi in pulmonary vasculature (see “Pathophysiology” above), our interpretation of the data is that the risks outweigh the benefits at this time, unless documented DVT or PE.

1. Similarly, TPA has been proposed as a possible therapeutic. We recommend against this for the same reasons.

Prognosis:


Disseminated Intravascular Coagulation (DIC)

Incidence/pathophysiology:


Time course:

1. Median time to onset of DIC was 4 days into hospital admission (Tang et al, J Thromb Haemost, 2020).

Workup:
1. Identify and treat underlying condition
2. ISTH DIC score (MDcalc online calculator): If score < 5, no DIC; recalculate in 1-2 days
3. Elevated PT/PTT and D-dimer correlate with worse prognosis: trend PT/INR, PTT, D-dimer, fibrinogen every 3 days until discharge or death

**Management:**

1. If not bleeding, supportive care:
   1. If fibrinogen < 150: FFP, cryoprecipitate or fibrinogen concentrate
   2. Transfuse platelets if < 30K
   1. Consider holding anticoagulation if the patient requires blood products for supportive care, though clinician should weigh risks and benefits.
3. If bleeding, give blood products:
   1. For elevated PT/PTT and bleeding, use FFP or 4F-PCC
   2. Hold anticoagulation for active bleeding.
4. Start systemic anticoagulation only if:
   1. Overt thromboembolism or organ failure due to clot (*i.e.*, purpura fulminans)
   2. There has been no mortality benefit of therapeutic anticoagulation in DIC (Levi et al, *Blood*, 2018).

**Prognosis:**

1. DIC is associated with worse survival in COVID-19 patients. Out of 183 COVID-19 patients in Wuhan, 71% of non-survivors had DIC (ISTH score ≥ 5; MDcalc online calculator) compared to 0.6% of survivors (Tang et al, *J Thromb Haemost*, 2020).
Nephrology
Acute Kidney Injury

Incidence and Pathophysiology

1. Incidence of AKI in COVID-19 varies widely, but estimates range from 2.1% to 29%.
2. Likely that the most common pathophysiology will be acute tubular necrosis (ATN) driven by shock (Xianghong et al, *Natl Med J China*, 2020) and in some cases cytokine storm.

1. Areas for future research: Some have hypothesized that there could direct cellular injury by the virus via angiotensin converting enzyme II (ACE2). COVID-19 uses ACE2 for cell entry. ACE2 is expressed in proximal renal tubules more than glomeruli (Fan et al, *medRxiv*, 2020).

Workup:

1. Monitor Creatinine at least daily


2. If evidence of rising BUN and/or creatinine, order urinalysis

   1. Patients may present with proteinuria (44%), hematuria (26.9%)  https://www.kidney-international.org/article/S0085-2538(20)30255-6/pdf

Management:

1. Consult Nephrology early at the first sign of renal injury for all COVID-19 confirmed patients

   1. Do not wait until need for RRT (renal replacement therapy)/dialysis for consultation.

2. Managing AKI:

   1. Minimize nephrotoxic agents
   2. Give judicious fluids for suspected prerenal insults, but discuss with renal if any ambiguity

Renal Replacement Therapy (RRT)
1. Estimates for RRT range from 1 to 5% of hospitalized patients. Among critically ill patients, need for CRRT ranges from 5 to 23%

1. Few studies have reported outcomes of RRT. One case series reported that out of 191 patients, 10 received CRRT, and all 10 died (Zhou et al, Lancet, 2020).

2. Renal will be coordinating RRT continuation and initiation

1. Indications for dialysis in COVID-19 patients are the same as the indications for all patients.

**Prognosis**

1. Increased serum creatine, BUN, AKI, proteinuria, or hematuria are each independent risk factors for in-hospital death (Cheng et al, medRxiv, 2020 preprint)

1. In two other studies, non-survivors had higher BUN and creatinine and higher rates of AKI (Wang et al, JAMA, 2020; Yang et al, Lancet Respir Med, 2020).

2. Another study found that higher BUN and creatinine are associated with progression to ARDS, and higher BUN (though not creatinine) is associated with death (HR 1.06-1.20) (Wu et al, JAMA Intern Med, 2020).

3. In SARS, AKI correlated with poor prognosis and 91.7% of patients with AKI died (vs 8.8% without AKI, p < 0.0001) (Chu et al, Kidney Int, 2005).
Neurology

Incidence and Pathology


Autopsy results of patients with COVID-19 showed that the brain tissue was hyperemic and edematous and some neurons degenerated. http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989/files/ce3e6945832a438eaae415350a8ce964.pdf

In a case series of 214 patients with coronavirus disease 2019, neurologic symptoms were seen in 36.4% of patients and were more common in patients with severe infection (45.5%) according to their respiratory status, which included acute cerebrovascular events, impaired consciousness, and muscle injury. (https://jamanetwork.com/journals/jamaneurology/fullarticle/2764549)

The three major categories of presentation included central nervous system manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure), peripheral nervous system manifestations (taste impairment, smell impairment, vision impairment, and nerve pain), and skeletal muscular injury manifestations. (https://jamanetwork.com/journals/jamaneurology/fullarticle/2764549)

Most neurologic manifestations occurred early in the illness (median time, 1-2 days up to 14-21 days) https://jamanetwork.com/journals/jamaneurology/fullarticle/2764549 https://jamanetwork.com/journals/jamaneurology/fullarticle/2764548

One case of Gullian Barre associated with COVID-19. Unclear as to whether this was causal, and cannot be definitively linked. DOI: https://doi.org/10.1016/S1474-4422(20)30109-5

Work-Up

Consideration for the following labs is acute mental status, ataxia, headache or skeletal muscle weakness occurs (these labs are ordered on admission):

1. Creatine kinase
2. Lactate dehydrogenase
3. D-Dimer
Consideration for CT and MRI in patients with persistent encephalopathy as this may represent COVID-19–associated acute necrotizing hemorrhagic encephalopathy, although this is based on one anecdotal case report.

The most characteristic imaging feature includes symmetric, multifocal lesions with invariable thalamic involvement. Other commonly involved locations include the brain stem, cerebral white matter, and cerebellum. Lesions appear hypoattenuating on CT images and MRI demonstrates T2 FLAIR hyperintense signal with internal hemorrhage. Postcontrast images may demonstrate a ring of contrast enhancement.

If patients develop ascending paralysis or signs and symptoms consistent with Guillain-Barre, consideration for neurological consultation and LP to examine for albuminocytologic disassociation.

**Management**

Management for neurologic manifestations should be done in conjunction with Neurology.

The AAN has a COVID-19 Neurology Resource Center that can be accessed for assistance as well. It is located at: [http://www.aan.com/](http://www.aan.com/)

Neurology will proceed with telephonic consultation and chart review to minimize exposure of healthcare personnel.

**Prognosis**

Acute cerebrovascular disease is not uncommon in COVID-19. Findings suggest that older patients with risk factors are more likely to develop CVD. The development of CVD is an important negative prognostic factor, which require further study to identify optimal management strategy to combat the COVID-19 outbreak.
Gastroenterology
Incidence and Pathology

COVID-19 GI manifestations are likely occur because the virus enters target cells through angiotensin converting enzyme 2 (ACE2), a receptor found in both the upper and lower gastrointestinal tract where it is expressed at nearly 100-fold higher levels than in respiratory organs. DOI: [https://doi.org/10.1053/j.gastro.2020.02.055](https://doi.org/10.1053/j.gastro.2020.02.055)

In the meta-analysis, pooled prevalence of GI manifestations was 18%. The most common symptom was anorexia (27%), followed by diarrhea (12%), nausea and vomiting (10%), and abdominal pain (9%). Prevalence of GI symptoms was 17% in patients with severe disease compared with 12% in those with non-severe disease and was similar among adults, children, and pregnant women. The overall concomitant viral RNA positivity rate of stool and respiratory samples was 48%. In studies reporting serial testing, 70% of patients had persistently positive stool RNA even after respiratory tests had become negative. [https://www.jwatch.org/na51324/2020/04/09/gastrointestinal-aspects-covid-19](https://www.jwatch.org/na51324/2020/04/09/gastrointestinal-aspects-covid-19)

Work-Up

Based on incidence and prevalence, continue to work up diarrhea with simple 5 step approach to the patient with diarrhea described by Mayo Clinic. [https://www.mayoclinicproceedings.org/article/S0025-6196(12)00382-5/fulltext](https://www.mayoclinicproceedings.org/article/S0025-6196(12)00382-5/fulltext)

1. Does the patient really have diarrhea? Beware of fecal incontinence and impaction.
2. Rule out medications as a cause of diarrhea (drug-induced diarrhea).
3. Distinguish acute from chronic diarrhea.
4. Categorize the diarrhea as inflammatory, fatty, or watery.
5. Consider factitious diarrhea.

BUN/Cr to evaluate for dehydration.

Management

Symptomatic Treatment
Primary focus is to ensure adequate hydration

Nausea: Ondansteron, Metaclopramaide
Diarrhea: Loperamide
Abdominal Discomfort: Consideration for antacids including PPI and H2 blockers

**Caution if on treatments like plaquenil as there is a risk for QT prolongation**

**Prognosis**

Studies do not directly confirm that viral particles in stool are infectious and capable of disease transmission, but offer evidence that COVID-19 can present with digestive symptoms. Further research is vital to determine if COVID-19 can spread via the fecal-oral route

[https://journals.lww.com/ajg/Documents/COVID19_Han_et_al_AJG_Preproof.pdf](https://journals.lww.com/ajg/Documents/COVID19_Han_et_al_AJG_Preproof.pdf)

**Liver disease**

**Overview**

1. **Incidence:**

   1. The incidence of direct hepatic injury is confounded by pre-existing liver disease, drug-induced liver injury, and shock

      1. The only reported post-mortem liver biopsy from a patient with COVID-19 showed only microvesicular steatosis, a common finding in sepsis

   2. Up to 53% of patients have abnormal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [Zhang et al, *Lancet Gastroenterol Hepatol*, 2020].

      1. Given often elevated CK, this may also represent a myositis similar to that observed in severe influenza infections [Bangash et al, Lancet Gastroenterol Hepatol, 2020].

   3. Bilirubin and alkaline phosphatase tend to be spared

      1. 54% of patients hospitalized for COVID-19 at a single center in China had elevated gamma-glutamyl transferase (GGT).

   2. **Clinical course:**
1. In general, liver injury in mild COVID-19 disease is transient and self-resolving. However, liver injury correlates with severity

   2. AST is associated with progression to ARDS but not death; total bilirubin is associated with both progression to ARDS and death (Wu et al, *JAMA Intern Med*, 2020).

2. Acute liver failure has not been reported [Ong et al, *BMJ*, 2020].

3. **Pathophysiology:**

   1. Possible mechanisms of liver injury include:

      1. Direct liver injury (viral hepatitis)

         1. In SARS direct liver injury is seen in up to 60% of patients. Liver biopsies from 3 patients with SARS showed mild to moderate lobular inflammation, apoptosis, and prominent mitotic activity of hepatocytes [Chau et al, *Hepatology*, 2004].

         2. ACE2 receptors are highly expressed within the biliary tree but not in hepatocytes [Chai et al, *BioRxiv*, 2020].

      2. Drug hepatotoxicity

      3. Hepatic congestion (impaired venous return and elevated RAP associated with high levels of PEEP)

      4. Cytokine/ immune effects

         1. Other respiratory viruses produce similar elevations of LFTs, thought to involve intrahepatic cytotoxic T cells and Kupffer cells.[Bangash et al, *Lancet Gastroenterol Hepatol*, 2020].

      5. Shock

4. **Workup**

   1. Baseline CK, LDH, LFT’s, INR

   2. If normal LFTs on presentation, monitor LFTs every third day

      1. If on hepatotoxic medications, monitor more frequently in conjunction with pharmacy.

   3. Workup for other etiologies of liver injury with RUQUS, doppler ultrasound, hepatitis serologies, etc., as clinically indicated.
Management

1. Follow for acute liver failure (defined as severe liver injury with elevated bilirubin, INR >1.5, and encephalopathy).
2. Review medication list for all possible offending agents and discontinue if possible.
3. N-Acetyl-Cysteine is not recommended at this time due to significant volume load.

   1. Chinese studies refer to giving “liver protective drugs” in case of severe liver injury but we recommend against this for now.
**Oncology**

**General Management**

1. **Data:**

   1. Based on early descriptive studies from China, patients with cancer - particularly those on active treatment for cancer - appear to have a worse prognosis. This includes higher prevalence, higher risk of severe disease, and higher risk of death from COVID-19 in patients with cancer compared to those without. (WHO-China Joint Mission on COVID-19, Yu et al, JAMA Oncology 2020, anecdotal reports)
   2. In univariate Cox proportional hazards model, cancer patients who received antitumor treatment within 14 days of COVID-19 diagnosis had a higher risk of developing severe events. Moreover, patchy consolidation on the first CT on admission suggested an elevated risk of developing severe events than those cases without consolidation. [https://www.esmo.org/oncology-news/findings-from-a-retrospective-case-study-of-covid-19-infection-in-cancer-patients-in-wuhan-an-emphasis-on-severe-events](https://www.esmo.org/oncology-news/findings-from-a-retrospective-case-study-of-covid-19-infection-in-cancer-patients-in-wuhan-an-emphasis-on-severe-events)

2. **Oncology Consultation/Coverage:**

   1. Contact primary oncologist to establish the best means of ongoing communication.

3. **Prognosis:**

   1. Many patients have a reasonable or even good oncologic prognosis with current therapies. Do not assume an oncologic prognosis, even with metastatic disease: involve the primary oncologist.

4. **Meds:**

   1. Ensure that an appropriate medication reconciliation for immunosuppressive medications

5. **Workup:**

   1. Additional labs to standard workup:
      
      1. Weekly galactomannan in neutropenic/transplant patients.
      2. Specific patient populations may require additional monitoring (such as CMV, EBV monitoring in transplant patients – consult with primary oncologist).

6. **Exam:**

   1. Examine catheters (port, CVC, others) daily.
2. Avoid rectal exams and any per-rectum therapies in neutropenic patients, but examine the perirectal area if symptoms or persistent fevers.
3. In patients with heme malignancy or SCT: findings are more subtle or absent in neutropenic and immune suppressed patients.

7. **Pain management:**

   1. Patients with cancer-related pain may have high opiate needs at baseline. Opiates should not be stopped but type may need to be adjusted in the setting of respiratory failure, renal injury, or liver injury.

8. **Goals of Care:**

   1. Involve primary oncologist whenever possible (recognizing that in critical/emergent situations, this may not be possible).

9. **Anticoagulation:**

   1. Thrombosis prophylaxis for all unless contraindicated
      
      1. Hold pharmacologic prophylaxis if platelet count < 30K, use TEDS/SCD’s
      2. Both COVID-19 infection and malignancy increase thrombotic risk, particularly with solid tumors.

10. **Transfusions:**

    1. If a transfusion is needed, suggest using irradiated, leukoreduced CMV negative blood
    2. See “Blood Transfusions” section for additional details

<table>
<thead>
<tr>
<th>Patient</th>
<th>DVT ppx</th>
<th>Transfusion Thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfuse 1 unit at a time</td>
<td>RBC</td>
<td>Platelets</td>
</tr>
<tr>
<td>No bleeding, Plts &gt; 30k</td>
<td>LMWH daily or SC UFH TID</td>
<td>Hgb &lt; 7 if ACS, ** Hgb &gt; 10</td>
</tr>
<tr>
<td>No bleeding, but patient requires anticoagulation</td>
<td>Heparin gt</td>
<td>PTT goal depends on indication</td>
</tr>
</tbody>
</table>
No bleeding, Plts < 30k | SCDs*  
|  
| * Hold pharmacologic  
|  
| Plts < 10k  
|  
Mild Bleeding, Rigors, or Minor Procedures (a-lines, CVCs) | Continue pharmacologic ppx in most patients  
|  
| SCDs* if not using pharmacologic  
|  
| Plts < 20k  
|  
| INR > 3  
|  
Serious Bleeding or Major Procedure (includes LP) | + SCDs*  
|  
| * Hold pharmacologic if able  
|  
| Transfuse for active bleeding  
|  
| Plts < 50k or higher  
|  
| INR > 1.5  

3. * SCDs = sequential compression devices  
4. ** ACS = Acute Coronary Syndrome

Febrile Neutropenia

1. Definition:
   1. ANC < 500 cells/mm3 AND T ≥ 100.4F

2. Workup:
   1. Blood cultures from peripheral (ideally two sets), and each lumen of central line (label clearly); UA/sed with urine culture (UA may not be as informative with neutropenia); glucan and galactomannan (if not checked recently), sputum if able; CXR  
      1. Continue DAILY blood cultures while febrile.  
      2. Monitor serum galactomannan and 1-3-beta glucan once weekly.  

3. Initial Empiric Antibiotics:
   1. Cover GNRs in all patients: Ceftazidime 2g Q8h or Cefepime 2g Q8h  
      1. Alternatives: Piperacillin-tazobactam (2nd line, high dose 4.5g Q6h) or meropenem (3rd line, 1g Q8h).  
   2. GPCs: add Vancomycin if hemodynamically unstable, or if MRSA pneumonia or catheter-associated infection is suspected. Check dosing with pharmacy if able.

4. Removal of lines:
1. Catheter removal should be discussed if associated infection is suspected - involve primary oncologist and/or ID team to weigh risks and benefits, given that not all lines require removal.

5. **Persistent Neutropenic Fever:**

   1. If fever persists x3 days despite antibiotics
      
      1. Add Micafungin 100mg IV daily
      2. Consideration of further imaging even if the patient appears stable (discuss with oncology / ID).

6. **Anti-infective course:**

   1. Anti-Infectives should be continued until the patient has met all of these criteria:
      
      1. clinically improved, and
      2. has been afebrile for 48h, and
      3. has been non-neutropenic for 48h.

**Immune Checkpoint Inhibitors**

1. **Overview**

   1. Immune Checkpoint Inhibitors (ICIs) are not immunosuppressive when used alone, but the steroid dosages used to treat immune toxicities are often immunosuppressive.
   2. Most common ICIs are CTLA-4 inhibitor (ipilimumab) and PD-1/PD-L1 inhibitors (pembrolizumab, nivolumab, durvalumab, atezolizumab and avelumab).

2. **Immune toxicity**

   1. If patient develops organ dysfunction, it may be due to immune toxicity
      
      1. Consult primary oncologist.
      
      2. Common immune toxicities include pneumonitis / respiratory failure (may be difficult to distinguish between COVID19 disease or may be aggravated by COVID19 infection), colitis, endocrine dysfunction (thyroid, pituitary / hypothalamic, adrenal), nephritis. Less common hepatitis, meningitis, dermatitis.
      
      1. Check TSH, ACTH, cortisol if hypotension or concern for endocrine dysfunction.
3. Immune toxicities are usually treated with high dose steroids

1. risks and benefits must be weighed immediately with primary oncologist and ID consult teams if immune toxicity is suspected concurrent with COVID19 infection.

**Prognosis for those with a concomitant oncology diagnosis:**

The most common complication was ARDS in 8 patients (28.6%), followed by septic shock in 1 patient (3.6%), and acute myocardial infarction (AMI) in 1 patient (3.6%). Two patients (7.1%) were suspected to have pulmonary embolism.

Ten of 28 patients (35.7%) had been discharged with a median hospital stay of 13.5 days; 10 patients (35.7%) were still inpatients with a median stay of 19.0 days.

Of the 28 patients, 8 patients (28.6%) died, with a median time of 16.0 days from admission to death. The cause of death included ARDS in 5 patients (62.5%), followed by pulmonary embolism in 1 patient (12.5%), septic shock in 1 patient (12.5%) and AMI in 1 patient (12.5%).

Intubation and Anesthesiology

Intubation Personal Protective Equipment, Materials, and Set Up

PPE for All Floor/ICU/ED intubations

1. Treat all floor/ICU/ED intubations as a presumed COVID positive patient
2. Intubating with the necessary PPE is often unfamiliar/difficult to many providers - consider practicing via simulation (APSF Considerations for Airway Manipulation, 3/20/2020)
3. Our current recommendation includes:
   1. Disposable hair bouffant or cap
   2. eye protection (face shield only vs face shield AND protective eyewear)
   3. either N95 or PAPR (N95 + hood for neck protection)
   4. fluid resistant gowns (blue impermeable)
   5. double gloves
   6. leg protection (boot covers) to below the knee

PPE for Perioperative Anesthesia Intubations

1. Unknown Status/Not Suspected (i.e. outpatient laparoscopic appendectomy):
   1. If possible, screen patients for: fever, sore throat, cough, runny nose or nasal congestion, loss of sense of smell, muscle aches, shortness of breath. At this time treat all patients as COVID positive unless they have definitive testing that suggests otherwise.
   1. If the patient has any of these symptoms or cannot provide a history: Defer the procedure until symptoms resolve and consider COVID-19 testing
   2. If procedure cannot be deferred, proceed as above for COVID-19 confirmed/ suspected case

Intubation Materials

1. Airway boxes (nasopharyngeal airways, oral airway, syringes, needles, LMA’s, blue “bougie” stylet, extra ETT’s 6.0-8.0)
2. Medication boxes (paralytics, phenylephrine, ephedrine, epinephrine, lidocaine, labetalol, esmolol, propofol/etomidate, midazolam)
3. Dedicated video laryngoscope.
4. With the exception of the video laryngoscope, DO NOT take these boxes into the room - only remove what you may need and discard materials taken into the room after intubation even if not used.

Ventilator Circuit Configuration for Viral Filtration

1. **Anesthesia Machine set up:**
   1. Place HME filter between patient and in-line EtCO₂ monitoring (APSF Machine Protection) then place a HEPA filter **closest** to the anesthesia machine on the expiratory limb as shown below.
   2. May also consider adding another HEPA filter closest to the patient before HME filter if your facilities HME filters are not VFE > 99.99% rated.

   ![Anesthesia Machine Circuit Configuration](image)

   **Preferred Filter Configuration**
   VFE > 99.99% for each filter. Gas sampling on machine side of filter. (Courtesy Draeger Medical)

2. **ICU Ventilator set up:**
   1. Place HEPA filter between patient and EtCO₂ monitor to avoid contaminating sample line (mandatory).
   2. If available, place HEPA filter on expiratory limb closest to the ventilator (preferred).
   3. If EtCO₂ monitor utilizes infrared measurement (i.e. Does not actually pull sample gas into machine) then may utilize single HEPA filter either between ETT and Y-piece or at expiratory limb closest to ventilator.

1. In the event of shortage of ICU ventilators, anesthesia machines may be used for prolonged ICU ventilation (ASA/ASPF Ventilator Guidance)
2. A quick reference sheet to set up and monitor a repurposed anesthesia machine are provided (ASA/APSF Quick Setup Instructions) [file:///Users/mousumisom/Downloads/Quick%20Reference.pdf](file:///Users/mousumisom/Downloads/Quick%20Reference.pdf)

Intubation in Operating Room (COVID positive or suspected)

Preparation

1. If possible, intubate the patient via dedicated airway teams in a negative pressure room in the ER or ICU in anticipation of surgical intervention. This allows for a closed circuit during transport and minimizes transmission
2. Ensure OR is set to be on negative pressure
   1. hang signage to prevent unnecessary entry
3. 3-person team (or 2 person team with one anesthesiology attending and one resident) is the preferred method:
   1. Intubator - most senior provider, will manipulate airway only
   2. “Clean anesthesia provider” will manipulate anesthesia machine, administer medications, chart, and read checklists
   3. Circulating RN/resident as assistant to intubator. If this is the case, this will remove the RN from direct exposure.
4. Perform routine anesthesia machine check and pre-induction checklist:
   1. consider removing all medications you may need for **entire case** to minimize omnicell contamination/movement in and out of room
5. Gather supplies:
   1. Place ETT, airway adjuncts, temperature probe, OG tube, eye protection, bite block and tape in a basin and hand to circulating RN positioned at side of bed
6. Position equipment:
1. video laryngoscope plugged in and working within reach
2. trash cans open and near table

**Procedure**

1. **Personal Protective Equipment:**
   1. don appropriate PPE via “read/do” checklist prior to entering OR

2. **Transition patient to OR oxygen delivery**
   1. Move patient to OR table
   2. If patient has supplemental O₂ (i.e. nasal cannula) then continue until ready to pre-oxygenate with anesthesia machine. Ensure flow of supplemental O₂ is turned “OFF” before manipulating device
   3. The “clean anesthesia provider” ensures APL at “zero” and all flows “OFF”, remove patient facemask and immediately use 2-hand technique to place circuit face mask on patient

3. **Preoxygenate:**
   1. Turn O₂ flow to 2L/min and allow patient to preoxygenate for 3-5 minutes at tidal breathing to minimize facemask leak that may occur with vital capacity breathing

4. **Intubate:**
   1. “Clean anesthesia provider” will push RSI medications once preoxygenation is complete.
   2. Avoid hand ventilation if possible. If hand ventilation needed, intubating provider to maintain 2-hand mask and “clean anesthesia provider” will touch bag/APL valve
   3. “Clean anesthesia provider” turns off gas flows
   4. Intubating provider disconnects facemask and place next to patient’s head, and uses video laryngoscopy to intubate patient

5. **After successful intubation**
   1. Circulating RN/resident pulls stylet, intubating anesthesia provider occludes end of ETT with finger, circulating RN/resident inflates cuff, and then connects circuit
   2. “Clean anesthesia provider” turns on gas flows and ventilator and confirms EtCO₂ (gold standard > 3 breaths with consistent waveform and value)
   3. Intubator monitors for bilateral chest rise and “fogging” of ETT
      1. avoid listening to breath sounds as can cause contamination of providers
4. Circulating RN/resident will take control of ETT while the intubating provider tapes
5. Intubator will place OG tube, temperature probe, eye protection and bite block
6. “Clean anesthesia provider” will start appropriate anesthetic i.e. inhaled volatile vs TIVA and chart as needed

6. Clean equipment:

1. Intubating provider and circulating RN/resident will change top gloves with and then clean video laryngoscope/any other equipment that may have been contaminated

7. Allow **18 minutes to facilitate 99% aerosolized virus removal** (assumes ACH of 15/hr) from time of intubation then allow other OR personnel(i.e. Surgeons/scrub tech) into the OR with proper PPE

**Transporting from the OR to the ICU**

1. Place HEPA filter between patient and Y-piece to prevent viral contamination of circuit
2. Maintain patient in a negative pressure environment with PPE including N95 or PAPR prior to transitioning to transport ventilator
3. Clamp ETT, remove from anesthesia circuit and then place onto transport ventilator.
4. Unclamp the tube and confirm ventilation. If EtCO2 monitoring is used for transport, ensure it is **POST** HEPA filter(EtCO2 closer to ventilator)

**Extubation**

**Perioperative/OR Extubation**

1. Don clean gloves on top of baseline PPE
2. Confirm patient will tolerate extubation:
   1. <0.4 FiO₂
   2. chemical paralysis reversed
   3. maintaining adequate minute ventilation and tidal volumes with minimal support (i.e. PSV 5/5)
   4. hemodynamically stable
   5. airway reflexes intact
3. “Clean anesthesia provider” places patient on 1.0 FiO₂, “Extubator” loosen tape securing ETT, suction mouth, remove OG tube, eye protection and temperature probe
4. “Extubator” places a nasal cannula in the patient’s nares with oxygen flow “OFF”
5. Consider placing a plastic drape on top of patient to prevent exposure to any coughing that may occur (i.e. Clear plastic head piece from Bair hugger)
6. “Clean anesthesia provider” turns all gas flows to “OFF” and “extubator” extubates the patient.
7. Circulating RN/resident will remove plastic drape and ETT as one item and discard while “extubator” will immediately place anesthesia facemask over patient with good seal and connect circuit, “clean anesthesia provider” will increase gas flows to confirm that the patient is ventilating appropriately
8. Once the patient is confirmed to be supporting their own oxygenation/ventilation - the “clean anesthesia provider” will turn “OFF” gas flows.
9. “Extubator” will remove the anesthesia face mask and immediately place surgical face mask down from forehead to cover the patient’s mouth/nares
10. “Clean anesthesia provider” will turn on supplemental nasal cannula O₂ to appropriate L/min flow
11. All providers will sanitize/change gloves while maintaining base layer PPE. Do not allow anyone into the room for at least 18 minutes after extubation to facilitate 99% of aerosolized virus removal by negative pressure room (assumes ACH of 15/hr)

**ICU Extubation**

1. Don appropriate PPE via “read/do” checklist
2. Only respiratory therapist and/or airway provider should be in the room
3. Confirm patient will tolerate extubation (See “vent weaning” section of respiratory chapter)
4. Place patient on 1.0 FiO₂ and ensure non-rebreather mask ready with flow “OFF”
5. Place “chuck” or towel on patient chest and ensure yankauer suction on ready readily available
6. Respiratory therapist to cut tape holding ETT, turn vent flows to “OFF” and extubate patient
7. Immediately discard of ETT and chuck or towel and immediately place non-rebreather, then turn oxygen flow to 10-15L/min
8. Ensure patient is oxygenating and ventilating
9. All providers will sanitize/change gloves while maintaining base layer PPE. Minimize personnel in the room for at least 47 minutes after extubation. All providers re-entering the room must be donned in full PPE.
Surgical Recommendations

At this time all elective surgeries are being recommended not to be performed. Guidance is based on the American College of Surgeons and CMS and based on the current COVID situation that is site specific.

Information is constantly being reviewed by the surgical COVID task force, and can be found at the following website: https://www.facs.org/covid-19/clinical-guidance/elective-case

On this website, specific surgical guidance is based on the type of surgery (Cancer related surgery, Emergency General Surgery, Gynecology, Metabolic-Bariatric Surgery, Neurosurgery, Ophthalmology, Orthopedic Procedures, Otolaryngology, Pediatric Surgery, Urology, Vascular Surgery)

Some overarching principles for all cases include the following:

1. Be aware that while some of the following triaging guidelines include a “Level 1” (e.g., lowest level of COVID-19 acuity) in the recommendations, one must be aware that the rates of COVID-19 are predicted to skyrocket in the next few weeks, and the overarching recommendation is to prepare for markedly increased rates when triaging elective cases at present.
2. Patients should receive appropriate and timely surgical care, including operative management, based on sound surgical judgment and availability of resources.
3. Consider nonoperative management whenever it is clinically appropriate for the patient.
4. Consider waiting on results of COVID-19 testing in patients who may be infected.
5. Avoid emergency surgical procedures at night when possible due to limited team staffing.
6. Aerosol generating procedures (AGPs) increase risk to the health care worker but may not be avoidable. For patients who are or may be infected, AGPs should only be performed while wearing full PPE including an N95 mask or powered, air-purifying respirator (PAPR) that has been designed for the OR. Examples of known and possible AGPs include:
   a. Intubation, extubation, bag masking, bronchoscopy, chest tubes
   b. Electrocautery of blood, gastrointestinal tissue, any body fluids
   c. Laparoscopy/endoscopy
      2. This does not apply to upper and lower GI bleeding, dysphagia impeding oral intake, impending cholangitis (ERCP), symptomatic pancreaticobiliary disease, palliation of GI obstruction, patients with a time sensitive diagnosis https://www.asge.org/home/advanced-education-training/covid-19-asge-updates-for-members/gastroenterology-professional-society-guidance-on-endoscopic-procedures-during-the-covid-19-pandemic
7. There are insufficient data to recommend for/against an open versus laparoscopy approach; however, the surgical team should choose an approach that minimizes OR time and maximizes safety for both patients and healthcare staff. Refer to Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guidelines for these patients.

Children are not as adversely affected by COVID than adults. Epidemiological Characteristics of 2143 Pediatric Patients with 2019 Coronavirus Disease in China,” examined the cases of 731 children with confirmed laboratory-tested cases of the coronavirus and 1,412 children who were suspected of having COVID-19.

Out of all 2,143 cases, one child died, and most cases were mild. Nearly 6% of the children’s cases were severe or critical compared with 18.5% of adults. (https://www.aap.org/en-us/about-the-aap/aap-press-room/Pages/Children-with-COVID-19-Impacted-Less-Severely-Than-Adults-Study.aspx)


**Neonatal Protocol for Neonates born to Mothers who are PUI or confirmed positive for COVID 19 recommendations based off of AAP guidance**

1. Delivery team will consist of those members essential to the anticipated care of the newborn per NRP guidelines and current hospital protocol. Maternal COVID-19 alone does not change these guidelines.

2. Members of the delivery team will wear gown, gloves, N95 mask, eye protection.

3. Upon delivery, any urgent, initial resuscitation will occur in delivery room, then neonate will be moved to a separate room for remainder of resuscitation and remainder of newborn care.
   
a. Separation of mother and infant should be discussed with mother as soon as possible after admission and before delivery of newborn.

4. If asymptomatic, neonate will remain in a separate room with a designated asymptomatic caregiver to provide care wearing appropriate PPE. Per hospital policy, all visitors must leave hospital by 7 pm. Assigned baby advocate will provide overnight care.
a. If needed, infants can be kept in cohort in a designated room, in isolettes and maintained at least 6 feet apart.

b. Caregiver and clinical providers should use gown, gloves, standard procedural mask, and eye protection.

c. For bag-mask ventilation, CPAP (or other positive pressure ventilation, including nasal cannula at higher than 2 L/min flow, intubation, tracheal suctioning or any form of mechanical ventilation, gown, gloves, N95, and eye protection should be worn.

d. A kangaroo bag will be designated for use in this room only.

5. Newborn should be bathed as soon as reasonably possible after birth.

6. If mother chooses to express breast milk using precautions, such as wearing a mask and washing hands and breast prior to expressing milk, neonate will be fed mother’s expressed breast milk.

7. If mother refuses separation, despite recommendations, infant will be cared for by mother and baby advocate in mother’s room wearing appropriate PPE. COVID +/PUIs are not allowed visitors at all (per hospital policy). Infants will be cared for by mother & nurse. Infants will stay in an isolette in mother’s room. If mother desires to direct breastfeed, despite recommendations to the contrary, she should wear gloves and mask and wash breasts prior to direct breastfeeding.

a. Newborns will be tested at approximately 24 hours of age, using a single swab to swab first the throat then nasopharynx, placing swab in one viral transport media tube and sent to lab for a single SARS-CoV-2 PCR test to be performed.

b. This test may be repeated at around 48 hours regardless of results of the first test if newborn has not been discharged from hospital. Second test must be approved to be ordered.

i. Note: There have been reports of newborns with negative first test and positive test at 48 hours of age.

8. If neonate remains asymptomatic, he/she will be given routine newborn care with the addition of separation, PPE and testing listed above. The neonate will be discharged according to current newborn discharge protocol.

a. Discharge of positive or PUI newborns will need plans for frequent outpatient follow-up over 14 days of life. Specific guidelines should be provided for caregiver(s) as outlined in AAP recommendations
9. If neonate demonstrates initial symptoms of distress, he/she will be provided care according to current protocols outlined by NRP and newborn nursery protocols. Caregivers will wear PPE as outlined previously (CDC and AAP recommendations). If symptoms resolve or show improvement within one hour, will continue to treat patient per protocol. If neonate’s symptoms are severe or fail to resolve or improve within one hour, the Saint Francis neonatologist on call will be notified for further consultation or for transfer request.

Initial Protocol proposal 4/6/20; adapted directly from document Initial Guidance: Management of Infants Born to Mothers with COVID-19 by the AAP Committee on Fetus and Newborn, Section on Neonatal Perinatal Medicine, and Committee on Infectious Disease April 2020—Document attached for reference.
Palliative Care

Anxiety

1. **Non-pharmacologic:**
   1. Counseling (Spiritual, Psychocological, SW), Reiki

2. **Pharmacologic**
   1. Benzodiazepines (if patient is not delirious; can use in either intubated or non-intubated pts)
      1. Lorazepam (longer half-life) 0.5-2 mg PO/SI q4-6h PRN; 0.5-2 mg IV q2h PRN
      2. Midazolam (shorter half-life) 0.2-0.5 mg IV slowly q 15 min PRN or 0.1-0.3 mg/hr IV infusion
   2. SSRI/SNRI: Continue home dose if possible. If NPO, replace with prn benzodiazepine

Dyspnea & Acute Pain

Non-opioid management

1. **Non-Pharmacologic for Dyspnea:**
   1. Positioning: sitting patient up in bed, if possible. See also Anxiety above.

2. **Pharmacologic:**
   1. Please see “Therapeutics” for discussion about NSAID use vs acetaminophen. No recommendation is made at this time
   2. Ativan (as above) can be used to ease the anxiety associated with dyspnea, but would avoid in patients who have had a previous paradoxical reaction (i.e. worsened agitation).
   3. **Opioids** can be used for both dyspnea and acute pain *(see below)*

Opioid management

1. **General principles:**
1. ALWAYS use PRN boluses to address acute, uncontrolled symptoms. PRN bolus dosing should be 10-20% of the 24-hour opioid dose

2. For opioid naive patients:

<table>
<thead>
<tr>
<th>Renal function</th>
<th>COPD</th>
<th>Morphine 5-10mg PO q3h PRN (use the 20mg/ml concentrate)</th>
<th>Hydromorphone 1-2mg PO q3h PRN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>No</td>
<td>Morphine 2-4mg IV q2h PRN</td>
<td>Hydromorphone 0.1-0.2mg IV q2h PRN</td>
</tr>
<tr>
<td>Abnormal (GFR&lt;50)</td>
<td>Yes</td>
<td>Morphine 2-5mg PO q4h PRN (use the 20 mg/ml concentrate)</td>
<td>Hydromorphone 2-4mg PO q4h PRN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Morphine 1-2 mg IV q2h PRN</td>
<td>Hydromorphone 0.2-0.4mg IV q2h PRN</td>
</tr>
</tbody>
</table>

3. If patient is not well managed with the above, add opioid infusion:

   1. Consider drip if > 3 bolus doses in 8 hours
   2. Calculate initial dose with total mg used/8 hours
      
      1. e.g. 1+2+2+2= 7 mg; begin drip at 7mg/8 hr = 1 mg/h
      2. Depending on symptoms and goals of care, consider reducing hourly rate by 30-50%. If patient is at end of life, would use 100% of hourly rate.

   3. Continue PRN dosing at current dose (if effective) or titrate as per above.

3. For Opioid tolerant patients:

   1. If able to take PO:
      
      1. Continue current long-acting doses if renal and hepatic function tolerate
      2. Continue current oral PRN dose if effective q4h prn

      1. If ineffective, increase dose by 50% and order range of up to 3 x basal dose
         
         1. e.g. 5 mg PO MS q3h prn; increase to 7.5 mg; 7.5-22 mg PO q3h PRN

   2. If unable to take PO, severe or rapidly escalating symptoms:
1. Convert as-needed PO doses to IV pushes as needed

1. Use the IV Conversion chart
2. Decrease PRN dose by ⅓ for incomplete cross-tolerance when switching between opioid classes

1. e.g. to convert 20 mg of oxycodone to IV hydromorphone: 20 mg oxy = 1.5 mg IV hydromorphone; 1.5 mg x ⅓ =1 mg IV

2. Convert PO long-acting/ sustained release opioids to an infusion:

1. Calculate 24-hour dose of PO sustained release (SR) morphine
   1. Divide by 3 for the total 24h mg IV (Morphine PO/IV = 3:1)
2. Divide the 24h mg IV total by 24h for the hourly drip rate (mg)
   1. e.g. 30 mg SR PO morphine q8 hr = 90 mg PO in 24 h; 90 mg /3 = 30 mg IV dose; 30 mg / 24 h~ 1 mg/hr IV morphine infusion

3. Continue PRN dosing. PRN dose should be 100-200% of opioid drip rate
   1. e.g. 1 mg/hr IV morphine infusion; PRN dose is 1-2 mg IV q2h

**Abbreviated Opioid Equianalgesic Table**

<table>
<thead>
<tr>
<th>Opioid Equianalgesic Doses</th>
<th>PO/PR (mg)</th>
<th>Subcut/IV (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td>n/a</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Fentanyl (See table below for transdermal conversions)</td>
<td>n/a</td>
<td>0.1 (100 mcg)</td>
</tr>
</tbody>
</table>

**Delirium**

1. **Diagnosis: CAM method**
1. Use the **Confusion Assessment Method (CAM)**

2. CAM is positive if (1) AND (2) and EITHER (3) or (4) are present

   1. Acute often fluctuating change in mental status (vs dementia)
   2. Difficulty focusing attention
   3. Disorganized thinking (rambling, illogical flow of ideas)
   4. Altered level of consciousness (too sedated or too hyperactive)

2. **Treatment:**

   1. Non-pharmacologic:

      1. Daytime lights, nighttime dark. Frequent reorientation. Reverse contributing medical conditions as able.
      2. Consult Psychiatry; for terminal delirium, consult Palliative Care

   2. Pharmacologic

      1. Additional information available at: Guidelines for Acute Hospital Acquired Delirium (Partners login required)
      2. Alter existing medications and treat comorbid symptoms.
      3. QTc prolonging agents <65 yo or DNR/I +LLST Comfort Measures

         1. Haloperidol, Mild agitation: 0.5-1.0 mg IV or 1 to 2 mg PO q6h and 1-2 mg q2h PRN.; Moderate agitation: 2-4 mg IV; Severe agitation: 4-10 mg Maximum dose: 20 mg / 24 hours
         2. If refractory, olanzapine, 2.5 to 5 mg (PO, SL, or IV) q12 hr and 2.5 mg q4h PRN; Maximum dose: 30mg / 24 hours
      4. QTc prolonging agents ≥ 65 yo or frail

         1. Haloperidol, Mild agitation 0.25 -0.5 mg IV or 1 to 2 mg PO q6h and 1 mg q2h PRN; Moderate agitation: 1-2 mg IV; Severe agitation: 2 mg IV Maximum dose: 20 mg / 24 hours
      5. Non-QTc prolonging agents

         1. Aripiprazole (Abilify), 5 mg PO daily; maximum dose 30 mg daily
         2. Valproic Acid 125-250mg IV q8h PRN.
Nausea and Vomiting

1. Match treatment to etiology of nausea:
   1. Chemoreceptor Trigger Zone (blood brain barrier breakdown)
      1. haloperidol, metoclopramide, ondansetron, olanzapine
   2. Gastrointestinal:
      1. ondansetron, metoclopramide, dexamethasone (if malignant obstruction)
   3. CNS cortical centers:
      1. lorazepam for anticipatory nausea, dexamethasone (tumor burden causing ICP)
   4. Vestibular:
      1. meclizine, scopolamine, diphenhydramine

Constipation

1. If able to take oral agents, start:
   1. Senna 2 tabs PO qhs, can increase up to 2 tabs PO TID if needed
   2. Polyethylene Glycol 17gm packet PO QD-BID prn
   3. Avoid Docusate given lack of data demonstrating benefit

2. If unable to take oral agents, suggest Bisacodyl suppository PR daily prn signs of abdominal discomfort/distention likely due to constipation.

Care of the imminently dying patient

1. Signs and symptoms of imminent death
   1. Somnolence
   2. Warmth, and later cooling and mottling of extremities
   3. Change in respiratory pattern, intermittent apnea, Cheyne-Stokes pattern
   4. Gurgling sounds from oropharynx (often more distressing to family than patient)
2. Symptom management

   1. Should follow the guidelines provided in sections above
   2. Intensive Comfort Measures Guidelines

3. Ensure good communication with family members

**Excessive Salivary Secretions at the End of Life**

1. For secretions with significant mucous, evaluate benefit/burden of repositioning and deep suctioning
2. Communicate with families to expect sounds:

   1. Reassure them that although the “rattling” sound is distressing to hear, the patient is not experiencing difficulty breathing or having to clear phlegm from his or her throat. The rattling sound comes from the movement of air over secretions pooled in the throat and airways.

3. Pharmacologic management (not to be used with secretions with significant mucous)

   1. Glycopyrrolate 0.2 – 0.4mg IV q2hrs prn secretions, rattling sound
   2. Hyoscyamine 0.125-0.25mg PO q4hrs prn secretions, rattling sound
   3. Scopolamine 1.5mg TD q72hrs if patient not awake and no apparent delirium or history of delirium. NB The patch will take ~ 12 hours to take effect
   4. Avoid using > 2 of these at the same time; if more than one is required, monitor for development of anticholinergic crisis

**Documenting Important Conversations**

1. The **Advance Care Planning (ACP) Module in Epic** is the single BEST place to document serious illness conversations for patients with COVID-19 and their families. Where to find and how to use the ACP Module in Epic.
2. In conscious patients, review or sign Health Care Proxy form.
**CMS Changes during COVID Pandemic**

CMS has made sweeping changes to protocols and procedures for billing, management and treatment during this pandemic. Referral to the following website will provide basic information to help guide through these practices:


CMS is allowing healthcare systems and hospitals to provide services in locations beyond their existing walls to help address the urgent need to expand care capacity and to develop sites dedicated to COVID-19 treatment.

CMS waivers will also permit doctor-owned hospitals to increase their number of beds without incurring sanctions.

Ambulances can transport patients to a wider range of locations when other transportation is not medically appropriate.

CMS is issuing guidance to dialysis facilities to allow for the establishment of special purpose facilities to just care for patients with COVID-19.

The new CMS guidelines allows healthcare systems, hospitals, and communities to set up testing and screening sites exclusively for the purpose of identifying COVID-19 positive patients in a safe environment.

Medicare Specific: Medicare will pay laboratory technicians to travel to a beneficiary’s home to collect a specimen for COVID-19 testing, eliminating the need for the beneficiary to travel to a healthcare facility for a test and risk exposure to themselves or others.

CMS is issuing a blanket waiver to allow hospitals to provide benefits and support to their medical staffs, such as multiple daily meals, laundry service for personal clothing, or child care services while the physicians and other staff are at the hospital providing patient care.

CMS also will permit wider use of verbal orders rather than written orders by hospital doctors so they can focus more of their time on taking care of patients.

CMS is waiving the requirements for a nurse to conduct an onsite visit every two weeks for home health and hospice.
CMS is temporarily eliminating paperwork requirements and allowing clinicians to spend more time with patients. Hospitals will not be required to have written policies on processes and visitation of patients who are in COVID-19 isolation. Hospitals will also have more time to provide patients a copy of their medical record.

Virtual Check-In services, or brief check-ins between a patient and their doctor by audio or video device, could previously only be offered to patients that had an established relationship with their doctor. Now, doctors can provide these services to both new and established patients.

CMS will now pay for more than 80 additional services when furnished via telehealth. These include emergency department visits, initial nursing facility and discharge visits, and home visits, which must be provided by a clinician that is allowed to provide telehealth.

Handbook Updates: (Adapted from Brigham and Women’s Hospital COVID-19 Guidelines)
4/13/2020

Disclaimer:
These guidelines were developed at Brigham and Women’s Hospital in Boston, MA and adapted to OSU Medicine in Tulsa, OK based on practice patterns and infrastructure at OSU Medical Center in Tulsa, OK. Local resources and factors should be taken into account if utilized at other hospitals.