MEDICINE

COVID19 HANDBOOK-VERSION 2.0
UPDATED 11/09/20

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; 8/10/2020; 8/17/2020; 8/31/20; 10/5/2020; 10/12/2020; 10/19/2020; 10/26/2020;
11/09/2020

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. NIH guideline updates: **Page 33**
2. Banlanivibimab granted EUA on 11.10.2020 for non-hospitalized patients not requiring O2 with COVID-10: **Page 48**
3. Tocilizumab updates: **Page 49**

Clinical Course and Prognosis

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 >= 38°C (of note, they used solely > 38°C but we would advocate for >= 38°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)   A study published in PLOS I 10.2020 demonstrates that anosmia may be a good predictor of COVID-19. A total of 77.6% of 567 participants with acute smell and/or taste loss had SARS-CoV-2 antibodies

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) https://www.mdcalc.com/neutrophil-lymphocyte-ratio-nlr-calculator#evidence

                   (a) 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)   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)   Varies with local epidemiology and season

           i)   A respiratory panel virus turned up in 3.3% (15 of 459) of the specimens that also tested positive for SARS-CoV-2 by RT-PCR at University of Chicago Medicine from March 12 through April 15, 2020. (https://www.medpagetoday.com/infectiousdisease/covid19/87483)

           ii)   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

        (1) Of the 116 specimens positive for SARS-CoV-2, 24 (20.7%) were positive for 1 or more additional pathogens

        (2) The most common co-infections were rhinovirus/enterovirus (6.9%), respiratory syncytial virus (5.2%), and non–SARS-CoV-2 Coronaviridae (4.3%)

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, https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html):
   a) Sepsis, median 9 days (range 7-13 days)
   b) ARDS, median 12 days (range 8-12 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/
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)
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, 8-12 days (Zhou et al, *Lancet*, 2020).Hypoxemic respiratory failure is the most common indication for ICU. 60–70% of patients admitted to the ICU (https://doi.org/10.1016/S2213-2600(20)30161-2)
2) Presentation with shock rare; however, vasopressors used in 67% of critically-ill patients (Arentz et al, *JAMA*, 2020).
3) Myocardial injury noted in 19,7% of 416 critically-ill patients, with the rate was roughly 13-fold higher in patients with severe disease treated in the intensive care unit compared with patients without severe disease https://jamanetwork.com/journals/jamacardiology/fullarticle/2768165)

Death and Hospital Discharge

1) Case Fatality Rates are largely unknown based on multiple factors https://www.who.int/news-room/commentaries/detail/estimating-mortality-from-covid-19
    a) Some studies measured this to 1-7% but likely inaccurate (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.
    i) The American Journal of Infection Control describes the most common comorbidities in July 2020: HTN, diabetes, CAD, cerebrovascular disease. 27.4% hypertension, 17.4% diabetes, 8.9% cardiovascular disease, 7.5% chronic obstructive pulmonary disease (COPD), 3.6%

chronic kidney disease, and 3.5 % malignancy. (https://www.ajicjournal.org/article/S0196-6553(20)30637-4/fulltext)

  (1) 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. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

  i) An article published in circulation shows an a 7 fold higher risk for mechanical ventilation in patients with a BMI of > 35 (when compared to BMI < 25) in a French Study. In NYC a BMI between 30 to 34 kg/m2 and >35 kg/m2 were 1.8 times and 3.6 times more likely to be admitted to critical care, respectively, than individuals with a BMI <30 kg/m2. https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.120.047659

2) OSA was found to have an increased risk for hospitalization after review of ~ 9000 patients after adjustments for diabetes, hypertension and BMI were made. https://dgalerts.docguide.com/study-finds-obstructive-sleep-apnea-associated-greater-risk-covid-19-infection-hospitalization-and?nl_ref=newsletter&pk_campaign=newsletter&nl_eventid=71604&nl_campaignid=3641&pw_siteID=25&ncov_site=covid-19&MemberID=302411139

3) Risk Calculators while caring for COVID patients

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

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

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

IDSA guidelines for who should be tested: https://www.idsociety.org/globalassets/idsa/public-health/covid-19-prioritization-of-dx-testing.pdf

How Are We Testing Currently?

2 validated modes of testing for acute COVID-19 infection: molecular tests, such as RT-PCR tests, that detect the virus's genetic material, and antigen tests that detect specific proteins on the surface of the virus. https://www.fda.gov/consumers/consumer-updates/coronavirus-testing-basics

Molecular Testing: virus's genetic material in a sample from the patient's nose or throat

The nuances of testing with RT-PCR described and how it is an imperfect test:
https://www.nejm.org/doi/full/10.1056/NEJMp2015897

Differentiation between salivary testing and nasopharyngeal testing provide support for salivary testing.
https://www.nejm.org/doi/full/10.1056/NEJMc2016359?query=C19&cid=DM97750_NEJM_Registered_Users_and_InActive&bid=248546496

Antigen Testing: Detect the presence of viral proteins in a biological sample. The pro's? Antigen tests 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)

The nuances of testing with antigens and how it is an imperfect test:
https://www.sciencemag.org/news/2020/05/coronavirus-antigen-tests-quick-and-cheap-too-often-wrong

Different Types of Coronavirus Tests

	Molecular Test	Antigen Test	Antibody Test
Also known as...	Diagnostic test, viral test, molecular test, nucleic acid amplification test (NAAT), RT-PCR test, LAMP test	Rapid diagnostic test (Some molecular tests are also rapid tests.)	Serological test, serology, blood test, serology test
How the sample is taken...	Nasal or throat swab (most tests) Saliva (a few tests)	Nasal or throat swab	Finger stick or blood draw
How long it takes to get results...	Same day (some locations) or up to a week	One hour or less	Same day (many locations) or 1-3 days
Is another test needed...	This test is typically highly accurate and usually does not need to be repeated.	Positive results are usually highly accurate but negative results may need to be confirmed with a molecular test.	Sometimes a second antibody test is needed for accurate results.
What it shows...	Diagnoses active coronavirus infection	Diagnoses active coronavirus infection	Shows if you've been infected by coronavirus in the past
What it can't do...	Show if you ever had COVID-19 or were infected with the coronavirus in the past	Definitively rule out active coronavirus infection. Antigen tests are more likely to miss an active coronavirus infection compared to molecular tests. Your health care provider may order a molecular test if your antigen test shows a negative result but you have symptoms of COVID-19.	Diagnose active coronavirus infection at the time of the test or show that you do not have COVID-19

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)

The following website looks at serology based testing and EUA authorized testing: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance

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

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.

Transmission dynamics

  a) Transmission of SARS-CoV-2 is incompletely understood, and new data continue to emerge.
   i) Theoretical Considerations and Review of Current Evidence published in JAMA suggest that it is impossible to conclude that aerosol-based transmission never occurs but the balance of currently available evidence suggests that long-range aerosol-based transmission is not the dominant mode of SARS-CoV-2 transmission. https://jamanetwork.com/journals/jama/fullarticle/2768396
   ii) 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
   iii) CDC Guidance published 10.2020 suggests that primary means of transmission are droplet with special circumstances having aerosolized transmission (enclosed spaces, poor ventilation and prolonged exposure). https://www.cdc.gov/coronavirus/2019-ncov/more/scientific-brief-sars-cov-2.html
   iv) 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
    (1) Aerosolizing procedures are proposed to include intubation, nebulization, non-invasive positive pressure (CPAP, BiPAP), and high-flow nasal cannula.
     (a) 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 of 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

    v) 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).

2) 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) A study published in JAMA continue to support the ongoing need for quarantine of asymptomatic individuals and population based surveillance: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2769235

3) Duration of viral shedding from illness onset in survivors varies based on severity of illness (https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html)
   a) For patients with mild to moderate COVID-19, replication-competent virus has not been recovered after 10 days following symptom onset (CDC, unpublished data, 2020; Wölfel et al., 2020; Arons et al., 2020; Bullard et al., 2020; Lu et al., 2020; personal communication with Young et al., 2020; Korea CDC, 2020).
   b) Recovery of replication-competent virus between 10 and 20 days after symptom onset has been documented in some persons with severe COVID-19 that, in some cases, was complicated by immunocompromised state (van Kampen et al., 2020).
   c) Although replication-competent virus was not isolated 3 weeks after symptom onset, recovered patients can continue to have SARS-CoV-2 RNA detected in their upper respiratory specimens for up to 12 weeks (Korea CDC, 2020; Li et al., 2020; Xiao et al, 2020)

4) Basic reproduction number (R0): Measure of transmissibility, denoting the theoretical expected number of secondary cases from any given case. An R0 > 1 is consistent with ongoing outbreak potential.
   a) Difficulty predicting R0 for COVID-19 https://www.the-scientist.com/features/why-r0-is-problematic-for-predicting-covid-19-spread-67690
      i) Silent spreaders are playing a role which is different from the viruses we were using to model how to create an R0 for COVID-19
      ii) Variability in infective rates of individuals who are infected
      iii) Contact rates of infected individuals is also widely variable

5) 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) Superspreading and COVID-19 explained with incidents. https://www.scientificamerican.com/article/how-superspreading-events-drive-most-covid-19-spread1/

6) 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) An 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/
   c) Recent articles demonstrate re-infection based on serological analysis that shows a patient's second diagnosis had numerous differences between the two viruses https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1275/5897019

Vulnerable populations and special settings

1) Long-term care facilities at high risk for morbidity and mortality associated with COVID-19. https://jamanetwork.com/journals/jama/article-abstract/2767062

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

3) Long-standing systemic health and social inequities have put many people from racial and ethnic minority groups at increased risk of getting sick and dying from COVID-19 https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/race-ethnicity.html

4) Rural Communities may not receive regular medical care, and have a higher prevalence of diabetes or other conditions, putting them at higher risk for severe infection with an estimated 10% decrease in available hospital beds.
   a) 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

5) Patients with behavioral health conditions because of inherent grief, fear of the virus, financial hardship, prolonged social isolation and limited behavioral health capacity have a higher risk of suffering severe illness from COVID-19. https://www.mckinsey.com/industries/healthcare-systems-and-services/our-

insights/a-holistic-approach-to-addressing-the-us-behavioral-health-crisis-in-the-face-of-the-global-covid-19-pandemic

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
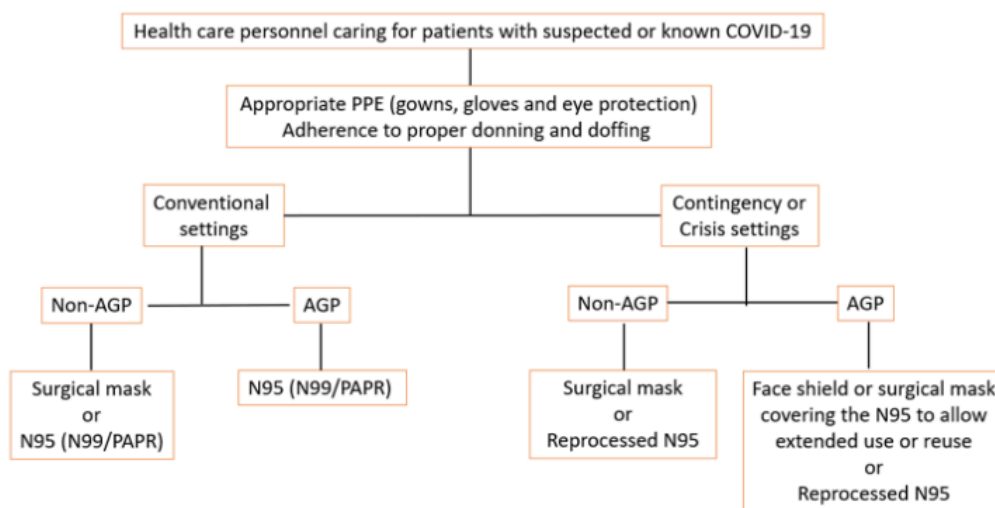
(e.g., fomites) is not a concern, non-emergency reuse has been practiced for decades. For example, for tuberculosis prevention, CDC recommends that a respirator classified as disposable can be reused by the same worker as long as it remains functional and is used in accordance with local infection control 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, must be using a surgical grade mask at all times .

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

North 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) when providing patient care. Each room has been created to be negative pressure, so outside of rooms it is acceptable to be wearing a surgical mask.

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

5W: **(**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.

7W: **(**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.

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

7E: All providers are to wear basic surgical mask and gloves while interacting with any patient.

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. This is required on all floors if COVID status is unknown.

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

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

Chest imaging

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
     a) 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. (https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection)
     b) 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)
     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 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
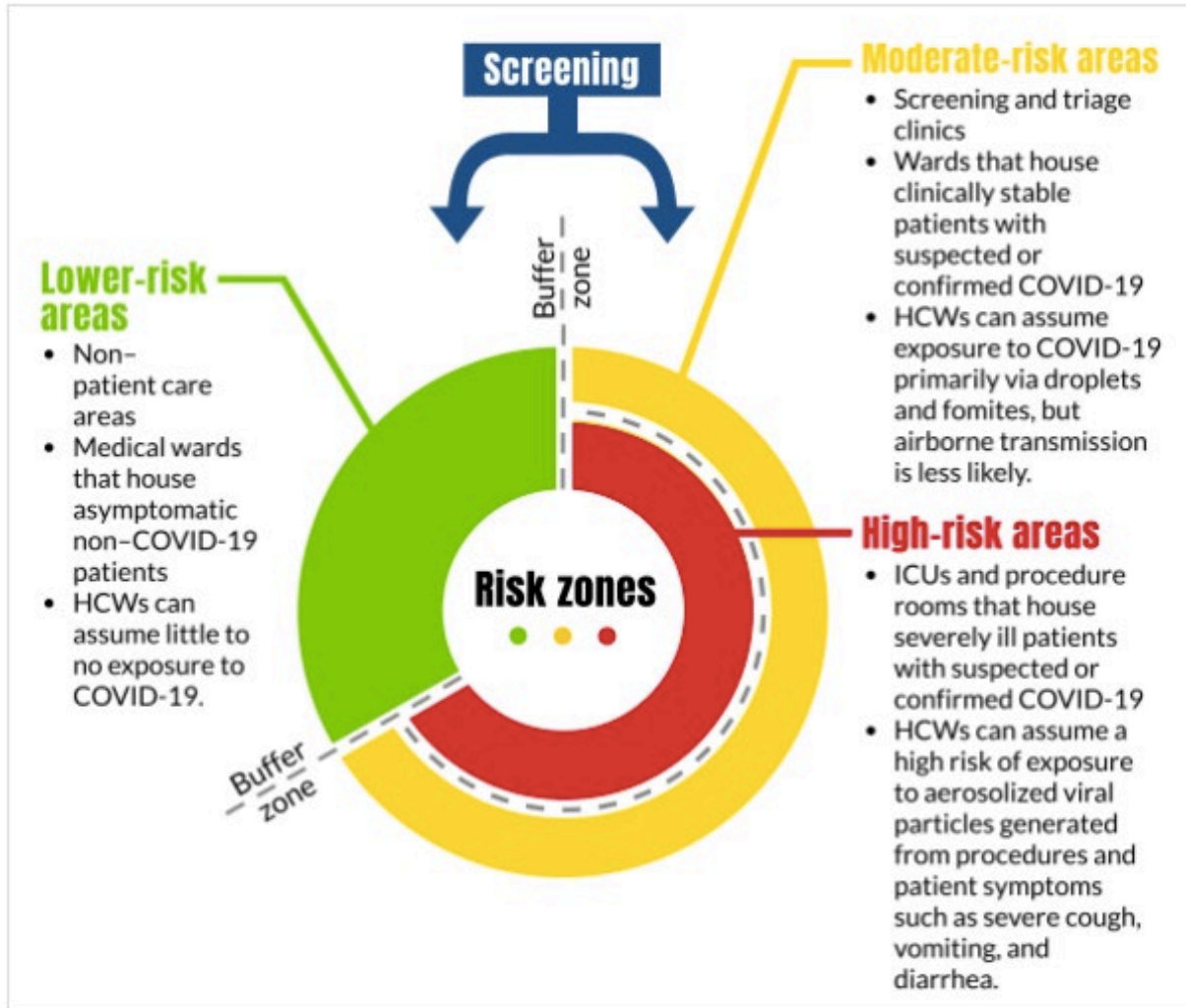
Patients that need further evaluation are then sent to their appropriate designation for COVID risk. If the patient is suspected to need any type of aerosolized procedure, they are moved to the negative pressure rooms in the ED (rooms 13-17 at OSU).
https://www.acep.org/corona/covid-19-field-guide/triage/how-covid-19-moves-within-a-hospital/

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

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

Quarantine and Repeat Testing

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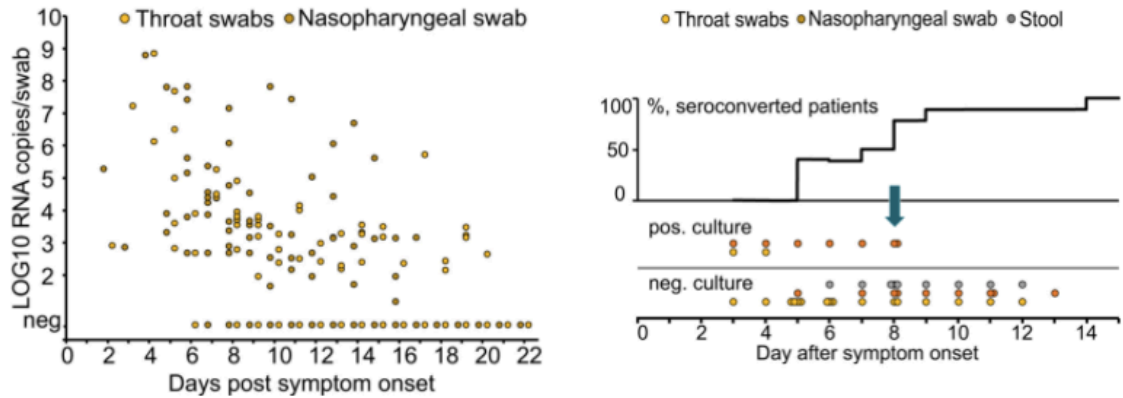
Note that typically for viruses, patients with compromised immune systems have prolonged viral shedding. The CDC guidelines state to extend the patient's isolation for the duration of symptoms based on the clinical judgement of the provider.

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).

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

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 $PaCO_2$ on the ventilatory response to hypoxia, hypoxia threshold that precipitates dyspnea, limited accuracy of SpO_2 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: https://qxmd.com/calculate/calculator_724/rox-index-to-predict-risk-of-intubation

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. 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

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

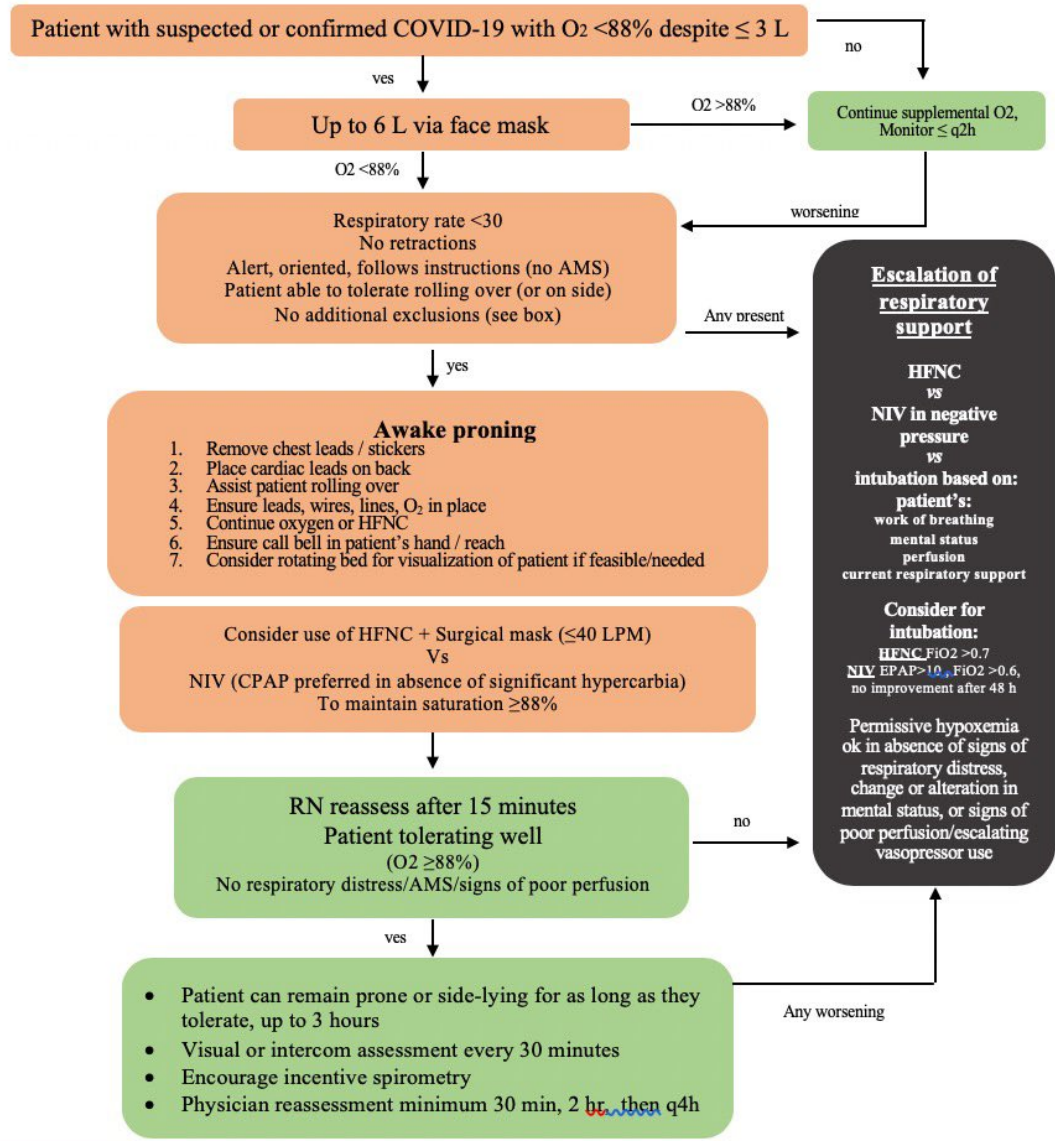Additional evidence supporting the use of high flow nasal canula to reduces intubation and subsequent invasive mechanical ventilation, with no affect on case fatality
https://www.atsjournals.org/doi/pdf/10.1164/rccm.202005-2007LE

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

Patient with suspected or confirmed COVID-19 with O2 <88% despite ≤ 3 L — no →

yes ↓

O2 >88% → **Continue supplemental O2, Monitor ≤ q2h**

Up to 6 L via face mask

O2 <88% ↓

worsening ↑

Respiratory rate <30
No retractions
Alert, oriented, follows instructions (no AMS)
Patient able to tolerate rolling over (or on side)
No additional exclusions (see box)

Any present →

yes ↓

Awake proning
1. Remove chest leads / stickers
2. Place cardiac leads on back
3. Assist patient rolling over
4. Ensure leads, wires, lines, O$_2$ in place
5. Continue oxygen or HFNC
6. Ensure call bell in patient's hand / reach
7. Consider rotating bed for visualization of patient if feasible/needed

Consider use of HFNC + Surgical mask (≤40 LPM)
Vs
NIV (CPAP preferred in absence of significant hypercarbia)
To maintain saturation ≥88%

RN reassess after 15 minutes
Patient tolerating well
(O2 ≥88%)
No respiratory distress/AMS/signs of poor perfusion

no →

yes ↓

- Patient can remain prone or side-lying for as long as they tolerate, up to 3 hours
- Visual or intercom assessment every 30 minutes
- Encourage incentive spirometry
- Physician reassessment minimum 30 min, 2 hr, then q4h

Any worsening ↑

Escalation of respiratory support

HFNC
vs
NIV in negative pressure
vs
intubation based on:
patient's:
work of breathing
mental status
perfusion
current respiratory support

Consider for intubation:
HFNC FiO2 >0.7
NIV EPAP>10, FiO2 >0.6, no improvement after 48 h

Permissive hypoxemia ok in absence of signs of respiratory distress, change or alteration in mental status, or signs of poor perfusion/escalating vasopressor use

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: proned 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.vapotherm.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) Rapid Sequence Induction (RSI) should be performed, avoiding bagging
2) By the most experienced airway provider
3) 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

Initial ARDS Ventilation Settings

Basic Guidance

https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-019-0540-9/figures/1
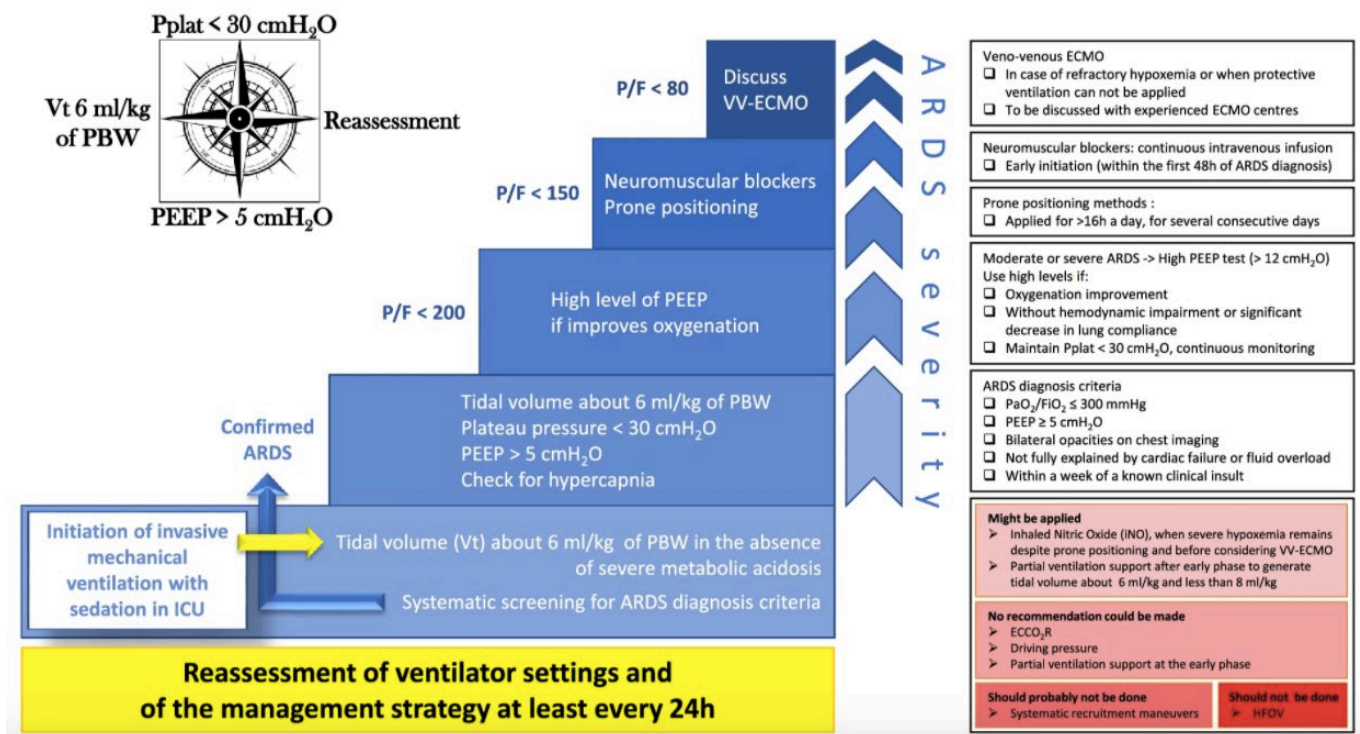
Special consideration: anecdotal reports of COVID-19 patients describe a compliant, highly PEEP dependent phenotype in which PEEP management may not strictly adhere to specified ARDSnet tables (*e.g.,* FiO2 0.4 - 0.5 but does not tolerate PEEP <10)

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 H_2O when the PEEP

is set at 18 cm H_2O, F_{IO_2} at 100%, and the tidal volume at 6 ml/kg according to the F_{IO_2} and PEEP table. The widely used practice in Wuhan, after lung recruitment maneuvers, is to set PEEP at 20 cm H_2O and titrate down in a decrement of 2 to 3 cm H_2O 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 H_2O.
(https://anesthesiology.pubs.asahq.org/article.aspx?articleid=2763453)

b) ATS indicates very little difference in physiology.
https://www.atsjournals.org/doi/pdf/10.1164/rccm.202005-2025LE

   i) Conclusive statement: The main features of respiratory mechanics, the response to treatment (such as the oxygenation response to LRM or prone position) and prognosis are similar in COVID-19 and nonCOVID-19 ARDS. The oxygenation response to LRM and a high PEEP appear to be very heterogeneous in COVID-19 ARDS; this would argue in favor of a personalized ventilation strategy.

Sedation and Ventilator Synchrony

1) **If unparalyzed, target sedation to ventilator synchrony or RASS -2 to -3 or Ramsey of 2 (see table below)** https://doctorguidelines.com/2016/07/21/sedation-scales-ramsay-rass-and-sas/**:**
   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

min: minute; NA: not applicable; RSI: rapid sequence intubation.
Source: References 5-7, 12, 25, 31, 32.

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

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)

Oxygenation parameters

1) **Minimize oxygen toxicity:** PEEP and Fi02 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) Goal FiO2 < 60%
   c) 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) http://www.ardsnet.org/tools.shtml

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)

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 contraindications

   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) Utilize the OSU Proning Protocol in conjunction with pulmonary consultation.

ECMO consultation

The use of ECMO in COVID-19 is unknown. There is some supporting literature for the use of ECMO, but it is limited and appears to be very patient specific:

(DOI:https://doi.org/10.1016/S2213-2600(20)30161-2)
https://jamanetwork.com/journals/jamasurgery/fullarticle/2769429

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 (> 65)

        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

Therapeutics and Clinical Trials:

There are no proven therapies for COVID-19. All therapies are based off 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. 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.

Overview

COVID-19 Therapeutics Guidelines
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/
   d) ATS: https://err.ersjournals.com/content/errev/29/157/200287.full.pdf?utm_campaign=ATS%20General&utm_medium=email&_hsmi=97033690&_hsenc=p2ANqtz-_T0DjnnnxNEkNfdXMdiQ_zu5wcXh3PFLRExxJ3sUKs3WthJKI-lEvyz5pF4TySC1I_XO_ct6-tM3BqzgbyT6ywx4r2bA&utm_content=97033690&utm_source=hs_email

Helpful Therapeutic Articles, Meta-analyses, and Images:
   - Siemieniuk R, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ 2020; 370 doi: https://doi.org/10.1136/bmj.m2980 (Published 30 July 2020).
   - Sanders JM, et al. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19). JAMA 2020;323(18):1824-1836. https://jamanetwork.com/journals/jama/fullarticle/2764727 (Published April 13, 2020).
   - ASHP.org. Assessment of Evidence for COVID-19-Related Treatments. Accessed at https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx. Updated weekly.
   - Figure provided by the NIH for use of dexamethsone and remdesivir based on Oxygen need https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/

This section will review medications in the following order of organization:
   1. Antiviral Therapy: Remdesivir, chloroquine/hydroxychloroquine, lopinavir/ritonavir and other antiretrovirals
   2. Immune-Based Therapy: Convalescent plasma, systemic corticosteroids, IL-6 inhibitors, Janus kinase inhibitors
   3. Adjunctive Therapy: Thromboprophylaxis, vitamin D

4. Respiratory Therapy: MDI vs. Nebulizers, non-intubated patients, intubated patients, airway clearance, inhaled corticosteroids
5. Concomitant Medications: ACE-inhibitors and Angiotensin Receptor Blockers, NSAIDS, tissue plasminogen activator (tPA), nitric oxide

Antiviral Therapy

Remdesivir

Physiology

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.

Evidence

1) 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)

2) Compassionate Use: Sixty-one patients with COVID-19 treated with remdesivir via a compassionate use program were included in a case series.
   a) 53 patients who received at least 1 dose of remdesivir showed some improvement in oxygen support status (68%) and an overall 13% mortality rate. Multiple issues including no established control group and baseline data on disease biomarkers or markers of global physiologic severity were not collected. The duration of remdesivir 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.)

3) Wang, et al: 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.
   a) 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. 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.   (Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. T*he Lancet* 2020; https://doi.org/10.1016/ S0140-6736(20)31022-9.)

4) SIMPLE-Severe (Goldman et al, Gilead Sponsored): 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 ≤ 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 65% of patients in the 5-day treatment group and 54% of patients in the 10-day treatment group. The most common adverse events observed were nausea, acute respiratory failure and elevated ALT. (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) SIMPLE-Moderate (Spinner, et al, Gilead Sponsored): This multi-center, randomized, placebo-controlled, open-label trial evaluated the impact of 5 or 10 days of remdesivir vs. standard of care on clinical status in hospitalized patients ≥12 years of age, with SARS-CoV-2 infection and moderate pneumonia. Patients were randomly assigned in a 1:1:1 ratio. Patients who clinically improved could be discharged prior to completion of the remdesivir course. Exclusion criteria included patients with LFTs > 5x ULN or CrCl <50 mL/min. The primary end point was clinical status on Day 11 on a 7-point ordinal scale. The secondary endpoint was the proportion of patients with adverse events. 589 patients were included in the study: 193 in the 10 day remdesivir group, 191 in the 5 day remdesivir group and 200 in the standard of care group. Median duration of symptoms and days of hospitalization prior to study day 1 was 9 days and 2 days, respectively. Patients in the 5 day remdesivir group had significantly higher odds of improvement in clinical status compared to the standard of care group (odds ratio. 1.65; 95% CI, 1.09-2.48; P=0.02) on Day 11. This difference was not statistically significant in the 10 day remdesivir group vs. standard of care group. A significant

difference in adverse events was noted between the 10 day remdesivir and standard of care groups with nausea, hypokalemia and headache being most commonly reported in the remdesivir group. (Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard of Care on Clinical Status at 11 Days in Patients with Moderate COVID-19: A Randomized Clinical Trial. JAMA. 15 September 2020;324 (11):1048-1057.)

6) ACTT-1 (Beigel et al, NIAID-sponsored): The first phase of the Adaptive COVID-19 Treatment Trial evaluated the clinical efficacy and safety of remdesivir. This trial was double-blind, randomized and placebo-controlled. 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 during the 28 days after enrollment utilizing an 8-point ordinal scale. 1062 patients were randomized, 517 in the remdesivir group and 508 in the placebo group completed the trial, recovered or died.   The median time between symptom onset and randomization was 9 days. Patients in the remdesivir group had a faster time to recovery compared to those in the placebo group. The median time to recovery was 10 days and 15 days for patients treated with remdesivir and placebo, respectively (rate ratio for recovery, 1.29; 95% CI, 1.12-1.49; p<0.001). Patients with a baseline ordinal scale of 5 had the largest rate ratio for recovery as well as patients who were randomized in the first 10 days of symptom onset. A survival benefit by day 15 was noted, with a mortality rate of 6.7% for the remdesivir group versus 11.9% for the placebo group (hazard ratio for death, 0.55; 95% CI, 0.36-0.83), with the incidence rising to 11.4% and 15.2 %, respectively by day 29.   The largest difference in mortality between-groups was among patients with a baseline ordinal score of 5. No new safety signals were noted. (Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19 - final report. N Engl J Med; DOI: 10.1056/NEJMoa2007764. [Epub ahead of print (Oct 8, 2020).

   a) ACTT-2 will evaluate 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. (https://clinicaltrials.gov/ct2/show/NCT04401579)

7) 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)

8) FDA approves remdesivir for treatment of COVID-19. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19

9) The WHO challenges the use of remdesivir based on findings of 11,000 patients. This was challenged by many who state is was poorly conducted as it was not double blinded. Results showed Death rates after 28 days, the need for breathing machines and time in the hospital were relatively similar for those given remdesivir versus usual care. https://apnews.com/article/virus-outbreak-donald-trump-united-nations-07353942476703499ed0e668eba52178

Recommendations
   1) If eligible, use of remdesivir
       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. Should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care

Dosing Regimen

1) 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. Currently OSU practice suggests 5 days

Monitoring and Toxicity

1) Elevated liver function tests (AST, ALT), phlebitis, constipation, headache, nausea
   a) Increased transaminitis may require discontinuation of remdesivir, and based on two patients may be treated successfully with NAC. https://www.empr.com/home/news/acetylcysteine-treatment-for-acute-liver-failure-associated-with-remdesivir/?utm_source=newsletter&utm_medium=email&utm_campaign=mpr-dailydose-hay-20201011&cpn=&hmSubId=dmL_U-IjanY1&hmEmail=_6Ym_Xl5ytac09PBhOn4zZlS2gCqT7BY0&NID=1730350034&c_id=&email_hash=abe4c36a01e3c92cd22cb264da83f798&dl=0&mpweb=1323-107983-6339279

2) Renal considerations:
   a) 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. (Health Care Provider EUA for Remdesivir. https://www.gilead.com/-/media/files/pdfs/remdesivir/eua-fact-sheet-for-hcps.pdf)
   b) Remdesivir is co-formulated with sulfobutyl ether β-cyclodextrin (SBECD) which are renally eliminated, so there is a theoretical risk of accumulation in renal failure promoting further renal injury, similar to intravenous voriconazole. 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. In addition, RRT and HD remove SBECD and therefore significant accumulation is expected to occur when dialysis is held for a prolonged time. 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 2020; 31 (7) 1384-1386.)

3) Drug Interactions
   a) Hydroxychloroquine or chloroquine plus remdesivir 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. This is supported by preliminary findings from the Phase 3 Simple Severe Study where rates of recovery were lower in patients who received remdesivir and hydroxychloroquine versus those who only received remdesivir.

Hydroxychloroquine and Chloroquine

Pathophysiology

HCQ was hypothesized to act through multiple mechanisms including inhibition of viral entry and release into the host cell, reduction of viral infectivity, and potential immune modulation through reduction of pro-inflammatory cytokines. (Devaux et al, *Int J Antimicrob Agent*, 2020) Initial in vitro data supported its potential involvement in treatment of SARS-CoV-2 (Yao, et al Clin Infect Dis 2020; Liu, et al. Cell Discov 2020), so further studies of in vivo use were conducted.

Evidence

Randomized, Controlled Trials
1) Treatment of hospitalized patients
    a. Tang et al: A study conducted in China on 150 patients (148 with mild-moderate COVID-19) compared hydroxychloroquine to standard of care. Results showed no difference in negative seroconversion by day 28 or time to negative seroconversion. (Tang W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomized controlled trial. BMJ. 2020 May 14; 369:m1849. PMID: 32409561 DOI: 10.1136/bmj.m1849)
    b. Cavalcanti et al: Adult patients in Brazil not requiring supplemental oxygen or requiring rates lower than 4 L/min were randomized 1:1:1 to receive hydroxychloroquine (n=159), hydroxychloroquine plus azithromycin (n=172), or standard of care (n=173). No significant difference was seen in primary endpoint of clinical status at day 15, or secondary outcomes of need for mechanical ventilation, duration of hospitalization, or in-hospital death. (Cavalcanti AB, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. N Eng J Med. 2020 Jul 23 [Epub ahead of print]. PMID: 32706953 DOI: 10.1056/NEJMoa2019014.)
    c. RECOVERY Trial (not peer-reviewed or published): The hydroxychloroquine arm of this adaptive trial was stopped early because of no benefit seen in the hydroxychloroquine arm in 28-day mortality or duration of hospitalization. (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)
2) Treatment of outpatients
    a. Skipper et al: In 423 patients randomized to hydroxychloroquine vs placebo where symptoms were present for no more than 4 days, no difference was seen in symptom severity, hospitalization, or death. (Skipper CP, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. Ann Intern Med. 2020 July 16 [Epub ahead of print]. PMID: 32673060 DOI: 10.7326/M20-4207.)
    b. Mitja et al: A total of 293 patients who were classified as having mild COVID-19 not requiring hospitalization were randomized 1:1 to hydroxychloroquine or usual care. No difference was seen in primary outcome of reduction of viral RNA load at days 3 or 7 or secondary outcomes of time to resolution of symptoms or hospitalization. (Mitja O, et al. Hydroxychloroquine for early treatment of adults with mild Covid-19: a randomized-controlled trial. Clin Infect Dis. 2020 Jul 16; ciaa1009 [Epub ahead of print]. PMID: 32674126 DOI: 10.1093/cid/ciaa1009.)
3) Post-exposure prophylaxis

a. Boulware et al: 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. Subgroup analysis comparing patients taking hydroxychloroquine with zinc versus those not taking zinc showed no difference in prevention of COVID-19 infection. (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).])

4) Pre-exposure prophylaxis

a. Abella et al: Randomized, double-blind, placebo-controlled trial evaluating conversion of seropositivity SARS-COV-2 in patients taking hydroxychloroquine (n=64) versus placebo (n=61) showed no difference in rate of positivity in healthcare personnel working 20 hours or more per week. Trial was halted at second planned interim analysis. (Abella BS, et al. Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: a randomized clinical trial. JAMA Intern Med. 2020 Sep 30 [Epub ahead of print].)

Retrospective/Observational Trials:

1) Geleris, NYC: Hydroxychloroquine administration was not associated with a lowered or increased risk of intubation or death in hospitalized patients with respiratory failure in a New York City large medical center. (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)].

2) Rosenberg, NYC: 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)

3) Arshad et al, Henry Ford: 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. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. IJID 2020;97:396-403. https://doi.org/10.1016/j.ijid.2020.06.099)

Recommendations

1) TREATMENT: Hydroxychloroquine should not be used as treatment for hospitalized patients with SARS-CoV-2.
   a. 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. (https://www.fda.gov/media/138945/download) Reasons include:
      i. Dosage regimens detailed are unlikely to produce antiviral effect.
      ii. Decreased viral shedding has not been replicated.
      iii. U.S. treatment guidelines do not recommend use outside of clinical trials.
      iv. Randomized, controlled studies do not show improvement in mortality, hospital length of stay, or prevention of mechanical ventilation.
         1. RECOVERY Trial halts Hydroxychloroquine arm early: 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
         2. SOLIDARITY Trial halts hydroxychloroquine arm early: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments
         3. Novartis, makers of hydroxychloroquine, halt COVID-19 clinical trial because of slow enrollment: https://www.novartis.com/news/media-releases/novartis-discontinues-hydroxychloroquine-clinical-trial-based-slow-enrollment-remains-committed-pandemic-research-efforts
2) POST-EXPOSURE PROPHYLAXIS: Hydroxychloroquine should not be used as post-exposure prophylaxis in the setting of high-risk exposure to SARS-CoV-2.

Monitoring and Toxicity

1) Hydroxychloroquine is contraindicated in epilepsy and porphyria. Known adverse effects include:
   a) Bone marrow suppression, hypoglycemia, methemoglobinemia, cardiomyopathy and retinopathy, QT-segment prolongation and therefore torsades de pointes
      i) For a full list of QTc prolonging medications, please visit https://www.crediblemeds.org/
      ii) 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
2) Drug Interactions

a) Decreased antiviral activity of remdesivir when combined with hydroxychloroquine/chloroquine
   i) https://www.fda.gov/media/137566/download
   ii) 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

Lopinavir/ritonavir

Pathophysiology

Lopinavir/ritonavir (Kaletra, LPV/r) has been available since 2000 as an antiretroviral agent in the treatment of human immunodeficiency virus (HIV). 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. Lopinavir was thought to work against coronaviruses like SARS-CoV-2 by inhibiting 3-chymotrypsin-like protease (3CL^{pro}).

Evidence

1) A randomized, controlled, open-label trial assessed lopinavir-ritonavir (n=99) vs. standard of care (n=100) in SARS-CoV-2 patients. Treatment with LPV/r was not associated with a difference in time to clinical improvement or mortality. Randomization didn't occur until a median of 13 days after symptom onset however, suggesting the window for benefit may already have already closed. (Cao et al, *N Engl J Med*, 2020)

2) 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)

3) The lopinavir/ritonavir arm (vs. standard of care) of the Solidarity Trial, which was established by WHO, has been discontinued. Interim results 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 for treatment of COVID-19.

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 https://www.ahajournals.org/doi/10.1161/CIRCEP.120.008798

Immune-Based Therapy

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) Recommend patient that have severe or critical illness related to COVID-19 be considered for plasma
   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) Patients interested in donating plasma
    i) Patient needs to register on the my biolink website at my.biolinked.org website OBI will call patient to schedule once the order has been received from the physician and the biolink has been completed by patient.
        (1) Donors can donate plasma as frequently as every 28 days
        (2) 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).
        (3) 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.
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) Convalescent Plasma has received EUA as of August 2020. https://www.npr.org/sections/coronavirus-live-updates/2020/08/23/905277083/fda-authorizes-convalescent-plasma-as-emergency-treatment-for-covid-19
    a) This has been met with some opposition based on limited evidence of the degree of efficacy in COVID-19 https://www.thoracic.org/covid/atscovid19-082820.pdf?utm_campaign=ATS%20General&utm_medium=email&_hsmi=94149338&_hsenc=p2ANqtz---L4jN5haLkDG_xoYFA3UIDt988F2mX-uM9uvIHvWPmb3hEGhbHt1P3MyxDRNjd4DUbHBWvEdYh1OLACPXu2TjhW4Ytg&utm_content=94149338&utm_source=hs_email

Evidence:

1) Several uncontrolled case series show the benefit of critically ill patients with COVID-19.
        a. https://jamanetwork.com/journals/jama/fullarticle/2763983
        b. https://www.pnas.org/content/early/2020/04/02/2004168117
2) A study published in the American Journal of Pathology shows benefit of transfusing convalescent plasma within 72 hours and with high anti-RBD titers, preferably > 1:1350. Confounding factors included concomitant medications being administered between groups. https://ajp.amjpathol.org/article/S0002-9440(20)30370-9/fulltext
3) 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.
        a. 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

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

5) 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

6) An open label, parallel arm, phase II, multicenter, randomized controlled trial in 39 public and private hospitals across India found no association with a reduction in progression to severe covid-19 or all-cause mortality. https://www.bmj.com/content/371/bmj.m3939

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 as follows:

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 or until hospital discharge, whichever comes first.
   a. If dexamethasone is unavailable, the NIH supports using equivalent dosing to dexamethasone (6 mg) with prednisone (40 mg, once daily or divided twice daily), methylprednisolone (32 mg, once daily or divided twice daily), or hydrocortisone (160 mg, divided two to four times daily).

2) 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 10/15/2020.)

3) IDSA supports the use of corticosteroids in hospitalized patients with COVID who are severe (SpO2 ≤94% on room air or requiring supplemental oxygen) or critically ill (mechanically ventilated, ECMO, or patients with end-organ dysfunction/ARDS). (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-5, accessed 10/15/2020)

4) WHO supports steroids for COVID-19 treatment in patients with severe or critical COVID. https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1

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:

Dexamethasone:

1) RECOVERY Trial, RCT: Preliminary results are available from the RECOVERY trial evaluating dexamethasone as a treatment for the novel coronavirus. The dose of dexamethasone used was 6 mg (PO or IV) once daily for 10 days. 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). Dexamethasone as a treatment for the novel coronavirus reduced 28 day mortality rates in 36% in ventilated patients (29.3% vs. 41.4%; OR 0.64; 95% CI 0.51-0.81) and by 18% in other patients receiving oxygen therapy only (23.3% vs. 26.2%; OR 0.82; 95% CI 0.72-0.94). Results were not statistically significant in patients not requiring mechanical ventilation or supplemental oxygen support (17.8% vs. 14.0%; OR 1.19; 95% CI 0.91-1.55). 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. These results prompted the NIH and IDSA to revise their treatment recommendation for corticosteroids in patients with COVID-19 who require supplemental oxygen, echoed in the recommendation above. (The Recovery Collaborative Group. Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report. N Engl J Med 2020; DOI: 10.1056/NEJMoa2021436 [Epub ahead of print (July 17, 2020)].)
   a. 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&m_bt=922415890

Methylprednisolone

1) MetCOVID Trial, RCT: MetCOVID is a double-blind, placebo-controlled phase 2b trial comparing the efficacy of methylprednisolone (MP) 0.5 mg/kg BID x5 days vs. placebo in hospitalized patients with suspected COVID-19. All patients with ARDS were also initiated on ceftriaxone + azithromycin (or clarithromycin) per hospital protocol. The primary outcome was 28-day mortality. From April18-June 16, 2020, 416 patients were enrolled and 393 patients completed follow-up. No major

differences in baseline characteristics were noted and a median of 10 doses were administered. IL-6 inhibitors, IL-1 inhibitors, remdesivir and convalescent plasma were not available during the trial period. 28-day mortality was 38.2% and 37.1% in the placebo and MP arms (p=0.629), respectively. In a post hoc analysis, patients >60 years of age were noted to have reduced mortality. These patients had a higher CRP compared to those </= 60 years of age. The authors hypothesize that a late initiation of MP therapy, a study site receiving transfers of critically ill patients and short treatment duration may have contributed to the overall high mortality. (Jeronimo C, et al. Methylprednisolone as Adjunctive Therapy for Patients Hospitalized with COVID-19 (MetCOVID): A Randomised, Double-Blind, Phase 2b, Placebo-Controlled Trial. Clin Infect Dis, 12 Aug 2020, https://doi.org/10.1093/cid/ciaa1177)

2) Nelson et al, case-control: A propensity-score matched case control study of 117 patients who received methylprednisolone was evaluated for ventilator free days at day 28. Ventilator free days were significantly higher in the methylprednisolone group compared to the no-methylprednisolone group (6.21±7.45 versus 3.14±6.22; P = 0.044). Also seen was an increased probability of getting extubated if patients were on methylprednisolone, but no significant difference in mortality between groups. (Nelson BC et al. Clinical outcomes associated with methylprednisolone in mechanically ventilated patients with COVID-19. Clin Infect Dis 2020;https://doi.org/10.1093/cid/ciaa1163 [Epub ahead of print (August 9, 2020)].)

3) Wu et al, retrospective: A retrospective cohort of 201 patients with COVID-19 pneumonia showed a lower mortality in patients with COVID-19 who developed 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. [Epub ahead of print (March 13, 2020).])

4) Wang et al, retrospective: A 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.)

JAK Inhibitors (Baricitinib, fedratinib, ruxolitinib)

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

Recommendation

Baricitinib should only be used in the context of a clinical trial and in conjunction with the COVID-19 Task Force and ID. **OSU is actively enrolling patients as of July 2020 into the COV-BARRIER trial.**

COV-BARRIER: 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. Dose of baricitinib is 4mg by mouth daily, adjusted if eGFR is <59. Baricitinib is not recommended if eGFR is <30. The primary endpoint is the proportion of patients requiring non-invasive ventilation/high-flow oxygen or invasive mechanical ventilation by day 28. (U.S. National Library of Medicine. ClinicalTrials.gov. Accessed 2020 Aug 22. Available from: https://clinicaltrials.gov/ct2/show/NCT04421027)

ACTT-2: Early and non-peer-reviewed results from the NIAID and NIH-funded study ACTT-2 show the addition of baricitinib to remdesivir decreases hospital stay by an additional day. Patients were considered recovered if they were able to be discharged from the hospital on no supplemental oxygen. Based on these results, Lilly has announced they will be seeking Emergency Use Authorization from the FDA for baricitinib. (Lilly News Release. Accessed at https://investor.lilly.com/news-releases/news-release-details/baricitinib-combination-remdesivir-reduces-time-recovery Published Sept 14, 2020.)

Monocolonal Antibodies in preventing COVID-19

Physiology

Use of neutralizing IgG1 monoclonal antibodies directed against the spike protein of SARS-CoV, it is theorized that use can block viral attachment and entry into human cells, thus neutralizing the virus, potentially preventing and treating COVID-19.

Evidence

Lilly has successfully completed dosing of LY-CoV555 in a Phase 1 study of hospitalized patients with COVID-19 (NCT04411628) and long-term follow-up is ongoing. BLAZE-1, a Phase 2 study in people recently diagnosed with COVID-19 in the ambulatory setting (NCT04427501), is ongoing. Based on current trends, enrollment is estimated to be completed in September, with initial data readout soon thereafter followed by full data in Q4. LY-CoV555 has been well tolerated at all doses tested and no drug-related severe adverse events (SAEs) have been observed to date. Efficacy data are not yet available.

Regeneron is also studying a monoclonal antibody named REGN-COV2 and is currently in a Phase 1/Phase 2/Phase 3 trial for the treatment of COVID-19 in hospitalized adults (NCT04426695) and in adults being treated in the ambulatory care setting (NCT04425629). This drug is also being studied in patients who are household contacts of a SARS-COV2 infected individual (NCT04452318) and as a part of the RECOVERY trial group in the U.K. (https://newsroom.regeneron.com/news-releases/news-release-details/recovery-covid-19-phase-3-trial-evaluate-regenerons-regn-cov2)

NIH puts pause on monoclonal antibody trial secondary to safety signal in either the pharmaceutical or placebo arm. This study was examining use of monoclonal antibodies in conjunction with remdesivir. https://www.statnews.com/2020/10/13/nih-paused-eli-lilly-covid-19-antibody-trial-because-of-safety-concerns/#:~:text=The%20National%20Institutes%20of%20Health,19%20treatment%20from%20Gilead%20Sciences.

The FDA has granted an EUA for bamlanivimab for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients on 11.10.2020. Bamlanivimab is not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19. A benefit of bamlanivimab treatment has not been shown in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19

Recommendations

Monoclonal Antibodies should only be used in the context of a clinical trial and in conjunction with the COVID-19 Task Force and ID. **OSU is actively enrolling patients as of October 2020 into the BLAZE-2 trial.**

Anti-IL6 Agents (Tocilizumab, Siltuximab, Sarilumab)

Pathophysiology

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

Evidence
1) 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)]

2) 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 [Epub ahead of print (June 24, 2020)].)

3) 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)].)

4) Patients receiving tocilizumab were more likely to have late-onset infections >48 hours after admission. (Pettit NN, et al. Late onset infectious complications and safety of tocilizumab in the management of COVID-19. J Med Virol 2020;1-10. DOI: 10.1002/jmv.26429 [epub ahead of print (August 10, 2020)].)

5) The COVACTA Trial is a phase 3, randomized, double-blind, placebo-controlled trial assessing tocilizumab vs placebo in hospitalized patients with severe COVID pneumonia failed to meet its primary endpoint of improved clinical status (p=0.36; OR 1.19, 95% CI 0.81-1.76) and a key secondary endpoint of a difference in mortality at week 4 (tocilizumab 19.7% vs placebo 19.4% with a difference [95% CI] of 0.3% [-7.6%, 8.2%], p=0.9410). A positive trend in time to hospital discharge was noted in the tocilizumab arm. No new safety signals were noted. Further analysis of the data is pending. (F. Hoffman-La Roche Ltd. https://www.roche.com/media/releases/med-cor-2020-07-29.htm. Accessed 14 August 2020)

6) Tocilizumab did not reduce the risk of clinical worsening in patients with COVID-19 pneumonia. (Salvarani C, Dolci G, Massari M, et al. Effect of Tocilizumab vs Standard of Care on Clinical Worsening in Patients Hospitalized with COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA Intern Med. Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6615.)

7) A double-blind placebo controlled trial assessing the efficacy of tocilizumab in patients with confirmed SARS-CoV-2 was undertaken to determine the impact of early tocilizimab therapy in preventing the progression of COVID-19. 10.6% of patients in the tocilizumab group and 12.5% in the placebo group required intubation or died by Day 28. Benefit of IL-6 blockade was not shown in this trial. (Stone JH, Frigault (MJ, Serling-Boyd NJ, et al. Efficacy of Tocilizumab in

Patients Hospitalized with COVID-19. NEJM. Published online October 21, 2020. DOI: 10.1056/NEJMoa2028836).

Recommendations

1) Anti-IL-6 agents are not recommended unless part of a clinical trial or recommended by ID.
2) For severe cases of COVID-19 with suspicion of cytokine activation syndrome, 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.

Adjunctive Therapy

Thromboprophylaxis

Please reference Hematology – Thrombotic Disease section in handbook for detailed recommendations.

Thromboprophylaxis with enoxaparin or heparin should be considered for patients in the usual doses. There 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
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.

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. For patients that are improving and transferring out of the ICU to the medical ward, it is reasonable to de-escalate to standard VTE prophylaxis dosing. Individual hospitals should determine which regimens best align with institutional experience and workflow. (Barnes GD, Burnett A, Allen A, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum [published online ahead of print, 2020 May 21]. J Thromb Thrombolysis. 2020;1-10.PMID: 32440883 DOI:10.1007/s11239-020-02138-z)

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

Respiratory Therapy

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

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.
   b) Ask patients / families to bring in their home inhalers if possible.
2) In patients WITHOUT suspicion for COVID-19 but with Universal Screening results pending:
   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
Anecdotal reports from Wuhan and Italy indicate that some patients develop very thick secretions causing dangerous mucus plugging. 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) 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.

Inhaled Corticosteroids
1) If a patient uses inhaled corticosteroids for daily management of asthma or COPD, the NIH recommends patients continue those inhalers. (National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines (updated July 30, 2020). From NIH website (https://www.covid19treatmentguidelines.nih.gov/).)
2) A small case series from Japan evaluated the use of ciclesonide and observed benefit in 3 patients. (Iwabuchi K, Yoshie K, Kurakami Y, et al. Therapeutic potential of ciclesonide inhalation for COVID-19 pneumonia: Report of three cases. J Infect Chemother. 2020; 26:625-32. PMID: 32362440. DOI: 10.1016/j.jiac.2020.04.007.)
3) More research is needed to support benefits of using inhaled corticosteroids exclusively for COVID-19 outside of other concomitant diagnoses.

Concomitant Medications

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

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

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. [Epub ahead of print (May 14, 2020)].)

Non-steroidal anti-inflammatory drugs (NSAIDs)

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).

Tissue Plasminogen Activator (TPA)

Recommendations

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).

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.)

Although clinical trials are underway to assess tPA for salvage therapy in COVID-19 patients, at this time there is insufficient evidence to support the use of tPA for COVID-19 unless other conditions are present (National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2020 Jun 1.).

Nitric Oxide

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 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_TuMiELQNZlRKdw&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%202%20COVID-19%20Vaccines

Cardiology

Acute Cardiac Injury

Definition and incidence

Definition: Defined as troponin > 99th percentile per the ACC with an incidence that is difficult to ascertain based on variations in assays. https://www.acc.org/latest-in-cardiology/articles/2020/07/17/08/00/key-points-about-myocardial-injury-and-cardiac-troponin-in-covid-19

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

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).

An article published by HeartRhythm indicates that the likelihood of arrhythmias were likely related to systemic illness, and not COVID-19 directly. https://www.heartrhythmjournal.com/article/S1547-5271(20)30594-4/fulltext

Workup

1) Telemetry, 12-lead EKG, cardiac troponin, BNP

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):

Management

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

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7296319/pdf/main.pdf

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.
3) **For STEMI** with no contraindications, cath lab will take COVID-19 patients, even if ventilated.
    a) 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.
    b) ACC guidelines recommend the following (if cardiac catheterization cannot be performed)

      i) Emergency intravenous thrombolysis is considered the first choice for acute ST-segment elevation myocardial infarction (STEMI)
      ii) 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)*
  For elevated Troponin, but unclear diagnosis of coronary occlusion
    a) **Advanced CV Imaging (Stress Testing, TEE, CT, CTA, MRI, Invasive Coronary Angiography)**
      i) 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.
      (1) Specific considerations:

(a) 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.
(b) TEE
    (i) Only for absolute necessity
(2) Consider alternative noninvasive imaging modalities (e.g. cardiac CT to rule out left atrial appendage thrombus, cardiac CT or PET/CT for endocarditis complications).
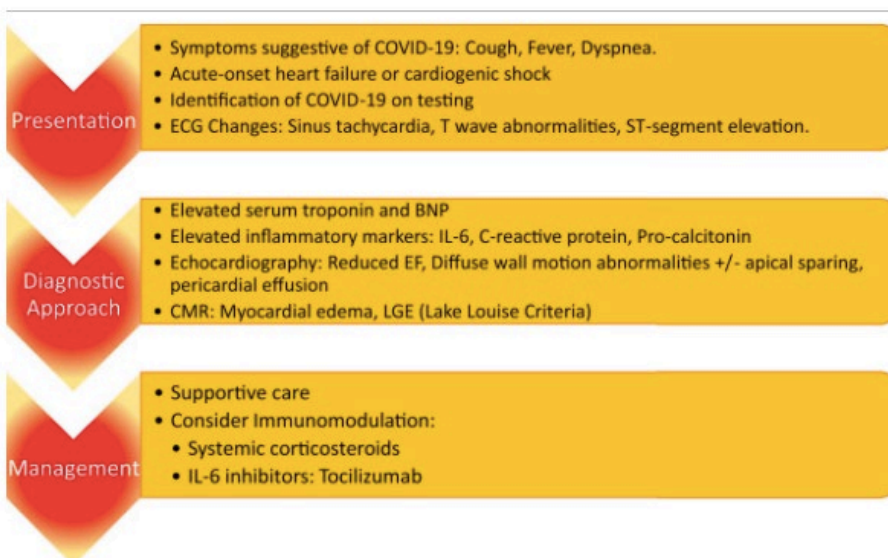
Pericarditis and Myocarditis

Incidence

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).

Clinically suspected myocarditis is a rare cause of myocardial injury, has heterogeneous clinical presentations, and may be underdiagnosed in critically ill patients with COVID-19. Because of the potential for rapid deterioration in COVID-19 patients with myocarditis, it is imperative to be aware of myocarditis as a sequela of COVID-19 and a multidisciplinary team should be formed for all COVID-19 patients with clinically suspected myocarditis. The approach to a patient with myocarditis can be further reviewed here. https://www.sciencedirect.com/science/article/pii/S2589790X20300640

Workup and Management

1) Likely no role for endomyocardial biopsy

Presentation
- Symptoms suggestive of COVID-19: Cough, Fever, Dyspnea.
- Acute-onset heart failure or cardiogenic shock
- Identification of COVID-19 on testing
- ECG Changes: Sinus tachycardia, T wave abnormalities, ST-segment elevation.

Diagnostic Approach
- Elevated serum troponin and BNP
- Elevated inflammatory markers: IL-6, C-reactive protein, Pro-calcitonin
- Echocardiography: Reduced EF, Diffuse wall motion abnormalities +/- apical sparing, pericardial effusion
- CMR: Myocardial edema, LGE (Lake Louise Criteria)

Management
- Supportive care
- Consider Immunomodulation:
  - Systemic corticosteroids
  - IL-6 inhibitors: Tocilizumab

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) 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

Septic Shock and Secondary Infections

Incidence
1) The reported rates of sepsis and septic shock are not reported consistently in currently available literature
    a) Secondary bacterial infections are reported:
        i) 20% of non-survivors (Zhou et al, *Lancet*, 2020)
        ii) 16% of non-survivors (Ruan et al, *Intensive Care Med*, 2020)
        iii) 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) Recommendations of a conservative over a liberal fluid resuscitation strategy is recommended. Recommendations for titration of fluids as well as choice of fluids can be found at the following. https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-US
2) **Pressors**
    a) Norepinephrine is drug of choice, followed by Vasopressin or epinpherine https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-US

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

2) **Corticosteroids for Refractory Shock**

1) Low dose corticosteroid treatment for refractory shock is supported.
   https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-US
   https://www.covid19treatmentguidelines.nih.gov/critical-care/

Cytokine Activation Syndrome

https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2767939

Pathophysiology

1) A subgroup of patients with severe COVID-19 may have cytokine activation syndrome. Patients who had cytokine activation developed rapid progression to ARDS, shock, and multiorgan failure (Chen et al*, Lancet,* 2020)
2) Much discussion over the nomenclature of cytokine storm
   a) https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2767939
3) Suspected 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

Management

Refer to the Clinical Therapeutics Section for targeted therapies to cytokines

Hematology

Thrombotic Disease

Pathophysiology and Evidence:
1) Case reports suggest there may be increased venous thromboembolism (VTE) in COVID-19 patients.
    a) This may be associated with an increased risk of lupus anticoagulant
       https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2769229
    b) Overexpression of tissue factor, endothelial dysfunction, and activation of the contact and complement systems are potential candidates for the increased risk of thrombosis.
       https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.048020

Management:
1) 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).
2) Current recommendations support VTE prophylaxis in standard doses, and should not be withheld if there is an elevated PTT (https://www.onlinejacc.org/content/accj/75/23/2950.full.pdf, https://www.covid19treatmentguidelines.nih.gov/adjunctive-therapy/antithrombotic-therapy/, https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation)
3) Some discussion in regards to higher level of VTE prophylaxis in the critically ill.
   https://link.springer.com/article/10.1007%2Fs11239-020-02138-z
4) Universal thromboprophylaxis is not recommended 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.
5) Speculative use of therapeutic anticoagulation or tissue plasminogen activator (TPA)
   While therapeutic anticoagulation has been used empirically in some severe COVID-19 patients, 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.

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) Data is routinely being updated, most recently suggesting the incidence of thrombotic complications is between 16–49% in patients with COVID-19 admitted to intensive care.
https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(20)30151-4/fulltext
2) Interim guidance recommends regularly monitoring of coagulation parameters, namely D-dimers, prothrombin time, and platelet count—in all patients presenting with COVID-19 and prophylactic use of low molecular weight heparin (LMWH) in all hospitalized patients, unless there are contraindications.
https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(20)30151-4/fulltext

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).

Nephrology

Acute Kidney Injury

Incidence and Pathophysiology
1) Incidence of AKI in COVID-19 varies widely, but estimates range from 1.3% to 36.4%
   https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03065-4
2) Varied theories on the pathophysiology on COVID 19 and the renal system include COVID-19 associated cytokine storm, activation of coagulation factors increasing hypercoagulability and activation of the membrane attack complex. https://jasn.asnjournals.org/content/31/7/1380

Workup:
1) Monitor Creatinine
   a) Studies find variable onset of AKI 6 days after admission in most COVID-19 patients while only 2 days after admission in patients with elevated baseline of serum creatinine.
   https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03065-4
   b) If evidence of rising BUN and/or creatinine, order urinalysis
   c) Patients may present with proteinuria (44%), hematuria (26.9%)
   https://www.kidney-international.org/article/S0085-2538(20)30255-6/pdf

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

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).

2) References frequently updated by The American Society of Nephrology https://www.asn-online.org/covid-19/ASN#ASN_Recommendations

Neurology

Incidence and Pathology

Although neurological complications are rare in SARS, MERS, and COVID-19, the scale of the current pandemic means that even a small proportion could build up to a large number of cases.
Given the 4·8 million cases of COVID-19 globally, these prevalence project to a total of 1805–9671 patients with CNS complications and 2407–7737 with PNS complications. These numbers, which do not include the increasingly important syndromes of stroke-associated COVID-19 infection, will rise as the pandemic continues. https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(20)30221-0/fulltext

Damage within the CNS or PNS might be caused directly by the virus or by the body's innate and adaptive immune responses to infection. Data so far do not suggest that SARS-CoV-2 or related coronaviruses are highly neurovirulent, unlike herpes simplex virus, some enteroviruses, and some arthropod-borne viruses, which can cause rampant destruction of neurons.
https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(20)30221-0/fulltext

The Lancet Neurology describes the potential associated neurological complications that may be seen with COVID-19.
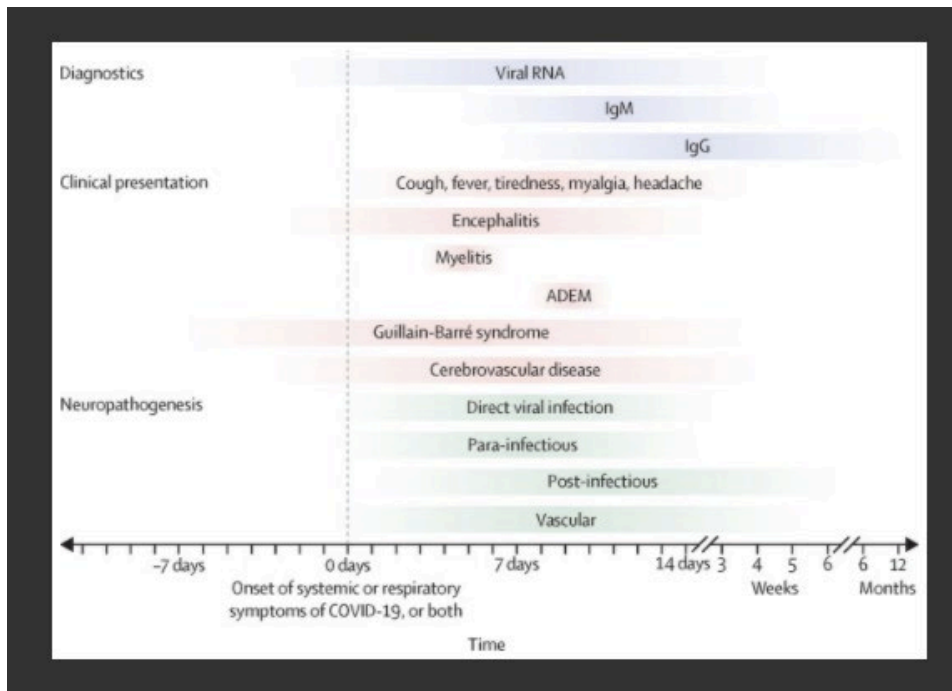
https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(20)30221-0/fulltext

In addition, case reports describing cerebral venous sinus thrombosis, posterior reversible encephalopathy syndrome and others have been described. https://www.aan.com/tools-and-resources/covid-19-neurology-resource-center/covid-19-articles-and-publications/
Work-Up

Clinicians must adopt a methodical approach to investigating patients with possible COVID-19-associated neurological disease, and must systematically consider the evidence for viral infection and the presenting clinical diagnosis, using definitions that distinguish confirmed, probable, and possible cases. https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(20)30221-0/fulltext

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/,
https://cp.neurology.org/content/early/2020/06/30/CPJ.0000000000000897

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.jwatch.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

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.

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

There is current lack of evidence on the relevance of the fecal-oral transmission of SARS-Cov-2, this paper raises the need for more in-depth research to ascertain the actual role of water and sanitation interventions in preventing this route of transmission.
https://onlinelibrary.wiley.com/doi/10.1002/ncp.10554

Management
Symptomatic Treatment

Primary focus is to ensure adequate hydration

The Role of PPI's and contracting COVID-19

Some studies indicate higher risk of contracting COVID being on chronic PPI that may be dose dependent. (https://journals.lww.com/ajg/Documents/AJG-20-1811_R1(PUBLISH%20AS%20WEBPART).pdf), https://www.medscape.com/viewarticle/934332

A Korean Study did not support increased rate of infectivity with chronic PPI use, but did suggest higher severity of illness.
https://gastroenterology.acponline.org/archives/2020/08/28/1.htm?utm_campaign=FY20-21_NEWS_GASTRO_DOMESTIC_082820_EML&utm_medium=email&utm_source=Eloqua

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
   b) Multivariate analysis revealed an association between abnormal liver tests and severe COVID-19, including ICU admission, mechanical ventilation, and death; associations with age, male gender, BMI, and diabetes mellitus were also observed. Transaminases seem to be the most affected (more so than Alkaline phosphatase and bilirubin)
   https://aasldpubs.onlinelibrary.wiley.com/doi/abs/10.1002/hep.31487
      i) Up to 53% of patients have abnormal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [Zhang et al, *Lancet Gastroenterol Hepatol,* 2020].
      ii) Bilirubin and alkaline phosphatase tend to be spared, bilirubin more so than alkaline phosphatase (both < 10%)
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

1) ASCO provides an excellent overview of patients with a concomitant diagnosis of malignancy and COVID-19 https://www.asco.org/asco-coronavirus-information/care-individuals-cancer-during-covid-19
    a) The best available evidence available at this time suggests that patients with cancer are at increased risk of death compared to patients without cancer.
    b) Disease specific information (according to malignancy type) can be found here https://www.asco.org/asco-coronavirus-resources/care-individuals-cancer-during-covid-19/disease-specific-information

2) **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) 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.

For those with febrile neutropenia and COVID, follow standard guidelines:

https://acphospitalist.org/archives/2016/02/expert-analysis-neutropenic-fever.htm

MD Anderson has an excellent flow sheet

https://www.mdanderson.org/content/dam/mdanderson/documents/for-physicians/algorithms/clinical-management/clin-management-neutropenic-fever-inpt-solid-web-algorithm.pdf

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: https://link.springer.com/article/10.1007/s11154-020-09569-2

Fig. 1
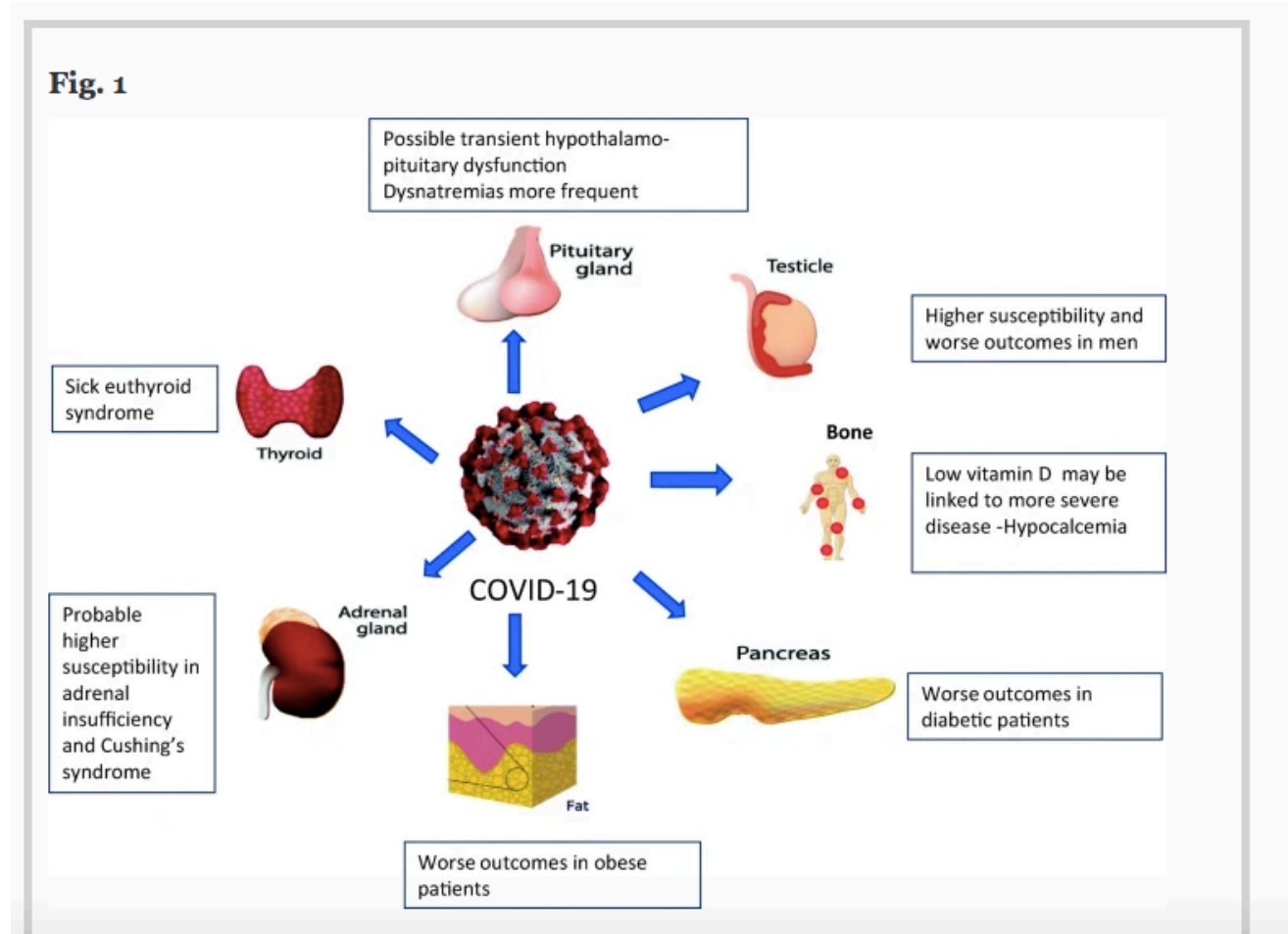
Diabetes

Diabetes has an increased risk of morbidity and mortality in patients that are affected by COVID with 78% of those admitted to the hospital having a diagnosis of diabetes, with a suspected higher case fatality rate. Center for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html, Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323:1239.

Obesity
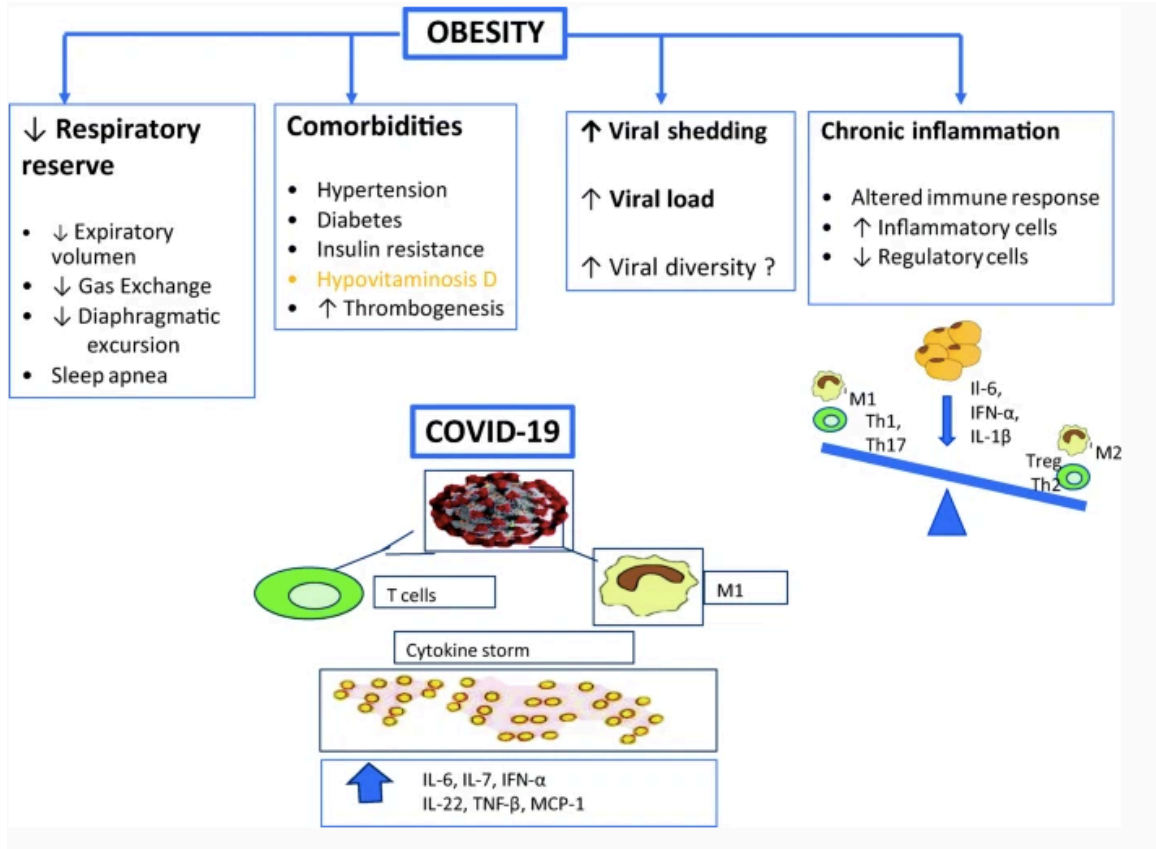
Potential mechanisms that link obesity to worse outcomes in COVID-19. Obese patients have 1) a impaired respiratory function; 2) associated cardiovascular, metabolic and thrombotic comorbidities which reduce the capability to cope with COVID-19. In addition, obese patients have 3) increased viral shedding and viral load and 4) an amplified immune response due to altered balance between inflammatory and regulatory cells. During COVID-19 infection there is also an altered immune response that is amplified by the dysregulated immune system of the obese patients

https://link.springer.com/article/10.1007/s11154-020-09569-2

Among 4103 patients in New York City, BMI >40 kg/m2 was the second strongest independent predictor of hospitalization, after old age. https://www.medrxiv.org/content/10.1101/2020.04.08.20057794v1

Surgical Recommendations

Some **overarching principles** for all cases include the following:

1) Patients should receive appropriate and timely surgical care, including operative management, based on sound surgical judgment and availability of resources.
    a) As there is no way to determine when the pandemic will be over, patients that need surgical intervention must receive the care they need. However, resource utilization and careful strategy and prioritization must continue.
2) Consider nonoperative management whenever it is clinically appropriate for the patient.
3) Consider waiting on results of COVID-19 testing in patients who may be infected.
    a) The following is a list of principles and considerations that was developed by the American College of Surgeons and the American Society of Anesthesiologists to guide physicians, nurses and local facilities in their care in operating rooms and all procedural areas during the ongoing pandemic. https://www.facs.org/covid-19/clinical-guidance/roadmap-maintain-essential-surgery
4) 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) https://www.jwatch.org/na51278/2020/04/03/advice-performing-endoscopy-during-covid-19-pandemic

There exists some concern that surgery may accelerate the development/progression of COVID.
https://www.thelancet.com/pdfs/journals/eclinm/PIIS2589-5370(20)30075-4.pdf
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31182-X/fulltext)
https://jamanetwork.com/journals/jamasurgery/fullarticle/2767370

Pediatrics

A brief overview of COVID and its impact on pediatric populations: https://www.kff.org/coronavirus-covid-19/issue-brief/what-do-we-know-about-children-and-coronavirus-transmission/

Box 1: Data on COVID-19 in Children in the United States

Children, under the age of 18, to date, account for:

- **7%** (more than 200,000) of reported COVID-19 cases* (source CDC)
- **<1%** of reported COVID-19 deaths* (source: CDC)
- **1%** of reported COVID-19 hospitalizations (source: CDC)

The number of reported cases of Multisystem Inflammatory Syndrome in Children (MIS-C) is **342**, including 6 deaths, among states reporting data (source: CDC)

*Based only on data for which age group information was available.

Coronavirus in Children and Transmission

Transmission dynamics and COVID-19 is still not clear. The degree of infectivity, severity of illness and transmission is still unknown. There is some speculation that younger children transmit less than older children (age breakpoint 10). https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30249-2/fulltext

https://www.kff.org/coronavirus-covid-19/issue-brief/what-do-we-know-about-children-and-coronavirus-transmission/

https://pediatrics.aappublications.org/content/146/2/e2020004879

Multisystem inflammatory syndrome related to COVID-19

The most feared complication for COVID-19 in the pediatric patient:

Criteria for MISC as directed by the AAP:

An individual aged <21 years presenting with fever,[1] laboratory evidence of inflammation,[2] and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); **AND**

No alternative plausible diagnoses; **AND**

Positive for current or recent SARS-CoV-2 (COVID-19) infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

Diagnostic testing and treatment can be found at the following website: https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/

Pediatric Clinical Characteristics and Outcomes with COVID-19

A review of ~ 8000 pediatric patients published in the lancet describes fever (59·1%) and cough (55·9%) as the most frequent symptoms. 19·3% of children were asymptomatic. Patchy lesions (21·0%) and ground-glass opacities (32·9%) depicted lung radiograph and computed tomography findings, respectively. Immunocompromised children or those with respiratory/cardiac disease comprised the largest subset of COVID-19 children with underlying medical conditions (152 of 233 individuals). Coinfections were observed in 5.6% of children and abnormal laboratory markers included serum D-dimer, procalcitonin, creatine kinase, and interleukin-6. Seven deaths were reported (0·09%) and 11 children (0·14%) met inclusion for multisystem inflammatory syndrome in children. https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30177-2/fulltext

Treatment for COVID-19 in Children

As COVID-19 continues to evolve, treatments continue to evolve and we recommend those treating COVID-19 in the pediatric population to frequently review the most up to date guidelines.

https://www.covid19treatmentguidelines.nih.gov/overview/children/
https://www.chkd.org/uploadedFiles/Documents/COVID-19/CHKD%20COVID%2019%20treatment%20guideline.pdf

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

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

Obstetrics and Gynecology

Prenatal Care
It is reasonable to space out appointments and provide alternate or reduced prenatal care schedule (group together vaccinations, glucose screenings) and elective ultrasounds are reasonable to discontinue. https://www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics

Increased Maternal Risk with COVID during Pregnancy
An *MMWR* study suggests that pregnant women with COVID-19 are more likely to be hospitalized and are at increased risk for intensive care unit (ICU) admission and receipt of mechanical ventilation than nonpregnant women. https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/special-populations/pregnancy-data-on-covid-19.html

Breast Feeding
Guidance from ACOG indicates that breast feeding should continue based on the benefit to the infant in COVID suspected or confirmed mothers. If possible use electronic breast pumps to collect milk vs. Using a face mask and good hand hygiene if mom is suspected or confirmed positive. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/03/novel-coronavirus-2019

Vertical Transmission and COVID-19
COVID-19 infection has caused higher incidence of fetal distress and premature labor in pregnant women. Although the possibility of vertical transmission in infected pregnant women is rare, four neonates' test results for COVID-19 infection were positive in this review. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7362089/

ACOG recommendations for COVID assessment
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

Assess Patient's Symptoms
Symptoms typically include fever ≥38°C (100.4°F) or one or more of the following:
• Cough   • Difficulty breathing or shortness of breath   • Gastrointestinal symptoms

— No → Routine Prenatal Care

Yes ↓

Conduct Illness Severity Assessment
• Does she have difficulty breathing or shortness of breath?
• Does she have difficulty completing a sentence without gasping for air or needing to stop to catch breath frequently when walking across the room?
• Does patient cough more than 1 teaspoon of blood?
• Does she have new pain or pressure in the chest other than pain with coughing?
• Is she unable to keep liquids down?
• Does she show signs of dehydration such as dizziness when standing?
• Is she less responsive than normal or does she become confused when talking to her?

Any Positive Answers →

Elevated Risk
Recommend she immediately seek care in an emergency department or equivalent unit that treats pregnant women. When possible, send patient to a setting where she can be isolated.
Notifying the facility that you are referring a PUI is recommended to minimize the chance of spreading infection to other patients and/or healthcare workers at the facility
Adhere to local infection control practices including personal protective equipment

No Positive Answers ↓

Assess Clinical and Social Risks
• Comorbidities (Hypertension, diabetes, asthma, HIV, chronic heart disease, chronic liver disease, chronic lung disease, chronic kidney disease, blood dyscrasia, and people on immunosuppressive medications)
• Obstetric issues (eg, preterm labor)
• Inability to care for self or arrange follow-up if necessary

Any Positive Answers →

Moderate Risk
See patient as soon as possible in an ambulatory setting with resources to determine severity of illness.
When possible, send patient to a setting where she can be isolated. Clinical assessment for respiratory compromise includes physical examination and tests such as pulse oximetry, chest X-ray, or ABG as clinically indicated.
Pregnant women (with abdominal shielding) should not be excluded from chest CT if clinically recommended.

No Positive Answers ↓

Low Risk
• Refer patient for symptomatic care at home including hydration and rest
• Monitor for development of any symptoms above and re-start algorithm if new symptoms present
• Routine obstetric precautions

← If no respiratory compromise or complications and able to follow-up with care

If yes to respiratory compromise or complications ↓

Admit patient for further evaluation and treatment. Review hospital or health system guidance on isolation, negative pressure and other infection control measures to minimize patient and provider exposure

Abbreviations: ABG, arterial blood gases; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus.
Healthcare providers should immediately notify their local or state health department in the event of a PUI for COVID-19 and should contact and consult with their local and/or state health department for recommendations on testing PUIs for COVID-19.

Intrapartum Care

No indication for scheduling C-sections in mothers that are COVID positive.

Inductions of labor and cesarean deliveries should continue to be performed as indicated. Decisions on how to schedule these procedures in the time of the COVID-19 pandemic are best made at the local facility and systems level, with input from obstetric care professionals and based on health care personnel availability, geography, access to readily available local resources, and coordination with other centers.

Delayed cord clamping is still acceptable.

https://www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics

ON THE HORIZON

New treatment options

1. hIVIG in combination by remdesivir is being evaluated by the NIH in Phase II trials based the theory that highly concentrated antibodies against coronavirus will provide cover if given early on in an acute coronavirus infection.
   https://dgalerts.docguide.com/nih-trial-testing-hyperimmune-intravenous-immunoglobulin-plus-remdesivir-treat-covid-19-begins?nl_ref=newsletter&pk_campaign=newsletter&nl_eventid=71604&nl_campaignid=3641&pw_siteID=25&ncov_site=covid-19&MemberID=302411139

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