



MEDICINE

COVID19 HANDBOOK

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Handbook Updates: (Adapted from Brigham and Women's Hospital COVID-19 Guidelines)

4/13/2020; 4/20/20; 4/27/20; 5/4/2020; 5/11/2020; 5/18/2020; 5/25/2020; 6/1/2020;
6/8/2020; 6/15/2020; 6/22/2020; 6/29/2020; 7/6/2020; 7/13/2020; 7/20/2020; 7/27/2020;
8/3/2020

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.

Recent Updates:

1. Ongoing debates about aerosolization; the perspective of an aerosol scientist: **Page 11**
2. Ongoing debate about the scientific reasoning behind antibody decay, the humoral and T cell response: **Page 13**
3. Using the CRP to help guide which patients will benefit from steroids: **Page 56**
4. Dexamethasone in Hospitalized Patients with COVID-19- Preliminary Report: **Page 57**
5. Consideration for long term hearing loss as a neuropathic consequence of COVID-19: **Page 113**
6. Rationale for why PPI's may increase risk for COVID-19, and the dose dependent increased risk?: **Page 116**
7. Update from the AAP for neonates born to PUI or COVID positive mothers and guidelines for multi-system inflammatory syndrome in pediatric patients associated with COVID :**Page 132-133**

Clinical Course, Prognosis, and Epidemiology

Clinical Presentation

- 1) Can be extremely varied; however, most common is a non-specific flu-like illness with mixed initial symptoms (Arentz et al, *JAMA*, 2020; Chen et al, *Lancet*, 2020; Guan et al, *N Engl J Med*, 2020; Li et al, *N Engl J Med*, 2020; Wu et al, *JAMA Internal Medicine* 2020; WHO-China Joint Mission on COVID-19; Young et al, *JAMA*, 2020):
 - a) Fever, 44-94%
 - i) No clear consensus definition, with numerous criteria used in different studies.
 - ii) Recommendation, based on Washington State data (Arentz et al, *JAMA*, 2020), would be to use $\geq 38^{\circ}\text{C}$ (of note, they used solely $> 38^{\circ}\text{C}$ but we would advocate for $\geq 38^{\circ}\text{C}$).
 - iii) Must also take into account: patient's immune status, medication regimen (steroids, chemotherapy, etc.), and recent use or administration of antipyretics.
 - b) Cough, 68-83%
 - c) Sore throat, 14-61%
 - d) Shortness of breath, 19-40%
 - e) Fatigue, 43%

- f) Headache 14%
 - g) Muscle aches, 11%
 - h) Upper respiratory symptoms (sore throat, rhinorrhea, nasal or sinus congestion), 5-25%
 - i) GI symptoms (nausea, vomiting, diarrhea), 4-9%, can present before respiratory symptoms
 - j) 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>).
 - i) Rapidly accumulating anecdotal evidence that anosmia (with resultant dysgeusia (change in taste) are frequently reported symptoms associated with the COVID-19 pandemic. The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) has established the COVID-19 Anosmia Reporting Tool. This tool was developed by the AAO-HNS Infectious Disease and Patient Safety Quality Improvement Committees to allow healthcare providers of all specialties and patients worldwide to submit data to confidentially report on anosmia and dysgeusia related to COVID-19.
 - ii) <https://www.entnet.org/content/reporting-tool-patients-anosmia-related-covid-19>
- 2) The majority of patients present with more than one sign/symptom on admission (Chen et al, *Lancet*, 2020).
 - 3) Several characteristic laboratory abnormalities have been described on patient admission (Arentz et al, *JAMA*, 2020; Chen et al, *Lancet*, 2020; Young et al, *JAMA*, 2020; Zhang et al, *Lancet Gastroenterol Hepatol*, 2020; Zhou et al, *Lancet*, 2020):
 - a) Lymphopenia, 35-83%
 - i) Evaluation of the neutrophil and lymphocyte ratio linked to increased mortality in patients affected by COVID, and is used in the risk score that was recently published from China in 5.2020.
(<https://www.sciencedirect.com/science/article/pii/S0163445320302085?via%3Dihub>)
(1) 8% higher risk of in-hospital mortality for each unit increase in NLR
 - b) Mild hepatocellular injury pattern with elevated AST / ALT (~200s), 28-38%
 - c) GGT elevated in ~54% of COVID-19 cases in one center (Zhang et al, *Lancet Gastroenterol Hepatol*, 2020).
 - d) Alk Phos elevations rare, ~2% (Zhang et al, *Lancet Gastroenterol Hepatol*, 2020).
 - e) Anemia, 51%
 - f) Increased D-dimer, 36%
 - g) Elevated CK, 13%
 - h) Elevated LDH, 76%
 - i) Low/normal procalcitonin, 94%
 - j) Elevated inflammatory markers (IL-6, ESR, CRP, or ferritin), 38-86%
 - i) 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)
 - 4) Abnormal diagnostic imaging findings are common.
 - 5) 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).

- a) This is going to vary greatly with local epidemiology and season
- b) Early reports from China suggested that co-infection with other respiratory viruses suggests higher rates of co-infection between SARS-CoV-2 and other respiratory pathogens than previously reported (JAMA Published online April 15, 2020 doi:10.1001/jama.2020.6266
 - i) Of the 116 specimens positive for SARS-CoV-2, 24 (20.7%) were positive for 1 or more additional pathogens
 - ii) The most common co-infections were rhinovirus/enterovirus (6.9%), respiratory syncytial virus (5.2%), and non-SARS-CoV-2 Coronaviridae (4.3%)
- 6) Respiratory co-infection in article that looked at patients in New York suggested a 2.1% co-infection rate (Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*. Published online April 22, 2020. doi:10.1001/jama.2020.6775)
 - a) This may also suggest that this will vary greatly based on local epidemiology and season

Disease Course and Progression

- 1) Duration of symptoms:
 - a) Fever, median 12 days (interquartile range 8-13 days) in survivors.
 - b) Dyspnea, median 13 days (interquartile range 8-13 days)
 - c) 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).
 - d) 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>)
- 2) Timing of development of complications from illness onset (Zhou et al, *Lancet*, 2020):
 - a) Sepsis, median 9 days (range 7-13 days)
 - b) ARDS, median 12 days (range 8-15 days)
 - i) Respiratory decompensation can progress rapidly with duration between symptom onset and ventilator need ranging from 3-12.5 days, median 10 days (Chen et al, *Lancet*, 2020; Zhou et al, *Lancet*, 2020).
 - ii) 53% of vented, critically-ill patients developed ARDS within 72 hours of initiation of mechanical ventilation (Arentz et al, *JAMA*, 2020).
 - iii) 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/>)
 - (2) A study published in JAMA reviews a risk calculator to help providers determine the severity of disease a patient may suffer from that looks at 10 variables that appear to be

well established in this disease

((<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2766086>))

- (a) CXR findings
- (b) LDH
- (c) Age
- (d) Hemoptysis
- (e) Dyspnea
- (f) Unconsciousness
- (g) Number of co-morbidities
- (h) Cancer History
- (i) Neutrophil to Lymphocyte Ratio
- (j) Direct Bilirubin

(3) Additional calculators have been produced for care of COVID patients

- (a) COVID ventilation protocol (<https://reference.medscape.com/calculator/735/covid-19-ventilation-protocol>)

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)

- a) Incidence rates as high as 15% (data from Wuhan)
- b) 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](https://www.ajkd.org/article/S0272-6386(20)30618-1/pdf))

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

- a) Time from initiation of invasive ventilation to VAP occurrence, median 8 days (interquartile range 2-9 days) (Zhou et al, *Lancet*, 2020).

6) Severity of disease:

- a) 81% have mild to moderate symptoms (mild symptoms to mild pneumonia)
- b) 14% have severe symptoms (hypoxemia, or >50% lung involvement)
- c) 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](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).

3) Myocardial injury noted in 20–30% of critically-ill patients (Arentz et al, *JAMA*, 2020) ([https://doi.org/10.1016/S2213-2600\(20\)30161-2](https://doi.org/10.1016/S2213-2600(20)30161-2)); some progress to cardiogenic shock late in course (anecdotal reports).

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](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30165-X/fulltext))
- 2) Cause of death (Ruan et al, *Intensive Care Med*, 2020)
 - a) Respiratory failure alone, 53%
 - b) Circulatory failure alone (in the setting of myocardial damage), 7%
 - c) Mixed respiratory and circulatory failure, 33%
 - d) Unknown cause, 7%
- 3) Time from illness onset:
 - a) To discharge, median 22 days (interquartile range 18-25 days) (Zhou et al, *Lancet*, 2020)
 - b) 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).
- 4) Duration of hospitalization, median 12 days (Guan et al, *N Engl J Med*, 2020)

Prognostic Indicators

- 1) Comorbidities: Present in 41-51% of COVID-19 patients (Chen et al, *Lancet*, 2020; Tang et al, *J Thromb Haemost*, 2020) and more prevalent in those with severe cases.
 - a) Most common comorbidities: HTN, diabetes, CAD, cerebrovascular disease. 17% hypertension, 8% diabetes, 4% cardiovascular disease, 2% cerebrovascular disease, 2% chronic obstructive pulmonary disease (COPD), 1% chronic kidney disease, and 1% malignancy. (Fang et al, *Lancet Respir Med*, 2020; Guan et al, *N Engl J Med*, 2020; Yang et al, *Lancet Respir Med*, 2020; Zhang et al, *Allergy*, 2020; Zhou et al, *Lancet*, 2020).
 - i) Higher odds of in-hospital death with diabetes or CAD (Zhou et al, *Lancet*, 2020)
 - b) Obesity is being recognized as a risk factor for severe COVID-19. In addition, this may be more of a risk than hypertension according to the CDC. This may even be linked to a BMI of > 30.
(https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html)
- 2) Other comorbidities associated with poor outcomes: chronic respiratory disease, malignancy, chronic liver disease, and chronic kidney disease (Tang et al, *J Thromb Haemost*, 2020).
- 3) Diabetes has emerged as a major comorbidity for COVID-19 severity. However, the phenotypic characteristics of diabetes in COVID-19 patients are unknown. In the Coronado trial they found that in people with diabetes hospitalized for COVID-19, BMI, but not long-term glucose control, was positively and independently associated with tracheal intubation and/or death within 7 days.
(<https://link.springer.com/article/10.1007/s00125-020-05180-x>)

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.

<https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html>

How Are We Testing Currently?

PRIORITIES FOR COVID-19 TESTING

(Nucleic Acid or Antigen)

High Priority

- Hospitalized patients **with** symptoms
- Healthcare facility workers, workers in congregate living settings, and first responders **with** symptoms
- Residents in long-term care facilities or other congregate living settings, including prisons and shelters, **with** symptoms

Priority

- Persons **with** symptoms of potential COVID-19 infection, including: fever, cough, shortness of breath, chills, muscle pain, new loss of taste or smell, vomiting or diarrhea, and/or sore throat.
- Persons **without** symptoms who are prioritized by health departments or clinicians, for any reason, including but not limited to: public health monitoring, sentinel surveillance, or screening of other asymptomatic individuals according to state and local plans.

<https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html>

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>

JAMA research letter suggests that there may be an increased need for symptom screening in health care providers. Screening only for fever, cough, shortness of breath, or sore throat might have missed 17% of symptomatic HCP at the time of illness onset; expanding criteria for symptoms screening to include myalgias and chills may still have missed 10%. (https://www.healio.com/infectious-disease/emerging-diseases/news/online/%7B5d37b55b-7bc7-42fe-9ed7-daf8826e961f%7D/screening-for-only-common-covid-19-symptoms-may-miss-symptomatic-cases-among-hcp?utm_source=selligent&utm_medium=email&utm_campaign=infectious%20disease%20news&m_bt=922415890)

Sensitivity: 70% <https://www.livescience.com/covid19-coronavirus-tests-false-negatives.html>

Specificity: Close to 100% <https://www.livescience.com/covid19-coronavirus-tests-false-negatives.html>

Further data in regards to false negatives is described in the Annals of Internal Medicine. A summary of findings showed that the probability of a false-negative result in an infected person decreases from 100% (95% CI, 100% to 100%) on day 1 to 67% (CI, 27% to 94%) on day 4. On the day of symptom onset, the median false-negative rate was 38% (CI, 18% to 65%).
(<https://www.acpjournals.org/doi/10.7326/M20-1495>)

Using data for 20,912 patients from two large academic health systems, we analyzed the frequency of SARS-CoV-2 RT-PCR test-discordance among individuals initially testing negative by nasopharyngeal swab who were retested on clinical grounds within 7 days. The frequency of subsequent positivity within this window was 3.5% and similar across institutions. (<https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa722/5854366>)

A study published by CHEST on June 10, tried to identify factors that would predict a positive test result. It included more than 10,000 patients tested for SARS-CoV-2 by Cleveland Clinic, including 818 positive results in a development cohort and 290 in a validation cohort. The study found that in addition to known exposure to COVID-19, being male, African-American, or older was associated with a positive result. Positive results were less likely in those who had received a pneumococcal polysaccharide or influenza vaccine or who were taking melatonin, paroxetine, or carvedilol.
([https://journal.chestnet.org/article/S0012-3692\(20\)31654-8/fulltext](https://journal.chestnet.org/article/S0012-3692(20)31654-8/fulltext))

Is there a place for looking at the CT (cycle threshold) PCR when determining releasing someone from quarantine in regards to infectivity.
<https://www.infectiousdiseaseadvisor.com/home/topics/covid19/ct-value-may-inform-when-patients-with-covid-19-can-be-safely-discharged/>

In addition, listen to the following from virologists: <http://www.microbe.tv/twiv/twiv-640/>

Data supporting the use of nasopharyngeal swab over oropharyngeal swab is limited, but drawn from two small studies. <https://www.cebm.net/covid-19/comparative-accuracy-of-oropharyngeal-and-nasopharyngeal-swabs-for-diagnosis-of-covid-19/>

The mechanism in which we are collecting these specimens is through nasopharyngeal swab.
https://www.youtube.com/watch?v=7g4aeMDe_tc&feature=youtu.be

Information provided by the NIH recommends that if there is question in certainty of diagnosis, it may be acceptable to consider lower respiratory specimens based on discordant shedding from upper respiratory and lower respiratory specimens. (<https://covid19treatmentguidelines.nih.gov/critical-care/laboratory-diagnosis/>)

Recently there has been increasing interest in Saliva testing as there is reported increase in sensitivity with saliva testing. OSU Stillwater is in the midst of validating testing. Validating testing requires positive patients that will receive simultaneous Nasopharyngeal Swabs and saliva testing to ensure consistency to gain validity.
<https://www.medrxiv.org/content/10.1101/2020.04.16.20067835v1.full.pdf>

The FDA has recently authorized the first at-home saliva collection test for COVID-19, which people could use to sample their own saliva and send it into a lab for results. <https://www.livescience.com/at-home-saliva-test-for-covid19.html>

The FDA has also granted an EUA 5.2020 for the use of antigen testing. Antigen testing is new to this market as of 5.2020 and looks at fragments of proteins from the nasal cavity through swab collection. One of the main advantages of an antigen test is the speed of the test, which can provide results in minutes. Antigen tests are very specific for the virus, but are not as sensitive as molecular PCR tests. This means that positive results from antigen tests are highly accurate, but there is a higher chance of false negatives, so negative results do not rule out infection.

With this in mind, negative results from an antigen test may need to be confirmed with a PCR test prior to making treatment decisions or to prevent the possible spread of the virus due to a false negative.

Antigen tests are also important in the overall response against COVID-19 as they can generally be produced at a lower cost than PCR tests and once multiple manufacturers enter the market, can potentially scale to test millions of Americans per day due to their simpler design, helping our country better identify infection rates closer to real time. (<https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-antigen-test-help-rapid-detection-virus-causes>)

Abbott Rapid Testing: Reported to provide results within 5 minutes.

<https://www.npr.org/sections/health-shots/2020/04/21/838794281/study-raises-questions-about-false-negatives-from-quick-covid-19-test>

A study in Australia is looking at a rapid blood test that looks at agglutination and can possibly detect positivity in as fast as 20 minutes. <https://www.sciencedaily.com/releases/2020/07/200717101037.htm>

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>)

A recent article was published in JAMA in 4.2020 in regards to the use of serology testing. Many concerns in regards to utilization are described well in this article. One of the biggest emphasis is the use for health care workers, and perhaps release from social distancing.

<https://jamanetwork.com/journals/jama/fullarticle/2764954>

A preprint study published by medrxiv, is looking at COVID direct observation of, and risk factors for, seroconversion and incident COVID disease (among those with or without antibodies to SARS/COV2) in areas of active transmission.

<https://www.medrxiv.org/content/10.1101/2020.04.28.20080630v1.article-info>

IDSA primer on the utility and applicability of antibody testing leaves many questions still on the table about how these will be used in the future. <https://www.idsociety.org/globalassets/idsa/public-health/covid-19/idsa-covid-19-antibody-testing-primer.pdf>

CDC guidance on the use of antibody testing: It is important to minimize false positive test results by choosing an assay with high specificity and by testing populations and individuals with an elevated

likelihood of previous exposure to SARS-CoV-2. Alternatively, an orthogonal testing algorithm (i.e., employing two independent tests in sequence when the first test yields a positive result) can be used when the expected positive predictive value of a single test is low.

(https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html?deliveryName=USCDC_2067-DM29085)

Federal health officials announced Thursday they will require laboratories to report racial, ethnic and other information about each person tested for the COVID-19. The new guidance compels all labs running tests to diagnose the coronavirus or determine whether someone might have antibodies to the virus to collect and submit information on people's age, sex, location, and test result, as well as on race and ethnicity. In total, 18 pieces of information are required. The rule takes effect Aug. 1.

(https://www.washingtonpost.com/health/race-ethnicity-data-to-be-required-with-coronavirus-tests-starting-aug-1/2020/06/04/402fc58a-a68f-11ea-b473-04905b1af82b_story.html)

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.

- 2) Route of transmission: Human-to-human (Li et al, *N Engl J Med*, 2020), following a suspected zoonotic-to-human initiating event. Most often transmitted by large droplets and fomites; transmission by aerosolized particles possible (WHO-China Joint Mission on COVID-19).
- a) 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 Doremalen 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.”
 - i) <https://www.nature.com/articles/d41586-020-00974-w>)
 - ii) A new study published in Nature shows that in households may have decreased infectivity, but the study was extremely small. Ricarda Schmithausen at the University of Bonn in Germany and her colleagues looked for traces of the virus SARS-CoV-2 in 21 households that each included at least one infected person. The team found viral RNA in just 3% of samples from the most frequently touched objects, such as doorknobs, and in 15% of samples taken from bathroom drains and toilets. The team could not grow infectious virus from any of the samples. ((M. Döhla *et al.* Preprint at medRxiv <http://doi.org/dxqn>; 2020))
 - b) The WHO also suggests that transmission is primarily through droplets, although exceptions can occur. <https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions>
 - c) The perspective of an aerosolization from an aerosol scientist and the argument of why the virus can be aerosolized. <https://www.medscape.com/viewarticle/934837>
 - d) Aerosolizing procedures are proposed to include intubation, nebulization, non-invasive positive pressure (CPAP, BiPAP), and high-flow nasal cannula.
 - i) The following document discusses the modes of transmission and suggests those procedures with higher risk of aerosolization. The ATS still does not document determine if COVID is transmitted by droplets or aerosols and is clear that more research needs to be done here.
https://www.atsjournals.org/doi/pdf/10.1164/rccm.2020C11?utm_campaign=ATS%20General&utm_medium=email&_hsmi=90669244&_hsenc=p2ANqtz--Ur5bVjSyre0gp9U314m1-EkcUS1Bo_NcBV_xEEZ09WMD2wXXLvp2KsqSlcB7g_Ne-9zRfVzq6uxMpg_Q-tQcBXMJUuw&utm_content=90669244&utm_source=hs_email
 - ii) The WHO supports that transmission during aerosolizing procedures can occur. In addition to the traditional aerosolizing procedures, some outbreak reports related to indoor crowded spaces have suggested the possibility of aerosol transmission, combined with droplet transmission, for example, during choir practice, in restaurants or in fitness classes. (<https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions>)
 - e) 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).

- f) A cohort study published in JAMA found that SARS-CoV-2 can be present in the semen of patients with COVID-19, and SARS-CoV-2 may still be detected in the semen of recovering patients. 38 participants who provided a semen specimen, 23 participants (60.5%) had achieved clinical recovery and 15 participants (39.5%) were at the acute stage of infection. Results of semen testing found that 6 patients (15.8%) had results positive for SARS-CoV-2, including 4 of 15 patients (26.7%) who were at the acute stage of infection and 2 of 23 patients (8.7%) who were recovering. This study is limited by the small sample size and the short subsequent follow-up. The implications of these findings is unclear as far as infectivity, however if SARS-CoV-2 can be transmitted sexually in future studies, sexual transmission might be a critical part of the prevention of transmission, especially considering the fact that SARS-CoV-2.
- https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2765654?utm_source=For_The_Media&utm_medium=referral&utm_campaign=ftm_links&utm_term=050720
- 3) Viral shedding and symptoms: Nasopharyngeal viral load peak within days of symptom onset followed by decline (Young et al, *JAMA*, 2020).
- a) 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
- i) In several patients, SARS-CoV-2 remained detectable in sputum after symptomatic recovery (Rothe et al, *N Engl J Med*, 2020) or without detectable virus in serum (Holshue et al, *N Engl J Med*, 2020).
- ii) A recent study published in the American Journal of Pathology show that those that are asymptomatic, and not hospitalized may have higher shedding risk which could have important indications for COVID containment. [https://ajp.amjpathol.org/article/S0002-9440\(20\)30328-X/fulltext](https://ajp.amjpathol.org/article/S0002-9440(20)30328-X/fulltext)
- b) Duration of viral shedding from illness onset in survivors, median 20 days (interquartile range 17-24 days); virus detectable to death in nonsurvivors (Zhou et al, *Lancet*, 2020; Young et al, *JAMA*, 2020).
- i) Viral shedding duration longer in more severe disease status (Zhou et al, *Lancet*, 2020).
- 4) Incubation period: Mean of 5 days, median of 3-4 days, with wide range up to 24 days (common range 2-7 days) (Li et al, *N Engl J Med*, 2020; Guan et al, *N Engl J Med*, 2020; Velavan and Meyer, *Trop Med Int Health*, 2020; Chan et al, *Lancet*, 2020).
- 5) Basic reproduction number (R0): Measure of transmissibility, denoting the theoretical expected number of secondary cases from any given case. An $R_0 > 1$ is consistent with ongoing outbreak potential.
- a) Various different models place estimates for R0 in the approximate range of 2-5, with min/max mean/median values ranging from 1.4-5.7 and decline in R0 since outbreak onset in China and regions of Europe (Zhao et al, *Int J Infect Dis*, 2020; Riou and Althaus, *Euro Surveill*, 2020; Flaxman et al, *Imperial College London*, 2020 preprint; Read et al, *medRxiv*, 2020 preprint; Shen et al, *medRxiv*, 2020 preprint).
- b) These estimates are comparable to those estimated for the 2002-2003 SARS outbreak (Lipsitch et al, *Science*, 2003; Bauch et al, *Epidemiology*, 2005; Wallinga and Teunis, *Am J Epidemiol*, 2004).

- 6) 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).
 - a) 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)
 - b) Additional evidence to support superspreading COVID-19 following a 2.5-hour choir practice attended by 61 persons, including a symptomatic index patient, 32 confirmed and 20 probable secondary COVID-19 cases. This was likely due to close proximity (< 6 feet during practice) occurred (<https://www.cdc.gov/mmwr/volumes/69/wr/mm6919e6.htm>)
- 7) 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 data used (Guan et al, *N Engl J Med*, 2020; Wang et al, *JAMA*, 2020), with initial estimates as high as 15% (Huang et al, *Lancet*, 2020).
 - a) Conservative estimates may still be an overestimate according to some (Guan et al, *N Engl J Med*, 2020; Klompas M, *Ann Intern Med*, 2020).
 - b) 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
- 8) Reinfection and immunity: Possibility or risk of reinfection in humans is not yet known nor are details around development of immunity.
 - a) Preprint studies report evidence of SARS-CoV-2-specific neutralizing antibodies generated by B-cells of convalescent patients (Ju et al, *bioRxiv*, 2020 preprint) and resistance to reinfection after recovery in non-human primates (Bao et al, *bioRxiv*, 2020 preprint).
 - b) A recent article published in the NEJM does show rapid decay of Anti-SARS-COV2 antibodies in those with mild infection, which may suggest less long term protection, although this is difficult to extrapolate beyond 90 days. <https://www.nejm.org/doi/full/10.1056/NEJMc2025179>
 - i) Concerns for antibody decay and the debate that exists. Scientists still do not know what level of immune response might be protective against future infection. Only longer-term studies will be able to answer that question. <https://www.scientificamerican.com/article/concerns-about-waning-covid-19-immunity-are-likely-overblown/>

Vulnerable populations and special settings

- 1) ICU Patients may have less of a mortality risk based on the knowledge gained since the pandemic began. Rates have dropped from 60% to 42%. Although this may seem promising, this is still higher than patients afflicted with other viral pneumonias, which is estimated to be at 22%. <https://www.reuters.com/article/us-health-coronavirus-survival/covid-icu-patients-survival-rate-has-improved-study-idUSKCN24G38S>

- 2) 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).
- 3) 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.
- 4) Possible increased risk in African American Populations based on reviews of affected and death rates based on state analysis including: Michigan, Illinois and Wisconsin. (<https://www.statnews.com/2020/04/06/flying-blind-african-americans-disparities-covid-19-data-limited/>)
- 5) 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).
 - i) Virologist cited in Nature News suggests cat owners should not yet be alarmed, noting deliberate high-dose inoculation of said cats - unrepresentative of day-to-day pet/owner interactions, and that none of the infected cats developed symptoms in the aforementioned study (Mallapaty S, *Nature News*, 2020).
- 6) An article in the Autoimmune Learning Network suggests that those patients that are on chronic immunosuppressive treatments appear not to be at a heightened risk of becoming infected with the SARS-COV-2 virus, concluded panelists in a roundtable discussion at the virtual Interdisciplinary Autoimmune Summit (IAS) 2020 on July 10. (<https://www.autoimmunelearningnetwork.com/web-content/does-immunosuppressive-therapy-increase-risk-covid-19-patients-imid?hmpid=bW91c3VtaS5zb21Ab2tzdGF0ZS5lZHU=>)
 - i) Only the use of steroids, along with the comorbidities that affect all populations, increase risk for complications of COVID-19 in patients with IBD.

Personal Protective Equipment and Infection Control

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 re-aerosolization 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>

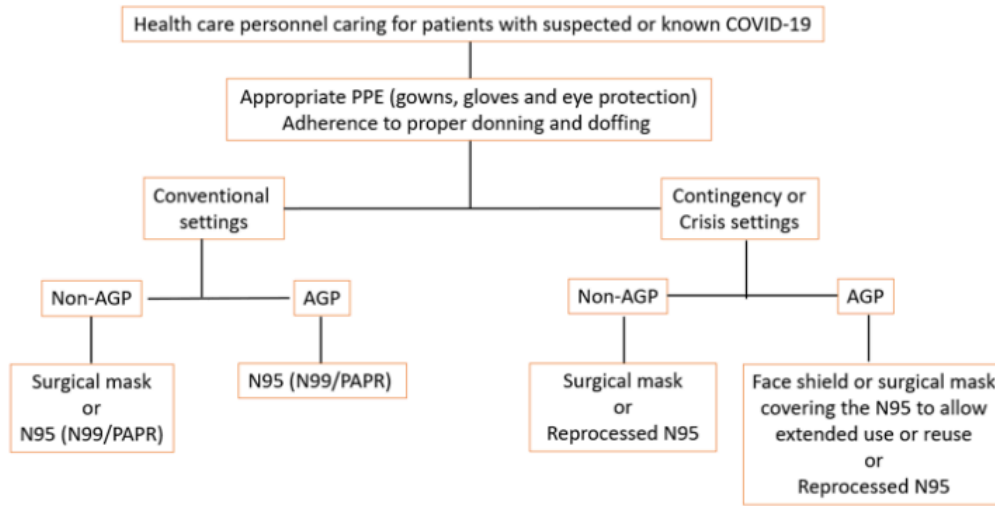
Safe Practices of Donning PPE and Doffing PPE: <https://www.cdc.gov/hai/pdfs/ppe/ppe-sequence.pdf>

Consideration for just in time training can also be watched at this website:

<https://www.youtube.com/watch?v=bG6zISnenPg&feature=youtu.be>

Information released from the IDSA also supports the following for appropriate PPE in the appropriate setting.

Figure 1. IDSA Algorithm for Appropriate PPE in Conventional and Contingency or Crisis Settings



AGP: aerosol-generating procedures; **PPE:** personal protective equipment

<https://www.idsociety.org/practice-guideline/covid-19-guideline-infection-prevention/#toc-9>

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

In the largest health care system in Massachusetts with more than 75 000 employees, in tandem with routine symptom screening and diagnostic testing of symptomatic HCWs for SARS-CoV-2 infection, leadership mandated a policy of universal masking for all HCWs as well as for all patients. New infections among HCWs with direct or indirect patient contact were increasing exponentially, from 0% to 21.3% (a mean increase of 1.16% per day). However, after the universal masking policy was in place, the proportion of symptomatic HCWs with positive test results steadily declined, from 14.7% to 11.5%

<https://jamanetwork.com/journals/jama/fullarticle/2768532>

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>

OSU Specific Reprocessing N-95 Respirators for Extended Use

<https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/decontamination-reuse-respirators.html>

<https://www.cdc.gov/coronavirus/2019-ncov/hcp/respirators-strategy/index.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.
 - a) Unit Clean Bin Delivery Area
 - i) ED: ED Breakroom
 - ii) MCH: MCH Breakroom
 - iii) ICUS: Room behind Nutrition
 - iv) 5E: Conference Room

- v) 7E: Conference Room
 - vi) RT: TBD
 - vii) 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 be stored at the end of a shift.
 - a) 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.
 - a) Wipe down the outer parts of the bin with a purple top wipe before transporting to CS.
 - b) 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.
 - c) Leave dirty bins in the wire rack shelf on the left as you enter CS.
 - d) CS staff will wipe down the dirty bins and return to the soiled utility rooms for each department.
 - 7) Packaging
 - a) Respirators can be only be processed two times.
 - b) 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.
 - c) After writing the reprocessing count inside the respirator, CS staff will place each individual respirator in a self-seal pouch (peel pack).
 - d) CS staff will label the outside of the peel pack with the employee's name and department.
 - e) Peel packs will be loaded, upright into the STERRAD Sterilizer.
 - 8) Sterilization Systems, Cycles and Loads
 - a) 40-50 respirators can be processed per load with each load taking 55 minutes.
 - b) After processing through the sterilizer is complete, respirators must aerate for one hour.
 - c) Approximately 200 respirators can be processed per day.
 - 9) Delivery
 - a) Once processed, CS staff will place peel packs in clean bins.
 - b) Each department will have a dedicated clean bin.
 - c) CS staff will return the clean bins to the appropriate department.
 - d) Clean bins will be left in a clean area designated by the department manager. See table above.
 - 10) Discardment process
 - a) Respirators cannot be identified (i.e. no name on respirator or paper bag)
 - b) Respirators that come to CS have already been reprocessed twice (i.e. x2)
 - c) 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
 - a) No air should be felt around the perimeter while blowing out.
 - b) If you feel air coming out it is not a tight seal.
 - c) When taking a small breath in, the mask should pucker in slightly.
 - d) If it does not, it is not re-usable.
 - e) If not a tight seal, the respirator cannot be re-used.
 - f) 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.
- 9) Don full face shield over N95

Diagnostic Testing in COVID Positive Patients for Prognostic Prediction

COVID testing

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

Laboratory studies and EKGs

On admission <i>If not obtained in ED, draw following morning</i>	<ul style="list-style-type: none"> • CBC with differential • CMP • Troponin, CK, BNP • LDH, CRP, Procalcitonin • PTT/INR, Ferritin, fibrinogen • Baseline EKG
Daily <i>Can change to every other day in stable floor patients</i>	<ul style="list-style-type: none"> • CBC with differential • CMP • <i>If ICU:</i> CMP, CBC with differential, LDH, Ferritin, CK
Every third day on wards, and day of discharge	<ul style="list-style-type: none"> • CPK • LDH, CRP, Ferritin
If clinical worsening	<ul style="list-style-type: none"> • CBC with differential • CMP • Troponin & CPK • LDH, CRP, Procalcitonin • PTT/INR, Fibrinogen, Ferritin • ABG preferred over VBG • Repeat EKG

Chest imaging

Findings:

- 1) Primary features are of atypical pneumonia or organizing pneumonia.
 - a) Distribution is typically bilateral, peripheral, and basal
 - i) Bilateral findings in about 85% of patients; 33 - 86% predominantly peripheral and 70 - 80% predominantly posterior (Chung, *RSNA*, 2020; Song, *RSNA*, 2020)
 - b) Parenchymal imaging findings are variable and depend on time course (Wang, *RSNA*, 2020, *American Journal of Roentgenology*: 1-7. 10.2214/AJR.20.23034)
 - i) Days 0-5: ~65% pure GGOs, 24% GGOs with intralobular lines
 - ii) Days 6-11: ~40% pure GGOs, 22% pure GGO with intralobular lines, 28% GGO with irregular lines and interfaces (can see crazy paving)
 - iii) Days 12 - 17: combination of the above, with more consolidations (38% show "mixed" pattern of consolidation, GGOs, and reticular opacities with architectural distortion)
 - iv) Late findings may include fibrotic changes
- 2) 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)

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

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

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

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](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30166-1/fulltext))
 - a) May help distinguishing cardiogenic pulmonary edema from ARDS. See table:

Table 1 Lung ultrasonography findings of ACPE and ARDS

	ACPE	ARDS
Clinical setting	Acute	Acute
B-lines	Always present	Always present
Distribution of B-lines	Bilateral and symmetric distribution	Non-homogeneous distribution, presence of spared areas
Pleural line abnormalities	Absent	Present, typical
Reduction or absence of lung sliding	Absent	Present
Lung pulse	Absent	Present
Consolidations	Absent	Frequent in the posterior areas

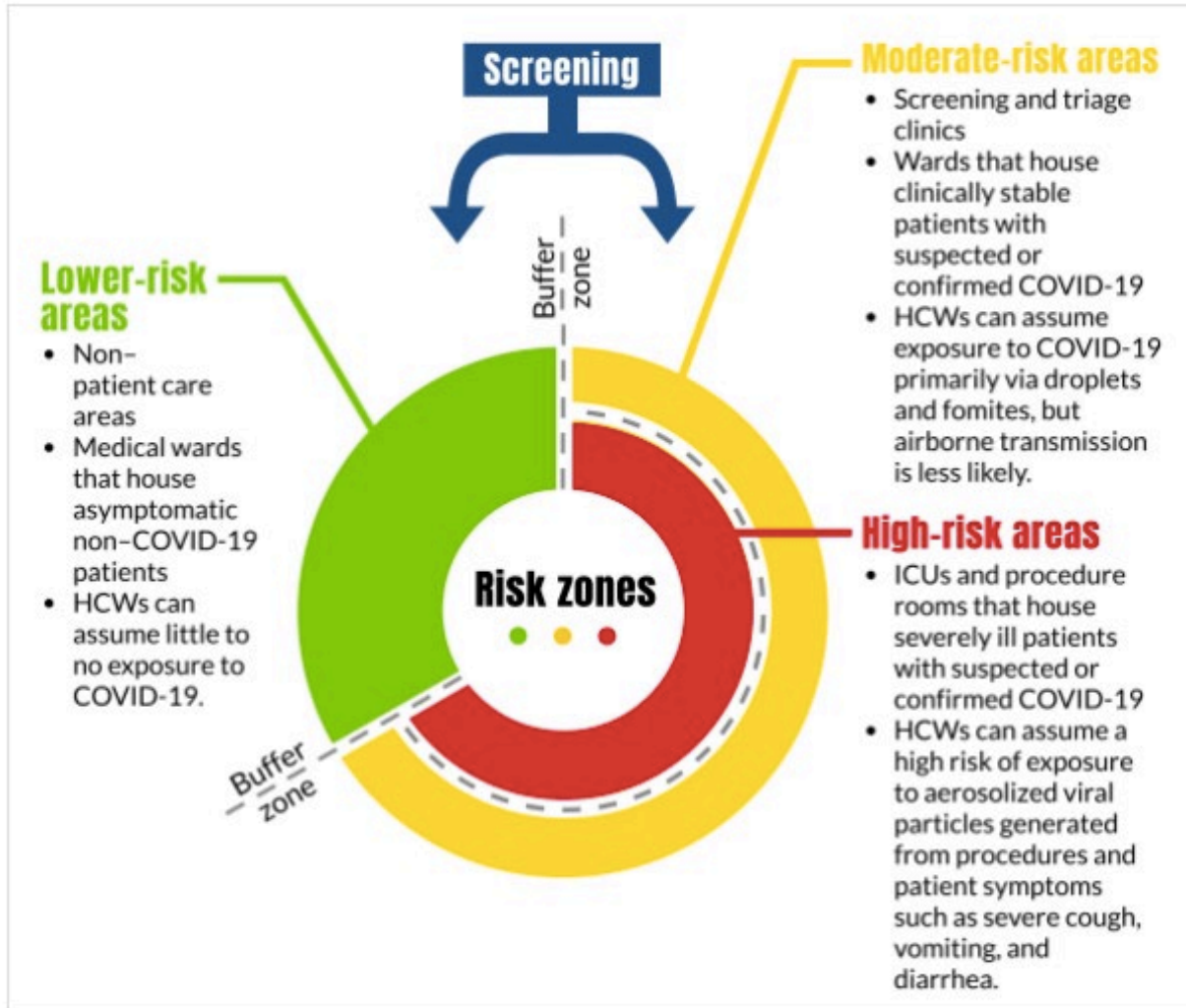
ACPE acute cardiogenic pulmonary edema, ARDS adult respiratory distress syndrome

Other Studies

- 1) Avoid other studies unless really necessary due to PPE limitations and transmission risk associated with transport.
 - a) Avoid routine TTEs (for cardiac studies, see: “Cardiac Complications of COVID” chapter).
 - b) Avoid routine CXR as this will unlikely change management unless acute change in clinical condition

ED Evaluation and Management

Basic Structure of Geographic Regions in the Emergency Department



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.

<https://www.acep.org/corona/covid-19-field-guide/triage/how-covid-19-moves-within-a-hospital/>

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/gso-20-15-hospital-cah-emptala-revised.pdf>

Risk Category	Clinical Presentation
Category 1 Consider Discharge to Home	Symptomatic patient with following clinical presentation Clinically well appearing, Resting O2 Sat >94% on room air No desaturation with ambulation No tachypnea, RR
Category 2 Consider Admission to COVID Stepdown	Symptomatic patient, Resting O2 sat < 93% on room air Desaturation on ambulation, Patients requiring bronchodilator treatment OR , any two (or even one criterion based on clinical presentation): Age >60 Existing conditions such as Diabetes Mellitus, HTN, CHF, CAD, COPD (or any chronic or severe lung disease), CKD, Cancer, Immunosuppression Change in mentation Respiratory Rate >20/min Pulse <120 bpm but > 100 Systolic BP is normal
Category 3 Consideration Admission to COVID ICU	Patient appears toxic and in distress O2 Saturation is < 93% on 6 Liters Patient is requiring vasopressors Patient is on mechanical ventilation 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**
 - a) Continue standard practices
- 2) **Noninvasive ventilation, high flow nasal cannula:**
 - a) Indications remain the same (including OSA)
 - b) Because rates of asymptomatic carriage in the community are unknown, and aerosolization risk is unknown, wherever possible:
 - i) Consider alternate options as available (e.g., nocturnal nasal cannula.)
 - ii) Use airborne precautions (Strict isolation, N95, negative pressure room)
 - iii) Use a closed circuit: BWH NIPPV machine with dual limb with a HEPA filter and BWH mask without anti-asphyxia valve.
 - iv) Ensure masks/devices fit well and there is minimal air leak
 - v) Avoid use of home NIV devices (particularly if single limb with anti-asphyxia valve)
 - c) Treat as though this person is a PUI (see below)
- 3) **Cardiac Arrest:**
 - a) Treat as though this person is a PUI (see below)

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

- 1) **Nasal Cannula:**
 - a) 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 tolerate. If possible, utilize a protocol that the patient (if able to do independently) uses oxygen supplied by nasal cannula and independently prones themselves for 30 minutes-3 hours at least three times daily. They should be monitored. *This patient does not necessarily need to be intubated at this or needs immediate ICU transfer.* (<https://rebelem.com/covid-19-hypoxemia-a-better-and-still-safe-way/>)

b). Additional information from UC DAVIS offers a combined literature review supporting prone in awake patients. 30 minutes to two hours a day show significant overall improvement. (<https://onlinelibrary.wiley.com/doi/epdf/10.1111/acem.14067>)

c) In addition, consideration can be given to the ROX score for closer monitoring. Although this was validated for high flow nasal cannula, 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: https://qxmd.com/calculate/calculator_724/rox-index-to-predict-risk-of-intubation

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.

<https://www.atsjournals.org/doi/pdf/10.1164/rccm.202003-0817LE>

- a) 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 cannula 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/>)
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Some data shows that the failure rate was 15% among COVID patients with severe acute respiratory failure (Wang, K., Zhao, W., Li, J. et al. The experience of high-flow nasal cannula in hospitalized patients with 2019 novel coronavirus-infected pneumonia in two hospitals of Chongqing, China. Ann. Intensive Care 10, 37 (2020). <https://doi.org/10.1186/s13613-020-00653-z>)

A small observational study in the NEJM showed that there was a benefit of self-proning. This was only 5 patients, but suggests that a portion of patients will avoid intubation.

<https://www.jwatch.org/na51452/2020/05/01/self-proning-covid-19?query=C19>

3) BIPAP/CPAP (NIVV)

- a) Consideration for BIPAP/CPAP as a means to avoid intubation
- b) Has a risk for aerosolization
 - i) If using, should be used with appropriate filter
- c) Select DNI patients as a bridge to family arrival or intervention
- d) If NIPPV/HFNC is used, it should be under strict airborne precautions including a negative pressure room with providers in PPE for aerosolized procedures
- e) 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>)

4) Intubation:

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

- b) Rapid Sequence Induction (RSI) should be performed, avoiding bagging
 - i) By the most experienced airway provider
 - ii) Using a video laryngoscope (SCCM COVID19 Guidelines) (APSF Considerations for Airway Manipulation, 3/20/2020).

A dedicated video laryngoscope is available in the COVID ICU. If an acrylic box is unavailable attempt to use a drape.

(<https://www.nejm.org/doi/pdf/10.1056/NEJMc2007589?articleTools=true>)

<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
 - a) Assign roles and airway plan (who will “hold/do” what)
- 3) Perform a “pre-induction” checklist prior to starting:
 - a) Suction available
 - b) Audible pulse oximetry
 - c) NIBP cycling
 - d) Ventilator setup and ready with quantitative EtCO₂ monitor in-line and ready (avoid color change device if possible)
 - e) Acrylic Box or plastic drape to protect airway team and reduce aerosolization
 - (1) (<https://www.nejm.org/doi/pdf/10.1056/NEJMc2007589?articleTools=true>)
 - (2) <https://www.youtube.com/watch?v=oROw6VgOpD8>
 - (3) <https://www.youtube.com/watch?v=8tgfqOgK7ns>
 - f) Free-flowing IV access
 - g) Post-intubation sedation ready
 - h) HEPA filter in-line
 - i) Medications ready
 - j) Non-rebreather, flow “OFF” until ready to preoxygenate
 - k) 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
 - a) Option 1: 3-5 minutes of tidal breathing 1.0 FiO₂ on non-rebreather at 15L/min flow
 - b) Option 2: facemask attached to AMBUbag with HEPA filter (2 hand technique to maintain seal)
 - c) 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:
 - a) use 2-hand technique with oral airway to create tight seal
 - b) use AMBUbag with HEPA filter in-line with high frequency/low tidal volume
 - c) do not remove mask for 2nd attempt intubation until end exhalation
- 6) After successful intubation:
 - a) Inflate cuff
 - b) connect patient directly to ventilator with HEPA filter with EtCO₂ gas sampling line post-filter or use an infrared CO₂ analyzer with no gas sampling
 - c) confirm via quantitative in-line EtCO₂ (gold standard > 3 breaths), bilateral chest rise, “fogging” of ETT, cuff palpation and possibly increasing SpO₂
 - d) avoid listening bilaterally for risk of contamination(touching ears with stethoscope/hands)
 - e) secure ETT per hospital policy
- 7) Clean the laryngoscope:
 - a) Remove soiled gloves and replace with clean gloves
 - b) Clean the video laryngoscope and allow it to dry - 3 minutes if PURPLE Sani-Cloth (Sani-Cloth Technical Sheet).
 - c) Push video laryngoscope out of room with clean gloves on
- 8) 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:

In conscious patients, review or sign Health Care Proxy form and discuss and document goals of care on admission (<https://www.nia.nih.gov/health/advance-care-planning-healthcare-directives>)

- 1) Educate patient and family on disease course and prognosis
- 2) 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
 - a) Need O₂ > 6 LPM to maintain SpO₂ > 90% or PaO₂ > 65.
 - b) Rapid escalation of oxygen requirement.
 - c) Significant work of breathing.
- 3) Hemodynamic instability after initial **conservative** fluid resuscitation
 - a) SBP < 90, Mean arterial pressure < 65, or Heart rate > 120.
- 4) Persistent Acidosis
 - a) VBG with pH < 7.3 or PCO₂ > 50 or above patient's baseline.
 - b) 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.
 - a) If the patient is on HFNC, a surgical mask should be over this device
 - b) If the patient is NIV, the patient should have the appropriate viral filter
- 3) Providers wear standard PPE during transport.
- 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
 - a) 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
 - a) 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:
 - a) Resolution of fever >48 hours without antipyretics
 - b) Improvement in illness signs and symptoms (cough, SOB, and oxygen requirement)

Confirmed COVID-19 Discharge Checklist

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:

- 1) Verify and document contact number for patient and primary support person; ensure active phone service, voicemail functioning, and language preference correctly documented
- 2) Verify residence with private room, ability to adhere to home isolation instructions and risk of transmission to persons with immunocompromising conditions in the home
- 3) Confirm ability to manage ADL/iADLs with degree of support at home
- 4) Confirm that patient has resources/social support to receive 1-2 weeks of food and other necessary supplies while under quarantine
 - a) For those in the Tulsa Areas
 - i) Wheels online - they can deliver 7 frozen meals 1 x per week
 - ii) 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.
 - iii) 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
 - iv) <https://www.reasors.com/shipt-home-delivery>
- 5) Perform DME needs assessment and consider sponsorship from hospital if item unable to be delivered or obtained by primary support person

Discharge medications/supplies

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

Transportation

- 1) Verify patient has a ride by private vehicle or arrange transportation via ambulance (infected person should wear mask in vehicle)
 - a) **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)
 - b) **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.

- c) **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

- 1) Ensure that you are using the stock discharge instructions at OSU through Meditech
- 2) 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

- 1) Verify and document patient's primary care provider
- 2) 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
- 3) 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:
 - a) Virtual visit through OSU Internal Medicine
 - i) Cortext Melissa Cox
 - (1) Patient name
 - (2) DOB
 - (3) Phone Number
 - (4) COVID status (Positive or Pending Result)
 - ii) If it is a new patient, fax new patient paperwork to 918-382-3589
 - iii) Melissa will send date, time and doxy information to requester
 - iv) Information for doxy.me/drurname 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.

Guidance on Removal from Quarantine and Return to Work Once Discharged Non-Test Based Strategy (Most Recent Update of 7.17.2020)

<https://www.cdc.gov/coronavirus/2019-ncov/hcp/return-to-work.html>

The CDC now recommends using the non-test based strategy to return to work for health care workers with mild to moderate symptoms.

- 1) At least 10 days have passed *since symptoms first appeared* and
- 2) At least 24 hours have passed *since last fever* without the use of fever-reducing medications and
- 3) Symptoms (e.g., cough, shortness of breath) have improved

The CDC now recommends using the non-test based strategy to return to work for health care workers with severe to critical symptoms.

- 4) At least 20 days have passed *since symptoms first appeared*
- 5) At least 24 hours have passed *since last fever* without the use of fever-reducing medications and
- 6) Symptoms (e.g., cough, shortness of breath) have improved

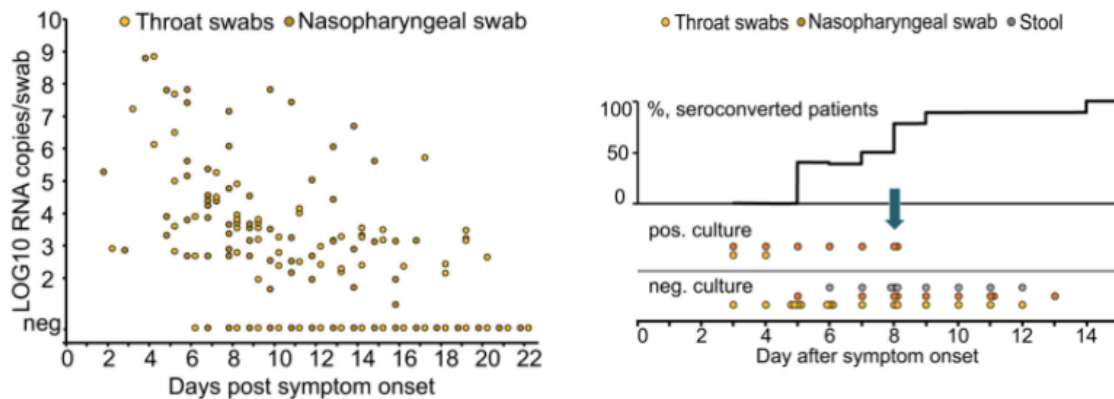
****An estimated 95% of severely or critically ill patients, including some with severe immunocompromise, no longer had replication-competent virus 15 days after onset of symptoms; no patient had replication-competent virus more than 20 days after onset of symptoms. Because of their often extensive and close contact with vulnerable individuals in healthcare settings, the more conservative period of 20 days was applied in this guidance. However, because the majority of severely or critically ill patients no longer**

appear to be infectious 10 to 15 days after onset of symptoms, facilities operating under critical care shortages might choose to allow HCP to return to work after 10 to 15 days, instead of 20 days.**

After returning to work, HCP should:

- 7) Wear a facemask for source control at all times while in the healthcare facility until all symptoms are completely resolved or at baseline. A facemask instead of a cloth face covering should be used by these HCP for source control during this time period while in the facility. A facemask for source control does not replace the need to wear an N95 or equivalent or higher-level respirator (or other recommended PPE) when indicated, including when caring for patients with suspected or confirmed SARS-CoV-2 infection.
- 8) Self-monitor for symptoms, and seek re-evaluation from occupational health if symptoms recur or worsen

Figure 1: From Wölfel et al. demonstrating declining viral burden in upper respiratory specimens as illness progresses and decreasing capacity to isolate replication-competent virus from these same specimens as the number of patients with detectable IgM and IgG increases.



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.

Information regarding viral CT values overtime is depicted at the following website:

https://www.cdc.gov/coronavirus/2019-ncov/community/strategy-discontinue-isolation.html?deliveryName=USCDC_2067-DM27395

Test Based Strategy (Although not recommended because of prolonged viral shedding)

- 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.
 - a) 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, *aqaa062*, <https://doi.org/10.1093/ajcp/aqaa062>)
 - b) *Vascular angiogenesis and its role in COVID-19*: Researchers compared lung samples of seven patients who died from COVID-19 with seven who died from acute respiratory distress syndrome related to influenza A (H1N1) and 10 uninfected controls. The lungs of both COVID-19 and influenza patients had diffuse alveolar damage and infiltrating perivascular lymphocytes. However, the lungs of COVID-19 patients also had severe endothelial injury associated with intracellular SARS-CoV-2 and disrupted endothelial cell membranes, widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries, and significant new blood vessel growth through intussusceptive angiogenesis.
- 2) There is also some evidence of direct viral injury to lung tissue. (Xu et al, *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:
 - a) Acute (onset over 1 week or less)
 - b) Bilateral opacities detected on CT or chest radiograph
 - c) PF ratio <300mmHg with a minimum of 5 cmH₂O PEEP (or CPAP)
 - d) Must not be fully explained by cardiac failure or fluid overload

Severity	PaO ₂ /FiO ₂ (on PEEP/CPAP >5)	Mortality (all cause, cohort)
Mild	200-300	27%
Moderate	100-200	32%
Severe	<100	45%

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:
 - a) Development of ARDS: 8-12 days (Wang et al, *JAMA*, 2020; Zhou et al, *Lancet*, 2020; Huang et al, *Lancet*, 2020)
 - b) Mechanical ventilation: 10.5-14.5 days (Huang et al, *Lancet*, 2020; Zhou et al, *Lancet*, 2020)

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 tolerate. If possible, utilize a protocol that the patient (if able to do independently) uses oxygen supplied by nasal cannula 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/>)

The concept of Happy Hypoxia in the patient from COVID 19 including the effect of hypoxia on the respiratory centers, effect of PaCO₂ on the ventilatory response to hypoxia, hypoxia threshold that precipitates dyspnea, limited accuracy of SpO₂ below 80%, shifts in the oxygen-dissociation curve, tolerance of low oxygen levels, and the definition of hypoxemia. In addition, diabetes and elderly age blunt the response to hypoxia. A disproportionate number of individuals affected by COVID are hypoxic. (<https://www.atsjournals.org/doi/pdf/10.1164/rccm.202006-2157CP>)

In addition, consideration can be given to the ROX score for closer monitoring. Although this was validated for high flow nasal cannula, 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:
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Evidence for the ROX score comes from a 2-year multicenter prospective observational cohort study including patients with pneumonia treated with HFNC. 36% of the patients went on to intubation & mechanical ventilation. Cox proportional hazards modeling of ROX association with HFNC outcome. Among the 191 patients treated with HFNC in the validation cohort, 68 (35.6%) required intubation. The prediction accuracy of the ROX index increased over time (area under the receiver operating characteristic curve: 2 h, 0.679; 6 h, 0.703; 12 h, 0.759). ROX greater than or equal to 4.88 measured at 2 (hazard ratio, 0.434; 95% confidence interval, 0.264–0.715; P = 0.001), 6 (hazard ratio, 0.304; 95% confidence interval, 0.182–0.509; P, 0.001), or 12 hours (hazard ratio, 0.291; 95% confidence interval, 0.161–0.524; P, 0.001) after HFNC initiation was consistently associated with a lower risk for intubation. A ROX less than 2.85, less than 3.47, and less than 3.85 at 2, 6, and 12 hours of HFNC initiation, respectively, were predictors of HFNC failure. Patients who failed presented a lower increase in the values of the ROX index over the 12 hours. Among components of the index, oxygen saturation as measured by pulse oximetry/FIO₂ had a greater weight than respiratory rate. *Am J Respir Crit Care Med.* 2019 Jun 1;199(11):1368-1376. doi: 10.1164/rccm.201803-0589OC.

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>)

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 cannula 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/>)

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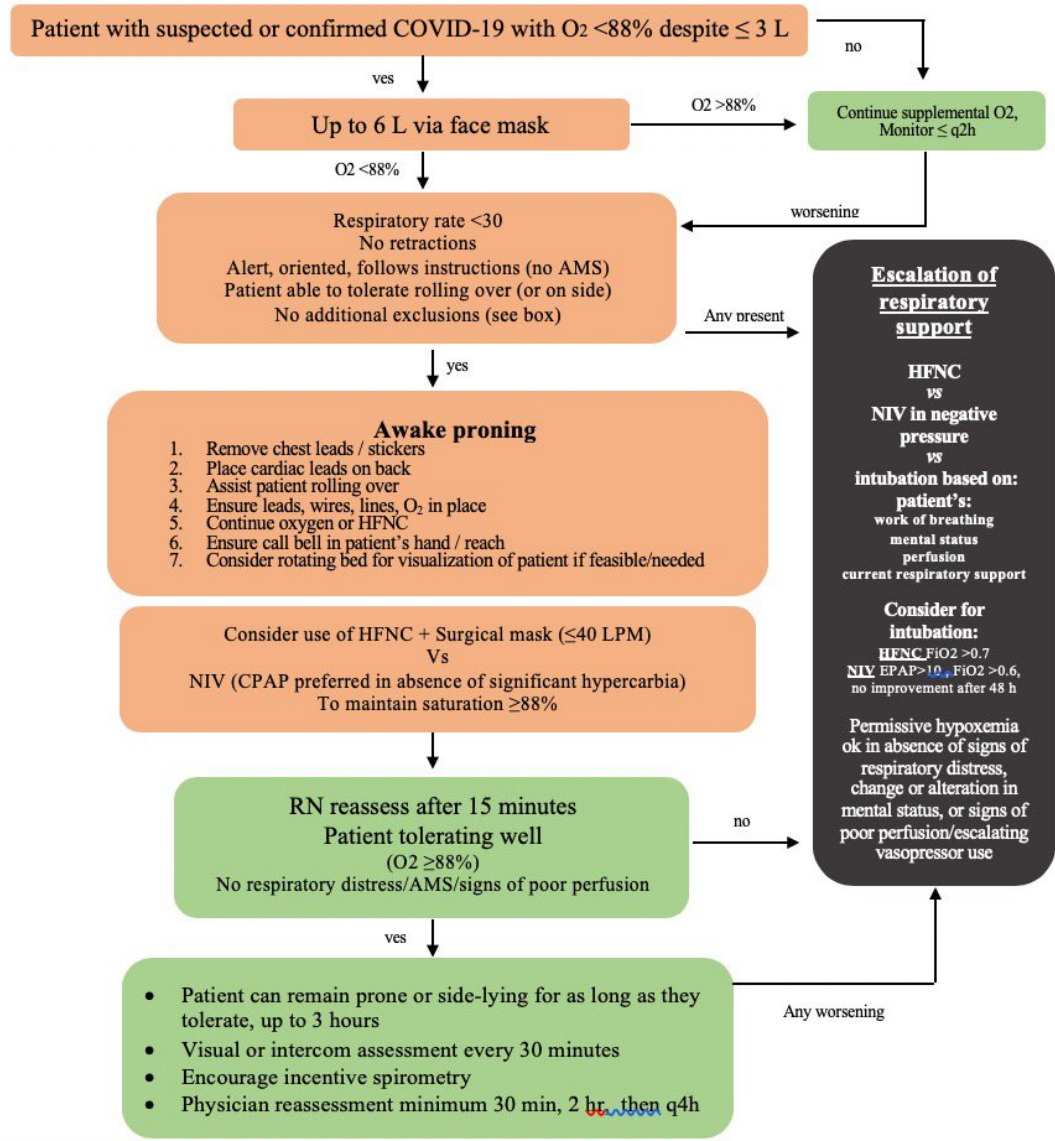
BIPAP/CPAP (NIVV)

Consideration for BIPAP/CPAP as a means to avoid intubation

- 1) Has a risk for aerosolization
- 2) If using, should be used with appropriate filter
- 3) 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>)



Why early awake proning?

- Early proning while awake has been used in COVID-19 and other scenarios with viral pneumonia, both with HFNC and NIV and *may* result in ↓ intubations
- These patients require close monitoring for tolerance and any decompensation as some patients may eventually need intubation.
- Target: prone three times daily

Sun et al. Intensive Care. 2020 10(33)
Ding et al. Critical Care. 2020 24(28)

Why the shift from early intubation?

- Patients often have prolonged course on ventilator (higher resource utilization, morbidity)
- Our understanding of the pathophysiology of severe COVID-19 continues to evolve but many countries/hospitals are having success with HFNC/NIV. The key is finding ways to mitigate risk to healthcare workers by reducing aerosols. HFNC ≤40 LPM + surgical mask generates minimal aerosols
- A proportion of these patients demonstrate pathophysiology atypical for ARDS (relatively ↑ compliance)

Gattinoni et al. AJRCCM 2020.
<https://content.vanonthem.com/hubfs/COVID-19%20Transmission%20Assessment%20Report.pdf>

Additional Exclusions for awake proning:

- Pregnancy
- Elevated ICP
- Massive hemoptysis
- Serious facial trauma/facial surgery within 15 days
- Tracheal surgery or sternotomy within 15 days
- Cardiac pacemaker inserted within 48 h
- DVT treated <48 h
- Single anterior chest tube with air leak
- Unstable spine, femur, or pelvis fractures
- ECMO
- Frequent ventricular arrhythmia
- Mean arterial pressure <65 mmHg (ok if receiving vasoactive)

STEPWISE APPROACH TO WORSENING HYPOXIA AT OSU

- 1) For patients with progressive O2 requirements consider awake proning
 - <https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-020-00650-2>
 - a) 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>)
 - b) Encourage proning for as long as they will tolerate it (ideally 16 hours a day)
 - c) 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)
 - a) Anesthesia 0700-1900
 - b) ED 1900-0700
 - i) 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
- 4) Using a video laryngoscope (SCCM COVID19 Guidelines) (APSF Considerations for Airway Manipulation, 3/20/2020).
 - a) A dedicated video laryngoscope is available in the COVID ICU (<https://www.nejm.org/doi/pdf/10.1056/NEJMc2007589?articleTools=true>)

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)
 - a) Evidence to suggest that using a simple surgical mask over high flow nasal cannula will reduce the incidence of aerosolized risk (Performed by Vapotherm (HFNC company).** Using computational fluid dynamic (CFD) simulation, modeled HFNC on simulated architecture of a petite adult female, sinusoidal breathing a 500ml tidal volume at 32 breaths per minute and a 1:1 Inspiratory/expiratory. HVNI flow was modeled at 40 LPM through a model of Vapotherm Adult Small/Pediatric cannula. Low Flow Oxygen delivery was modeled using a similar cannula delivering 6 LPM continuous flow. Simulated surgical mask placed on model.)

Table 1		% particles trapped in mask	% particles <1m spread	% particles >1m spread
No oxygen	No Mask		69.0%	31.0%
No oxygen	Mask	87.2%	7.8%	5.0%
40 L/min HFNC	Mask	83.2%	0.9%	15.9%
6 L/min NC	Mask	73.6%	19.5%	6.9%

- 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:
 - a) Initiate ARDS ventilation as described below
 - b) Determine PEEP and mechanics as described below
 - c) Assure adequate sedation as described below
- 2) Obtain STAT portable CXR to confirm endotracheal tube location
 - a) 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
 - a) Calculate P/F ratio from initial post-intubation ABG. Adjust oxygenation as described below
 - b) Goal pH 7.25 to 7.45 adjust ventilation as described below

Use of Single Ventilator for Multiple Patients

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):
 - a) Vt = 6 ml/kg (based on ideal body weight [IBW] from ARDSnet table, see table below)
 - i) IBW men (kg) = 50 + 2.3 (height in inches – 60)
 - ii) IBW women (kg) = 45.5 + 2.3 (height in inches – 60)

NIH PREDICTED BODY WEIGHT (PBW) / TIDAL VOLUME CHART															
MALES								FEMALES							
HEIGHT		PBW	4	5	6	7	8	HEIGHT		PBW	4	5	6	7	8
Feet	Inches	Male	ml/kg	ml/kg	ml/kg	ml/kg	ml/kg	Feet	Inches	Female	ml/kg	ml/kg	ml/kg	ml/kg	ml/kg
4' 10"	58	45.4	180	230	270	320	360	4' 7"	55	34	140	170	200	240	270
4' 11"	59	47.7	190	240	290	330	380	4' 8"	56	36.3	150	180	220	250	290
5' 0"	60	50	200	250	300	350	400	4' 9"	57	38.6	150	190	230	270	310
5' 1"	61	52.3	210	260	310	370	420	4' 10"	58	40.9	160	200	250	290	330
5' 2"	62	54.6	220	270	330	380	440	4' 11"	59	43.2	170	220	260	300	350
5' 3"	63	56.9	230	280	340	400	460	5' 0"	60	45.5	180	230	270	320	360
5' 4"	64	59.2	240	300	360	410	470	5' 1"	61	47.8	190	240	290	330	380
5' 5"	65	61.5	250	310	370	430	490	5' 2"	62	50.1	200	250	300	350	400
5' 6"	66	63.8	260	320	380	450	510	5' 3"	63	52.4	210	260	310	370	420
5' 7"	67	66.1	270	330	400	460	530	5' 4"	64	54.7	220	270	330	380	440
5' 8"	68	68.4	280	340	410	480	550	5' 5"	65	57	230	290	340	400	460
5' 9"	69	70.7	280	350	420	490	570	5' 6"	66	59.3	240	300	360	420	470
5' 10"	70	73	290	370	440	510	580	5' 7"	67	61.6	250	310	370	430	490
5' 11"	71	75.3	300	380	450	530	600	5' 8"	68	63.9	260	320	380	450	510
6' 0"	72	77.6	310	390	470	540	620	5' 9"	69	66.2	260	330	400	460	530
6' 1"	73	79.9	320	400	480	560	640	5' 10"	70	68.5	270	340	410	480	550
6' 2"	74	82.2	330	410	490	580	660	5' 11"	71	70.8	280	350	420	500	570
6' 3"	75	84.5	340	420	510	590	680	6' 0"	72	73.1	290	370	440	510	580
6' 4"	76	86.8	350	430	520	610	690	6' 1"	73	75.4	300	380	450	530	600
6' 5"	77	89.1	360	450	530	620	710	6' 2"	74	77.7	310	390	470	540	620
6' 6"	78	91.4	370	460	550	640	730	6' 3"	75	80	320	400	480	560	640

3) Set Initial respiratory rate

- a) Typical starting rates will be 16-24 titrated to goal minute ventilation of 5-8 L/min
- b) 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):

- a) BMI < 35: PEEP 5
- b) 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

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:

a) **BMI < 35:** titrate PEEP and FiO2 as per the ARDSnet LOW PEEP table

Lower PEEP/higher FiO2

FiO ₂	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO ₂	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24

b) **BMI ≥ 35:** titrate PEEP and FiO2 as per the ARDSnet HIGH PEEP table

Higher PEEP/lower FiO2

FiO ₂	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16

FiO ₂	0.5	0.5-0.8	0.8	0.9	1.0	1.0
PEEP	18	20	22	22	22	24

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)

a) 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.

(<https://anesthesiology.pubs.asahq.org/article.aspx?articleid=2763453>)

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

Obtain respiratory mechanics:

- 1) Plateau pressure (goal ≤ 30 cm/H₂O)
- 2) Static compliance

Sedation and Ventilator Synchrony

- 1) **If unparalyzed, target sedation to ventilator synchrony or RASS -2 to -3 (see table below):**
 - a) 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, and other ventilator alarms).
 - i) Titrate sedatives/analgesics to ventilator synchrony allowing for deeper RASS.
 - ii) If patient remains dyssynchronous despite deep sedation (RASS -5), initiate continuous paralytics (ensure BIS 40 to 60 prior to initiating and during paralysis).
 - (1) Continuous paralytics have some evidence correlating to the development to critical illness myopathy and critical illness polyneuropathy. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5167093/>
 - (2) A table comparing pharmacokinetics is listed (<https://www.uspharmacist.com/article/neuromuscular-blocking-agents-use-and-controversy-in-the-hospital-setting>)

Table 1. Pharmacokinetics of Neuromuscular Blockers

Agent	Dosing	Time to Peak (min)	Duration of Action (min)	Metabolism	Side Effects
NONDEPOLARIZING					
Aminosteroids					
Pancuronium	0.05-0.1 mg/kg bolus; 0.8-1.7 mcg/kg/min infusion	2-3	60-100	Renal	Tachycardia, hypotension, and increased cardiac output
Vecuronium	0.08-0.1 mg/kg bolus; 0.8-1.7 mcg/kg/min infusion	3-4	20-45 (prolonged as active metabolite builds up)	Hepatic via hydrolysis, then bile; metabolites excreted renally	Hemodynamic instability
Rocuronium	0.6-1 mg/kg bolus; 8-12 mcg g/kg/min infusion; RSI: 1-1.2 mg/kg bolus	1-2	20-35 for bolus dose; 60-80 for RSI dose	Hepatic; no active metabolites	NA
Benzylisoquinoliniums					
Atracurium	0.4-0.5 mg/kg bolus; 5-20 mcg g/kg/min infusion	3-4	20-35	Hoffmann reaction	Seizures associated with neurotoxic metabolite (laudanosine), hypotension (histamine release)
Cisatracurium	0.1-0.2 mg/kg bolus; 3 mcg g/kg/min initial infusion; 1-2 mcg g/kg/min maintenance infusion	2-3	30-60	Hoffmann reaction	Bronchospasm
DEPOLARIZING					
Succinylcholine	1 mg/kg bolus; infusions rarely used	<1	5-10	Plasma cholinesterase	Bradycardia, malignant hyperthermia, and hyperkalemia
<i>min: minute; NA: not applicable; RSI: rapid sequence intubation. Source: References 5-7, 12, 25, 31, 32.</i>					

- 2) **If paralyzed, target sedation to BIS 40 to 60 and titrate level of neuromuscular blockade to ventilator synchrony:**
- a) Maintain deep sedation immediately post-intubation while paralyzed (assume 60 minutes for Rocuronium, 10 minutes for succinylcholine)
 - i) Preferred initial sedation regimen:
 - (1) Fentanyl (boluses +/- infusion) + Propofol: target analgosedation and optimize analgesia first while decreasing sedative requirements
 - (2) 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).
 - (a) 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
 - b) Adjunct agent: Midazolam
 - c) Use dexmedetomidine only when nearing extubation

RASS		
Score	Term	Description
+4	Combative	Overly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	Alert and calm
-1	Drowsy	Not fully alert, but has sustained awakening on verbal stimulation
-2	Light sedation	Briefly awakens with eye contact to voice on verbal stimulation
-3	Moderate sedation	Movement or eye opening to voice on verbal stimulation
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

d) Consideration for the use of opioids in patients with air hunger and COVID-19 based off of the physiology of opiates in relieving these symptoms. This was reviewed at Mass General who worries about mass psychological trauma in the survivors induced by untreated air hunger during this pandemic. (<https://www.thoracic.org/about/newsroom/press-releases/resources/air-hunger-and-psychological-trauma-in-covid1.pdf>)

Ventilator Adjustments and Daily Management

General management of ventilated patients

- 1) Consider whether patient requires daily CXR:
 - a) CXR clearly indicated for:
 - i) Clinical change
 - ii) 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
- 2) Ventilator consults:
 - a) 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:**
 - a) 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:**
 - a) Titrate ventilatory parameters to pH and not PCO₂.
 - i) To achieve low tidal volumes will tolerate hypercapnia (functionally no limitation unless clinical sequelae) and acidemia (pH > 7.2).
 - ii) Because tidal volumes are low, the respiratory rate often has to be high to accommodate; typical RR is 20-35 breaths/minute.
- 3) **pH goal is normally 7.25-7.45:** http://www.ardsnet.org/files/ventilator_protocol_2008-07.pdf
 - a) If pH > 7.45, decrease respiratory rate
 - b) If pH 7.15-7.30, then increase respiratory rate until pH > 7.30, or PaCO₂ < 25 (maximum RR= 35 breaths/minute)
 - c) If pH < 7.15, then increase respiratory rate to 35 breaths/minute
 - i) 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
 - a) PaO₂ / SpO₂ are widely debated; PaO₂ > 55 and SpO₂ >88% are also commonly used http://www.ardsnet.org/files/ventilator_protocol_2008-07.pdf
 - b) Extensive mammalian animal data demonstrates that hyperoxic injury occurs at a FiO₂ ≥ 75% (at sea level) with the rate of injury increasing as FiO₂ exceeds that threshold. In multiple mammalian models, a 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:**
 - a) PEEP should be set and titrated as explained above using the ARDSNET PEEP tables to guide FiO₂ and PEEP determination
 - b) 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).
 - c) **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:**
 - a) Goal FiO₂ < 60%; if FiO₂ >60%; patient requires ventilator optimization. If you need assistance, pulmonary consultation is available (pager 11957)

- b) 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:**
 - a) Check plateau pressure with every change in tidal volume, PEEP, or clinical deterioration (worsening oxygenation) but not as part of routine practice
 - b) If plateau pressure is >30 cm H₂O, then decrease tidal volume by 1 mL/kg (minimum 4 mL/kg)
 - c) 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
 - d) 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:

- a) If patient is hypoxic (PaO₂ <75) on individualized PEEP setting from PV tool (or PEEP based on ARDSnet table)
 - i) and FiO₂ ≥ 0.6 or PaO₂ / FiO₂ ratio < 150
 - (1) Perform the following in this order:
 - (a) Optimize volume status by diuresing;
 - (b) if no improvement then:
 - (i) Deep sedation, advancing to RASS -5 if needed;
 - (c) if no improvement then:
 - (i) Initiate continuous paralysis (cisatracurium bolus 0.2mg/kg followed by infusion at 0-5 mcg/kg/min titrated to patient-ventilator synchrony);
 - (d) if no improvement then:
 - (i) Initiate prone ventilation early: Discuss proning when PaO₂/FiO₂ < 150 and a requirement of 12 hours of FIO₂ of > 75%.
 - ii) For adults receiving mechanical ventilation who have moderate to severe ARDS, prone ventilation for 12 to 16 hours is suggested over no prone ventilation

- b) 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)
 - i) if no improvement then:
 - (1) 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)
 - ii) if no improvement then:
 - (1) Consider ECMO consultation (see below) if, despite the above steps:
 - (a) Persistent PaO₂ < 75 requiring FiO₂ > 0.75
 - (b) Plateau pressure >30
 - (c) Refractory hypercapnia and pH < 7.2
 - (d) Absence of contra-indications (see ECMO section)

Prone Ventilation

- 1) **Prone early:**
 - a) 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:**
 - a) The only absolute contraindications to proned ventilation are spinal cord injury, open chest or abdomen, and unstable airway; BMI and patient size are not absolute contra-indications
 - b) 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.
 - c) RRT can be performed while proned (e.g, by femoral vein catheter) but should be discussed with renal consultation prior to proning
- 3) **Managing a proned patient:**
 - a) 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\(3\).pdf](file:///Users/mousumisom/Downloads/DoD%20COVID19%20Practice%20Management%20Guide%20V10%20(3).pdf)
 - i) An example of proning patients on mechanical ventilation can be found t the following youtube video: https://cdn.embedly.com/widgets/media.html?src=https%3A%2F%2Fwww.youtube.com%2Fembed%2FE_6jT9R7WJs%3Ffeature%3Doembed&display_name=YouTube&url=https%3A%2F%2Fwww.youtube.com%2Fwatch%3Fv%3DE_6jT9R7WJs&image=https%3A%2F%2Fi.ytimg.com%2Fvi%2FE_6jT9R7WJs%2Fhqdefault.jpg&key=40cb30655a7f4a46adaaf18efb05db21&type=text%2Fhtml&schema=youtube
 - b) Prone >16 hrs per 24 hrs. Supine >4 hrs per 24 hrs.
 - c) 1 hour post-initiation of prone ventilation:

- i) Adjust oxygen parameters: re-assess lung mechanics (plateau pressure and re-optimize PEEP, see above)
- ii) 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 cm/H₂O
- d) 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:
 - (a) PaO₂ / FiO₂ ratio > 200
 - (b) Ppl < 30
 - (c) pH > 7.25
 - (d) FiO₂ < 60%
- e) 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))

OSU ECMO guidelines

- 1) **Indications:**
 - a) Persistent PaO₂ / FiO₂ ratio < 75 mmHg despite optimized ARDS management (optimized PEEP, neuromuscular blockade, proning).
 - b) Plateau pressure > 30 cm H₂O on ARDSnet ventilation.
 - i) pH < 7.2
 - c) No potentially reversible causes (*e.g.*, pulmonary edema, mucus plug, abdominal compartment syndrome)
- 2) **Contraindications:** Each patient is assessed on a case-by-case basis.
 - a) Absolute or relative contra-indications can include:
 - i) Advanced age
 - ii) Active malignancy
 - iii) Severe shock; high cardiac output state
 - iv) Multi-system organ failure
 - v) Prolonged ventilation or ARDS with poor chance of pulmonary recovery or severe chronic lung disease.

- vi) Severe neurologic injury or intra-cranial hemorrhage
- vii) Overall poor life expectancy (*e.g.*, < 6 months); poor functional status at baseline; poor potential to recover functional status.
- viii) Active hemorrhage or inability to anti-coagulate
- ix) Thrombocytopenia (plt < 50)
- x) Neutropenia (ANC < 500)
- xi) BMI > 35 / total body weight > 300 pounds

Ventilator Weaning and Extubation

- 1) Clinical goal is to liberate patients from mechanical ventilation as soon as safe and feasible.
 - a) 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:
 - a) Improving or stable respiratory disease
 - b) FiO₂ ≤ 50%, PEEP ≤ 10 with SpO₂ >92%
 - c) Hemodynamically stable (minimal to no vasopressor requirements to maintain target MAPs)
- 3) Assess patient readiness for weaning at least once daily
 - a) 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:
 - i) Patients are in supine position
 - ii) 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
 - iii) Hemodynamically stable (defined as HR < 120, MAP > 65, and vasopressor requirement of levophed gtt < 10 mcg/min)
 - iv) SpO₂ > 92% or PaO₂ > 75 with an FiO₂ ≤ 50% and PEEP ≤ 10 (and most recent Ppl < 30)
 - b) A daily spontaneous breathing trial (SBT) is considered for all patients who meet the requirements for a daily SAT
 - i) SBT consists of Pressure Support ventilation mode with a PS = 5 and PEEP = 5
 - c) SBT discontinued if the patient develops
 - i) Evidence of increased work of breathing with RR > 30
 - ii) Hypoxia (SpO₂ < 92%)
 - iii) Hemodynamic instability
 - iv) Rapid shallow breathing index (RSBI) = RR/TV > 105
 - d) Terminate all SBTs after 30 minutes and return to prior VC settings if patients are deemed not ready to extubate
- 4) Extubation readiness:
 - a) Extubation should be considered if patients meet the following criteria
 - i) Breathing spontaneously
 - ii) RASS 0 to -1

- iii) Able to follow commands
 - iv) Intact cough and able to protect airway
 - v) Requiring airway suctioning for secretion < q2h
 - b) Other considerations include:
 - i) FiO2 < 40% at the time of extubation
 - ii) 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:
 - a) Respiratory factors:
 - i) Ongoing pneumonia or pulmonary inflammation
 - ii) Bronchoconstriction
 - iii) Glottic and airway edema, sputum production, impaired cough
 - b) Cardiac factors:
 - i) Cardiac dysfunction or shock
 - c) Neuromuscular factors
 - i) Weakness and prolonged immobility
 - ii) Effects of steroids or neuromuscular blockade
 - d) Neuropsychological factors
 - i) Delirium
 - ii) Sedating medications
 - e) Metabolic factors
 - i) Malnutrition
 - ii) Electrolyte disturbances (hypophosphatemia, etc)

Special Considerations from ATS

This week, ATS issued a [statement](https://www.thoracic.org/about/newsroom/press-releases/journal/2020/tear-gas-use-during-covid-19-pandemic-irresponsible-moratorium-needed,-says-american-thoracic-society.php?utm_campaign=Washington%20Letter&utm_medium=email&_hsmi=89441318&_hsenc=p2ANqtz--YDEe79T9xEIwv0YTvmA2aDdZNcR1f0lu5q1XOXIePAB90r099NivgGodwX6CknYX25faSlccZmSy0b3TdO5ICPFLTlg&utm_content=89441318&utm_source=hs_email) calling for a moratorium on tear gas use. “The use of chemical crowd control agents is outlawed in the time of war. They cause significant short- and long-term respiratory health injury and likely propagate the spread of viral illnesses, including COVID-19,” said ATS President Juan C. Celedón, MD, DrPH, ATSF. (https://www.thoracic.org/about/newsroom/press-releases/journal/2020/tear-gas-use-during-covid-19-pandemic-irresponsible-moratorium-needed,-says-american-thoracic-society.php?utm_campaign=Washington%20Letter&utm_medium=email&_hsmi=89441318&_hsenc=p2ANqtz--YDEe79T9xEIwv0YTvmA2aDdZNcR1f0lu5q1XOXIePAB90r099NivgGodwX6CknYX25faSlccZmSy0b3TdO5ICPFLTlg&utm_content=89441318&utm_source=hs_email)

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

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.

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>

Organizations such as the Infectious Diseases Society of America, the Society of Critical Care Medicine, and the National Institutes of Health have all released living guidelines that will be updated as new research is known. Links to these documents can be found here:

- a) IDSA: <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>
- b) SCCM: <https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19>
- c) NIH: <https://www.covid19treatmentguidelines.nih.gov/>

Infectious Diseases Consultation

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.

Re-consultation should occur if the patient develops ARDS (mechanically-ventilated with P/F ratio < 300) or shock/cytokine activation syndrome.

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

Clinical reports indicate that rates of bacterial superinfection of COVID19 are low (10-20%), but when present increase mortality risk. Anecdotal reports suggest less MRSA superinfection than is often seen

with influenza. Unnecessary antibiotics carry risks of fluid overload and drug-resistance, as well as the possibility that antibiotics may become a limited resource. (Zhou et al, *Lancet*, 2020; Yang et al, *Lancet Respir Med*, 2020; Lippi and Plebani, *Clinica Chimica Acta*, 2020; WHO, *COVID-19 Interim guidance*, March 2020).

The SCCM does recommend broad spectrum antibiotics in the patient that is critically ill. (Alhazzani W, Moller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Intensive Care Med* 2020; <https://doi.org/10.1007/s00134-020-06022-5>. [file:///Users/mousumisom/Downloads/Surviving Sepsis Campaign Guidelines on the.95707.pdf](file:///Users/mousumisom/Downloads/Surviving%20Sepsis%20Campaign%20Guidelines%20on%20the%2095707.pdf))

- 1) Antibiotics should reflect IDSA guidelines, presumed source, and MDRO risk.
 - a) For empiric coverage for a presumed pulmonary source of infection:
 - i) 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.)
 - ii) 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.)
 - b) Consideration for calculation of the SHORR score if determining if vancomycin should not be utilized based on its negative predictive value and concerns for vancomycin induced renal toxicity. <https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2019.199.1-MeetingAbstracts.A3688>
- 2) For coverage of potential coinfections:
 - a) 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:
 - a) Clinical status is not deteriorating.
 - b) 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

Nebulization may aerosolize viral particles and contribute to disease transmission. COVID-19 clinical reports do not indicate wheeze as a common symptom, and not all patients require bronchodilators (Zhou et al, *Lancet*, 2020; Yang et al, *Lancet Respir Med*, 2020; Guan et al, *N Engl J Med*, 2020; WHO, *COVID-19 Interim guidance*, March 2020).

Do not use common canister protocols.

<https://assets.ecri.org/PDF/COVID-19-Resource-Center/COVID-19-Clinical-Care/COVID-ISMP-Safe-Medication-Safety-Alert-2020-0326.pdf>

Inhaled Corticosteroids

A review of the literature shows that clinicians should be aware that there is no evidence to support the withdrawal of ICS in patients treated with these drugs, and to do so is likely to be harmful. Patients with

asthma and COPD who are stable while using ICS should continue on their treatment. If there is uncertainty about the diagnosis, physicians should be more careful about initiating ICS or ICS/LABA in patients without clear objective evidence of asthma. Studies are underway to determine the effect of ICS or ICS/LABA used to treat and/or mitigate symptoms of COVID-19 and the results will be updated here when known.

<https://erj.ersjournals.com/content/early/2020/04/20/13993003.01009-2020>

<https://www.cebm.net/covid-19/inhaled-corticosteroids-a-rapid-review-of-the-evidence-for-treatment-or-prevention-of-covid-19/>

<https://clinicaltrials.gov/ct2/show/NCT04330586>

<https://clinicaltrials.gov/ct2/show/NCT04331054>

Non-intubated patients

- 1) If COVID-19 is confirmed or suspected:
 - a) Use metered dose inhalers (MDIs), NOT nebulizers, due to increased aerosol risk associated with nebulization. Because MDI supply is limited, only prescribe when needed.
 - b) Ask patients / families to bring in their home inhalers if possible.
- 2) In patients WITHOUT suspicion for COVID-19:
 - a) 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):
 - a) 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.
- 2) 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.
- 2) 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
 - a) **Only use in ventilated patients on strict airborne precautions in a negative-pressure room.**
 - b) Options include:
 - i) Normal (0.9%) saline nebulizer BID.
 - ii) 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

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
- 3) Dexamethasone has less mineralocorticoid activity than most corticosteroids, which may be more favorable in patients in whom fluid retention should be avoided

Recommendations:

Corticosteroid recommendations are conflicting between major guidelines.

- 1) The NIH supports the use of dexamethasone for COVID-19 positive patients who are mechanically ventilated, or for patients who require supplemental oxygen but who are not mechanically ventilated. Dosing for this recommendation is 6mg IV or PO daily for up to 10 days. The NIH recommends against using dexamethasone in patients with COVID-19 who do not require supplemental oxygen. (COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at <https://www.covid19.treatmentguidelines.nih.gov/>. Accessed 6/26/2020.)
- 2) The WHO does 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. (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:

The RECOVERY Trial further looked at a subanalysis looked at CRP in relation to steroid use. For patients with an elevated CRP (> 20) showed early glucocorticoid use reduced mortality or mechanical ventilation. In patients with CRP less than 10, there may be an increased risk for mortality or mechanical ventilation.

https://www.healio.com/news/primary-care/20200722/steroid-treatment-benefits-some-may-harm-others-with-covid19?utm_source=selligent&utm_medium=email&utm_campaign=news&utm_bt=922415890

Evidence suggests that corticosteroid use in patients with SARS, MERS, and influenza was associated with no survival benefit and possible harm (e.g., delayed viral clearance, avascular necrosis, psychosis, diabetes) (World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance. 2020 Mar 13. From WHO website. Accessed 2020 Mar 19. [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected).) (Lee et al, *J Clin Virol*, 2004; Stockman et al, *PLoS Med*, 2006; Arabi et al, *Am J Respir Crit Care Med*, 2018; WHO, *COVID-19 Interim guidance*, March 2020; Wu et al, *JAMA Int Med*, 2020).

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, et al. *Lancet* 2020;395:473-5. DOI: 10.1016/S0140-6736(20)30317-2. PMID: 32043983)

Although no randomized controlled clinical studies with corticosteroids for COVID-19 or other coronaviruses have been peer-reviewed and published, preliminary results from the RECOVERY trial have been released showing dexamethasone as a treatment for the novel coronavirus reduced death in 35% in ventilated patients (OR 0.65, 95% CI 0.48-0.88, $p=0.0003$) and by 20% in other patients receiving oxygen therapy only (OR 0.80, 0.67-0.96, $p=0.0021$). The dose of dexamethasone used was 6 mg (PO or IV) once daily for 10 days. These results prompted the NIH to revise their treatment recommendation for corticosteroids in patients with COVID-19 who require supplemental oxygen, echoed in the recommendation above. (RECOVERY Trial, <https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19>, published and accessed on 6/16/2020.)

A retrospective cohort of 201 patients with COVID-19 pneumonia showed a lower mortality in patients with COVID-19 and ARDS (HR 0.38, 95% CI, 0.20-0.72), although this estimate did not adjust for confounders. Among patients with ARDS who took methylprednisolone, 23 of 50 (46%) died, while of those who did not receive methylprednisolone, 21 of 34 (61.8%) died. (Wu C, et al. *JAMA Intern Med* 2020; doi:[10.1001/jamainternmed.2020.0994](https://doi.org/10.1001/jamainternmed.2020.0994). [Epub ahead of print (March 13, 2020).])

Another retrospective, observational, single-center study (n=46) from Wuhan, China showed the use of methylprednisolone was associated with improvement in fever and hypoxia and had a shortened

disease course versus patients who did not receive the drug. However death occurred in 3 patients during hospitalization, 2 of whom were taking methylprednisolone. (Wang Y, et al. medRxiv. 2020.03.06.20032342; doi: <https://doi.org/10.1101/2020.03.06.20032342>.)

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 al, *Lancet Resp Med*, 2020) but this has not been replicated as of yet.

Dexamethasone in Hospitalized Patients with COVID-19- Preliminary Report

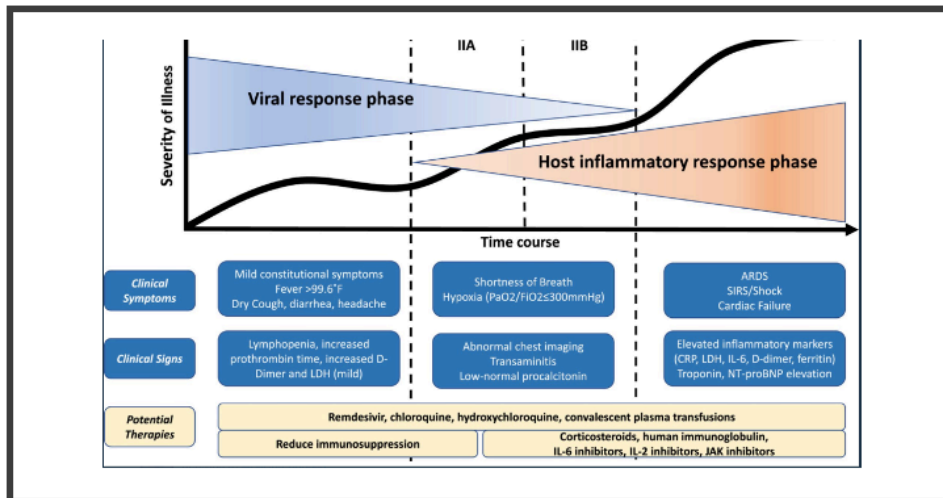
Preliminary results of the RECOVERY Trial have been published. The RECOVERY Trial is a controlled, open-label study that is designed to evaluate various treatments in hospitalized patients with COVID-19 across 176 National Health Service organizations in the UK. Patients with suspected or confirmed SARS-CoV-2 infection were included in the trial. Eligible patients were assigned to receive standard of care alone or standard of care plus dexamethasone 6 mg daily for up to 10 days or one of the other available treatments being evaluated in the trial. In situations where dexamethasone use was definitely indicated or contraindicated or the drug was unavailable, those patients were excluded. The primary outcome was all-cause mortality within 28 after randomization. Baseline characteristics between dexamethasone and standard of care group were similar. At randomization, 16% were receiving invasive mechanical ventilation or ECMO, 60% were receiving oxygen only, with or without noninvasive ventilation and 24% required neither. In the dexamethasone group, 95% of the patients received at least one dose and the median duration of therapy was 7 days. Eight percent of patients in the standard of care group received dexamethasone as a part of their care. Following the availability of remdesivir in the UK, 3 patients in the dexamethasone group and 2 patients in the standard of care group received it as a part of their regimen. At 28 days, there was a significant difference in mortality between the two groups. Deaths were reported in 22.9% and 25.7% of patients in the dexamethasone and standard of care groups, respectively (rate ratio, 0.83; 95% CCI, 0.75-0.93; P<0.001). In the dexamethasone group, the incidence of death was the lower in patients requiring invasive mechanical ventilation and oxygen support without invasive mechanical ventilation at randomization, compared to usual care. A clear benefit of dexamethasone therapy was not noted in patients not requiring respiratory support. In patients receiving dexamethasone, a reduction in 28-day mortality was noted in patients who had a longer

duration of symptoms (>7 days) compared to recent onset. (The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with COVID-19- Preliminary Report. NEJM. July17, 2020. DOI: 10.1056/NEJMoa2021436)

An article out of JAMA describes targets for potential drug therapies for SARS-COV2: A link to this article can be found here: <https://jamanetwork.com/journals/jama/fullarticle/2764727>

Adapted from “Pharmacologic Treatment for Coronavirus Disease 2019 (COVID-19) A Review,” by JM Sanders, 2020, JAMA, p. E1-E13. Copyright 2020 by the American Medical Association.

In addition, this image is commonly seen in the medical literature that is being posted, and describes the phases of COVID that a patient can go through and also identifies targets based on phases.



Remdesivir

Physiology

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/>
2. 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. Remdesivir has shown *in vitro* activity against SARS-CoV-2 (Wang et al, *Cell Research*, 2020)

Evidence

- 1) There is not yet adequate evidence for remdesivir against SARS-CoV-2 *in vivo*
 - a) 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)
 - b) Animal models have shown reduced lung viral loads when remdesivir is used for both SARS-CoV-1 and MERS-CoV (Sheahan et al, *Sci Transl Med*, 2017; Sheahan et al, *Nat Commun* 2020; de Wit et al, *Proc Nat Acad Sci* 2020)
 - c) The efficacy of remdesivir treatment vs. placebo was tested in a rhesus macaque model with SARS-CoV-2 infection. Treatment was initiated 12 hours after inoculation and continued daily for 6 dpi. Animals in the treatment arm lacked obvious signs of respiratory disease and demonstrated reduced viral replication in the lungs following treatment. First effects were noted as early as 12 hours following remdesivir administration. Interestingly, there was no reduction in viral shedding. These data support a potential benefit of early treatment initiation in patients with COVID-19 to prevent progression to severe disease. (Williamson, BN, Feldmann F, Schwarz, B, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *bioRxiv*. Preprint, doi: <https://doi.org/10.1101/2020.04.15.043166>)
- 2) 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)
- 3) Sixty-one patients with COVID-19 treated with remdesivir via a compassionate use program were included in a case series. Analysis included data from 53 patients who received at least 1 dose of remdesivir. Although the trial showed some improvement in oxygen support status (68%) and an overall 13% mortality rate, there were multiple issues with this trial. There was no established control group and baseline data on disease biomarkers or markers of global physiologic severity were not collected. Moreover, the duration of remdesivir therapy was not entirely uniform in the study, largely because clinical improvement enabled discharge from the hospital. Lastly, no viral load data was collected to confirm the antiviral effects of remdesivir or any association between baseline viral load and viral suppression, if any, and clinical response. (Grein J, et al. Compassionate use of remdesivir for patients with severe COVID-19. *N Engl J Med* 2020; DOI: 10.1056/NEJMoa2007016.)
- 4) The SIMPLE severe trial, a Study to Evaluate the Safety and Antiviral Activity of Remdesivir in Participants with Severe Coronavirus Disease was a randomized, open-label, phase 3 trial conducted to determine whether there was a difference in outcomes in patients receiving a 5-day vs 10-day course of remdesivir. Children ≥ 12 years of age and adults with SARS-CoV-2 confirmed by PCR, evidence of pulmonary infiltrates and SpO₂ $\leq 94\%$ or requiring supplemental oxygen at screening were included. Participants requiring mechanical ventilation and ECMO at the time of study entry,

CrCl <50 ml/min and ALT/AST >5x ULN were excluded. The primary endpoint was clinical status at Day 14 based on a 7-point ordinal scale. The secondary endpoint was the proportion of patients experiencing adverse events up to 30 days after the last dose of remdesivir. The time to clinical improvement for 50% of patients was 10 days and 11 days in the 5-day and 10-day treatment groups, respectively. More than half of the patients in both groups were discharged from the hospital by Day 14 (5-day: 60%, n=120/200 vs. 10-day: 52% n=103/197; p=0.14). At Day 14, clinical recovery was achieved in 64% of patients in the 5-day treatment group and 54% of patients in the 10-day treatment group. After pooling data across treatment arms, 62% of patients who received remdesivir within the first 10 days of symptom onset were able to be discharged from the hospital by Day 14 compared to 49% of patients treated after 10-plus days of symptoms. The most common adverse events observed were nausea, acute respiratory failure and elevated ALT. Grade 3 or higher liver enzyme elevations were noted in 7.3% of patients, with 3.0% requiring remdesivir discontinuation. This data combined with preliminary positive efficacy and safety data from the NIH sponsored trial, Adaptive COVID-19 Treatment Trial, resulted in the issuance of an Emergency Use Authorization for remdesivir on May 1, 2020. (Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in Patients with Severe COVID-19. *N Engl J Med*; DOI: 10.1056/NEJMoa2015301. [Epub ahead of print (May 27, 2020).

- a) A pre-planned comparative analysis of 312 patients from the SIMPLE severe trial and 818 patients from a retrospective cohort of patients with similar baseline characteristics and disease severity who received standard of care during the same period was conducted. Remdesivir treatment was associated with improved clinical recovery and a 62% reduction in mortality vs. standard of care. By Day 14, 74% and 59% of patients receiving remdesivir and standard of care, respectively, recovered. Clinical improvement was defined as an improvement based on a 7-point ordinal scale. The mortality rate for patients treated with remdesivir was 7.6% at Day 14 vs 12.5% in the standard of care group (adjusted odds ratio 0.38, 95% confidence interval 0.22-0.68, p=0.001). (“Gilead Presents Additional Data on Investigational Antiviral Remdesivir for the Treatment of COVID-19” Gilead Sciences, Inc, 10 July 2020. <https://www.gilead.com/news-and-press/press-room/press-releases/2020/7/gilead-presents-additional-data-on-investigational-antiviral-remdesivir-for-the-treatment-of-covid-19> Press Release.)
- 5) The Adaptive COVID-19 Treatment Trial sponsored by the NIH is currently evaluating the clinical efficacy and safety of different investigational therapeutics compared to a control arm. The initial treatment arms evaluated were remdesivir vs. placebo. Adult patients with SARS-CoV-2 infection confirmed by RT-PCR with one of the following: radiographic infiltrates by imaging, SpO₂ < / = 94% on room air or requiring supplemental oxygen, mechanical ventilation or ECMO were included. Patients with ALT or AST >5x ULN, eGFR < 30 ml/min and pregnant women were excluded. The primary endpoint was time to recovery. Preliminary results showed that patients in the remdesivir group had a faster time to recovery compared to those in the placebo group. The median time to recovery was 11 days and 15 days for patients treated with remdesivir and placebo, respectively (rate ratio for recovery, 1.32; 95% CI, 1.12-1.55; p<0.001). A survival benefit at 14 days was also noted, with a mortality rate of 7.1% for the remdesivir group versus 11.9% for the placebo group (hazard ratio for death, 0.70; 95% CI, 0.47-1.04). Estimates of mortality at Day 28 are not yet available as this data represents a preliminary analysis. This data combined with preliminary results from the SIMPLE severe trial, Study to Evaluate the Safety and Antiviral Activity of Remdesivir in Participants with Severe Coronavirus Disease, resulted in the issuance of an Emergency Use Authorization for remdesivir on May 1, 2020. (Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19 - preliminary report. *N Engl J Med*; DOI: 10.1056/NEJMoa2007764. [Epub ahead of print (May 22, 2020).

- a) The next phase of this adaptive trial, ACTT2, will evaluate the benefit of using baricitinib in combination with remdesivir. Patients with confirmed SARS-CoV-2 infection and evidence of lung involvement (need for supplemental oxygen, abnormal chest X-rays or requiring mechanical ventilation) will be included. Patients will randomly be assigned to remdesivir IV (up to 10 days of treatment) and baricitinib 4 mg PO/NG daily (up to 14 days of treatment) vs. remdesivir and placebo. Investigators will evaluate time to recovery until Day 29. An independent data and safety board will continue to monitor ongoing results. (“NIH clinical trial testing antiviral remdesivir plus anti-inflammatory drug baricitinib for COVID-19 begins.” National Institutes of Health, 8 May 2020. <https://www.nih.gov/news-events/news-releases/nih-clinical-trial-testing-antiviral-remdesivir-plus-anti-inflammatory-drug-baricitinib-covid-19-begins>. News Release.)
- 6) A multi-center investigator initiated, randomized, placebo-controlled, double-blind trial was initiated in Wuhan, China to assess the safety and efficacy of adult patients with severe COVID-19. Patients with pneumonia confirmed by chest imaging, oxygen saturation $\leq 94\%$ on room air or $\text{paO}_2/\text{FiO}_2 \leq 300$ mmHg and were within 12 days of symptom onset were included. Use of treatments including lopinavir/ritonavir and interferon alfa-2b was permitted. Patients were randomized 2:1 to receive either remdesivir or placebo. The primary endpoint was time to clinical improvement within 28 days after randomization. Assuming an 80% event rate within 28 days across both groups and a dropout rate of 10%, about 453 patients should have been recruited for this trial, however, due to control of the outbreak, only 236 patients were recruited and the statistical power was dropped to 58%. Based on termination criteria, the study was halted and available data analyzed. In the ITT and per protocol population, the time to clinical improvement in the remdesivir group was not significantly different compared to the control group. In the ITT population, patients that received remdesivir within 10 days of symptom onset had a faster time to clinical improvement than those receiving placebo (median 18 days [IQR 12–28] vs 23 days [15–28]; HR 1.52 [0.95–2.43]), however, this finding was not statistically significant. 28-day mortality was not significantly different between the two groups. Adverse events were reported in 66% of patients treated with remdesivir compared to 64% that received placebo. Treatment was stopped early in 12% of patients treated with remdesivir compared to 5% of patients in the placebo group. (Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet* 2020; [https://doi.org/10.1016/S0140-6736\(20\)31022-9](https://doi.org/10.1016/S0140-6736(20)31022-9).)
- 7) Gilead released topline results from the SIMPLE trial assessing outcomes in patients with moderate COVID-19 pneumonia receiving remdesivir + standard of care for 5 days vs. 10 days to standard of care alone. The primary endpoint was clinical status assessed via 7-point ordinal scale at Day 11. Results demonstrated that patients in the 5-day treatment group were 65% more likely to have clinical improvement at Day 11 compared to standard of care group (OR 1.65 [95% CI 1.09-2.48]; $p=0.017$). The odds of clinical improvement in patients who received 10 days of remdesivir vs standard of care were favorable but not statistically significant (OR 1.31 [95% CI 0.88-1.95]; $p=0.18$). Gilead will submit the full data for publication in the coming weeks. (“Gilead Announces Results from Phase 3 of Remdesivir in Patients with Moderate COVID-19.” Gilead Sciences, Inc, 1 June 2020. <https://www.gilead.com/news-and-press/press-room/press-releases/2020/6/gilead-announces-results-from-phase-3-trial-of-remdesivir-in-patients-with-moderate-covid-19>. Press Release.)
- 8) Gilead received approval from the FDA to begin Phase 1a clinical study with an inhaled, nebulized formulation of remdesivir to be used in earlier stages of disease. (<https://www.gilead.com/news-and-press/company-statements/gilead-sciences-statement-on-the-initiation-of-clinical-testing-of-an-inhaled-solution-of-remdesivir-for-potential-outpatient-treatment-of-covid19>)

Recommendations

- 1) If eligible, use of remdesivir via Emergency Use Authorization (EUA) may be considered. The authorization covers:
 - a. Treatment of adults and children with suspected or laboratory confirmed COVID-19 and severe disease defined as SpO₂ ≤ 94% on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)
 - b. For additional information, please refer to Fact Sheet for Healthcare Providers issued by the FDA <https://www.fda.gov/media/137566/download>
- 2) If not eligible for EUA or state awaiting remdesivir allocation, enrollment in clinical trials, emergency access program or compassionate use program may be considered.

Dosing Regimen

- 1) Remdesivir is only available as an investigational agent through clinical trials, compassionate use or through the Emergency Use Authorization.
 - a) 200 mg IV loading dose, followed by 100 mg IV daily for a total of 5 or 10 days, depending on severity. The optimal duration of treatment for COVID-19 is unknown.

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
 - a) There is a paucity of information surrounding the use of remdesivir in patients with acute or chronic kidney disease and COVID-19 as this population has traditionally been excluded from clinical trials (eGFR < 30 or 50 mL/min/1.73 m²). The EUA Fact Sheet for health care providers states that remdesivir should not be used in patients with eGFR < 30 ml/min/1.73 m² unless the potential benefit outweighs the potential risk. Patients with ESRD however are at a greater risk for exposure to SARS-CoV-2 and severe disease. Further, infection leads to AKI in 20-40% of patients with critical illness. The authors of this perspective paper present what is known about remdesivir administration in patients with impaired kidney function.

Remdesivir and its active metabolite are primarily renally eliminated. In patients with acute or chronic kidney disease there is a concern that the accumulation of remdesivir and its vehicle, sulfobutylether-β-cyclodextrin (SBECD) can result in toxicity. Remdesivir however is a weak inhibitor of mammalian RNA and DNA polymerases and is not expected to cause mitochondrial toxicity, given treatment duration is short, not exceeding 5 or 10 days. SBECD is excreted primarily via glomerular filtration. In animal studies, SBECD accumulation resulted in liver necrosis and renal tubule obstruction when administered in doses 50-100 fold higher than expected for a remdesivir course. Voriconazole IV, which contains SBECD is given to patients with IFI and renal failure who are not able to adequately absorb the oral formulation. In this setting, short courses have been tolerated. In addition, RRT and HD remove SBECD and therefore significant accumulation is expected to occur when dialysis is held for a prolonged time. Overall exposure to SBECD in this population is higher than those with normal function. Well-designed trials assessing efficacy and safety of remdesivir in patients with kidney disease are needed. (Adamsick ML, Gandhi RG, Bidell MR, et al. Remdesivir in Patients with Acute or Chronic Kidney Disease and COVID-19. JASN. DOI: <https://doi.org/10.1681/ASN.2020050589>. Epub Ahead of Print July 2020).

- 3) All patients must have an eGFR determined before dosing. Remdesivir is not recommended in adult and pediatric patients (>28 days old) with eGFR less than 30 mL/min or in full-term neonates (≥7 days to ≤28 days old) with serum creatinine greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk.
- 4) Drug Interactions
 - a) Avoid combination of hydroxychloroquine or chloroquine and remdesivir. This combination can decrease the antiviral activity of remdesivir, based on in vitro data showing an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir.
 - i) FACT SHEET FOR HEALTH CARE PROVIDERS: EMERGENCY USE AUTHORIZATION (EUA) OF REMDESIVIR (GS-5734™). Updated June 2020. Accessed at <https://www.fda.gov/media/137566/download> on 6/16/2020.
 - b) An analysis of clinical outcomes with patients treated with both remdesivir and hydroxychloroquine vs those treated with remdesivir alone was conducted by Gilead. During a median follow-up of 14 days, the rates of recovery were lower in patients who received concomitant hydroxychloroquine vs patients treated with remdesivir alone (57% vs. 69%, covariate-adjusted HR [95% CI] 0.61 [0.45, 0.83], p=0.002). Concomitant hydroxychloroquine use was not associated with increased mortality during this time period. Patients in the concomitant hydroxychloroquine group had overall higher rates of adverse events, demonstrating a significant difference in Grade 3-4 adverse events. (“Gilead Presents Additional Data on Investigational Antiviral Remdesivir for the Treatment of COVID-19” Gilead Sciences, Inc, 10 July 2020. <https://www.gilead.com/news-and-press/press-room/press-releases/2020/7/gilead-presents-additional-data-on-investigational-antiviral-remdesivir-for-the-treatment-of-covid-19> Press Release.)

Hydroxychloroquine and Chloroquine

Pathophysiology

Hydroxychloroquine (HCQ) is an anti-malarial 4-aminoquinoline shown to have *in vitro* (but not yet *in vivo*) activity against diverse RNA viruses, including SARS-CoV-1 (Touret and de Lamballerie, *Antivir Res*, 2020) and SARS-CoV-2 (Yao, et al *Clin Infect Dis* 2020; Liu, et al. *Cell Discov* 2020).

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, *Virology*, 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

Efficacy for Treatment of SARS-CoV-2

- 1) Hydroxychloroquine was found to be more potent than chloroquine in inhibiting SARS-CoV-2 *in vitro* (Yao et al, *Clin Infect Dis*, 2020).
- 2) A prospective study of 30 patients in China randomized patients to hydroxychloroquine, 400 mg, daily for 5 days plus standard of care (supportive care, interferon, and other antivirals) or standard care alone in a 1:1 fashion; there was no difference in virologic outcomes. At day 7, virologic clearance was similar, with 86.7% vs 93.3% clearance for the hydroxychloroquine plus standard of care group and standard care group, respectively ($P > .05$). (Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *J Zhejiang Univ (Med Sci)* 2020; published online March 6. DOI:10.3785/j.issn.1008-9292.2020.03.03.)
- 3) An expert consensus group out of China suggests that chloroquine improved lung imaging and shortened disease course (Zhonghua et al, *CMAJ*, 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).
- 4) An ongoing study has halted its high dose chloroquine arm (600 mg BID for 10 days) due to cardiotoxicity, specifically prolonged QT intervals and a trend toward higher fatality rate. All patients randomized to the high dose arm have been unblinded and transitioned to the low dose arm for completion of the study (450 mg BID on day 1 and 450 mg daily for days 2-5). (Borba MGS, et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). *JAMA Network Open*. 2020;3(4.23):e208857. doi:10.1001/jamanetworkopen.2020.8857.)
- 5) A retrospective analysis was conducted from 368 patients across U.S. Veterans Health Administration medical centers analyzing differences in outcomes of death and the need for mechanical ventilation in three groups: hydroxychloroquine (HCQ) alone plus standard supportive management (n=97), hydroxychloroquine plus azithromycin (HCQ+Azith) plus standard supportive management (n=113), and standard supportive management alone (SSM) (n=158). Rates of death were 27.8%, 22.1%, and 11.4% respectively. The risk of death was higher in the HCQ group when compared to SSM ($p=0.03$). Rates of ventilation were 13.3%, 6.9%, and 14.1%, respectively. No difference was found when comparing the HCQ and HCQ+Azith groups with SSM ($p=0.48$ and $p=0.09$ respectively). Based on the increased mortality with the HCQ group, the authors caution against widespread adoption of these drugs in COVID-19 patients until more ongoing prospective, randomized controlled studies have found results. (Magagnoli J, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. Preprint. MedRxiv. <https://doi.org/10.1101/2020.04.16.20065920>.)
- 6) An observational study examining the association between hydroxychloroquine use and respiratory failure in 1376 patients at a large medical center in New York City showed no significant difference between groups for incidence of intubation or death (hazard ratio 1.04, 95% CI 0.82-1.32). Patients in the hydroxychloroquine were sicker at baseline (median Pao₂:Fio₂, 223 vs. 360). Authors conclude hydroxychloroquine administration was not associated with a lowered or increased risk of intubation or death. Randomized, controlled trials are needed to examine this treatment. (Geleris J, et

- al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med* 2020; DOI: 10.1056/NEJMoa2012410 [Epub ahead of print (May 7, 2020)].
- 7) A retrospective cohort of 1438 patients in New York, evaluated in-hospital mortality in patients who received hydroxychloroquine, hydroxychloroquine and azithromycin, azithromycin alone, or neither. Overall, in-hospital mortality was 20.3%. The probability of death was as follows: 25.7% (hydroxychloroquine + azithromycin), 19.9% (hydroxychloroquine alone), 10.0% (azithromycin alone), and 12.7% (neither drug). Using adjusted cox proportional hazard modeling, there were no significant differences in in-hospital mortality between treatment arms compared to neither therapy. Despite finding no significant ECG changes between groups, cardiac arrest was significantly higher in the group taking both hydroxychloroquine and azithromycin in combination [HR 2.13 (95% CI 1.12-4.05)]. (Rosenberg ES, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. *JAMA*. Published online May 11, 2020. doi:10.1001/jama.2020.8630)
 - 8) A retrospective trial out of China evaluated 568 critically ill patients with COVID-19 also receiving basic therapy. A subset (n=48) received hydroxychloroquine and these patients showed lower mortality compared to the group who did not receive hydroxychloroquine (18.8% versus 45.8%, p<0.001). The group who received hydroxychloroquine also had a reduction in their IL-6 level from beginning to end of treatment. (Yu B, et al. Low dose hydroxychloroquine reduces fatality of critically ill patients with COVID-19. *Sci China Life Sci* 2020; 63: <https://doi.org/10.1007/s11427-020-1732-2>. [epub ahead of print (5/15/2020)]
 - 9) A study initially published in *Lancet* on May 22, 2020 by Mehra et al. reported an increase in mortality and ventricular arrhythmias associated with hydroxychloroquine and chloroquine. This study has now been retracted by the authors after independent third-party peer review could not confirm the data from the Surgisphere database was in fact accurate or reliable. (Mehra MR, et al. Retraction – Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet* 2020; [https://doi.org/10.1016/S0140-6736\(20\)31324-6](https://doi.org/10.1016/S0140-6736(20)31324-6) [Epub ahead of print June 5, 2020].)
 - 10) The RECOVERY trial has halted its hydroxychloroquine arm as of June 5, 2020 because of no benefit on 28 day mortality, decreased hospital stay, or other outcomes in patients who are hospitalized with COVID-19. (<https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19>) In addition, the investigators of the Solidarity trial have halted enrollment into the hydroxychloroquine arm of the study (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments>).
 - 11) The Henry Ford COVID-19 Task Force published a retrospective cohort study on hydroxychloroquine, azithromycin, and combination therapy in hospitalized patients (n=2541) on June 28, 2020. After a mean follow-up of 28 days, and a total mortality rate of patients of 18.1%, 13.5% in the hydroxychloroquine alone group, 20.1% in the combination therapy, and 26.4% in the group who received neither therapy (p<0.001). Adjunct corticosteroids (prednisone, methylprednisolone) were given in 68% of patients, as were anti-IL-6 agents in 4.5%. The authors postulate this benefit may be due to the earlier administration of the medication(s) compared to other studies, where 82% of participants received the medication(s) within 24 hours of admission and 91% within the first 48 hours, although duration of symptoms prior to hospitalization was not captured. (Arshad S, et al. *IJID* 2020; <https://doi.org/10.1016/j.ijid.2020.06.099> [Epub ahead of print (June 28, 2020)].

Efficacy for Post-Exposure Prophylaxis

- 1) Hydroxychloroquine was tested against placebo to determine if it could prevent COVID-19 infection after a person is exposed to the virus SARS-CoV-2 either through household or occupational contact. Out of 821 asymptomatic patients enrolled in the study, 87.6% had a high-risk exposure. Thirteen percent of the population developed COVID-19 after exposure, but the incidence of infection did not differ significantly between treatment and placebo groups ($p=0.35$). No arrhythmias or deaths were reported. (Boulware DR, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for COVID-19. *N Engl J Med* 2020; DOI: 10.1056/NEJMoa2016638 [Epub ahead of print (June 3, 2020).])

Safety Studies

- 1) A report of patients who received at least 1 day of hydroxychloroquine and were positive for COVID-19 were evaluated to determine change in QT interval. Out of 90 patients who received hydroxychloroquine, 53 also received azithromycin. Incidence of QT >500 msec was higher in hydroxychloroquine + azithromycin group versus hydroxychloroquine group alone (21% versus 13%). Patients on loop diuretics or who had baseline QTc of 450 or greater were more likely to have a prolonged QTc. Ten patients discontinued treatment early, one of whom experienced torsades de pointes. (Mercurio NJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for Coronavirus Disease 2019. *Jama Cardiol*; doi: 10.1001/jamacardio.2020.1834. Available online May 1, 2020.)
- 2) The ISMP describes a patient going into cardiac arrest after discontinuing azithromycin and starting hydroxychloroquine. Even though these medications were not taken simultaneously, the long half-life of azithromycin ($t_{1/2} = 68-72$ hours) and added QT prolonging risk of hydroxychloroquine was determined to be the likely cause of the arrest. Patient's QTc upon admission was 460 msec, then 490 msec upon starting hydroxychloroquine, and 605 msec after ROSC was achieved post arrest. Patient taking hydroxychloroquine right after discontinuing azithromycin develops QTc prolongation and cardiac arrest. (Acute Care ISMP Medication Safety Alert 2020;25(7):1,3. Published online at <https://ismp.org/sites/default/files/newsletter-issues/20200409.pdf> on April 9, 2020.)

Recommendations

TREATMENT: Hydroxychloroquine should not be used as treatment for hospitalized patients with SARS-CoV-2.

POST-EXPOSURE PROPHYLAXIS: Hydroxychloroquine should not be used as post-exposure prophylaxis in the setting of high-risk exposure to SARS-CoV-2.

The Emergency Use Authorization for chloroquine and hydroxychloroquine in the treatment of COVID-19 has been revoked by the FDA as of June 15, 2020. It was initially issued on March 28, 2020 and the FDA has since reviewed new information that led them to conclude the original criteria for use of these drugs under this EUA are no longer met. Reasons for revocation:

1. Suggested dosage regimens detailed in the EUA fact sheet are unlikely to produce an antiviral effect.
2. Early observations of decreased viral shedding have not been replicated.
3. Current U.S. treatment guidelines do not recommend the use of these agents in hospitalized patients with COVID-19 outside of a clinical trial. The NIH recommends against their use outside of a clinical trial.
4. Recent randomized controlled trials show no evidence of benefit in mortality, hospital length of stay, or mechanical ventilation using these medications.

(US Food and Drug Administration. Letter regarding revocation of emergency use authorization (EUA) for emergency use of chloroquine phosphate and hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of Coronavirus disease 2019. 2020 Jun 15. Available at <https://www.fda.gov/media/138945/download>.)

The NIH Treatment Guidelines recommend against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19, except in a clinical trial. The panel also recommends against the use of hydroxychloroquine or chloroquine plus azithromycin for the treatment of COVID-19, except in a clinical trial. (COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at <https://www.covid19.treatmentguidelines.nih.gov/>. Accessed 6/26/2020.)

Monitoring and Toxicity

- 1) Hydroxychloroquine is contraindicated in epilepsy and porphyria. Known adverse effects include:
 - a) Bone marrow suppression
 - b) Cardiomyopathy and retinopathy
 - i) 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).
 - c) QT-segment prolongation and therefore torsades de pointes, especially if administered in combination with azithromycin or other QT-prolonging medications.
 - i) For a full list of QTc prolonging medications, please visit <https://www.crediblemeds.org/>
 - ii) Given this, the following monitoring is required for patients being treated with hydroxychloroquine:
 - (1) Obtain baseline ECG, ECG 4 hours after first dose, and daily ECG thereafter.
 - (2) Discontinue all other QT-prolonging agents if at all possible.
 - (3) Maintain continuous telemetry while under treatment.
 - (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.
 - (a) 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.ncbi.nlm.nih.gov/pmc/articles/PMC7048442/)

- d) Increased risk of hypoglycemia also seen with the use of hydroxychloroquine (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf)
- e) Methemoglobinemia

(Naymagon L, et al. Am J Hematol. 2020; <https://onlinelibrary.wiley.com/doi/epdf/10.1002/ajh.25868> [Epub ahead of Print (May 10, 2020).])

2) Drug Interactions

- a) Avoid combination of hydroxychloroquine or chloroquine and remdesivir. This combination can decrease the antiviral activity of remdesivir, based on in vitro data showing an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir.
 - i) FACT SHEET FOR HEALTH CARE PROVIDERS: EMERGENCY USE AUTHORIZATION (EUA) OF REMDESIVIR (GS-5734™). Updated June 2020. Accessed at <https://www.fda.gov/media/137566/download> on 6/16/2020.
- b) An analysis of clinical outcomes with patients treated with both remdesivir and hydroxychloroquine vs those treated with remdesivir alone was conducted by Gilead. During a median follow-up of 14 days, the rates of recovery were lower in patients who received concomitant hydroxychloroquine vs patients treated with remdesivir alone (57% vs. 69%, covariate-adjusted HR [95% CI] 0.61 [0.45, 0.83], p=0.002). Concomitant hydroxychloroquine use was not associated with increased mortality during this time period. Patients in the concomitant hydroxychloroquine group had overall higher rates of adverse events, demonstrating a significant difference in Grade 3-4 adverse events. (“Gilead Presents Additional Data on Investigational Antiviral Remdesivir for the Treatment of COVID-19” Gilead Sciences, Inc, 10 July 2020. <https://www.gilead.com/news-and-press/press-room/press-releases/2020/7/gilead-presents-additional-data-on-investigational-antiviral-remdesivir-for-the-treatment-of-covid-19> Press Release.)

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 (3CL^{pro})

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)
 - a) Treatment with LPV/r was **not** associated with a difference in time to clinical improvement or mortality
 - b) 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) Combination therapy with lopinavir/ritonavir, ribavirin and interferon beta-1b vs lopinavir/ritonavir was evaluated in a phase 2, multicenter, open-label randomized trial in adults with mild-moderate COVID-19. Lopinavir and interferon beta, have demonstrated *in vitro* activity against SARS and MERS, and some *in vivo* data suggests that they can be used synergistically with ribavirin. Lopinavir/ritonavir and interferon beta-1b have shown to reduce viral load and improve lung pathology in animal models. In this trial, patients were randomized 2:1 to the combination group or the lopinavir/ritonavir group (control). Treatment duration was 12 days. The primary endpoint was time to negative RT-PCR result by nasopharyngeal swab. 127 patients were recruited, 86 patients and 41 patients in the combination and control groups, respectively. Median days from symptom onset to treatment initiation was 5 days in the combination group and 4 days in the control group. Median time to negative nasopharyngeal swab was significantly shorter in the combination group (7 days [IQR 5–11]) vs control group (12 days [8–15]; HR 4.37 [95% CI 1.86–10.24], p=0.0010). Patients in the combination group demonstrated significantly better clinical and virologic response resulting in a shorter hospital length of stay (9 days [7–13] vs 14.5 days [9.3–16.0]; HR 2.72 [1.2–6.13], p=0.016). Patients in the combination group who started treatment less than 7 days after symptom onset had better clinical and virologic outcomes than in the control group. Larger trials are needed to confirm efficacy of interferon beta-1b alone or in combination with other agents in COVID-19 disease. (Hung I, Lung K, Tso E, et al. Triple combination of interferon beta-1b, lopinavir/ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *The Lancet* 2020; DOI:[https://doi.org/10.1016/S0140-6736\(20\)31042-4](https://doi.org/10.1016/S0140-6736(20)31042-4))
- 5) 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).
- 6) The lopinavir/ritonavir arm (vs. standard of care) of the Solidarity Trial, which was established by WHO, has been discontinued. Interim results which were evaluated by the trial's International Steering Committee, demonstrated that lopinavir/ritonavir demonstrated little or no reduction in mortality with some associated safety signals. (<https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19>)

Recommendations

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

Dosing Regimen if recommended by Infectious Disease

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
- 3) Lopinavir plus ritonavir may pose a risk for bradycardia in COVID-19 patients, Of 41 COVID-19 patients treated with lopinavir-ritonavir at a French hospital, 22% developed bradycardia at least 48 hours after treatment began. Patients who developed bradycardia were older than those who did not (mean, 73 vs. 62 years). <https://www.ahajournals.org/doi/10.1161/CIRCEP.120.008798>.

Anti-IL6 Agents (Tocilizumab, Siltuximab, Sarilumab)

Pathophysiology

- 1) Elevated levels of IL-6 strongly associated with the need for mechanical ventilation ($p=1.2 \cdot 10^{-5}$). In addition, the maximal IL-6 level (cutoff 80 pg/ml) for each patient during disease predicted respiratory failure with high accuracy ($p=1.7 \cdot 10^{-8}$, 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>
- 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).

Evidence

- 1) 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.
- 2) A single center retrospective analysis in 15 patients with moderate-critical COVID-19 infection demonstrated near normalization of CRP in 11 patients and a decline in IL-6 in 10 patients following a transient increase after tocilizumab administration. Three of seven critically ill patients died and notably, all 3 patients received a single dose of tocilizumab. Doses ranged from 80 mg-600 mg per dose, administered as single or multiple doses. In critically ill patients or patients with extremely high baseline IL-6 levels, the authors suggest that repeat tocilizumab administration at a reduced dose and frequency may be beneficial. (Reference: Pan L (2020). Tocilizumab treatment in COVID-19: a single center experience. *J Med Virol*. Advance online publication, doi: 10.1002/jmv.25801.)

- 3) Tocilizumab was evaluated in 21 patients in a retrospective, uncontrolled study where all patients required O₂ at enrollment. Within 24 hours, fevers resolved, O₂ intake was lowered in 75%, O₂ saturation levels stabilized or improved in all patients, and CT scans showed improved lung lesion opacities in 90.5%. Two patients who were ventilated were weaned. All patients were discharged alive. More randomized, controlled trials are needed to confirm effectiveness, as this population is small and observational. (Xu X, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020 Apr 29. pii: 202005615. doi: 10.1073/pnas.2005615117. [Epub ahead of print])
- 4) Retrospective review of hypoxic and hospitalized COVID-19 patients: This retrospective cohort study model was similar as Guaraldi et al's model in that patients with severe COVID-19 patients treated with standard of care (e.g. hydroxychloroquine, azithromycin, and a systemic steroid) were either treated or not treated with tocilizumab then compared. The sample size was small (n=51) and divided into 28 who received tocilizumab and 23 who did not. Those who received tocilizumab required more invasive ventilation at baseline and during hospital stay. Time to clinical improvement and invasive ventilation rates were not statistically significant between groups, but vasopressor support duration was lower in the tocilizumab group (2 days vs. 5 days, p=0.039). (Kewan T, et al. EClinicalMedicine; <https://doi.org/10.1016/j.eclinm.2020.100418> [Epub ahead of print (May 30, 2020)])
- 5) Use in severe COVID-19 patients to prevent mechanical ventilation: A retrospective, observational cohort study of severe COVID-19 patients were treated with standard of care (i.e. O₂, hydroxychloroquine, azithromycin, antiretrovirals, and low molecular weight heparin), some of whom received 2 intravenous infusions or subcutaneous injections of tocilizumab. Although raw unmatched numbers do not favor a statistically significant improvement in mechanical ventilation in patients treated with tocilizumab versus not (16% vs. 18%, p=0.41), when adjustments were made to match cases based on sex, age, center, duration of symptoms, and SOFA score, tocilizumab was associated with a reduced risk of mechanical ventilation or death (HR 0.61, 95% CI 0.40-0.92, p=0.020). Seventy-three (20%) of the standard of care group died compared to 13 (7%) of the standard of care plus tocilizumab (n<0.0001). Superinfection rate was higher in the tocilizumab group (p<0.0001). (Guaraldi G, et al. Lancet Rheumatol 2020; [https://doi.org/10.1016/S2665-9913\(20\)30173-9](https://doi.org/10.1016/S2665-9913(20)30173-9) [Epub ahead of print (June 24, 2020)].)
- 6) Use in already-mechanically-ventilated patients: An observational, controlled study of 154 patients with severe COVID-19 requiring mechanical ventilation were given tocilizumab. Treatment group did differ from the control group in age (55 years vs. 60 years), chronic pulmonary disease incidence (10% vs. 28%), and d-dimer levels at time of intubation (2.4 vs. 6.5 mg/dL). Treatment group showed a 45% reduction in mortality rates at 28 days versus untreated controls. Patients in the treatment group did experience more superinfections (e.g. VAP, ~50% as *S. aureus*) (54% versus 26%), although those with superinfection did not have a higher mortality rate than those without superinfection (22% vs. 15%, p=0.42). (Somers EC, et al. Clinical Infectious Diseases 2020; <https://doi.org/10.1093/cid/ciaa954> [Epub ahead of print (July 11, 2020)].)

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 retrospective and observational 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.

a) 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.

a) Common adverse effects of tocilizumab include:

- i) Transaminitis (AST, ALT), >22%
- ii) Infusion reaction, 4-20%
- iii) Hypercholesterolemia, 20%
- iv) Upper respiratory tract infection, 7%
- v) Neutropenia, 2-7%

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

a) Common adverse effects of siltuximab include:

- i) Edema, >26%
- ii) Upper respiratory infection, >26%
- iii) Pruritus / skin rash, 28%
- iv) Hyperuricemia, 11%
- v) Lower respiratory tract infection, 8%
- vi) Thrombocytopenia, 8%
- vii) Hypotension, 4%

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

a) Common adverse effects of sarilumab include:

- i) Transaminitis (AST, ALT), 28-47%
- ii) Neutropenia, 7-10%
- iii) Infusion reactions, 7%
- iv) Upper respiratory tract infections, 4%
- v) 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.

5) **JAK Inhibitors**

Baricitinib

Physiology

Baricitinib, fedratinib, and ruxolitinib are potent and selective JAK inhibitors approved for indications such as rheumatoid arthritis and myelofibrosis. All three are powerful anti-inflammatories that, as JAK–STAT signaling inhibitors, are likely to be effective against the consequences of the elevated levels of cytokines (including interferon- γ) typically observed in people with COVID-19.

Although the three candidates have similar JAK inhibitor potencies, a high affinity for AAK1 suggests baricitinib is the best of the group, especially given its once-daily oral dosing and acceptable side-effect profile. https://www.ema.europa.eu/en/documents/product-information/olumiant-epar-product-information_en.pdf, [https://doi.org/10.1016/S1473-3099\(20\)30132-8](https://doi.org/10.1016/S1473-3099(20)30132-8)

Recommendation

Recommend use of baricitinib only in conjunction with ID with consideration of enrollment into a clinical trial. This is a trial that is being launched at OSU 7.2020.

Arm ①	Intervention/treatment ②
Experimental: Baricitinib 4 milligrams (mg) of baricitinib given orally with background therapy.	Drug: Baricitinib Given orally Other Name: LY3009104
Placebo Comparator: Placebo Placebo given orally with background therapy.	Drug: Placebo Given orally

<https://clinicaltrials.gov/ct2/show/NCT04421027>

Evidence

- 1) No evidence currently exists for baricitinib to treat COVID-19. The NIAID sponsored trial will test baricitinib in hospitalized patients with Covid-19 at the end April, with data expected two months later.
- 2) The ACTT2 trial will evaluate the benefit of using baricitinib in combination with remdesivir. Patients with confirmed SARS-CoV-2 infection and evidence of lung involvement (need for supplemental oxygen, abnormal chest X-rays or requiring mechanical ventilation) will be included. Patients will randomly be assigned to remdesivir IV (up to 10 days of treatment) and baricitinib 4 mg PO/NG daily (up to 14 days of treatment) vs. remdesivir and placebo. Investigators will evaluate time to recovery until Day 29. An independent data and safety board will continue to monitor ongoing results. (“NIH clinical trial testing antiviral remdesivir plus anti-inflammatory drug baricitinib for COVID-19 begins.” National Institutes of Health, 8 May 2020. <https://www.nih.gov/news-events/news-releases/nih-clinical-trial-testing-antiviral-remdesivir-plus-anti-inflammatory-drug-baricitinib-covid-19-begins>. News Release.)
- 3) A randomized, double-blind, placebo-controlled, parallel group phase 3 trial assessing the safety and efficacy of baricitinib in hospitalized patients with SARS-CoV-2 not requiring invasive mechanical ventilation is underway. Patients must have at least one inflammatory marker (CRP, D-dimer, LDH, ferritin) >ULN within 2 days before study entry. Baricitinib 4 mg PO/NG daily vs placebo will be administered in addition to standard of care. The primary endpoint is the proportion of patients requiring non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation by day 28. This is a trial that is being launched at OSU 7.2020. (U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Jul 12. Available from: <https://clinicaltrials.gov/ct2/show/NCT04421027>)

Tyrosine Kinase Inhibitors

Abivertinib

Physiology

Abivertinib irreversibly binds to the Bruton's tyrosine kinase (BTK) receptor, preventing the phosphorylation of the receptor and inhibits key pro-inflammatory cytokine production, including IL-1beta, IL-6 and TNF-alpha.

Evidence

Abivertinib is an investigational tyrosine kinase inhibitor cleared by the FDA to enter Phase 2 for hospitalized patients with moderate to severe disease pulmonary disease. (NCT04440007)

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>

Recommendations

- 1) OSU has established 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.
 - a) 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.
 - b) Severe COVID: Dyspnea, RR > 30/min, O2 saturation < 93%, PaO2/Fio2 < 300 or lung infiltrates > 50% within 24 to 48 hours.
 - c) Life-Threatening COVID: Respiratory failure, septic shock or multiple organ dysfunction syndrome.
 - d) 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.
 - a) Our current working process to get patients enrolled statewide at no charge to the patient:
 - i) Completing one virtual visit with patient to discuss CPP information needed:
 - (1) Date of confirmed diagnosis
 - (2) Date of last symptom
 - (3) If female has she been pregnant? Does she know her HLA antibody if previous history of pregnancy?

- ii) During this visit, the physician determines if the patient is willing to donate. If so the following are evaluated:
 - (1) Has the patient been symptoms free for 14-28 days? If yes, order COVID-19 test to verify negative status.
 - (2) **Or** Is the patient more than 28 days past last COVID symptoms? Then no re-testing required.
 - iii) If patient is willing to donate and has the negative re-test/ 28 days past COVID symptoms, the physician fills out the request for CCP donation form. Information on closest OBI donation site given to patient
 - iv) The form gets faxed to OBI (fax number is located on form 87).
 - v) Patient needs to register on the my biolink website at my.biolinked.org website (this information is on the PDF that is given to patient prior to discharge from hospital and it is attached to this email.)
 - vi) OBI will call patient to schedule once the order has been received from the physician and the biolink has been completed by patient.
 - vii) Will confirm with OBI 24 hours after faxing form that patient has been scheduled
- 3) Transfusing incompatible plasma may be safer than transfusing other types of incompatible blood products <https://onlinelibrary.wiley.com/doi/abs/10.1111/trf.14415>
- 4) Other FAQ's
- a) Donors can donate plasma as frequently as every 28 days
 - b) Transfusion of blood products is a 12 month deferral (recently the FDA revised this deferral period to 3 months under pandemic conditions—OBI is still evaluating an implementation process for this).
 - c) Exclusion criteria for donation: CCP donors must meet all of the allogeneic blood donation criteria—medication and travel deferral criteria that must be qualified in a CCP donor. The infectious disease screening tests include HIV+HBV+HCV (serology & nucleic acid), HTLV I/II (serology), West Nile virus + Zika (nucleic acid), and syphilis. T. cruzi (Chagas) is a one time screening test for all first-time donors.

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) Study published in MedRxiv showed that only 2 (of 36) SAEs were judged as definitely related to the convalescent plasma transfusion, according to the PI's. Early indicators suggest that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19. <https://www.medrxiv.org/content/10.1101/2020.05.12.20099879v1>
- 4) 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. <https://www.ncbi.nlm.nih.gov/pubmed/18014217>
- 5) 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>

- 6) 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).
- 7) Among patients with severe or life-threatening COVID-19, convalescent plasma therapy added to standard treatment did not significantly improve the time to clinical improvement within 28 days, although the trial was terminated early and may have been underpowered to detect a clinically important difference. <https://jamanetwork.com/journals/jama/article-abstract/2766943>. The early termination of the trial most likely resulted in an underpowered study, thereby precluding any definitive conclusions about the role and potential efficacy of convalescent plasma for patients with COVID-19. In addition, the open-label design, the possibility of an element of subjectivity for the primary outcome, lack of a protocolized approach to standard therapy, and variability among study centers also must be considered when interpreting the study findings.
<https://jamanetwork.com/journals/jama/fullarticle/2766940>

Anakinra

Pathophysiology

Recombinant IL-1 receptor antagonist that may potentially combat cytokine release syndrome symptoms in severely ill patients

OSU Recommendations

Anakinra is **not** yet recommended as overall evidence is lacking. If infectious diseases recommends, the dosage showing effectiveness in COVID-19 patients was 5 mg/kg intravenously twice daily, infused over 1 hour until sustained clinical benefit defined as a 75% reduction in serum C-reactive protein and sustained respiratory improvement (PaO₂:FiO₂ >200 mmHg) for at least 2 days. Monitor for signs of infection/bacteremia.

Evidence

A retrospective cohort study in Italy studied high dose anakinra in 29 patients with COVID-19, moderate-to-severe ARDS, and hyperinflammation who were managed with non-invasive ventilation outside of the ICU, compared to 16 patients retrospectively matched as the control group. Patients treated also received hydroxychloroquine and lopinavir/ritonavir. The cohort was divided into 3 treatment groups, low dose anakinra (n=7, 100 mcg *subcutaneously* BID), high dose anakinra (n=29, 5 mg/kg *intravenously* BID), and standard treatment (n=16), but the low dose arm was abandoned for no effect in the middle of the study. Results showed improved respiratory function in 21 of 29 patients (72%), 5 who received mechanical ventilation (17%), and 3 who died (10%), compared to the controls where 8 (50%) showed respiratory improvement, 1 (6%) on mechanical ventilation, and 7 (44%) who died. Survival at 21 days was statistically different between groups (95% versus 56%, p=0.009) favoring high dose anakinra. Median duration of treatment was 9 days (IQR 7-11). (Cavalli G, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *The Lancet Rheumatology*. May 2020. doi:[10.1016/s2665-9913\(20\)30127-2](https://doi.org/10.1016/s2665-9913(20)30127-2))

52 consecutive patients received 100 mg doses of subcutaneous anakinra twice per day for 72 hours, followed by 100 mg daily for 7 days, as well standard treatment. Additionally, 44 patients in the

historical control group received standard treatment and supportive care. ICU admissions for invasive ventilation or death occurred in 25% of patients in the anakinra group, compared with 73% in the historical control group (HR = 0.22; 95% CI, 0.11-0.41). This impact remained significant in the multivariate analysis (HR = 0.22; 95% CI, 0.10-0.49). Regarding safety, an increase in liver aminotransferases occurred in 13% of patients who received anakinra, and in 9% of those in the historical control group.

https://www.healio.com/news/rheumatology/20200629/anakinra-reduces-ventilation-need-mortality-in-covid19?utm_source=selligent&utm_medium=email&utm_campaign=news&utm_bt=922415890

Regeneron

Physiology

The human immune system typically produces antibodies to fight the viruses and bacteria. Vaccination involves injecting a dead or weakened virus, or a critical small piece of a virus, to induce this protective immune response, resulting in the same antibodies the immune system would typically make in a person who actually had the infectious disease. Regeneron's core technologies allow for rapid and efficient generation of these protective anti-viral antibodies outside of the body, derived from either genetically-humanized mice or convalescent humans. The resulting antibodies correspond to the most potent of anti-viral antibodies that could be elicited by a vaccine or through exposure to a pathogen. These antibodies can be delivered to people via injection, providing "passive immunity" and protection from the disease immediately, though they must be re-administered to remain effective over time. These antibodies can also treat an existing infection, unlike vaccines which can only be used preventatively.

OSU Recommendations

Recommend use of Regeneron only in conjunction with ID with consideration of enrollment into a clinical trial

Evidence

Regeneron Pharmaceuticals, Inc announced initiation of the first clinical trial of REGN-COV2, its investigational dual antibody cocktail for the prevention and treatment of COVID-19. The REGN-COV2 clinical program will consist of four separate study populations: hospitalized COVID-19 patients, non-hospitalized symptomatic COVID-19 patients, uninfected people in groups that are at high-risk of exposure (such as healthcare workers or first responders) and uninfected people with close exposure to a COVID-19 patient (such as the patient's housemate). The placebo-controlled trials will be conducted at multiple sites.

BTK Inhibitors (ibrutinib and acalabrutinib)

Pathophysiology

- 1). BTK inhibition also has been shown to abrogate pulmonary inflammatory cytokines, regulate macrophage signaling and rescue mice from lethal influenza-induced acute lung injury, sparking interest in its potential to treat COVID-19.

Recommendations

Recommend use of BTK inhibitors only in conjunction with ID with consideration of enrollment into a clinical trial.

Evidence

A case series of six patients with Waldenstrom macroglobulinemia and concomitant COVID-19 received full doses of ibrutinib and experienced no dyspnea or hospitalization.

Another study by Roschewski used acalabrutinib to 19 hospitalized patients with 11 patients on supplemental O₂ and 8 on mechanical ventilation. Results of this off label study showed reductions in oxygen need, CRP and IL-6 over 10-14 days.

(<https://immunology.sciencemag.org/content/5/48/eabd0110>)

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

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

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).

The American College of Cardiology, American Heart Association and Heart Failure Society of America joint statement recommends against discontinuing ACE-I and ARBs in patients with COVID-19 (Bozkurt et al, *HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19*, 2020).

A study in the European Heart Journal measured ACE2 concentrations in 1485 men and 537 women with heart failure (index cohort). In two independent cohorts of patients with heart failure, plasma concentrations of ACE2 were found to be higher in men than in women. In addition the use of ACE inhibitors, angiotensin receptor blockers (ARBs), or mineralocorticoid receptor antagonists (MRAs) was not an independent predictor of plasma ACE2. (<https://www.escardio.org/The-ESC/Press-Office/Press-releases/Men-s-blood-contains-greater-concentrations-of-enzyme-that-helps-COVID-19-infect-cells>)

A study in the Lancet evaluated whether patients on renin-angiotensin-aldosterone system inhibitors were at risk of COVID-19 and hospitalization. Each patient case with COVID-19 was matched with 10 control patient cases. No increased risk was observed in patients taking ACE-inhibitors (adjusted OR 0.80, 95% CI 0.64-1.00) or ARBs (1.10, 0.88-1.37). The researchers concluded RAAS inhibitors do not increase the risk of COVID-19 requiring admission to the hospital, including fatal cases and those admitted to ICUs, supporting the notion that these medications should not be discontinued to prevent a severe case of COVID-19. (de Abajo FJ, et al. Use of renin–angiotensin–aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. *Lancet* 2020; [https://doi.org/10.1016/S0140-6736\(20\)31030-8](https://doi.org/10.1016/S0140-6736(20)31030-8). [Epub ahead of print (May 14, 2020)].)

An observational study including 8910 patients by Mehra et al. Evaluating the association between cardiovascular disease, medications, and mortality has been retracted because of the inability to access raw data reported or validate the findings. (Mehra et al. Retraction: Cardiovascular Disease, Drug Therapy, and Mortality in COVID-19. *N Engl J Med*. DOI: 10.1056/NEJMoa2007621. [Epub ahead of print June 4, 2020].)

Non-steroidal anti-inflammatory drugs (NSAIDs)

Pathophysiology

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

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

Reports from France indicate possible increase in mortality with ibuprofen in COVID-19 infection, but these reports have not been corroborated (Fang et al, *Lancet Respir Med*, 2020; Day M, *BMJ*, 2020). WHO clarified on 3/20/20 it does not recommend avoiding NSAIDs as initially stated 3/18/20 (WHO, *COVID-19 Interim guidance*, March 2020).

Statins

Recommendations

Persons with COVID-19 who are prescribed statin therapy for the treatment or prevention of cardiovascular disease should continue these medications (AIII).

(<https://covid19treatmentguidelines.nih.gov/concomitant-medications/>)

The Panel recommends against the use of statins for the treatment of COVID-19 outside of the setting of a clinical trial (AIII). (<https://covid19treatmentguidelines.nih.gov/concomitant-medications/>)

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 Erythropoietin (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

Currently we are not recommending EPO as a treatment option for COVID-19 based on the paucity of evidence. This was one anecdotal study. If the patient has other indications for receiving EPO, we will not prohibit its use.

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.

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. These 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

Ivermectin has shown *in vitro* activity against some human and animal viruses (Yang SNY, Atkinson SC, Wang C, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β 1 heterodimer. *Antiviral Res.* 2020. PMID: 32134219 DOI: 10.1016/j.antiviral.2020.104760.)

Ivermectin has shown *in vitro* evidence of activity against SARS-CoV-2 in Vero -hSLAM cells infected with the virus (Caly L, Druce JD, Catton MG et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*. *Antiviral Res.* 2020. Preprint. (<https://www.sciencedirect.com/science/article/pii/S0166354220302011?via%3Dihub>))

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

Famotidine (Pepcid)

Pathophysiology

Presumed that famotidine will bind to the viral enzyme called the papainlike protease, which helps the pathogen replicate.

Recommendations

GI prophylaxis with famotidine should be considered for patients in the usual doses, and not at the doses that are being conducted in this trial until more information is garnered or the patient is entered into a clinical trial, or advised by ID.

Evidence

On 7 April, the first COVID-19 patients at Northwell Health in the New York City area began to receive famotidine intravenously, at nine times the heartburn dose.

187 COVID-19 patients in critical status, including many on ventilators, have been enrolled in the trial, which aims for a total of 1174 people.

Hospitalized COVID-19 patients on famotidine appeared to be dying at a rate of about 14% compared with 27%

Out of 6,000 reviewed, patients found a slightly higher number of those taking famotidine recovered than those who didn't take the medicine. The number wasn't high enough to be statistically significant, meaning it could just as easily be attributed to chance.

To find out if it was meaningful, Callahan contacted Kevin Tracey at Northwell Health in New York City. A double-blind randomized study, partly funded by the U.S. Biomedical Advanced Research and Development Authority, was launched on April 14, according to Science.

<https://www.sciencemag.org/news/2020/04/new-york-clinical-trial-quietly-tests-heartburn-remedy-against-coronavirus>

MPR discussed the use of famotidine for patients in a small group of nonhospitalized patients with coronavirus disease 2019 (COVID-19). Self-administration of high-dose oral famotidine was found to be associated with improvements in disease-related symptoms, according to a recently published case series. Findings of the analysis revealed that treatment with famotidine was both well tolerated and beneficial, with rapid improvements noted within 24 to 48 hours after starting the drug. “In addition, for all patients who were able to provide data, temperature readings, oxygen saturations and activity improved in correlation with taking famotidine,” the authors stated.

Moreover, symptoms continued to improve to close to pre-illness levels 14 days after the first dose was administered. The study patients reported that airway-related symptoms (ie, cough, shortness of breath) improved faster than systemic symptoms (ie, fatigue) while taking famotidine (<https://www.medrxiv.org/content/10.1101/2020.05.01.20086694v2>)

Remestemcel-L

Physiology

Culture-expanded mesenchymal stem cells derived from the bone marrow of an unrelated donors which is believed to work by down-regulating the production of proinflammatory cytokines, increasing production of anti-inflammatory cytokines, and enabling recruitment of naturally occurring anti-inflammatory cells to involved tissues

Recommendations

OSU does not routinely recommend Remestemcel-L for patients with COVID-19. This would be done under the guidance of an ID infection, and would be in the setting of a clinical trial.

Evidence

A current randomized, placebo-controlled trial is being conducted at Mount Sinai hospital in New York City. Patients were treated with a variety of experimental agents prior to receiving remestemcel-L. Findings from the study showed 83% survival in ventilator-dependent COVID-19 patients with moderate/severe ARDS (n=10/12) following 2 intravenous infusions of remestemcel-L within the first 5 days; 75% of patients (n=9/12) were able to successfully come off ventilator support at a median of 10 days. There have been 7 patients discharged from the hospital as of now.

PB1046

Physiology

PB1046 is a novel, once-weekly, subcutaneously-injected vasoactive intestinal peptide (VIP) receptor agonist that targets VPAC receptors in the cardiovascular, pulmonary and immune systems. VIP is a neurohormone known to have anti-inflammatory, antifibrotic, inotropic, lusitropic and vasodilatory effects and several cardiopulmonary disorders are associated with alterations in levels of VIP or its receptors, VPAC1 and VPAC2. Importantly, VIP has also been observed to have potent bronchodilatory and immunomodulatory effects in the respiratory system. Specifically, VIP has been shown to regulate proinflammatory cytokines including TNF- α , IFN- γ , IL-12, IL-17A and IL-6. In animal models, treatment with VIP peptide prevented acute lung injury and inhibited cytokine-mediated inflammatory responses that are characteristic of ARDS.

Recommendations

OSU does not routinely recommend PB1046 for patients with COVID-19. This would be done under the guidance of ID and would be in the setting of a clinical trial.

Evidence

The FDA has given the go ahead for a trial looking a PB1046 as a treatment to prevent progression to ARDS.

The VANGARD trial (VIP ANalogue, in hospitalized COVID-19 patients at hiGh risk for rapid clinical deterioration and ARDS) is a multi-center, randomized, double-blind, parallel group clinical trial that will assess the efficacy and safety of once-weekly subcutaneous injections of PB1046 in hospitalized COVID-19 patients at high risk for rapid clinical deterioration and ARDS. Approximately 210 patients will be targeted to be enrolled at approximately 20 sites nationwide. The primary endpoint will measure days alive and free of respiratory failure.

Having received FDA clearance to initiate the VANGARD trial, PhaseBio expects to begin dosing patients by the end of June. Subject to the pace of enrollment and any further impacts from the COVID-19 pandemic, PhaseBio is targeting to report trial results late in the fourth quarter of 2020. Based on feedback from the FDA, PhaseBio believes that positive, clearly interpretable and clinically meaningful results from this trial may enable PhaseBio to submit a Biologics License Application.

Dapagliflozin

Not used as a treatment for COVID-19, but presumed to favorably influence the underlying mechanistic processes dysregulated in the setting of acute illness, including effects on energy metabolism, autophagy, oxidative stress, and inflammation.

The DARE-19 trial will assess both the efficacy and the safety of dapagliflozin in this patient population in the closely monitored environment of a rigorously designed clinical trial aimed at identifying if dapagliflozin will prevent serious complications such as organ failure. The DARE-19 trial is designed to enroll 900 adults with confirmed SARS-CoV-2 infection and oxygen saturation of 94% or greater. (<https://www.clinicaltrials.gov/ct2/show/NCT04350593>)

This has generated a lot of controversy in the public, as many societies have given the advice to avoid oral medications, and primarily treat with insulin in the acutely ill COVID patient.

Tissue Plasminogen Activator (TPA)

Physiology

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.

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).

OSU Recommendations

Thromboprophylaxis with enoxaparin should be considered for patients in the usual doses. TPA is not recommended for the treatment of COVID, unless it is being used to treat other conditions in which TPA has a documented benefit (CVA, VTE, arterial occlusion).

gThere is some evidence to suggest higher intensity thromboprophylaxis in patients with COVID-19, but this will be determined by the physician providing care to the patient. Evidence is listed below.

Evidence

ARDS is a known risk for increased thrombogenicity. Coagulopathy in ARDS is thought to involve alveolar fibrin deposition, depressed fibrinolysis and activation of coagulation pathways by damage to the alveolar endothelium leading to exposure of tissue factor (Sebag SC, Bastarache JA, Ware LB. Therapeutic modulation of coagulation and fibrinolysis in acute lung injury and the acute respiratory distress syndrome. *Curr Pharm Biotechnol*. 2011;12(9):1481-1496. doi:10.2174/138920111798281171)

No trial in humans to date has reported a significant clinical benefit in ARDS, although there is research into inhaled therapies that have an anticoagulant activity. This emphasizes the use of avoiding systemic thrombolytics for the treatment of ARDS. (Camprubí-Rimblas M, Tantinyà N, Bringué J, Guillamat-Prats R, Artigas A. Anticoagulant therapy in acute respiratory distress syndrome. *Ann Transl Med*. 2018;6(2):36. doi:10.21037/atm.2018.01.08).

Evidence from an anticoagulation forum states that for all non-critically ill hospitalized patients (i.e., not in an ICU) with confirmed or highly suspected COVID-19, be started on a standard dose VTE prophylaxis as per existing societal guidelines for medically ill and surgical hospitalized patients. Dose adjustments for renal function or extremes of weight should follow product labeling and/or institutional protocols. (https://acforum-excellence.org/Resource-Center/resource_files/1549-2020-05-07-133522.pdf)

For critically ill patients (i.e., in an ICU) with confirmed or highly suspected COVID-19, there is some evidence to support increased doses of VTE prophylaxis (e.g., enoxaparin 40 mg subcutaneous twice daily, enoxaparin 0.5 mg/kg subcutaneous twice daily, heparin 7500 units subcutaneous three times daily, or low-intensity heparin infusion. This suggestion is based largely on expert opinion. Dose adjustments for renal function or extremes of weight should follow product labeling and/or institutional protocols. Individual hospitals should determine which regimens best align with institutional experience and workflow. Several examples of institutional protocols for COVID-19 are available for review and use within the Anticoagulation Forum's Centers of Excellence Resources Center (<https://acforum-excellence.org/Resource-Center/index.php>).

Nitric Oxide

Physiology: The anatomic target of inhaled nitric oxide (NO) is the vascular smooth muscle cells that surround the small resistance arteries in the lungs. As NO diffuses through the alveolar membrane, it reaches these smooth muscle cells, causing an increase in the levels of cyclic guanosine monophosphate that in turn sets off a chain of events resulting in the reduction of smooth muscle tone. Inhaled NO therapy is used in adult respiratory distress syndrome because it reduces pulmonary artery pressure and vasodilates the blood vessels in ventilated regions. This reduces the shunt fraction and simultaneously increases PaO₂.

OSU Recommendations:

Inhaled Nitric Oxide is not recommended for the treatment of COVID, unless it is recommended by pulmonology or if it is in the context of a clinical trial.

Evidence:

The FDA recently granted INOpulse emergency expanded access for the treatment of patients with COVID-19. The agency also recently accepted Bellerophon Therapeutics' investigational new drug application to initiate a phase 3 study of INOpulse, according to a company press release.

The ATS published a non-peer reviewed article on the use of Nitric Oxide to reduce shunting and increase PAO₂/FIO₂ ratio. This may be a promising treatment option for patients with COVID-19. (https://www.atsjournals.org/doi/pdf/10.1164/rccm.202004-0940LE?utm_campaign=ATS%20General&utm_medium=email&_hsmi=90669244&_hsenc=p2ANqtz-z1H1BVNjwgGwUJGAVUbKtzWMGdcudP4i1OA50Z2XXbl1auYLS7G8EZt56pRXSIN-p3Jbq8-yYUGZ_TuMiELQNZIRKdw&utm_content=90669244&utm_source=hs_email)

Vaccinations

An excellent website from the WHO has been released to show all the recent vaccines that are coming to the market and where they are in clinical phase trials:

<https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>

No current vaccines exist but are in active phases of development. Vaccines for human use will be instrumental but will take time to develop.

The FDA has also fast tracked two COVID-19 vaccination. https://www.contagionlive.com/news/fda-fast-tracks-2-covid19-vaccines?utm_medium=email&utm_campaign=7-13-20-CTGNE%20Coronavirus%20Update%20eNL&utm_content=7-13-20-CTGNE%20Coronavirus%20Update%20eNL+CID_1cc5c1d6f191da33d4d78cbb0a498adb&utm_source=CM%20Contagion&utm_term=FDA%20Fast%20Tracks%20%20COVID-19%20Vaccines

Preliminary results are available for a vaccine made from mRNA showing promising results. Forty-five patients, aged 18 to 55 years, received two vaccinations dosed 28 days apart in doses of 25 mcg, 100 mcg, and 250 mcg per dose. After the second dose, immune response was noted in all participants, with those in the upper half of the distribution showing similar immune reactions as to those who had received convalescent plasma. Adverse effects reported include fatigue, chills, headache, myalgia, and pain at the injection site. More systemic adverse effects were seen after the second dose in the highest dosage arm. (Jackson LA, et al. NEJM: DOI: 10.1056/NEJMoa2022483 [Epub ahead of print (July 14, 2020)]. Additional studies will look at adults over age 55. Phase II and III studies are already underway for this vaccine. (<https://www.nih.gov/news-events/news-releases/experimental-covid-19-vaccine-safe-generates-immune-response>)

Jackson et al - NEJM July 14 - mrna vaccine against sars-cov-2 prelim report - two vaccinations 28 days apart in a dose of 25, 100, 250 micrograms. All experienced seroconversion by day 15. 2 higher doses had responses similar to cpp. No SAE, 1 hives after dose 1. Systemic AE more common after 2nd dose and occurred in all pts receiving 250 mcg. One developed a fever. Phase 2 trial of this vaccine ongoing and phase 3 of 100 mcg dose expected this summer. An Mrna vaccine against sars-cov-2.

PiCoVacc: A purified inactivated SARS-CoV-2 virus vaccine candidate (PiCoVacc) confers complete protection in non-human primates against SARS-CoV-2 strains circulating worldwide by eliciting potent humoral responses devoid of immunopathology. <https://www.biorxiv.org/content/10.1101/2020.04.17.046375v1.full.pdf>

SARS-CoV-2 vaccines currently in clinical trials

Entity	Vaccine	Clinicaltrials.gov#	Stage	Phase
University of Oxford	ChAdOx1 nCoV-19	NCT04324606	Recruiting	Phase I
CanSino Biologics Inc.	Ad5 Vectors	NCT04313127	Active, not recruiting	Phase I
CanSino Biologics Inc.	Ad5 Vectors	NCT04341389	Recruiting	Phase II
Sinovac	Inactivated virus vaccine	NCT04352608	Recruiting	Phase I/II
Symvivo Corporation	Bifidobacterium vector	NCT04334980	Not yet recruiting	Phase I
NIAID	mRNA-1273	NCT04283461	Recruiting	Phase I
Inovio	DNA	NCT04336410	Recruiting	Phase I

<https://clinicaltrials.gov/ct2/show/NCT04352608?term=sinovac+covid19&draw=2&rank=1>

A new prototype DNA vaccines expressing various S immunogens and assessed protective efficacy against intranasal and intratracheal SARS-CoV-2 challenge in rhesus macaques is being investigated and shows some promise, with much further study needed to be completed. This is the second study that

looks at sustained responses in Rhesus monkey's, but the first to be looked at in relation to a vaccine. (<https://science.sciencemag.org/content/early/2020/05/19/science.abc6284>)

Llama Antibodies as a Possible Therapeutic Option?

Coronaviruses make use of a large envelope protein called spike (S) to engage host cell receptors and catalyze membrane fusion. Because of the vital role that these S proteins play, they represent a vulnerable target for the development of therapeutics. Here, we describe the isolation of single-domain antibodies (VHHs) from a llama immunized with prefusion-stabilized coronavirus spikes. These VHHs neutralize MERS-CoV or SARSCoV-1 S pseudotyped viruses, respectively. Crystal structures of these VHHs bound to their respective viral targets reveal two distinct epitopes, but both VHHs interfere with receptor binding. We also show cross-reactivity between the SARS-CoV-1 S-directed VHH and SARS-CoV-2 S and demonstrate that this cross-reactive VHH neutralizes SARS-CoV-2 S pseudotyped viruses as a bivalent human IgG Fc-fusion. These data provide a molecular basis for the neutralization of pathogenic betacoronaviruses by VHHs and suggest that these molecules may serve as useful therapeutics during coronavirus outbreaks.

The consideration would thus be given to prophylactic and therapeutic interventions because of their favorable biophysical properties and their potent neutralization capacity. MERS VHH-55, SARS VHH-72, and VHH-72-Fc may serve as both useful reagents for researchers and as potential therapeutic candidates. ([https://www.cell.com/cell/pdf/S0092-8674\(20\)30494-3.pdf](https://www.cell.com/cell/pdf/S0092-8674(20)30494-3.pdf))

OSU Recommendations:

There are no recommendations for this type of therapy. This is purely investigational at the molecular level.

Vitamin D

Physiology

Severe deficiency is defined as a serum 25(OH)D lower than 30nmol/L. Previous studies identified associations between higher levels of ACE2 and better coronavirus disease health outcomes. In the lung, ACE2 protects against acute lung injury. Calcitriol (1,25-dihydroxyvitamin D3) exerts pronouncedly impacts on ACE2/Ang(1-7)/MasR axis with enhanced expression of ACE2 which is being investigated in diseases and physiology. (<https://www.ncbi.nlm.nih.gov/pubmed/29351514>)

Recommendations

It is appropriate to check Vitamin D levels in the outpatient clinics and in the hospital and treat to guidelines. No recommendations for superphysiologic doses of vitamin D in the acutely ill patients should be made off of this study.

Evidence

CRP is a surrogate marker for severe COVID-19 and is associated with Vit D deficiency. A study in prepublication looked at the recovery and deceased rate data for patients with COVID-19 from countries with a large number of confirmed patients (Germany, South Korea (S. Korea), China (Hubei), Switzerland, Iran, UK, US, France, Spain, Italy) as of April 20, 2020 were used. The finding suggests that Vit D may reduce COVID-19 severity by suppressing cytokine storm in COVID-19 patients. Further research is needed to account for other factors through direct measurement of Vit D levels. This study needs further exploration. <https://www.medrxiv.org/content/10.1101/2020.04.08.20058578v3>

NICE states that vitamin D supplements are not specifically licensed for preventing or treating any infection, including the novel coronavirus infection that causes COVID-19. However there was inherent bias to this study that was admitted, although their rapid review summary did not show evidence to support Vitamin D supplementation as a means to prevent or treat COVID-19. <https://www.nice.org.uk/advice/es28/chapter/Key-messages>

Cardiology

Acute Cardiac Injury

Definition and incidence

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

Incidence: Incidence of 7-22% in hospitalized patients with COVID-19 in China (Ruan et al, *Intensive Care Med*, 2020; Wang et al, *JAMA*, 2020; Chen et al, *Lancet*, 2020; Shi et al, *JAMA Cardiology*, 2020; Guo 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)
 - a) Possible direct toxicity through viral invasion into cardiac myocytes (*i.e.*, myocarditis)
 - b) Acute coronary syndrome and demand ischemia
 - c) Stress cardiomyopathy (*i.e.*, Takotsubo's)
 - d) Myocardial suppression in the setting of profound inflammatory response/cytokine storm (Siddiqi & Mehra, *Journal Heart Lung Transpl*, 2020)

Time course and prognostic implication

- 1) Troponin rise and acute cardiac injury may be late manifestations of COVID-19.
 - a) Troponin increased rapidly from ~14 days from illness onset, after the onset of respiratory failure (Zhou et al, *Lancet*, 2020).
 - b) 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
 - a) ACI is higher in non-survivors (59%, n=32) than survivors (1%, n=1) (Zhou et al, *Lancet*, 2020).
 - b) ACI is higher in ICU patients (22%, n=22) compared to non-ICU patients (2%, n=2) (Wang et al, *JAMA*, 2020)
 - c) 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>

Consultation of Cardiovascular Medicine

Cardiology Consultation

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:**
 - a) All patients: check Trop, BNP and CPK on admission
 - b) Check 12 lead EKG on admission
 - c) Consideration for performing point-of-care US (POCUS) to assess for gross abnormalities in LV or RV function; upload to centricity/PACs
 - i) If either are abnormal, obtain virtual or bedside cardiology consultation. Consider formal echocardiogram in discussion with cardiology consultation.
 - ii) If no new ECG or echocardiographic abnormalities, continue to monitor Trop, BNP,
- 2) **Telemetry:**
 - a) 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.
 - b) If patients are receiving plaquenil, they should be on telemetry
 - c) For hospitals, with resource-limitations, telemetry is most important for patients who meet AHA criteria (Sandau et al, *Circulation*, 2017).
- 3) **ECGs:**
 - a) Daily ECGs are reasonable for individuals who are receiving treatment for COVID-19.
 - i) When possible, print ECGs from the in-room monitor to minimize contamination of equipment
- 4) **TTE:**
 - a) Do not order routine TTEs on COVID-19 patients.
 - b) Indications for POCUS:
 - i) Marked elevation in troponin or BNP
 - ii) Shock
 - iii) New heart failure (not pre-existing heart failure)
 - iv) New persistent arrhythmia
 - v) Significant ECG changes
 - c) 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)**
 - a) 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.
 - b) Specific considerations:

- i) 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.
- ii) TEE
 - (1) Only for absolute necessity
- iii) 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

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
 - a) Beta blockade if no evidence of heart failure or shock
 - b) If significant heart failure or borderline BPs, use amiodarone. There is no known increased concern for amiodarone lung toxicity
 - c) If unstable, synchronized DCCV with 200 Joules biphasic
- 2) Ventricular tachycardia (VT)
 - a) Unstable/pulseless: initiate ACLS
 - b) Stable:
 - i) **Cardiology consult** (may represent evolving myocardial involvement)
 - ii) Amiodarone 150mg IV x 1

Acute Coronary Syndromes

Incidence

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:
 - a) Coronary thrombosis
 - b) Demand-related ischemia
 - c) Myocarditis
 - d) Toxic myocardial injury (e.g. sepsis)
- 2) Determination of ACS will rely on all evidence available:
 - a) Symptoms (if able to communicate): New dyspnea, chest pain, anginal equivalents
 - b) Regional ECG changes
 - c) Rate of change of Troponin changes (*i.e.*, steep rise suggests ACS)
 - d) 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**

<https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2020/04/06/11/32/recommendations-from-the-peking-union-medical>

- 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.

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 catheterization cannot be performed)
 - a) If lytics infused, a safe and efficient medical environment should be ensured
 - b) Emergency intravenous thrombolysis is considered the first choice for acute ST-segment elevation myocardial infarction (STEMI)
 - i) 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*)
 - c) 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.

- d) Patients without thrombolytic contraindications should first start intravenous thrombolysis and then transfer to the local designated medical institution of infectious disease for further treatment.
- e) 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:
 - i) Monitor closely; conduct emergency coronary intervention immediately after elimination of COVID-19.
 - ii) 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.
- f) 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

One cross-sectional study showed a higher incidence of myocarditis as the etiology of cardiac biomarker elevation. This was detected by cardiac MRI, and scar from myocarditis may be permanent.

<https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.120.049252>

Myocarditis and pericarditis are potential manifestations of COVID-19 and source of Acute Cardiac Injury, based on case reports/case series (Ruan et al, *Intensive Care Med*, 2020; Zeng et al, *Preprints*, 2020; Hu et al, *Eur Heart J*, 2020; Inciardi et al, *JAMA Cardiology*, 2020). One case report had cMRI proven myocarditis and a concomitant reduction in LVEF to 35% with rapid resolution after antiviral treatment and systemic glucocorticoids (Inciardi, et al, *JAMA Cardiology*, 2020).

Workup

- 1) Likely no role for endomyocardial biopsy
- 2) Clinical surveillance and laboratory testing, including troponin levels, in individuals with recent symptoms of an acute illness to guarantee appropriate identification and prompt isolation of patients at risk of COVID-19 and eventually to reduce further transmission. (Inciardi RM, Lupi L, Zaccone G, et al. Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. Published online March 27, 2020. doi:10.1001/jamacardio.2020.1096)

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:**
 - a) 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:**
 - a) Patients rarely present in shock on admission
 - b) Natural history seems to favor the development of shock after multiple days of critical illness.
- 3) **Etiology:**
 - a) The range of reasons for shock is wide and more variable than for most patients and may include:
 - i) Myocardial dysfunction
 - ii) Secondary bacterial infection
 - iii) Cytokine storm

Workup

- 1) Assess for severity of **end organ damage:**
 - a) UOP, mental status, lactate, BUN/creatinine, electrolytes, LFTs
- 2) Obtain a **FULL infectious/ septic workup**, which includes all of the following:
 - a) 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
 - b) Portable CXR (avoid CT unless absolutely necessary)
 - c) Full skin exam
- 3) Assess for **cardiogenic shock**
 - a) Assess extremities: warm or cool on exam
 - b) Assess patient volume status: JVP, CVP, edema, CXR
 - c) 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)
 - d) Perform POCUS, if able, to assess for gross LV/RV dysfunction (upload to PACS/Centricity)
 - e) Labs: Obtain an SCV02 or MV02 if the patient has central access, troponin x2, BNP, lipid profile, TSH
 - f) EKG (and telemetry)
 - g) **Obtain cardiology consultation** if any suspicion of cardiogenic shock
- 4) Assess for **other causes of shock:**

- a) Vasoplegia:
 - i) Run medication list for recent cardiosuppressive medications, vasodilatory agents, antihypertensives
- b) Adrenal insufficiency:
 - i) Unless high pretest probability of adrenal insufficiency, we recommend against routine cortisol stimulation testing
- c) Obstruction:
 - i) 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>
 - ii) Tamponade (given elevated risk of pericarditis)
 - iii) Obstruction from PEEP
- d) Cytokine storm (see “Cytokine Activation Syndrome” section in this chapter below)
- e) Allergic reactions to recent medications
- f) Neurogenic shock is uncommon in this context
- g) Hypovolemia:
 - i) Bleeding
 - ii) Insensible losses from fever
 - iii) Diarrhea/vomiting

Differentiating Shock

The table below is a helpful tutorial.

Type of Shock	Cardiac Output	SVR	CVP/Wedge	ScvO₂, MvO₂	Other features
Cardiogenic	↓	↑	↑	↓	
Distributive (sepsis, cytokine, anaphylaxis)	↑	↓	↓	↑	
Obstructive	↓	↑	↑	↓	
Hypovolemic	↓	↑	↓	↓	
Neurogenic	↓	↓	↓ /normal	↓	Decreased HR

Septic Shock and Secondary Infections

Incidence

- 1) The reported rates of sepsis and septic shock are not reported consistently in currently available case series
- 2) Secondary bacterial infections are reported:
 - a) 20% of non-survivors (Zhou et al, *Lancet*, 2020)
 - b) 16% of non-survivors (Ruan et al, *Intensive Care Med*, 2020)
 - c) 12-19% In H1N1 epidemic (MacIntyre et al, *BMC Infect Dis*, 2018)

Management

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>)

Pressors and Fluid Management:

- 1) **Goal MAP > 65mmHg**
 - a) 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**
 - a) Start Norepinephrine while determining the etiology of undifferentiated shock <https://jamanetwork.com/journals/jama/fullarticle/2763879>
 - b) 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

Conservative fluid management:

- 1) **Do not give conventional 30cc/kg resuscitation**
 - a) 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](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30161-2/fulltext#fig2)
 - b) 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:**
 - a) Increase > 2 in CVP
 - b) Increase in MAP or decrease in pressor requirement

- i) 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**
- a) 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 <https://www.acep.org/how-we-serve/sections/critical-care-medicine/news/april-2016/tips-and-tricks-pulse-pressure-variation/>
 - b) 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/>
 - c) 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>
 - d) For further guidance, Conservative Fluid Management protocols are available from from FACCT Lite trial (Grissom et al, *Crit Care Med*, 2015).

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.
 - a) Mechanism is unknown, potentially direct viral toxicity, ACS, stress or inflammatory cardiomyopathy
- 2) **Incidence:**
 - a) Heart failure or cardiogenic shock **was observed**
 - i) 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),
 - ii) 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:**
 - a) Heart failure or myocardial damage **contributed to death**
 - i) 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:**

- a) 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):
 - a) Elevated BNP
 - b) 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:
 - a) 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)
 - b) Daily EKGs or prn with clinical deterioration
 - c) Trend troponin to peak

Management

- 1) Close collaboration with the **cardiovascular medicine consultation service** is recommended. Consideration for pulmonary artery catheter placement.
 - a) Goals: MAPs 65-75, CVP 6-14, PCWP 12-18, PAD 20-25, SVR 800-1000, SCvO₂ > 60%, CI > 2.2
 - i) Note: Achieving MAP goal is first priority, then optimize other parameters
 - b) How to achieve goals:
 - i) Continue titration of norepinephrine gtt for goal MAP 65-75
 - ii) Initiate diuretic therapy for CVP > 14, PCWP >18, PAD > 25
 - iii) 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.
 - iv) 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:
 - a) Dobutamine gtt at 5mcg/kg/min (or unable to tolerate dobutamine due to tachyarrhythmias) and ScvO₂ < 60% or CI < 2.2
 - b) 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.

- a) Consideration for ECMO consultation for cardiogenic shock can be considered if the following are met
 - i) Younger age
 - ii) Expected life expectancy >6 months pre-hospitalization
 - iii) No evidence of solid or liquid malignancy
 - iv) Able to tolerate anticoagulation
 - v) Platelets >50,000
 - vi) Absence of severe peripheral arterial disease
 - vii) No evidence of irreversible neurological injury
 - viii) Able to perform ADLs at baseline prior to illness
 - ix) 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 secondary HLH (Mehta et al, *Lancet*, 2020).
 - a) Patients who had cytokine activation developed rapid progression to ARDS, shock, and multiorgan failure (Chen et al, *Lancet*, 2020)
- 2) Pathophysiology:
 - a) 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)
 - b) Similar patterns of cytokine storm and ARDS have been seen with SARS, MERS (Kim et al, *J Korean Med Sci*, 2016)
 - c) 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)
 - d) An editorial in JAMA has an interesting perspective on cytokine storm in patients with COVID, and indicate that too much stock may be put into monitoring inflammatory markers as well as developing targeted treatments for individual components. They see little difference between the well established systemic inflammatory response syndrome. They believe the current data does not support its use as a definition or a target and believe that until new data establish otherwise, the linkage of cytokine storm to COVID-19 may be nothing more than a tempest in a teapot. <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2767939>

Workup

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)
 - a) CRP seems to correlate with disease severity and prognosis of COVID-19 (Ruan et al, *Intensive Care Med*, 2020; Young et al, *JAMA*, 2020)

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

Management

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:
 - a) 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:
 - a) Use an automated compression device where available to minimize personnel.
 - b) If not available, minimize the number of individuals doing compressions
- 3) Prepare code equipment:
 - a) 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.
 - b) Use of video laryngoscopy should be primary mode of intubation

Early goals of care conversations

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

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

2) Circulation

- a) 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).
- b) If patient has shockable rhythm (VF/VT), defibrillate as soon as possible.

3) Airway

a) Initial Airway Management, Prior to Intubation:

- i) 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.
- ii) Prior to securing a definitive airway, oxygen should be applied via a non-rebreather mask at 15L/min without humidification
- iii) Avoid BVM ventilation, high-flow nasal cannula, and non-invasive ventilation (CPAP, BiPAP) to minimize aerosolized virus (Cheung, *Lancet Resp Med*, 2020; Tran et al, *PLoS One*, 2012).
- iv) If passive oxygen is not available, place a surgical face-mask and a blanket over the patient's face prior to chest compressions.
- v) If the patient does not have a shockable rhythm, proceed with Rapid Sequence Intubation as early as possible to limit aerosolization

b) Endotracheal Intubation

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

- iii) If the pause in chest compressions is excessive and endotracheal intubation does not seem likely, consider LMA or other extraglottic airway device.
- iv) Code responders should distance themselves from the head of the bed during the intubation procedure (6 ft. distance).
- v) Continuous capnography device should be used to monitor ventilation (Cheung, *Lancet Resp Med*, 2020).
- vi) 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

- a) Data from a retrospective study in Wuhan (Ruan et al, *Intensive Care Med*, 2020) revealed cause of death to be:
 - i) Respiratory failure (53%)
 - ii) Heart failure with respiratory failure (33%)
 - iii) Myocardial damage (7%)
 - iv) Unknown cause (7%)
- b) It is important to attempt to identify and treat reversible causes (5H's, 5T's) before stopping the code.

5) Terminating Resuscitative Efforts

- a) Avoid prolonged resuscitation if there is no easily reversible etiology identified.
- b) 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.
- c) 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

- a) Dispose of, or clean, all equipment used during CPR. Any work surfaces used for airway/resuscitation equipment will also need to be cleaned.
- b) After the resuscitation has ended adhere to strict doffing procedure to limit exposure.
- c) 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

Evidence:

- 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]).
- 3) 31% incidence of thrombotic complications in ICU patients with COVID-19 infections is remarkably high. Our findings reinforce the recommendation to strictly apply pharmacological thrombosis prophylaxis (<https://www.sciencedirect.com/science/article/pii/S0049384820301201>)
- 4) In a study published in NEJM, most patients with Covid-19 who were admitted to the hospital with a prolonged aPTT were positive for lupus anticoagulant (91%) and often had an associated factor XII deficiency. Factor XII is not required for hemostasis, and the presence of lupus anticoagulant, if persistent, can be associated with a thrombotic tendency within the antiphospholipid syndrome. They recommend further study to determine the role, if any, of lupus anticoagulant in the pathogenesis of Covid-19 thrombosis. Heparin was detected in 28 of the 35 specimens, the DRVVT assay contains heparinase, which neutralizes any heparin effect that might lead to false positive detection of lupus anticoagulant

Pathophysiology:

- 1) The mechanism for VTE are unknown and likely multifactorial:
 - a) Systemic inflammatory response as seen in sepsis
 - b) Stasis/critical illness
 - c) 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.
 - a) 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
 - a) If CrCl > 30: Lovenox 40 mg SC daily
 - b) If CrCl < 30 or AKI: Heparin 5000 units SC TID
 - c) 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).

- 4) Based on findings from the 5.2020 NEJM study, patients who have a prolonged PTT should not be automatically considered to have a higher bleeding risk and have anticoagulation, particularly thromboprophylaxis, withheld. This should also be looked at closely for patients who develop VTE, and should not be a criteria to not anticoagulate.
- 5) An anticoagulation forum does not suggest universal thromboprophylaxis on patients being discharged to home, but particular situations may warrant consideration that will have to be individualized based on the patient's clinical condition and provider recommendations. If it is chosen, the recommendations are for use with betrixaban, rivaroxaban or enoxaparin. (https://acforum-excellence.org/Resource-Center/resource_files/1549-2020-05-07-133522.pdf)
 - a) Choosing who may be considered for extended anticoagulation is based on previous data collected from non-COVID studies (<https://covid19treatmentguidelines.nih.gov/antithrombotic-therapy/>)
 - i) Modified IMPROVE-VTE score ≥ 4 ; *or*
 - ii) Modified IMPROVE-VTE score ≥ 2 and D-dimer level > 2 times the upper limit of normal; *or*
 - iii) Age ≥ 75 years; *or*
 - iv) Age > 60 years and D-dimer level > 2 times the upper limit of normal; *or*
 - v) Age 40 to 60 years, D-dimer level > 2 times the upper limit of normal, and previous VTE event or cancer.

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

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.

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

Prognosis

Higher D-dimer and FDP levels track with multi-organ dysfunction syndrome and poorer prognosis (Wang et al, *JAMA*, 2020; Zhou et al, *Lancet*, 2020).

Disseminated Intravascular Coagulation (DIC)

Incidence/pathophysiology

- 1) Limited data: 16 of 183 hospitalized patients in Wuhan had DIC (Tang et al, *J Thromb Haemost*, 2020).
- 2) Laboratory changes in coagulation parameters and FDP track with multi-organ dysfunction (Zhou et al, *Lancet*, 2020).

Time course

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:
 - a) If fibrinogen < 150: FFP, cryoprecipitate or fibrinogen concentrate
 - b) Transfuse platelets if < 30K
 - c) Consider holding anticoagulation if the patient requires blood products for supportive care, though clinician should weigh risks and benefits.
- 2) If bleeding, give blood products:
 - a) For elevated PT/PTT and bleeding, use FFP or 4F-PCC
 - b) Hold anticoagulation for active bleeding.
- 3) Start systemic anticoagulation only if:
 - a) Overt thromboembolism or organ failure due to clot (*i.e.*, purpura fulminans)
 - b) There has been no mortality benefit of therapeutic anticoagulation in DIC (Levi et al, *Blood*, 2018).

Prognosis

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).

Blood Type and Affect on COVID

There has been much debate on blood type and its impact on COVID-19. A study looking at 1,980 patients with Covid-19 respiratory failure at seven centers in the Italian and Spanish epicenters of the SARS-CoV-2 pandemic in Europe found that two human gene variants that could make people more susceptible to lung failure associated with COVID-19. One variant lies in the swathe of the genome that determines blood groups. A follow-up analysis found that people with blood type A+ had an increased risk of lung failure compared with those with other blood types, whereas those with type O blood were protected to some extent. The study flagged a second variant, on chromosome 3, that is near six genes, including one that interacts with the molecular receptor the virus uses to enter human cells. (<https://www.medrxiv.org/content/10.1101/2020.05.31.20114991v1>)

Challenging the findings that blood types are associated with protective effects or increased effects of developing severe COVID, Dr. Poland encourages people to look at the findings published with a sense of biologic plausibility but understand that findings need to be confirmed through studies that can more precisely account for a variety of statistical and clinical factors. <https://www.healio.com/news/primary->

Blood Products

Red blood cells

- 1) Restrictive transfusion strategy (Hct > 21, Hgb > 7) is recommended.
 - a) If hemodynamically stable, transfuse 1 unit at a time and reassess needs.
 - b) Transfusion thresholds for pRBCs are recommended as follows:
 - i) Acute coronary syndrome: consider transfusion for Hgb < 10.
 - ii) Oncology patients: transfuse for Hgb < 7.
 - iii) All others: transfuse for Hgb < 7.
- 2) Parsimony is encouraged given:
 - a) Limited supply (blood drives are limited by social distancing).
 - b) Volume overload is of particular concern in COVID patients.
 - i) Randomized controlled trials of ICU patients have shown that a conservative transfusion strategy (Hgb > 7) is associated with less pulmonary edema, fewer cardiac events and no evidence of harm compared to a liberal transfusion strategy (Hébert et al, *N Engl J Med*, 1999; Holst et al, *N Engl J Med*, 2014; Gajic et al, *Crit Care Med*, 2006).

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:

<i>Procedure or trauma scenario</i>	<i>Platelets</i>	<i>FFP or 4F-PCC</i>	<i>Notes</i>
Central venous catheter	Transfuse for plt < 10 K	Transfuse if INR > 3	Avoid subclavian
Arterial line	Transfuse for plt < 10 K	Transfuse if INR > 3	
Lumbar puncture	Transfuse for plt < 50 K	Transfuse if INR > 1.4	
Trauma, no intracranial bleed	Transfuse for plt < 50 K	Transfuse if INR > 2	
Trauma with intracranial bleed	Transfuse for plt < 75 K	Transfuse if INR > 1.7	

Blood donation

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.

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.
 - a) 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).
 - b) A study in the NEJM found three of 6 patients with a detectable SARS-CoV-2 viral load in all kidney compartments examined, with preferential targeting of glomerular cells
 - i) This suggests that renal tropism is a potential explanation of commonly reported new clinical signs of kidney injury in patients
<https://www.nejm.org/doi/full/10.1056/NEJMc2011400?query=TOC>

Workup:

- 1) Monitor Creatinine at least daily
 - a) Studies find variable onset of AKI, from 7 days (Cheng et al, *medRxiv*, 2020 preprint) to 15 days after illness onset (Zhou et al, *Lancet*, 2020). Onset of AKI more rapid and severe in patients with underlying CKD (Cheng et al, *medRxiv*, 2020 preprint)
- 2) If evidence of rising BUN and/or creatinine, order urinalysis
 - a) Patients may present with proteinuria (44%), hematuria (26.9%)
[https://www.kidney-international.org/article/S0085-2538\(20\)30255-6/pdf](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
 - a) Do not wait until need for RRT (renal replacement therapy)/dialysis for consultation.
- 2) Managing AKI:
 - a) Minimize nephrotoxic agents
 - b) 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%
 - a) 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
 - a) Indications for dialysis in COVID-19 patients are the same as the indications for all patients.

Prognosis

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

- b) 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).
- c) 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

ACE2 was identified as the functional receptor for SARS-CoV-2, which is present in multiple human organs, including nervous system and skeletal muscles. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCoV. *bioRxiv*. 2020. doi:[10.1101/2020.01.26.919985](https://doi.org/10.1101/2020.01.26.919985)

According to an article published in SAGE journals, patients with COVID-19 have a high risk of developing acute stroke. The reasoning as to why, remains unclear. This may be secondary to hypercoagulability. In patients with COVID, there is a relatively high concentration of inflammation and hypercoagulability markers such as CRP and D-Dimer. These are not contraindications to rt-PA, but previous studies show that patients with acute ischemic stroke without COVID-19 demonstrate a higher rate of death and disability post thrombolytic ICH. <https://journals.sagepub.com/doi/10.1177/1747493020923234>

Preliminary clinical data indicate that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with neurological and neuropsychiatric illness according to a multi-disciplinary meeting was established at the National Hospital, Queen Square, in early March 2020. The high incidence of acute disseminated encephalomyelitis, particularly with haemorrhagic change, is striking. This complication was not related to the severity of the respiratory COVID-19 disease. Early recognition, investigation and management of COVID-19-related neurological disease is challenging. Further clinical, neuroradiological, biomarker and neuropathological studies are essential to determine the underlying pathobiological mechanisms, which will guide treatment. Longitudinal follow-up studies will be necessary to ascertain the long-term neurological and neuropsychological consequences of this pandemic. <https://academic.oup.com/brain/article/doi/10.1093/brain/awaa240/5868408>

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>

One case of Guillain 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](https://doi.org/10.1016/S1474-4422(20)30109-5)

A small study reviewing autopsies in patients in Germany suggest pronounced CNS involvement with pan-encephalitis, meningitis, and brainstem neuronal cell damage were key events in all our cases. In patients younger than 65 years, CNS haemorrhage was a fatal complication of COVID-19.

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31282-4/fulltext?dgcid=raven_jbs_etoc_email](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31282-4/fulltext?dgcid=raven_jbs_etoc_email)

Some concerns expressed in a letter *International Journal of Audiology*, add to a growing body of anecdotal evidence that SARS-CoV-2 has long term impacts on hearing. They caution their review in June identified reports of hearing loss and tinnitus, but there were only a small number of studies and the quality of evidence was low. <https://www.sciencefocus.com/news/more-than-1-in-10-report-post-covid-19-hearing-deterioration/>

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

<https://jamanetwork.com/journals/jamaneurology/fullarticle/2764549>

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 <https://pubs.rsna.org/doi/10.1148/radiol.2020201187>

Although MRI may detect these findings, guidance from the ACR does not support MRI as a tool to diagnose COVID-19. The American College of Radiology (ACR) recommends that practitioners minimize the use of MR except where absolutely necessary, and postpone all non-urgent or non-emergent exams. In some cases, the use of alternative imaging methods such as point of care or portable imaging may be appropriate. As with all imaging, the impact of the results of the imaging must potentially affect imminent clinical management.

https://www.diagnosticimaging.com/covid-19/avoid-mri-scans-covid-19-patients-unless-necessary?rememberme=1&elq_mid=11565&elq_cid=954218&GUID=21E05F1B-7AE4-481B-9684-C96AE2BCD7EA

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/>

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>

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.iwatch.org/na51324/2020/04/09/gastrointestinal-aspects-covid-19>

Of those with GI symptoms, typical complaints include:

- 1) Anorexia (seen in 78-98% of those with gastrointestinal symptoms)
- 2) Diarrhea (seen in 34-37% of those with gastrointestinal symptoms)
- 3) High volume or clinically severe diarrhea is not common
- 4) Nausea (seen in 73% of those with gastrointestinal symptoms)
- 5) Vomiting (seen in <5-65% of those with gastrointestinal symptoms)
- 6) Abdominal pain (seen in <5-25% of those with gastrointestinal symptoms)
- 7) Sources: ([Luo et al, Clinical Gastroenterology and Hepatology, 2020](#); [Pan et al, The Am. J. Gastroenterol, 2020](#))

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.

It is not necessary to immediately test every individual for COVID with GI complaints.

Management

Symptomatic Treatment

Primary focus is to ensure adequate hydration

Nausea: Ondansteron, Metoclopramide (Caution for increasing QT prolongation with select antiemetics)

Diarrhea: Loperamide

Abdominal Discomfort: Consideration for antacids including H2 blockers

Consideration for H2 blocker over PPI in patients that have GERD. This was based on a study that may show an increased risk of COVID positivity for those that are on chronic PPI therapy. This may be linked to intragastric pH. 3,386 (6.4%) participants reported a positive COVID-19 test (Table 1). In multivariable regression analysis, PPI use was independently associated with increased odds for reporting a positive test, even after adjusting for a wide range of sociodemographic, lifestyle, and clinical variables. ([https://journals.lww.com/ajg/Documents/AJG-20-1811_R1\(PUBLISH%20AS%20WEBPART\).pdf](https://journals.lww.com/ajg/Documents/AJG-20-1811_R1(PUBLISH%20AS%20WEBPART).pdf))

Investigators suggest that taking PPIs once daily increases your risk for COVID-19 by twofold, whereas taking them twice daily can increase your risk by over three and a half fold. Coronavirus sheds into saliva and can rapidly invade and replicate within cells lining the intestinal tract. As stomach acid can be protective against acquisition of coronavirus, and certainly PPIs induce hypochlorhydria, this can facilitate an environment in which coronavirus may thrive. This was part of the biological plausibility for why PPIs can increase the risk for COVID-19 acquisition.

<https://www.medscape.com/viewarticle/934332>

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

Liver disease

Overview

1) Incidence:

- a) The incidence of direct hepatic injury is confounded by pre-existing liver disease, drug-induced liver injury, and shock
 - i) The only reported post-mortem liver biopsy from a patient with COVID-19 showed only microvesicular steatosis, a common finding in sepsis
- b) Up to 53% of patients have abnormal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [Zhang et al, *Lancet Gastroenterol Hepatol*, 2020].
 - i) 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].
- c) Bilirubin and alkaline phosphatase tend to be spared, bilirubin more so than alkaline phosphatase (both < 10%)
 - i) 54% of patients hospitalized for COVID-19 at a single center in China had elevated gamma-glutamyl transferase (GGT).

2) Clinical course:

- a) In general, liver injury in mild COVID-19 disease is transient and self-resolving. However, liver injury correlates with severity
 - i) ALT > 40 is associated with higher odds of in-hospital death (Zhou et al, *Lancet*, 2020).

- ii) 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).
- b) Acute liver failure has not been reported [Ong et al, *BMJ*, 2020].

3) Pathophysiology:

- a) Possible mechanisms of liver injury include:
 - i) 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].
 - ii) Drug hepatotoxicity
 - iii) Hepatic congestion (impaired venous return and elevated RAP associated with high levels of PEEP)
 - iv) 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].
 - (2) Besides, SARS patients with HBV/HCV infection were more prone to develop liver damage and severe hepatitis, which is probably due to enhanced replication of hepatitis virus during SARS-CoV infection Huang Y, Gao Z. Study of the relationship SARS and hepatitis virus B *Chin J Clini Hepatol*. 2003;6:342-343

Workup

- 1) Baseline CK, LDH, LFT's, INR
- 2) If normal LFTs on presentation, monitor LFTs every third day
 - a) 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.
- 4) Consideration for Hepatitis serology given worsening with concomitant infection

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.
 - a) N-Acetyl-Cysteine is not recommended at this time due to significant volume load. If worsening condition, it is reasonable to consult with hepatology at Integris

Oncology

General Management

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>
- 3) In contrast to recent studies, the largest cohort presented so far of cancer patients with coronavirus disease 2019 (COVID-19) has concluded that recent chemotherapy use is not a significant contributor to more severe disease or a predictor of death from COVID-19. Moreover, there were similar observations for immunotherapy, hormonal therapy, targeted therapy and radiotherapy. ([https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31173-9/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31173-9/fulltext))

Oncology Consultation/Coverage:

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

Prognosis:

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.

Meds:

Ensure that an appropriate medication reconciliation for immunosuppressive medications

Workup:

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).

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.

Pain management:

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.

Goals of Care:

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

Anticoagulation:

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

Transfusions:

- 1) If a transfusion is needed, suggest using irradiated, leukoreduced CMV negative blood
- 2) See "Blood Transfusions" section for additional details

Patient	DVT ppx	Transfusion Thresholds <i>Transfuse 1 unit at a time</i>			
		RBC	Platelets	Cryo	FFP
No bleeding, Plts > 30k	LMWH daily or SC UFH TID	Hgb < 7 <i>If ACS, ** Hgb > 10</i>	n/a	Fibrinogen < 100	INR > 10
No bleeding, but patient requires anticoagulation	Heparin gtt <i>PTT goal depends on indication</i>		Plts < 30k		
No bleeding, Plts < 30k	SCDs* <i>Hold pharmacologic</i>		Plts < 10k		
Mild Bleeding, Rigors, or Minor Procedures (<i>a-lines, CVCs</i>)	<i>Continue pharmacologic ppx in most patients</i> SCDs* if not using pharmacologic		Plts < 20k	INR > 3	
Serious Bleeding [#] or Major Procedure (<i>includes LP</i>)	+ SCDs* <i>Hold pharmacologic if able</i>	Transfuse for active bleeding	Plts < 50k or higher	INR > 1.5	

* SCDs = sequential compression devices

** ACS = Acute Coronary Syndrome

Febrile Neutropenia

Definition:

ANC < 500 cells/mm³ AND T ≥ 100.4F

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
 - a) Continue DAILY blood cultures while febrile.
 - b) Monitor serum galactomannan and 1-3-beta glucan once weekly.

Initial Empiric Antibiotics:

- 1) Cover GNRs in all patients: Ceftazidime 2g Q8h or Cefepime 2g Q8h
 - a) 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.

Removal of lines:

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.

Persistent Neutropenic Fever:

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).

Anti-infective course:

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

Overview

Immune Checkpoint Inhibitors (ICIs) are not immunosuppressive when used alone, but the steroid dosages used to treat immune toxicities are often immunosuppressive.

Most common ICIs are CTLA-4 inhibitor (ipilimumab) and PD-1/PD-L1 inhibitors (pembrolizumab, nivolumab, durvalumab, atezolizumab and avelumab).

Immune toxicity

- 1) If patient develops organ dysfunction, it may be due to immune toxicity
 - a) 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.

- a) Check TSH, ACTH, cortisol if hypotension or concern for endocrine dysfunction.
- 3) Immune toxicities are usually treated with high dose steroids
 - a) 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%).

<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>

ENDOCRINE

Diabetes

In a letter to the editor in NEJM, there is a suggestion that there is a link to the development of diabetes as a result of SARS COV-2. However, more exploration to this needs to be conducted. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes Covid-19, binds to angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed in key metabolic organs and tissues, including pancreatic beta cells, adipose tissue, the small intestine, and the kidneys.⁴ Thus, it is plausible that SARS-CoV-2 may cause pleiotropic alterations of glucose metabolism that could complicate the pathophysiology of preexisting diabetes or lead to new mechanisms of disease.

<https://www.nejm.org/doi/full/10.1056/NEJMc2018688>

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:
 - a) Disposable hair bouffant or cap
 - b) Eye protection (face shield only vs face shield AND protective eyewear)
 - c) Either N95 or PAPR (N95 + hood for neck protection)
 - d) Fluid resistant gowns (blue impermeable)
 - e) Double gloves
 - f) Leg protection (boot covers) to below the knee

PPE for Perioperative Anesthesia Intubations

Unknown Status/Not Suspected (i.e. outpatient laparoscopic appendectomy):

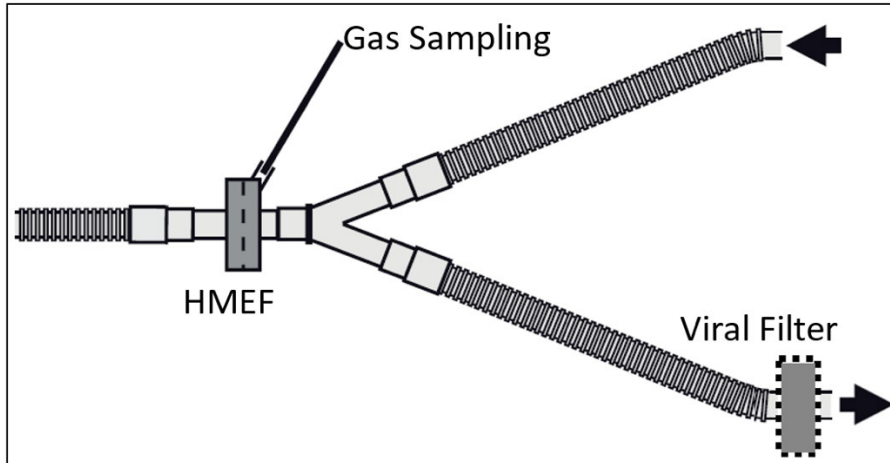
- 1) If possible, screen patients for: fever, sore throat, cough, runny nose or nasal congestion, loss of sense of smell, muscle aches, shortness of breath. At this time treat all patients as COVID positive unless they have definitive testing that suggests otherwise.
 - a) If the patient has any of these symptoms or cannot provide a history: Defer the procedure until symptoms resolve and consider COVID-19 testing
 - b) 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:**
 - a) 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
 - b) 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



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

2) ICU Ventilator set up:

- a) Place HEPA filter between patient and EtCO₂ monitor to avoid contaminating sample line(mandatory)
- b) If available, place HEPA filter on expiratory limb closest to the ventilator (preferred)
- c) 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

Use of Anesthesia Machine for Prolonged ICU Ventilation

<https://www.asahq.org/in-the-spotlight/coronavirus-covid-19-information/purposing-anesthesia-machines-for-ventilators>

In the event of shortage of ICU ventilators, anesthesia machines may be used for prolonged ICU ventilation(ASA/ASPF Ventilator Guidance)

A quick reference sheet to set up and monitor a repurposed anesthesia machine are provided(ASA/ASPF Quick Setup Instructions) <file:///Users/mousumisom/Downloads/Quick%20Reference.pdf>

Intubation in Operating Room (COVID positive or suspected)

Preparation

- 1) 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 Ensure OR is set to be on negative pressure

- a) Hang signage to prevent unnecessary entry
- 2) 3-person team (or 2-person team with one anesthesiology attending and one resident) is the preferred method:
 - a) Intubator - most senior provider, will manipulate airway *only*
 - b) "Clean anesthesia provider" will manipulate anesthesia machine, administer medications, chart, and read checklists
 - c) Circulating RN/resident as assistant to intubator. If this is the case, this will remove the RN from direct exposure.
- 3) Perform routine anesthesia machine check and pre-induction checklist:
 - a) consider removing all medications you may need for **entire case** to minimize omnicell contamination/movement in and out of room
- 4) Gather supplies:
 - a) 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
- 5) Position equipment:
 - a) video laryngoscope plugged in and working within reach
 - b) trash cans open and near table

Procedure

- 1) Personal Protective Equipment:
 - a) don appropriate PPE via "read/do" checklist prior to entering OR
- 2) Transition patient to OR oxygen delivery
 - a) Move patient to OR table
 - b) 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
 - c) The "clean anesthesia provider" ensures APL at "zero" and all flows "OFF"², remove patient facemask and immediately use 2-hand technique to place circuit face mask on patient
- 3) Preoxygenate:
 - a) 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:
 - a) "Clean anesthesia provider" will push RSI medications once preoxygenation is complete.
 - b) 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
 - c) "Clean anesthesia provider" turns off gas flows
 - d) Intubating provider disconnects facemask and place next to patient's head, and uses video laryngoscopy to intubate patient
- 5) After successful intubation
 - a) Circulating RN/resident pulls stylet, intubating anesthesia provider occludes end of ETT with finger, circulating RN/resident inflates cuff, and then connects circuit
 - b) "Clean anesthesia provider" turns on gas flows and ventilator and confirms EtCO₂(gold standard > 3 breaths with consistent waveform and value)
 - c) Intubator monitors for bilateral chest rise and "fogging" of ETT
 - i) avoid listening to breath sounds as can cause contamination of providers
 - d) Circulating RN/resident will take control of ETT while the intubating provider tapes

- e) Intubator will place OG tube, temperature probe, eye protection and bite block
 - f) "Clean anesthesia provider" will start appropriate anesthetic i.e. inhaled volatile vs TIVA and chart as needed
- 6) Clean equipment:
- a) 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:
 - a) <0.4 FiO₂
 - b) chemical paralysis reversed
 - c) maintaining adequate minute ventilation and tidal volumes with minimal support (i.e. PSV 5/5)
 - d) hemodynamically stable
 - e) 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
 - i) Screening and surveillance via upper and lower end endoscopy should be postponed <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>
 - ii) 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.

CMS has also issued guidance. Not only is delay of elective surgeries to minimize ongoing risks, it is also to conserve PPE, beds and ventilators. <https://www.cms.gov/files/document/cms-non-emergent-elective-medical-recommendations.pdf>

An article published in Lancet suggests that surgery may accelerate the development of COVID symptoms. Individuals in this study received “elective surgery,” in the likely incubation period and had a rapid development of SARSs-COV2 findings suggesting that caution needs to be taken when dealing with surgical decisions. Criticisms include a small retrospective trial. [https://www.thelancet.com/pdfs/journals/eclinm/PIIS2589-5370\(20\)30075-4.pdf](https://www.thelancet.com/pdfs/journals/eclinm/PIIS2589-5370(20)30075-4.pdf)

An additional study published by the Lancet supports increased risk of post-pulmonary complications. just over half of patients with perioperative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection went on to develop at least one pulmonary complication within 30 days of their procedure. In addition, pulmonary complications were experienced by over 80% of patients who died in the study. ([https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31182-X/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31182-X/fulltext))

Plan on reopening Surgical Service Lines as a joint statement by the American College of Surgeons, American Society of Anesthesiologists, Association of peri-Operative Registered Nurses and the American Hospital Association:

<https://www.asahq.org/about-asa/newsroom/news-releases/2020/04/joint-statement-on-elective-surgery-after-covid-19-pandemic>

The above link describes the following:

1. Timing for Reopening of Elective Surgery
2. COVID-19 Testing Within a Facility
3. Personal Protective Equipment

4. Case Prioritization and Scheduling **S**
5. Post-COVID-19 Issues for the Five Phases of Surgical Care
6. Collection and Management of Data
7. COVID-related Safety and Risk Mitigation surrounding Second Wave
8. Additional COVID-19 Related Issues

Pediatrics

In a study published in Emerging Infectious Disease, there was evidence that suggested that household transmission of SARS-CoV-2 was highest from ages 10-19. This may have implications for schools re-opening and strategies to take to mitigate risk. https://wwwnc.cdc.gov/eid/article/26/10/20-1315_article

Coronavirus in Children and Transmission

Study suggesting that children develop symptoms after or concurrent with adult HHCs, suggesting that the child was not the source of infection and that children most frequently acquire COVID-19 from adults, rather than transmitting it to them.

<https://pediatrics.aappublications.org/content/early/2020/07/08/peds.2020-004879>

Coinfection and other Clinical Characteristics of COVID-19 in Children

<https://pediatrics.aappublications.org/content/146/1/e20200961?cct=2287>

COVID-19 Transmission and Children: The Children are Not to Blame

<https://pediatrics.aappublications.org/content/pediatrics/early/2020/05/22/peds.2020-004879.full.pdf>

Coronavirus disease 2019: Clinical Manifestations and Diagnosis

“limited evidence suggests that transmission by children is uncommon”

<https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-clinical-manifestations-and-diagnosis-in-children>

Covid-19 in Children: The link in the transmission chain

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7156154/>

Fecal-oral transmission of sars-cov-2 in children

<https://www.cebm.net/study/covid-19-fecal-oral-transmission-of-sars-cov-2-in-children/>

Children may play a major role in community-based viral transmission.

<https://pediatrics.aappublications.org/content/early/2020/03/16/peds.2020-0702.1>

Multisystem inflammatory syndrome related to COVID-19

AAP releases new interim guidance on multi-system inflammatory syndrome in children

<https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/faqs-management-of-infants-born-to-covid-19-mothers/>

American College of Rheumatology Clinical Guidance for Pediatric patients with MIS-C

<https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-C-Hyperinflammation.pdf>

Pediatric Clinical Characteristics and Outcomes with COVID-19

Characteristics and Outcomes of Children with Coronavirus disease 2019 (COVID 19) Infection Admitted to US and Canadian Pediatric Intensive Care Units

Lara S. Shekerdemian, MD, MHA; Nabihah R. Mahmood, MD; Katie K. Wolf, MD; et al. *JAMA Pediatr.* Published online May 11 2020. doi:10.1001/jamapediatrics.2020.1948
<https://jamanetwork.com/journals/jamapediatrics/fullarticle/2766037>

Ask The Expert: What Are the Presenting Signs and Symptoms in Children with Confirmed COVID-19 disease? H Cody Meissner, MD, FAAP
<https://www.aappublications.org/news/2020/05/11/covid19askexpert051120>

Case studies suggest that children are less commonly and less severely affected by SARS-CoV-2 in comparison with adults.

Zimmermann, Petra MD, PhD*,†,‡; Curtis, Nigel FRCPCH, PhD†,‡,§ Coronavirus Infections in Children Including COVID-19, *The Pediatric Infectious Disease Journal*: May 2020 - Volume 39 - Issue 5 - p 355-368
doi: 10.1097/INF.0000000000002660
https://journals.lww.com/pidj/Fulltext/2020/05000/Coronavirus_Infections_in_Children_Including.1.aspx)

Children are not as adversely affected by COVID than adults. Epidemiological Characteristics of 2143 Pediatric Patients with 2019 Coronavirus Disease in China.
<https://www.aap.org/en-us/about-the-aap/aap-press-room/Pages/Children-with-COVID-19-Impacted-Less-Severely-Than-Adults-Study.aspx>

An article in JAMA explores why children may be less affected than adults, and finds that it may be related to the nasal ACE 2 levels which are much lower in children < 10, but then increased after 10. The importance of nasal ACE 2 levels could suggest that this a target in treatment in the future and is being investigated further. <https://jamanetwork.com/journals/jama/fullarticle/2766522>

Treatment for COVID-19 in Children

Covid 19 Treatment Guidelines

<https://www.covid19treatmentguidelines.nih.gov/overview/children/>

CHKD Treatment Guideline

<https://www.chkd.org/uploadedFiles/Documents/COVID-19/CHKD%20COVID%2019%20treatment%20guideline.pdf>

Kathleen Chiotos, et al., Multicenter initial guidance on use of antivirals for children with COVID-19/SARS-CoV-2, *Journal of the Pediatric Infectious Diseases Society*, p1aa045,
<https://academic.oup.com/jpids/advance-article/doi/10.1093/jpids/piaa045/5823622>)

Thromboembolism and Anticoagulant Treatment during the COVID-19 Pandemic: Interim Clinical Guidance from the Anticoagulation Forum. Geoffrey D Barnes MD MSc, Allison Burnett PharmD, PhD, CACP, et al. *The Journal of Thrombosis and Thrombolysis*. Pre-print of article May 2020.

Updates to AAP neonatal guidance for neonates born to mothers who are PUI or confirmed positive for COVID 19 include

-delayed cord clamping should occur per usual practice; mother should don a mask while holding neonate during delayed cord clamping

- mothers and newborns may room in according to usual practice
- mother should maintain a reasonable distance from her infant when possible; when providing hands-on care, mother should wear a mask and perform hand-hygiene
- breastfeeding is not contra-indicated; when breastfeeding, mother should perform hand-hygiene and wear mask

<https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/faqs-management-of-infants-born-to-covid-19-mothers/>

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

<https://downloads.aap.org/AAP/PDF/COVID%2019%20Initial%20Newborn%20Guidance.pdf>

- 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) According to a Scientific Brief published by the World Health Organization (WHO), there are insufficient data at present to conclude vertical transmission of COVID-19 through breastfeeding. Therefore, "WHO recommendations on the initiation and continued breastfeeding of infants and

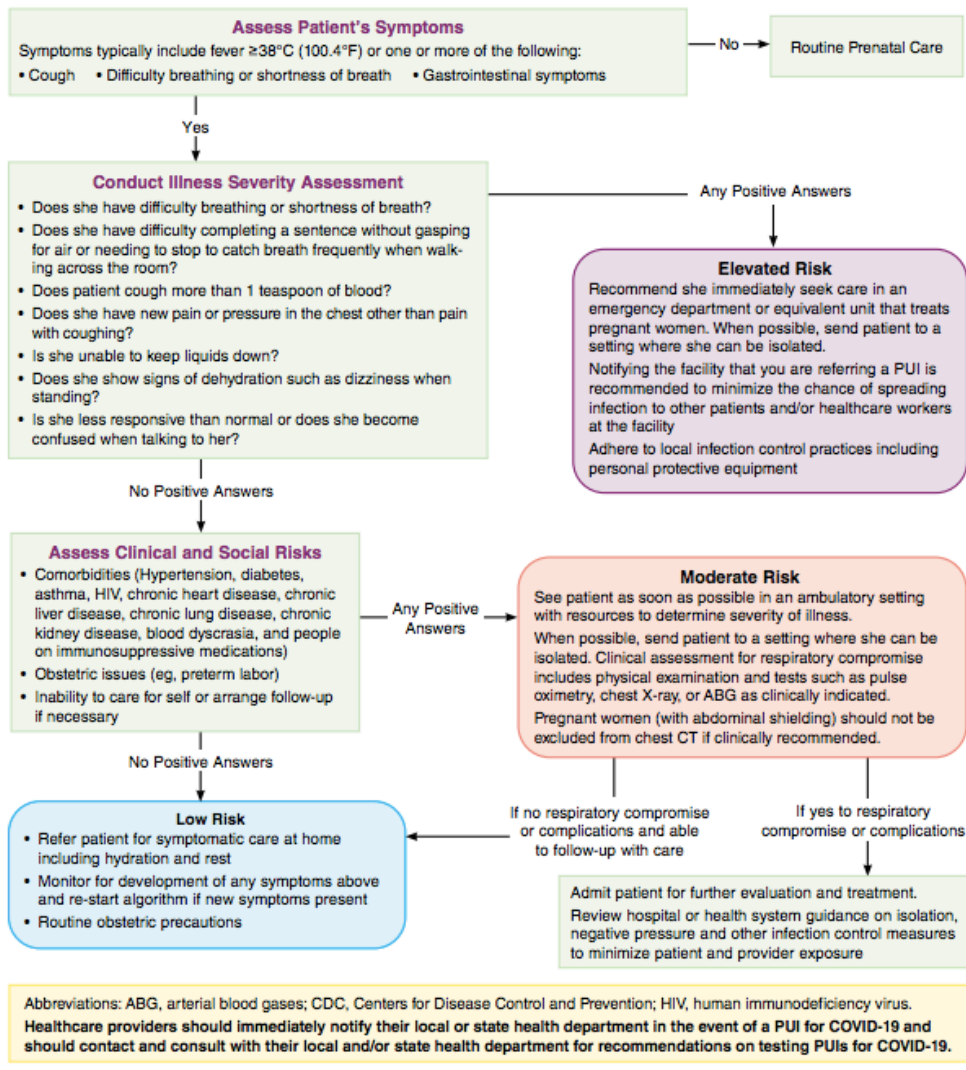
young children also apply to mothers with suspected or confirmed COVID-19," the report added. (https://dgalerts.docguide.com/who-scientific-brief-insufficient-data-conclude-vertical-transmission-covid-19-through-breastfeeding?nl_ref=newsletter&pk_campaign=newsletter&nl_eventid=49314&nl_campaignid=3641&pw_siteID=25&ncov_site=covid-19&MemberID=104196194)

- 9) 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
- 10) 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.

Obstetrics and Gynecology

- 1) The clinical characteristics of COVID-19 pneumonia in pregnant women were similar to those reported for non-pregnant adult patients who developed COVID-19 pneumonia. There is currently no evidence for intrauterine infection caused by vertical transmission in women who develop COVID-19 pneumonia in late pregnancy. [https://doi.org/10.1016/S0140-6736\(20\)30360-3](https://doi.org/10.1016/S0140-6736(20)30360-3)
- 2) A study published in JAMA showed that the clinical symptoms from 33 neonates with or at risk of COVID-19 were mild and outcomes were favorable. Of the 3 neonates with symptomatic COVID-19, the most seriously ill neonate may have been symptomatic from prematurity, asphyxia, and sepsis, rather than SARS-CoV-2 infection. (Zeng L, Xia S, Yuan W, et al. Neonatal Early-Onset Infection With SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China. *JAMA Pediatr*. Published online March 26, 2020. doi:10.1001/jamapediatrics.2020.0878)
- 3) A study published in JAMA showed that 6 mothers with confirmed COVID-19, SARS-CoV-19 had negative nasopharyngeal swabs for RT-PCR in their newborns. However, virus-specific antibodies were detected in neonatal blood sera samples. The IgG concentrations were elevated in 5 infants. IgG is passively transferred across the placenta from mother to fetus beginning at the end of the second trimester and reaches high levels at the time of birth. However, IgM, which was detected in 2 infants, is not usually transferred from mother to fetus because of its larger macromolecular structure. In a study of mothers with SARS, the placentas of 2 women who were convalescing from SARS-CoV infection in the third trimester of pregnancy had abnormal weights and pathology. Whether the placentas of women in this study were damaged and abnormal is unknown. Alternatively, IgM could have been produced by the infant if the virus crossed the placenta. (Zeng H, Xu C, Fan J, et al. Antibodies in Infants Born to Mothers With COVID-19 Pneumonia. *JAMA*. Published online March 26, 2020. doi:10.1001/jama.2020.4861)



For recommendations from ACOG, visit the website below.

<https://www.acog.org/-/media/project/acog/acogorg/files/pdfs/clinical-guidance/practice-advisory/covid-19-algorithm.pdf>

Quick Hits

Gynecology Practice Recommendations- ACOG

In-person visits: limit to urgent/emergent complaints, for example, concern for ectopic pregnancy or profuse vaginal bleeding

Telehealth visits (video or telephone): contraceptive counseling and prescribing.
Management of menopausal symptoms

Defer visits: annual exams and management of abnormal cervical cancer screening (low-grade paps needing colposcopy can be deferred for 6-12 months and high-grade paps needing colposcopy should be performed within 3 months)

Contraception- IUD and contraceptive implant insertion procedures should continue where possible. Removal procedures should be delayed - patient should be counseled about evidence of their extended use.

Prenatal visits- limit in-person visits to visits where ultrasound or labs needed. Typical schedule is 12, 20, 28 and 36 weeks. All other interval visits can be telemedicine visits (patient to take BP at home if has cuff)

Scheduled C-Sections and Induction Guidance

(<https://www.sciencedirect.com/science/article/pii/S2589933320300409>)

Ideally, this should be determined when screening the patient by phone the day before admission to avoid travel to the hospital.

Evaluation should be conducted to determine if rescheduling in 2–3 days is feasible to allow for results of COVID-19 testing if necessary.

For COVID-19–positive patients with mild or moderate symptoms not requiring immediate care, it is important to recognize that the severity of disease peaks often in the second week; therefore, planning delivery before that time is optimal.

Palliative Care

Anxiety

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

Dyspnea & Acute Pain

Non-opioid management

- 1) **Non-Pharmacologic for Dyspnea:**
 - a) Positioning: sitting patient up in bed, if possible. See also *Anxiety* above.
- 2) **Pharmacologic:**
 - a) Please see “Therapeutics” for discussion about NSAID use vs acetaminophen. No recommendation is made at this time
 - b) 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).
 - c) **Opioids** can be used for both **dyspnea** and **acute pain (see below)**

Opioid management

- 1) **General principles:**
 - a) 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:**

		Renal function	
		Normal	Abnormal (GFR<50)
COPD	No	Morphine 5-10mg PO q3h PRN (use the 20mg/ml concentrate) Morphine 2-4mg IV q2h PRN	Hydromorphone 1-2mg PO q3h PRN Hydromorphone 0.1-0.2mg IV q2h PRN
	Yes	Morphine 2-5mg PO q4h PRN (use the 20 mg/ml concentrate) Morphine 1-2 mg IV q2h PRN	Hydromorphone 2-4mg PO q4h PRN Hydromorphone 0.2-0.4mg IV q2h PRN

- 3) If patient is not well managed with the above, add opioid infusion:
 - a) Consider drip if > 3 bolus doses in 8 hours

- b) Calculate initial dose with total mg used/8 hours
 - i) e.g. 1+2+2+2= 7 mg; begin drip at 7mg/8 hr = 1 mg/h
 - ii) 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.
 - c) Continue PRN dosing at current dose (if effective) or titrate as per above.
- 4) **For Opioid tolerant patients:**
- a) If able to take PO:
 - i) Continue current long-acting doses if renal and hepatic function tolerate
 - ii) 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
 - (a) e.g. 5 mg PO MS q3h prn; increase to 7.5 mg; 7.5-22 mg PO q3h PRN
 - b) If unable to take PO, severe or rapidly escalating symptoms:
 - i) Convert as-needed PO doses to IV pushes as needed
 - (1) Use the IV Conversion chart
 - (2) Decrease PRN dose by 1/3 for incomplete cross-tolerance when switching between opioid classes
 - (a) e.g. to convert 20 mg of oxycodone to IV hydromorphone: 20 mg oxy = 1.5 mg IV hydromorphone; 1.5 mg x 2/3 = 1 mg IV
 - ii) Convert PO long-acting/ sustained release opioids to an infusion:
 - (1) Calculate 24-hour dose of PO sustained release (SR) morphine
 - (a) 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)
 - (a) 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
 - (a) e.g. 1 mg/hr IV morphine infusion; PRN dose is 1-2 mg IV q2h

Abbreviated Opioid Equianalgesic Table

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

Delirium

Diagnosis: CAM method

- 1) Use the **Confusion Assessment Method (CAM)**
- 2) CAM is positive if (a) AND (b) and EITHER (c) or (d) are present

- a) Acute often fluctuating change in mental status (vs dementia)
- b) Difficulty focusing attention
- c) Disorganized thinking (rambling, illogical flow of ideas)
- d) Altered level of consciousness (too sedated or too hyperactive)

Treatment:

- 1) Non-pharmacologic:
 - a) Daytime lights, nighttime dark. Frequent reorientation. Reverse contributing medical conditions as able.
 - b) Consult Psychiatry; for terminal delirium, consult Palliative Care
- 2) Pharmacologic
 - a) Additional information available at: Guidelines for Acute Hospital Acquired Delirium (Partners login required)
 - b) Alter existing medications and treat comorbid symptoms.
 - c) QTc prolonging agents <65 yo or DNR/I +LLST Comfort Measures
 - i) 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
 - ii) 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
 - d) QTc prolonging agents ≥ 65 yo or frail
 - i) 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
 - e) Non-QTc prolonging agents
 - i) Aripiprazole (Abilify), 5 mg PO daily; maximum dose 30 mg daily
 - ii) Valproic Acid 125-250mg IV q8h PRN.

Nausea and Vomiting

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

Constipation

- 1) If able to take oral agents, start:
 - a) Senna 2 tabs PO qhs, can increase up to 2 tabs PO TID if needed
 - b) Polyethylene Glycol 17gm packet PO QD-BID prn

- c) 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
 - a) Somnolence
 - b) Warmth, and later cooling and mottling of extremities
 - c) Change in respiratory pattern, intermittent apnea, Cheyne-Stokes pattern
 - d) Gurgling sounds from oropharynx (often more distressing to family than patient)
- 2) Symptom management
 - a) Should follow the guidelines provided in sections above
 - b) 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:
 - a) 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)
 - a) Glycopyrrolate 0.2 – 0.4mg IV q2hrs prn secretions, rattling sound
 - b) Hyoscyamine 0.125-0.25mg PO q4hrs prn secretions, rattling sound
 - c) 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
 - d) 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) In conscious patients, review or sign Health Care Proxy form.

Toolkit provided by the Center for Advanced Palliative Care

- 1)** The following website provides a tremendous amount of information in regards to difficult conversations, advanced directives, symptom management, and CMS support of alternative mechanisms to provide palliative care during this time. <https://www.capc.org/toolkits/covid-19-response-resources/>

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: <https://www.aamc.org/advocacy-policy/washington-highlights/cms-releases-interim-final-rule-covid-19-regulatory-changes>

Highlights from the CMS FAQ Sheet can be found below (<https://www.cms.gov/newsroom/fact-sheets/additional-backgroundsweeping-regulatory-changes-help-us-healthcare-system-address-covid-19-patient>):

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.

Resources

Community Resources in the Time of COVID Crisis

211 Eastern Oklahoma - 211 Eastern Oklahoma is a free and confidential link to help and hope for those in need, whatever the need, 24/7. Get connected to thousands of community resources and services near you, including crisis support. www.csctulsa.org/211eok/

Catholic Charities - Amended Hours: Wednesday and Friday 9 a.m. - 2 p.m., Tuesday and Thursday 9 a.m. to 4 p.m., First and Third Saturdays of each month from 9 a.m. - 11 a.m.
www.cceok.org/emergency-assistance

Emergency Infant Services – Provides basic needs help for children five and under.
<https://www.eistulsa.org/>

Technology Incentives – List of companies that have responded to the Keep Americans Connected Pledge.
<https://sde.ok.gov/sites/default/files/COVID-19%20Technology%20Incentives.pdf>

Tulsa Area United Way – COVID -19 Resources List www.tauw.org/tauw/COVID-19.asp

Evictions and Foreclosures in OK

Due to the coronavirus, the Oklahoma Supreme Court has ordered that the courts remain closed until May 15, 2020. This means that no court hearings will be held and no eviction orders will be issued until after the courts reopen.

https://www.csctulsa.org/wp-content/uploads/2020/03/Notice-to-Tenants-about-Mediation_3.31.20.pdf

Food Pantries

Aldersgate United Methodist Church 3702 S 90th E Ave in Tulsa, OK 74145 918-627-4165 3rd Saturday of each month from 2 p.m. and 4 p.m.

Christ for Humanity 6314 E 13th St in Tulsa, OK 74112 918-836-2424 Monday through Thursday from 10 a.m. - 3 p.m.

Common Ground Food Pantry - Mondays 6 p.m. - 8 p.m. and Thursdays 10 a.m. - 12 p.m. Food distributed outside the building. Do not arrive early if you are coming for food. Have your ID and proof of residence ready. www.cg.church

Eastland Assembly of God Food Pantry - These ministries are available to our community on the first and third Tuesday of each month from 6 p.m. - 7 p.m. Our guests should park on the East side of the building towards the back and come in the East doors. www.eastlandag.org/outreach

Guts Church Distribution Center - Every Friday at 10 a.m. we provide FREE GROCERIES and FREE CLOTHING to those in need. (NO ID REQUIRED). Guts Distribution Center is located at 4352 S 91st E Ave in Tulsa, OK 74145.

<https://www.gutschurch.com/friday-groceries/>

Iron Gate Tulsa - Our grocery pantry is open on Wednesday and Friday from 12:00 p.m. - 1 p.m. and Saturdays from 11a.m. - 12:00 p.m. The grocery pantry provides a self-serve grocery bag of basics and fresh produce with no required documentation. <https://www.irongatetulsa.org/programs>

John 3:16 Mission Youth & Family Center - To receive help with supplemental groceries or clothing, you will need to contact our Family & Youth Center and set up an appointment. Make an appointment by calling 918-592-1186.

www.john316mission.org/groceries-and-clothing

Loaves and Fishes - Those who feel they are in the group that is most vulnerable to COVID-19 should contact the ministry to make an appointment, 918-234-8574 between the hours of 8 a.m. and noon.

www.loavesandfishes.net/#needhelp

Restore Hope - Provides emergency food pantry located at Asbury United Methodist Church. Restore Hope will only be open at our SOUTH location. Our food service hours will be Monday-Thursday from 12:30 - 3:30 p.m.

<https://www.restorehope.org/>

Mental Health Resources

COPES - It's a free and confidential 24/7 telephone crisis line and mobile crisis service, provides emotional support children and adults in suicidal crisis or emotional distress. Please call COPES at 918-744-4800. www.fcsok.org/services/crisisservices/

Disaster Helpline 1-800-985-5990 – for information, updates and help

The Calm Center Call 918-394-2256 anytime of day or night for help with a behavioral or substance abuse crisis affecting youth ages 10-17. www.crsok.org/the-calm-center/

Reopening, a strategic plan

Guidelines for outpatient areas and “non-essential clinic services,” have been developed by the American Medical Association, which draws on multiple resources including recommendations by CMS and the White House.

1. Comply with governmental guidance
2. Develop an operational strategic plan
 - a. Include dates, and proceed with a “soft re-opening,” if at all possible
 - i. This will increase your volumes in a staggered fashion
 - b. Determine how many days of PPE you have on hand, and how easily it will be access more as you increase your patient care
 - c. Determine how cleaning will transpire between patients
3. Institute safety measures for patients
 - a. Use telehealth/virtual health when possible
 - b. Maintain adequate distancing between patients in the waiting room
 - c. Separate sick and well patients if room allows
 - d. Encourage all patients to wear masks to the office
 - e. Consider expanding times between appointments to allow for less interaction
4. Ensure workplace safety for clinicians and staff
 - a. Staggered work schedules
 - b. Restructure the workspace to minimize interaction
 - c. Continue screening employees
 - d. Be clear about what should trigger the employee to stay at home
 - e. Clinicians and staff should be masked if possible
5. Screen patients before in-person visits
 - a. Call the patient 24 hours prior and screen them again prior to entering spaces that have high interaction
6. Limit visitors

<https://www.ama-assn.org/delivering-care/public-health/covid-19-physician-practice-guide-reopening>
<https://www.cms.gov/files/document/covid-flexibility-reopen-essential-non-covid-services.pdf>

Procedural Recommendations

At this time, elective surgeries have been resumed per the governor’s strategic reopening plan. Governor Stitt gave an executive order allowing elective surgeries to resume on May 1, 2020. The following scale is a three-tiered system from the governor’s memorandum.

OSUMC, based on these recommendations, instituted a strategic reopening plan to begin non-essential surgeries as of May 4, 2020. A procedural review committee was formed to create requirements and guidelines to follow during the reopening process. Guidance was pulled from multiple sources and communities on both a national and state level and includes the American College of Surgeons and CMS.

This decision is multifactorial and based upon available PPE, hospital beds, and number of current COVID patients. Elective/Non-essential surgeries may proceed unrestricted as long as the following criteria are met:

14 day supply of PPE is available

Less than 15 COVID positive patients or PUIs currently inpatient
Available ICU beds

The Medical Executive Committee, COVID task force, and Procedural Review Committee are reviewing the above daily, and procedures will be scaled back as needed. Information is constantly being reviewed by the surgical COVID task force, and can also 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)
Scheduling Procedures:

OUTPATIENT:

All patients are required to be tested within 5 days of the scheduled procedure. Only patients with a negative test will be allowed to proceed. If positive, retesting is based on the current CDC guidelines. Patients can be retested 7 days following their positive test and require 2 negative tests performed >24 hours apart. <https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html>

Nasopharyngeal swab testing is being performed either during the pre-anesthesia (PAT) visit or is available as a drive through test at west side of the hospital. The drive through testing site is currently open 1-3 PM Monday – Friday, but accommodations will be made for those that cannot make this time slot. The tests will be sent to the Saint Francis lab. Patients that are not in Tulsa area may have testing through their local health department, as long as the test is within the 5 day window. Patients are required to self-quarantine after their test until the date of their procedure to avoid exposure.

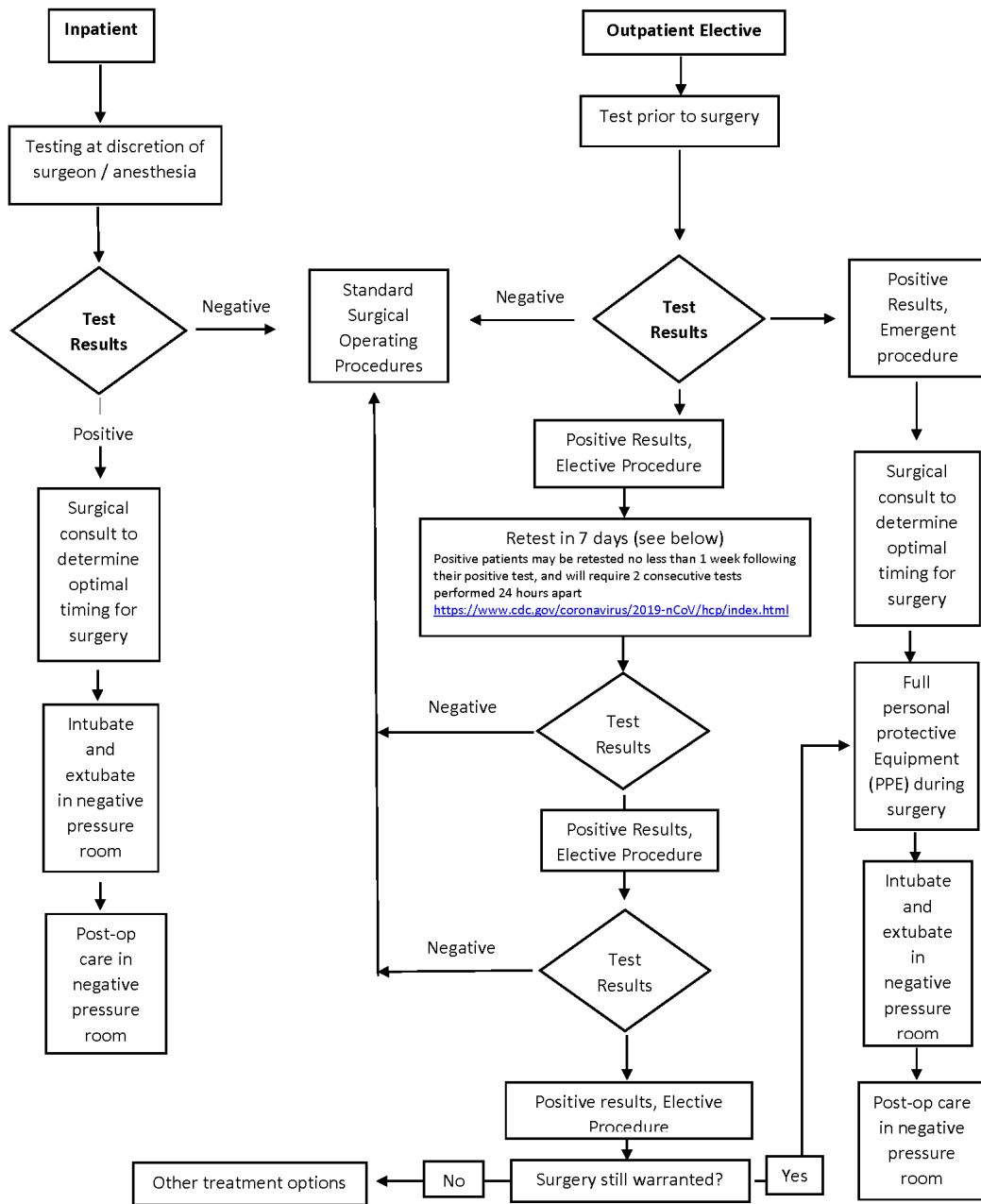
The test is to be ordered by the scheduling physician's office at the time the procedure is scheduled. The patient will be contacted by the hospital scheduling department and an appointment will be made for testing.

All patients will be notified of their test results. If negative, the hospital will notify the patient. If positive, the case will be canceled and the results will be sent to the physician's office performing the procedure. It is their responsibility to contact the patient with the positive result and arrange repeat testing.

INPATIENT:

Inpatient testing will be at the discretion of the physician providing the procedure and anesthesia. Emergent/Urgent procedures do not require testing if delaying the procedure to await the results would be harmful to the patient. Appropriate PPE will be used during the procedure. If delaying the procedure to allow for testing is an option, it is our current recommendation the patient be tested.

Pre-Procedure Testing for COVID-19
Oklahoma State University Medical Center



ADDITIONAL INFORMATION:

Some overarching principles for all cases include the following:

1. Be aware that this is a very fluid situation and subject to change at any moment.
2. Patients should receive appropriate and timely surgical care, including operative management, based on sound surgical judgment and availability of resources.
3. Consider non-operative management whenever it is clinically appropriate for the patient.
4. Avoid emergency surgical procedures at night when possible due to limited team staffing.
5. 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
6. Screening and surveillance via upper and lower end endoscopy should be postponed <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>
 - a. 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.

CMS has also issued guidance. Not only is delay of elective surgeries to minimize ongoing risks, it is also to conserve PPE, beds and ventilators.

<https://www.cms.gov/files/document/cms-non-emergent-elective-medical-recommendations.pdf>

An article published in Lancet suggests that surgery may accelerate the development of COVID symptoms. Individuals in this study received “elective surgery,” in the likely incubation period and had a rapid development of SARSs-COV2 findings suggesting that caution needs to be taken when dealing with surgical decisions. Criticisms include a small retrospective trial.

[https://www.thelancet.com/pdfs/journals/eclinm/PIIS2589-5370\(20\)30075-4.pdf](https://www.thelancet.com/pdfs/journals/eclinm/PIIS2589-5370(20)30075-4.pdf)

Plan on reopening Surgical Service Lines as a joint statement by the American College of Surgeons, American Society of Anesthesiologists, Association of peri-Operative Registered Nurses and the American Hospital Association:

<https://www.asahq.org/about-asa/newsroom/news-releases/2020/04/joint-statement-on-elective-surgery-after-covid-19-pandemic>

The above link describes the following:

1. Timing for Reopening of Elective Surgery
2. COVID-19 Testing Within a Facility
3. Personal Protective Equipment
4. Case Prioritization and Scheduling S
5. Post-COVID-19 Issues for the Five Phases of Surgical Care
6. Collection and Management of Data
7. COVID-related Safety and Risk Mitigation surrounding Second Wave
8. Additional COVID-19 Related Issues

What Should We Expect in the Days to Come?

- 1) Discussion about a second wave that may be more significant than the first
<https://www.livescience.com/covid-19-second-wave-flu-season.html>
- 2) Will we be hit worse in Oklahoma? Some data suggests that Rural States will be hit hardest.
 - a. In an article from infectious disease, they suggest that because many people in rural areas are not receiving regular medical care, they may also have a higher prevalence of diabetes or other conditions, putting them at higher risk for severe infection https://www.healio.com/infectious-disease/emerging-diseases/news/online/%7Bb231754d-976e-4a74-b8fe-947f3ad67371%7D/idsa-covid-19-in-rural-america-will-be-a-long-sustained-outbreak?utm_source=selligent&utm_medium=email&utm_campaign=infectious%20disease%20news&utm_bt=922415890
 - b. A precision tool developed that combines indicators specific to COVID per the CDC and the social vulnerability index which measures the negative impact of any type of disaster shows that Oklahoma may be in trouble <https://precisionforcovid.org/ccvi>
- 3) Advice from Washington DC on re-opening in multiple areas including hospitals, schools, etc.
<https://www.cdc.gov/coronavirus/2019-ncov/community/reopen-guidance.html>

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